Assessing the implications of the NICE budget impact test: how many oncology regimens will be affected and what will be the impact on patient outcomes?

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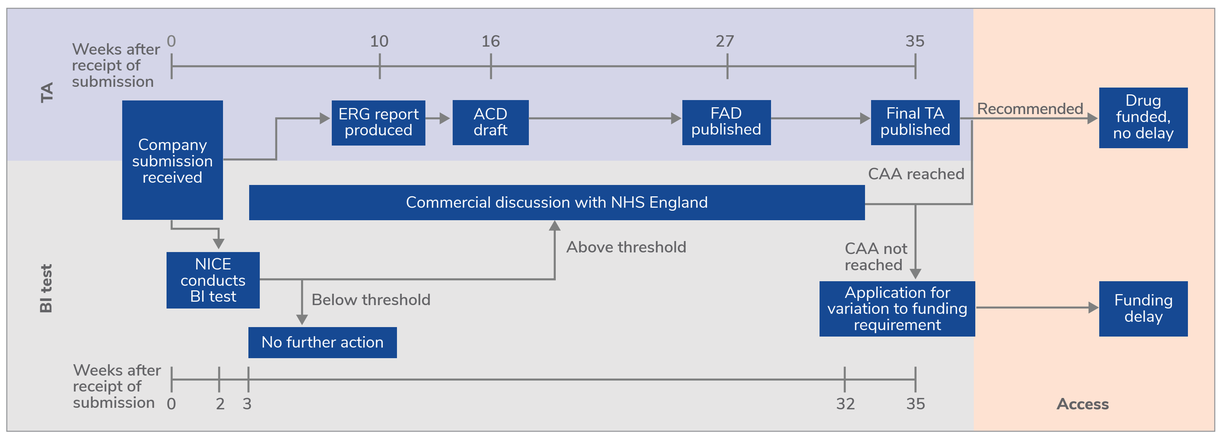
Introduction

- In response to increasing funding pressures on the UK National Health Service (NHS), the National Institute for Health and Care Excellence (NICE) introduced the budget impact (BI) test for technology appraisal (TA) and Highly Specialised Technology (HST) programs in April 2017. The test determines whether action needs to be taken to mitigate the impact of funding a technology on the rest of the NHS (1).
- A technology fails the test if the BI is expected to exceed £20 mn in any of the first 3 years of use, triggering commercial discussions between NHS England and the manufacturer to manage the net BI (1). These discussions take place in parallel with the NICE TA (see Figure 1) but are not taken into account for the cost-effectiveness assessment of the technology (2).
- If an agreement does not result in a BI of less than £20 mn per year in each of the first 3 years of use, NHS England may request consideration of a longer time to implement the statutory funding requirement from NICE, thereby delaying reimbursement by up to 3 years (1-3).
- This has raised concerns that access to treatments with the potential to provide clinical benefit to large numbers of patients may be delayed (4).

Figure 1: Timing of TA and BI test processes



Based on (2) and (5)
ACD, appraisal consultation document; BI, budget impact; CAA, commercial access agreement; ERG, evidence review group; FAD, final appraisal determination; TA, technology appraisal

Objective

- This study aimed to identify whether oncology regimens assessed in the last year (before the introduction of the test) would pass the new BI test, and to estimate the potential impact on patient outcomes of delays in the funding of treatments that fail the test.

Methods

- TAs of oncology drugs launched in the UK with final guidance documentation published between May 2016 and May 2017 were identified. TAs were excluded if they were re-assessments.
- Where available, BI data were extracted from the submission documents for TAs where routine funding was recommended by NICE.
- The number of oncology regimens with a BI of more than £20 mn (i.e., those that would fail the BI test) was then determined.
- For TAs that would have failed the BI test, projections of the eligible patient population were extracted from the company submission document.
- To estimate the potential impact on patients of delays in funding, data on survival gains were extracted from the company submission documents or pivotal trial publications.
- The potential number of additional deaths due to delays in funding was then calculated for a number of scenarios based on assumptions about the length of the delay, the proportion of patients who would be eligible to receive the new treatment, and survival gains.
- In addition, the following assumptions were made in all scenarios:
  - All eligible patients receive treatment from the day of the NICE recommendation onwards.
  - All patients receive either the new therapy or the trial comparator. This is unlikely to reflect clinical practice, where patients receive a variety of treatment options.
  - The market share of a treatment applies from the date of the NICE recommendation and does not change over time.

Results

Calculating the proportion of drugs that would fail the BI test

- Eighteen relevant TAs were identified and routine funding was recommended by NICE in 13 of these (see Table 1).
- Among these 13 recommended treatments, BI data were marked as confidential in four TAs; of the remaining nine treatments, eight had a BI of less than £20 mn and would therefore pass the BI test. The remaining one treatment (11% of all treatments included in he analysis) would fail the BI test.
- This treatment, nivolumab combined with ipilimumab for advanced melanoma (TA 400), was estimated to have a BI of approximately £12.1 mn in 2016 (based on list prices), increasing to approximately £26.9 mn by 2018. Even assuming a patient access scheme discount of 25% on the drug cost of the combination, the BI was still estimated to be more than £20 mn in 2018.

Table 1: TAs of oncology drugs launched in the UK with final guidance documentation published between May 2016 and May 2017 and recommended for funding by the NHS

Drug	Indication	Estimated BI before PAS[a]	Likely to pass BI test
Pembrolizumab (Keytruda) TA 428	Locally advanced or metastatic PD-L1+ NSCLC in adults who have had ≥1 chemotherapy (and targeted treatment if they have an EGFR+ or ALK+ tumor)	Year 1: £0.8 mn Year 2: £4.7 mn Year 3: £4.6 mn	✓
Ibrutinib (Imbruvica) TA 429	CLL in adults who have had ≥1 prior therapy, or who have a 17p deletion or TP53 mutation, and in whom chemo-immunotherapy is unsuitable	Year 1: £0.3 mn Year 2: £0.4 mn Year 3: £0.5 mn	✓
Pertuzumab (Perjeta) + trastuzumab (Herceptin) + chemotherapy TA 424	In combination with trastuzumab and chemotherapy for the neoadjuvant treatment of adults with HER2+locally advanced, inflammatory or early-stage breast cancer at high risk of recurrence	Year 1: £5.0 mn Year 2: £6.6 mn Year 3: £8.3 mn	✓
Nivolumab (Opdivo) TA 417	Previously treated advanced renal cell carcinoma in adults	Costs confidential	–
Osimertinib (Tagrisso) TA 416	Locally advanced or metastatic EGFR T790M+ NSCLC in adults whose disease has progressed after first-line treatment with an EGFR TKI (use within the CDF)	Costs confidential	–
Crizotinib (Xalkori) TA 406	Untreated ALK+ advanced NSCLC in adults	Year 1: £5.1 mn	✓
Pegaspargase (Oncaspar) TA 408	As part of antineoplastic combination therapy, for untreated newly diagnosed ALL in children, young people, and adults	Year 1: £0.0 mn Year 2: £0.0 mn Year 3: £0.0 mn	✓
Talimogene laherparepvec (Imlygic) TA 410	Unresectable, regionally or distantly metastatic (Stage IIIB, IIIC, or IVM1a) melanoma in adults	Costs confidential	–
Degarelix (Firmagon) TA 404	Advanced hormone-dependent prostate cancer in people with spinal metastases	Year 1: £0.2 mn Year 2: £0.0 mn Year 3: -£0.1 mn	✓
Trifluridine–tipiracil (Lonsurf) TA 405	Metastatic colorectal cancer in adults who have had previous treatment	Year 1: £3.2 mn Year 2: £6.5 mn Year 3: £9.4 mn	✓
Nivolumab (Opdivo) + ipilimumab (Yervoy) TA 400	In combination with ipilimumab for treating advanced (unresectable or metastatic) melanoma in adults	Year 1: 12.1 mn Year 2: 22.1 mn Year 3: 26.9 mn	×
Ceritinib (Zykadia) TA 395	Advanced ALK+ NSCLC in adults who have previously received crizotinib	Year 1: £1.3 mn Year 2: £1.4 mn Year 3: £1.4 mn	✓
Trametinib (Mekinist) + dabrafenib (Tafinlar) TA 396	In combination with dabrafenib for treating unresectable or metastatic melanoma in adults with a BRAF V600 mutation	Costs confidential	–

ALK, anaplastic lymphoma kinase; ALL, acute lymphoblastic leukemia; BRAF, v-Raf murine sarcoma viral oncogene homolog B1; CDF, Cancer Drugs Fund; CLL, chronic lymphocytic leukemia; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; NSCLC, non-small cell lung cancer; PD-L1, programmed cell death ligand 1; TKI, tyrosine kinase inhibitor
[a]A PAS was proposed for all treatments but the discount was confidential; therefore, the BI reported is based on list prices without a PAS for all treatments except trifluridine–tipiracil (Lonsurf), where the PAS discount was not confidential.
Source: TAs were identified from (6)

Potential impact of delays to funding on patient outcomes

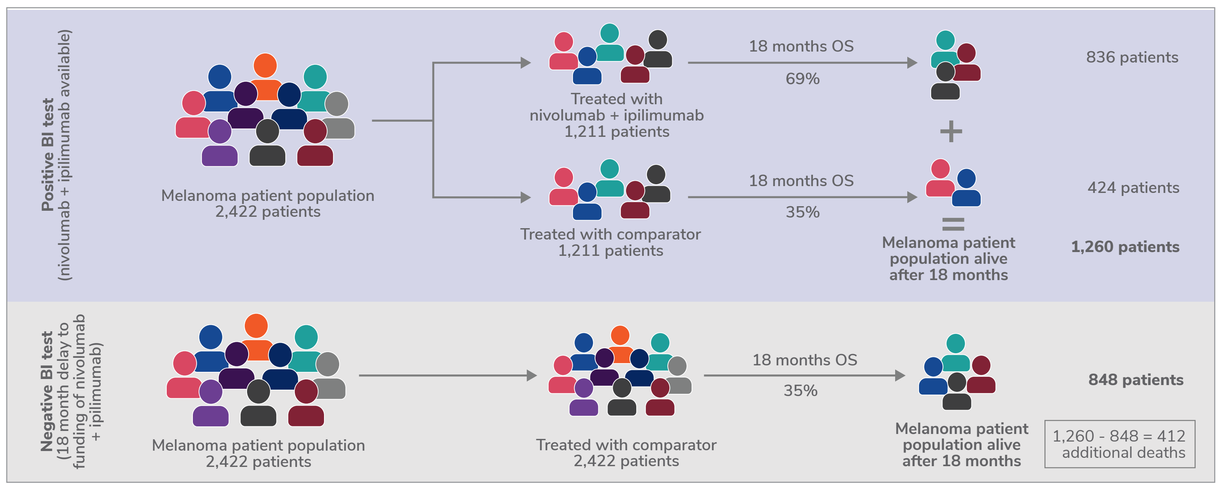
- We assessed the potential impact of 18 and 24 month delays in funding for the one treatment that failed the BI test (nivolumab in combination with ipilimumab for advanced melanoma), assuming that the delay would apply from the time of publication of the TA (July 2016).
- According to the evidence submitted by the company, the combination provides an 18 month survival gain of 34% over ipilimumab monotherapy. More recent publications suggested that a 24 month survival gain of 5–19% compared with ipilimumab or nivolumab monotherapy could be achieved (7–9) (Table 2).

Table 2: Survival gains reported for nivolumab in combination with ipilimumab

Study	Landmark OS	Combination treatment	Comparator		Survival gain for new treatment
CheckMate-069 (7)	18 months	69%	35%	Ipilimumab pooled analysis	34%
CheckMate-069 (8)	24 months	64%	54%	Ipilimumab monotherapy	10%
CheckMate-067 (9)	24 months	64%	59%	Nivolumab monotherapy	5%
			45%	Ipilimumab monotherapy	19%

- The estimated patient population eligible for treatment with the combination was 2,422 patients over 18 months, or 3,268 over 24 months (7).
- Assuming that 50% of patients with advanced melanoma would receive nivolumab in combination with ipilimumab after the NICE recommendation, 1,211 patients would benefit from the overall survival gain over 18 months, and 1,634 patients over 24 months.
- The delay in funding due to failing the BI test could therefore result in 82–412 additional deaths (see Figure 2 for illustrative calculation).

Figure 2: Illustrative calculations of the impact of failing the BI test on patient survival



Calculations are based on an 18 month delay to funding and assuming 50% of patients would be treated with the combination.

- The impact and number of additional deaths remained considerable even when it was assumed that a smaller proportion of patients would receive the combination (see Table 3).

Table 3: Additional deaths expected due to delays in funding nivolumab and ipilimumab

Delay	Proportion of eligible patients receiving nivolumab in combination with ipilimumab		
	10%	25%	50%
18 months	82	206	412
24 months	16–62	41–155	82–310

The range for a 24 month delay is based on varying estimates of survival gains from CheckMate-069 and CheckMate-067 studies

Discussion and conclusions

- The findings of the analysis are limited by the small number of assessments that would fail the BI test. However, our analysis suggests that delays in funding due to a failed test will have a substantial impact on patient outcomes and even result in additional deaths.
- All TA and HST programs are expected to be subject to the BI test, so the appraisal process for a substantial number of technologies will be affected.
- It is expected that the result of the BI test will be shared only with the submitting company. The outcome will not be in the public domain, and therefore the process may not be transparent.
- Companies are encouraged to approach NHS England at the earliest opportunity to mitigate any risk of delays in funding.
- NICE and the NHS plan to review the impact of the application of the BI test in 2020 (1).

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