A Targeted Review of Treatment Beyond Progression in NICE HTA Oncology Submissions

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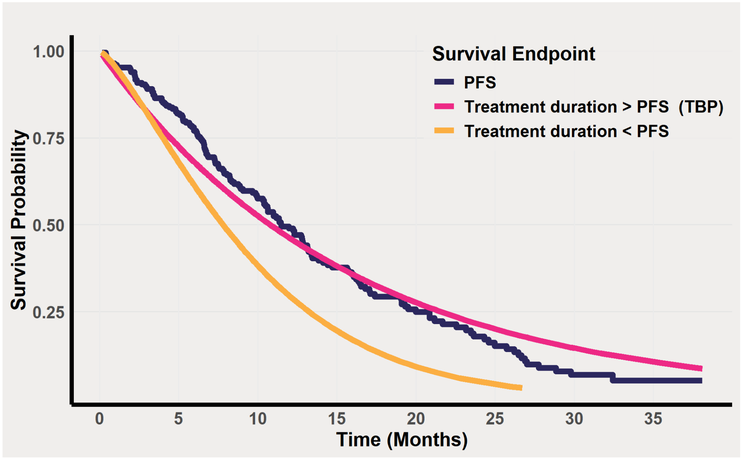
Background

- In oncology, treatment beyond progression (TBP) refers to the continuation of current therapy despite disease progression.[1]
- TBP has been reported across multiple oncology indications, including melanoma and lung cancer, particularly with the growing use of immunotherapy interventions.[1-4]
- The TBP approach may be chosen due to several factors, including unconventional response patterns (e.g., pseudo-progression), potential for delayed tumour regression, sustained clinical benefits despite clinically defined progression, and observed improvements in overall survival.[4-6]
- Traditional oncology partitioned survival models (PSM) use a 'treat-to-progression' approach, assuming treatment duration, as measured by clinical trial endpoints (e.g., time to treatment discontinuation [TTD] or time on treatment [ToT]), does not exceed disease progression, as indicated by measures such as progression-free survival (PFS).
- **Figure 1** illustrates the Kaplan Meier (KM) curves used to model treatment duration in a typical 'treat-to-progression' approach as well as a TBP scenario.
- When clinical trials demonstrate TBP, economic modellers face the challenge of appropriately incorporating extended treatment durations into both cost calculations and efficacy estimates, complicating the accurate modelling of treatment costs for economic evaluations, health technology assessment (HTA) submissions, and subsequent reimbursement decisions.[7-9]

Objective

The objective of the current study was to examine manufacturer approaches to modelling TBP and the impact of these approaches on HTA decisions by the National Institute for Health and Care Excellence (NICE) in the United Kingdom (UK).

Figure 1. Example TBP KM

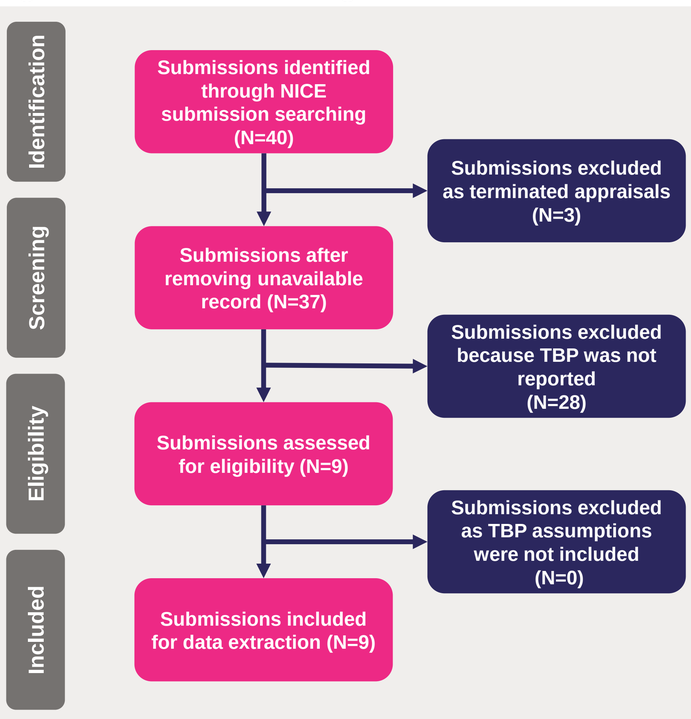


Note: hypothetical data for illustration purposes only. Abbreviations: KM, Kaplan Meier; PFS, progression-free survival; TBP, treatment beyond progression.

Methods

- A targeted review was conducted to identify PSM-based oncology NICE submissions (April 2023 to April 2024) from the NICE database.
- As per the study objective, only submissions for which trial TTD or ToT exceeded progression-free survival (PFS) were included (**Figure 2**).
- TBP modelling approaches and External Assessment Group (EAG) critique were extracted from the submissions utilising a pre-defined data extraction table.

Figure 2. PRISMA flow diagram



Abbreviations: N, number of submissions; NICE, National Institute for Health and Care Excellence; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; TBP, treatment beyond progression.

Results

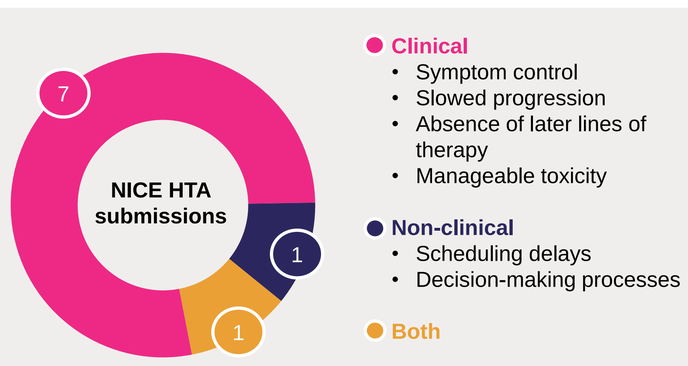
- Of 40 identified HTA submissions, nine submissions reporting TBP were included.
- All EAGs critiqued TBP assumptions, considering it a key cost-effectiveness driver and noting that it was important to match costs to the clinical benefits of extended treatment already incorporated into models (**Table 1**).
- TBP assumptions were employed in all economic models. The rationales for TBP inclusion are presented in **Figure 3**, and **Figure 4** summarises the specific assumptions applied.
- In the six submissions artificially limiting TTD/ToT, EAGs requested scenarios without capping, resulting in substantial incremental cost-effectiveness ratio increases.
- Contrastingly, in the two submissions without TBP restrictions, EAGs recommended introducing a cap to align with clinical guidelines and ensure consistency.
- Two submissions were rejected with TBP assumptions contributing to the decisions.

Table 1. Summary of TBP in NICE oncology submissions and EAG assessment

TA	TBP assumption	Stated reason for TBP	Impact of TBP assumption on ICER	EAG critique	Recommended?
TA962[10]	TTD was capped at 2 years for patients with CR	● Clinical benefits or scheduling delays or decision-making	▼	• Clinicians could continue tx beyond 2 years for partial responders (5% in trial; generalisable to UK clinical practice). • EAG requested a scenario removing the cap to check robustness. • Tx remained cost-effective without the cap.	✓
TA950[11]	TTD was capped to PFS	● Clinical benefits or manageable toxicity	▲	• Manufacturer assumed that in clinical practice no patients remain on 1L tx post progression; therefore, TTD was capped to PFS. • EAG argued to remove cap as they stated it would better reflect clinical practice and the clinical benefit of TBP observed in trial. • The manufacturer maintained their original base case and the EAG accepted the proposed cap (aligning with clinical guidelines).	✓
TA948[12]	TTD was capped to PFS	● TBP was permitted in trial to capture full potential benefit	▼	• EAG expressed concerns that by capping TTD, tx costs and benefit do not align, should be modelled as observed in trial. • Committee followed manufacturer's base case, noting TBP is unlikely in clinical practice, based on expert advice.	✓
TA944[13]	TTD = PFS PFS as proxy for TTD	● TBP permitted in trial to align with immunotherapy practices (delayed clinical benefit)	▼	• EAG argued that PFS was a poor proxy for TTD, as TTD typically exceeds PFS in clinical practice, resulting in underestimated treatment costs. • The base case was adjusted to model tx costs on TTD trial data.	✓
TA928[14]	TTD was capped to PFS	● Clinical benefits and absence of later tx lines	▲	• EAG expressed concerns that the selected extrapolation for TTD remained lower than PFS when in clinical practice some TBP would be expected, therefore the tx costs and benefit do not align. • EAG preferred a scenario that applied a different distribution without a cap to allow for some TBP, adopting a more conservative approach for the revised base-case analysis.	✗
TA911[15]	Allowed TBP	● Progressed patients often stay on tx until after two additional scans	▼	• EAG preferred a different parametric fit for TTD, arguing that the chosen fit underestimated TTD and contradicted clinical expert observation of typical 3-month post-progression treatment. • EAG scenario aligning TTD with expert input and trial post-progression data increased the ICER.	✓
TA908[16]	Allowed TBP TTD was modelled on mature KM data	● Clinical benefits ● Continuation until initiation of 3L tx	▲	• EAG contended that TTD should not exceed PFS, citing clinical practice and the product label, which specifies treatment until progression or unacceptable toxicity. • TTD was capped to PFS based on EAG recommendations.	✓
TA904[17]	Allowed TBP	● Clinical benefits and tolerability	▲	• EAG opposed TBP, arguing that ToT typically aligns with PFS, as progression usually results in treatment changes/discontinuation. • TTD was capped to PFS based on EAG recommendations.	✓
TA881[18]	TTD = PFS	● Clinical benefits and absence of later tx lines	▼	• EAG criticised the approach, arguing that it did not follow tx guidelines, and highlighting misalignment of tx costs and benefits. • An exploratory scenario by the EAG that allowed for post-progression treatment substantially increased the ICER. • The manufacturer's decision to maintain their original base case, despite these recommendations, influenced the final outcome.	✗

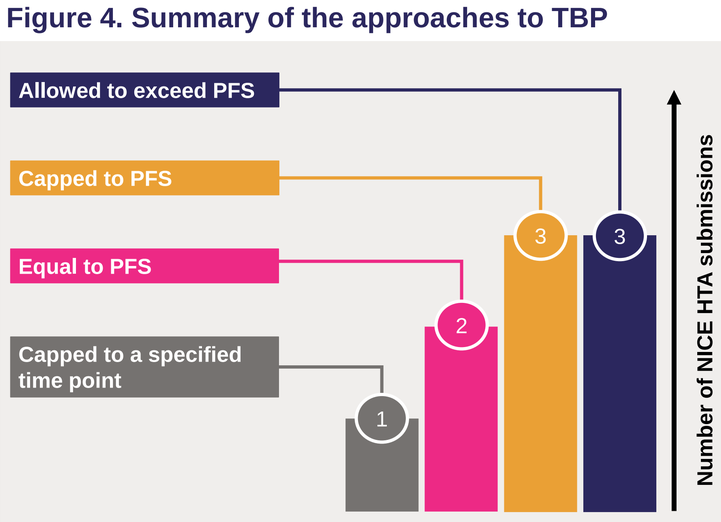
Legend: ● Clinical; ● Non-clinical; ● Both; ▼ ICER decreased; ▲ ICER increased; ✓ Recommended; ✗ Not recommended. Abbreviations: 1L, first-line; 3L, third-line; CR, complete response; EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; KM, Kaplan Meier; NICE, National Institute for Health and Care Excellence; PFS, progression-free survival; TA, technology appraisal; TBP, treatment beyond progression; ToT, time on treatment; TTD, time to treatment discontinuation; tx, treatment; UK, United Kingdom.

Figure 3. Rationales for TBP inclusion



Abbreviations: HTA, health technology appraisal; TBP, treatment beyond progression.

Figure 4. Summary of the approaches to TBP



Abbreviations: PFS, progression-free survival; TBP, treatment beyond progression.

Conclusions

- Correctly incorporating the cost and efficacy impact of TBP is key for economic evaluation to avoid bias in treatment duration estimates.
- There is no single accepted approach and guidance on the approach is context specific, depending on factors such as the clinical setting, line of therapy, and available alternative treatments.
- Guidance from NICE on TBP in modelling would be beneficial. In its absence, manufacturers should consider the clinical context, seek clinical advice on expected real-world use, consider precedent, and explore scenarios with and without capping.

References

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Disclosures

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