INTRODUCTION

There is large unmet need in non-small cell lung cancer (NSCLC), which remains the most common cause of cancer-related death worldwide. 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 option 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 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.

RESULTS

EMA has granted 12 products approval in NSCLC since 2012, of which four received CMA (Table 1). All CMA products were approved based on pivotal single arm phase III or II trials. None of the other II trials applied for CMA and all received full MA based on RCT phase III trials with the exception of Mekinist + Tafinlar, which received full MA based on uncontrolled phase IIA 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 short relative 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 incorporated into the OS extrapolation, allowing for more realistic OS estimates better representative of the UK population, thereby contributing to meeting the end-of-life criteria

Although to a lesser extent, some HTAs on NSCLC products approved via full MA mentioned utilization of non-trial evidence. The sponsor of Portanza incorporated data from a retrospective medical chart review trial 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.

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

<table>
<thead>
<tr>
<th>Brand (1st approval year)</th>
<th>Open-label extension</th>
<th>Early access program</th>
<th>Expanded access</th>
<th>Non-trial evidence consideration in HTA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Xalkori</strong> (ALK+, adv., 2012)</td>
<td>NA</td>
<td>ATU (FR; n=152)</td>
<td>NA</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Zykadia</strong> (ALK+, adv., 2015)</td>
<td>NA</td>
<td>ATU (FR; n=151)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Tagrisso</strong> (EGFR T790M+; LA, met. 2016)</td>
<td>NA</td>
<td>EAMS (UK; n=145)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Alecensa</strong> (ALK+, adv., 2017)</td>
<td>NA</td>
<td>ATU (UK; n=47)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Giotrif</strong> (EGFR T790M+; LA, met. 2015)</td>
<td>NA</td>
<td>EAMS (UK; n=145)</td>
<td>NA</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Opdivo</strong> (LA, met. LR, 2014)</td>
<td>NA</td>
<td>EAMS for 1st line pts (US, FR; n=477)</td>
<td>N/A</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Tafinlar</strong> (BRAF V600+; adv. 2017)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

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 III 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, SMIC) 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, final early access programs (EAPs) run in France (cohort Temporary Access Program [CAP]), which allowed for more realistic survival estimates relevant to the UK population, thereby contributing to meeting the end-of-life criteria.

**The pharmacovigilance safety data collected the cohort ATU did not provide new information on the benefit / risk balance of Opdivo.**

**The EMA noted that exclusion of retrospective chart reviews in the company’s SLR may have overlooked important information on the benefit / risk balance of Opdivo and to assess plausibility of extrapolations used in CE analysis.**

In the NICE, positive recommendation, 1st line ALK+ NSCLC NICE acknowledged the use of the retrospective U/S/C 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.

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.

NICE (2016), positive, reweight, recommendation, 2nd line EFG T790M+ NSCLC NICE acknowledged that ATU patients’ characteristics and treatment history provided valuable insight in the French clinical practice, but ATU efficacy data was not assessed as data only collected for 48% of the total patient group.

NICE (2017), positive recommendation, 1st line ALK+ NSCLC

The EMA noted that exclusion of retrospective chart reviews in the company’s SLR may have overlooked important information on the benefit / risk balance of Opdivo.

HAS (2015), positive recommendation, ASMR II, 2nd line NSCLC

The pharmacovigilance safety data collected the cohort ATU did not provide new information on the benefit / risk balance of Opdivo.

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.

**In the NICE, positive, reweight, recommendation, 1st line EGFR+ NSCLC**

Keytruda is made available within the CDF. This requires data collection through the SACT database, currently the primary source for the phase III KEYNOTE-024 trial.

**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.