Evidence generation in an early access strategy for oncology therapies: a comparison in NSCLC

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INTRODUCTION

There is large unmet need in non-small cell lung cancer (NSCLC), which remains the most common cause of cancer-related mortality worldwide (1). In order to address this unmet need in a timely manner, patients should be provided early access to new treatment options. Conditional marketing authorization (CMA) is a regulatory route offered by the European Medicines Agency (EMA) specifically designed to accelerate patient access to new treatments in areas of high unmet need. CMA is associated with less comprehensive clinical trial data than is required for a standard "full" MA, on the condition that the applicant will provide this data within a specified timeframe. Besides trial data, sponsors may explore other evidence generation approaches. It is hypothesized that such non-trial evidence generation is utilized to a greater extent for CMA products to gain a better understanding of the product's safety and efficacy early on and potentially to provide as additional evidence in submissions to Health Technology Assessment (HTA) bodies.

This study aims to investigate the use of CMA in NSCLC, their timeline from development to market access and trial evidence generation compared to standard approved NSCLC products.

METHODOLOGY

Drugs that received CMA or full MA in NSCLC from EMA since 2012 were identified through IQVIA's proprietary database HTA Accelerator. The start date of phase I or phase I/II trials included in EMA assessments were derived from TrialTrove. Start of the EMA assessment and European Commission (EC) decision dates were collected from the EMA website. Decision date of the first positive (with restrictions) HTA outcome in France (HAS), UK (NICE, SMC) and Germany (G-BA) was accessed from HTA Accelerator. To obtain the NSCLC benchmark, results for the above timeline metrics were averaged across non-CMA products.

Sponsors-initiated non-trial evidence generation approaches in NSCLC were identified through a TrialTrove and PubMed search. The scope included: open-label extension studies, expanded access programs and retrospective studies that were initiated prior to the product's latest MA extension in NSCLC granted by the EC. Retrospective analyses on trial populations were excluded. In addition, formal early access programs (EAPs) run in France (cohort Temporary Authorisation for Use; ATU or Recommendation for Temporary Use; RTU) or the UK (Early Access to Medicines Scheme; EAMS) were identified through the MHRA and ANSM website, respectively. Relevant HTAs from NICE and HAS were analyzed on submitted evidence to identify if non-trial evidence was assessed by HTA bodies.

RESULTS

EMA has granted 12 products approval in NSCLC since 2012, of which four received CMA (Table 1). All CMA products received approval based on pivotal single arm phase I/II or II trials. None of the other 8 products applied for CMA and all received full MA based on RCT phase III studies with the exception of Mekinst + Tafinlar, which received full MA based on uncontrolled phase II data. All CMA products are relatively quicker to market compared to the NSCLC benchmark, largely based on their shorter absolute clinical development timeline. Out of all products, only Tagrisso was reviewed through accelerated assessment, which explains its relative short EMA assessment period.

Overall, sponsors of CMA products generated more non-trial evidence compared to full MA products. The majority of these studies allowed for collection of both efficacy and safety data. In addition, two retrospective studies were conducted to collect healthcare utilization and cost data specifically (Zykadia, Alecensa).

As CMA products have less comprehensive data at the moment of HTA submission than full MA products, it is hypothesized that non-trial evidence could be provided as additional evidence in submissions to HTA bodies. This was observed for Xalkori and Zykadia, although the evidence was not used to support trial efficacy and safety data. In the NICE assessment of Xalkori, patient characteristics from a retrospective medical chart review study were incorporated into the OS extrapolation, allowing for more realistic OS estimates better representative of the UK population. In the HAS assessment of Zykadia, patient characteristics and treatment history data collected through the cohort ATU was considered valuable, but efficacy data collected for only a subset of the ATU population was not considered. Although non-trial evidence collected for Tagrisso and Alecensa was not used in HTAs, NICE did acknowledge the relevance of this type of data. Tagrisso is marketed through the Cancer Drug Fund (CDF) and requires data collection through Systemic Anti-cancer Therapy (SACT) dataset. NICE also criticized the lack of retrospective chart reviews in the assessment of Alecensa.

Although to a lesser extent, some HTAs on NSCLC products approved via full MA mentioned utilization of non-trial evidence. The sponsor of Portrazza incorporated data from a retrospective medical chart review in their economic model for NICE, whilst safety data from a large-scale ATU program for Opdivo was submitted to HAS. Similar to Tagrisso, Opdivo (not shown in table) and Keytruda were made available through CDF, both requiring data collection through the SACT database during their managed access period.

Figure 1. Development, approval and access timelines

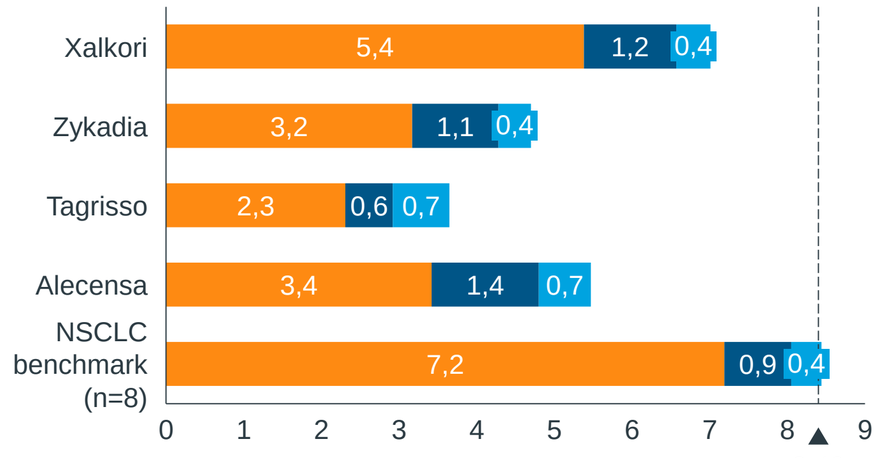

Table 1. Sponsor initiated non-trial evidence generation in NSCLC

	Brand (1st approval; year)	Open-label extension	Early access program	Expanded access	Retrospective studies	Non-trial evidence consideration in HTA
CMA	**Xalkori** (ALK+ adv.; 2012)	N/A	ATU (FR; n=130) RTU for ROS1+ ALK+ (FR; n=N/A)	N/A	Xalkori-treated pts as ≥1st line (US, CA; n=212) Xalkori or chemo-treated pts (CN; n=291) Xalkori-treated pts w. brain metastases (EU; n=23) Xalkori-treated pts (global; n=158) ROS1+ pts off-label Xalkori (EU; n=32)	**NICE (2016), positive recommendation, 1st line ALK+ NSCLC** NICE accepted the use of the retrospective US/CA cohort to model baseline patient characteristics, which allowed for more realistic survival estimates relevant to the UK population, thereby contributing to meeting the end-of life criteria
CMA	**Zykadia** (ALK+ adv.; 2015)	Global; n=N/A	ATU (FR; n=161)	pts pre-exposed to an ALK inhibitor (global, n=N/A)	Healthcare costs of Zykadia-treated pts (US; n=164) Xalkori- or Zykadia or chemo-treated pts (CA; n=97) Zykadia-treated pts post-Xalkori (US; n=58)	**HAS (2015), positive recommendation, ASMR IV, 2nd line ALK+ NSCLC** HAS acknowledged that ATU patients' characteristics and treatment history provided valuable insights in the French clinical practice, but ATU efficacy data was not assessed as data only collected for 48% of the total patient group
CMA	**Tagrisso** (EGFR T790M+ LA or met.; 2016)	N/A	ATU (FR; n=229) EAMS (UK; n=25)	pts pre-exposed to EGFR-TKI (US, n=248 pts) Compassionate use for EGFR TKI-treated pts (JA; n=18)	N/A	**NICE (2016), positive w. restr. recommendation, 2nd line EGFR T790M+ NSCLC** Tagrisso is available through CDF. This requires data collection through the SACT database to inform real world treatment patterns with Tagrisso in the UK, which will support the primary data source: results of the phase III AURA3 trial
CMA	**Alecensa** (ALK+ adv.; 2017)	Global; n=N/A	EAMS for 1st line ALK+ (UK; n=N/A)	Alecensa in Xalkori-treated pts (US; n=129)	Online study in pts treated with Xalkori and subsequent Alecensa (US; n=207) Healthcare costs of brain metastases in Xalkori- or Alecensa-treated pts (US; n=405)	**NICE (2018), positive recommendation, 1st line ALK+ NSCLC** The ERG noted that exclusion of retrospective chart reviews in the company's SLR may have overlooked important evidence to validate OS and to assess plausibility of extrapolations used in CE analysis
Standard MA	**Giotrif** (EGFR TKI-naïve; LA or met.; 2013)	Roll-over Ph I (SK; n=N/A)	N/A	Access for EGFR+ pts (US; n=573) Access for EGFR+ pts failed erlotinib or gefitinib (US, Pacific, EU; n=N/A)	N/A	HTA agency did not comment on non-trial evidence generation
Standard MA	**Vargatef** (LA, met. LR; 2014)	FR, DE; n=41	N/A	N/A	N/A	HTA agency did not comment on non-trial evidence generation
Standard MA	**Opdivo** (LA, or met. sq.; 2015)	N/A	EAMS for sq. pts (UK; n=47) ATU for 2nd line treatment (FR; n=1148)	Access for 2nd-line pts (US, CA, BR, n=N/A)	N/A	**HAS (2015), positive recommendation, ASMR III, 2nd line NSCLC** The pharmacovigilance safety data collected the cohort ATU did not provide new information on the benefit / risk balance of Opdivo
Standard MA	**Cyramza** (LA or met.; 2016)	N/A	N/A	N/A	N/A	HTA agency did not comment on non-trial evidence generation
Standard MA	**Portrazza** (EGFR+ sq. LA or met.; 2016)	N/A	N/A	N/A	Cohort study to assess treatment patterns and resource utilization in sq. pts (UK; n=203)	**NICE (2016), negative recommendation, 1st line squamous NSCLC** A retrospective medical chart review fed into the economic model for UK disease monitoring and supportive care estimates; no specific commentary by NICE was provided
Standard MA	**Keytruda** (2nd line; 2016)	N/A	EAMS for 2nd line PDL-1+ pts (UK; n = 231)	N/A	N/A	**NICE (2017), positive w. restr. recommendation, 1st line PD-L1+ NSCLC** Keytruda is made available within the CDF. This requires data collection through the SACT database, supportive of the primary data source: the ongoing phase III KN-024 trial
Standard MA	**Tecentriq** (LA, or met.; 2017)	Global; n=N/A	N/A	N/A	N/A	HTA agency did not comment on non-trial evidence generation
Standard MA	**Mekinst +Tafinlar** (BRAF V600+ adv. 2017)	N/A	N/A	N/A	N/A	HTA agency did not comment on non-trial evidence generation

Type of data collected: Efficacy (and safety) · Safety · Demographics, clinical characteristics, treatment patterns and/or costs · Data collection unknown

Conclusion

The unmet need in NSCLC is high, as evidenced by one-third of the products being approved through CMA since 2012, which resulted in earlier access to the market. Sponsors of CMA NSCLC products are using a full range of evidence generation opportunities to complement their main clinical trials to a greater extent than standard approvals. HTAs from HAS and NICE illustrate that this type of data is accepted or even required/desired by European HTA bodies.

(1) McGuire S. World Cancer Report 2014. Geneva, Switzerland: World Health Organization, International Agency for Research on Cancer, WHO Press, 2015. Adv. Nutr. 2016;7:418-9.
Abbreviations: adv.: advanced; LA: locally advanced; LR: locally recurrent; met.: metastatic; sq.: squamous; TKI: tyrosine kinase inhibitor

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