Critiques of survival analysis methods used in immuno-oncology appraisals assessed by NICE in the UK, 2011-2020

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Immuno-oncology treatments: the promise

Overall survival (OS) is the main efficacy outcome considered by health technology assessment (HTA) bodies, including the UK National Institute for Health and Care Excellence (NICE), when assessing novel oncology therapies.

Immuno-oncology treatments: the challenge

Given the short follow-up in most clinical trials, extrapolation of the OS beyond the trial cut-off is necessary to estimate the lifetime benefit associated with treatment.

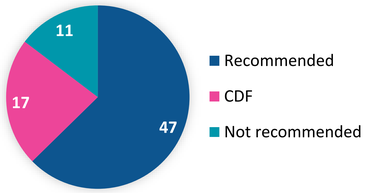
We evaluated factors associated with OS extrapolation that have influenced the success of immuno-oncology (I-O) therapies for reimbursement in the UK by NICE from 2011 until 2020.

Identifying NICE critiques to survival analyses

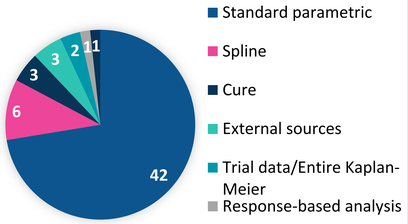
- **75 technology appraisals of I-O therapies,** as defined by the Cancer Research Institute's classification of immunotherapies,[1] **were identified on** the NICE website for the period between 2011 and 2020 (excluding terminated appraisals).[2] General appraisal information and NICE recommendations for each I-O technology were extracted from NICE Final Appraisal Documents.
- Information was extracted about the type of model, the time horizon, the method to extrapolate OS as well as NICE's critiques of these aspects. Cost-effectiveness results were also extracted.

Outcomes of I-O appraisals submitted to NICE

NICE recommendation (n = 75)



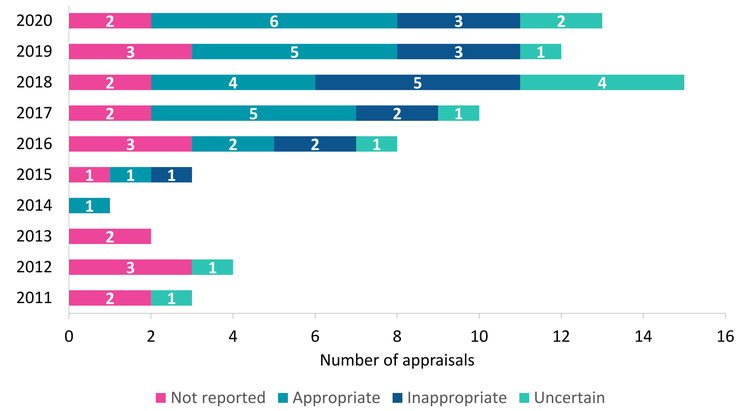
OS extrapolation method (n = 58)



- 62% of I-O treatments were **recommended** for reimbursement by the NHS and 22% for reimbursement **within the Cancer Drug Fund (CDF),** while 14.7% were **not recommended** for reimbursement.
- **All appraisals** reported clinical data on OS: **54.7%** reported a **statistically significant** improvement in OS following I-O treatment, of which 68.3% were recommended, 14.6% were recommended for CDF reimbursement, and 17.1% were not recommended for reimbursement.
- NICE **rejected the extrapolation method in 27.6%** of appraisals that used one.

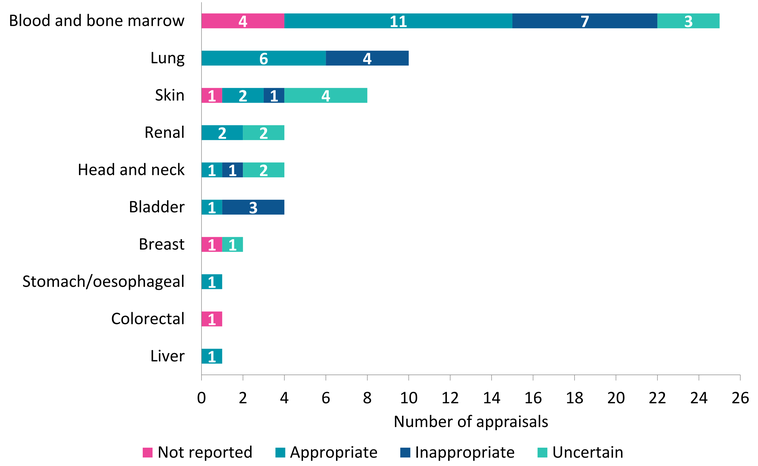
NICE's assessment of OS extrapolation method in I-O appraisal

Stratified by year



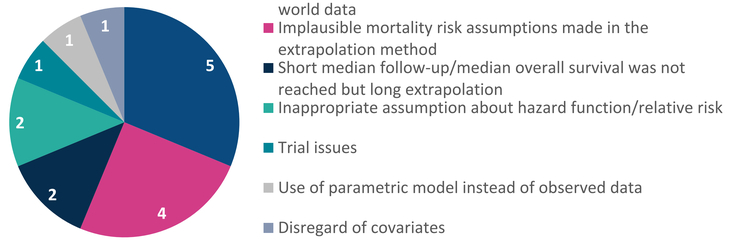
- Compared to older submissions, recent ones have tended to apply OS extrapolation methods that NICE considered appropriate.

Stratified by cancer type



- Submissions involving lung and blood and bone marrow cancers were most likely to use OS extrapolation methods that NICE considered appropriate, while submissions involving skin cancer were most likely to use methods that NICE considered uncertain.

NICE's reasons for rejecting the OS extrapolation method in 16 appraisals



- The most frequent critiques were that OS estimates were **implausible** and **inconsistent** with clinical trial evidence or real-world data (5 appraisals), or that estimates assumed that future mortality rate would be **no higher** than that in the general population (4 appraisals).
- Other critiques were extrapolation of OS over a long horizon even though median survival was not met or follow-up was short; failure to account for change in risk over time when calculating the hazard ratio or relative risk; trial issues such as censoring; use of parametric models instead of observed data; and disregard of covariates.

Immuno-oncology treatments: lessons learned for reimbursement success

Conclusions:

- The number of I-O therapies assessed by NICE has increased **exponentially** in recent years.
- OS was reported by manufacturers in all I-O appraisals, but a statistically **significant improvement** was observed in only **54.7%**.
- To extrapolate OS, most appraisals have used standard parametric models, which are very common in traditional chemotherapeutic regimens.[3]
- OS extrapolation methods were used in most appraisals and **rejected** by NICE in just under **one third**.
- **Lack** of significant survival benefit and **uncertainty** in long-term OS impacts the cost-effectiveness of I-O treatments.[4]
- Given the mechanism of action of I-O treatments, **more flexible extrapolation methods** may be needed to address such challenges as non-proportional hazards, the plateau effect, and unobserved patient heterogeneity.[4]
- Companies should **validate the plausibility** of OS benefit and mortality risk assumptions; otherwise NICE is more likely to reject the extrapolation method.

Limitations:

- Additional information was not examined in other NICE documents, such as manufacturer's submissions or reports from the Evidence Review Group.
- NICE appraisals were carried out by different appraisal committees, so critiques may vary by committee.

References:

(1) Cancer Research Institute . Available from: https://www.cancerresearch.org/immunotherapy/treatment-types; (2) NICE guidance. Available from https://www.nice.org.uk/guidance . Accessed March 2021.; (3) Latimer, N. NICE DSU Technical Support Document 14: Undertaking survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data. 2011.; (4) Quinn C, Garrison LP, Pownell AK, et al. Current challenges for assessing the long-term clinical benefit of cancer immunotherapy: a multi-stakeholder perspective. J Immunother Cancer. 2020;8(2):e000648. doi:10.1136/jitc-2020-000648