Clinical and Translational Imaging
https://doi.org/10.1007/s40336-021-00477-2

MINI-REVIEW

Clinical application of radioiodinated antibodies: where are we?

Maria Cristina Oliveira[1] · **João D. G. Correia**[1]

Received: 8 October 2021 / Accepted: 9 December 2021

Abstract
Eradication of cancer still remains an upsetting issue despite our increased understanding of the molecular basis of carcinogenesis. Factors such as the molecular heterogeneity of some tumours and initial diagnosis at advanced stages hamper effective disease treatment. Given the ineffectiveness of current treatments, the development of newer therapeutic modalities to address clinical unmet needs is still mandatory. Radioimmunotherapy (RIT) that combines the use of specific antibodies against tumour-associated antigens with the cytotoxic properties of therapeutic radionuclides is amongst those approaches. The potential of monoclonal antibodies to complement current treatment protocols may bring a significant improvement to the overall therapeutic outcomes of oncologic disorders. RIT permits the delivery of a high dose of therapeutic radiation to cancer cells, while minimizing the exposure of normal cells. ^{131}I and ^{90}Y have been used in > 95% of clinical RIT trials and represent the current standard to which all other radionuclides are compared. Both β-particle-emitting isotopes qualify for RIT because of their favourable emission characteristics and availability and flexible radiochemistry. The importance of radioiodine in nuclear medicine together with the success of radioiodinated antibody-based drugs in the clinical setup prompted us to provide an updated overview of the application of radioiodinated antibodies in RIT and anticipate potential relevant accomplishments in the near future.

Keywords Antibodies · Hematologic malignancies · Radioimmunotherapy · Radioiodine · Solid tumours

Abbreviations

L8A4	EGFRvIII-targeting monoclonal antibodies
Hepama-1	Anti-HCC monoclonal antibody
L6	Tumour-associated antigen
[^{125}I]-SGMIB	N-succinimidyl 4-guanidinomethyl-3-[^{125}I]iodobenzoate
^{131}I-*ch*TNT-1/B mAb	Cotara®
^{131}I-ERIC-1	Labelled monoclonal antibody against NCAM
^{131}I-L19SIP	Radretumab
^{131}I-UJ13A	Labelled monoclonal antibody against NCAM
^{18}F-FDG	18F-fluorodeoxyglucose
3F8	Murine monoclonal IgG3 antibody against GD2
A33 antigen	Transmembrane protein expressed almost exclusively by intestinal epithelial cells
AFP	Alpha-fetoprotein
alpha-IFN	Alpha interferon
ASCO	American Society of Clinical Oncology
B72.3	Monoclonal anti-TAG-72 antibody
BC	Breast cancer
BC-2, BC-4, 81C6, ST2146, ST2485, F16, P12	Murine antibodies against tenascin-C
BT-474	Human breast carcinoma cell line (HER2+, ER+)
BTD	Breakthrough therapy designation
c, ch	Chimeric
C5	Complement protein

✉ Maria Cristina Oliveira
cristinaoliveira@ctn.tecnico.ulisboa.pt

✉ João D. G. Correia
jgalamba@ctn.tecnico.ulisboa.pt

[1] Departamento de Engenharia e Ciências Nucleares (DECN) e Centro de Ciências e Tecnologias Nucleares (C2TN), Instituto Superior Técnico, Universidade de Lisboa, CTN, Estrada Nacional 10 (km 139,7), 2695-066 Bobadela, LRS, Portugal

Published online: 11 January 2022

CA125	Cancer antigen 125
CaPan1	Human pancreatic ductal adenocarcinoma cell line
CC49	Monoclonal anti-TAG-72 antibody
CD	Cluster of differentiation
CDR	Complementarity-determining region
CEA	Carcinoembryonic antigen
CED	Convection-enhanced delivery
*ch*81C6	Chimeric antibody against tenascin-C
CHOP	Cyclophosphamide-Adriamycin-Oncovin-prednisone
CLM	Colorectal liver metastasis
COL-1	Monoclonal antibody specific for CEA
CR	Complete response
CRC	Colorectal cancer
cRIT	Compartmental radioimmunotherapy
CT	Computed tomography
CTV	Clinical target volume
CVP	Cyclophosphamide–vincristine–prednisolone
DLBCL	Diffuse large B-cell lymphoma
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
EDB	Extra domain B of fibronectin
EGF	Epidermal growth factor
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
EpCAM, KSA, KS1/4 or 17–1 antigen	Epithelial cell adhesion molecule
F(ab′), F(ab′)2	Antibody fragments
FA8H1	Murine–human anti-VEGFR2 chimeric Fab
FDA	Food and Drug Administration
FL	Follicular lymphoma
FN	Fibronectin
GBM	Glioblastoma multiforme
GD2	Disialoganglioside
GLOBOCAN	Global cancer incidence, mortality and prevalence
GP38	Glycoprotein 38
GSK	Glaxo Smith Kline
HAb18G/CD147	Hepatocellular carcinoma-associated antigen
HAMA	Human anti-murine antibody
HACA	Human anti-chimeric antibody
HCC	Hepatocellular carcinoma
HER2	Human epidermal growth factor receptor 2
HMFG	Human milk fat globule
IgE, IgG	Immunoglobulin
IL	Interleukin
ic	Intracavitary
ip	Intraperitoneal
it	Intratumoural
iv	Intravenous
kDa	Kilodalton
LNCaP cells	Androgen-sensitive human prostate adenocarcinoma cells
LQC	Last qualifying chemotherapy
LS-174 T	Human colon cancer cell line
m	Murine
MA	Meconium antigen
mAb	Monoclonal antibody
mAb806	EGFRvIII-targeting monoclonal antibodies
mCRPC	Metastatic castration-resistant prostate cancer
MDA-MB-453	Breast cancer cell line (AR^+, ER^-, PR^-, $HER2/neu^-$)
MG	Malignant glioma
MOv	Murine monoclonal antibody against the epitope of human folate-binding protein
MSKCC	Memorial Sloan Kettering Cancer Center
MTD	Maximum tolerated dose
MUC	Mucin
NCA	Nonspecific cross-reacting antigen
NCAM	Neural cell adhesion molecule
NED	No evidence of disease
NHL	Non-Hodgkin's lymphoma
NP	Antibody against CEA
OC	Ovarian cancer
OC125	Murine monoclonal antibody that recognizes the antigenic determinant CA125
OS	Overall survival

PAM4	Monoclonal antibody with high specificity for pancreatic ductal adenocarcinoma
PD1	Programmed cell death protein
PET	Positron emission tomography
PFS	Progression-free survival
PLAP	Placental alkaline phosphatase
PR	Partial remission
PSA	Prostate-specific antigen
PSMA	Prostate-specific membrane antigen
rec	Recombinant
RIS	Radioimmunoscintigraphy
RIT	Radioimmunotherapy
RSV	Respiratory syncytial virus
scFv	Single-chain variable fragment
SCRC	Surgery-created resection cavities
SIP	Small immunoprotein
SPECT	Single-photon emission computed tomography
SWOG	Southwest Oncology Group
TAG-72	Tumour-associated glycoprotein 72
TNF	Tumour necrosis factor
TNT	Tumour necrosis therapy
VEGF	Vascular endothelial growth factor
WBRT	Whole brain radiation treatment

Introduction

Radioimmunotherapy (RIT) is a form of targeted radionuclide therapy that uses a monoclonal antibody to deliver localized radiation. It is most appropriate for treatment of multiple tumour sites that cannot be readily excised surgically or irradiated using external beam radiation or brachytherapy. RIT has been established over the past 20 years and is still an important therapeutic approach in haematological malignancies.

Target specificity in the prevention or treatment of diseases such as infection, cancer and autoimmune disorders became more viable through the development of monoclonal antibodies. The mouse hybridoma technology described by Köhler and Milstein in 1975 was a significant step in the development of antibody technology and opened the way for the onset of therapeutic monoclonal antibodies [1]. The first therapeutic murine monoclonal antibody, indicated for the prevention of kidney transplant rejection (Orthoclone, OKT3 from Ortho Pharmaceuticals), was approved by the US Food and Drug Administration (FDA) in 1986. However, monoclonal antibodies of mouse origin were shown to have limited use because of the immunogenicity of murine proteins in humans and the rapid development of a human anti-murine antibody (HAMA) response in the patients. The HAMA response neutralized the efficacy of the murine antibodies and resulted in their rapid clearance from the body. One way to reduce the immunogenicity of murine monoclonal antibodies is the use of recombinant DNA technology to generate a chimeric mouse/human antibody construct in which the epitope-specific variable region of the murine mAb is combined with the constant region of a human immunoglobulin.

In the early 1990s, "chimeric" antibodies were shown to elicit much lower HAMA responses in patients. This class of antibodies include the highly successful anti-CD20 Rituxan® and anti-EGFR Erbitux®, as well as the anti-inflammatory product anti-TNF-α Remicade® [2]. Although superior to murine antibodies, the chimeric versions still pose a moderate risk of immunogenicity due to their residual murine components.

"Humanized" antibodies, in which the complementarity-determining regions (CDRs) of a human antibody gene have been replaced by those from a CDR of a murine mAb gene, were generated in an attempt to further reduce HAMA response in patients. Successful examples of CDR-grafted human antibodies currently in the market include Synagis® (anti-RSV), Herceptin® (anti-HER2), Mylotarg® (anti-CD33)®, Xolair® (anti-IgE), and Avastin® (anti-VEGF-A) [3].

The latest advance in creating less immunogenic antibody-based drugs is the ability to generate fully human monoclonal antibodies (mAbs). Two general methodologies have been developed to prepare fully human antibodies: in vivo strategies using a murine system in which the immunoglobulin genes have been replaced by their human counterparts or in vitro approaches using libraries containing millions of variations of antibody sequences coupled with a mechanism to express and screen these antibodies in vitro, such as *phage display*. The anti-TNF-α antibody Humira®, the first fully human antibody to be approved by the FDA for treatment of rheumatoid arthritis, is still the best selling monoclonal antibody therapy in the market [3]. Some examples of successful therapeutic antibodies that have been approved for clinical use are summarized in Table 1.

The clinical utility of antibodies for both therapeutic and diagnostic applications has been somehow limited mostly by their slow blood clearance and the relatively long time needed to optimally accumulate in tumours, as well as the extensive optimization required for each antibody-tracer

Table 1 Some examples of successful therapeutic antibodies

mAb	Trade name	mAb type (target antigen)	Technology	Therapeutic indication	First EU approval year	First US approval year
Muromanab-CD3	Orthoclone, OKT3	Murine IgG2a CD3	Hybridoma	Kidney transplant rejection	1986	1986
Rituximab	Rituxan® MabThera	Chimeric IgG1 CD20	Hybridoma	Non-Hodgkin's lymphoma	1998	1997
Cetuximab	Erbitux®	Chimeric IgG1 EGFR	Hybridoma	Colorectal cancer	2004	2004
Infliximab	Remicade®	TNF-α	Hybridoma	Crohn's disease	1999	1998
Palivizumab	Synagis®	Humanized IgG1 RSV	Hybridoma	Prevention of RSV infection	1999	1998
Trastuzumab	Herceptin®	Humanized IgG1 HER2	Hybridoma	Breast cancer	2000	1998
Gemtuzumab ozogamicin	Mylotarg®	Humanized IgG4 CD33	Hybridoma	CD33-acute myeloma	NA	2000
Omalizumab	Xolair®	Humanized IgG1 IgE	Hybridoma	Asthma	2005	2003
Bevacizumab	Avastin®	Humanized IgG1 VEGF-A	Hybridoma	Colorectal cancer	2005	2004
Adalimumab	Humira	Human IgG1 TNF-α	Phage display	Rheumatoid arthritis	2003	2002
Ibritumomab tiuxetan	Zevalin	Murine IgG1 Y-90 CD20	Hybridoma	Non-Hodgkin's lymphoma	2004	2002
Tositumomab and iodine-131	Bexxar	Murine IgG2a I-131 CD20	Hybridoma	Non-Hodgkin's lymphoma	NA	2003
Nimolumab	Opidivo	Human IgG4 PD1	Hybridoma	Melanoma, NSCLC, and others	2015	2014
Pembrozilumab	Keytruda	Humanized IgG4 PD1	Hybridoma	Melanoma, NSCLC, and others	2015	2014
Ustekinumab	Stelara	Human IgG1 IL12/23	Transgenic mice	psoriasis	2009	2009
Eculizumab	Soliris	Humanized IgG2/4 C5	Hybridoma	Paroxysmal nocturnal, haemoglobinuria	2007	2007

RSV respiratory syncytial virus, *TNF-α* tumour necrosis factor alpha

system [4, 5]. Regarding radiolabelled antibodies for imaging or therapeutic applications (RIT), almost all early clinical trials have used whole IgG [6–8]. The slow blood clearance of IgG stimulates tumour uptake, but also exposes the red bone marrow, a highly radiation-sensitive tissue, to a continuous source of low-dose radiation, leading, in some cases, to myelosuppression even before a tumouricidal dose can be achieved [9].

Most of the unwanted properties of intact IgGs that restrict their use in RIT result from their large size (120 kDa). The latter can be reduced by modifying the antibody design, namely by altering the antibody structure to generate lower molecular weight fragments without distressing their specific antigen binding. The first strategy to increase tumour penetration and clearance from normal tissues comprised the use of smaller enzymatically derived antibody fragments $F(ab')_2$ and Fab' that exhibited fast and homogenous tumour localization and shorter serum half-lives. With the advent of genetic engineering, smaller antibody fragments, ranging from 30 to 120 kDa, such as single-chain Fvs (scFv), diabodies, and minibodies, have been developed (Fig. 1).

Current progress in innovative engineered antibodies has been recently reviewed [10]. These new-generation antibody fragments, when compared with intact mAbs and more conventional enzymatically derived fragments, offer several advantages, including as carriers for selective delivery of radionuclides to tumours. An overview of relevant properties of intact antibodies, enzymatic fragments, and other engineered constructs is presented in Table 2.

The rate of clearance of scFv from the blood pool and normal tissues is much faster than that seen for intact IgG, $F(ab')_2$ or Fab' fragments. Faster clearance reduces red marrow exposure, allowing the total administered activity to be

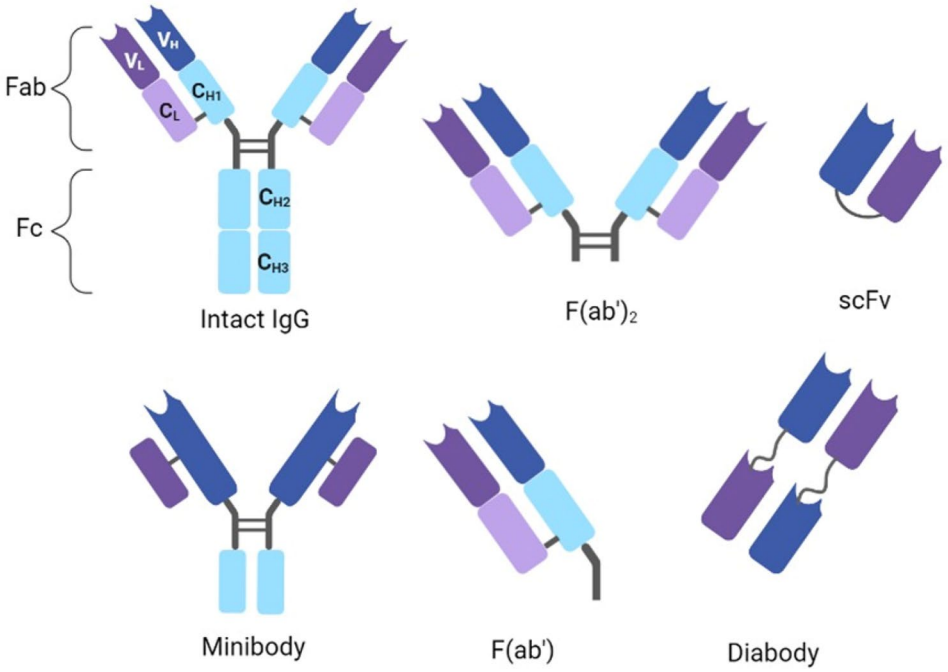

Fig. 1 Schematic representation of an intact antibody and other engineered antibody fragments. Created with BioRender.com. *Fv* variable fragment, *scFv* single-chain variable fragment, *VH* variable heavy region, *VL* variable light region, *CH* constant heavy region, *CL* constant light region, *Fab* antigen-binding fragment, *Fc* constant region fragment

Table 2 Overview of relevant properties of intact antibodies, enzymatic fragments, and other engineered constructs

Format	Intact IgG	F(ab')2	Minibody	Diabody	F(ab)	scFv
MW	150 kDa	120 kDa	80 kDa	55 kDa	55 kDa	25 kDa
Composition	$(V_H+V_L)_2$	$(V_HC_H1+V_L+C_{L)2}$	$(scFv+C_H3)_2$	$(scFv)_2$	$V_HC_H1+V_L+C_L$	(V_H+V_L)
Source		Enzymatic	Engineered	Engineered	Enzymatic	Engineered
Half-life in blood	1–3 weeks	8–10 h	5–10 h	3–5 h	12–20 h	2–4 h
Valency	Bivalent	Bivalent	Bivalent	Bivalent	Monovalent	Monovalent
Clearance route	Liver	Liver, kidney	Liver	Kidney	Kidney	Kidney

increased. Also, autoradiographic studies have indicated that scFv constructs penetrate into the tumour more efficiently than intact IgG or larger fragments. Pharmacokinetics and biodistribution of genetically engineered antibodies have been discussed in detail elsewhere [11, 12].

Most antibodies are "naked" antibodies, meaning that they rely on either blocking an important biological function or on activating the immune system, to elicit a therapeutic effect. However, antibodies are also useful as targeting agents to deliver potent chemo- or radioactive agents, specifically to target cells. Successful examples are the immunoconjugate Mylotarg (an anti-CD33 linked to a cytotoxic agent from the class of calicheamicins) and the anti-CD20 radioimmunoconjugates Zevalin (^{90}Y-ibritumomab tiuxetan) and Bexxar (iodine-131 tositumomab). The first therapeutic clinical trials focused on using radioiodinated antibodies but, over time, advances in chelation chemistry have allowed other new therapeutic radionuclides to be explored (Table 3).

Table 3 Therapeutic radionuclides used for radioimmunotherapy

Radionuclide	Energy (MeV_{max})†	Range†	Half-life
β-emitter			
Yttrium-90	2.28	11.3 mm	2.7 days
Iodine-131*	0.61	2.3 mm	8.0 days
Lutetium-177	0.50	1.8 mm	6.7 days
Rhenium-188	2.12	10.4 mm	0.7 days
Copper-68	0.58	2.1 mm	2.6 days
α-emitter			
Bismuth-213	8.3	60–85 µm	0.8 h
Astatine-211	6.8		7.2 h
Actinium-225	6.8		10 days
Auger electrons			
Iodine-125		2–500 nm	60.5 days

†As reported by Kassis [13]. *Iodine-131 also emits γ-rays with a minimum energy of 364 keV. MeV_{max} maximum range of particulate energy in tissue

Iodine-131 has a long successful history in the treatment of several malignancies due to its short path-length β particles emission, γ emission, long half-life and well-established radiochemistry. Whereas β emission permits the irradiation of small and large foci of targeted tumour tissue with relatively little exposure of neighbouring normal tissues, γ ray emission allows non-invasive tumour imaging, as well as quantitative tumour and organ dosimetry.

The main advantages of ^{131}I are the relatively low cost, and the physical characteristics, which allow its use for both imaging and therapy (*Theranostics*). The main disadvantage is related with the fact that radioiodine is non-residualizing and once internalized in the cell escapes by diffusion across the cell membrane, causing unwanted irradiation of non-targeted tissues (e.g. thyroid and stomach). In addition, the γ rays emitted by ^{131}I may pose a radiation risk to family members and health-care personnel.

Haematopoietic toxicity can also occur due to an extensive radiation exposure resulting from the medium-long range β and γ emissions associated with ^{131}I. Thus, an alternative approach to killing individual tumour cells while sparing the bone marrow would be the use of low-energy Auger electron emitters, such as ^{125}I, conjugated to antibodies that internalize only into the target cells [14]. RIT using Auger electron emitters has been regarded disadvantageous, since the localization of the radionuclide, after receptor binding, is not the nucleus, as required for effective cell killing, but the cytoplasm (internalizing mAbs) or the cell membrane (non-internalizing mAbs). However, clinical trials in patients with advanced colon cancer have demonstrated that RIT with ^{125}I-labelled internalizing antibodies can be achieved without significant patient toxicity or radiation hazard, but only modest antitumour effects were observed [14–16]. Conversely, a preclinical study reported in 2009 by Santoro et al. has suggested that the use of internalizing mAbs, which drive radioactivity in cells near the nucleus, was not a prerequisite to the success of ^{125}I therapy, and ^{125}I-labelled non-internalizing mAbs could be suitable for RIT of small solid tumours [17]. Unfortunately, as far as we are aware, there have not been any subsequent clinical RIT trials attempted with ^{125}I-labelled mAbs in the past decade.

The aim of the present review article is to give an overview of published clinical trials of radioimmunotherapy with radioiodinated monoclonal antibodies for the treatment of solid cancers and haematological malignancies.

Radioiodinated monoclonal antibodies for radioimmunotherapy of solid tumours

Throughout the last sixty decades, several radioimmunotherapeutic drugs have been explored for the treatment of a variety of solid malignancies, including ovarian, colorectal, breast, prostate, pancreatic, hepatocellular, and primary brain tumours. However, up to now, no drug of that class has entered the market. Several new radioimmunotherapeutic agents are still under active clinical investigation, either as single agents or combined with radiosensitizing chemotherapy or with external beam radiotherapy. Progress in chimerization and humanization of antibodies (and antibody fragments), improved pre-targeting methods and dosimetric models, as well as the availability of novel radionuclides have expanded the therapeutic window for these agents.

Ovarian cancer

Ovarian cancer is still a lethal gynaecological malignancy, especially due to late diagnosis in most patients. In 2020 the estimated number of new cases worldwide was 313,959 (1.6%) with 207,252 deaths (2.1%) (GLOBOCAN2020) [18]. Even with the evolution of surgical procedures and the advent of novel targeted therapies, ovarian cancer is in the top ten most common cancers for women in 2020 [18]. The poor prognosis is mainly related to the clinically occult nature of the disease. The lack of specificity associated to conventional therapies together with the heterogeneity that characterizes malignant cells also hampers the possibility of treatment. The most relevant ovarian cancer RIT/RIS clinical trials with radioiodinated antibodies are summarized in Table 4.

Targeting folate receptor α

Folate-binding protein GP38 is a membrane-associated glycoprotein (38 kDa) that mediates the intracellular transport of folates. It is overexpressed in more than 90% of the ovarian carcinomas and in 60% of other gynaecological carcinomas [19]. GP38 is identified by two murine monoclonal antibodies (MOv18 and MOv19) that recognize different epitopes [19].

Immunohistochemical studies with both MOv18 and MOv19 were reported in the literature [20, 21]. MOv18 presented restricted specificity for both malignant and benign ovarian tumours, with no significant immunoreaction towards normal ovary [21, 22]. The administration of murine (m) or chimeric (c) MOv18 IgG to ovarian cancer patients suggested therapeutic benefit without evident associated toxicity. Findings from the first clinical study with ^{131}I-m-MOv18, conducted in 1991 by Crippa et al. [23] suggested its potential application for radioimmunoscintigraphy of ovarian cancer patients. Subsequent preclinical and clinical studies with $^{125/131}$I-m-MOv18 demonstrated good localizing properties in ovarian tumours, both as the whole immunoglobulin G (IgG) and as fragments ($F(ab')_2$) [24, 25]. The efficacy of radioimmunotherapy with ^{131}I-MOv18 was later

Table 4 Relevant RIT/RIS clinical trials in ovarian cancer patients

Antigen/antibody	Trial/phase	Route	Dose/frequency	Remarks /outcomes	Ref.
Folate receptor α (GP38)					
^{131}I-*m*MOv18 IgG	RIS	30 OC *i.p.* (n = 10) *i.v.* (n = 20)	114 MBq *i.p* 103 MBq *i.v*	MOv18 is a suitable mAb for in vivo radiolocalization of OC lesions, with better biodistribution following *i.p.* administration	[23]
^{131}I-*m*MOv18 IgG	RIT/II	*i.p* 16 OC patients	Single mean dose of 14 mg of MOv18 (8–21 mg) labelled with 3700 MBq of ^{131}I	Negligible RIT toxicity HAMA response in 94% (15/16) of patients CR (5/16); NC (6/16); PD (5/16) very effective in the treatment of minimal residual disease	[26]
^{131}I-*m*MOv18 IgG ^{131}I-*c*MOv18 F(ab')2	RIS	*i.v.* (n = 1)	-	Good and specific tumour localization of *m*MOv18 and *c*MOv18 Mab in one patient with ovarian cancer	[24]
$^{131/125}$I-cMOv18 IgG $^{131/125}$I-cMOv18F(ab')2	RIS	*i.v.* (n = 24)	cMOvl8 IgG and cMOv18 F(ab')2 labelled with a low tracer dose of ^{131}I and ^{125}I	Both the highest tumour uptake and the longest retention time are achieved with intact cMOv18 compared to F(ab')2, whereas there is no difference in tumour:non-tumour ratio between IgG and F(ab')2	[25]
^{131}I-cMOv18	RIT/ I	*i.v.* (n = 15)	Single infusion of increasing doses of *c*MOv18 (5–75 mg) 1.4 MBq and 7.4 MBq (laparotomy 2 and 6 days p.i., respectively)	i.v. administration of c-MOv18 IgG in a dose up to 75 mg is safe, inducing only minor side effects at doses of 50 mg or higher No HACA response, no DLT c-MOv18 might be applicable as an unmodified antibody/immunoconjugate in OC treatment	[27]
^{131}I-*c*MOv18 IgG	Dosimetric analysis	*i.p.* (n = 8) *i.v.* (n = 4)	150 MBq *i.p* single infusion 7.50 MBq *i.v* single infusion	Therapeutic tumour doses can be achieved in patients with intraperitoneal ovarian cancer lesions with no normal organ toxicity *i.p.* route seems to be preferable to *i.v.*: tumour uptake at least as high after *i.p.* while haematopoietic toxicity is reduced	[29]
$^{125/131}$I-*c*MOv18 IgG	Comparing *i.p.* and *i.v.* routes	*i.p.* (^{131}I) & *i.v.* (^{125}I) (n = 15)	1.85 MBq 1.85 MBq	Patients were simultaneously injected *i.p.* and *i.v.* with different radionuclides No HACA response Haematological toxicity was observed in both routes of administration. *i.p.* route could be advantageous with respect to bone marrow toxicity, but no advantage could be demonstrated for the *i.p.* route with respect to tumour uptake	[30]
MUC1					
^{131}I-HMFG1 IgG1 ^{131}I-HMFG2 IgG1 ^{131}I-AUA1 IgG1 ^{131}I- H17E2 IgG1		*i.p* 24 adv. OC	Escalating doses 740–7585 MBq	Doses > 5180 MBq more effective than lower doses Antibody-guided irradiation is certainly less toxic and probably as effective as *i.p.* chemotherapy. Possible benefit in patients with small-volume stage III OC	[35]
CA125					
^{131}I-OC125F(ab')2	I	Single *i.p* 29 EOC patients	Escalating doses 740-5180 MBq	Haematologic/gastrointestinal toxicity is predictable and related to antibody dose and clearance rate	[44]
^{131}I-OC125F(ab')2	II	*i.p.* (n = 6)	440 MBq	HAMA in all patients. Toxicity mainly haematological, little therapeutic benefit from *i.p.* RIT in patients with residual ovarian carcinoma	[45]

adv advanced, *OC* ovarian cancer, *DLT* dose-limiting toxicity, *HACA* human anti-chimeric antibody, *HAMA* human anti-murine antibody, *CR* complete response, *NC* no change, *PD* progressive disease

demonstrated in a clinical study enrolling 19 ovarian cancer patients with minimal residual disease [26]. Although low toxicity was reported in this study, most of the treated patients (94%) developed HAMA responses.

Aimed at reducing the immunogenicity of murine MOv18, a chimeric form of the antibody (c-MOv18) was prepared and compared to m-MOvl8. However, both the affinity and immunoreactivity of c-MOv18 were reported to be identical to the murine form [24]. Later, both the efficacy and safety of i.v. administration of ^{131}I-c-MOv18 were established in a dose-escalating phase I trial, suggesting its clinical application as an unmodified antibody or as an immunoconjugate in the treatment of ovarian carcinomas [27].

The influence of the route of administration of radiolabelled c-MOv18 was investigated by two distinct studies where ^{131}I-c-MOv18 was administered by *i.p.* and *i.v.* routes to ovarian cancer patients [28–30]. However, the results from these studies were controversial. The first scintigraphic images showed better accumulation of ^{131}I-c-MOv18 in the ovarian cancer lesions of the patients that had received intraperitoneal administration [29]. Contrary to these findings, van Zanten-Przybysz et al. could not demonstrate any advantage for the *i.p.* route of ^{125}I-labelled c-MOv18 with regard to tumour uptake in suspected ovarian cancer patients [30]. According to van Zanten-Przybysz et al. the better accumulation of ^{131}I-c-MOv18 found in ovarian cancer lesions of patients following *i.p.* administration [29] was probably due the fact that the background radioactivity was not defined and the uptake values were extracted from the images using region of interest (ROI) analysis, which is not as accurate as the direct tissue counting method. Moreover, in some cases, the favourable results for the *i.p.* route are influenced by a persistent nonspecific accumulation of ^{131}I-m-MOv18 in pelvic tissues. Also, *i.v.* and *i.p.* routes of administration were not compared in the same patient in the initial clinical trial [29].

Targeting MUC1

Human milk fat globule membrane protein antibodies (HMFG-1 and HMFG-2) are murine monoclonal antibodies directed at specific epitopes of the MUC-1 gene product, a large and heavily glycosylated mucin expressed on the apical surface of the majority of secretory epithelial cells [31]. MUC-1 is an attractive target for immunotherapy due to its overexpression in 90% of adenocarcinomas, including cancers of the ovary, breast, and pancreas. Moreover, as a result of under glycosylation or aberrant glycosylation in cancerous tissue MUC1 is antigenically distinct from normal tissue mucin [32].

Radiolabelled ^{131}I-HMFG2 has been successful used to image lesions in patients with primary and metastatic ovarian cancers [33]. In selected regions of the body such as the pelvis, where CT scanning and ultrasonography have some limitations, antibody scanning with ^{123}I-HMFG2 has the potential to detect accurately very small lesions such as ovarian tumours with masses less than 0.8 cm in diameter [34].

Promising results from a RIT clinical trial with ^{131}I-HMFG-1 and ^{131}I-HMFG-2, enrolling 24 patients with persistent epithelial ovarian cancer after chemotherapy [35], prompted the use of other therapeutic radionuclides. To this end, yttrium-90, a pure β-emitter, seemed to be a more promising candidate for ovarian cancer radioimmunotherapy [36]. A nonrandomized, extended phase I/II clinical trial suggested that patients with advanced ovarian cancer who had achieved complete remission following conventional therapy might benefit from further treatment with *i.p.* administered ^{90}Y-HMFG-1 [37]. However, a multinational, open-label, randomized phase III trial comparing ^{90}Y-HMFG-1 plus standard treatment versus standard treatment alone in ovarian cancer patients in complete clinical remission after cytoreductive surgery and platinum-based chemotherapy showed no extended survival or time to relapse in patients who had a negative second-look laparoscopy [38]. Although no survival benefit was found as consolidation treatment for epithelial ovarian cancer, an improved control of intraperitoneal disease was demonstrated in a retrospective analysis of this trial [39].

Targeting CA-125

CA125 is an ovarian cancer-associated antigen expressed on tumour cells in over 90% of patients with advanced epithelial ovarian cancer [40]. Preliminary animal and clinical studies with a specific murine monoclonal antibody labelled with ^{131}I, ^{131}I-OC125, have demonstrated selective tumour uptake and favourable tumour to non-tumour ratios suitable for intraperitoneal RIT [41, 42]. Phase I and II clinical trials demonstrated that *i.p.* administration of ^{131}I-OC125 was effective against residual macroscopic or microscopic disease and that a dose of up to 140 mCi of ^{131}I could be safely administered [43, 44]. However, a phase II clinical study with ^{131}I-OC125 F(ab')$_2$ showed little therapeutic benefit in patients with residual ovarian carcinoma after primary treatment with surgery and chemotherapy [45].

Several other ^{131}I-labelled mAbs for RIT in ovarian cancer have also been reported in the literature, but with little or no clinical experience. These include the monoclonal antibodies ^{123}I-Hu2LAP, ^{131}I-H317, and ^{131}I-H17E2, specific for placental-type alkaline phosphatase (PLAP), a surface-membrane enzyme expressed in most ovarian carcinomas

[46, 47]. The human IgG Hu2LAP labelled with ^{123}I and the mouse IG_1 H317 and IG_1 H17E2 labelled with ^{131}I have also been used for ovarian tumour detection [48, 49]. However, no therapeutic studies have been reported so far.

Colorectal cancer

Colorectal cancer (CRC) ranks third in terms of incidence and second in terms of mortality. Indeed, more than 1.9 million new colorectal cancer cases and 935,000 deaths were estimated to occur in 2020, which accounts for about one in ten cancer cases and deaths [50]. In this manuscript, colorectal cancer will be defined as the combination of cancers of the colon, rectum, and anus. The more important RIT/RIS clinical trials conducted in colorectal cancer patients are outlined in Table 5.

Targeting CEA

Carcinoembryonic antigen (CEA), a glycosylated cell surface glycoprotein (molecular weight = 200 kDa), was first identified from extracts of human adenocarcinoma of the colon by Gold and Freedman [51]. As CEA is highly overexpressed in breast, lung and pancreatic cancer and, particularly, in CRC [52, 53], it has become one of the first tumour-associated antigens to be explored at the clinical level. CEA is routinely detected in serum as a tumour biomarker.

The first clinical trial testing the efficacy of RIT with an anti-CEA radiolabelled antibody was reported by Lane et al. in 1994 [54]. The murine anti-CEA antibody ^{131}I-A5B7, either as the intact immunoglobulin IgG or as the F(ab')2 fragment, was administered to 19 patients with metastatic colorectal tumours. Four hours after injection the tumour uptake of F(ab')2 fragments was higher than that of the intact antibody, which was consistent with the faster penetration of the smaller F(ab')2 into tumour masses as already found earlier in animal models of CRC [55–57].

Four other anti-CEA antibodies reactive with four distinct epitopes expressed on CEA have also been described in the literature [58, 59]. These antibodies, NP-1, NP-2, NP-3 and NP-4, were classified into three main classes according to their reactivity towards CEA and the CEA-related antigens, meconium antigen (MA) and nonspecific cross-reacting antigen (NCA) [59, 60]. The class I antibody, NP-1, had high affinity for CEA and MA, but low affinity for NCA, while the class II antibodies, NP-2 and NP-3, had moderate affinities for CEA and MA. The class III antibody, NP-4, appeared to recognize determinants unique to CEA and had no affinity for NCA or MA. The immunological, pharmacokinetic, and targeting properties of ^{131}I-labelled murine NP-2, NP-3 and NP-4 were evaluated after *i.v.* injection in patients with diverse cancers [8, 61]. Owing to its specificity towards CEA, good targeting properties in patients and limited complexation with circulating CEA, ^{131}I- NP-4, in the form of intact IgG, was considered the candidate of choice for imaging and therapy of CEA-expressing tumours.

Goldenberg and co-workers were also involved in the study of other anti-CEA candidates for therapy, either in animal or in human models [8, 59, 61–64]. The pharmacokinetics, toxicity, dosimetry as well as antitumour activity of ^{131}I-labelled NP4 IgG1 (IMMU-4; Immunomedics. Inc., Morris Plains, NJ) were investigated in a phase I/II clinical trial enrolling 57 patients with small-volume CEA-expressing metastatic cancers (including 29 CRC). The clinical response rates in these patients were comparable to the response rates of conventional chemotherapeutic regimens, but with fewer side effects, suggesting that in small-volume disease RIT might be superior to conventional chemotherapy [62]. Tumour dosimetry indicated that small tumours received substantially higher radiation doses, supporting the findings of earlier preclinical studies that tumour dose and consequently the potential therapeutic success is inversely related to tumour size.

The use of two fragments of ^{123}I-labelled NP-4 (F(ab')2 and Fab') to image colorectal cancer was reported in a prospective, randomized multicentre study enrolling 62 CRC patients [64]. Clinical findings suggested that ^{123}I-labelled NP-4 Fab' combined with CT provided greater accuracy in the detection and localization of recurrent or metastatic colorectal cancer sites than CT alone (100% versus 78%). The clinical feasibility of RIT with ^{131}I-labelled NP-4 F(ab')2 was later demonstrated in 13 patients with small-volume (3 cm in diameter) or minimal residual disease [63]. Favourable tumour targeting was observed and the therapy resulted in disease stabilization in some of the patients. However, the efficacy of the treatment was modest despite the small volume of the tumours. In brief, it has been concluded that RIT of patients with small-volume disease was possible and, because of their generally poor prognosis, future dose-intensification trials should be considered in these patients.

A second-generation panel of anti-CEA monoclonal antibodies was generated and compared to the first-generation panel of NP mAbs [65]. Four of them, identified as MN-2, MN-6, MN-14 and MN-15, showed similar specificities. MN-15, like its NP-1 equivalent, reacts with NCA, MA and CEA. MN-2 has properties similar to NP-2, being reactive with MA and CEA. In animal studies, both MN-2 and MN-6 showed similar imaging limitations in CEA-expressing tumours as observed before for NP-2 and NP-3. Like NP-2, both MN-2 and MN-3 targeted bone marrow, and MN-6 accumulates in normal colon as found for NP-3. The murine mAb MN-14, with a tenfold higher affinity (9×10^9 M^{-1}) than NP-4, has demonstrated superior tumour-targeting ability in a human colon carcinoma xenograft model compared with NP-4 [65]. In a phase I clinical trial enrolling 22

cancer patients, Sharkley et al. have demonstrated the safety and excellent targeting sensitivity of ^{131}I-labelled MN-14 mAb for detecting CEA-rich tumours, even in patients with extremely elevated serum CEA levels [66].

To circumvent immunogenicity issues associated with the murine form of MN-14, a less immunogenic, humanized, CDR-grafted, version has been developed (hMN-14) [67]. Human MN-14 (hMN, labetuzumab from Immunomedics, Inc., Morris Plains, NJ) has shown high affinity, and good tumour targeting in a human colon carcinoma xenograft model, as well as clinically, in a pilot trial enrolling 19 patients with a prior history of CEA-expressing cancers. Biodistribution, tumour targeting, and pharmacokinetic behaviour of ^{131}I-hMN-14 IgG (^{131}I-labetuzumab) were similar to those of the murine form. Based on these preclinical and clinical data, a phase I clinical therapy trial was initiated to determine the pharmacokinetics, organ and tumour dosimetry, and dose-limiting toxicity (DLT) of ^{131}I-labetuzumab in patients with advanced metastatic gastrointestinal and colorectal cancer. In general, ^{131}I-labetuzumab showed good tumour targeting and an acceptable toxicity profile, although no objective responses were observed in this subset of patients [68].

Hepatic resection still remains the gold standard treatment for patients with colorectal liver metastasis (CLM). Yet, approximately 70% of patients will eventually relapse, probably because of occult micrometastases present at the time of resection. Thus, adjuvant systemic therapeutic regimens have been explored to improve the outcome of patients who underwent complete resection of CLM. However, such trials had failed to provide significant survival benefit [69, 70]. In up to 40% of these patients, the liver remains the only site of metastasis [71]. Consequently, innovative therapeutic strategies are still needed to improve patient outcomes such as prolonging the time to progression and increasing overall survival. In previous reports, Liersch and colleagues have demonstrated that RIT with a single administration of ^{131}I-labetuzumab after complete resection of colorectal liver metastases was well tolerated by CRC patients and significantly improved survival compared with a control group that did not receive RIT [72, 73]. This promising result of single RIT after salvage resection of colorectal liver metastases has encouraged the same researchers to investigate the safety and long-term therapeutic effects of repeated RIT in a phase II prospective clinical trial enrolling a larger group of CRC patients [74]. The main conclusion drawn from this study was that repeated RIT with ^{131}I-labetuzumab was feasible, but was associated with higher than anticipated acute haematotoxicity. Nevertheless, median time to progression (16 months) and overall survival (55 months) observed were encouraging enough to provide a proof of concept for the effectiveness of this adjuvant treatment option in the case of occult, micrometastatic disease after salvage resection of colorectal liver metastases.

Targeting TAG-72

Tumour-associated glycoprotein 72 (TAG-72) is a high molecular weight glycoprotein (240–400 KDa) with mucin-like characteristics isolated from the LS-174 T human colon cancer xenograft [75]. Owing to its expression in most adenocarcinomas, TAG-72 was considered a potential antigen target for RIT in several carcinomas, including colorectal cancer. TAG-72 is expressed in 80% of colorectal carcinomas, with relatively little expression in normal tissues [76].

The murine monoclonal antibody B72.3 (m-B72.3) against TAG-72 was initially generated by immunization of mice with a membrane-enriched fraction of a human breast carcinoma [77]. The potential of $^{125/131}$I-labelled-m-B72.3 to selectively localize primary and metastatic lesions in colorectal cancer patients has been demonstrated by several research groups [6, 78, 79]. However, it has been observed that one administration of a relatively low dose of m-B72.3 (1–5 mg range) led to a HAMA response in approximately 50% of patients [80]. In an effort to overcome this limitation, chimeric mouse/human antibodies were generated aiming to reduce the amount of foreign protein while preserving antitumour specificity. The IgG4 chimeric version of murine B72.3 (ch-B72.3) was accomplished by fusion of cDNA sequences encoding the heavy and light chain variable regions of B72.3 with genomic DNA encoding human IgG4 and K constant regions [81, 82]. ^{131}I-labelled-ch-B72.3 was evaluated by Meredith et al. in a phase I clinical trial involving 12 CRC patients [83]. Since ch-B72.3 had demonstrated limited utility as a means of delivering multiple therapeutic doses of ^{131}1 in the majority of patients enrolled in this clinical study, the authors suggested that other alternative strategies, such as the use of anti-TAG-72 monoclonal antibodies with higher affinity should be followed. Also, the use of other chimeric isotypes, chimeric antibody fragments or novel genetically engineered molecules could eventually provide better radioimmunotherapeutic agents [84]. A rec/ch-B72.3 with a human IgG1 constant region, designated cB72.3(IgG1), was labelled with ^{131}I and its in vitro/in vivo biological behaviour was compared with both ^{131}I-B72.3 and ^{131}I-ch-B72.3(IgG4) [85]. However, no clinical studies have been reported.

A second generation of anti-TAG-72 monoclonal antibodies, named as CC (for colon cancer), was proposed [86, 87]. Among them, the murine IgG CC49, with a sixfold higher affinity for TAG-72 than B72.3, has been the most explored. In a comparative clinical study, ^{131}I-CC49 was superior to ^{131}I-B72.3 for localizing colorectal carcinoma [88]. Ten patients with CRC metastasis received B72.3 and CC49 simultaneously prior to biopsy. Although both

Table 5 Relevant clinical trials of RIT/RIS in colorectal cancer patients

Antigen/antibody	Phase	Route	Dose/frequency	Remarks/outcomes	Ref.
CEA					
^{131}I-*m*A5B7 IgG ^{131}I-*m*A5B7 F(ab')2	I/II	*i.v* 19 unresectable, locally recurrent or metastatic tumours	Repeated doses 1.2–5.5 GBq	Similar toxicities in both groups Higher tumour uptake of F(ab')2 in metastatic CRC	[54]
^{131}I-*m*NP4 IgG1	I/II	57 metastatic patients with CEA-expressing tumours	Therapeutic dose (4-23 mg/1628-9916 MBq)	HAMA responses (94%) Antitumour effects in 12 of 35 assessable patients	[62]
^{123}I-NP4 F(ab')2 ^{123}I-NP4 F(ab')	RIS	62 CR patients	1–10 mg 296–370 MBq	RIS with NP4 (IMMU-4) is safe and able to disclose CR sites at least 1 cm in size 1 mg of Fab' confirmed as many lesions as did 10 mg of Fab, or either dose of F(ab')2	[64]
^{131}I-*m*MN-14 IgG	RIT/I	22 patients with CEA-expressing tumours	15: 178-426 MBq (0.45–1.1 mg) 7: 2590-2960 MBq (4.8–6.2 mg) Phase I therapy trial	Patients injected with 5 mg were more likely to have HAMA than patients who were injected with less mAb MMN-14 (IMMU-14) targets tumours effectively, even in the presence of elevated circulating CEA	[66]
CDR-grafted version of ^{131}I-*m*MN-14 (^{131}I-hMN-14)	Pilot imaging study/RIT	30 patients with advanced CEA-expressing tumours	19: 296-1110 MBq ^{131}I-hMN-14 (0.5-20 mg) 11: ^{131}I-*m*MN-14	Similar biodistribution, tumour-targeting and pharmacokinetic behaviour ^{131}I-hMN-14 is less immunogenic	[67]
^{131}I-hMN-14 IgG (^{131}I-labetuzumab)	I	A 8 patients with prior external beam radiation therapy B 13 patients who received standard chemotherapy	21: diagnostic infusion 296 MBq 17/21: infusional therapy of escalating radioactive doses 1110-1850 MBq/m^2	^{131}I-hMN-14 IgG has good targeting, good tumour to normal organs radiation absorbed ratios, and an acceptable toxicity profile in advanced metastatic GI/CR cancer patients No objective responses were seen in this group of heavily pre-treated and mostly advanced patients	[68]
^{131}I-labetuzumab	Adjuvant RIT II	*i.v* 23 CR patients after salvage resection of liver metastases and at a median follow-up of 91 months	Single dose 1480–2220 MBq/m^2	Both the median OS and 5-year survival rates seem to improve with adjuvant RIT after complete LM resection in CRC after 91 months follow-up: first evidence of a statistically significant survival advantage for adjuvant RIT, as compared with controls	[72, 73]

Table 5 (continued)

Antigen/antibody	Phase	Route	Dose/frequency	Remarks/outcomes	Ref.
^{131}I-labetuzumab	RIT II	*i.v* 63 patients after resection of CR liver metastases at a median follow-up of 54 months 39/63 with normal CEA levels and no suspicious lesions observed by PET/CT	Two RIT courses 1480–1850 MBq/m^2	Repeated RIT is feasible, but associated with higher than anticipated acute haematotoxicity compared with previous single RIT study Survival was encouraging, especially for truly adjuvant patients (n = 39). However, maximum safe dose is a single administration of 1850 MBq	[74]
TAG-72					
^{131}I-*m*B72.3 IgG	RIS	*i.p* 12 metastatic CRC	185-370 MBq	No adverse reactions 8/12 positive scans. In 3/8 the MoAb scan depicted tumours that were not found by other means	[6]
^{131}I-*m*B72.3 IgG		*i.v* 27 CRC	74-370 MBq (0.16–20 mg)	No adverse reactions 50% HAMA response	[80]
^{131}I-*ch*B72.3 IgG4	I	12 metastatic CRC	666 MBq/m^2 999 MBq/m^2 1332 MBq/m^2	No acute side effects Excessive whole-body radiation due to the long plasma half-life of ^{131}I-*ch*B72.3 Therapeutic gain is low than might be achieved with an isotope having a longer half-life due to relatively short effective half-life compared to the time required for tumour localization Limited utility as a means of delivering multiple therapeutic doses	[83]
^{125}I-*m*B72.3 ^{131}I-*m*CC49	RIS Clinical comparison of 2 mAbs	*i.v* 10 pre-surgical CRC metastases	A. 5 patients ^{125}I-*m*B72.3 + ^{131}I-*m*CC49 1 mg «74 MBq B. 5 patients ^{125}I-*m*B72.3 + ^{131}I-*m*CC49 20 mg «74 MBq	B72.3 and CC49 show comparable tumour uptake, with a trend of cancer towards improved CC49 tumour uptake at the 20 mg dose CC49 with better tumour:serum ratios is the preferred mAb for RIS/RIT	[88]

Table 5 (continued)

Antigen/antibody	Phase	Route	Dose/frequency	Remarks/outcomes	Ref.
^{131}I-CC49	II	*i.v* 15 refractory metastatic colon cancer patients	2775 MBq/m^2 (20 mg)	Despite minimal toxicity and favourable ^{131}I-CC49, tumour uptake efficacy was limited The lack of therapeutic benefit could be due to many physical/immunologic factors (i.e. heterogeneity of uptake, rapid clearance, increased HAMA, etc.) that overall prevent sufficient tumour uptake	[89]
^{131}I-CC49	I	*i.v* 24 advanced CRC patients expressing TAG-72	Escalating doses 555-3330 MBq/m^2 (20 mg)	Excellent targeting (<95%) of tumour lesions and relative lack of haematologic toxicity. No major responses. All patients developed HAMA response within 4 wks of therapy Concordance between length of disease as measured by CT scans, and as measured by RIS following administration of mAb	[90]
TAG-72 and CEA					
^{131}I-CC49 and ^{131}I-COL-1	Dual therapy II	14 metastatic CRC patients	2775 MBq/m^2 injected simultaneously *plus* *s.c* α-IFhN (3×10^6 IU)	The combination of complementary COL-1 (anti-CEA) and CC49 (anti-TAG-72) with α-IFN administration increases localization intensity and radiation doses at tumour sites as compared to historical controls The amount of radiation delivered to tumour sites was still below that required to cause tumour regressions in metastatic CRC	[97]
A33					
$^{125/131}$I-A33*m*Ab	I	3 + 23 CRC with LM	*i.v* (1406-2886 MBq/m^2)	Quantitative analysis of mAb localization in human metastatic CRC shows excellent localization to metastatic CR tumours	[105]

Table 5 (continued)

Antigen/antibody	Phase	Route	Dose/frequency	Remarks/outcomes	Ref.
^{131}I-A33*m*Ab	I/II	23 adv CC patients	*i.v* escalating doses (1110–3478 MBq/m^2)	All patients developed HAMA after one cycle of treatment. Toxicity is mostly haematologic and more pronounced in patients with compromised bone marrow due to prior chemotherapy 20 patients showed localization of mAb to sites of disease. No major responses were observed	[106]
^{131}I-huA33	I	12 CRC patients	*i.v* dose escalating to 400 MBq (0.25, 1.0, 5.0, and 10 mg/m^2)	^{131}I-huA33 is safe at the doses used (no DLT) and shows selective and rapid localization to colorectal carcinoma in vivo. The excellent targeting characteristics indicate clear potential for the targeted therapy of CRC	[110]
^{131}I-huA33	RIT I	15 pre-treated metastatic CRC patients	*i.v* dose escalating 740-1850 MBq/m^2 (10 mg/m^2 huA33)	4 patients developed HAHA. At restaging, 4 patients had SD, whereas 11 patients had PD RIT with ^{131}I-huA33 shows promise in targeting CRC at a max. tolerated dose of 1480 MBq/m^2	[111]

Adv advanced, *CC* colon cancer, *CRC* colorectal cancer, *DLT* dose-limiting toxicity, *HAHA* human anti-human antibody, *HAMA* human anti-murine antibody, *LM* liver metastases, *MDS* myelodysplastic syndrome, *OS* overall survival, *wk* week

antibodies showed comparable uptake in tumour, tumour to serum ratios were significantly higher for ^{131}I-CC49. Two RIT trials with ^{131}I-CC49 to determine dose-limiting toxicity and therapeutic efficacy were reported later in metastatic colorectal cancer patients [89, 90]. In a phase II clinical trial, 15 refractory metastatic CRC patients were treated with ^{131}I-CC49 [89. Despite good visualization of metastasis, no objective tumour responses were observed. In a subsequent phase I trial enrolling 24 patients with advanced CRC, Divgi et al. confirmed the excellent localization characteristics and relative lack of toxicity of ^{131}I-CC49 [90]. Although the treatment was well tolerated, no major responses were observed.

Further studies were performed aiming to improve tumour uptake using the biologic response modifier interferon, which has been shown to upregulate TAG-72 and CEA expression in tumour cells [91–93], or to reduce bone marrow toxicity by using interleukin 1 (IL-1) or other growth factors [69, 94].

Meredith et al. carried out a dual-antibody clinical trial directed to TAG-72 and carcinoembryonic antigen (CEA) in an attempt to enhance antibody localization and efficacy as compared to prior trials with ^{131}I-CC49 alone [89, 90, 95] or combined with interleukin 1 [96]. ^{131}I-CC49 (anti-TAG-72) and ^{131}I-COL-1 (anti-CEA) were simultaneously given to 14 patients with metastatic CRC. Interferon (α-IFN) was also administered subcutaneously to enhance the expression of both antigens in the tumour. No relevant responses were achieved, with four patients remaining stable while ten progressed. The combination of these two complementary antibodies with α-IFN seemed to increase radiation doses at tumour sites as compared to historical controls. Yet, the amount of radiation delivered to the tumour was below the required to cause tumour regression in metastatic CRC [97].

In an attempt to overcome the shortcomings of murine and intact IgG and to profit from the excellent specific reactivity of CC49, Slavin-Chiorini bioengineered a CDR-grafted humanized monoclonal antibody with a C_H2 domain deletion (ΔCH2) [98]. Deletion of the C_H2 domain of IgG had already been reported to result in faster tumour uptake and more rapid blood clearance [99–101]. The recombinant IgG molecule HuCC49ΔCH2 combined, for the first time, a fast blood clearance with the reduced potential for eliciting a HAMA response. As anticipated, radioiodinated ($^{125/131}$I) HuCC49ΔCH2 constructs demonstrated faster blood clearance in both athymic and SCID mice bearing human colon carcinoma xenografts and effective localization to tumour xenographs while showing minimal deposition in healthy tissues [98, 101, 102]. Despite favourable pharmacokinetics and relevant tumour accumulation of radioiodinated HuCC49ΔCH2, together with the reduced ability to elicit HAMA responses, no clinical studies have been reported to date.

Targeting A33

The human A33 antigen is a transmembrane glycoprotein member of the immunoglobulin superfamily that is overexpressed in normal human colonic and small bowel epithelium and in > 95% of human colon cancers [103, 104]. It is absent in most other human tissues and tumour types and is not secreted or shed into the blood stream. In several preclinical and clinical studies, this antigen has been targeted using the radioiodinated murine IgG2a mAb A33 [16, 105, 106]. The latter accumulated selectively in tumour metastases of advanced colorectal cancer patients [105]. Welt et al. conducted two phase I/II clinical trials to determine the therapeutic efficacy, the toxicity and the maximum tolerated dose of $^{125/131}$I-mAb A33 [16, 106]. In the first trial, 23 patients with advanced colorectal cancer were treated with escalating doses of ^{131}I-mAb A33. No major responses were observed, but three patients had evidence of mixed responses to therapy and the serum CEA levels decreased in two patients. In the second clinical study, 21 patients with advanced chemotherapy-resistant colon cancer were treated with ^{125}I-mAb A33. The modest antitumour activity observed was still encouraging because of the lack of toxicity in the bowel and bone marrow at the doses studied (up to 350 mCi/m^2).

The excellent characteristics of anti-A33, such as long retention time in tumour, high tumour uptake, and minimal gut toxicity, observed in these trials, led to the generation of a humanized version, huA33, to allow repeated dosing without HAMA response [107]. The safety and efficacy of huA33, alone and combined with chemotherapy, was demonstrated in patients with colorectal carcinoma [108, 109]. Subsequent phase I clinical trials, conducted in patients with metastatic colorectal carcinoma, have shown the ability of radiolabelled huA33 to selectively and rapidly target primary and metastatic colorectal tumours and to penetrate into large necrotic metastatic lesions [110, 111]. Although radioimmunotherapy using ^{131}I-huA33 held some promise in targeting colorectal tumours, its clinical application has not been explored further.

Targeting EpCAM

The epithelial cell adhesion molecule (EpCAM) was initially described as a colorectal carcinoma-specific antigen [112, 113]. This glycosylated transmembrane protein (40-kDa) gained interest as a potential therapeutic target for antibody-based approaches due to its wide-spectrum expression in many epithelial malignancies, including colorectal carcinomas. The different designations proposed for EpCAM, including KSA, KS1/4 or 17-1 antigen, are associated with the monoclonal antibodies specific for the cell

surface antigen or cDNA clones used to characterize the antigen [114, 115]. Unlike CEA, EpCAM is not generally shed into circulation, which made this antigen a promising target for RIT. EpCAM-binding antibodies are rapidly internalized into the cell, displaying excellent tumour uptake and retention. A phase I clinical trial enrolling 53 patients (25 with CRC) that were treated with ^{125}I-CO 17-1A, a radioiodinated murine anti-EpCAM antibody, was reported [15]. The results of this study underlined the potential clinical utility of therapy with monoclonal antibodies to treat certain patients with gastrointestinal malignancy, even at late stages of disease.

A chimeric version of 17-lA (c-17-lA) has been generated by joining the variable region of the murine 17-lA with human IgG1 heavy chain and kappa light chain sequences [116]. It has been shown that both ^{125}I-c-17-1A and ^{125}I-murine 17-lA exhibited identical biological behaviour concerning internalization, cytotoxicity and growth inhibition of human colon cancer xenografts in nude mice. Moreover, both forms were equally effective in producing antibody-dependent cell-mediated cytotoxicity [117]. A pilot clinical trial with ^{125}I-c17-lA, enrolling patients with metastatic colorectal cancer, has subsequently demonstrated that high-dose outpatient radioimmunotherapy with an ^{125}I-labelled internalizing antibody can be achieved without significant patient toxicity or radiation hazard [14].

Breast cancer

Breast cancer (BC), the most common cancer among women worldwide, is still characterized by high morbidity and mortality. According to GLOBOCAN 2020, female BC has surpassed lung cancer as the leading cause of global cancer incidence, with an estimated 2.3 million new cases, representing 11.7% of all cancer cases. It is the fifth leading cause of cancer mortality worldwide, with 685,000 deaths [50]. Among women, BC accounts for one in four cancer cases and for one in six cancer deaths, ranking first for incidence and mortality in the vast majority of countries [50]. BC is a heterogeneous disease characterized by a variety of clinical and histological forms, ranging from discrete metastatic lesions to diffuse and multiple organ involvement, with variable outcomes. Thus, one of the major challenges has been to identify predictive and prognostic biomarkers that can help to select the patients who can benefit most from more aggressive and potentially curative options. Nowadays, breast cancer patients have many more therapeutic choices to treat the disease; however, when failure to conventional therapies occurs, newer treatment options such as RIT could offer some benefit.

Several active targets useful for RIT have been identified in BC, including TAG-72, MUC-1, L6, and CEA, and antibodies targeting these antigens have also been evaluated in BC over the years. The anti-TAG-72 monoclonal antibody CC49, labelled with either ^{177}Lu or ^{131}I, has been evaluated in breast cancer patients [118–120]. Tumour localization was excellent, and in the patients receiving ^{131}I-CC49, α-IFN was also administered to upregulate the expression of the TAG-72 antigen. As expected, α-IFN was capable of enhancing TAG-72 antigen expression and, to a lesser degree, tumour uptake of ^{131}I-labelled CC49 in breast cancer patients. However, this was not sufficient to significantly increase the accumulation of radioactivity in tumours [119].

Tumour-associated antigen L6, a 24-kDa cell surface glycoprotein overexpressed in several oncologic malignancies, including breast carcinoma [121], has also attracted some interest as a therapeutic target for murine humanized antibodies [122–125]. In a phase I dose escalation trial, a radioiodinated human chimeric antibody, ^{131}I-chL6, was administered in multiple cycles to ten women with metastatic breast cancer who had failed standard therapy. All the patients received an imaging dose of ^{131}I-chL6, followed by a therapeutic dose of ^{131}I-chL6 (20–70 mCi/m^2). Clinically measurable tumour responses (5 lasting 1.5–5 months) were reported, suggesting that the responses could be related to the combined effects of targeted radiation and the biological activity of the antibody [124]. Although some effort was made to generate antibodies with high affinity to target breast cancer antigens, ^{131}I-labelled antibodies have not played a particularly important role in radioimmunotherapy of breast cancer.

The role of HER2-directed antibodies, affibodies and nanobodies. as vehicles for imaging and therapy approaches in breast cancer, has been reviewed in detail recently [126]. Anti-HER2-VHH1 was explored as a lead compound to target HER2-receptor, which is also overexpressed in some breast carcinomas. A ^{68}Ga-labelled anti-HER2-VHH1 nanobody (^{68}Ga-NOTA-HER2) is under clinical development for PET imaging of HER2 receptor expression in cancer. A phase I trial enrolling 20 breast cancer patients has been successfully conducted and multiple phase II trials are still ongoing [127, 128]. Recent preclinical studies have demonstrated the excellent tumour-targeting characteristics and most adequate in vivo biodistribution of ^{131}I-labelled anti-HER2-VHH1 (^{131}I-GMIB-anti-HER2-VHH1). The favourable biological profile, combined with the theranostic features of ^{131}I had triggered interest in the use of this antibody as a potential theranostic tool in cancer treatment [129]. The encouraging results of this study have prompted a multicenter dose escalation and therapeutic clinical investigation (NCT02683083) of ^{131}I-GMIB-anti-HER2-VHH1 in patients with HER2-positive breast cancer.

Trastuzumab, used either alone or in combination with chemotherapy, is considered as a standard treatment option

as it significantly improves the survival time in patients with HER2+ metastatic breast cancer compared with treatment with chemotherapy alone [130]. Recent preclinical studies in both BT-474 and MDA-MB-453 cells and in tumour-bearing animals have demonstrated the potential of ^{131}I-trastuzumab for breast cancer treatment [131].

Prostate cancer

Prostate cancer is the third most frequent malignancy (after breast and lung cancer) and the fifth leading cause of cancer death in men worldwide, accounting for almost 1.4 million new cases, and 375,000 deaths in 2020 [18, 50]. Targeted therapies based on radiolabelled specific antibodies may play an important role towards improving the clinical efficacy and overall survival of prostate cancer patients.

The first successful radiolabelled antibody was reported approximately 40 years ago by Goldenberg and co-workers who showed that ^{131}I-labelled rabbit antibody IgG against prostatic acid phosphatase could locate primary and metastatic tumours of prostatic origin [132]. Later, in 1994, results from a phase II clinical trial of ^{131}I-CC49, targeting TAG-72 in 15 patients with hormonally unresponsive metastatic prostate cancer, were reported by Meredith et al. [95]. No acute adverse reactions occurred, but all patients had evidence of an immune response to CC49 by 4 weeks. Although six of ten symptomatic patients had bone pain relief, neither of them met the radiographic or PSA criteria for objective response. The results of a following phase II trial using ^{131}I-CC49 with adjuvant α-IFN, conducted in 15 hormone-resistant metastatic prostate cancer patients, showed a tendency for enhanced tumour uptake and antitumour effects as compared to the prior phase II trial of ^{131}I-CC49 alone [133].

One of the most important membrane antigens anticipated for targeted therapy is prostate-specific membrane antigen (PSMA), also known as N-acetyl-alpha-linked acidic dipeptidase I (NAALA-Dase), glutamate carboxy-peptidase II (EC 3.4.17.21) or folate hydrolase. PSMA, a type II membrane glycoprotein of about 100 kDa, is highly expressed in prostate cells. The expression of PSMA is upregulated in malignant disease, with the highest level detected in metastatic androgen-independent prostate cancer. PSMA, a cell surface protein, is not released into circulation, being internalized after antibody binding by receptor-mediated endocytosis. These features make PSMA an excellent target for prostate cancer and have encouraged the development of a set of potential PSMA ligands for SPECT/PET imaging and therapy [134, 135]. Radiolabelled monoclonal antibody therapy that targets PSMA showed some promise and has been an area of active investigation. J591, a IgG monoclonal antibody, has demonstrated to be the most successful for targeting the extracellular domain of PSMA. This antibody has been thoroughly tested in preclinical studies and has also been humanized for clinical studies. Preclinical studies evaluating ^{131}I-, ^{177}Lu-, and ^{90}Y-labelled J591 in LNCaP cells, subcutaneously implanted in mice, showed dose-dependent responses with all radionuclides. However, ^{90}Y- and ^{177}Lu-labelled J591 could be given as fractionated doses and showed a favourable dosimetry over ^{131}I-J591 due to the shorter intracellular half-life of ^{131}I [136]. More recently, PSMA-targeted radionuclide therapy with a small urea-based molecule and lutetium-177 has emerged as a promising new approach for treating metastatic castration-resistant prostate cancer (mCRPC) [137]. The phase III VISION clinical trial NCT03511664 demonstrated that ^{177}Lu-PSMA-617 significantly improved overall survival and radiographic progression-free survival for men with progressive PSMA-positive mCRPC [138]. Based on this unprecedented accomplishment, the US Food and Drug Administration has granted Breakthrough Therapy designation (BTD) to ^{177}Lu-PSMA-617 [139].

Pancreatic cancer

Pancreatic ductal adenocarcinoma, or pancreatic cancer, is one of the most severe cancers and is predicted to rise up to the number two cancer killer by 2030. Based on GLOBOCAN 2020 estimates, pancreatic cancer accounts for almost as many deaths (466,000) as cases (496,000) because of its poor prognosis, and is the seventh leading cause of cancer death worldwide [50]. Particularly for unresectable cases, the median survival is shorter than 1 year, with few long-term survivors [140]. Pancreatic cancer is still one of the cancers with the poorest outcome due mainly to the ineffective treatment options available as well as to its silent course and late clinical symptoms.

MUC-1 is an attractive target for RIT since the vast majority of pancreatic cancers cases are mucin-expressing adenocarcinomas [141, 142]. Early preclinical studies have demonstrated the ability of murine monoclonal antibody PAM4 directed against MUC-1 to target CaPan1 human pancreatic carcinoma in athymic nude mice [143]. A pilot investigation performed in two patients with pancreatic cancer indicated the favourable tumour-targeting potential in vivo of ^{131}I-PAM4, with the overall results of the study encouraging further clinical studies [144]. Although some RIT studies using ^{131}I-PAM4 have demonstrated significant antitumour effects in mice bearing human pancreatic cancer xenografts [143, 145], a study reported by Cardillo et al. has demonstrated the advantage of ^{90}Y over ^{131}I as

the radionuclide of choice for PAM4-targeted radioimmunotherapy of xenografted pancreatic cancer [146].

Hepatocellular carcinoma

Primary liver cancer, which includes hepatocellular carcinoma (HCC—comprising 75%–85% of cases) and intrahepatic cholangiocarcinoma (10%–15%), as well as other rare types, is the sixth most commonly diagnosed cancer and the third leading cause of cancer death worldwide in 2020, with approximately 906,000 new cases and 830,000 deaths [50, 147]. Chronic liver disease and cirrhosis remain the most important risk factors for the development of HCC, of which viral hepatitis and excessive alcohol intake are the leading risk factors worldwide [148]. Only 15% of HCC patients are eligible for surgical management involving hepatic resection or transplantation. Five-year survival rates of > 70% can be achieved in these patients, but recurrences are inevitable. The vast majority of HCC patients are not candidates for surgical intervention and the long-term survival for these patients is poor, with a median survival shorter than 1 year [149]. In the majority of cases, treatment of HCC is largely palliative. Cytoreduction and sequential tumour excision give a new hope for non-operable HCC patients. RIT using radiolabelled antibodies could be an encouraging approach for tumour cytoreduction.

The first RIT clinical trials with ^{131}I–anti-alpha-fetoprotein (AFP) and ^{131}I–anti-ferritin in unresectable HCC patients have yielded mixed results [150–152]. However, these studies suggested that, in some cases, RIT could successfully convert unresectable tumours to resectable status. ^{131}I-Hepama-1 mAb (DGDK-1) was the first RIT agent developed for targeting a membrane antigen of liver carcinoma cells. In a phase I clinical study the treatment of 32 unresectable HCC patients with a peripheral intravenous infusion of ^{131}I-Hepama-1 mAb has demonstrated to be safe and well tolerated and the 1-year overall survival rate was reported to be 31% (60% for patients without metastases) [153].

The expression of CD147/HAb18G in hepatocellular carcinoma represents a significantly unfavourable prognostic factor. This HCC-associated antigen, expressed in approximately 60% of HCC patients, is associated with increased metastatic potential and worse disease outcomes compared with those who are CD147 negative [154]. Blocking CD147 with CD147 mAb or ^{131}I-metuximab, the bivalent F(ab')2 fragment of a murine monoclonal antibody specifically raised against CD147, has been reported to inhibit HCC growth and metastasis in vivo [155]. Treatment with ^{131}I-metuximab (Licartin) provided survival benefits in patients with unresectable HCC in several non-randomised studies [155–158]. The clinical efficacy of adjuvant ^{131}I-metuximab treatment in preventing tumour recurrence and prolonging survival have also been shown in advanced HCC patients undergoing liver transplantation, and in those who have undergone ablative treatment for early HCC [159, 160]. Results from a recent randomized controlled trial, reporting on the use of radioimmunotherapy as an adjuvant strategy after hepatectomy for HCC, support the clinical efficacy of ^{131}I-metuximab as an adjuvant treatment after surgical resection of HCC [161].

Vascular endothelial growth factor receptor 2 (VEGFR2) is traditionally regarded as an important therapeutic target in a wide variety of malignancies, including HCC. High VEGFR2 expression in liver cancer, as compared to normal liver tissues, has been associated with the poor outcome of these patients [162]. The murine–human chimeric Fab antibody, FA8H1, a potential therapeutic agent against solid tumours overexpressing VEGFR2, was labelled with ^{131}I (^{131}I-FA8H1) and its therapeutic efficacy was investigated in two HCC xenograft models. The reduction in tumour weight and volume observed after ^{131}I-FA8H1 administration has confirmed its therapeutic effect, suggesting a potential application for targeted therapy of VEGFR2 overexpressing HCC [164].

Brain tumours

With an incidence of 308,102 new cases in 2020, primary brain tumours account for 1.6% of all cancer cases. [50]. These malignant tumours still remain the most lethal of all cancer types with an estimated annual mortality rate of 251,329 worldwide according to GLOBOCAN2020 [50]. Gliomas, cancer cells that originate from glial precursors, represent about 75% of all malignant primary brain tumours in adults and are characterized by a poor outcome. In children, primary brain tumours are the most common of the solid tumours and the second most frequent cause of cancer death after leukaemia. The most common benign intracranial tumour is meningioma comprising 10–15% of all brain neoplasms. Gliomas are the most prevalent type of adult brain tumour (approximately 30% of all brain tumours) [165]. Glioblastoma multiforme (GBM) is a fast-growing glioma that develops from star-shaped glial cells (astrocytes and oligodendrocytes). GBM, often referred to as a grade IV astrocytoma (or grade IV glioma), is the deadliest primary brain tumour. These gliomas are very aggressive and spread very rapidly and their outcome is still very disappointing, as they usually do not respond effectively to conventional therapies such as surgery, radiotherapy or chemotherapy. All treatments tried so far are merely palliative and associated with severe side effects. GBM patients usually present a median overall survival of less than 1 year [166].

The global incidence of brain metastases in patients with systemic cancer is about ten times higher than that of primary brain tumours, and approximately 10–30% of patients with metastatic cancer will develop brain metastases [167]. Metastasis to the central nervous system is an indicator of poor prognosis and is almost always lethal [168–170]. While lung cancer accounts for the majority of metastatic brain disease, melanoma has the highest propensity to disseminate to the brain and nearly 50% of patients with advanced melanoma will eventually develop brain metastases [170].

Several antigens, such as epidermal growth factor receptor (EGFR) or tenascin, have been reported in the literature as potential therapeutic targets for brain disorders and some preclinical and clinical trials were carried out with promising results. A brief overview of the more relevant studies using radioiodinated antibodies is given below (Table 6).

EGFR targeting

The epidermal growth factor receptor is a transmembrane glycoprotein whose expression has been identified in 19–85% of primary malignant gliomas, mainly in GBM, but is very low in normal brain [171]. Earlier studies showed that all gliomas with the amplified EGFR gene overexpressed EGFR protein. Overexpression without gene amplification was observed in some of the low-grade gliomas and few GBM.

The monoclonal antibody anti-EGFR-425 is an IgG2a that binds to human EGFR [172]. Early evidence of the efficacy of anti-EGFR-425 was demonstrated in a pilot study reported by Brady et al. in 1990 [173]. Fifteen patients with recurrent malignant glioma were treated with ^{125}I-labelled anti-EGFR-425. In this study there was one surgically documented complete response, two partial responders and five patients with stable disease. A phase II trial with the same radioiodinated antibody enrolling 25 patients with malignant astrocytoma (10 astrocytoma with anaplastic foci and 15 GBM) was later reported by the same researchers [174]. The patients received multiple infusions and cumulative doses following surgical resection and adjuvant external beam radiotherapy. A significant and promising increase in median survival was reported for both groups, with more than 60% of patients still alive 1 year after treatment. In a following phase II clinical study, 180 patients, of which 118 had a glioblastoma diagnosis, received intravenous or intra-arterial RIT as an adjuvant therapy after surgery or radiotherapy, with and without chemotherapy. The overall median survival for the glioblastoma group was reported to be 13.4 months, with a subgroup of patients less than 40 years old showing a median survival of 25.4 months [175].

Some years later, Li and colleagues published the results of a phase II clinical trial to assess the efficacy of adjuvant RIT with ^{125}I-labelled anti-EGFR-425 in 192 patients with newly diagnosed GBM [176]. Among these 192 patients, 132 were treated with ^{125}I-labelled anti-EGFR-425 alone, and 60 were treated with ^{125}I-labelled anti-EGFR-425 plus temozolomide. An additional 81 GBM patients served as a historical control group. Both therapeutic options demonstrated to be safe and well tolerated with little added toxicity. Median survival following RIT alone was reported to be 14.5 months, while acombination of RIT and temozolomide provided the greatest survival benefit with a median survival of 20.4 months.

Approximately, one-half of patients with EGFR amplification also present a specific mutation, known as EGFRvIII, which results in the deletion of an extracellular domain segment of the EGFR, including the ligand-binding region [177]. Further studies to develop improved RIT agents have been carried out with EGFRvIII-targeting monoclonal antibodies, such as mAb806 and L8A4 [178–181]. The monoclonal antibody L8A4 labelled with N-succinimidyl 4-guanidinomethyl-3-[^{125}I]iodobenzoate ([^{125}I]SGMIB-L8A4) was compared to various ^{177}Lu-labelled conjugates of L8A4 in an animal study [180, 181]. However, better results were obtained with the radiometallated antibodies [^{177}Lu]-1B4M-DTPA-L8A4 and [^{177}Lu]-MeO-DOTA-L8A4, suggesting no clear advantage of [^{125}I]SGMIB-L8A4 for clinical RIT of malignant brain tumours.

Tenascin targeting

Tenascin, which has probably been the most investigated target for brain tumours, is an extracellular matrix hexabrachion glycoprotein expressed ubiquitously in the extracellular matrix of gliomas [182, 183]. Tenascin is also expressed in breast, lung, and squamous cell carcinomas, but not in normal adult or foetal brain [184]. The primary structure of human tenascin has been established in 1991 by sequencing cDNA clones which cover its complete coding region [185]. Tenascin is mainly made up of three groups of sequences with a high homology to epidermal growth factor (EGF), fibronectin (FN) type Ill repeat and fibrinogen. The deduced amino acid sequence shows that human tenascin is mainly made up of 14 and half EGF-like repeats and 15 FN-like repeats, fibrinogen-like sequences and potential N-glycosylation sites. Several murine antibodies have been developed against tenascin C, including BC-2, BC-4, 81C6, ST2146, ST2485, F16, and P12. All these antibodies have been labelled with ^{131}I. A chimeric antibody against tenascin C, ch81C6, has been reported as well [186].

BC-2 and BC-4 are IgG monoclonal antibodies that react with two distinct epitopes on the tenascin molecule [185]. BC-4 recognizes an epitope within the EGF-like sequence, while BC-2 recognizes an epitope within the FN-like type Ill repeats. ^{131}I-BC-2 was used to treat ten patients with bulky brain glioblastoma, recurring after surgery, radiotherapy or

chemotherapy. Although RIT failed to show any encouraging results in four patients, a favourable outcome, classified as partial (2) or complete remission (1), was observed in three of the ten patients (30%). At the same time, stabilization of the disease was observed in three other patients for a median of 8 months, thus improving survival and quality of life [187]. This therapeutic approach was later confirmed using the other anti-tenascin monoclonal antibody. Both antibodies, labelled with ^{131}I, were given intratumourally to 30 patients with recurrent glioblastomas with comparable results and no evidence of systemic adverse effects were observed [188]. Fifty patients with recurrent (26) or newly diagnosed (24) malignant glioma were later treated locally with ^{131}I-BC-2 and ^{131}I-BC-4 [189]. The overall response rate was 40% (34.6% recurrent and 45.8% newly diagnosed), which represents an encouraging result in such highly aggressive and untreatable tumours. No systemic or cerebral adverse effects were detected. Progression of tumour was only reported in 19 cases (13 recurrent and 6 newly diagnosed). A major phase I/II clinical trial enrolled 111 malignant glioma patients, including 91 with glioblastoma, that were treated with ^{131}I-BC-2 and ^{131}I-BC-4 injected directly into the tumour site. Overall, 58 were newly diagnosed and 53 were recurrent tumours. 20 patients (17 with GBM) were recruited in a phase I study and 91 (74 with GBM) in a phase II trial [190]. The results for phase I patients revealed a maximal tolerated dose of 2,590 MBq. Among the 70 GBM patients evaluated in phase II, 33 have experienced favourable outcomes (1CR + 9PR + 23NED) and most of them were free of disease for at least 20 months.

81C6 is a murine immunoglobulin G_{2b} that binds an epitope within the alternatively spliced fibronectin type III region of tenascin [184, 191]. Cell studies and a preclinical study in xenograft model systems have confirmed the specificity and efficacy of ^{131}I-labelled m81C6 therapy [192–194]. In clinical studies, Zalutsky's research group first confirmed the specificity and selectivity of ^{131}I-labelled m81C6 in patients with malignant glioma (MG) [182, 195, 196]. A series of phase I clinical trials was performed by Zalutsky and colleagues to establish the maximum tolerated dose (MTD) of ^{131}I-labelled murine 81C6 (m81C6) mAb injected directly into surgery created resection cavities (SCRC) in malignant glioma patients. Dose-limiting toxicity was neurologic and defined the MTD to be 3.7 GBq for recurrent patients and 4.44 GBq for newly diagnosed patients [197, 198]. Patients with recurrent and newly diagnosed glioblastoma multiforme (GBM) treated on these phase I studies had achieved median survivals of 56 and 69 weeks, respectively [198, 199]. A subsequent phase II study demonstrated a median survival of 79 weeks among newly diagnosed GBM patients treated with 4.44 GBq (120 mCi) of ^{131}I-m81C6 [200]. The difficulties found in producing murine 81C6 in sufficient quantity to support a multi-institutional randomized trial led the same researchers to develop a human/mouse chimeric 81C6 mAb (ch81C6) that could allow bulk production [186]. The specificity and binding affinity of both ch81C6 and m81C6 were virtually identical, but the chimeric isoform unexpectedly also demonstrated increased tumour uptake in human glioma xenografts and enhanced in vivo stability when compared to m81C6 [201]. A phase I therapeutic trial to determine the MTD, dosimetry and evidence of clinical benefit was performed in either newly diagnosed or untreated (19), newly diagnosed following radiotherapy (16) or recurrent patients (12) [186]. Median survival was 89 and 65 weeks for newly diagnosed and recurrent patients, respectively. Although median survival was encouraging, ^{131}I-ch81C6 was associated with greater haematologic toxicity, probably due to the enhanced stability of the IgG2 construct, as compared with ^{131}I-murine 81C6 and its clinical development has been discontinued.

Other human recombinant antibodies (F16 and P12) specific to the alternatively spliced domains A1 and D of the large isoform of tenascin-C were generated by antibody phage technology [202]. The tumour-targeting properties of F16 and P12 labelled with ^{125}I were assessed by biodistribution studies in tumour xenografts using the antibodies in small immunoprotein (SIP) format. ^{125}I-labelled SIP(F16) selectively accumulated in tumour in a U87 glioblastoma model and was rapidly cleared from other organs. Tumour accumulation of ^{125}I-labelled SIP(P12) was lower and persistent levels of radioactivity were observed in the intestine. As far as we are aware no clinical trials have been reported to date with any of these antibodies.

Other molecular targets in brain tumours

Other promising molecular targets aimed to treat brain tumours have also been identified, including human neural cell adhesion molecule (NCAM), the extra domain B of fibronectin (EDB) or disialoganglioside GD2. These targets have not been so extensively explored, but some clinical trials using ^{131}I-labelled mAbs have been reported in the literature and are briefly summarized below.

The neural cell adhesion molecule is an immunoglobulin-like neuronal surface glycoprotein that binds to a variety of other cell adhesion proteins to mediate adhesion, guidance, and differentiation during neuronal growth [203]. Due to its ubiquitous localization in several cancers, including brain cancers, NCAM-based target therapy has attracted considerable interest. Several radiolabelled monoclonal antibodies have been developed against NCAM, namely ^{131}I-ERIC-1 and ^{131}I-UJ13A, and evaluated in preclinical and clinical trials [204–206].

Tumour angiogenesis has been established as a cancer hallmark, and thus, considerable efforts have been made

Table 6 More relevant clinical trials of RIT in brain tumours

Antigen/antibody	Phase	Route	Dose/frequency	Remarks/outcomes	Ref.
EGFR					
^{125}I-anti-EGFR425	Pilot study t	15 recurrent malignant astrocytomas	One to three *i.a.* infusions total dose 925–4810 MBq	No significant toxicities. No significant life-threatening reactions Average survival time: 8 ± 6.6 months This therapy alone was probably not adequate and its use in the adjuvant setting should be evaluated	[173]
^{125}I-anti-EGFR425	II Adjuvant therapy	10 AAF 15 GBM	*i.v.* or *i.a* one or multiple doses after surgical debulking or biopsy 1295–3330 MBq/infusion total cumulative doses: 1480–8288 MBq	No HAMA response 60% survival at 1 year for both AAF and GBM	[174]
^{125}I-anti-EGFR425	II Adjuvant therapy 10 years follow-up	Outpatients 55 AAF 118 GBM	*i.v.* or *i.a* median total dose: AAF 5.2 GBq GBM 5.1 GBq	Minimal toxicity Significant increase in MS. Overall medium survival: 13.4 mos (AAF) and 50.9 (GBM) mos ^{125}I-Mab 425 therapy represents a promising therapeutic regimen for high-grade gliomas	[175]
^{125}I-anti-EGFR425 ^{125}I-anti-EGFR425 + TMZ	II Adjuvant therapy 20-year outcomes of NCT00589706 study	192 GBM	Course of 3 weekly 1.8 GBq *i.v.* injections following surgery and radiation therapy 132 RIT 60 RIT + TMZ 81 CTL	This study spans over 20 years and remains one of the most encouraging large phase II experiences examining an experimental treatment for GBM Treatment was safe and well tolerated with an MS of 15.7 months. No significative HAMA or acute side effects RIT + TMZ provided the greatest survival benefit with an MS of 20.4 months	[176]
Tenascin					
^{131}I-BC-2	I	10 patients with brain glioblastoma	Direct *i.t.* administration of 555 MBq (1.93 mg)	Very low HAMA Encouraging results: 30% PR or CR; 30% SD (for 8 mos)	[187]

Table 6 (continued)

Antigen/antibody	Phase	Route	Dose/frequency	Remarks/outcomes	Ref.
^{131}I-BC-2 ^{131}I-BC-4		26 recurrent disease 24 newly diagnosed tumour	Local infusion after surgery and chemotherapy Multiple RIT cycles 26 185–2405 MBq 24 1850-2405 MBq	No systemic or cerebral adverse effects 20 months total MS (18 in recurrent tumours and 23 in newly diagnosed lesions). MS 17 months in bulky tumours (recurrent and newly diagnosed); 26 months in minimal/microscopic disease. Median time to progression: 3 months in recurrent; 7 in newly diagnosed 3 CR, 6 PR and 11 SD. PD in 19 cases. 11 patients treated by RIT when their disease was minimal and nondetectable remained disease free (NED). Overall response rate (NED + CR + PR) = 40% Promising therapeutic technique to apply in an adjuvant setting	[189]
^{131}I-BC-2 ^{131}I-BC-4	I/II Locoregional RIT 7 years follow-up	111 malignant gliomas (58 newly diagnosed and 53 recurrent) phase I 20 phase II 91)	Phase I escalating doses (185, 370, 740, 110, 1480, 1850, 2220, 2590 and 2775 MBq) Phase II Mean dose 2035 MBq (range 1295–2775 MBq)	74 phase II glioblastoma patients: 10 SD, 9 PR, 23 NED 1 CR. MS = 19 months. Response rate (CR + PR + NED) = 17.8% for bulky lesions (17 months MS), 66.6% for small lesions (25 months MS) LR-RIT can produce favourable effects and can be used safely as a clinical therapy	[190]
^{131}I-*m*81C6	I	34 patients with recurrent malignant gliomas	administered clinically into SCRCs dose escalation from 1740 to 4440 MBq	^{131}I-*m*81C6 treatment through the SCRC of previously irradiated patients with recurrent primary/metastatic brain tumours is well tolerated with little toxicity at the MTD dose level of 3770 MBq The estimated MS for GBM patients and for all 34 patients was 56 and 60 weeks, respectively Further studies for comparison of increased survival with other therapeutic modalities are needed	[199]

Table 6 (continued)

Antigen/antibody	Phase	Route	Dose/frequency	Remarks/outcomes	Ref.
^{131}I-m81C6	I	42 patients with newly diagnosed malignant gliomas	Administered clinically into SCRC dose escalation from 1740 to 6660 MBq	The MTD for administration of ^{131}I-labelled 81C6 into the SCRC of newly diagnosed patients with no prior radiation therapy or chemotherapy was 4440 MBq None of the patients developed major haematologic toxicity. MS for the 32 GBM patients and for all 42 patients was 69 and 79 weeks, respectively A randomized study to compare other local therapies with this adjuvant therapy modality should be conducted	[198]
^{131}I-*m*81C6	II	23 patients with newly diagnosed malignant gliomas	4440 MBq injected directly into SCRC	MS for all patients and those with GBM was 86.7 and 79.4 weeks, respectively. 11 remain alive at a median follow-up of 93 weeks (49 to 220 weeks). 9 patients (27%) developed reversible haematologic toxicity, and histologically confirmed, treatment-related neurologic toxicity occurred in 5 (15%). The results confirm the efficacy of ^{131}I-*m*81C6 for this group of patients and suggest that a randomized phase III study is indicated	[200]
^{131}I-*ch*81C6		47 patients with newly diagnosed (35) and recurrent malignant (12) gliomas	Initial doses 2.96 GB Dose escalation was empirically set in 0.74-GBq increments Doses up to 4.44 GBq injected directly into the SCRC	MS was 88.6 wk and 65.0 wk for newly diagnosed and recurrent patients, respectively The MTD of ^{131}I-ch81C6 is 2.96 GBq because of dose-limiting haematologic toxicity. Although encouraging survival was observed, 131I-*ch*81C6 was associated with greater haematologic toxicity than ^{131}I-*m*81C6	[186]
NCAM					
^{131}I-ERIC-1	Pilot study	*i.t*	Escalating dose ranging from 1329 to 2193 MBq	Minimal toxicity	[204]
^{131}I-UJ13A		*i.v.* (n = 9)		No toxicity was encountered	[205]
EDB					
^{131}I-L19-SIP plus WBRT		(n = 4)	4.107 GBq/m^2		[217]

Table 6 (continued)

Antigen/antibody	Phase	Route	Dose/frequency	Remarks/outcomes	Ref.
GD2					
^{131}I-*m*3F8	Children with metastatic neuroblast	*i.v*	222–1036 /kg	No survival benefit compared to unlabelled3F8	[224]
^{131}I-3F8 + bevacizumab	I patient with relapsed/refractory neuroblast	*i.v*		Responses were similar to those with ^{131}I-3F8 alone	*
^{131}I-*m*3F8 (cRIT)	Patients with relapsed central nervous system neuroblast			Improvement in overall survival	[225]
^{131}I-*m*3F8 (cRIT)	I 10 years follow-up			cRIT with ^{131}I-*m*3F8 is safe, maintains remission in high-risk/recurrent medulloblastomas when added to salvage therapy	[226]

AAF astrocytoma with anaplastic foci, *cRIT* compartmental radioimmunotherapy, *CTL* control group, *GBM* glioblastoma multiforme, *i.v.* intravenous, *i.a.* intra-arterial, *i.t.* intratumoural, *mos* months, *MS* median survival, *TMZ* temozolomide, *NED* no evidence of the disease, *SCRC* surgically created resection cavities, *NCT00450827

recently to image and to disrupt tumour blood vessels.[207, 208]. One striking target for both approaches is the splice variant of fibronectin containing extra domain B (EDB). The latter is abundantly expressed around the vasculature of a variety of human cancers (both primary tumours and metastases), but is absent in the majority of normal tissues [209–211]. A human recombinant scFv fragment, designated L19, targeting an epitope of EDB of fibronectin was developed [212]. Several other L19 formats were constructed, including dimeric scFv [(scFv)2], a human bivalent "small immunoprotein" (SIP, ~80 kDa), and a full human IgG1 [213]. Radiolabelled L19 constructs have been evaluated in tumour-bearing nude mice to select a conjugate for clinical RIT, and the most favourable therapeutic index was found for ^{131}I-L19-SIP [213–216]. RIT with ^{131}I-L19-SIP at maximum tolerated dose improved survival in several animal models [214–216]. Preliminary results of a study with the human antibody ^{131}I-L19SIP (radretumab) in combination with whole brain radiation treatment (WBRT) were reported by Virotta et al.[217]. 4 patients with brain metastatic lesions were treated with radretumab and underwent PET/CT scans with ^{18}F-FDG and ^{124}I-L19SIP for diagnostic and dosimetric purposes. The significant reduction of glucose metabolism observed in the lesions has suggested the potential clinical efficacy of radretumab. However, no further studies were reported to confirm these preliminary results, particularly in patients with lower stage of disease.

Anti-disialoganglioside (GD2) antibodies have been widely evaluated in preclinical and clinical studies in the past two decades and GD2-targeted immunotherapy and radioimmunotherapy have already been extensively reviewed elsewhere [218]. Gangliosides are lipid-sugar compounds thought to influence a variety of cellular functions including those affecting tumourigenesis. A murine monoclonal IgG3 antibody (3F8) that recognizes disialoganglioside GD2, which is homogeneously distributed on the cell membrane of solid tumours of neuroectodermal origin, including medulloblastoma [218–220], retains its immunoreactivity when labelled with ^{124}I or ^{131}I [221, 222]. Intravenous anti-GD2 therapy is standard of care for patients with metastatic neuroblastoma [223, 224]. Intravenous anti-GD2 ^{131}I-3F8 has been tested in children with metastatic neuroblastoma at high doses (6–28 mCi/kg), but did not add any survival benefit compared to unlabelled 3F8 [224]. In a subsequent phase I trial of ^{131}I-3F8 in combination with bevacizumab (NCT00450827) in patients with relapsed/refractory neuroblastoma, the responses were similar to those with ^{131}I-3F8 alone. Improvement in overall survival has been noted with the incorporation of intraventricular ^{131}I-labelled 3F8 compartmental radioimmunotherapy (cRIT) in patients with relapsed central nervous system neuroblastoma [225]. On a phase II clinical trial carried out at Memorial Sloan Kettering Cancer Center (MSKCC), between 2006 and 2016,

cRIT with ^{131}I-labelled 3F8 has demonstrated to be safe and has suggested some clinical utility in maintaining remission in high-risk or recurrent medulloblastomas when added to salvage therapy [226]. The clinical feasibility of cRIT with ^{131}I-labelled 3F8 was also demonstrated in another phase I study enrolling patients with GD2-expressing leptomeningeal neoplasms [227].

In an attempt to improve tumour specificity, targeted antineoplastic agents, such as tumour necrosis therapy (TNT) agents, have emerged as an alternative treatment to solid tumours. [228–230]. ^{131}I-chTNT-1/B mAb (Cotara®, Peregrine Pharmaceuticals Inc., CA, USA) is a TNT agent that provides targeted radioimmunotherapy for the treatment of cancers such as high-grade glial neoplasms [231]. Clinical experience with Cotara as a treatment agent for malignant gliomas has been reviewed in detail elsewhere.[232]. Cotara is a genetically engineered chimeric murine mAb with variable regions specific for an universal intracellular antigen (i.e. histone H1 complexed to deoxyribonucleic acid) exposed in the necrotic core of malignant solid tumours [231, 233, 234]. Although several variants of radiolabelled TNT-1/B mAb were investigated in a number of malignancies, such as cervical [230] colon [235] and lung [236, 237] cancers as well as hepatic metastases [238]. The largest clinical experience with Cotara has been in the treatment of malignant gliomas [233, 234, 239]. Patel et al. reported the findings of a phase I dose-defining clinical study [233]. In this study 12 patients with recurrent glioblastoma received Cotara infusions by convection-enhanced delivery (CED). Data from this trial indicated that 1.0 and 1.5 mCi/cm^3 clinical target volume (CTV) could be administered to patients safely and produced a tolerable radiation effect. CTV was defined for these studies as the baseline gadolinium-enhanced tumour volume, including non-enhancing areas of central necrosis. These activities were then administered alone and in combination to treat an expanded patient population in a phase II study. A total of 39 patients were treated, 16 of whom received two infusions at least 8 weeks apart, with each infusion at the above determined dosage. A phase II trial with Cotara for dose confirmation in patients with GBM at first relapse (NCT00677716) has been completed in November 2011 [240]. In this open-label, dose confirmation study, 41 patients received CED infusions of Cotara. Interim results were presented at the Annual Meeting of the American Society of Clinical Oncology (ASCO). [239]. Survival analysis showed a promising 41-week median survival, with two patients still alive at least 3 years after the treatment. However, this result has not been confirmed in a phase III trial and as far as we are aware no further clinical developments using Cotara for GBM treatment have been reported since 2011.

Radioimmunotherapy of B-cell non-Hodgkin lymphoma (NHL)

Both Hodgkin's disease (sometimes referred to as Hodgkin's lymphoma) and non-Hodgkin's lymphoma (NHL) are cancers that originate in lymphocytes, which are important components of the immune system. The distinction between Hodgkin's disease and non-Hodgkin's lymphoma is made upon examination of the cancer cells from a biopsy or aspiration of the tumour tissue. The type of abnormal cells identified in the sample determines whether a lymphoma is classified as Hodgkin's disease or non-Hodgkin's lymphoma. Non-Hodgkin's lymphoma is much more common than Hodgkin's disease. NHL comprises a very large group of diseases, often with very different symptoms, treatment, and outcomes. Non-Hodgkin lymphoma is responsible for 544,000 new cases and 260,000 deaths in 2020 worldwide [50].

Aggressive non-Hodgkin's lymphoma, such as high-grade or intermediate-grade lymphoma, usually grows fast in the body. Surprisingly, aggressive NHL often responds better to treatment, and the majority of patients with aggressive NHL achieve remission after initial treatment with chemotherapy with or without radiation therapy if they are diagnosed early. The most common aggressive lymphoma is diffuse large B-cell lymphoma (DLBCL).

Low-grade NHL, on the other hand, grows slowly, and these lymphomas are therefore called indolent NHL. The most common indolent lymphoma is follicular lymphoma (FL). This kind of lymphoma does not give rise to too many symptoms, but they are also long-standing and are less likely to be cured. In approximately one third of patients, low-grade NHL transforms into a higher-grade histology that is associated with an accelerated rate of growth and a poorer prognosis. Advanced-stage follicular B-cell lymphoma is considered incurable. Rituximab, a genetically engineered monoclonal chimeric antibody targeting the CD20 antigen expressed on B cells, was the first monoclonal antibody approved by FDA in 1997, for the treatment of relapsed or refractory low-grade or follicular non-Hodgkin's lymphoma and by the European Agency for the Evaluation of Medicinal Products (now European Medicines Agency, EMA) in 1998, for therapy of patients with stage III/IV, follicular, chemoresistant or relapsed NHL. However, only few patients can be permanently cured with single-agent therapy: fewer than half of follicular NHL patients respond to rituximab with median response duration of about a year, since they may not respond or may develop resistance to antibody therapy [241, 242].

Therapeutic strategies incorporating the use of radiolabelled monoclonal antibodies reactive with lymphoid-associated antigens have shown some promise for NHL

treatment, as lymphomas are highly radiosensitive and a variety of lymphoid lineage-specific antigens have been identified as potential targets for antibody-based therapies. The CD20 B-lymphocyte-associated surface-membrane antigen presents favourable features as a target for NHL radioimmunotherapy. This 35-kd transmembrane glycoprotein is abundantly expressed by more than 95% of B-cell NHL [243, 244]. Upon antibody binding CD20 is not shed into the circulation nor is internalized, which provides a prolonged antibody residence time on the cell surface and, consequently, an extended exposure of the tumour to radiation [245, 246].

Two anti-CD20 radiolabelled murine monoclonal antibodies have been approved in the USA for the treatment of relapsed follicular or transformed lymphoma (Zevalin, ^{90}Y-ibritumomab tiuxetan, IDEC-Y2B8; from IDEC Pharmaceuticals, San Diego, CA; and Bexxar, ^{131}I-tositumomab; from Corixa Corp, Seattle, WA). Several studies have demonstrated the efficacy of both antibodies in relapsed/ refractory indolent B-cell lymphoma and indolent lymphoma in the front-line setting, and available evidence for the preclinical and clinical development of these two agents have been extensively reviewed in the literature [247–249]. In this manuscript we briefly examine the clinical trials with ^{131}I-tositumomab reported in the literature (Table 7).

Chemotherapy-relapsed/refractory indolent B-cell NHL

Tositumomab (previously referred to as anti-B1 antibody) is a mouse immunoglobulin G2a (IgG2a) monoclonal antibody specific for CD20 [243]. Given the favourable preclinical data already available on tositumomab [250], a phase I/II study of ^{131}I-tositumomab was initiated in 1990 (from April 1990 to January 1996) enrolling NHL patients who had relapsed after having received at least one chemotherapy regimen or who had had no response to at least one regimen. Early results obtained in this study suggested high response rates and an excellent tolerability to the drug [251–253]. The updated results on the entire cohort of this unique set of patients, including long-term safety and survival data up to 8 years after treatment were reported in 2000 by Kaminski and colleagues [254]. Forty two (71%) of 59 patients with relapsed/refractory follicular lymphoma enrolled in the study responded. 20 (34%) complete responses and 22 (36%) partial responses were observed. Response rates were higher for low-grade or transformed NHL than for de novo intermediate-grade NHL (83% vs 41%). For all 42 responders, the median progression-free survival was 12 months and 20.3 months for those with complete responses.

A multicentre phase II study confirmed the efficacy and safety of ^{131}I-tositumomab [255]. In this trial 45 of 47 patients with chemotherapy-relapsed/refractory low-grade or transformed low-grade NHL were treated with a single dosimetric and therapeutic dose of ^{131}I-tositumomab. 27 patients (57%) responded to the treatment. The overall response rate was similar in patients with low-grade or transformed low-grade NHL (57% vs 60%) with a median duration of 9.9 months. A complete response with a median duration of 19.9 months was observed in 15 (32%) patients, including five patients with transformed low-grade NHL. The median PFS was 12 months for all responders and 22 months for complete responders.

The encouraging results from these two trials led to a phase III multicentre study enrolling 60 patients with an even poorer prognosis. This group of patients had failed multiple chemotherapy regimens and had either not responded to or responded and experienced disease progression within 6 months of completion of their last qualifying chemotherapy regimen (LQC) were treated with ^{131}I-tositumomab [256]. This clinical trial was designed to compare the therapeutic efficacy of LQC regimen with the efficacy of ^{131}I-tositumomab treatment. After treatment with a single course of ^{131}I-tositumomab, a partial or complete response was observed in 39 (65%) patients compared with 17 (28%) after their LQC regimen. The median duration of response after ^{131}I-tositumomab was longer than that on the LQC regimen (6.5 vs 3.4 months). Only two (3%) of 60 patients had achieved a CR on the LQC regimen, while 12 (20%) achieved a CR on ^{131}I-tositumomab. The promising results have demonstrated that a single course of ^{131}I-tositumomab was significantly more efficacious than the LQC received by this poor-prognostic and heavily pre-treated group of patients.

In 2003, following a prospective phase II study, ^{131}I-tositumomab (Bexxar) was then approved by FDA for the treatment of patients with CD20-positive, relapsed or refractory, low-grade, follicular, or transformed non-Hodgkin's lymphoma, including patients with rituximab-refractory non-Hodgkin's lymphoma. Other studies have also demonstrated the benefit of ^{131}I-tositumomab in rituximab failure [257]. In a clinical trial enrolling 40 patients with low-grade or transformed low-grade or follicular large-cell lymphoma whose disease had not responded to or had progressed after rituximab therapy, the safety and efficacy of Bexxar therapeutic regimen (tositumomab and ^{131}I tositumomab) has been demonstrated. 80% of patients met the definition of "rituximab refractory" (defined as no response or response of less than 6 months in duration). Clinical benefit was based on evidence of durable responses without any evidence of an effect on survival. Confirmed overall response (65%) and complete response (38%) rates were not significantly associated with prior rituximab response. With a median follow-up of 3.3 years, the median progression-free survival was 10.4 months and 24.5 months for responders. The results of this study were supported by demonstration of durable objective responses in 4 single-arm studies enrolling 190 patients evaluable for efficacy with

rituximab-naïve, follicular non-Hodgkin's lymphoma with or without transformation, who had relapsed following or were refractory to chemotherapy. In these studies, the overall response rates ranged from 47 to 64% and the median durations of response ranged from 12 to 18 months.

Indolent lymphoma in the front-line setting

Given the encouraging results observed in patients who had a relapse after extensive chemotherapy or whose disease was refractory to chemotherapy or to rituximab, the safety and efficacy of Bexxar therapeutic regimen was then evaluated as initial treatment for advanced follicular lymphoma. Between June 1996 and April 1999, in a phase II single-center study, 76 patients with previously untreated stage III/IV follicular lymphoma [258] received as initial therapy a single course of treatment consisting of a dosimetric dose of tositumomab and ^{131}I-tositumomab that was followed 1 week later by a therapeutic dose of 75 cGy of radiation. 72 patients (95%) responded to the therapy with most of them presenting regression of palpable tumours within 2 weeks. CR were observed in 57 patients (75%). An estimated 77% of patients with a complete remission remained disease-free at five years. The study demonstrated that a single one-week treatment with ^{131}I-tositumomab therapy induced rates of overall and complete responses higher than those observed with ^{131}I-tositumomab therapy in previously treated patients. Although the reason for this difference was not very clear the promising results greatly suggested the early use of RIT in the course of follicular lymphoma. Updated results of this phase II trial (reporting period June 1996 to May 2009) were reported later in 2009 and had demonstrated that a single course of treatment with Bexxar therapeutic regimen could produce durable responses, especially durable complete responses lasting over a decade in patients with untreated follicular lymphoma [259]. After a median follow-up of 10 years, the median duration of response was 6 years, with approximately 40% remaining progression-free at 10 years. For the 57 complete responders, median progression-free survival was 10.9 years. Ten-year overall survival was approximately 82%.

Although the high response rates achieved with ^{131}I-tositumomab in first-line management of FL were encouraging, combination regimens of chemotherapy followed by RIT could offer some potential benefits. Debulking before RIT can reduce both overall tumour burden and bone marrow involvement improving treatment efficacy, thus allowing RIT in patients who would otherwise be ineligible for RIT because of extensive marrow disease. Three clinical trials were reported in previously untreated subjects with low- to intermediate-grade NHL. Patients were treated with ^{131}I-tositumomab immediately after completion of systemic chemotherapy either with cyclophosphamide–adriamycin–oncovin–prednisone (CHOP), fludarabine or with cyclophosphamide–vincristine–prednisolone (CVP). All these studies showed initial promise, with patients attaining very high overall response rates (80% to 100%) with minimal toxicities [260–262].

The safety and efficacy of a sequential treatment regimen consisting of an abbreviated course (three cycles) of fludarabine followed 6–8 weeks later by iodine ^{131}I-tositumomab was evaluated in 35 patients with previously untreated follicular NHL [260]. The single-agent fludarabine is a purine analogue that typically achieves response rates of 29% to 75% in indolent lymphoma. After fludarabine, the overall response rate was 89% (31 of 35 patients). Three of these 31 patients (9%) achieved a complete response (CR), 28 achieved a PR, and 4 patients (11%) demonstrated stable disease. All 35 patients (100%) responded to the full regimen of fludarabine plus ^{131}I-tositumomab, 30 (86%) patients achieved CR, and 5 (14%) achieved partial response, with a 5-year estimated PFS rate of 60%. This sequential treatment regimen has shown to be highly effective as front-line therapy for follicular lymphoma and can reduce bone marrow involvement, when needed, to allow the use of RIT.

Since fludarabine has been sometimes associated with immunosuppression, cytopenias, and secondary malignancies [263], Link et al. sought to investigate the efficacy and safety of a sequential regimen consisting of six cycles of CVP followed by one cycle of tositumomab and ^{131}I-tositumomab therapy in a group of 30 patients with untreated low-grade FL [261]. The efficacy results of this study were encouraging because all patients responded to this regimen, with 53% of patients achieving CR after the CVP chemotherapy and 93% achieving a confirmed CR following the combination therapy. Five-year progression-free and overall survival rates were 56% and 83%, respectively. Furthermore, 12 of 14 patients with bone marrow involvement and 14 of 15 patients with bulky disease achieved a complete response.

Although Bexxar had a good opportunity when it was approved in June 2003 it missed its last big chance in 2011 when the Southwest Oncology Group (SWOG) together with Cancer and Leukemia Group B compared the safety and efficacy of two immunochemotherapeutic regimens for follicular non-Hodgkin lymphoma in a phase III *randomized* intergroup protocol (SWOG S0016). Data from this long-term study, between March 2001 and September 2008, and that enrolled 554 patients was presented at the American Society of Hematology [264]. In one arm of the study, patients received six cycles of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy at 3-week intervals with six doses of rituximab (CHOP-R). In another arm of the study, patients received six cycles of CHOP followed by tositumomab and ^{131I}-tositumomab consolidative RIT (CHOP-RIT). Both regimens used in this trial produced outstanding outcomes in advanced follicular

Table 7 More relevant clinical trials of RIT in NHL tumours

Antigen/antibody	Phase	Route	Dose/frequency	Remarks/outcomes	Ref.
CD20 *Chemotherapy-relapsed/refractory indolent B-cell NHL*					
^{131}I-tositumomab	I/II 8 years follow-up	59 Relapsed/refractory NHL patients	*i.v* 1258-5957 MBq	42/59 (71%) patients responded: 0 CR (34%) 22 PR (36%) Higher response rates for low-grade/transformed NHL than for de novo intermediate-grade NHL (83% vs 41%) Median progression-free survival: CR:12 months; PR: 20.3 months 10 (17%) HAMA responses	[254]
^{131}I-tositumomab	II	47 chemotherapy-relapsed/refractory low-grade or transformed low-grade NHL	Single dosimetric and therapeutic dose	27 (57%) responders. Similar overall response rate: 57% vs 60% in low-grade or transformed low-grade NHL, with a median duration of 9.9 months. 15 CR (32%) with a median duration of 19.9 months (including 5 transformed low-grade NHL). Median PFS: 12 months for all responders and 22 months for CR	[255]
^{131}I-tositumomab	III Comparison of LQC regimen with ^{131}I-tositumomab	60 patients treated with at least two protocol-specified qualifying chemotherapy regimens and had not responded or progressed within 6 months after their LQC	Single course	39 (65%) CR or PR vs 17 (28%) after LQC Median duration of response after ^{131}I-tositumomab was longer than that on the LQC regimen (6.5 vs 3.4 months). Only 2/60 (3%) had achieved a CR on the LQC regimen, while 12 (20%) achieved a CR on ^{131}I-tositumomab A single course of ^{131}I-tositumomab was significantly more efficacious in this group than LQC	[256]
^{131}I-tositumomab	Prospective phase II	47 patients with B-cell lymphoma, progressive after rituximab	Median therapeutic dose 3282 MBq (range, 1946–6238 MBq)	^{131}I-tositumomab is effective in CD20-positive lymphoma progressive after rituximab Confirmed OR (65%) and CR (38%) rates were not significantly associated with prior rituximab response. With a median follow-up of 3.3 years, the median PFS was 10.4 months and 24.5 months for responders	[257]
CD20 *indolent lymphoma in the front-line setting*					
^{131}I-tositumomab	II	76 previously untreated stage III/IV follicular lymphoma	Single 1-week course Dosimetric and therapeutic dose	72/76 (95%) responders, most of them presenting regression of palpable tumours within 2 weeks. 57 CR (75%). An estimated 77% of patients with a complete remission remained disease free at 5 years The rates of overall and complete responses with a single 1-week ^{131}I-tositumomab treatment were higher than those observed with ^{131}I-tositumomab therapy in previously treated patients	[258]
^{131}I-tositumomab Bexxar	10 years follow-up			Overall response rate was 97% with 57 CR (75%) Median duration of response: 6 years, after a median follow-up of 10 years, with approximately 40% remaining progression free at 10 years. For the 57 CR, median PFS was 10.9 years. 10-year overall survival was approximately 82% A single course of treatment with ^{131}I-tositumomab therapeutic regimen could produce durable responses, especially durable complete responses lasting over a decade in patients with untreated	[259]
^{131}I-tositumomab plus fludarabine		35 untreated follicular NHL	3 cycles of fludarabine, followed by ^{131}I-tositumomab	Fludarabine: overall response rate 31/35 (89%). 3/31 CR, 28/31 PR and 4/31 SD Full regimen: overall response rate 35/35 (100%). 30/35 CR, 5/35 PD with a 5-year PFS estimated of 60% Highly effective sequential treatment regimen as front-line FL therapy	[260]
^{131}I-tositumomab plus CPV		30 untreated low-grade FL	6 cycles of CPV followed by one cycle of ^{131}I-mAb	100% responders, 53% CR after CVP chemotherapy and 93% CR after combination therapy 5-year progression-free and overall survival rates were 56% and 83%, respectively. 12/14 patients with bone marrow involvement and 14/15 CR in bulky disease patients	[261]

Table 7 (continued)

Antigen/antibody	Phase	Route	Dose/frequency	Remarks/outcomes	Ref.
^{131}I-tositumomab + CHOP		554 NHL patients 7 years long-term phase III study	Arm 1. 6 cycles of CHOP + 6 doses of rituximab CHOP-R Arm 2. 6 cycles of CHOP + ^{131}I-mAb CHOP-RIT	Both regimens are well tolerated with no significant differences in PFS, OS, or serious toxicities. Median follow-up time among patients still alive is 4.9 years. 106/267 pts on the CHOP-R arm have progressed/died vs 86/265 pts on the CHOP-RIT arm. 2-year PFS estimate was 76% on the CHOP-R arm vs 80% on the CHOP-RIT arm. 26/267 pts on the CHOP-R arm had died compared to 40/265 pts on the CHOP-RIT arm. OS 2-year estimate was 97% on the CHOP-R arm vs 93% on the CHOP-RIT arm	[264] [265] [266]
^{131}I-rituximab	II	142 low-grade predominantly follicular relapsed NHL	*i.v* 200 MBq ^{131}I-rituximab plus 375 mg rituximab /m^2	Objective response rates of 67% with 50% CR and median OS of 32 months. 18 months overall PFS 32 months in CR.RIT with ^{131}I-rituximab in routine clinical outpatient practice provides cost-effective, safe treatment of relapsed/ refractory indolent NHL, with half of patients achieving durable, complete remission with potential for repeat RIT on relapse	[267]
^{131}I-rituximab	Prospective phase II	68 7 years follow-up		First-line ^{131}I-rituximab RIT of advanced follicular NHL is effective and safe with early response rates similar to those observed with combination chemotherapy and rituximab regimens 98% OR at 3 months with 38 CR (76%) and 11 PR (22%). 0.4/11 PR patients (36%) at 3 months converted to CR in the year following treatment, so that 84% of patients were in CR at 1 year. During median follow-up of 33 months, only one patient (2.6%) among those who had achieved CR had relapsed, while PD was seen in seven patients (64%) of those with PR at first post-treatment assessment. Toxicity was limited to haematological grade 4 neutropenia in five patients (10%) and thrombocytopenia in five patients (10%). 3 patients died	[268] [269]

CHOP cyclophosphamide, doxorubicin, vincristine, and prednisone; *CVP* cyclophosphamide–vincristine–prednisolone, *FL LQC* last qualifying chemotherapy, *OR* overall response, *OS* overall survival, *PD* progressive disease; follicular lymphoma, *PFS* progression-free survival, *pts* patients

lymphoma, with more than 60% of patients estimated to be in progression-free 5 years after treatment. Overall survival was similarly impressive, with 80% of patients estimated to be alive 8 years after treatment with either regimen. The excellent progression-free survival (PFS) and overall survival (OS) rates observed for the CHOP-RIT arm in this trial were already predicted by the preceding phase II study (SWOG S9911) [265, 266]. Both treatments were excellent, but no statistically significant improvement in complete response rate, or survival time, was observed for patients receiving Bexxar (CHOP-RIT) [262]. On February 2014 GlaxoSmithKline (GSK) announced that the withdrawal of the drug would be voluntarily discontinued due to a projected decline in sales and to the availability of other anti-CD20 monoclonal antibodies.

Although not so used in routine practice, radioimmunotherapy of indolent NHL has achieved objective response rates in clinical trials comparable with standard rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy. In a phase II clinical trial of ^{131}I-rituximab RIT carried out by Leahy and colleagues and enrolling 142 consecutive patients, objective response rates of 67%, with complete response in 50% and median overall survival of 32 months, matched the response rates and compared favourably with those reported for ^{131}I-tositumomab or ^{90}Y-ibritumomab tiuxetan [267]. Building upon on their former experience with ^{131}I-rituximab RIT in recurrent and refractory indolent NHL, the same research group performed a prospective phase II study of first-line ^{131}I-rituximab outpatient RIT in 68 newly diagnosed, advanced stage, symptomatic follicular non-Hodgkin lymphoma patients followed for up to 7 years [268, 269]. Overall response rate at 3 months was 99%. Clinical results have demonstrated that ^{131}I-rituximab RIT in this newly diagnosed subset of NHL patients is an effective, practical and affordable alternative to existing conventional chemotherapies, with lower toxicity and durable remissions.

Conclusions and future perspectives

Owing to their unique nuclear properties, iodine radioisotopes (^{123,124,125,131}I) have reached a key role in biomedicine and nuclear medicine. ^{125}I-labelled molecules are routinely used in radiometric binding assays as well as relevant tools for translating preclinical results into humans since the replacement of ^{125}I by ^{123}I delivers a probe with suitable characteristics for SPECT imaging. Additionally, translation to PET molecular imaging can also be accomplished with the positron emitter ^{124}I. Finally, the β/γ emitter ^{131}I is the "classic theranostic agent" as coined by Silberstein [270] and can be used for both diagnostic and therapy. The latter radioisotope together with ^{90}Y have been used in > 95% of RIT trials and represent the current standard to which all other radionuclides are compared to. Their efficacy for the treatment of both haematological and solid malignancies has been demonstrated in a wide variety of published clinical trials. ^{131}I is a relatively inexpensive radioisotope with a long successful history of treating several malignancies, especially the simplest inorganic form, ^{131}I^{-}, which is used since the 1940s to treat thyroid cancer. As regards biomedical applications of radioiodinated high molecular weight molecules such as antibodies, further achievements must take into consideration both the in vivo dehalogenation of proteins by endogenous enzymes and their usually long half-lives (e.g. around 24 h for IgG antibodies). Whereas the first is mainly dependent on the molecule, the latter can be tuned upon reduction of the molecular weight while keeping the antigen binding properties with improvement of certain features such as stability. Within this context, engineered antibody fragments such as diabodies, single-chain variable fragments or single-domain antibody fragments hold great potential for molecular imaging and/or radionuclide therapy and important breakthroughs are expected in the near future. For the sake of example, let us refer to the work of D' Huyvetter et al. where a new ^{131}I-labelled single-domain antibody, namely ^{131}I-GMIB-anti-human epidermal growth factor receptor type 2 (HER2)-VHH1, has been proposed for HER2-targeted radionuclide therapy in breast cancer patients [271]. Moreover, an extensive clinical trial enrolling 70 patients (NCT04467515) is currently underway to evaluate the safety, tolerability, dosimetry, and preliminary efficacy of an HER2-targeting single-domain antibody linked to iodine-131 in patients with advanced/metastatic HER2-positive breast, gastric, and gastro-esophageal junction cancer [272]. Brought together, these studies confirm that engineered target-specific antibody fragments linked to therapeutic radionuclides such as iodine-131 hold potential to address clinical unmet needs in clinical oncology.

Author contributions Both authors, M-CNO and JDGC, have contributed equally to the conceptualization, writing, review and editing of this manuscript.

Funding This study was partially supported by Fundação para a Ciência e Tecnologia (UID/Multi/04349/2020 and PTDC/QUINUC/30147/2017.)

Declarations

Conflict of interest Author Maria-Cristina N Oliveira declares that she has no conflict of interest. Author João D. G. Correia declares that he has no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. Kohler G, Milstein C (1975) Continuous cultures of fused cells secreting antibody of predefined specificity. Nature 256:495–497. https://doi.org/10.1038/256495a0
2. Shepard H, Phillips G, Thanos C, Feldnnann M (2017) Developments in therapy with monoclonal antibodies and related proteins. Clin Med 17:220–232. https://doi.org/10.7861/clinmedicine.17-3-220
3. Lu R, Hwang Y, Liu I, Lee C, Tsai H, Li H et al (2020) Development of therapeutic antibodies for the treatment of diseases. J Biomed Sci. https://doi.org/10.1186/s12929-019-0592-z
4. Jain M, Gupta S, Kaur S, Ponnusamy M, Batra S (2013) Emerging trends for radioimmunotherapy in solid tumours. Cancer Biother Radiopharm 28:639–650. https://doi.org/10.1089/cbr.2013.1523
5. Jain M, Venkatraman G, Batra S (2007) Optimization of Radioimmunotherapy of solid tumours: biological impediments and their modulation. Clin Cancer Res 13:1374–1382. https://doi.org/10.1158/1078-0432.CCR-06-2436
6. Carrasquillo J, Sugarbaker P, Colcher D, Reynolds J, Esteban J, Bryant G et al (1988) Peritoneal carcinomatosis-Imaging with intraperitoneal injection of i–131-labeled b723 monoclonal-antibody. Radiology 167:35–40. https://doi.org/10.1148/radiology.167.1.3347742
7. Milenic D, Yokota T, Filpula D, Finkelman M, Dodd S, Wood J et al (1991) Construction, binding-properties, metabolism, and tumour targeting of a single-chain FV derived from the pancarcinoma monoclonal-antibody CC49. Can Res 51:6363–6371 (**PMID: 1933899**)
8. Sharkey R, Mottahennessy C, Pawlyk D, Siegel J, Goldenberg D (1990) Biodistribution and radiation-dose estimates for yttrium-labeled and iodine-labeled monoclonal-antibody IGG and fragments in nude-mice bearing human colonic tumour xenografts. Cancer Res 50:2330–2336
9. Sharkey R, Goldenberg D (2011) Cancer radioimmunotherapy. Immunotherapy 3:349–370. https://doi.org/10.2217/imt.10.114|10.2217/IMT.10.114
10. Strohl W (2018) Current progress in innovative engineered antibodies. Protein Cell 9:86–120. https://doi.org/10.1007/s13238-017-0457-8
11. Batra S, Jain M, Wittel U, Chauhan S, Colcher D (2002) Pharmacokinetics and biodistribution of genetically engineered antibodies. Curr Opin Biotechnol 13:603–608. https://doi.org/10.1016/S0958-1669(02)00352-X
12. Russeva M, Adams G (2004) Radioimmunotherapy with engineered antibodies. Expert Opin Biol Ther 4:217–231. https://doi.org/10.1517/14712598.4.2.217
13. Kassis A (2008) Therapeutic radionuclides: biophysical and radiobiologic principles. Semin Nucl Med 38:358–366. https://doi.org/10.1053/j.semnuclmed.2008.05.002
14. Meredith R, Khazaeli M, Plott W, Spencer S, Wheeler R, Brady L et al (1995) Initial clinical-evaluation of iodine-125-labeled chimeric 17–1A for metastatic colon-cancer. J Nucl Med 36:2229–2233 (**PMID: 8523110**)
15. Markoe A, Brady L, Woo D, Amendola B, Karlsson U, Fisher M et al (1990) Treatment of gastrointestinal cancer using monoclonal antibodies. Front Radiat Ther Oncol 24:214–224. https://doi.org/10.1159/000417788
16. Welt S, Scott A, Divgi C, Kemeny N, Finn R, Daghighian F et al (1996) Phase I/II study of iodine 125-labeled monoclonal antibody A33 in patients with advanced colon cancer. J Clin Oncol 14:1787–1797. https://doi.org/10.1200/JCO.1996.14.6.1787
17. Santoro L, Boutaleb S, Garambois V, Bascoul-Mollevi C, Boudousq V, Kotzki P et al (2009) Noninternalizing monoclonal antibodies are suitable candidates for I-125 radioimmunotherapy of small-volume peritoneal carcinomatosis. J Nucl Med 50:2033–2041. https://doi.org/10.2967/jnumed.109.066993
18. Ferlay J, Colombet M, Soerjomataram I, Parkin D, Pineros M, Znaor A et al (2021) Cancer statistics for the year 2020: an overview. Int J Cancer 149:778–789. https://doi.org/10.1002/ijc.33588
19. Miotti S, Canevari S, Menard S, Mezzanzanica D, Porro G, Pupa S et al (1987) Characterization of human ovarian carcinoma-associated antigens defined by novel monoclonal-antibodies with tumour-restricted specificity. Int J Cancer 39:297–303. https://doi.org/10.1002/ijc.2910390306
20. Mantovani L, Miotti S, Menard S, Canevari S, Raspagliesi F, Bottini C et al (1994) Folate binding-protein distribution in normal-tissues and biological-fluids from ovarian-carcinoma patients as detected by the monoclonal-antibodies MOV18 and MOV19. Eur J Cancer 30A:363–369. https://doi.org/10.1016/0959-8049(94)90257-7
21. Veggian R, Fasolato S, Menard S, Minucci D, Pizzetti P, Regazzoni M et al (1989) Immunohistochemical reactivity of a monoclonal-antibody prepared against human ovarian-carcinoma on normal and pathological female genital tissues. Tumouri 75:510–513
22. Li P, DelVecchio S, Fonti R, Carriero M, Potena M, Botti G et al (1996) Local concentration of folate binding protein GP38 in sections of human ovarian carcinoma by in vitro quantitative autoradiography. J Nucl Med 37:665–672 (**PMID: 2481353**)
23. Crippa F, Buraggi G, Dire E, Gasparini M, Seregni E, CanevarI S et al (1991) Radioimmunoscintigraphy of ovarian-cancer with the MOV18 monoclonal-antibody. Eur J Cancer 27:724–729. https://doi.org/10.1016/0277-5379(91)90174-C
24. Molthoff C, Buist M, Kenemans P, Pinedo H, Boven E (1992) Experimental and clinical analysis of the characteristics of a chimeric monoclonal-antibody, MOV18, reactive with an ovarian cancer-associated antigen. J Nucl Med 33:2000–2005
25. Buist M, Kenemans P, Denhollander W, Vermorken J, Molthoff C, Burger C et al (1993) Kinetics and tissue distribution of the radiolabeled chimeric monoclonal-antibody MOV18 IGG and F(AB')(2) fragments in ovarian-carcinoma patients. Can Res 53:5413–5418
26. Crippa F, Bolis G, Seregni E, Gavoni N, Scarfone G, Ferraris C et al (1995) single-dose intraperitoneal radioimmunotherapy with the murine monoclonal-antibody I-131 MOV18 - Clinical-results in patients with minimal residual disease of ovarian-cancer. Eur J Cancer 31A:686–690. https://doi.org/10.1016/0959-8049(94)00454-D
27. Molthoff C, Prinssen H, Kenemans P, van Hof A, den Hollander W, Verheijen R (1997) Escalating protein doses of chimeric monoclonal antibody MOv18 immunoglobulin G in ovarian carcinoma patients: A phase I study. Cancer 80:2712–2720. https://doi.org/10.1002/(SICI)1097-0142(19971215)80:12+%3c2712::AID-CNCR50%3e3.0.CO;2-B
28. van Rijswijk R, Hoekman K, Burger C, Verheijen R, Vermorken J (1997) Experience with intraperitoneal cisplatin and etoposide and iv sodium thiosulphate protection in ovarian cancer patients with either pathologically complete response or minimal residual disease. Ann Oncol 8:1235–1241. https://doi.org/10.1023/A:1008296202198
29. Buijs W, Tibben J, Boerman O, Molthoff C, Massuger L, Koenders E et al (1998) Dosimetric analysis of chimeric monoclonal antibody cMOv18 IgG in ovarian carcinoma patients after intraperitoneal and intravenous administration. Eur J Nucl Med 25:1552–1561. https://doi.org/10.1007/s002590050335
30. Van Zantenr-Pzybysz I, Molthoff C, Roos J, Verheijen R, Van Hof A, Buist M, et al. Influence of the route of administration on targeting of ovarian cancer with the chimeric monoclonal antibody MO: I.v. vs. i.p. Int J Cancer. 2001;92:106–14. doi:https://doi.org/10.1002/1097-0215(200102)9999:9999<::AID-IJC1145>3.0.CO;2-I.

31. Gendler S (2001) MUC1, the renaissance molecule. J Mammary Gland Biol Neoplasia 6:339–353. https://doi.org/10.1023/A:1011379725811
32. Mukherjee P, Madsen C, Ginardi A, Tinder T, Jacobs T, Parker J et al (2003) Mucin 1-specific immunotherapy in a mouse model of spontaneous breast cancer. J Immunother 26:47–62. https://doi.org/10.1097/00002371-200301000-00006
33. Epenetos A, Mather S, Granowska M, Nimmon C, Hawkins L, Britton K et al (1982) Targeting of iodine-123-labeled tumour-associated monoclonal-antibodies to ovarian, breast, and gastrointestinal tumours. Lancet 2:999–1005
34. Epenetos A, Shepherd J, Britton K, Mather S, Taylor-Papadimitriou J, Granowska M et al (1985) I-123 Radioiodinated antibody imaging of occult ovarian-cancer. Cancer 55:984–987. https://doi.org/10.1002/1097-0142(19850301)55:5%3C984::AID-CNCR2820550511%3E3.0.CO;2-E
35. Epenetos A, Munro A, Stewart S, Rampling R, Lambert H, Mckenzie C et al (1987) Antibody-guided irradiation of advanced ovarian-cancer with intraperitoneally administered radiolabeled monoclonal-antibodies. J Clin Oncol 5:1890–1899. https://doi.org/10.1200/JCO.1987.5.12.1890
36. Wessels B, Rogus R (1984) Radionuclide selection and model absorbed dose calculations for radiolabeled tumour associated antibodies. Med Phys 11:638–645. https://doi.org/10.1118/1.595559
37. Hird V, Maraveyas A, Snook D, Dhokia B, Soutter W, Meares C et al (1993) Adjuvant therapy of ovarian-cancer with radioactive monoclonal-antibody. Br J Cancer 68:403–406. https://doi.org/10.1038/bjc.1993.349
38. Verheijen R, Massuger L, Benigno B, Epenetos A, Lopes A, Soper J et al (2006) Phase III trial of intraperitoneal therapy with yttrium-90-labeled HMFG1 murine monoclonal antibody in patients with epithelial ovarian cancer after a surgically defined complete remission. J Clin Oncol 24:571–578. https://doi.org/10.1200/JCO.2005.02.5973
39. Oei A, Verheijen R, Seiden M, Benigno B, Lopes A, Soper J et al (2007) Decreased intraperitoneal disease recurrence in epithelial ovarian cancer patients receiving intraperitoneal consolidation treatment with yttrium-90-labeled murine HMFG1 without improvement in overall survival. Int J Cancer 120:2710–2714. https://doi.org/10.1002/ijc.22663
40. Madiyalakan R, Sykes T, Dharampaul S, Sykes C, Baum R, Hor G et al (1995) Antiidiotype induction therapy - evidence for the induction of immune-response through the idiotype network in patients with ovarian-cancer after administration of anti-CA125 murine monoclonal-antibody B43.13. Hybridoma 14:199–203. https://doi.org/10.1089/hyb.1995.14.199
41. Moseley K, Battaile A, Knapp R, Haisma H (1988) Localization of radiolabeled f(ab')2 fragments of monoclonal-antibodies in nude-mice bearing intraperitoneally growing human ovarian-cancer xenografts. Int J Cancer 42:368–372. https://doi.org/10.1002/ijc.2910420311
42. Haisma H, Moseley K, Battaile A, Griffiths T, Knapp R (1988) Distribution and pharmacokinetics of radiolabeled monoclonal-antibody OC-125 After intravenous and intraperitoneal administration in gynecologic tumours. Am J Obstet Gynecol 159:843–848. https://doi.org/10.1016/S0002-9378(88)80150-9
43. Finkler N, Muto M, Kassis A, Weadock K, Tumeh S, Zurawski V et al (1989) Intraperitoneal radiolabeled OC 125 in patients with advanced ovarian-cancer. Gynecol Oncol 34:339–344. https://doi.org/10.1016/0090-8258(89)90169-8
44. Muto M, Finkler N, Kassis A, Howes A, Anderson L, Lau C et al (1992) Intraperitoneal radioimmunotherapy of refractory ovarian-carcinoma utilizing iodine-131-labeled monoclonal-antibody OC125. Gynecol Oncol 45:265–272. https://doi.org/10.1016/0090-8258(92)90302-Y
45. Mahe M, Fumoleau P, Fabbro M, Guastalla J, Faurous P, Chauvot P et al (1999) A phase II study of intraperitoneal radioimmunotherapy with iodine-131-labeled monoclonal antibody OC-125 in patients with residual ovarian carcinoma. Clin Cancer Res 5:3249S-S3253
46. Benham F, Povey M, Harris H (1978) Placental-like alkaline-phosphatase in malignant and benign ovarian tumours. Clin Chim Acta 86:201–215. https://doi.org/10.1016/0009-8981(78)90134-1
47. Sunderland C, Davies J, Stirrat G (1984) Immunohistology of normal and ovarian-cancer tissue with a monoclonal-antibody to placental alkaline-phosphatase. Can Res 44:4496–4502
48. Kosmas C, Kalofonos H, Hird V, Epenetos A (1998) Monoclonal antibody targeting of ovarian carcinoma. Oncology 55:435–446. https://doi.org/10.1159/000011892
49. Epenetos A, Carr D, Johnson P, Bodmer W, Lavender J (1986) Antibody-guided radiolocalization of tumours in patients with testicular or ovarian-cancer using 2 radioiodinated monoclonal-antibodies to placental alkaline-phosphatase. Br J Radiol 59:117–125. https://doi.org/10.1259/0007-1285-59-698-117
50. Sung H, Ferlay J, Siegel R, Laversanne M, Soerjomataram I, Jemal A et al (2021) Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 71:209–249. https://doi.org/10.3322/caac.21660
51. Gold P, Freedman S (1965) Specific carcinoembryonic antigens of human digestive system. J Exp Med 122:467. https://doi.org/10.1084/jem.122.3.467
52. Shively J, Beatty J (1985) CEA-related antigens - molecular-biology and clinical-significance. CRC Crit Rev Oncol Hematol 2:355–399. https://doi.org/10.1016/S1040-8428(85)80008-1
53. Hefta L, Neumaier M, Shively J (1998) Kinetic and affinity constants of epitope specific anti-carcinoembryonic antigen (CEA) monoclonal antibodies for CEA and engineered CEA domain constructs. Immunotechnology 4:49–57. https://doi.org/10.1016/S1380-2933(98)00004-9
54. Lane D, Eagle K, Begent R, Hopestone L, Green A, Casey J et al (1994) Radioimmunotherapy of metastatic colorectal tumours with iodine-131-labeled antibody to carcinoembryonic antigen - Phase I/II study with comparative biodistribution of intact and F(ab')(2) antibodies. Br J Cancer 70:521–525. https://doi.org/10.1038/bjc.1994.338
55. Wahl R, Parker C, Philpott G (1983) Improved radioimaging and tumour-localization with monoclonaL F(ab')2. J Nucl Med 24:316–325
56. Buchegger F, Pelegrin A, Delaloye B, BischofdelaloyE A, Mach J (1990) Iodine-131-labeled mAb F(ab')2 fragments are more efficient and less toxic than intact anti-CEA antibodies in radioimmunotherapy of large human colon-carcinoma grafted in nude-mice. J Nucl Med 31:1035–1044
57. Pedley R, Boden J, Boden R, Dale R, Begent R (1993) Comparative radioimmunotherapy using intact of F(ab')2 fragments of I-131 anti-CEA antibody in a colonic xenograft model. Br J Cancer 68:69–73. https://doi.org/10.1038/bjc.1993.288
58. Primus F, Newell K, Blue A, Goldenberg D (1983) Immunological heterogeneity of carcinoembryonic antigen-antigenic determinants on carcinoembryonic antigen distinguished by monoclonal-antibodies. Can Res 43:686–692
59. Primus F, Kuhns W, Goldenberg D (1983) Immunological heterogeneity of carcinoembryonic antigen—immunohistochemical detection of carcinoembryonic antigen determinants in colonic tumours with monoclonal-antibodies. Can Res 43:693–701

60. Burtin P, Chavanel G, Hendrick J, Frenoy N (1986) Antigenic variants of the nonspecific cross-reacting antigen (NCA). J Immunol 137:839–845
61. Sharkey R, Goldenberg D, Goldenberg H, Lee R, Ballance C, Pawlyk D et al (1990) murine monoclonal-antibodies against carcinoembryonic antigen—immunological, pharmacokinetic, and targeting properties in humans. Can Res 50:2823–2831
62. Behr T, Sharkey R, Juweid M, Dunn R, Vagg R, Ying Z et al (1997) Phase I/II clinical radioimmunotherapy with an iodine-131-labeled anti-carcinoembryonic antigen murine monoclonal antibody IgG. J Nucl Med 38:858–870
63. Juweid M, Sharkey R, Swayne L, Behr T, Dunn R, Goldenberg D (1996) Radioimmunotherapy in patients with CEA-producing cancers and small-volume disease using I-131-labeled anti-CEA monoclonal antibody NP-4 F(ab')(2). J Nucl Med 37:735
64. Goldenberg D, Wlodkowski T, Sharkey R, Silberstein E, Serafini A, Garty I et al (1993) Colorectal-cancer imaging with iodine-123-labeled CEA monoclonal-antibody fragments. J Nucl Med 34:61–70
65. Hansen H, Goldenberg D, Newman E, Grebenau R, Sharkey R (1993) Characterization of 2nd-generation monoclonal-antibodies against carcinoembryonic antigen. Cancer 71:3478–3485. https://doi.org/10.1002/1097-0142(19930601)71:11%3c3478::AID-CNCR2820711104%3e3.0.CO;2-A
66. Sharkey R, Goldenberg D, Murthy S, Pinsky H, Vagg R, Pawlyk D et al (1993) Clinical-evaluation of tumour targeting with a high-affinity, anticarcinoembryonic-antigen specific, murine monoclonal-antibody, MN-14. Cancer 71:2082–2096. https://doi.org/10.1002/1097-0142(19930315)71:6%3c2082::AID-CNCR2820710625%3e3.0.CO;2-Q
67. Sharkey R, Juweid M, Shevitz J, Behr T, Dunn R, Swayne L et al (1995) Evaluation of a complementarity-determining region-grafted (humanized) anticarcinoembryonic antigen monoclonal-antibody in preclinical and clinical-studies. Cancer Res 55:5935–45
68. Hajjar G, Sharkey RM, Burton J, Zhang C-H, Yeldell D, Matthies A, Alavi A, Losman MJ, Brenner A, Goldenberg DM (2002) Phase I radioimmunotherapy trial with iodine-131—labeled humanized MN-14 anti-carcinoembryonic antigen monoclonal antibody in patients with metastatic gastrointestinal and colorectal cancer. Clin Colorectal Cancer 2:31–42
69. Blumenthal R, Sharkey R, Snyder D, Hansen H, Goldenberg D (1988) Reduction of radioantibody-induced myelotoxicity in hamsters by recombinant interleukin-1. Can Res 48:5403–5406
70. Nordlinger B, Sorbye H, Glimelius B, Poston G, Schlag P, Rougier P et al (2013) Perioperative FOLFOX4 chemotherapy and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC 40983): long-term results of a randomised, controlled, phase 3 trial. Lancet Oncol 14:1208–1215. https://doi.org/10.1016/S1470-2045(13)70447-9
71. de Jong M, Pulitano C, Ribero D, Strub J, Mentha G, Schulick R et al (2009) Rates and patterns of recurrence following curative intent surgery for colorectal liver metastasis an international multi-institutional analysis of 1669 patients. Ann Surg 250:440–448. https://doi.org/10.1097/SLA.0b013e3181b4539b
72. Liersch T, Meller J, Kulle B, Behr T, Markus P, Langer C et al (2005) Phase II trial of carcinoembryonic antigen radioimmunotherapy with I-131-labletuzumab after salvage resection of colorectal metastases in the liver: five-year safety and efficacy results. J Clin Oncol 23:6763–6770. https://doi.org/10.1200/JCO.2005.18.622
73. Liersch T, Meller J, Bittrich M, Kulle B, Becker H, Goldenberg D (2007) Update of carcinoembryonic antigen radioimmunotherapy with (131)supercript stopI-Labetuzumab after salvage resection of colorectal liver metastases: comparison of outcome to a contemporaneous control group. Ann Surg Oncol 14:2577–2590. https://doi.org/10.1245/s10434-006-9328-x
74. Sahlmann C, Homayounfar K, Niessner M, Dyczkowski J, Conradi L, Braulke F et al (2017) Repeated adjuvant anti-CEA radioimmunotherapy after resection of colorectal liver metastases: safety, feasibility, and long-term efficacy results of a prospective phase 2 study. Cancer 123:638–649. https://doi.org/10.1002/cncr.30390
75. Johnson V, Schlom J, Paterson A, Bennett J, Magnani J, Colcher D (1986) Analysis of a human tumour-associated glycoprotein (TAG-72) identified by monoclonal-antibody B72.3. Cancer Res 46:850–7
76. Molinolo A, Simpson J, Thor A, Schlom J (1990) Enhanced tumour binding using immunohistochemical analyses by 2nd generation anti-tumour-associated glycoprotein-72 monoclonal-antibodies versus monoclonal antibody-B72.3 in human tissue. Cancer Res 50:1291–8
77. Colcher D, Hand P, Nuti M, Schlom J (1981) A spectrum of monoclonal-antibodies reactive with human mammary-tumour cellS. Proc Natl Acad Sci USA Biol Sci 78:3199–3203. https://doi.org/10.1073/pnas.78.5.3199
78. Brown CK, Modzelewski RA, Johnson CS, Wong MKK (2000) A novel approach for the identification of unique tumour vasculature binding peptides using an *E. coli* peptide display library. Ann Surg Oncol 7:743–749. https://doi.org/10.1007/s10434-000-0743-0
79. Cohen A, Martin E, Lavery I, Daly J, Sardi A, Aitken D et al (1991) Radioimmunoguided surgery using I-125 B72.3 in patients with colorectal-cancer. Arch Surg 126:349–52
80. Colcher D, Milenic D, Ferroni P, Carrasquillo J, Reynolds J, Roselli M et al (1990) Invivo fate of monoclonal-antibody B723 in patients with colorectal-cancer. J Nucl Med 31:1133–42
81. Colcher D, Milenic D, Roselli M, Raubitschek A, Yarranton G, King D et al (1989) Characterization and biodistribution of recombinant and recombinant chimeric constructs of monoclonal-antibody B72.3. Cancer Res 49:1738–45
82. Whittle N, Adair J, Lloyd C, Jenkins L, Devine J, Schlom J et al (1987) Expression in cos cells of a mouse human chimaeric B723-antibody. Protein Eng 1:499–505. https://doi.org/10.1093/protein/1.6.499
83. Meredith R, Khazaeli M, Plott W, Saleh M, Liu T, Allen L et al (1992) Phase-I trial of iodine-131-chimeric B723 (human IGG4) in metastatic colorectal-cancer. J Nucl Med 33:23–9
84. Morrison S (1985) Transfectomas provide novel chimeric antibodies. Science 229:1202–1207. https://doi.org/10.1126/science.3929380
85. Hutzell P, Kashmiri S, Colcher D, Primus F, Hand P, Roselli M et al (1991) Generation and characterization of a recombinant/chimeric B72.3 (human gamma-1). Cancer Res 51:181–9
86. Muraro R, Kuroki M, Wunderlich D, Poole D, Colcher D, Thor A et al (1988) Generation and characterization of B72.3 2nd-generation monoclonal-antibodies reactive with the tumour-associated glycoprotein-72 antigen. Cancer Res 48:4588–96
87. Colcher D, Minelli M, Roselli M, Muraro R, Simpsonmilenic D, Schlom J (1988) Radioimmunolocalization of human carcinoma xenografts with B723 2nd-generation monoclonal-antibodies. Cancer Res 48:4597–603
88. Divgi C, Scott A, Mcdermott K, Fallone P, Hilton S, Siler K et al (1994) clinical comparison of radiolocalization of 2 monoclonal-antibodies (mAbs) against the TAG-72 antigen. Nucl Med Biol 21:9–15. https://doi.org/10.1016/0969-8051(94)90124-4
89. Murray J, Macey D, Kasi L, Rieger P, Cunningham J, Bhadkamkar V et al (1994) Phase-II radioimmunotherapy trial with I-131 CC49 in colorectal-cancer. Cancer 73:1057–1066.

https://doi.org/10.1002/1097-0142(19940201)73:3+%3c1057::AID-CNCR2820731345%3e3.0.CO;2-3
90. Divgi C, Scott A, Dantis L, Capitelli P, Siler K, Hilton S et al (1995) Phase-I radioimmunotherapy trial with iodine-131-CC49 in metastatic colon-carcinoma. J Nucl Med 36:586–592
91. Greiner J, Hand P, Noguchi P, Fisher P, Pestka S, Schlom J (1984) Enhanced expression of surface tumour-associated antigens on human-breast and colon-tumour cells after recombinant human-leukocyte alpha-interferon treatment. Can Res 44:3208–3214
92. Greiner J, Guadagni F, Goldstein D, Borden E, Ritts R, Witt P et al (1991) Evidence for the elevation of serum carcinoembryonic antigen and tumour-associated glycoprotein-72 levels in patients administered interferons. Can Res 51:4155–4163
93. Greiner J, Ullmann C, Nieroda C, Qi C, Eggensperger D, Shimada S et al (1993) Improved radioimmunotherapeutic efficacy of an anticarcinoma monoclonal-antibody (I-131-CC49) when given in combination with gamma-interferon. Can Res 53:600–608
94. Blumenthal R, Sharkey R, Goldenberg D (1992) Dose escalation of radioantibody in a mouse model with the use of recombinant human interleukin-1 and granulocyte-macrophage colony-stimulating factor intervention to reduce myelosuppression. J Natl Cancer Inst 84:399–407. https://doi.org/10.1093/jnci/84.6.399
95. Meredith R, Bueschen A, Khazaeli M, Plott W, Grizzle W, Wheeler R et al (1994) treatment of metastatic prostate carcinoma with radiolabeled antibodY CC49. J Nucl Med 35:1017–1022
96. Wheeler RH MR, Saleh MN (1994) A phase II trial of IL-1+ radioimmunotherapy (RIT) in patients (pts) with metastatic colon cancer. Proc Annu Met Am Soc Clin Oncol (meeting abstract) 295
97. Meredith R, Khazaeli M, Plott W, Grizzle W, Liu T, Schlom J et al (1996) Phase II study of dual I-131-labeled monoclonal antibody therapy with interferon in patients with metastatic colorectal cancer. Clin Cancer Res 2:1811–1818
98. SlavinChiorini D, Kashmiri S, Lee H, Milenic D, Poole D, Bernon E et al (1997) A CDR-grafted (humanized) domain-deleted antitumour antibody. Cancer Biother Radiopharm 12:305–316. https://doi.org/10.1089/cbr.1997.12.305
99. Chinn P, Morena R, Santoro D, Kazules T, Kashmiri S, Schlom J et al (2006) Pharmacokinetics and ibmor localization of In-111-labeled HuCC49 Delta C(H)2 in BALB/c mice and athymic murine colon carcinoma xenograft. Cancer Biother Radiopharm 21:106–116. https://doi.org/10.1089/cbr.2006.21.106
100. Mueller B, Reisfeld R, Gillies S (1990) serum half-life and tumour-localization of a chimeric antibody deleted of the CH2 domain and directed against the disialoganglioside-GD2. Proc Natl Acad Sci USA 87:5702–5705. https://doi.org/10.1073/pnas.87.15.5702
101. Slavinchiorini D, Hand P, Kashmiri S, Calvo B, Zaremba S, Schlom J (1993) Biologic properties of a CH2 domain-deleted recombinant immunoglobulin. Int J Cancer 53:97–103. https://doi.org/10.1002/ijc.2910530119
102. Slavinchiorini D, Kashmiri S, Schlom J, Calvo B, Shu L, Schott M et al (1995) Biological properties of chimeric domain-deleted anticarcinoma immunoglobulins. Cancer Res 55:5957–67
103. Heath J, White S, Johnstone C, Catimel B, Simpson R, Moritz R et al (1997) The human A33 antigen is a transmembrane glycoprotein and a novel member of the immunoglobulin superfamily. Proc Natl Acad Sci USA 94:469–474. https://doi.org/10.1073/pnas.94.2.469
104. Ritter G, Cohen L, Nice E, Catimel B, Burgess A, Moritz R et al (1997) Characterization of posttranslational modifications of human A33 antigen, a novel palmitoylated surface glycoprotein of human gastrointestinal epithelium. Biochem Biophys Res Commun 236:682–686. https://doi.org/10.1006/bbrc.1997.6966
105. Welt S, Divgi C, Real F, Yeh S, Garinchesa P, Finstad C et al (1990) quantitative-analysis of antibody localization in human metastatic colon cancer—a phase-I study of monoclonal antibody-A33. J Clin Oncol 8:1894–1906. https://doi.org/10.1200/JCO.1990.8.11.1894
106. Welt S, DivgI C, Kemeny N, Finn R, Scott A, Graham M et al (1994) Phase I/II study of iodine 131-LABELED monoclonal-antibody A33 in patients with advanced colon-canceR. J Clin Oncol 12:1561–1571. https://doi.org/10.1200/JCO.1994.12.8.1561
107. King D, Antoniw P, Owens R, Adair J, Haines A, Farnsworth A et al (1995) Preparation and preclinical evaluation of humanized A33 immunoconjugates for radioimmunotherapy. Br J Cancer 72:1364–72. https://doi.org/10.1038/bjc.1995.516
108. Welt S, Ritter G, Williams C, Cohen L, John M, Jungbluth A et al (2003) Phase I study of anticolon cancer humanized antibody A33. Clin Cancer Res 9:1338–1346
109. Welt S, Ritter G, Williams C, Cohen L, Jungbluth A, Richards E et al (2003) Preliminary report of a phase I study of combination chemotherapy and humanized A33 antibody immunotherapy in patients with advanced colorectal cancer. Clin Cancer Res 9:1347–1353
110. Scott A, Lee F, Jones R, Hopkins W, MacGregor D, Cebon J et al (2005) A phase I trial of humanized monoclonal antibody A33 in patients with colorectal carcinoma: Biodistribution, pharmacokinetics, and quantitative tumour uptake. Clin Cancer Res 11:4810–4817. https://doi.org/10.1158/1078-0432.CCR-04-2329
111. Chong G, Lee F, Hopkins W, Tebbutt N, Cebon J, Mountain A et al (2005) Phase I trial of I-131-huA33 in patients with advanced colorectal carcinoma. Clin Cancer Res 11:4818–4826. https://doi.org/10.1158/1078-0432.CCR-04-2330
112. Koprowski H, Steplewski Z, Mitchell K, Herlyn M, Herlyn D, Fuhrer P (1979) colorectal-carcinoma antigens detected by hybridoma antibodies. Somatic Cell Genetics 5:957–972. https://doi.org/10.1007/BF01542654
113. Herlyn M, Steplewski Z, Herlyn D, Koprowski H (1979) Colorectal carcinoma-specific antigen—detection by means of monoclonal antibodies. Proc Natl Acad Sci USA 76:1438–1442. https://doi.org/10.1073/pnas.76.3.1438
114. Trzpis M, McLaughlin P, de Leij L, Harmsen M (2007) Epithelial cell adhesion molecule—more than a carcinoma marker and adhesion molecule. Am J Pathol 171:386–395. https://doi.org/10.2353/ajpath.2007.070152
115. Gottlinger H, Funke I, Johnson J, Gokel J, Riethmuller G (1986) The epithelial-cell surface-antigen 17–1A, a target for antibody-mediated tumour-therapy—its biochemical nature, tissue distribution and recognition by different monoclonal-antibodies. Int J Cancer 38:47–53
116. Sun L, Curtis P, Rakowiczszulczynska E, Ghrayeb J, Chang N, Morrison S et al (1987) chimeric antibody with human constant regions and mouse variable regions directed against carcinoma-associated antigen 17–1A. Proc Natl Acad Sci USA 84:214–218. https://doi.org/10.1073/pnas.84.1.214
117. Shaw D, Khazaeli M, Sun L, Ghrayeb J, Daddona P, Mckinney S et al (1987) Characterization of a mouse human chimeric monoclonal-antibody (17–1A) to a colon cancer tumour-associated antigen. J Immunol 138:4534–4538
118. Macey D, Grant E, Kasi L, Rosenblum M, Zhang H, Katz R et al (1997) Effect of recombinant alpha-interferon on pharmacokinetics, biodistribution, toxicity, and efficacy of I-131-labeled monoclonal antibody CC49 in breast cancer: A phase II trial. Clin Cancer Res 3:1547–1555
119. Murray J, Macey D, Grant E, Rosenblum M, Kasi L, Zhang H et al (1995) Enhanced tag-72 expression and turner uptake of

radiolabeled monoclonal-antibody CC49 In metastatic breast-cancer patients following alpha-interferon treatment. Can Res 55:S5925–S5928
120. Mulligan T, Carrasquillo J, Chung Y, Milenic D, Schlom J, Feuerstein I et al (1995) Phase I study of intravenous Lu-177-labeled CC49 murine monoclonal antibody in patients with advanced adenocarcinoma. Clin Cancer Res 1:1447–1454
121. Marken J, Schieven G, Hellstrom I, Hellstrom K, Aruffo A (1992) Cloning and expression of the tumour-associated antigen-L6. Proc Natl Acad Sci USA 89:3503–3507. https://doi.org/10.1073/pnas.89.8.3503
122. Goodman G, Hellstrom I, Brodzinsky L, Nicaise C, Kulander B, Hummel D et al (1990) Phase-I trial of murine monoclonal antibody-L6 in breast, colon, ovarian, and lung-cancer. J Clin Oncol 8:1083–1092. https://doi.org/10.1200/JCO.1990.8.6.1083
123. Svensson H, Vrudhula V, Emswiler J, Macmaster J, CosanD W, Senter P et al (1995) In-vitro and in-vivo activities of a doxorubicin prodrug in combination with monoclonal-antibody beta-lactamase conjugates. Can Res 55:2357–2365
124. DeNardo S, OGrady L, Richman C, Goldstein D, ODonnell R, DeNardo D et al (1997) Radioimmunotherapy for advanced breast cancer using I-131-ChL6 antibody. Anticancer Res 17:1745–51
125. DeNardo S, Richman C, Goldstein D, Shen S, Salako Q, Kukis D et al (1997) Yttrium-90/indium-111-DOTA-peptide-chimeric L6: Pharmacokinetics, dosimetry and initial results in patients with incurable breast cancer. Anticancer Res 17:1735–1744
126. Altunay B, Morgenroth A, Beheshti M, Vogg A, Wong N, Ting H et al (2020) HER2-directed antibodies, affibodies and nanobodies as drug-delivery vehicles in breast cancer with a specific focus on radioimmunotherapy and radioimmunoimaging. Eur J Nucl Med Mol Imaging. https://doi.org/10.1007/s00259-020-05094-1
127. Xavier C, Vaneycken I, Dhuyvetter M, Heemskerk J, Keyaerts M, Vincke C et al (2013) Synthesis, preclinical validation, dosimetry, and toxicity of Ga-68-NOTA-Anti-HER2 nanobodies for iPET imaging of HER2 receptor expression in cancer. J Nucl Med 54:776–84. https://doi.org/10.2967/jnumed.112.111021
128. Keyaerts M, Xavier C, Heemskerk J, Devoogdt N, Everaert H, Ackaert C et al (2016) Phase I study of Ga-68-HER2-nanobody for PET/CT assessment of HER2 expression in breast carcinoma. J Nucl Med 57:27–33. https://doi.org/10.2967/jnumed.115.162024
129. D'Huyvetter M, De Vos J, Xavier C, Pruszynski M, Sterckx Y, Massa S et al (2017) I-131-labeled Anti-HER2 camelid sdAb as a theranostic tool in cancer treatment. Clin Cancer Res 23:6616–6628. https://doi.org/10.1158/1078-0432.CCR-17-0310
130. Perez E, Romond E, Suman V, Jeong J, Sledge G, Geyer C et al (2014) Trastuzumab plus adjuvant chemotherapy for human epidermal growth factor receptor 2-positive breast cancer: planned joint analysis of overall survival from NSABP B-31 and NCCTG N9831. J Clin Oncol 32:3744. https://doi.org/10.1200/JCO.2014.55.5730
131. Kameswaran M, Gota V, Ambade R, Gupta S, Dash A (2017) Preparation and preclinical evaluation of I-131-trastuzumab for breast cancer. J Labelled Compd Radiopharm 60:12–19. https://doi.org/10.1002/jlcr.3465
132. Goldenberg D, Deland F, Bennett S, Primus F, Nelson M, Flanigan R et al (1983) Radioimmunodetection of prostatic-cancer—invivo use of radioactive antibodies against prostatic acid-phosphatase for diagnosis and detection of prostatic-cancer by nuclear imaging. JAMA J Am Med Assoc 250:630–635. https://doi.org/10.1001/jama.250.5.630
133. Meredith R, Khazaeli M, Macey D, Grizzle W, Mayo M, Schlom J et al (1999) Phase II study of interferon-enhanced I-131-labeled high affinity CC49 monoclonal antibody therapy in patients with metastatic prostate cancer. Clin Cancer Res 5:3254S-S3258
134. Bouchelouche K, Turkbey B, Choyke P (2016) PSMA PET and radionuclide therapy in prostate cancer. Semin Nucl Med 46:522–535. https://doi.org/10.1053/j.semnuclmed.2016.07.006
135. Haberkorn U, Eder M, Kopka K, Babich J, Eisenhut M (2016) New strategies in prostate cancer: prostate-specific membrane antigen (PSMA) ligands for diagnosis and therapy. Clin Cancer Res 22:9–15. https://doi.org/10.1158/1078-0432.CCR-15-0820
136. Tagawa S, Beltran H, Vallabhajosula S, Goldsmith S, Osborne J, Matulich D et al (2010) Anti-prostate-specific membrane antigen-based radioimmunotherapy for prostate cancer. Cancer 116:1075–1083. https://doi.org/10.1002/cncr.24795
137. Sadaghiani M, Sheikhbahaei S, Werner R, Pienta K, Pomper M, Solnes L et al (2021) A systematic review and meta-analysis of the effectiveness and toxicities of lutetium-177-labeled prostate-specific membrane antigen-targeted radioligand therapy in metastatic castration-resistant prostate cancer. Eur Urol 80:82–94. https://doi.org/10.1016/j.eururo.2021.03.004
138. Morris M, De Bono J, Chi K, Fizazi K, Herrmann K (2021) Phase III study of lutetium-177-PSMA-617 in patients with metastatic castration-resistant prostate cancer (VISION). J Clin Oncol
139. Novartis. Novartis receives FDA breakthrough therapy designation for investigational 177Lu-PSMA-617 in patients with metastatic castration-resistant prostate cancer (mCRPC). https://www.novartis.com/news/novartis-receives-fda-breakthrough-therapy-designation-investigational-177lu-psma-617-patients-metastatic-castration-resistant-prostate-cancer-mcrpc. Accessed 27 Nov 2021
140. Wilkowski R, Wolf M, Heinemann V (2008) Primary advanced unresectable pancreatic cancer. Recent Results Cancer Res 177:79–93
141. Qu C, Li Y, Song Y, Rizvi S, Raja C, Zhang D et al (2004) MUC1 expression in primary and metastatic pancreatic cancer cells for in vitro treatment by Bi-213-C595 radioimmunoconjugate. Br J Cancer 91:2086–2093. https://doi.org/10.1038/sj.bjc.6602232
142. Winter J, Tang L, Klimstra D, Brennan M, Brody J, Rocha F et al (2012) A novel survival-based tissue microarray of pancreatic cancer validates MUC1 and mesothelin as biomarkers. PLoS ONE. https://doi.org/10.1371/journal.pone.0040157
143. Gold D, Alisauskas R, Sharkey R (1995) Targeting of xenografted pancreatic-cancer with a new monoclonal-antibodY, PAM4. Can Res 55:1105–1110
144. Mariani G, Molea N, Bacciardi D, Boggi U, Fornaciari G, Campani D et al (1995) Initial turner targeting, biodistribution, and pharmacokinetic evaluation of the monoclonal-antibody PAM4 in patients with pancreatic-cancer. Cancer Res 55:S5911–S5
145. Gold D, Cardillo T, Vardi Y, Blumenthal R (1997) Radioimmunotherapy of experimental pancreatic cancer with I-131-labeled monoclonal antibody PAM4. Int J Cancer 71:660–667
146. Cardillo T, Ying Z, Gold D (2001) Therapeutic advantage of (90) Yttrium-versus (131)Iodine-labeled PAM4 antibody in experimental pancreatic cancer. Clin Cancer Res 7:3186–3192
147. El-Serag H, Rudolph L (2007) Hepatocellular carcinoma: epidemiology and molecular carcinogenesis. Gastroenterology 132:2557–2576. https://doi.org/10.1053/j.gastro.2007.04.061
148. Nordenstedt H, White D, El-Serag H (2010) The changing pattern of epidemiology in hepatocellular carcinoma. Dig Liver Dis 42:S206–S214. https://doi.org/10.1016/S1590-8658(10)60507-5
149. Finn R (2010) Development of molecularly targeted therapies in hepatocellular carcinoma: where do we go now? (vol 16, pg

390, 2010). Clin Cancer Res 16:2696. https://doi.org/10.1158/1078-0432.CCR-10-0681
150. Order S, Stillwagon G, Klein J, Leichner P, Siegelman S, Fishman E et al (1985) I-131 antiferritin, a new treatment modality in hepatoma—a radiation-therapy-oncology-group study. J Clin Oncol 3:1573–1582. https://doi.org/10.1200/JCO.1985.3.12.1573
151. Liu Y, Yang K, Wu Y, Gang Y, Zhu D (1983) Treatment of advanced primary hepatocellular-carcinoma by I-131-labeled-anti-AFP. Lancet 1:531–532
152. Sitzmann J, Abrams R (1993) Improved survival for hepatocellular cancer with combination surgery and multimodality treatment. Ann Surg 217:149–154. https://doi.org/10.1097/00000658-199302000-00009
153. Chen S, Li B, Xie H, Xu L, Niu G, Fan K et al (2004) Phase I clinical trial of targeted therapy using I-131-hepama-1 mAb in patients with hepatocellular carcinoma. Cancer Biother Radiopharm 19:589–600
154. Zhang Q, Zhou J, Ku X, Chen X, Zhang L, Xu J et al (2007) Expression of CD147 as a significantly unfavorable prognostic factor in hepatocellular carcinoma. Eur J Cancer Prev 16:196–202. https://doi.org/10.1097/01.cej.0000236245.40619.c3
155. Chen Z, Mi L, Xu J, Song F, Zhang Q, Zhang Z et al (2006) Targeting radioimmunotherapy of hepatocellular carcinoma with iodine (I-131) metuximab injection: clinical phase I/II trials. Int J Radiat Oncol Biol Phys 65:435–444. https://doi.org/10.1016/j.ijrobp.2005.12.034
156. Zhang Z, Bian H, Feng Q, Mi L, Mo T, Kuang A et al (2006) Biodistribution and localization of Iodine-131-labeled metuximab in patients with hepatocellular carcinoma. Cancer Biol Ther 5:318–322. https://doi.org/10.4161/cbt.5.3.2431
157. Wu L, Yang Y, Ge N, Shen S, Liang J, Wang Y et al (2012) Hepatic artery injection of I-131-labelled metuximab combined with chemoembolization for intermediate hepatocellular carcinoma: a prospective nonrandomized study. Eur J Nucl Med Mol Imaging 39:1306–1315. https://doi.org/10.1007/s00259-012-2145-5
158. He Q, Lu W, Liu Y, Guan Y, Kuang A (2013) I-131-labeled metuximab combined with chemoembolization for unresectable hepatocellular carcinoma. World J Gastroenterol 19:9104–9110. https://doi.org/10.3748/wjg.v19.i47.9104
159. Xu J, Shen Z, Chen X, Zhang Q, Bian H, Zhu P et al (2007) A randomized controlled trial of licartin for preventing hepatoma recurrence after liver transplantation. Hepatology 45:269–276. https://doi.org/10.1002/hep.21465
160. Bian H, Zheng J, Nan G, Li R, Chen C, Hu C et al (2014) Randomized trial of [I-131] metuximab in treatment of hepatocellular carcinoma after percutaneous radiofrequency ablation. JNCI J Natl Cancer Inst. https://doi.org/10.1093/jnci/dju239
161. Li J, Xing J, Yang Y, Liu J, Wang W, Xia Y et al (2020) Adjuvant I-131-metuximab for hepatocellular carcinoma after liver resection: a randomised, controlled, multicentre, open-label, phase 2 trial. Lancet Gastroenterol Hepatol 5:548–560. https://doi.org/10.1016/S2468-1253(19)30422-4
162. Huang J, Zhang X, Tang Q, Zhang F, Li Y, Feng Z et al (2011) Prognostic significance and potential therapeutic target of VEGFR2 in hepatocellular carcinoma. J Clin Pathol 64:343–348. https://doi.org/10.1136/jcp.2010.085142
163. Huang J, Liang J, Tang Q, Wang Z, Chen L, Zhu J et al (2011) An active murine-human chimeric Fab antibody derived from Escherichia coli, potential therapy against over-expressing VEGFR2 solid tumours. Appl Microbiol Biotechnol 91:1341–1351. https://doi.org/10.1007/s00253-011-3335-y
164. Huang J, Tang Q, Wang C, Yu H, Feng Z, Zhu J (2015) Molecularly targeted therapy of human hepatocellular carcinoma xenografts with radio-iodinated anti-VEGFR2 murine-human chimeric fab. Sci Rep. https://doi.org/10.1038/srep10660
165. Goodenberger M, Jenkins R (2012) Genetics of adult glioma. Cancer Genet 205:613–621. https://doi.org/10.1016/j.cancergen.2012.10.009
166. Taylor O, Brzozowski J, Skelding K (2019) Glioblastoma multiforme: an overview of emerging therapeutic targets. Front Oncol. https://doi.org/10.3389/fonc.2019.00963
167. Zimm S, Wampler G, Stablein D, Hazra T, Young H (1981) Intra-cerebral metastases in solid-tumour patients—natural-history and results of treatment. Cancer 48:384–394. https://doi.org/10.1002/1097-0142(19810715)48:2%3c384::AID-CNCR2820480227%3e3.0.CO;2-8
168. Schouten L, Rutten J, Huveneers H, Twijnstra A (2002) Incidence of brain Metastases in a cohort of patients with breast, colon, kidney, and lung cancer, and melanoma. Neurology 58:A49
169. Lombardi G, Di Stefano A, Farina P, Zagonel V, Tabouret E (2014) Systemic treatments for brain metastases from breast cancer, non-small cell lung cancer, melanoma and renal cell carcinoma: an overview of the literature. Cancer Treat Rev 40:951–959. https://doi.org/10.1016/j.ctrv.2014.05.007
170. Lu-Emerson C, Eichler AF (2012) Brain metastases. Continuum Lifelong Learn Neurol 18:295–311
171. Marquez A, Wu R, Zhao J, Tao J, Shi Z (2004) Evaluation of epidermal growth factor receptor (EGFR) by chromogenic in situ hybridization (CISH (TM)) and immunohistochemistry (IHC) in archival gliomas using bright-field microscopy. Diagn Mol Pathol 13:1–8. https://doi.org/10.1097/00019606-200403000-00001
172. Murthy U, Basu A, Rodeck U, Herlyn M, Ross A, Das M (1987) Binding of an antagonistic monoclonal-antibody to an intact and fragmented egf-receptor polypeptide. Arch Biochem Biophys 252:549–560. https://doi.org/10.1016/0003-9861(87)90062-2
173. Brady LW, Markoe AM, Woo DV et al (1990) Iodine125 labeled anti-epidermal growth factor receptor-425 in the treatment of malignant astrocytomas: a pilot study. J Neurosurg Sci 34:243–9
174. Brady L, Miyamoto C, Woo D, Rackover M, Emrich J, Bender H et al (1992) Malignant astrocytomas treated with I-125 labeled monoclonal-antibody 425 against epidermal growth-factor receptor—a phase II trial. Int J Radiat Oncol Biol Phys 22:225–230. https://doi.org/10.1016/0360-3016(92)91009-C
175. Emrich J, Brady L, Quang T, Class R, Miyamoto C, Black P et al (2002) Radioiodinated (I-125) monoclonal antibody 425 in the treatment of high grade glioma patients—ten-year synopsis of a novel treatment. Am J Clin Oncol Cancer Clin Trials 25:541–546. https://doi.org/10.1097/00000421-200212000-00001
176. Li L, Quang T, Gracely E, Kim J, Emrich J, Yaeger T et al (2010) A Phase II study of anti-epidermal growth factor receptor radioimmunotherapy in the treatment of glioblastoma multiforme Clinical article. J Neurosurg 113:192–198. https://doi.org/10.3171/2010.2.JNS091211
177. An Z, Aksoy O, Zheng T, Fan Q, Weiss W (2018) Epidermal growth factor receptor and EGFRvIII in glioblastoma: signaling pathways and targeted therapies. Oncogene 37:1561–1575. https://doi.org/10.1038/s41388-017-0045-7
178. Jungbluth A, Stockert E, Huang H, Collins V, Coplan K, Iversen K et al (2003) A monoclonal antibody recognizing human cancers with amplification/overexpression of the human epidermal growth factor receptor. Proc Natl Acad Sci USA 100:639–644. https://doi.org/10.1073/pnas.232686499
179. Perera R, Zoncu R, Johns T, Pypaert M, Lee F, Mellman I et al (2007) Internalization, intracellular trafficking, and biodistribution of monoclonal antibody 806: a novel anti-epidermal growth factor receptor antibody. Neoplasia 9:1099–1110. https://doi.org/10.1593/neo.07721

180. Hens M, Vaidyanathan G, Welsh P, Zalutsky M (2009) Labeling internalizing anti-epidermal growth factor receptor variant III monoclonal antibody with Lu-177: in vitro comparison of acyclic and macrocyclic ligands. Nucl Med Biol 36:117–128. https://doi.org/10.1016/j.nucmedbio.2008.11.001
181. Hens M, Vaidyanathan G, Zhao X, Bigner D, Zalutsky M (2010) Anti-EGFRvIII monoclonal antibody armed with Lu-177: in vivo comparison of macrocyclic and acyclic ligands. Nucl Med Biol 37:741–750. https://doi.org/10.1016/j.nucmedbio.2010.04.020
182. Zalutsky M, Moseley R, Coakham H, Coleman R, Bigner D (1989) Pharmacokinetics and tumour-localization of I-131-Labeled anti-tenascin monoclonal antibody-81C6 In patients with gliomas and other intracranial malignancies. Can Res 49:2807–2813
183. Ventimiglia J, Wikstrand C, Ostrowski L, Bourdon M, Lightner V, Bigner D (1992) Tenascin expression in human glioma cell-lines and normal-tissues. J Neuroimmunol 36:41–55. https://doi.org/10.1016/0165-5728(92)90029-K
184. Bourdon M, Wikstrand C, Furthmayr H, Matthews T, Bigner D (1983) Human glioma-mesenchymal extracellular-matrix antigen defined by monoclonal-antibody. Can Res 43:2796–2805
185. Siri A, Carnemolla B, Saginati M, Leprini A, Casari G, Baralle F et al (1991) Human tenascin—primary structure, pre-messenger-rna splicing patterns and localization of the epitopes recognized by 2 monoclonal-antibodies. Nucleic Acids Res 19:525–531. https://doi.org/10.1093/nar/19.3.525
186. Reardon D, Quinn J, Akabani G, Coleman R, Friedman A, Friedman H et al (2006) Novel human IgG2b/murine chimeric antitenascin monoclonal antibody construct radiolabeled with I-131 and administered into the surgically created resection cavity of patients with malignant glioma: phase I trial results. J Nucl Med 47:912–918
187. Riva P, Arista A, Sturiale C, Moscatelli G, Tison V, Mariani M et al (1992) Treatment of intracranial human glioblastoma by direct intratumoural administration of I-131-Labeled anti-tenascin monoclonal-antibody BC-2. Int J Cancer 51:7–13. https://doi.org/10.1002/ijc.2910510103
188. Riva P, Arista A, Sturiale C, Tlson V, Lazzari S et al (1994) Glioblastoma therapy by direct intralesional administration of i-131 radioiodine labeled antitenascin antibodies. Cell Biophys 24/25
189. Riva P, Arista A, Franceschi G, Frattarelli M, SturialE C, Riva N et al (1995) Local treatment of malignant gliomas by direct infusion of specific monoclonal-antibodies labeled with I-131—comparison of the results obtained in recurrent and newly-diagnosed tumours. Cancer Res 55:5952–6
190. Riva P, Franceschi G, Frattarelli M, Riva N, Guiducci G, Cremonini A et al (1999) I-131 radioconjugated antibodies for the locoregional radioimmunotherapy of high-grade malignant glioma—Phase I and II study. Acta Oncol 38:351–359
191. Bourdon M, Matthews T, Pizzo S, Bigner D (1985) Immunochemical and biochemical-characterization of a glioma-associated extracellular-matrix glycoprotein. J Cell Biochem 28:183–195. https://doi.org/10.1002/jcb.240280302
192. Bourdon M, Coleman R, Blasberg R, Groothuis D, Bigner D (1984) Monoclonal-antibody localization in subcutaneous and intracranial human glioma xenografts - paired-label and imaging analysis. Anticancer Res 4:133–140
193. Lee Y, Bullard D, Wikstrand C, Zalutsky M, Muhlbaier L, Bigner D (1987) Comparison of monoclonal-antibody delivery to intracranial glioma xenografts by intravenous and intracarotid administration. Can Res 47:1941–1946
194. Lee Y, Bullard D, Zalutsky M, Coleman R, Wikstrand C, Friedman H et al (1988) Therapeutic efficacy of antiglioma mesenchymal extracellular-matrix I-131-radiolabeled murine monoclonal-antibody in a human glioma xenograft model. Can Res 48:559–566
195. Schold S, Zalutsky M, Coleman R, Glantz M, Friedman A, Jaszczak R et al (1993) distribution and dosimetry of I-123 labeled monoclonal antibody-81C6 in patients with anaplastic glioma. Invest Radiol 28:488–496
196. Zalutsky M, Moseley R, Benjamin J, Colapinto E, Fuller G, Coakham H et al (1990) Monoclonal-antibody and F(ab')2 fragment delivery to tumour in patients with glioma—comparison of intracarotid and intravenous administration. Can Res 50:4105–4110
197. Akabani G, Cokgor I, Coleman R, Trotter D, Wong T, Friedman H et al (2000) Dosimetry and dose-response relationships in newly diagnosed patients with malignant gliomas treated with iodine-131-labeled anti-tenascin monoclonal antibody 81C6 therapy. Int J Radiat Oncol Biol Phys 46:947–958. https://doi.org/10.1016/S0360-3016(99)00500-3
198. Cokgor I, Akabani G, Kuan C, Friedman H, Friedman A, Coleman R et al (2000) Phase I trial results of iodine-131-labeled antitenascin monoclonal antibody 81C6 treatment of patients with newly diagnosed malignant gliomas. J Clin Oncol 18:3862–3872. https://doi.org/10.1200/JCO.2000.18.22.3862
199. Bigner D, Brown M, Friedman A, Coleman R, Akabani G, Friedman H et al (1998) Iodine-131-labeled antitenascin monoclonal antibody 81C6 treatment of patients with recurrent malignant gliomas: phase I trial results. J Clin Oncol 16:2202–2212. https://doi.org/10.1200/JCO.1998.16.6.2202
200. Reardon D, Akabani G, Coleman R, Friedman A, Friedman H, Herndon J et al (2002) Phase II trial of murine I-131-labeled antitenascin monoclonal antibody 81C6 administered into surgically created resection cavities of patients with newly diagnosed malignant gliomas. J Clin Oncol 20:1389–1397. https://doi.org/10.1200/JCO.20.5.1389
201. He X, Archer G, Wikstrand C, Morrison S, Zalutsky M, Bigner D et al (1994) Generation and characterization of a mouse/human chimeric antibody-directed against extracellular-matrix protein tenascin. J Neuroimmunol 52:127–137. https://doi.org/10.1016/0165-5728(94)90106-6
202. Brack S, Silacci M, Birchler M, Neri D (2006) Tumour-targeting properties of novel antibodies specific to the large isoform of tenascin-C. Clin Cancer Res 12:3200–3208. https://doi.org/10.1158/1078-0432.CCR-05-2804
203. Weledji EP, Assob JC (2014) The ubiquitous neural cell adhesion molecule (N-CAM). Ann Med Surg 3:77–81
204. Papanastassiou V, Pizer B, Coakham H, Bullimore J, Zananiri T, Kemshead J (1993) Treatment of recurrent and cystic malignant gliomas by a single intracavity injection of I-131 monoclonal-antibody—feasibility, pharmacokinetics and dosimetry. Br J Cancer 67:144–151. https://doi.org/10.1038/bjc.1993.25
205. Goldman A, Vivian G, Gordon I, Pritchard J, Kemshead J (1984) Immunolocalization of neuroblastoma using radiolabeled monoclonal antibody UJ13A. J Pediatr 105:252–256
206. Jones D, Lashford L, Dicks-Mireaux C, Kemshead J (1987) Comparison of pharmacokinetics of radiolabeled monoclonal antibody UJ13A in patients and animal models NCI monographs. J Natl Cancer Inst 125–30
207. Neri D, Bicknell R (2005) Tumour vascular targeting. Nat Rev Cancer 5:436–446. https://doi.org/10.1038/nrc1627
208. Rybak J, Trachsel E, Scheuermann J, Neri D (2007) Ligand-based vascular targeting of disease. ChemMedChem 2:22–40. https://doi.org/10.1002/cmdc.200600181
209. Carnemolla B, Balza E, Siri A, Zardi L, Nicotra M, Bigotti A et al (1989) A tumour-associated fibronectin isoform generated by alternative splicing of messenger-rna precursors. J Cell Biol 108:1139–1148. https://doi.org/10.1083/jcb.108.3.1139

210. Castellani P, Viale G, Dorcaratto A, Nicolo G, Kaczmarek J, Querze G et al (1994) The fibronectin isoform containing the ED-B oncofetal domain—a marker of angiogenesis. Int J Cancer 59:612–618. https://doi.org/10.1002/ijc.2910590507
211. Ebbinghaus C, Scheuermann J, Neri D, Elia G (2004) Diagnostic and therapeutic applications of recombinant antibodies: targeting the extra-domain B of fibronectin, a marker of tumour angiogenesis. Curr Pharm Des 10:1537–1549. https://doi.org/10.2174/1381612043384808
212. Pini A, Viti F, Santucci A, Carnemolla B, Zardi L, Neri P et al (1998) Design and use of a phage display library—human antibodies with subnanomolar affinity against a marker of angiogenesis eluted from a two-dimensional gel. J Biol Chem 273:21769–21776. https://doi.org/10.1074/jbc.273.34.21769
213. Borsi L, Balza E, Bestagno M, Castellani P, Carnemolla B, Biro A et al (2002) Selective targeting of tumoural vasculature: comparison of different formats of an antibody (L19) to the ED-B domain of fibronectin. Int J Cancer 102:75–85. https://doi.org/10.1002/ijc.10662
214. Berndorff D, Borkowski S, Sieger S, Rother A, Friebe M, Viti F et al (2005) Radioimmunotherapy of solid tumours by targeting extra domain B fibronectin: identification of the best-suited radioimmunoconjugate. Clin Cancer Res 11:7053S-S7063. https://doi.org/10.1158/1078-0432.CCR-1004-0015
215. Tijink B, Neri D, Leemans C, Budde M, Dinkelborg L, Stigter-van Walsum M et al (2006) Radioimmunotherapy of head and neck cancer xenografts using I-131-labeled antibody L19-SIP for selective targeting of tumour vasculature. J Nucl Med 47:1127–1135
216. El-Emir E, Dearling J, Huhalov A, Robson M, Boxer G, Neri D et al (2007) Characterisation and radioimmunotherapy of L19-SIP, an anti-angiogenic antibody against the extra domain B of fibronectin, in colorectal tumour models. Br J Cancer 96:1862–1870. https://doi.org/10.1038/sj.bjc.6603806
217. Virotta G, Poli G, Bettini A, Bianchi C, Giovannoni L, Gerali A, et al. Radioimmunotherapy with 131I-L19SIP (Radretumab) in metastatic solid tumours: preliminary results. J Nucl Med. 2012;53
218. Dobrenkov K, Cheung N (2014) GD2-targeted immunotherapy and radioimmunotherapy. Semin Oncol 41:589–612. https://doi.org/10.1053/j.seminoncol.2014.07.003
219. Cheung N, Landmeier B, Neely J, Nelson A, Abramowsky C, Ellery S et al (1986) Complete tumour ablation with radiolabeled-I-131 disialoganglioside GD2-specific monoclonal-antibody against human neuroblastoma xenografted in nude-mice. J Natl Cancer Inst 77:739–745. https://doi.org/10.1093/jnci/77.3.739
220. Mennel H, Bosslet K, Geissel H, Bauer B (2000) Immunohistochemically visualized localisation of gangliosides G(lac)2 (GD(3)) and G(tri)2 (GD(2)) in cells of human intracranial tumours. Exp Toxicol Pathol 52:277–285
221. Yeh S, Larson S, Burch L, Kushner B, Laquaglia M, Finn R et al (1991) Radioimmunodetection of neuroblastoma with iodine-131-3F8—correlation with biopsy, Iodine-131-metaiodobenzylguanidine and standard diagnostic modalities. J Nucl Med 32:769–76
222. Larson S, Pentlow K, Volkow N, Wolf A, Finn R, Lambrecht R et al (1992) PET scanning of Iodine-124-3F8 as an approach to tumour dosimetry during treatment planning for radioimmunotherapy in a child with neuroblastoma. J Nucl Med 33:2020–2023
223. Yu A, Gilman A, Ozkaynak M, London W, Kreissman S, Chen H et al (2010) Anti-GD2 antibody with GM-CSF, interleukin-2, and isotretinoin for neuroblastoma. N Engl J Med 363:1324–1334. https://doi.org/10.1056/NEJMoa0911123
224. Cheung N, Cheung I, Kushner B, Ostrovnaya I, Chamberlain E, Kramer K et al (2012) Murine anti-GD2 monoclonal antibody 3f8 combined with granulocyte-macrophage colony-stimulating factor and 13-cis-retinoic acid in high-risk patients with stage 4 neuroblastoma in first remission. J Clin Oncol 30:3264–3270. https://doi.org/10.1200/JCO.2011.41.3807
225. Kramer K, Kushner B, Modak S, Pandit-Taskar N, Smith-Jones P, Zanzonico P et al (2010) Compartmental intrathecal radioimmunotherapy: results for treatment for metastatic CNS neuroblastoma. J Neurooncol 97:409–418. https://doi.org/10.1007/s11060-009-0038-7
226. Kramer K, Pandit-Taskar N, Humm J, Zanzonico P, Haque S, Dunkel I et al (2018) A phase II study of radioimmunotherapy with intraventricular I-131-3F8 for medulloblastoma. Pediatr Blood Cancer. https://doi.org/10.1002/pbc.26754
227. Kramer K, Humm J, Souweidane M, Zanzonico P, Dunkel I, Gerald W et al (2007) Phase I study of targeted Radioimmunotherapy for leptomeningeal cancers using intra-ommaya 131-I-3F8. J Clin Oncol 25:5465–5470. https://doi.org/10.1200/JCO.2007.11.1807
228. Epstein A, Chen F, Taylor C (1988) A novel method for the detection of necrotic lesions in human cancers. Can Res 48:5842–5848
229. Epstein A, Chen D, Ansari A, Najafi A, Siegel M, Lee K et al (1991) Radioimmunodetection of necrotic lesions in human tumours using I-131-labeled TNT-1 F(ab)2 monoclonal-antibody. Antibody Immunoconjug Radiopharmaceut 4:151–161
230. Chen F, Taylor C, Epstein A (1989) Tumour necrosis treatment of me-180 human cervical-carcinoma model with i-131-labeled TNT-1 monoclonal-antibody. Can Res 49:4578–4585
231. Peregrine Pharmaceuticals Inc. Cotara® oncology. www.peregrineinc.com/pipeline/cotara-oncology.html. Accessed 7 Jan 2021
232. Hdeib A, Sloan A (2012) Targeted radioimmunotherapy: the role of I-131-chTNT-1/B mAb (Cotara (R)) for treatment of high-grade gliomas. Future Oncol 8:659–669. https://doi.org/10.2217/FON.12.58
233. Patel S, Shapiro W, Laske D, Jensen R, Asher A, Wessels B et al (2005) Safety and feasibility of convection-enhanced delivery of cotara for the treatment of malignant glioma: Initial experience in 51 patients. Neurosurgery 56:1243–1252. https://doi.org/10.1227/01.NEU.0000159649.71890.30
234. Shapiro W, Carpenter S, Roberts K, Shan J (2006) I-131-chTNT-1/B mAb: tumour necrosis therapy for malignant astrocytic glioma. Expert Opin Biol Ther 6:539–545. https://doi.org/10.1517/14712598.6.5.539
235. Street H, Goris M, Fisher G, Wessels B, Cho C, Hernandez C et al (2006) Phase I study of I-131-chimeric(ch) TNT-1/B monoclonal antibody for the treatment of advanced colon cancer. Cancer Biother Radiopharm 21:243–256. https://doi.org/10.1089/cbr.2006.21.243
236. Chen S, Yu L, Jiang C, Zhao Y, Sun D, Li S et al (2005) Pivotal study of iodine-131-labeled chimeric tumour necrosis treatment radioimmunotherapy in patients with advanced lung cancer. J Clin Oncol 23:1538–1547. https://doi.org/10.1200/JCO.2005.06.108
237. Yu L, Ju D, Chen W, Li T, Xu Z, Jiang C et al (2006) I-131-chTNT radioimmunotherapy of 43 patients with advanced lung cancer. Cancer Biother Radiopharm 21:5–14. https://doi.org/10.1089/cbr.2006.21.5
238. Anderson P, Wiseman G, Lewis B, Charboneau J, Dunn W, Carpenter S et al (2003) A phase I safety and imaging study using radiofrequency ablation (RFA) followed by 131IchTNT-1/B radioimmunotherapy adjuvant treatment of hepatic metastases. Cancer Ther 1:297–306
239. Shapiro W, Gupta D, Mahapatra A, Gopal S, Judy K, Patel S et al (2011) Open-label, dose confirmation study of interstitial I-131-chTNT-1/b mab for the treatment of glioblastoma multiforme (GBM) at first relapse: interim results. J Clin Oncol. https://doi.org/10.1200/jco.2011.29.15_suppl.2035

240. Peregrine P (2011) Dose confirmation study of cotara for the treatment of glioblastoma multiforme at first relapse. ClinicalTrials.gov NCT00677716. Accessed 7 Jan 2021
241. Cheson B (2003) Radioimmunotherapy of non-Hodgkin lymphomas. Blood 101:391–398. https://doi.org/10.1182/blood-2002-06-1793
242. Green D, Press O (2017) Whither radioimmunotherapy: to be or not to be? Can Res 77:2191–2196. https://doi.org/10.1158/0008-5472.CAN-16-2523
243. Stashenko P, Nadler L, Hardy R, Schlossman S (1980) Characterization of a human lymphocyte-B-specific antigen. J Immunol 125:1678–1685
244. Einfeld D, Brown J, Valentine M, Clark E, Ledbetter J (1988) Molecular-cloning of the human B-cell CD20 receptor predicts a hydrophobic protein with multiple transmembrane domains. EMBO J 7:711–717. https://doi.org/10.1002/j.1460-2075.1988.tb02867.x
245. Press O, Farr A, Borroz K, Anderson S, Martin P (1989) Endocytosis and degradation of monoclonal-antibodies targeting human B-cell malignancies. Can Res 49:4906–4912
246. Press O, Howellclark J, Anderson S, Bernstein I (1994) Retention of B-CELL-specific monoclonal-antibodies by human lymphoma-cells. Blood 83:1390–1397
247. Rao AV, Akabani G, Rizzieri DA (2005) Radioimmunotherapy for non-Hodgkin's lymphoma. Clin Med Res 3:157–165
248. Tomblyn M (2012) Radioimmunotherapy for B-cell non-Hodgkin lymphomas. Cancer Control 19:196–203. https://doi.org/10.1177/107327481201900304
249. Bodet-Milin C, Ferrer L, Pallardy A, Eugène T, Rauscher A, Faivre-Chauvet A et al (2013) RIT of B-cell non-Hodgkin's lymphoma. Front Oncol. https://doi.org/10.3389/fonc.2013.00177
250. Buchsbaum D, Wahl R, Normolle D, Kaminski M (1992) Therapy with unlabeled and I-131-labeled Pan-B-cell monoclonal-antibodies in nude-mice bearing Raji Burkitt's-lymphoma xenografts. Can Res 52:6476–6481
251. Kaminski M, Zasadny K, Francis I, Fenner M, Ross C, Milik A et al (1996) Iodine-131—Anti-B1 radioimmunotherapy for B-cell lymphoma. J Clin Oncol 14:1974–1981. https://doi.org/10.1200/JCO.1996.14.7.1974
252. Wahl R, Zasadny K, MacFarlane D, Francis I, Ross C, Estes J et al (1998) Iodine-131 anti-B1 antibody for B-cell lymphoma: an update on the Michigan phase I experience. J Nucl Med 39:21S-S27
253. Kaminski M, Zasadny K, Francis I, Milik A, Ross C, Moon S et al (1993) Radioimmunotherapy of B-CELL lymphoma with [I-131] anti-B1 (ANTI-CD20) antibody. N Engl J Med 329:459–465. https://doi.org/10.1056/NEJM199308123290703
254. Kaminski M, Estes J, Zasadny K, Francis I, Ross C, Tuck M et al (2000) Radioimmunotherapy with iodine I-131 tositumomab for relapsed or refractory B-cell non-Hodgkin lymphoma: updated results and long-term follow-up of the University of Michigan experience. Blood 96:1259–1266. https://doi.org/10.1182/blood.V96.4.1259.h8001259_1259_1266
255. Vose J, Wahl R, Saleh M, Rohatiner A, Knox S, Radford J et al (2000) Multicenter phase II study of iodine-131 tositumomab for chemotherapy-relapsed/refractory low-grade and transformed low-grade B-cell non-Hodgkin's lymphomas. J Clin Oncol 18:1316–1323. https://doi.org/10.1200/JCO.2000.18.6.1316
256. Kaminski M, Zelenetz A, Press O, Saleh M, Leonard J, Fehrenbacher L et al (2001) Pivotal study of iodine I 131 Tositumomab for chemotherapy-refractory low-grade or transformed low-grade B-cell non-Hodgkin's lymphomas. J Clin Oncol 19:3918–3928. https://doi.org/10.1200/JCO.2001.19.19.3918
257. Horning S, Younes A, Jain V, Kroll S, Lucas J, Podoloff D et al (2005) Efficacy and safety of tositumomab and iodine-131 tositumomab (Bexxar) in B-Cell lymphoma, progressive after rituximab. J Clin Oncol 23:712–719. https://doi.org/10.1200/JCO.2005.07.040
258. Kaminski M, Tuck M, Estes J, Kolstad A, Ross C, Zasadny K et al (2005) I-131-tositumomab therapy as initial treatment for follicular lymphoma. N Engl J Med 352:441–449. https://doi.org/10.1056/NEJMoa041511
259. Kaminski M, Tuck M, Estes J, Kolstad A, Ross C, Regan D et al (2009) Tositumomab and iodine I-131 tositumomab for previously untreated, advanced-stage, follicular lymphoma: median 10 year follow-up results. Blood 114:1447. https://doi.org/10.1182/blood.V114.22.3759.3759
260. Leonard J, Coleman M, Kostakoglu L, Chadburn A, Cesarman E, Furman R et al (2005) Abbreviated chemotherapy with fludarabine followed by tositumomab and iodine I 131 tositumomab for untreated follicular lymphoma. J Clin Oncol 23:5696–5704. https://doi.org/10.1200/JCO.2005.14.803
261. Link B, Martin P, Kaminski M, Goldsmith S, Coleman M, Leonard J (2010) Cyclophosphamide, vincristine, and prednisone followed by tositumomab and iodine-131-tositumomab in patients with untreated low-grade follicular lymphoma: eight-year follow-up of a multicenter phase II study. J Clin Oncol 28:3035–3041. https://doi.org/10.1200/JCO.2009.27.8325
262. Press O, Unger J, Rimsza L, Friedberg J, LeBlanc M, Czuczman M et al (2013) Phase III randomized intergroup trial of CHOP Plus rituximab compared with CHOP chemotherapy plus (131) iodine-tositumomab for previously untreated follicular non-Hodgkin lymphoma: SWOG S0016. J Clin Oncol 31:314–320. https://doi.org/10.1200/JCO.2012.42.4101
263. Sacchi S, Marcheselli L, Bari A, Marcheselli R, Pozzi S, Luminari S et al (2008) Secondary malignancies after treatment for indolent non-Hodgkin's lymphoma: a 16-year follow-up study. Haematologica 93:398–404. https://doi.org/10.3324/haematol.12120
264. Press O, Unger J, Rimsza L, Friedberg J, LeBlanc M, Czuczman M et al (2011) A phase III randomized intergroup trial (SWOG S0016) of CHOP chemotherapy plus rituximab Vs CHOP chemotherapy plus iodine-131-tositumomab for the treatment of newly diagnosed follicular non-Hodgkin's lymphoma. Blood 118:48. https://doi.org/10.1182/blood.V118.21.98.98
265. Press O, Unger J, Braziel R, Maloney D, Miller T, LeBlanc M et al (2003) A phase 2 trial of CHOP chemotherapy followed by tositumomab/iodine I 131 tositumomab for previously untreated follicular non-Hodgkin lymphoma: Southwest Oncology Group Protocol S9911. Blood 102:1606–1612. https://doi.org/10.1182/blood-2003-01-0287
266. Press O, Unger J, Braziel R, Maloney D, Miller T, LeBlanc M et al (2006) Phase II trial of CHOP chemotherapy followed by tositumomab/iodine I-131 tositumomab for previously untreated follicular non-Hodgkin's lymphoma: five-year follow-up of southwest oncology group protocol S9911. J Clin Oncol 24:4143–4149. https://doi.org/10.1200/JCO.2006.05.8198
267. Leahy M, Turner J (2011) Radioimmunotherapy of relapsed indolent non-Hodgkin lymphoma with I-131-rituximab in routine clinical practice: 10-year single-institution experience of 142 consecutive patients. Blood 117:45–52. https://doi.org/10.1182/blood-2010-02-269753
268. McQuillan A, Macdonald W, Leahy M, Turner J (2011) First-line radio-immunotherapy of newly diagnosed, advanced follicular non-Hodgkin lymphoma with I-131-rituximab: the INITIAL study. Blood 118:1589
269. McQuillan AD, Macdonald WBG, Turner H (2014) Phase II study first-line Iodine-131-rituximab radioimmunotherapy follicular non-Hodgkin lymphoma and prognostic Fluorine-18 FDG-PET. Leukemia Lymphoma. https://doi.org/10.3109/10428194.2014.949260

270. Silberstein E (2012) Radioiodine: the classic theranostic agent. Semin Nucl Med 42:164–170. https://doi.org/10.1053/j.semnuclmed.2011.12.002
271. D'Huyvetter M, De Vos J, Caveliers V, Vaneycken I, Heemskerk J, Duhoux F et al (2020) Phase I trial of 131I-GMIB-Anti-HER2-VHH1, a new promising candidate for HER2-targeted radionuclide therapy in breast cancer patients. J Nucl Med. https://doi.org/10.2967/jnumed.120.255679
272. Precirix. A study to evaluate safety, tolerability, dosimetry, and preliminary efficacy of the HER2 directed radioligand CAM-H2 in patients with advanced/metastatic HER2-positive breast, gastric, and gastro-esophageal junction (GEJ) Cancer ClinicalTrials.gov Identifier: NCT04467515; 2020