



Next-Generation Anticancer Modalities: A Systematic Review of Antibody–Drug Conjugates, Bispecific Antibodies, CAR-T Cell Therapy, Cancer Vaccines, and Radioligand Therapy

Elmursieva Vakhidat Z.¹, Umaeva Amina M.¹, Maleeva Anna V.¹, Fokina Daria A.¹, Khordaeva Marina B.², Dadaeva Marina M.³, Machieva Laura A.⁴, Kottoev Albert A.⁴, Magomadova Khava R.⁴, Bisultanova Khadishat M.⁴, Malsagova Aminat R.⁴, Misaeva Muslimat S.⁴, Sulumova Khava Kh.⁴, Evloev Ibragim R.⁵, Bursagova Elina I.⁵, Shandulaev Shamil M.⁵, Belyavskiy Ivan A.⁶, Klimatova Hyadi S.⁷

¹ The Pavlov First Saint Petersburg State Medical University, Saint Petersburg, Russia

² Rostov State Medical University, Rostov-on-Don, Russia

³ North Ossetian State Medical Academy, Vladikavkaz, Russia

⁴ Kadyrov Chechen State University, Grozny, Russia

⁵ The Russian University of Medicine, Moscow, Russia

⁶ North-Western State Medical University I.I. Mechnikov, Saint Petersburg, Russia

⁷ Ingush State University, Magas, Russia

OPEN ACCESS

Article Citation:

Elmursieva Vakhidat Z.¹, Umaeva Amina M.¹, Maleeva Anna V.¹, Fokina Daria A.¹, Khordaeva Marina B.², Dadaeva Marina M.³, Machieva Laura A.⁴, Kottoev Albert A.⁴, Magomadova Khava R.⁴, Bisultanova Khadishat M.⁴, Malsagova Aminat R.⁴, Misaeva Muslimat S.⁴, Sulumova Khava Kh.⁴, Evloev Ibragim R.⁵, Bursagova Elina I.⁵, Shandulaev Shamil M.⁵, Belyavskiy Ivan A.⁶, Klimatova Hyadi S.⁷, "Next-Generation Anticancer Modalities: A Systematic Review of Antibody–Drug Conjugates, Bispecific Antibodies, CAR-T Cell Therapy, Cancer Vaccines, and Radioligand Therapy", International Journal of Recent Trends in Multidisciplinary Research, July-August 2026, Vol 6(04), 115-125.



©2026 The Author(s). This is an open access article distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited. Published by 5th Dimension Research Publication

Abstract: Cancer therapy is undergoing a paradigm shift driven by five distinct next-generation modalities. Despite advances in immune checkpoint inhibition and targeted therapy, a substantial proportion of patients with advanced malignancies fail to achieve durable responses [43,44]. This systematic review provides an integrated comparative analysis of antibody–drug conjugates (ADCs), bispecific antibodies (BsAbs), CAR-T cell therapy, mRNA cancer vaccines, and radioligand therapy (RLT), with attention to their histotype-specific versus pan-tumour applicability. A PRISMA 2020-compliant systematic search of PubMed/MEDLINE, Scopus, CENTRAL, and ClinicalTrials.gov was conducted covering January 2018 through May 2025 [45]. Phase 2–3 randomised controlled trials, pivotal single-arm trials, and regulatory submissions were eligible. Risk of bias was assessed using RoB 2.0 and ROBINS-I. 128 eligible studies were identified. ADCs – led by trastuzumab deruxtecan (T-DXd) – established the first tumour-agnostic ADC approval in 2024, with mPFS of 28.8 vs 6.8 months over T-DM1 in HER2+ breast cancer (HR 0.33) [2]. BsAbs yielded ORRs of 40–80% across haematological and solid tumour indications [13–20]. The first randomised CAR-T trial in a solid tumour (satri-cel vs TPC in gastric cancer) demonstrated significant PFS improvement in 2025 [26]. mRNA-4157 plus pembrolizumab reduced melanoma recurrence risk by 44% (HR 0.56) [31]. [¹⁷⁷Lu]Lu-PSMA-617 extended OS by 4 months over standard care in mCRPC (HR 0.62) [39]. All five modalities have achieved regulatory approvals and clinically meaningful efficacy. Combinatorial strategies, predictive biomarker development, and equitable access are the foremost challenges for the field.

Key Words: antibody–drug conjugates; bispecific antibodies; CAR-T; cancer vaccines; radioligand therapy; immunotherapy; precision oncology; systematic review

1. Introduction

Cancer remains the second leading cause of death worldwide, accounting for approximately 10 million deaths in 2022 [43]. Despite the transformative impact of immune checkpoint inhibitors (ICIs) and targeted small-molecule therapies, a substantial proportion of patients with advanced solid tumours and relapsed haematological malignancies fail to achieve durable responses [44,46]. Treatment resistance, tumour heterogeneity, and immune evasion continue to limit long-term outcomes.

Over the past five years, five distinct therapeutic platforms have reached clinical maturity: (1) ADCs, which conjugate a tumour-targeting antibody to a cytotoxic payload via a cleavable linker [47]; (2) bispecific antibodies (BsAbs), designed to simultaneously engage a tumour antigen and a cytotoxic immune effector [48]; (3) chimeric antigen receptor T-cell (CAR-T) therapy, in which T cells are engineered with a synthetic tumour-antigen receptor [49]; (4) personalised and fixed-antigen cancer vaccines leveraging mRNA lipid nanoparticle (LNP) delivery platforms [50]; and (5) radioligand therapy (RLT), coupling a tumour-specific ligand to a therapeutic radionuclide [51].

Each modality exploits a mechanistically distinct approach, creating opportunities for complementary or sequential use. Multiple agents within each class have received FDA and EMA approval between 2018 and 2025 [1–42], yet a comprehensive comparative synthesis across all five modalities – encompassing efficacy, safety, pan-tumour versus histotype-specific applicability, and combinatorial potential – has not been previously published.

This systematic review synthesises Phase 2–3 clinical evidence for all five modalities published or presented through May 2025. We address ORR, PFS, OS, safety, biomarker strategies, and emerging combination approaches with the objective of providing an integrated evidence-based overview for clinicians, researchers, and policymakers.

2. Methods

Protocol and Registration

This systematic review was conducted in accordance with the PRISMA 2020 guidelines [45]. The protocol was registered in PROSPERO (registration number: [PROSPERO ID]).

Search Strategy

A comprehensive electronic search was performed in PubMed/MEDLINE, Scopus, and CENTRAL, supplemented by ClinicalTrials.gov (results through 31 May 2025) and conference abstracts from ASCO, ESMO, ASH, and AACR (2022–2025). Core MeSH terms included: "Immunoconjugates" AND "Neoplasms"; "Antibodies, Bispecific"; "Receptors, Chimeric Antigen"; "Cancer Vaccines"; and "Radioligand Therapy" combined with "Lu-177", "PSMA", or "DOTA". Boolean operators and proximity filters were applied as appropriate. The search was restricted to English-language publications, January 2018 – May 2025.

Eligibility Criteria

Studies were included based on the PICO framework:

1. Population (P): adult patients (≥ 18 years) with confirmed malignant neoplasms;
2. Intervention (I): any approved or investigational ADC, BsAb, CAR-T construct, mRNA/neoantigen cancer vaccine, or RLT agent;
3. Comparator (C): standard-of-care chemotherapy, targeted therapy, ICI, or best supportive care; single-arm trials included when no randomised data were available;
4. Outcomes (O): ORR, PFS, OS, DOR, and safety (AEs grade ≥ 3 per CTCAE v5.0).

Exclusion criteria: preclinical studies, reviews, case reports, <20 evaluable patients, and studies reporting exclusively on pharmacokinetic or manufacturing endpoints.

Study Selection and Data Extraction

Two independent reviewers screened titles and abstracts, followed by full-text review. Discrepancies were resolved by consensus or a third reviewer. Pre-specified data extraction included: study design, phase, sample size, patient population, intervention, comparator, follow-up, primary and secondary endpoints, and safety data.

Risk of Bias Assessment

Risk of bias for RCTs was assessed using the Cochrane RoB 2.0 tool [52]. Non-randomised studies were assessed using ROBINS-I [53]. Evidence certainty was rated using GRADE [54].

3. Results

Study Selection

The initial search yielded 4,812 records. After duplicate removal ($n = 1,247$) and title/abstract screening ($n = 3,565$), 412 full-text articles were assessed for eligibility. Of these, 284 were excluded (wrong intervention $n = 96$; non-human data $n = 74$; insufficient sample size $n = 61$; reviews $n = 53$). A total of 128 studies were included: ADCs ($n = 41$), BsAbs ($n = 29$), CAR-T ($n = 24$), cancer vaccines ($n = 18$), and RLT ($n = 16$).

Antibody–Drug Conjugates

ADCs represent the most clinically advanced of the five modalities reviewed, with eight agents holding FDA approval for solid tumours as of May 2025 [47]. The ADC design couples a tumour-targeting antibody to a cytotoxic payload via a cleavable

Next-Generation Anticancer Modalities: A Systematic Review of Antibody–Drug Conjugates, Bispecific Antibodies, CAR-T Cell Therapy, Cancer Vaccines, and Radioligand Therapy

linker, enabling selective drug delivery to antigen-expressing cells while generating a 'bystander effect' through payload diffusion to neighbouring antigen-negative cells [55].

HER2-targeted ADCs

Trastuzumab emtansine (T-DM1; Kadcyla®) was the first ADC approved for solid tumours and demonstrated a median OS of 22.7 versus 15.8 months (HR 0.68, 95% CI 0.54–0.85) over treatment of physician's choice in heavily pre-treated HER2-positive metastatic breast cancer in the Phase 3 TH3RESA trial (n = 606) [1]. T-DM1 remains the standard adjuvant treatment for residual disease after neoadjuvant trastuzumab-based therapy.

Trastuzumab deruxtecan (T-DXd; Enhertu®) – incorporating a cleavable tetrapeptide linker, topoisomerase I inhibitor payload, and DAR of 8 – established superiority over T-DM1 in the pivotal Phase 3 DESTINY-Breast03 trial (n = 524): median PFS 28.8 versus 6.8 months (HR 0.33, 95% CI 0.26–0.43) and ORR 79% versus 35% [2]. Activity in HER2-low (IHC 1+ or 2+/ISH–) breast cancer was demonstrated in DESTINY-Breast04 [3], prompting redefinition of HER2-targeting beyond the traditional positive/negative binary. In April 2024, the FDA granted accelerated approval of T-DXd for adult patients with unresectable or metastatic HER2-positive (IHC 3+) solid tumours regardless of histotype after prior systemic therapy, based on pooled data from 192 patients across DESTINY-PanTumor02, DESTINY-Lung01, and DESTINY-CRC02 [4,5] – making T-DXd the first tumour-agnostic ADC approval. As of June 2025, two DXd-platform ADCs hold regulatory approval: T-DXd (Enhertu®) and datopotamab deruxtecan (Dato-DXd; Datroway®), the latter approved for HR+/HER2– metastatic breast cancer [6,56].

HER3-targeted ADCs and EGFR-resistance contexts

Patritumab deruxtecan (HER3-DXd), utilising the same DXd payload system, demonstrated an ORR of 29.8% and mPFS of 5.5 months in the Phase 2 HERTHENA-Lung02 trial in patients with EGFR-mutated NSCLC who had progressed on osimertinib [10]. Given near-ubiquitous HER3 expression in NSCLC and the absence of validated targeted options after third-generation EGFR TKI failure, HER3-DXd received FDA Breakthrough Therapy Designation and is under evaluation in a Phase 3 confirmatory trial.

Trop-2– and Nectin-4–targeted ADCs

Sacituzumab govitecan (SG; Trodelvy®) – a Trop-2-targeting ADC with SN-38 payload and DAR 7.5 – demonstrated a median OS of 12.1 versus 6.7 months (HR 0.48, 95% CI 0.35–0.66) in the Phase 3 ASCENT trial in triple-negative breast cancer (n = 468) [7]. Subsequent approval in HR+/HER2– metastatic breast cancer was supported by TROPiCS-02 [8]. Enfortumab vedotin (EV; Padcev®), targeting Nectin-4 with monomethyl auristatin E, combined with pembrolizumab achieved an ORR of 68% and mPFS of 12.5 months in the Phase 3 EV-302 trial in previously untreated locally advanced or metastatic urothelial carcinoma [9], establishing this combination as a new first-line standard of care. Table 1 summarises the key ADCs, targets, pivotal trials, and regulatory status

Agent	Target	Indication	Key trial / ref.	ORR / mPFS	Status
T-DM1 (Kadcyla®)	HER2	HER2+ mBC (2L+)	TH3RESA [1]	ORR 31%; mOS 22.7 vs 15.8 mo	FDA 2013
T-DXd (Enhertu®)	HER2	HER2+ mBC, HER2-low mBC, NSCLC, gastric, pan-tumour HER2+ IHC3+	DESTINY-Breast03 [2]; DESTINY-Breast04 [3]; DESTINY-PanTumor02 [4]; FDA 2024 [5]	mPFS 28.8 vs 6.8 mo (HR 0.33); ORR 79% (HER2+); ORR 52% (HER2-low)	FDA/EMA approved (2019–2024, multiple)
Dato-DXd (Datroway®)	Trop-2	HR+/HER2– mBC (2L+)	TROPION-Breast01 [6]	mPFS 6.9 vs 4.9 mo (HR 0.63); ORR 36%	FDA/EMA 2024–2025
Sacituzumab govitecan (Trodelvy®)	Trop-2	TNBC (2L+); HR+/HER2– mBC; urothelial	ASCENT [7]; TROPiCS-02 [8]	TNBC: mOS 12.1 vs 6.7 mo (HR 0.48); ORR 35%	FDA 2020/2023
Enfortumab vedotin + pembrolizumab (Padcev®)	Nectin-4	Locally adv./met. urothelial (1L)	EV-302 [9]	mPFS 12.5 mo; ORR 68%	FDA 2023
Patritumab deruxtecan (HER3-DXd)	HER3	EGFR-mut. NSCLC (post-osimertinib)	HERTHENA-Lung02 [10]	ORR 29.8%; mPFS 5.5 mo	FDA Breakthrough Designation

Table 1. Key antibody–drug conjugates: targets, pivotal trial data, and regulatory status (2013–2025). ADC, antibody–drug conjugate; mBC, metastatic breast cancer; NSCLC, non-small cell lung cancer; TNBC, triple-negative breast cancer; UC, urothelial carcinoma; ORR, overall response rate; mPFS, median PFS; mOS, median OS; FDA, Food and Drug Administration; EMA, European Medicines Agency; IHC, immunohistochemistry; HR, hormone receptor; L, treatment line.

Bispecific Antibodies

Bispecific antibodies are engineered to simultaneously bind two distinct antigens, most commonly linking a tumour-associated antigen to CD3 ϵ on T cells, thereby recruiting polyclonal cytotoxic T lymphocytes to mediate tumour lysis independent of MHC-I antigen presentation – a mechanism that circumvents a key immune evasion strategy of cancer [48,57]. As of mid-2025, more than nine BsAbs have received FDA approval in oncology [57].

Haematological malignancies

In B-cell lymphomas, CD20 $\times$ CD3 bispecific antibodies have transformed the treatment landscape. Mosunetuzumab (Lunsumio®, Roche) – the first BsAb approved for follicular lymphoma – achieved an ORR of 80% and CR rate of 60% in the GO29781 Phase 2 trial in R/R FL after ≥ 2 prior therapies (n = 90) [15]. At 3-year follow-up, the median duration of response had not been reached in patients achieving CR, indicating potentially curative remissions in a historically incurable disease [15,58]. Epcoritamab (Epkinly®) and glofitamab (Columvi®) have each been approved in more than 30 countries for R/R DLBCL after ≥ 2 prior therapies, with ORRs of 63% and 52%, and CR rates of 39% for both agents, respectively [16,17]. Glofitamab employs a unique 2:1 bivalent CD20-binding format and, critically, is delivered as a finite 12-cycle treatment, with durable CRs observed post-treatment [17]. Real-world registry studies from multiple institutions confirm that efficacy of both agents in routine practice is consistent with pivotal trial data [59].

In multiple myeloma, BCMA $\times$ CD3 BsAbs have collectively achieved ORRs of 60–73% in heavily pre-treated populations. Teclistamab (Tecvayli®) demonstrated an ORR of 63% with a median DOR of 18.4 months in the MajesTEC-1 Phase 1/2 trial [14]. Talquetamab (Talvey®), targeting the novel antigen GPRC5D expressed on myeloma cells and plasma cells, achieved an ORR of approximately 73% in MonumenTAL-1 [18], providing an alternative pathway in patients with prior BCMA-targeted exposure. Linvoseltamab (Lynozyfic®, Regeneron), a BCMA $\times$ CD3 BsAb approved by the FDA in 2025, further expands this class [57].

Solid tumours: tarlatamab and beyond

Tarlatamab (Imdelltra®, Amgen), approved by the FDA in 2024 for ES-SCLC after platinum-based chemotherapy, represents a landmark extension of BsAbs to solid tumours [13]. Targeting DLL3 – a Notch ligand aberrantly expressed on SCLC tumour cells but absent from most normal tissues – tarlatamab achieved an ORR of 40% and a median OS of 14.3 months in the DeLLphi-301 Phase 2 trial, compared to historical median OS of 5–7 months with second-line topotecan [13,60]. CRS occurred in approximately 50% of patients (predominantly grade 1–2), necessitating step-up dosing protocols and premedication.

Zanidatamab (Ziihera®), a biparatopic antibody binding two non-overlapping HER2 epitopes, received FDA approval in 2024 for HER2-amplified biliary tract cancer with an ORR of 52% and median DOR of 14.9 months in HERIZON-BTC-01 [19]. Zenocutuzumab (Bizengri®, Merus), targeting the HER2/HER3 heterodimer to block NRG1-mediated signalling, received tumour-agnostic FDA approval in 2024 based on an ORR of 34% in NRG1 fusion-positive solid tumours across multiple histotypes in the eNRGy basket trial [20]. Immunogenicity of approved BsAbs is low: anti-drug antibodies occur in <3% of patients treated with blinatumomab, mosunetuzumab, epcoritamab, glofitamab, and amivantamab [57]. Table 2 provides a comparative overview of key BsAbs, mechanisms, efficacy, and safety.

Agent	Targets	Indication	Key trial / ref.	Key efficacy	Year approved
Blinatumomab (Blincyto®)	CD19 $\times$ CD3	R/R B-ALL; MRD+ ALL	TOWER [11]; MT103-203 [12]	mOS 7.7 vs 4.0 mo (HR 0.71)	FDA 2014/2018
Tarlatamab (Imdelltra®)	DLL3 $\times$ CD3	ES-SCLC (2L+)	DeLLphi-301 Ph2 [13]	ORR 40%; mOS 14.3 mo	FDA 2024
Teclistamab (Tecvayli®)	BCMA $\times$ CD3	R/R multiple myeloma	MajesTEC-1 [14]	ORR 63%; mDOR 18.4 mo	FDA/EMA 2022
Mosunetuzumab (Lunsumio®)	CD20 $\times$ CD3	R/R follicular lymphoma ≥ 2 L	GO29781 Ph2 [15]	ORR 80%; CR 60%; 3-yr mDOR not reached in CR pts	FDA 2022
Epcoritamab (Epkinly®)	CD20 $\times$ CD3	R/R DLBCL ≥ 2 L	EPCORE NHL-1 [16]	ORR 63%; CR 39%	FDA 2023 (>30 countries)
Glofitamab (Columvi®)	CD20 $\times$ CD3 (2:1)	R/R DLBCL (finite 12 cycles)	NP30179 Ph1/2 [17]	ORR 52%; CR 39%	FDA 2023 (>30 countries)

Next-Generation Anticancer Modalities: A Systematic Review of Antibody–Drug Conjugates, Bispecific Antibodies, CAR-T Cell Therapy, Cancer Vaccines, and Radioligand Therapy

Talquetamab (Talvey®)	GPRC5D×CD3	R/R multiple myeloma	MonumenTAL-1 [18]	ORR ~73%; mDOR 9.5 mo	FDA/EMA 2023
Zanidatamab (Ziihera®)	HER2 biparatopic	HER2-amp. biliary tract cancer	HERIZON-BTC-01 [19]	ORR 52%; mDOR 14.9 mo	FDA 2024
Zenocutuzumab (Bizengri®)	HER2×HER3	NRG1 fusion+ solid tumors	eNRGy [20]	ORR 34%; mDOR 11.1 mo	FDA 2024

Table 2. Key bispecific antibodies in oncology: targets, efficacy, and regulatory status (2014–2025). BsAb, bispecific antibody; R/R, relapsed/refractory; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MM, multiple myeloma; ES-SCLC, extensive-stage small-cell lung cancer; CRS, cytokine release syndrome; ORR, overall response rate; DOR, duration of response; FDA, Food and Drug Administration.

CAR-T Cell Therapy

CAR-T cell therapy involves the ex vivo engineering of autologous or allogeneic T cells to express a synthetic receptor combining an extracellular scFv antigen-binding domain with intracellular signalling domains (CD3ζ, CD28, and/or 4-1BB) [49,61]. Following infusion and antigen engagement, CAR-T cells expand, secrete cytokines, and mediate direct tumour cytotoxicity. Six CAR-T products currently hold FDA approval for haematological malignancies [49].

Haematological malignancies

Tisagenlecleucel (Kymriah®, Novartis) was the first gene therapy approved by the FDA in 2017, achieving an ORR of 81% in paediatric R/R B-ALL in the ELIANA trial [21] and 52% in adult R/R DLBCL in JULIET [22]. Axicabtagene ciloleucel (Yescarta®, Gilead/Kite) demonstrated superiority over standard chemo-immunotherapy as second-line treatment for relapsed LBCL in ZUMA-7 (event-free survival 8.3 vs 2.0 months; HR 0.40, 95% CI 0.31–0.51) [24]. Ciltacabtagene autoleucel (Carvykti®, J&J/Legend Biotech) achieved landmark results in the Phase 3 CARTITUDE-4 trial: ORR 98%, median PFS 34.9 versus 11.8 months (HR 0.26, 95% CI 0.18–0.38) in lenalidomide-refractory multiple myeloma [25] – the strongest efficacy evidence for any CAR-T product in a randomised comparison.

CAR-T in solid tumours: a field in transition

Solid tumour CAR-T therapy faces three fundamental barriers: (1) tumour heterogeneity and antigen-negative escape; (2) the immunosuppressive tumour microenvironment (TME) characterised by T-cell exhaustion and checkpoint ligand upregulation; and (3) poor CAR-T cell trafficking and persistence within the tumour mass [49,62]. Engineering innovations including armoured CARs secreting IL-12, tandem or logic-gated constructs, and co-stimulatory domain optimisation are being actively investigated [62].

The most significant 2025 milestone was the first randomised controlled trial of CAR-T therapy in a solid tumour: satricabtagene autoleucel (satri-cel; CT041), a CLDN18.2-targeted autologous CAR-T, versus treatment of physician's choice (TPC) in 156 patients with previously treated advanced gastric or GEJ cancer in the CT041-ST-01 trial, published in The Lancet in 2025 [26,27]. Satri-cel treatment resulted in a statistically significant improvement in PFS with a manageable safety profile – grade ≥3 CRS was rare and no grade ≥3 ICANS was observed – representing proof-of-concept that CAR-T therapy can achieve randomised efficacy advantage in a solid tumour context.

GD2-targeting CAR-T cells have shown durable objective responses in H3K27M+ diffuse midline glioma following intraventricular and intravenous administration, with CAR-T cell persistence of up to 2 years in some patients (Nature, 2025) [28]. GCC19CART (bispecific GCC × CD19 CAR-T) achieved an ORR of 80% at dose level 2 in R/R metastatic colorectal cancer, albeit with significant gastrointestinal toxicity including one treatment-related death [30]. Extended CAR-T cell persistence correlating with better responses was observed in both GD2- and CLDN18.2-targeting trials, highlighting persistence as a key pharmacodynamic target [49,62]. Table 3 summarises key CAR-T products, targets, and clinical results.

Agent	Target	Disease	Key trial / ref.	Key result	Status
Tisagenlecleucel (Kymriah®)	CD19	R/R B-ALL (paed.); R/R DLBCL	ELIANA [21]; JULIET [22]	B-ALL: ORR 81%; DLBCL: ORR 52%	FDA 2017
Axicabtagene ciloleucel (Yescarta®)	CD19	R/R LBCL ≥2L; FL ≥3L	ZUMA-1 [23]; ZUMA-7 [24]	ZUMA-7: EFS 8.3 vs 2.0 mo (HR 0.40)	FDA 2017/2022
Ciltacabtagene autoleucel (Carvykti®)	BCMA	R/R MM ≥1 prior line (lenalidomide-ref.)	CARTITUDE-4 [25]	mPFS 34.9 vs 11.8 mo (HR 0.26); ORR 98%	FDA 2022/2024
Satricabtagene	CLDN18.2	Adv. gastric/GEJ	CT041-ST-01 Ph2	First RCT of CAR-T in solid	Phase 2

Next-Generation Anticancer Modalities: A Systematic Review of Antibody–Drug Conjugates, Bispecific Antibodies, CAR-T Cell Therapy, Cancer Vaccines, and Radioligand Therapy

autoleucel (satri-cel; CT041)		(≥2L)	RCT [26,27]	tumour; significant PFS improvement vs TPC (ASCO/Lancet 2025)	(landmark RCT)
GD2-CAR-T (GD2-CART01 / intraventricular)	GD2	H3K27M+ diffuse midline glioma; neuroblastoma	Nature 2025 [28]; NCT03373097 [29]	Glioma: durable objective responses; neuroblastoma: 57% RFS at high dose	Phase 1/2
GCC19CART	GCC×CD19	R/R metastatic CRC	NCT05319314 [30]	ORR 80% at DL2; severe diarrhea; 1 TRD	Phase 1, dose escalation

Table 3. CAR-T cell therapy: key agents, targets, clinical results, and development stage (2017–2025). CAR-T, chimeric antigen receptor T-cell; CLDN18.2, Claudin 18.2; R/R, relapsed/refractory; RCT, randomised controlled trial; mPFS, median PFS; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; TPC, treatment of physician's choice; GEJ, gastroesophageal junction; TRD, treatment-related death.

Cancer Vaccines

mRNA cancer vaccines exploit synthetic mRNA encoding personalised tumour neoantigens or shared tumour-associated antigens (TAAs), delivered via LNPs, resulting in in situ antigen expression, MHC-I/II presentation, and priming of tumour-specific CD8+ cytotoxic T lymphocytes and CD4+ helper T cells [50,63]. The COVID-19 pandemic substantially accelerated LNP manufacturing and regulatory infrastructure, reducing vaccine production timelines from approximately nine weeks to under four weeks for personalised constructs [64].

Personalised neoantigen vaccines

The most clinically advanced personalised neoantigen vaccine is mRNA-4157/V940 (Moderna/Merck), currently in Phase 3 development (NCT05933577). In the randomised Phase 2b KEYNOTE-942 trial in patients with resected high-risk (stage IIB–IV) melanoma, mRNA-4157 plus pembrolizumab reduced the risk of recurrence or death by 44% compared with pembrolizumab monotherapy (HR 0.56, 95% CI 0.32–0.99; $p = 0.0266$), with an 18-month RFS of 79% versus 62% [31]. At 3-year follow-up, benefit was maintained, and regulatory submissions are anticipated in 2026 [32].

The individualised neoantigen approach was validated in pancreatic ductal adenocarcinoma (PDAC) – historically resistant to immunotherapy due to a cold, desmoplastic TME. In a Phase 1 adjuvant trial at Memorial Sloan Kettering/BioNTech, autogene cevumeran (encoding up to 20 patient-specific neoantigens) was administered with atezolizumab and mFOLFIRINOX in resected PDAC patients [33]. Of 16 patients, 8 mounted detectable vaccine-induced T cell responses. After a median follow-up of 3.2 years, vaccine responders had a median RFS not yet reached, compared with 13.4 months in non-responders (HR 0.08), an effect maintained at nearly 4 years in some patients [34]. CD8+ neoantigen-specific T cell responses persisted for up to 4 years after vaccination, demonstrating durable immune memory [34].

Fixed-antigen mRNA vaccines

BNT111 (BioNTech), encoding four melanoma-associated antigens (NY-ESO-1, MAGE-A3, tyrosinase, TPTE), achieved an ORR of 22% as monotherapy in patients with anti-PD-1 relapsed/refractory unresectable melanoma in the LIPO-MERIT Phase 2b trial, including durable complete responses [35]. The KRAS-targeting mRNA vaccine mRNA-5671/V941 (Merck) demonstrated an acceptable safety profile in Phase 1 but limited single-agent activity, emphasising the importance of ICI combinations and challenges of KRAS immunogenicity [36,65]. As of 2025, more than 120 RNA cancer vaccine trials are registered across lung, breast, prostate, melanoma, PDAC, and brain tumours [64]. Personalised manufacturing costs exceeding \$100,000 per patient remain a fundamental barrier to equitable access [64]. Table 4 summarises key cancer vaccine platforms and clinical results.

Agent	Platform	Disease	Key trial / ref.	Key result	Status
mRNA-4157/V940 + pembrolizumab	Personalised mRNA LNP neoantigen	Resected high-risk melanoma	KEYNOTE-942 Ph2b [31,32]	44% reduction recurrence/death (HR 0.56, $p=0.0266$); 18-mo RFS 79% vs 62%; benefit sustained ≥30 mo	Phase 3 NCT05933577 (recruiting)
Autogene cevumeran + atezolizumab + mFOLFIRINOX	Personalised mRNA LNP (up to 20 neoantigens)	Resected PDAC	MSK/BioNTech Ph1 [33,34]	8/16 pts immune response; responders median RFS not reached vs 13.4 mo (HR 0.08); durable at 4 yr	Phase 2 expansion ongoing
BNT111 + cemiplimab	Fixed mRNA LNP (NY-ESO-1,	Anti-PD-1 relapsed	LIPO-MERIT Ph2b [35]	ORR 22% monotherapy; combination data pending	Phase 2b recruiting

Next-Generation Anticancer Modalities: A Systematic Review of Antibody–Drug Conjugates, Bispecific Antibodies, CAR-T Cell Therapy, Cancer Vaccines, and Radioligand Therapy

	MAGE-A3, tyrosinase, TPTE)	unresectable melanoma			
mRNA-5671/V941 ± pembrolizumab	mRNA (KRAS G12V/D/C/R)	CRC, PDAC, NSCLC (KRAS-mut.)	NCT03948763 Ph1 [36]	Safety established; limited single-agent activity; combination data exploratory	Phase 1 completed

Table 4. Cancer vaccines: platforms, indications, key trials, and development stage (2020–2025). LNP, lipid nanoparticle; PDAC, pancreatic ductal adenocarcinoma; RFS, recurrence-free survival; ORR, overall response rate; TAA, tumour-associated antigen; TME, tumour microenvironment.

Radioligand Therapy

RLT combines a tumour-targeting ligand with a therapeutic radionuclide – most commonly lutetium-177 (^{177}Lu , β -emitter) – delivering cytotoxic radiation selectively to antigen-expressing tumour cells while sparing adjacent normal tissue [51,66]. A defining advantage of RLT is its intrinsic theranostic capacity: the same targeting ligand labelled with a diagnostic radionuclide (e.g., ^{68}Ga for PET) enables patient selection based on quantitative target expression, treatment monitoring, and post-treatment dosimetry [42,66] – a capability unique among the five modalities reviewed.

Approved agents

^{177}Lu -DOTA-TATE (Lutathera®, Novartis) was approved by the EMA in 2017 and the FDA in 2018 for progressive, unresectable, well-differentiated, SSTR-positive GEP-NETs. The Phase 3 NETTER-1 trial ($n = 229$) demonstrated a dramatic improvement in PFS (HR 0.18, 95% CI 0.10–0.33; mPFS not reached vs 8.4 months for high-dose octreotide LAR), with ORR 18% and disease control rate >80% [37]. Interim results from the Phase 3 COMPETE trial, presented at ENETS 2025, demonstrated a median PFS of 29.3 months for ^{177}Lu -DOTA-TOC versus the comparator everolimus in G1–G2 GEP-NETs [38], further cementing RLT as the cornerstone of GEP-NET management.

^{177}Lu -PSMA-617 (Pluvicto®, Novartis) received FDA and EMA approval in 2022 for PSMA-positive mCRPC after prior ARPI and taxane-based chemotherapy. The pivotal Phase 3 VISION trial ($n = 831$) demonstrated a median OS of 15.3 versus 11.3 months (HR 0.62, 95% CI 0.52–0.74) and radiographic PFS of 8.7 versus 3.4 months (HR 0.40, 95% CI 0.29–0.57) [39]. The Phase 2 UpFrontPSMA trial (Lancet Oncology, 2024) demonstrated that sequential ^{177}Lu -PSMA-617 with docetaxel improved PSA50 response (73% vs 44%) over docetaxel alone in metastatic hormone-sensitive prostate cancer [41], supporting earlier-line potential.

Rechallenge and novel targets

A 2025 PRISMA-compliant systematic review and meta-analysis evaluating ^{177}Lu -PSMA rechallenge therapy in mCRPC patients who progressed after a first RLT course (literature through March 2025) found PSA50 response rates of 40–60% with manageable haematologic toxicity [40], suggesting clinically meaningful activity in a population with very limited options.

As of July 2025, more than 400 clinical trials explore novel RLT targets [42]. Fibroblast activation protein (FAP), overexpressed in cancer-associated fibroblasts across multiple solid tumour types, represents the most extensively investigated pan-tumour target, with early Phase 1/2 signals of activity and organ toxicity under evaluation [42]. Additional emerging targets include CAIX (clear-cell RCC), GRPR (breast and prostate cancers), and integrins ($\alpha\text{v}\beta 3$, $\alpha\text{v}\beta 6$) [42,66]. Alpha-emitting ^{225}Ac -PSMA is under clinical evaluation, offering higher linear energy transfer and potential for patients with low or heterogeneous PSMA expression [40]. Table 5 summarises key RLT agents, targets, pivotal trials, and development status.

Agent	Target	Disease	Key trial / ref.	Key result	Status
^{177}Lu -DOTA-TATE (Lutathera®)	SSTR2	Progressive SSTR+ GEP-NETs	NETTER-1 Ph3 [37]; COMPETE Ph3 (ENETS 2025) [38]	NETTER-1: mPFS NR vs 8.4 mo (HR 0.18); ORR 18%; COMPETE: mPFS 29.3 mo vs everolimus	FDA 2018, EMA 2017
^{177}Lu -PSMA-617 (Pluvicto®)	PSMA	mCRPC (post-ARPI + taxane)	VISION Ph3 [39]	mOS 15.3 vs 11.3 mo (HR 0.62); rPFS 8.7 vs 3.4 mo (HR 0.40)	FDA/EMA 2022
^{177}Lu -PSMA-617 rechallenge	PSMA	mCRPC progressed after 1st RLT	Systematic review & meta-analysis 2025 [40]	PSA50 response 40–60%; manageable haematologic toxicity	Retrospective; Ph2 trials ongoing
^{177}Lu -PSMA-617 + docetaxel (early-line)	PSMA	mHSPC	UpFrontPSMA Ph2 [41]	rPFS benefit vs docetaxel alone; PSA50 73% vs 44%	Phase 2, Lancet Oncol 2024

Next-Generation Anticancer Modalities: A Systematic Review of Antibody–Drug Conjugates, Bispecific Antibodies, CAR-T Cell Therapy, Cancer Vaccines, and Radioligand Therapy

FAP-targeted RLT (various)	FAP	Multiple solid tumours (pan-tumour stroma)	Global perspective review [42]; >400 trials registered (Jul 2025)	Early signals of activity; organ toxicity under evaluation	Phase 1/2
----------------------------	-----	--	---	--	-----------

Table 5. Radioligand therapy: agents, targets, pivotal trials, and regulatory status (2017–2025). RLT, radioligand therapy; PSMA, prostate-specific membrane antigen; SSTR, somatostatin receptor; GEP-NETs, gastroenteropancreatic neuroendocrine tumours; mCRPC, metastatic castration-resistant prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer; FAP, fibroblast activation protein; PFS, progression-free survival; OS, overall survival; FDA, Food and Drug Administration; EMA, European Medicines Agency.

2. Discussion

Comparative Efficacy Across Modalities

The five modalities differ substantially in their mechanisms, target accessibility, and depth and durability of response. ADCs and BsAbs have demonstrated the most consistent efficacy across haematological and solid tumour contexts, reflecting their antibody-based design, scalable manufacturing, and broad antigen targeting [47,48]. CAR-T therapy achieves the highest ORRs in haematological settings (>80–98% in certain populations) [21–25], but its translation to solid tumours has been historically limited – with the CT041-ST-01 RCT in gastric cancer representing a pivotal proof-of-concept in 2025 [26,27]. mRNA cancer vaccines remain at the earliest stage of regulatory maturity, with no approved product as of June 2025, though Phase 3 data for mRNA-4157 in melanoma are anticipated within 1–2 years [31,32]. RLT occupies a unique niche: its theranostic capacity enables prospective patient selection by quantitative imaging [39,66], and it achieves objective responses in diseases (GEP-NETs, mCRPC) where other systemic options have limited activity [37,39].

Pan-Tumour versus Histotype-Specific Approaches

A fundamental differentiator across modalities is feasibility of pan-tumour versus histotype-specific application. ADCs lead in tumour-agnostic potential: the 2024 FDA approval of T-DXd for any HER2+ (IHC3+) solid tumour [4,5], the tissue-agnostic NRG1-fusion approval of zenocutuzumab [20], and the pan-tumour potential of Trop-2-targeting agents [7,8] exemplify this approach – enabled by molecular biomarkers (HER2 IHC3+, NRG1 fusion) that are uniformly actionable

regardless of tissue of origin. BsAbs currently remain more histotype-restricted in solid tumours (tarlatamab targets DLL3 in SCLC [13]), though the bispecific T-cell-engaging principle is inherently pan-tumour if an appropriate tumour-restricted antigen can be identified. FAP-targeted CAR-T [62] and FAP-targeted RLT [42] both aim to exploit the near-universality of cancer-associated fibroblasts. Cancer vaccines are by definition personalised or shared-antigen-based [50,63], and are conceptually incompatible with traditional histotype-agnostic approval frameworks without neoantigen selection criteria.

Safety Profiles and Toxicity Management

Each modality carries a characteristic toxicity signature. ADCs produce haematological toxicity, interstitial lung disease (ILD – particularly with DXd-payload agents, occurring in 10–15% of patients on T-DXd across trials, with rare fatal events) [47,55], and payload-specific effects (peripheral neuropathy with auristatin-based agents, ocular toxicity with belantamab mafodotin). Prompt recognition of ILD and early corticosteroid therapy are essential [55].

BsAbs and CAR-T share the toxicity profile of T-cell engagement: CRS and ICANS [48,49]. In haematological settings, CRS is predominantly grade 1–2 and manageable with tocilizumab; grade ≥3 CRS occurs in 5–15% of cases [15,17,25]. Immunogenicity is low for most BsAbs (<3% ADA incidence) [57]. Infectious complications, particularly opportunistic infections driven by prolonged B-cell depletion, represent the most clinically significant late safety concern [48,57].

RLT has a favourable systemic toxicity profile: grade 3–4 thrombocytopenia in 3–9% and anaemia in 13% of patients in the VISION trial [39]. Radiation nephropathy, managed through renal dosimetry monitoring and co-administration of renal protective amino acids, is the other principal concern [66]. Cancer vaccines have the most benign safety profile of any modality – typically limited to injection-site reactions and transient flu-like symptoms; grade ≥3 immune-related AEs are rare [31,35].

Combinatorial Strategies and Emerging Approaches

Rational combination strategies exploiting mechanistic synergies are increasingly supported by clinical data. ADCs with immunogenic payloads – particularly topoisomerase I inhibitors – induce immunogenic cell death, potentially converting cold TMEs to hot ones and sensitising to subsequent ICI therapy [47,67]. The Phase 3 PSMAAddition trial demonstrated that [¹⁷⁷Lu]Lu-PSMA-617 plus enzalutamide significantly improved rPFS over enzalutamide alone in mCRPC (HR 0.60, 95% CI 0.49–0.74) [68]. RLT combined with PARP inhibitors is supported by a synthetic lethality rationale – radiation-induced DNA DSBs are exacerbated by PARP inhibition – with multiple Phase 1/2 trials ongoing [66,68]. BsAb plus ICI combinations are being explored in solid tumours based on complementary T-cell engagement mechanisms [57,67]. mRNA vaccines combined with CAR-T constructs to prime and amplify neoantigen-specific responses represent an emerging frontier [50,63], though clinical data remain preliminary.

Predictive Biomarkers

Biomarker-driven patient selection is critical across all five modalities. For ADCs, antigen expression level (HER2 IHC score, Trop-2 H-score) is the primary eligibility and response predictor [2,3,7]. The clinically meaningful benefit of T-DXd at

Next-Generation Anticancer Modalities: A Systematic Review of Antibody–Drug Conjugates, Bispecific Antibodies, CAR-T Cell Therapy, Cancer Vaccines, and Radioligand Therapy

HER2-low expression levels [3] demonstrates that the conventional binary HER2-positive/negative classification is insufficient, prompting redefinition of the HER2 spectrum. For BsAbs and CAR-T, tumour antigen density, TMB, and TME composition (T-effector/Treg ratio, immune infiltration) are critical predictors [48,57,62]. CD20 loss post-CD20 × CD3 BsAb therapy is a clinically important resistance mechanism, with high rates of CD20 negativity observed at relapse [69]. For mRNA vaccines, neoantigen clonality, HLA binding affinity, and tumour antigen presentation competence (B2M, HLA-A/B/C expression) determine immunogenicity [50,63,65]. For RLT, quantitative PSMA PET (SUVmean thresholds used in VISION eligibility criteria) and FAP PET imaging provide the theranostic basis for patient selection [39,42].

Access, Cost, and Regulatory Landscape

Equitable patient access to all five modalities is challenged by cost and geographic concentration. ADCs are priced at \$150,000–\$300,000 per year of therapy in high-income countries, with limited biosimilar competition expected before 2030 [44]. CAR-T products range from \$400,000 to \$500,000 per infusion, and personalised neoantigen vaccines cost in excess of \$100,000 per patient [64]. RLT using commercially produced [¹⁷⁷Lu]-labelled agents requires nuclear medicine infrastructure largely absent from low- and middle-income countries [42,66]. The FDA accelerated approval pathway, based on ORR as a surrogate endpoint, has enabled faster patient access but generated controversy where confirmatory trials have been delayed [5,44]. The FDA's tumour-agnostic approval framework – exemplified by T-DXd in 2024 – is expected to expand as basket trial methodology matures and companion diagnostics gain regulatory acceptance [4,5,20].

3. Limitations

This review has several limitations. First, substantial heterogeneity across studies in patient populations, prior treatment lines, endpoint definitions, and follow-up durations precludes formal meta-analysis across modalities. Second, late-breaking conference data (e.g., ASCO 2025) included herein have not always been fully peer-reviewed and should be interpreted with appropriate caution [26,38]. Third, cross-modality efficacy comparisons are confounded by differences in patient selection and lines of therapy. Fourth, long-term follow-up data are immature for most recently approved agents. Fifth, this review focused on Phase 2–3 data; comprehensive analysis of Phase 1 findings across hundreds of investigational agents was outside scope. Finally, cost-effectiveness analysis was beyond scope and requires dedicated systematic evaluation.

4. Conclusion

All five next-generation anticancer modalities – ADCs, BsAbs, CAR-T cell therapy, mRNA cancer vaccines, and RLT – have demonstrated clinically meaningful, in several cases practice-changing, efficacy and have earned regulatory approvals that are fundamentally expanding the therapeutic repertoire for patients with advanced cancer.

ADCs, particularly the deruxtecan platform, represent the broadest translational success, having achieved tumour-agnostic approval and superiority over prior standards in multiple Phase 3 trials [2–5]. BsAbs have transformed haematological oncology [14–18] and are achieving clinically significant activity in solid tumours [13,19,20]. CAR-T therapy achieved its first RCT evidence of superiority in a solid tumour in 2025 [26,27], signalling a potential paradigm shift. mRNA neoantigen vaccines have produced the first randomised evidence of recurrence prevention in resected melanoma [31,32] and durable immune responses in PDAC [33,34], with Phase 3 data anticipated within 1–2 years. RLT has established a distinctive theranostic niche with ongoing expansion into pan-tumour FAP-targeted applications [42].

Convergence of these modalities in rational combination strategies represents the most promising direction for further improving patient outcomes. Predictive biomarker development, manufacturing scale-up and cost reduction, and equitable global access remain the foremost challenges. Future systematic reviews should incorporate head-to-head trial data, long-term survival outcomes, and formal health economic analyses to guide rational treatment sequencing.

References

1. Krop IE, Kim SB, Martin AG, et al. Trastuzumab emtansine versus treatment of physician's choice in patients with previously treated HER2-positive metastatic breast cancer (TH3RESA): final overall survival results from a randomised open-label phase 3 trial. *Lancet Oncol.* 2017;18(6):743–754. doi:10.1016/S1470-2045(17)30313-3
2. Cortés J, Kim SB, Chung WP, et al. Trastuzumab Deruxtecan versus Trastuzumab Emtansine for Breast Cancer. *N Engl J Med.* 2022;386(12):1143–1154. doi:10.1056/NEJMoa2115022
3. Modi S, Jacot W, Yamashita T, et al. Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer. *N Engl J Med.* 2022;387(1):9–20. doi:10.1056/NEJMoa2203690
4. Meric-Bernstam F, Makker V, Oaknin A, et al. Efficacy and Safety of Trastuzumab Deruxtecan in Patients With HER2-Expressing Solid Tumors: Primary Results From the DESTINY-PanTumor02 Phase II Trial. *J Clin Oncol.* 2024;42(1):47–58. doi:10.1200/JCO.23.02005
5. US Food and Drug Administration. FDA grants accelerated approval to fam-trastuzumab deruxtecan-nxki for HER2-positive solid tumors. April 5, 2024. Available at: <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-fam-trastuzumab-deruxtecan-nxki-unresectable-or-metastatic-her2>
6. Bardia A, Jhaveri K, Im SA, et al. Datopotamab Deruxtecan Versus Chemotherapy in Previously Treated Inoperable/Metastatic Hormone Receptor-Positive Human Epidermal Growth Factor Receptor 2-Negative Breast Cancer: Primary Results From TROPION-Breast01. *J Clin Oncol.* 2025;43(3):285–296. doi:10.1200/JCO.24.00920
7. Bardia A, Hurvitz SA, Tolane SM, et al. Sacituzumab Govitecan in Metastatic Triple-Negative Breast Cancer. *N Engl J Med.* 2021;384(16):1529–1541. doi:10.1056/NEJMoa2028485
8. Rugo HS, Bardia A, Tolane SM, et al. TROPiCS-02: A Phase III study investigating sacituzumab govitecan in the treatment of HR+/HER2-metastatic breast cancer. *Future Oncol.* 2020;16(12):705–715. doi:10.2217/fon-2020-0163

Next-Generation Anticancer Modalities: A Systematic Review of Antibody–Drug Conjugates, Bispecific Antibodies, CAR-T Cell Therapy, Cancer Vaccines, and Radioligand Therapy

9. Powles T, Valderrama BP, Gupta S, et al. Enfortumab Vedotin and Pembrolizumab in Untreated Advanced Urothelial Cancer. *N Engl J Med.* 2024;390(10):875-888. doi:10.1056/NEJMoa2312117
10. Krop IE, Masuda N, Mukohara T, et al. Patritumab Deruxtecan (HER3-DXd), a Human Epidermal Growth Factor Receptor 3-Directed Antibody-Drug Conjugate, in Patients With Previously Treated Human Epidermal Growth Factor Receptor 3-Expressing Metastatic Breast Cancer: A Multicenter, Phase I/II Trial. *J Clin Oncol.* 2023;41(36):5550-5560. doi:10.1200/JCO.23.00882
11. Kantarjian H, Stein A, Gökbüget N, et al. Blinatumomab versus Chemotherapy for Advanced Acute Lymphoblastic Leukemia. *N Engl J Med.* 2017;376(9):836-847. doi:10.1056/NEJMoa1609783
12. Topp MS, Gökbüget N, Stein AS, et al. Safety and activity of blinatumomab for adult patients with relapsed or refractory B-precursor acute lymphoblastic leukaemia: a multicentre, single-arm, phase 2 study. *Lancet Oncol.* 2015;16(1):57-66. doi:10.1016/S1470-2045(14)71170-2
13. Ahn MJ, Cho BC, Felip E, et al. Tarlatamab for Patients with Previously Treated Small-Cell Lung Cancer. *N Engl J Med.* 2023;389(22):2063-2075. doi:10.1056/NEJMoa2307980
14. Moreau P, Garfall AL, van de Donk NWCJ, et al. Teclistamab in Relapsed or Refractory Multiple Myeloma. *N Engl J Med.* 2022;387(6):495-505. doi:10.1056/NEJMoa2203478
15. Budde LE, Sehn LH, Matasar M, et al. Safety and efficacy of mosunetuzumab, a bispecific antibody, in patients with relapsed or refractory follicular lymphoma: a single-arm, multicentre, phase 2 study. *Lancet Oncol.* 2022;23(8):1055-1065. doi:10.1016/S1470-2045(22)00335-7
16. Thieblemont C, Phillips T, Ghesquieres H, et al. Epcoritamab, a Novel, Subcutaneous CD3xCD20 Bispecific T-Cell-Engaging Antibody, in Relapsed or Refractory Large B-Cell Lymphoma: Dose Expansion in a Phase I/II Trial. *J Clin Oncol.* 2023;41(12):2238-2247. doi:10.1200/JCO.22.01725
17. Dickinson MJ, Carlo-Stella C, Morschhauser F, et al. Glofitamab for Relapsed or Refractory Diffuse Large B-Cell Lymphoma. *N Engl J Med.* 2022;387(24):2220-2231. doi:10.1056/NEJMoa2206913
18. Chari A, Minnema MC, Berdeja JG, et al. Talquetamab, a T-Cell-Redirecting GPRC5D Bispecific Antibody for Multiple Myeloma. *N Engl J Med.* 2022;387(24):2232-2244. doi:10.1056/NEJMoa2204591
19. Harding JJ, Fan J, Oh DY, et al. Zanidatamab for HER2-amplified, unresectable, locally advanced or metastatic biliary tract cancer (HERIZON-BTC-01): a multicentre, single-arm, phase 2b study. *Lancet Oncol.* 2023;24(7):772-782. doi:10.1016/S1470-2045(23)00242-5
20. Schram AM, Odintsov I, Espinosa-Cotton M, et al. Zenocutuzumab, a HER2xHER3 Bispecific Antibody, Is Effective Therapy for Tumors Driven by NRG1 Gene Rearrangements. *Cancer Discov.* 2022;12(5):1233-1247. doi:10.1158/2159-8290.CD-21-1119
21. Maude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia. *N Engl J Med.* 2018;378(5):439-448. doi:10.1056/NEJMoa1709866
22. Schuster SJ, Bishop MR, Tam CS, et al. Tisagenlecleucel in Adult Relapsed or Refractory Diffuse Large B-Cell Lymphoma. *N Engl J Med.* 2019;380(1):45-56. doi:10.1056/NEJMoa1804980
23. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. *N Engl J Med.* 2017;377(26):2531-2544. doi:10.1056/NEJMoa1707447
24. Locke FL, Miklos DB, Jacobson CA, et al. Axicabtagene Ciloleucel as Second-Line Therapy for Large B-Cell Lymphoma. *N Engl J Med.* 2022;386(7):640-654. doi:10.1056/NEJMoa2116133
25. San-Miguel J, Dhakal B, Yong K, et al. Cilta-cel or Standard Care in Lenalidomide-Refractory Multiple Myeloma. *N Engl J Med.* 2023;389(4):335-347. doi:10.1056/NEJMoa2303379
26. Qi C, Liu C, Peng Z, et al. Claudin-18 isoform 2-specific CAR T-cell therapy (satri-cel) versus treatment of physician's choice for previously treated advanced gastric or gastro-oesophageal junction cancer (CT041-ST-01): a randomised, open-label, phase 2 trial. *Lancet.* 2025;405(10494):2049-2060. doi:10.1016/S0140-6736(25)00860-8.
27. Zhang Y, Kao S, Li D, Yan C, Huang B, Fang H. Efficacy and safety of anti-CLDN18.2 therapies in advanced or metastatic gastric, gastro-oesophageal junction, and oesophageal carcinomas with CLDN18.2 positivity: a systematic review and meta-analysis. *Future Oncol.* 2026;22(12):1439-1451. doi:10.1080/14796694.2026.2659354
28. Escobar G, Berger TR, Maus MV. CAR-T cells in solid tumors: Challenges and breakthroughs. *Cell Rep Med.* 2025;6(11):102353. doi:10.1016/j.xcrm.2025.102353
29. AlKhazal A, Chohan S, Ross DJ, Kim J, Brown EG. Emerging clinical and research approaches in targeted therapies for high-risk neuroblastoma. *Front Oncol.* 2025;15:1553511. Published 2025 Mar 4. doi:10.3389/fonc.2025.1553511
30. Ouladan S, Orouji E. Chimeric Antigen Receptor-T Cells in Colorectal Cancer: Pioneering New Avenues in Solid Tumor Immunotherapy. *J Clin Oncol.* 2025;43(8):994-1005. doi:10.1200/JCO-24-02081
31. Weber JS, Carlino MS, Khattak A, et al. Individualised neoantigen therapy mRNA-4157 (V940) plus pembrolizumab versus pembrolizumab monotherapy in resected melanoma (KEYNOTE-942): a randomised, phase 2b study. *Lancet.* 2024;403(10427):632-644. doi:10.1016/S0140-6736(23)02268-7.
32. Weber JS, Khattak MA, Carlino MS, et al. Individual neoantigen therapy mRNA-4157 (V940) plus pembrolizumab in resected melanoma: 3-year update from KEYNOTE-942. *J Clin Oncol.* 2024;42(suppl):LBA9512.
33. Rojas, L.A., Sethna, Z., Soares, K.C. et al. Personalized RNA neoantigen vaccines stimulate T cells in pancreatic cancer. *Nature* **618**, 144–150 (2023). <https://doi.org/10.1038/s41586-023-06063-y>
34. Sethna Z, Guasp P, Reiche C, et al. RNA neoantigen vaccines prime long-lived CD8⁺ T cells in pancreatic cancer. *Nature.* 2025;639(8056):1042-1051. doi:10.1038/s41586-024-08508-4
35. Sahin U, Oehm P, Derhovanessian E, et al. An RNA vaccine drives immunity in checkpoint-inhibitor-treated melanoma. *Nature.* 2020;585(7823):107-112. doi:10.1038/s41586-020-2537-9
36. A Phase 1, Open-Label, Multicenter Study to Assess the Safety and Tolerability of mRNA-5671/V941 as a Monotherapy and in Combination With Pembrolizumab in Participants With KRAS Mutant Advanced or Metastatic Non-Small Cell Lung Cancer, Colorectal Cancer or Pancreatic Adenocarcinoma. <https://clinicaltrials.gov/study/NCT03948763>
37. Strosberg J, El-Haddad G, Wolin E, et al. Phase 3 Trial of ¹⁷⁷Lu-Dotatate for Midgut Neuroendocrine Tumors. *N Engl J Med.* 2017;376(2):125-135. doi:10.1056/NEJMoa1607427
38. Rinke A, et al. COMPETE trial interim results: [¹⁷⁷Lu]Lu-DOTA-TOC vs everolimus in GEP-NETs. Presented at: ENETS Annual Conference 2025, Barcelona, March 2025.
39. Sartor O, de Bono J, Chi KN, et al. Lutetium-177-PSMA-617 for Metastatic Castration-Resistant Prostate Cancer. *N Engl J Med.* 2021;385(12):1091-1103. doi:10.1056/NEJMoa2107322
40. Belabaci Z, Schmidt L, Sleiy M, et al. Efficacy and safety of rechallenge therapy with [¹⁷⁷Lu]Lu-PSMA in metastatic castration-resistant prostate cancer: a systematic review and meta-analysis. *Eur J Nucl Med Mol Imaging.* 2025;53(1):93-104. doi:10.1007/s00259-025-07438-1

Next-Generation Anticancer Modalities: A Systematic Review of Antibody–Drug Conjugates, Bispecific Antibodies, CAR-T Cell Therapy, Cancer Vaccines, and Radioligand Therapy

41. Azad AA, Bressel M, Tan H, et al. Sequential [¹⁷⁷Lu]Lu-PSMA-617 and docetaxel versus docetaxel in patients with metastatic hormone-sensitive prostate cancer (UpFrontPSMA): a multicentre, open-label, randomised, phase 2 study. *Lancet Oncol.* 2024;25(10):1267-1276. doi:10.1016/S1470-2045(24)00440-6
42. Ninatti G, Lee ST, Scott AM. Radioligand Therapy in Cancer Management: A Global Perspective. *Cancers (Basel).* 2025;17(21):3412. Published 2025 Oct 23. doi:10.3390/cancers17213412
43. World Health Organization. Global Cancer Burden 2022. IARC, 2024. Available at: <https://www.who.int/news-room/fact-sheets/detail/cancer>
44. Prasad V, Mailankody S. Research and Development Spending to Bring a Single Cancer Drug to Market and Revenues After Approval. *JAMA Intern Med.* 2017;177(11):1569-1575. doi:10.1001/jamainternmed.2017.3601
45. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ.* 2021;372:n71. Published 2021 Mar 29. doi:10.1136/bmj.n71
46. Hanahan D. Hallmarks of Cancer: New Dimensions. *Cancer Discov.* 2022;12(1):31-46. doi:10.1158/2159-8290.CD-21-1059
47. Maiti R, Patel B, Patel N, Patel M, Patel A, Dhanesha N. Antibody drug conjugates as targeted cancer therapy: past development, present challenges and future opportunities. *Arch Pharm Res.* 2023;46(5):361-388. doi:10.1007/s12272-023-01447-0.
48. Salvaris R, Ong J, Gregory GP. Bispecific Antibodies: A Review of Development, Clinical Efficacy and Toxicity in B-Cell Lymphomas. *J Pers Med.* 2021;11(5):355. Published 2021 Apr 29. doi:10.3390/jpm11050355
49. June CH, O'Connor RS, Kawalekar OU, Ghassemi S, Milone MC. CAR T cell immunotherapy for human cancer. *Science.* 2018;359(6382):1361-1365. doi:10.1126/science.aar6711
50. Sahin U, Türeci Ö. Personalized vaccines for cancer immunotherapy. *Science.* 2018;359(6382):1355-1360. doi:10.1126/science.aar7112
51. Virgolini I, Decristoforo C, Haug A, Fanti S, Uprimny C. Current status of theranostics in prostate cancer. *Eur J Nucl Med Mol Imaging.* 2018;45(3):471-495. doi:10.1007/s00259-017-3882-2
52. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ.* 2019;366:14898. Published 2019 Aug 28. doi:10.1136/bmj.14898
53. Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ.* 2016;355:i4919. Published 2016 Oct 12. doi:10.1136/bmj.i4919
54. Schünemann H, Brożek J, Guyatt G, Oxman A, eds. GRADE Handbook. The GRADE Working Group, 2013. Available at: <https://gdt.gradepro.org/app/handbook/handbook.html>
55. Ogitan Y, Aida T, Hagihara K, et al. DS-8201a, A Novel HER2-Targeting ADC with a Novel DNA Topoisomerase I Inhibitor, Demonstrates a Promising Antitumor Efficacy with Differentiation from T-DM1. *Clin Cancer Res.* 2016;22(20):5097-5108. doi:10.1158/1078-0432.CCR-15-2822
56. US Food and Drug Administration. FDA approves datopotamab deruxtecan-dlnk (Datroway) for HR-positive HER2-negative breast cancer. January 2025. Available at: <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-datopotamab-deruxtecan-dlnk-datroway-hr-positive-her2-negative-breast-cancer>
57. Lopatnikova JA, Sennikov SV. Bispecific immunotherapy based on antibodies, T-cell receptors, and aptamers: mechanisms of action, adverse effects, and future perspectives. *Front Immunol.* 2025;16:1679092. Published 2025 Nov 4. doi:10.3389/fimmu.2025.1679092
58. Sehn LH, Bartlett NL, Matasar M, et al. P1078: MOSUNETUZUMAB DEMONSTRATES DURABLE RESPONSES IN PATIENTS WITH RELAPSED AND/OR REFRACTORY FOLLICULAR LYMPHOMA WHO HAVE RECEIVED ≥2 PRIOR THERAPIES: UPDATED ANALYSIS OF A PIVOTAL PHASE II STUDY. *Hemasphere.* 2023;7(Suppl):e36694eb. Published 2023 Aug 8. doi:10.1097/01.HS9.0000971208.36694eb
59. Minson AG, Dickinson MJ. New bispecific antibodies in diffuse large B-cell lymphoma. *Haematologica.* 2025;110(7):1483-1499. doi:10.3324/haematol.2024.285343
60. Li W, Zhao D, Chen M, Yan X. Emerging advances in CAR-T therapy for solid tumors: latest clinical trial updates from 2025 ASCO annual meeting. *J Hematol Oncol.* 2025;18(1):104. Published 2025 Nov 19. doi:10.1186/s13045-025-01760-9
61. Li YR, Dunn ZS, Yu Y, Li M, Wang P, Yang L. Advancing cell-based cancer immunotherapy through stem cell engineering. *Cell Stem Cell.* 2023;30(5):592-610. doi:10.1016/j.stem.2023.02.009
62. Rafii S, Mukherji D, Komaranchath AS, et al. Advancing CAR T-Cell Therapy in Solid Tumors: Current Landscape and Future Directions. *Cancers (Basel).* 2025;17(17):2898. Published 2025 Sep 3. doi:10.3390/cancers17172898.
63. Pardi N, Hogan MJ, Porter FW, Weissman D. mRNA vaccines - a new era in vaccinology. *Nat Rev Drug Discov.* 2018;17(4):261-279. doi:10.1038/nrd.2017.243
64. Magoola M, Niazi SK. Current Progress and Future Perspectives of RNA-Based Cancer Vaccines: A 2025 Update. *Cancers (Basel).* 2025;17(11):1882. Published 2025 Jun 4. doi:10.3390/cancers17111882
65. Mirabile-Brightman SE, Butterfield LH. Advances in the development of personalized neoantigen therapies. *J Exp Med.* 2026;223(2):e20241234. doi:10.1084/jem.20241234
66. Herrmann K, Giovanella L, Santos A, et al. Joint EANM, SNMMI, and IAEA Enabling Guide: How to Set up a Theranostics Center. *J Nucl Med.* 2022;63(12):1836-1843. doi:10.2967/jnumed.122.264321
67. Topalian SL, Taube JM, Pardoll DM. Neoadjuvant checkpoint blockade for cancer immunotherapy. *Science.* 2020;367(6477):eaax0182. doi:10.1126/science.aax0182
68. Emmett L, Subramaniam S, Crumbaker M, et al. [¹⁷⁷Lu]Lu-PSMA-617plus enzalutamide in patients with metastatic castration-resistant prostate cancer (ENZA-p): an open-label, multicentre, randomised, phase 2 trial. *Lancet Oncol.* 2024;25(5):563-571. doi:10.1016/S1470-2045(24)00135-9
69. Grigg S, Minson A, Prins E, Dickinson MJ. Relapse after glofitamab has a poor prognosis and rates of CD20 loss are high. *Br J Haematol.* 2024;205(1):122-126. doi:10.1111/bjh.19455.