

# The impact of different HTA frameworks on time to patient access: a case study assessing the first commercial launch indications for five oncology medicines

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## Supplementary materials

### Additional methods

- Information on the methodology and data sources can be found in **Supplementary Tables 1–3**.
- Health technology assessment (HTA) recommendations (**Supplementary Table 4**) and benefit assessments (**Supplementary Table 5**) from first HTA submissions differ between countries.
  - The differences observed in decision and benefit ratings demonstrate the inconsistency in HTA process across the six countries.
  - France and Germany had low clinical benefit assessment ratings despite the medicines becoming standard of care.
  - In contrast, higher ratings were issued for durvalumab in the PACIFIC randomized controlled trial, which did not undergo accelerated clinical development.
  - Significant delays to access were observed in countries with negative HTA decisions (**Figure 2**).

### Additional conclusions

- Our study attempted to quantify the impact of the duration of the HTA process after regulatory approval on patients and families in terms of potential life-years lost.
- Our findings will be more pronounced for cancer medicines as drug development moves increasingly into earlier disease settings and strives for a cure because long-term outcomes will be more uncertain at launch.

Supplementary Table 1. Summary of data sources	
Parameter	Source
Clinical efficacy data	Published articles <sup>1–21</sup>
Regulatory assessment of clinical benefit–risk balance	Published European Public Assessment Reports (EMA) and Summary Basis of Decision (Health Canada)
Supplementary data and modelling for HTA submission	AstraZeneca HTA submissions
Epidemiology	© 2023 DR/Decision Resources, LLC. All rights reserved. Reproduction, distribution, transmission or publication is prohibited. Reprinted with permission
Payer assessment of clinical benefit–risk balance	IQVIA HTA Accelerator database (www.iqvia.com/landing/hta-accelerator)
Regulatory approval dates	
Reimbursement listing dates	NAVLIN database (https://data.navlin.com)

EMA, European Medicines Agency; HTA, health technology assessment.

Supplementary Table 2. Summary of HTA details		
Country	Accountable HTA agency	Early patient access overview
Canada	CADTH	No paid early access programme
England	NICE	Cancer Drug Fund: paid early access programme
France	HAS Five levels of additional clinical benefit compared with alternative comparative therapy are assigned, which influence pricing	Paid early access programme for unserved patient population or high unmet need within approved label
Germany	G-BA Six levels of additional clinical benefit compared with alternative comparative therapy are assigned, which influence pricing	Access granted from EMA approval
Italy	AIFA	No paid early access programme
Spain	AEMPS	No paid early access programme

AEMPS, Spanish Agency of Medicines and Medical Products; AIFA, Italian Medicines Agency; CADTH, Canadian Agency for Drugs and Technologies in Health; EMA, European Medicines Agency; G-BA, Federal Joint Committee; HAS, French National Authority for Health; HTA, health technology assessment; NICE, National Institute for Health and Care Excellence.

Supplementary Table 3. Overview of medicines included in the study: indication at first major launch and supporting trials				
Medicine	First major launch indication	Study design and phase (number of patients)	Control arm	Primary endpoint
Olaparib	Maintenance treatment in patients with platinum-sensitive, relapsed, high-grade serous ovarian cancer who had received two or more platinum-based regimens, and had had a partial or complete response to their most recent platinum-based regimen	Randomized 2 (265 patients)	Placebo	PFS (met)
		Randomized 3 (295 BRCAm patients)	Placebo	PFS (met)
Osimertinib	Non-small cell lung cancer in patients previously treated with an EGFR-TKI	1/2 single-arm trial (603 patients)	None	ORR (met)
		2 single-arm trial (472 T790M patients)	None	ORR (met)
		Randomized 3 (419 T790M patients)	SOC	PFS (met)
Durvalumab	Unresectable, stage 3 non-small cell lung cancer following concurrent chemoradiation	Randomized 3 (713 patients)	Placebo	PFS (met) OS (met)
Acalabrutinib	First-line and relapsed/refractory chronic lymphocytic leukaemia	Randomized 2 (535 patients)	SOC	PFS (met)
Trastuzumab deruxtecan	HER2-positive metastatic breast cancer in patients previously treated with trastuzumab emtansine	2 single-arm trial (253 HER2+ patients)	None	ORR (met)
		Randomized 3 (600 HER2+ patients)	SOC	PFS (met)

BRCAm, BReast CAncer gene mutated; EGFR-TKI, epidermal growth factor receptor tyrosine kinase inhibitor; HER2+, human epidermal growth factor receptor 2 positive; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; SOC, standard of care.

**Supplementary Table 4. Overview of HTA recommendations from the first submission**

Medicine	Canada	England	Germany	France	Italy	Spain
Olaparib	Negative	Restrictions	Non-quantifiable added benefit	Positive	Restrictions	Positive
Osimertinib	Positive	Restrictions	No added benefit	Positive	Positive	Positive
Durvalumab	Positive	Restrictions	Considerable added benefit	Positive	Positive	Restrictions
Acalabrutinib	Restrictions	Restrictions	Minor added benefit	Restrictions	Positive	Positive
Trastuzumab deruxtecan	Not submitted	Restrictions	Considerable added benefit	Positive	Not submitted	Negative

HTA, health technology assessment.

**Supplementary Table 5. Overview of benefit assessments from the HTA submission for the first indication**

Medicine	Germany	France
Olaparib	IV: Non-quantifiable added benefit	IV: Minor therapeutic improvement
	III: Minor added benefit on resubmission with mature OS data	
Osimertinib	V: No added benefit	V: No therapeutic improvement
	II: Considerable on resubmission with mature OS data	IV: Minor therapeutic improvement on resubmission with mature OS data
Durvalumab	II: Considerable added benefit	III: Moderate therapeutic improvement
Acalabrutinib	III: Minor added benefit	V: No therapeutic improvement
Trastuzumab deruxtecan	II: Considerable added benefit	V: No therapeutic improvement

OS, overall survival.

## References

- Friedlander M, Matulonis U, Gourley C *et al.* Long-term efficacy, tolerability and overall survival in patients with platinum-sensitive, recurrent high-grade serous ovarian cancer treated with maintenance olaparib capsules following response to chemotherapy. *British Journal of Cancer* 2018;119:1075–1085.
- Ledermann J, Harter P, Gourley C *et al.* Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. *New England Journal of Medicine* 2012;366:1382–1392.
- Ledermann J, Harter P, Gourley C *et al.* Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer: a preplanned retrospective analysis of outcomes by BRCA status in a randomised phase 2 trial. *The Lancet Oncology* 2014;15:852–861.
- Ledermann JA, Harter P, Gourley C *et al.* Overall survival in patients with platinum-sensitive recurrent serous ovarian cancer receiving olaparib maintenance monotherapy: an updated analysis from a randomised, placebo-controlled, double-blind, phase 2 trial. *The Lancet Oncology* 2016;17:1579–1589.
- Poveda A, Floquet A, Ledermann JA *et al.* Olaparib tablets as maintenance therapy in patients with platinum-sensitive relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a final analysis of a double-blind, randomised, placebo-controlled, phase 3 trial. *The Lancet Oncology* 2021;22:620–631.
- Pujade-Lauraine E, Ledermann JA, Selle F *et al.* Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial. *The Lancet Oncology* 2017;18:1274–1284.
- Ahn M-J, Tsai C-M, Shepherd FA *et al.* Osimertinib in patients with T790M mutation-positive, advanced non-small cell lung cancer: Long-term follow-up from a pooled analysis of 2 phase 2 studies. *Cancer* 2019;125:892–901.
- Goss G, Tsai C-M, Shepherd FA *et al.* Osimertinib for pretreated EGFR Thr790Met-positive advanced non-small-cell lung cancer (AURA2): a multicentre, open-label, single-arm, phase 2 study. *The Lancet Oncology* 2016;17:1643–1652.
- Mok TS, Wu Y-L, Ahn M-J *et al.* Osimertinib or platinum–pemetrexed in EGFR T790M–positive lung cancer. *New England Journal of Medicine* 2017; 376:629–640.
- Papadimitrakopoulou VA, Mok TS, Han J-Y *et al.* Osimertinib versus platinum–pemetrexed for patients with EGFR T790M advanced NSCLC and progression on a prior EGFR-tyrosine kinase inhibitor: AURA3 overall survival analysis. *Annals of Oncology* 2020;31:1536–1544.
- Wu Y-L, Mok TSK, Han J-Y *et al.* Overall survival (OS) from the AURA3 phase III study: Osimertinib vs platinum-pemetrexed (plt-pem) in patients (pts) with EGFR T790M advanced non-small cell lung cancer (NSCLC) and progression on a prior EGFR-tyrosine kinase inhibitor (TKI). *Annals of Oncology* 2019;30:ix158.
- Yang JC-H, Ahn M-J, Kim D-W *et al.* Osimertinib in pretreated T790M-positive advanced non-small-cell lung cancer: AURA study phase II extension component. *Journal of Clinical Oncology* 2017;35:1288–1296.
- Antonia SJ, Villegas A, Daniel D *et al.* Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC. *New England Journal of Medicine* 2018;379:2342–2350.
- Antonia SJ, Villegas A, Daniel D *et al.* Durvalumab after chemoradiotherapy in stage III non–small-cell lung cancer. *New England Journal of Medicine* 2017;377:1919–1929.
- Spigel DR, Faivre-Finn C, Gray JE *et al.* Five-year survival outcomes from the PACIFIC trial: Durvalumab after chemoradiotherapy in stage III non–small-cell lung cancer. *Journal of Clinical Oncology* 2022;40:1301–1311.
- Sharman JP, Egyed M, Jurczak W *et al.* Acalabrutinib with or without obinutuzumab versus chlorambucil and obinutuzmab for treatment-naïve chronic lymphocytic leukaemia (ELEVATE TN): a randomised, controlled, phase 3 trial. *Lancet* 2020;395:1278–1291.
- Sharman JP, Egyed M, Jurczak W *et al.* Acalabrutinib ± obinutuzumab vs obinutuzumab + chlorambucil in treatment-naïve chronic lymphocytic leukemia: 5-year follow-up of ELEVATE-TN [poster]. Presented at the American Society of Clinical Oncology Annual Meeting, 3–8 June 2022, Chigago, IL, USA.
- Krop I, Park YH, Kim S-B *et al.* Trastuzumab deruxtecan vs physician’s choice in patients with HER2+ unresectable and/or metastatic breast cancer previously treated with trastuzumab emtansine: Primary results of the randomized phase 3 study DESTINY Breast02 [poster]. Presented at San Antonio Breast Cancer Symposium 6–10 December 2022, San Antonio, Texas, USA.
- Modi S, Saura C, Yamashita T *et al.* Trastuzumab deruxtecan in previously treated HER2-positive breast cancer. *New England Journal of Medicine* 2020;382:610–621.
- Saura Manich C, Modi S, Krop I *et al.* Trastuzumab deruxtecan (T-DXd) in patients with HER2-positive metastatic breast cancer (MBC): Updated survival results from a phase 2 trial (DESTINY-Breast01) [poster]. Presented at the European Society for Medical Oncology (ESMO) 2021 Annual Meeting 16–21 September 2021 [virtual].
- Verma S, Miles D, Gianni L *et al.* Trastuzumab emtansine for HER2-positive advanced breast cancer. *New England Journal of Medicine* 2012;367:1783–1791.