Single-arm trials and reimbursement decision-making in Europe: a case study in non-small cell lung cancer

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Background & objective

- Randomised controlled trials (RCT) represent the gold standard for clinical evidence.
- Nevertheless, single-arm trials (SAT) have been accepted as pivotal evidence for marketing authorisations (MA), with the objective of expediting regulatory approval and accelerating access to new therapies in areas of high unmet need.
- SATs have increasingly been used to secure conditional MAs for the first indications of innovative, targeted oncology therapies.
- However, SATs do not provide the comparative evidence needed for robust value assessment by the health technology assessment (HTA) bodies which determine reimbursement in Europe.
- This research examines regulatory and HTA outcomes in non-small cell lung cancer (NSCLC), to estimate the overall impact of SATs on access in Europe.

Methods

- European Medicines Authority (EMA) data was used to identify all regulatory submissions for NSCLC therapies since the beginning of the EU centralised procedure in 1995.
- EMA public assessment reports were reviewed to identify therapies approved based on SATs, the evidence assessed and decision made in the regulatory process.
- Decision documents published by HAS (France), G-BA (Germany) and NICE (UK) were reviewed to identify the evidence assessed and decisions made in national HTA and reimbursement processes.
- Confirmatory and other subsequent clinical trials in NSCLC were identified and results reviewed for each therapy initially authorised with SAT evidence.
- Data were extracted, analysed and summarised.

Results

- 20 NSCLC therapies have been submitted to the EMA with pivotal evidence from SATs. All are therapies targeting oncogenic driver mutations (**Table 1**).

Table 1: NSCLC therapies submitted to EMA relying on SAT data

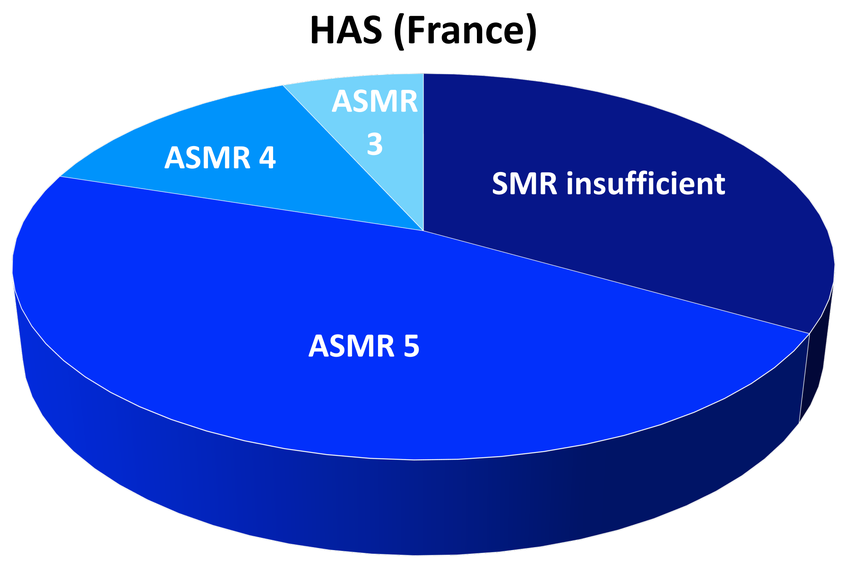
Therapy	Status	Year	Target	Pivotal study
Crizotinib	Authorised	2012	ALK	PROFILE 1001
Ceritinib	Authorised	2015	ALK	ASCEND-2
Osimertinib	Authorised	2016	EGFR T790M	AURA, AURA-2
Alectinib	Authorised	2017	ALK	NP28761, NP28673
Trametinib	Authorised	2017	BRAF V600	BRF113928
Brigatinib	Authorised	2018	ALK	ALTA
Lorlatinib	Authorised	2019	ALK	Ph2 EXP NCT01970865
Entrectinib	Authorised	2020	ROS1	ALKA, STARTRK-1 & -2
Selpercatinib	Authorised	2021	RET fusion	LIBRETTO-001
Amivantamab	Authorised	2021	EGFR exon 20	CHRYSALIS
Sotorasib	Authorised	2022	KRAS G12C	CodeBreak 100
Tepotinib	Authorised	2022	MET exon 14	VISION
Capmatinib	Authorised	2022	MET exon 14	GEOMETRY mono-1
Trastuzumab	Authorised	2023	HER2	DESTINY-Lung02
Adagrasib	Authorised	2024	KRAS G12C	KRYSTAL-1
Encorafenib	Authorised	2024	BRAF V600E	PHAROS
Reprotrectinib	Authorised	2025	ROS1	TRIDENT-1
Rociletinib	Withdrawn	2016	EGFR	TIGER-X, TIGER-2
Pralsetinib	Withdrawn	2021	RET fusion	ARROW
Mobocertinib	Withdrawn	2022	EGFR exon 20	AP32788-15-101

- None of the therapies have positive evidence for overall survival (OS) from subsequent randomised controlled trials (RCT) covering the original SAT indication.
- 3 therapies have positive evidence for OS in another NSCLC indication: alectinib (ALEX), osimertinib (ADAURA) and amivantamab (MARIPOSA).
- For most therapies, confirmatory trials included earlier treatment lines and used crossover designs, making demonstration of OS benefit challenging.
- 2 therapies were withdrawn prior to MA (rociletinib, mobocertinib) and one following MA (pralsetinib).

Results (continued)

- HAS assessed 15 therapies. 5 received SMR “insufficient”. 7 received ASMR 5. 3 therapies received better than ASMR 5, but only one of these assessments was based on SAT evidence alone.
- G-BA assessed 16 therapies. 14 received additional benefit (AB) not proven.
- NICE assessed 19 therapies. 6 appraisals were terminated or suspended, 3 therapies were not recommended and 4 entered the Cancer Drugs Fund.
- Re-evaluation using confirmatory RCTs improved some HTA value assessments, but decisions were always caveated with high uncertainty, mostly due to crossover designs in the confirmatory trials.

Figure 1: HTA outcomes



Conclusions

- Lack of comparative data in SATs and confounding from crossover in confirmatory RCTs present major impediments to value assessment of therapies first approved based on SATs.
- SATs have the potential to accelerate regulatory timelines for innovative medicines in areas of high unmet need, but this may not translate through to faster access for patients in Europe.
- Some NSCLC therapies with SAT evidence have been withdrawn, others were not assessed for reimbursement until RCT evidence became available, and, across 3 European HTA bodies, NSCLC therapies approved based on SATs mostly received unfavourable HTA outcomes.

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