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Assessing Trends in the EU's Health Technology Assessment Submissions of Antibody–Drug Conjugates

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INTRODUCTION

- Antibody–drug conjugates (ADCs) combine targeted therapies with chemotherapies and are among the fastest growing anti-cancer drugs, with numerous pipeline trials propelling their growth
- ADCs combine the benefits of highly specific targeting with potent cytotoxic effects, enabling the precise and efficient elimination of cancer cells.[1] As a result, they have become a key focus in the research and development of anti-cancer therapies

OBJECTIVES

- This review aimed to identify trends in health technology assessment (HTA) submissions of ADCs to European regulatory bodies, highlighting the driving factors necessary for future submissions

METHODS

- HTA recommendations and conclusions from key markets such as the UK (National Institute for Health and Care Excellence [NICE])[2], the Netherlands (Zorginstituut Nederland [ZIN])[3], France (Haute Autorité de Santé [HAS])[4] and Germany (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen [IQWiG])[5] were analysed for eight European Medicines Agency (EMA)-approved ADCs

RESULTS

- A list of the eight included ADCs, their brand names, and the submitting manufacturers is provided in Table 1

Table 1. Overview of included ADCs including their brand names and manufacturer

Drug	Brand name	Manufacturer
Brentuximab vedotin	Adcetris®	Takeda
Trastuzumab emtansine	Kadcyla®	Roche
Inotuzumab ozogamicin	Besponsa®	Pfizer
Gemtuzumab ozogamicin	Mylotarg®	Pfizer
Polatuzumab vedotin	Polivy®	Roche
Trastuzumab deruxtecan	Enhertu®	Daiichi Sankyo
Sacituzumab govitecan	Trodelvy®	Gilead Sciences
Loncastuximab tesirine	Zynlonta®	Swedish Orphan Biovitrum

NICE recommendations in the UK

- NICE has issued favourable recommendations for all eight EMA-approved ADCs, highlighting their ability to effectively delay disease progression within acceptable cost-effectiveness estimates. Detailed information about each individual ADC, along with the indications, is reported in Table 2
- NICE recommended brentuximab vedotin (Adcetris; Takeda) for CD30-positive Hodgkin's lymphoma, CD30-positive cutaneous T-cell lymphoma (after one systemic therapy), and relapsed/refractory diffuse large B-cell lymphoma (DLBCL) but issued a negative recommendation for untreated advanced Hodgkin's lymphoma due to lack of evidence submission
- Roche's polatuzumab vedotin (Polivy) with rituximab and bendamustine was recommended for relapsed/refractory DLBCL in adults ineligible for stem cell transplants, with an incremental cost-effectiveness ratio (ICER) of £35,663 to £48,839 per quality-adjusted life year (QALY). Polatuzumab vedotin with R-CHP (rituximab, cyclophosphamide, doxorubicin and prednisolone) was also recommended for untreated DLBCL (International Prognostic Index [IPI] score 2–5), with an ICER of £26,097 per QALY
- Sacituzumab govitecan (Trodelvy; Gilead Sciences) and loncastuximab tesirine (Zynlonta; Swedish Orphan Biovitrum) received positive recommendations for unresectable triple-negative advanced breast cancer and relapsed/refractory DLBCL after two or more therapies, respectively

Table 2. NICE recommendations for ADCs

Intervention	Indication(s)	Comparator	Reimbursement
Brentuximab vedotin	CD30-positive HL (TA524)	Single-agent chemotherapy	Yes
	CD30-positive cutaneous TCL (after at least one systemic therapy) (TA577)	Physician's choice	Yes
	R/R sALCL (TA478)	Chemotherapy	Yes
	Untreated advanced HL (TA594)	NR	No
Brentuximab vedotin + CHP	Untreated sALCL (TA641)	CHOP	Yes
Trastuzumab emtansine	HER2-positive advanced BC after trastuzumab + taxane (TA458)	Lapatinib + capecitabine	Yes
	HER2-positive early breast cancer[a] (TA632)	Pertuzumab + trastuzumab + chemotherapy	Yes
Inotuzumab ozogamicin	R/R B-cell ALL (TA541)	Standard care	Yes
Gemtuzumab ozogamicin + daunorubicin + cytarabine	Untreated AML aged 15 years and over (TA545)	Daunorubicin + cytarabine	Yes
Polatuzumab vedotin + rituximab + bendamustine	R/R DLBCL[b] (TA649)	Rituximab + bendamustine	Yes
Polatuzumab vedotin + R-CHP	Untreated DLBCL[c] (TA874)	R-CHOP	Yes
Trastuzumab deruxtecan	HER2-positive unresectable or metastatic breast cancer[d] (TA862)	Trastuzumab emtansine	Yes (through Cancer Drugs Fund)
	HER2-positive unresectable or metastatic BC after two or more anti-HER2 therapies (TA704)	Eribulin + capecitabine + vinorelbine	Yes (through Cancer Drugs Fund)
	HER2-mutated advanced NSCLC after platinum-based chemotherapy (TA976)	NR	No
	HER2-positive unresectable or metastatic gastric or GEJ cancer after anti-HER2 treatment (TA879)	NR	No
	HER2-low metastatic or unresectable breast cancer after chemotherapy (TA992)	Physician choice	No
Sacituzumab govitecan	Unresectable advanced TNBC after two or more therapies (TA819)	Physician's choice: eribulin, capecitabine, gemcitabine and vinorelbine	Yes
Loncastuximab tesirine	R/R DLBCL and HBCL in adults after 2 or more systemic treatments (TA947)	Polatuzumab + bendamustine + rituximab + chemotherapy	Yes

Key: ADC, antibody–drug conjugate; ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; DLBCL, diffuse large B-cell lymphoma; GEJ, gastro-oesophageal junction; HBCL, high-grade B-cell lymphoma; HL, Hodgkin's lymphoma; IPI, International Prognostic Index; NSCLC, non-small-cell lung cancer; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; R-CHP, rituximab, cyclophosphamide, doxorubicin, prednisone; sALCL, systemic anaplastic large-cell lymphoma; TCL, T-cell lymphoma; TNBC, triple-negative breast cancer.
Notes: [a] In patients who have residual invasive disease, in the breast and/or lymph nodes, after neoadjuvant taxane-based and HER2-targeted therapy. [b] In adults who cannot have a haematopoietic stem cell transplant. [c] With an IPI score of 2–5. [d] After one or more anti-HER2 treatments.

ZIN recommendations in the Netherlands

- The ZIN categorized all ADCs as 'expensive medicines' due to their high cost. The ZIN cited uncertainties about long-term effects like overall survival and quality of life, recommending negotiation with manufacturers before reimbursement. Table 3 provides a list of recommendations for ADCs by ZIN, along with their respective indications
- Trastuzumab deruxtecan was approved for reimbursement on 11th April 2024 for advanced HER2-positive breast cancer, while sacituzumab govitecan received temporary reimbursement for metastatic triple-negative breast cancer on 2nd October 2024. Polatuzumab vedotin was not reimbursed for relapsed/refractory diffuse large B-cell lymphoma, pending positive advice, appropriate use agreements, and successful price negotiations. The ZIN advised against reimbursing loncastuximab tesirine, due to a lack of demonstrated added value

HAS recommendations in France

- The HAS issued a favourable opinion for almost all ADCs with a Service Médical Rendu (SMR) 'important' status. However, most ADCs received a moderate-to-minor improvement status in actual benefit (Amélioration du Service Médical Rendu [ASMR] Level III/IV), primarily because the Transparency Committee expects a better toxicity and quality-of-life profile compared with existing treatments. Table 3 provides a list of ADCs along with their respective indications
- Inotuzumab ozogamicin had an insufficient SMR for relapsed/refractory Philadelphia chromosome-positive B-cell acute lymphoblastic leukaemia (ALL), offering no improvement in actual benefit (ASMR Level V). Gemtuzumab ozogamicin also received an important SMR, but showed no improvement in actual benefit (ASMR Level V) for treatment-naïve acute myeloid leukaemia (AML) with CD33-positive expression
- Brentuximab vedotin demonstrated an important SMR and moderate improvement (ASMR Level III) for previously untreated systemic anaplastic large-cell lymphoma (sALCL). Trastuzumab emtansine showed a significant SMR and moderate improvement (ASMR Level III) in HER2-positive early breast cancer with invasive residual disease after neoadjuvant treatment

IQWiG recommendations in Germany

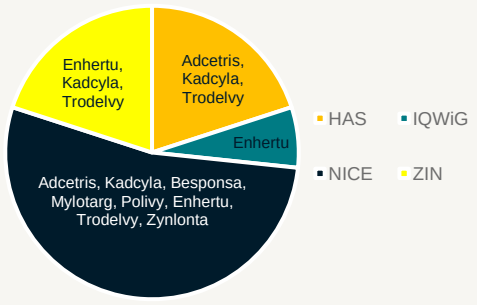
- In Germany, ADC submissions are increasingly being rated as having 'no additional benefit', apart from trastuzumab deruxtecan. Detailed information about the verdicts provided by IQWiG on trastuzumab deruxtecan is presented in Table 3
- Trastuzumab deruxtecan was identified by IQWiG as providing considerable added benefit for adults with unresectable or metastatic HER2-low breast cancer with visceral disease, and a major added benefit for those without visceral disease, who had prior chemotherapy or relapsed within 6 months of adjuvant chemotherapy

Table 3. ZIN, HAS and IQWiG recommendations for ADCs

Intervention	Indication(s)	Reimbursement
ZIN recommendations for ADCs		
Trastuzumab deruxtecan	HER2-positive breast cancer	Yes
Trastuzumab emtansine	Early HER2-positive breast cancer	Yes
Polatuzumab vedotin + bendamustine + rituximab	R/R DLBCL[a]	No
Sacituzumab govitecan	Inoperable or metastatic TNBC[b]	Yes
Loncastuximab tesirine	R/R DLBCL	No
Trastuzumab deruxtecan	HER2-positive breast cancer	Yes
HAS recommendations for ADCs		
Inotuzumab ozogamicin	ALL (B-precursor ALL with R/R CD22+ expression)	No, (ASMR Level V, compared to standard chemotherapies)
Gemtuzumab ozogamicin + daunorubicin + cytarabine	De novo, treatment-naïve AML with CD33+ expression	No (ASMR Level V, compared to daunorubicin + cytarabine)
Trastuzumab deruxtecan	Stomach cancer	No information reported
Brentuximab vedotin + CHP	sALCL	Yes (ASMR Level III, compared to CHOP)
Trastuzumab emtansine	Breast cancer	Yes (ASMR Level III, compared to trastuzumab)
Polatuzumab vedotin + R-CHP	Diffuse large B cell lymphoma	No (SMR: Insufficient)
Sacituzumab govitecan	Unresectable or metastatic TNBC	Yes, (ASMR Level III, compared to chemotherapy)
Sacituzumab govitecan	HR+ and HER2 negative unresectable or metastatic breast cancer	Yes, (ASMR Level IV, compared to chemotherapy
IQWiG recommendations for ADCs		
Trastuzumab deruxtecan [A23-115]	Advanced NSCLC tumours with HER2 mutation	Added benefit not proven
Trastuzumab deruxtecan [A23-52]	Unresectable or metastatic HER2-low breast cancer with prior chemotherapy in the metastatic setting or developed disease recurrence during/within 6 months of completing adjuvant chemotherapy	▪ With visceral disease: indication of minor added benefit ▪ Without visceral disease: indication of major added benefit
Trastuzumab deruxtecan [A23-08]	Advanced HER2+ gastric or gastroesophageal junction adenocarcinoma	Added benefit not proven
Trastuzumab deruxtecan [A22-126]	Patients with unresectable or metastatic HER2+ BC who have previously received one HER2-targeted therapy	For patients < 65 years of age, a hint of major added benefit in comparison with trastuzumab emtansine
Trastuzumab deruxtecan [A22-127]	Unresectable or metastatic HER2+BC with prior 2 or more HER2-targeted therapies	Considerable added benefit

Key: ADC, antibody-drug conjugate; ALL, acute lymphoblastic leukaemia; ASMR, Amélioration du Service Médical Rendu; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; CHP, cyclophosphamide, doxorubicin, prednisone; DLBCL, diffuse large B-cell lymphoma; NSCLC, non-small cell lung cancer; R-CHP, rituximab, cyclophosphamide, doxorubicin, prednisone; R/R, relapsed/refractory; sALCL, systemic anaplastic large-cell lymphoma; SMR, Service Médical Rendu; TNBC, triple-negative breast cancer
Notes: [a] Who are not candidates for haematopoietic stem cell transplantation. [b] With two or more prior systemic therapies, including one line of taxane-containing therapy and at least one for advanced disease.

Figure 1. Reimbursement of ADCs by various HTA bodies



CONCLUSIONS

- In summary, ADCs such as brentuximab vedotin, trastuzumab emtansine, trastuzumab deruxtecan and sacituzumab govitecan have achieved broad reimbursement across Europe, including in the UK, Netherlands, France, and Germany, highlighting their accessibility
- ADCs face divergent evaluations in Europe. The UK and France support their reimbursement, citing benefits and cost-effectiveness, while the Netherlands and Germany express concerns over high costs and uncertain long-term effects, advocating for cautious reimbursement and negotiation

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