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A review of differences in decision-making across NICE health technology assessments of nivolumab

JA Horscroft[1], J Casson[1], W Sullivan[1], D Ntais[2], C Kiff[2], D Tyas[2]

[1], BresMed Health Solutions Ltd, Sheffield, UK; [2], Bristol-Myers Squibb Pharmaceuticals Ltd, Uxbridge, UK

Background

A consistent approach to reimbursement decision-making at the National Institute for Health and Care Excellence (NICE) would add clarity for manufacturers developing submission materials and reduce the need for methodological adjustments during technology appraisal (TA). Cancer immunotherapies such as nivolumab present key challenges to decision-makers, including multi-indication licenses. The basic molecular biology and mode of action of nivolumab is the same regardless of tumour; a convergence in some assumptions for TAs and a reduction in uncertainty over time can be expected. Nivolumab has now been assessed by NICE in 10 different single technology appraisals (STAs), which provides the opportunity to assess if consistent approaches have been adopted across appraisals.

Objective

To explore differences in decision-making approaches across 10 completed NICE appraisals of nivolumab.

Methods

- Publicly available documents from 10 completed NICE STAs, available via nice.org.uk, were reviewed to identify and synthesise key themes.

Results

Table 1. Summary of appraisals reviewed

Code	Indication	Drug	Line of therapy	Other information	Guidance published	Result
TA384	Melanoma	NIVO	First line	Advanced (unresectable or metastatic)	Feb 2016	BLC
TA400	Melanoma	NIVO + IPI	First line	Advanced (unresectable or metastatic)	Jul 2016	BLC
TA417	RCC	NIVO	PT	–	Nov 2016	BLC
TA462	Hodgkin lymphoma	NIVO	PT	Relapsed or refractory classical Hodgkin lymphoma, after autologous SCT and treatment with brentuximab vedotin	Jul 2017	BLC
TA483	NSCLC	NIVO	PT	Squamous	Nov 2017	CDF
TA484	NSCLC	NIVO	PT	Non-squamous	Nov 2017	CDF
TA490	Head and neck cancer	NIVO	PT	Squamous cell carcinoma after platinum-based chemotherapy	Nov 2017	CDF
TA530	Urothelial cancer	NIVO	PT	Locally advanced unresectable or metastatic after platinum-containing chemotherapy	Jul 2018	Rejected
TA558	Melanoma	NIVO	Adjuvant	Completely resected melanoma with lymph node involvement or metastatic disease	Jan 2019	CDF
TA581	RCC	NIVO + IPI	First line	Adults with untreated advanced renal cell carcinoma that is intermediate or poor risk as defined in the IMDC	May 2019	CDF

Key: BLC, baseline commissioning; CDF, Cancer Drugs Fund; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; IPI, ipilimumab; NIVO, nivolumab; NSCLC, non-small cell lung cancer; PT, previously treated; RCC, renal cell carcinoma; SCT, stem cell transplantation; TA, technology appraisal.

Key: ●, accepted via baseline commissioning; ●, accepted via Cancer Drugs Fund; ●, rejected

Table 1 summarises some key features of each completed nivolumab STA, and illustrates the trend towards Cancer Drugs Fund (CDF) versus baseline commissioning recommendations following the re-launch of the CDF in 2016, further highlighted in the flow diagram immediately above.

Though not shown in Table 1, typical for oncology STAs, long-term treatment effect uncertainty was a theme across STAs. Sub-topics included the selection of parametric survival models, treatment (effect) waning assumptions and long-term immunotherapeutic survival assumptions.

Parametric survival analysis methods

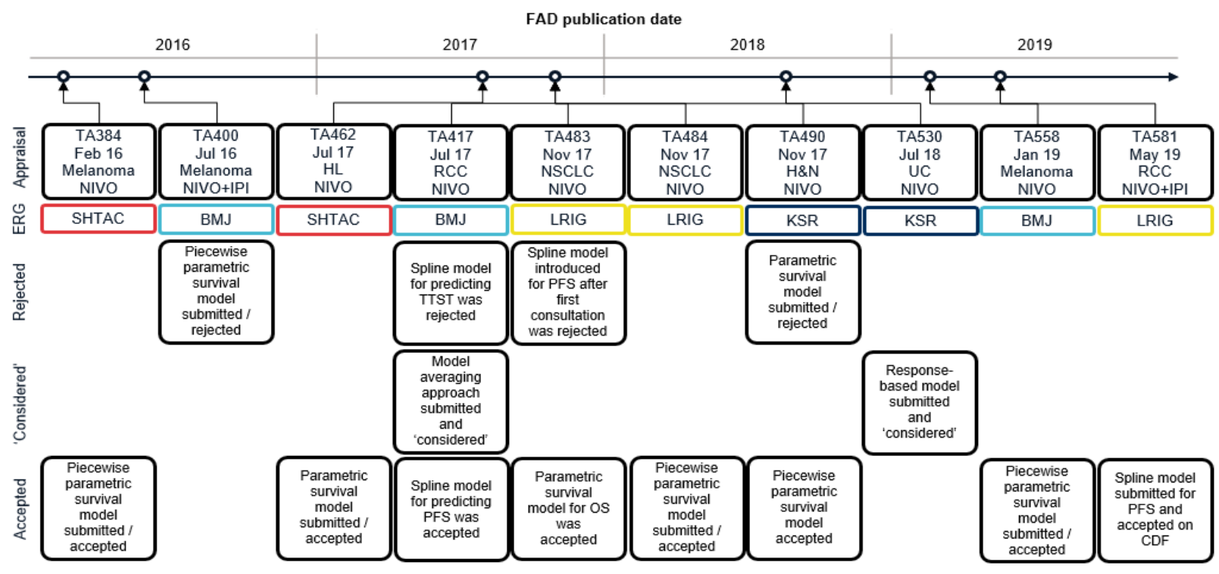
- Table 2 describes the proposed and accepted methods for the reviewed TAs. 'Standard' parametric extrapolations (Gompertz, Weibull, lognormal, loglogistic, exponential or generalized gamma models for time-to-event extrapolations) were accepted by Committees for survival extrapolations in Hodgkin lymphoma and squamous NSCLC (e.g. TA462, TA483); however, they were deemed inappropriate for immunotherapies in the head and neck cancer appraisal (TA490).
- In some cases, the Committee was willing to consider alternative techniques in its decision making, such as spline and piecewise parametric models, and in one case (TA417) an assumption that post-nivolumab survival may be similar to the general population (i.e. that some patients were effectively cured).
- Figure 1 shows similar data to Table 2, but illustrating trends over time. Acceptance of 'non-standard' modelling techniques has generally increased over time, potentially due to a developing understanding of the immunotherapeutic effect and/or the introduction of the updated CDF, although Committees still rarely accept the results of 'non-standard' approaches outright. A methodology timeline is presented above.
- There were no clear trends in the influence of Committees or Evidence Review Groups (ERGs) on the acceptance or rejection of specific approaches, other than Liverpool (LRiG) ERG illustrating their apparent preference for exponential assumptions for extrapolations.
- There seems little evidence that NICE are taking a holistic and knowledge building approach to survival assumptions for nivolumab appraisals as pan-indication clinical evidence grows.

Table 2. Parametric survival analysis methods proposed and accepted

Appraisal	• Committee • ERG	Proposed and accepted methodology for survival analysis
TA384: NIVO for advanced melanoma	• A • SHTAC	**TTP:** Piecewise KM data + Gompertz proposed and accepted
		pre-PS: Log-normal for 3 years before switching to long-term OS data
		post-PS: Log-logistic proposed and accepted
TA400: NIVO + IPI for advanced melanoma	• A • BMJ	**TTP:** Piecewise KM data + log-normal proposed and unchallenged
		post-PS: Log-logistic based on RCT for 3 years, then switch to long-term OS data proposed, extrapolation based on RCT data preferred
		pre-PS: Assumed equal to general population; adapted but accepted
TA558: Adjuvant NIVO for resected melanoma	• A • BMJ	**OS*:** GG proposed, Committee noted uncertainty due to data immaturity and OS benefit vs. IPI was removed
		RFS*: Piecewise KM/Log-logistic proposed; AJCC data used from 10 years onwards
TA417: NIVO for previously treated advanced RCC	• B • BMJ	**OS:** GG proposed and accepted
		PFS: Spline model with 2 knots proposed and accepted
		TTST: Spline model with 2 knots proposed, log normal or GG preferred
TA581: NIVO + IPI for untreated advanced RCC	• B • LRiG	**OS:** Log normal proposed and considered along with exponential
		PFS: Cubic spline model proposed and accepted (minimal effect on ICER)
		TTST: Gamma proposed and accepted (minimal effect on ICER)
TA462: NIVO for relapsed, refractory Hodgkin lymphoma	• C • SHTAC	**OS:** Weibull (NIVO) and exponential (SoC) proposed and accepted
		PFS: Log-normal (NIVO) and exponential (SoC) proposed and accepted
TA483: NIVO for previously treated squamous NSCLC	• C • LRiG	**OS:** Log-logistic proposed initially; exponential preferred; GG proposed after consultation and accepted
		PFS: Spline model with 2 knots proposed after first consultation; piecewise exponential accepted
TA484: NIVO for previously treated non-squamous NSCLC	• C • LRiG	**OS:** Piecewise KM data (12 months) + GG proposed initially, piecewise KM data (24 mo) + log-normal proposed after consultation, piecewise KM data + exponential preferred
		PFS: GG based on TTST proposed, exponential based on PFS preferred
TA530: NIVO for previously treated UC (locally advanced or worse)	• D • KSR	**OS:** Piecewise GG for responders and non-responders proposed and considered alongside standard GG
		PFS: Piecewise GG for responders and non-responders proposed and considered alongside standard GG
TA490: NIVO for previously treated squamous head and neck carcinoma	• D • KSR	**OS:** Log-normal proposed, piece-wise log-normal accepted instead of ERG's piecewise exponential (due to crossing curves)
		PFS: GG proposed and accepted with noted uncertainty
		TTST: GG proposed and accepted with noted uncertainty

Key: AJCC, American Joint Committee on Cancer; BMJ, British Medical Journal; ERG, Evidence Review Group; GG, generalized gamma; ICER, incremental cost-effectiveness ratio; IPI, ipilimumab; KM, Kaplan–Meier; KSR, Kleijnen Systematic Reviews; LRiG, Liverpool Reviews and Implementation Group; NIVO, nivolumab; NSCLC, non-small-cell lung cancer; OS, overall survival; PFS, progression-free survival; pre-/post-PS, pre-/post-progression survival; PSM, partitioned survival model; RFS, recurrence-free survival; RCC, renal cell carcinoma; RCT, randomized controlled trial; SA, scenario analysis; SHTAC, Southampton Health Technology Assessments Centre; SoC, standard of care; TA, technology appraisal; TTP, time-to-progression; TTST, time-to-stopping-treatment; UC, urothelial cancer; * applies only to PSM.

Figure 1. Changes in parametric survival methods over time



Key: BMJ, British Medical Journal; CDF, Cancer Drugs Fund; HL, Hodgkin lymphoma; IPI, ipilimumab; KSR, Kleijnen Systematic Reviews; LRIG, Liverpool Reviews and Implementation Group; NIVO, nivolumab; OS, overall survival; PFS, progression-free survival; RCC, renal cell carcinoma; SHTAC, Southampton Health Technology Assessments Centre; TTST, time to stopping treatment; UC, urothelial cancer; FAD, final appraisal document; NSCLC, non-small cell lung cancer; TA, technology appraisal; H&N, head and neck.

Treatment (effect) waning assumptions

- Formally incorporating an assumption that treatment effect (upon health outcomes) wanes over time is a typically cautious approach in an investment decision, but may be inappropriate for some nivolumab patients if a post-treatment immunotherapeutic survival benefit is plausible. Appropriate assumptions will vary by indication, based on the underlying biology of disease.
- Across the 10 nivolumab STAs, treatment waning assumptions incorporated into the base case have varied, from a constant treatment effect to waning of treatment effect after 3 years.
- The assumptions regarding the incorporation of treatment waning into analyses and the length of the waning period have often been challenged by the ERG and Committee, sometimes in tandem with treatment stopping rule assumptions. In TA581, the most recently completed of the 10 STAs, the committee rejected stopping rule assumptions proposed by the company. This may be due to differences in ERGs or a trend over time, but may also be explained by appropriateness given underlying biology.

Table 3. Treatment waning assumptions proposed and accepted

Appraisal	• Committee • ERG	Was waning of treatment effect after discontinuation incorporated into the company's base case?	Was waning of treatment effect after discontinuation incorporated into the Committee's accepted base case?
TA384: NIVO for advanced melanoma	• A • SHTAC	No	No
TA400: NIVO+IPI for advanced melanoma	• A • BMJ	No	No
TA558: Adjuvant NIVO for resected melanoma	• A • BMJ	No	No
TA417: NIVO for previously treated advanced RCC	• B • BMJ	No	No
TA581: NIVO+IPI for untreated advanced RCC	• B • LRiG	Initial submission: no; revised model: yes, after 3 years	Stopping rule was rejected
TA462: NIVO for relapsed, refractory Hodgkin lymphoma	• C • SHTAC	Not relevant due to focus on SCT access	
TA483: NIVO for previously treated squamous NSCLC	• C • LRiG	No	Yes, after 3 years
TA484: NIVO for previously treated non-squamous NSCLC	• C • LRiG	No	Yes, after 3 years
TA530: NIVO for previously treated UC (locally advanced or worse)	• D • KSR	No (waning after 3 and 5 years explored in SA)	Rejection of lifetime continued treatment effect
TA490: NIVO for previously treated squamous head and neck carcinoma	• D • KSR	No (waning after 5 and 10 years explored in SA)	Yes, after 5 years

Key: BMJ, British Medical Journal; ERG, Evidence Review Group; IPI, ipilimumab; KSR, Kleijnen Systematic Reviews; LRiG, Liverpool Reviews and Implementation Group; NIVO, nivolumab; NSCLC, non-small-cell lung cancer; RCC, renal cell carcinoma; SA, scenario analysis; SCT, stem cell transplant; SHTAC, Southampton Health Technology Assessments Centre; TA, technology appraisal; UC, urothelial cancer.

Immunotherapeutic survival assumptions

- A summary of immunotherapeutic survival assumptions is presented in Table 4. Overall, NICE has been reluctant to accept the notion that nivolumab has the potential to restore some patients to near-normal survival in the absence of long-term indication-specific evidence, as seen in melanoma, and there is only scant evidence of a cumulative knowledge building approach across indications.
- In the first appraisal of nivolumab for melanoma (TA384), 10-year registry data for overall survival from 5 years onwards was accepted as supportive that nivolumab can lead to near-normal survival for some.
- In 2 further STAs, potential restoration to near-normal survival was explicitly considered by decision-makers, though decision-making assumptions are not clear. In renal cell carcinoma (TA417), the Committee were 'willing to consider' a model that predicted nivolumab monotherapy would restore survival for previously treated patients alive after 5 years with a 50% probability. In squamous cell carcinoma of the head and neck (TA490), the Committee assumed that nivolumab's treatment effect on survival would last up to 5 years, but felt it was implausible that the risk of death would become similar to that of the general population. On the other hand, the Committee rejected an exponential extrapolation on clinical advice, on the grounds that a survival 'plateau' has been observed in other indications.
- In the remaining 7 nivolumab STAs, ERGs and Committees have rejected modelling assumptions that were consistent with the notion of nivolumab restoring survival to near-normal levels for some patients.

Table 4. Was the Committee base case consistent with the notion that nivolumab can restore some patients to near-normal survival?

	Melanoma		RCC		HL	NSCLC		UC	Head & neck
	Advanced	*Resected, adjuvant*	*Advanced, PT*	*Advanced, TN*	*RR*	*Squamous PT*	*Non-squamous, PT*	*Locally advanced or worse, PT*	*Squamous PT*
NIVO	**TA384.** Yes	**TA558.** Not relevant	**TA417.** Not clear	NA	**TA462.** Not relevant	**TA483.** No	**TA484.** No	**TA530.** No	**TA490.** Not clear
NIVO + IPI	**TA400.** No	NA	NA	**TA581.** No	NA	NA	NA	NA	NA

Key: ●, yes; ●, not clear; ●, no; ●, not relevant; ●, no appraisal; HL, Hodgkin lymphoma; IPI, ipilimumab; NA, no appraisal; NIVO, nivolumab; NSCLC, non-small-cell lung cancer; PT, previously treated; RCC, renal cell carcinoma; RR, relapsed refractory; TA, technology appraisal; TN, treatment-naïve; UC, urothelial cancer.

Discussion

From this review of nivolumab STAs, we have found that NICE decision-makers have generally considered each indication in isolation, in line with process but at the cost of growing pan-indication evidence. There is some evidence that committees have sought to consider assumptions in previous nivolumab STAs, but far from a consistent approach, and this may be at the cost of gold-standard evidence-based decision making.

Since the 2016 relaunch of the CDF, there has been a clear trend towards CDF versus routine use recommendations for emerging nivolumab indications. On the one hand, the new CDF provides a useful option for further data collection under uncertainty; on the other hand, more certainty around the value of nivolumab across indications may indicate that routine use recommendations are more likely as knowledge builds, if NICE were incorporating pan-indication nivolumab evidence into each decision.

Different decision-maker attitudes to the innovative nature of the intervention and high unmet need across nivolumab STAs should be expected given existing treatment and disease pathway differences across indications.

There is suggestive evidence of correlation between base case modelling assumptions and the involvement of certain ERGs. For example, the Liverpool Reviews and Implementation Group (LRiG) more frequently proposed exponential models for the survival extrapolation than other ERGs. Moreover, the assumption that treatment effect does not wane following discontinuation was accepted in all appraisals involving the Southampton Health Technology Assessments Centre (SHTAC) and the British Medical Journal Technology Assessment Group (BMJ-TAG), and rejected in all appraisals involving LRiG and Kleijnen Systematic Reviews (KSR). Whether such differences are justified by the principle of ERG independence is debatable.

The generalisability of this review is limited by its focus on nivolumab STAs only. Considering other STAs of immunotherapy products may draw out different trends, and this is a possible area of future research.

Recommendations: While we recognize that the freedom for independent thought of ERGs and Committees is inherently valuable, this review leads us to the following suggestions:

1. Further guidance for manufacturers for systematic and consistent incorporation of pan-indication evidence into STA dossier submissions
2. Further guidance and standards for ERGs and committees, for consistent consideration of pan-indication evidence

References

1. TA384: Nivolumab for treating advanced (unresectable or metastatic) melanoma; https://www.nice.org.uk/guidance/ta384
2. TA400: Nivolumab in combination with ipilimumab for treating advanced melanoma; https://www.nice.org.uk/guidance/ta400
3. TA558: Nivolumab for adjuvant treatment of completely resected melanoma with lymph node involvement or metastatic disease; https://www.nice.org.uk/guidance/TA558
4. TA417: Nivolumab for previously treated advanced renal cell carcinoma; https://www.nice.org.uk/guidance/ta417
5. TA581: Nivolumab with ipilimumab for untreated advanced renal cell carcinoma; https://www.nice.org.uk/guidance/ta581
6. TA462: Nivolumab for treating relapsed or refractory classical Hodgkin lymphoma; https://www.nice.org.uk/guidance/ta462
7. TA483: Nivolumab for previously treated squamous non-small-cell lung cancer; https://www.nice.org.uk/guidance/ta483
8. TA484: Nivolumab for previously treated non-squamous non-small-cell lung cancer; https://www.nice.org.uk/guidance/ta484
9. TA530: Nivolumab for treating locally advanced unresectable or metastatic urothelial cancer after platinum-containing chemotherapy; https://www.nice.org.uk/guidance/ta530
10. TA490: NIVO for previously treated squamous head and neck carcinoma; https://www.nice.org.uk/guidance/ta490

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Email: christopher.kiff@bms.com