

Treatment landscape and key drivers for HTA decisions in patients with non-small cell lung cancer without EGFR or ALK alterations

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PCN366

Introduction

- Advances in the understanding of the molecular pathogenesis of non-small cell lung cancer (NSCLC) are paving the way for new treatments targeting specific patient populations harbouring molecular biomarkers¹.
- In the last 10 years, 46.7% of the drugs approved by the European Medicines Agency (EMA) for NSCLC target endothelial growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) rearrangements²; however, up to 80% of patients do not have these genetic alterations^{3,4}.

- This study analyses the HTA decisions for treatments in patients without EGFR/ ALK mutations.
- The objectives of this study were:
 - To examine the overall trends in HTA decision making for patients with NSCLC without EGFR or ALK mutations.
 - To determine the key drivers for the HTA decisions in this indication.

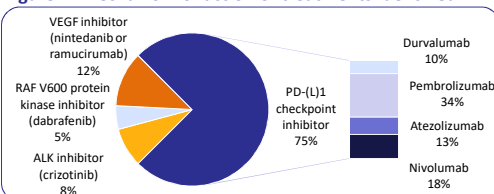
Methods

- HTAs for the treatment of NSCLC corresponding to EMA assessments from October 1st 2009 to 2019 were identified from the SIRIUS Oncology HTA database⁵.
- HTAs where the target indication was EGFR or ALK mutations were excluded; Crizotinib (an ALK inhibitor) was included, as it was indicated for ROS-1+ patients.
- HTAs by NICE (England and Wales), SMC (Scotland), HAS (France), G-BA (Germany), PBAC (Australia), and CADTH (Canada) were reviewed and the results analysed.

Results

- In patients without EGFR/ ALK mutations, 8 unique treatments were identified in 60 HTAs; 75% of HTAs were for PD-(L)1 checkpoint inhibitors (Figure 1).

Figure 1: Mechanism of action of treatments identified

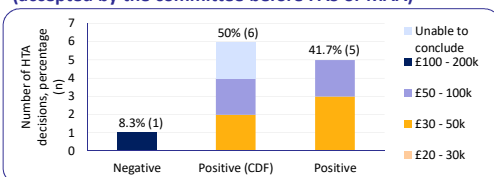


- In 78.3% of all HTAs, the treatment was recommended or demonstrated added benefit. This figure was higher at 91.1% for PD-(L)1 inhibitors.



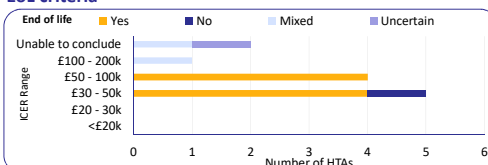
- NICE published guidance on 12 treatment regimens for NSCLC in patients without EGFR/ ALK mutations. A positive recommendation was issued in 91.7% of HTAs, of which 50% were recommended through the CDF.
- The ICER was an important element in decision making with the only negative assessment demonstrating an ICER in the range of £100,000-£200,000 per QALY gained. The committee were unable to conclude on the ICER for 16.7% of the technologies, and these were reimbursed through the CDF. Furthermore, a higher proportion of HTAs that had a positive outcome had an ICER of less than £50,000 (Figure 2).

Figure 2: Outcomes of NICE assessments and the ICER range (accepted by the committee before PAS or MAA)



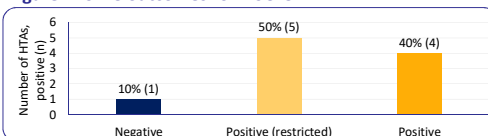
- Of all the treatments assessed, 75% met the criteria as an end-of-life (EoL) treatment, extending life by more than 3 months, allowing the NICE appraisal committee to consider ICERs greater than £30,000. A further 16.7% were mixed as they met the EoL criteria against at least one comparator or indication, and in one HTA (8.3%) it was uncertain at the time of assessment. Only one treatment with an ICER above £30,000 did not meet EoL criteria (it was recommended for the CDF) (Figure 3).

Figure 3: ICER ranges according to whether treatments met EoL criteria



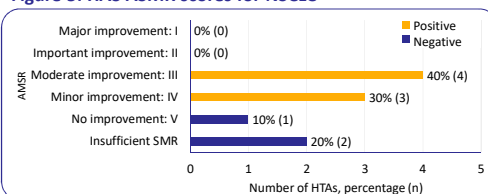
- 10 HTAs were identified from the SMC, where 90% were recommended, though 50% were restricted, due to two-year clinical stopping rules in place for PD-(L)1 inhibitors.
- Positive decisions were based on improved OS and PFS and were supported with a PACE meeting to allow for input from patient and clinician groups as well as a discount through a PAS.
- The negative decision was due to concerns over comparator appropriateness, estimated ICERs for PD-L1 subgroups, estimated OS benefit, and utility estimates in the economic analysis (Figure 4).

Figure 4: SMC outcomes for NSCLC



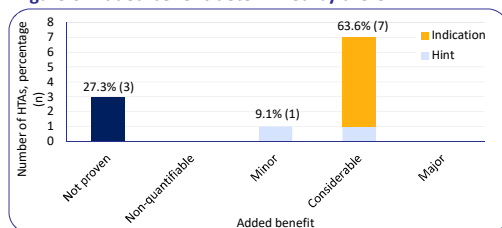
- In patients without EGFR/ ALK mutations, 10 HTAs were identified from HAS, where 80% were recommended for reimbursement, receiving an ASMR score of I-V.
- Added benefit was conferred in 70% of HTAs, with an ASMR score of IV or III, which would allow for similar or premium pricing compared to other EU countries. No technologies received an ASMR score of I or II.
- The reasons behind the negative outcomes were no RCT with the appropriate comparator (20%) and no demonstration of OS or QoL benefit (10%) (Figure 5).

Figure 5: HAS ASMR scores for NSCLC



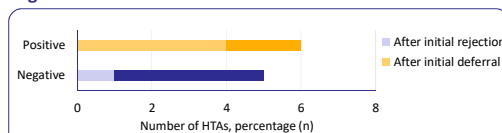
- The G-BA determined that there was an added benefit in 72.7% of the 11 HTAs that were identified. In 63.6% of HTAs there was a hint or an indication of a considerable added benefit due to a significant improvement in OS over the comparator treatments (Figure 6).
- Added benefit was not proven in 27.3% of HTAs due to the absence of an RCT with the appropriate comparator (18.2%) or possible effect modification due to differences in patient age in the clinical trial (9.1%).

Figure 6: Added benefit determined by the G-BA



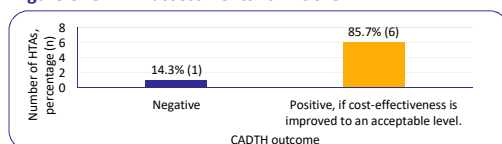
- PBAC provided a recommendation in 54.5% of HTAs, although this decision was originally deferred in 33.3% of cases.
- Negative decisions centered around there being no evidence of clinical benefit, immature trial data, or unfavourable cost-effectiveness (Figure 7).

Figure 7: Outcomes from PBAC assessments



- CADTH made 7 assessments, where 85.7% were recommended on a conditional basis, pending improvement of the cost-effectiveness to an acceptable level. This would occur during price negotiations with the individual provinces (Figure 8).

Figure 8: CADTH assessments for NSCLC



Conclusion

- The CDF, which allows provisional access while additional data is collected to support clinical/ cost-effectiveness, was a frequent access route for new treatments in NSCLC for patients without EGFR or ALK mutations in England and Wales, with more treatments being recommended through the CDF than outright. This was often due to uncertainty in the cost effectiveness, or an ICER of above £50,000 per QALY gained that could become lower than the threshold when mature data is available.
- The SMC had a similar proportion of positive outcomes,

which were supported by PACE meetings where clinicians and patient groups have a voice in decision making.

- HAS and the G-BA, whose decision making relies on comparison with available treatments, determined an added benefit in a high proportion of HTAs relative to general oncology⁶, with several treatments demonstrating a moderate improvement (HAS) or a hint/indication of a considerable added benefit (G-BA). The main reason behind the positive decisions was improved OS.
- PBAC provided the fewest number of positive outcomes.

Negative assessments were due to unfavourable trial results or cost-effectiveness. The high number of negative outcomes is also likely due to the nature of Australian HTAs, where resubmissions are often required before recommendation.

- CADTH had the lowest number of assessments, with one negative outcome due to uncertainties in the clinical data.
- There has been an increasing number of HTAs for targeted therapies in NSCLC in recent years, reflecting the trend towards personalised medicine in oncology.

ALK, anaplastic lymphoma kinase; ASMR, improvement in actual benefit; CADTH, Canadian Agency for Drugs and Technologies in Health; CDF, Cancer Drugs Fund; EGFR, endothelial growth factor receptor; EMA, European Medicines Agency; EU, European Union; G-BA, The Federal Joint Committee; HAS, Haute Autorité de Santé; HTA, health technology assessment; ICER, incremental cost-effectiveness ratio; NICE, National Institute for Health and Care Excellence; NSCLC, non-small cell lung cancer; OS, overall survival; PBAC, Pharmaceutical Benefits Advisory Committee; PACE, patient and clinician engagement; PAS, patient access scheme; PD-(L)1, programmed death-(ligand)-1; PFS, progression-free survival; QALY, quality-adjusted life year; QoL, quality of life; RCT, randomised control trial; ROS, reactive oxygen species; SMC, Scottish Medicines Consortium; VEGF, vascular endothelial growth factor