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Higher Termination Rates and Survival Trade-offs: A 10-Year Review of NICE Appraisals of Oncology Combination Therapies

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Objective

- Global valuation of oncology combination therapies* is impeded by the challenge of allocating value between components. This study aimed to quantify the proportion of oncology therapies terminated during the HTA appraisal process in England and estimate the potential survival impact for patients when therapies are not reimbursed

***Combination therapies:** Interventions using 2 or more targeted therapies together. **Non-combination therapies:** Interventions using 1 or no targeted therapies (may include chemotherapy).

Conclusions

- Oncology combination therapies are associated with higher termination rates in NICE appraisals compared to non-combination therapies, despite showing survival benefits
- These findings underscore the need for more flexible and innovative pricing models to ensure the cost-effectiveness and viability of combination therapies within current reimbursement systems
- Our findings reinforce other studies[1] by showing that many combinations with substantial survival gains were terminated in NICE appraisals, underscoring the urgent need for more flexible value frameworks to ensure timely patient access
- These terminations can hinder patient access to therapies with demonstrated survival benefits. Further work is needed to engage with HTA bodies to understand the barriers to valuing combination therapies and to identify solutions for all stakeholders

Disclosures

Vijay Joish is an employee of Genmab, where he receives a salary, stock and stock options.

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Abbreviations

BRAF, B-Raf proto-oncogene; CLL, chronic lymphocytic leukaemia; *EGFR*, epidermal growth factor receptor gene; HTA, health technology assessment; ICER, incremental cost-effectiveness ratio; MM, multiple myeloma; N/A, not applicable; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; NR, not reached; NSCLC, non–small cell lung cancer; OS, overall survival; QALY, quality-adjusted life year; RCT, randomised controlled trial; SoC, standard of care; TA, technology appraisal; UK, United Kingdom; V600E, valine to glutamic acid at position 600 (specific mutation of the *BRAF* gene).

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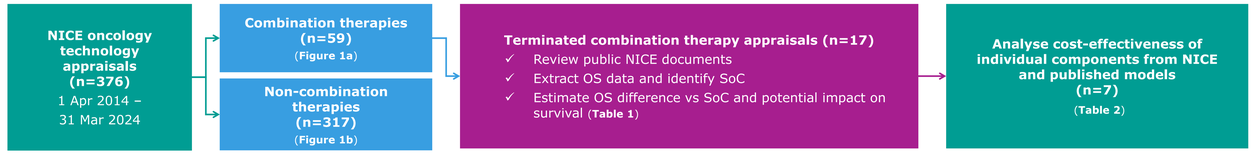
Introduction

- Recent analyses of the European oncology landscape highlight that combination therapies deliver transformative patient and health system value despite incremental benefit challenges[1]
- Oncology combination therapies face evaluation challenges in HTA including:
  - Assessment being based on standard cost-effectiveness principles, with value needing to be attributed across individual components[2]
  - Backbone therapies consuming most cost-effectiveness headroom, leaving limited remaining margin for add-ons[3,4]
  - Difficulty meeting overall cost-effectiveness thresholds
- These therapies could increase survival, but due to these known challenges, appraisals may be terminated even for therapies with proven clinical benefit, potentially limiting patient access and impacting survival
- This study examined the proportion of oncology combination therapies terminated during NICE appraisals in England over 10 years and estimated the potential survival impact of non-reimbursement

Methods

- A retrospective review of NICE oncology technology appraisals (1 April 2014 to 31 March 2024) was conducted.[5] Therapies were categorised as combination or non-combination, with outcomes recorded as recommended, not recommended, or terminated
- For terminated combination therapy appraisals, publicly available RCT publications and NICE technology appraisal documents were reviewed to identify OS data availability and comparator alignment with NHS SoC in England at the time of submission. Where available, the OS difference compared with SoC (in months) was calculated to estimate the potential survival benefit of terminated therapies
- Cost-effectiveness of the individual components (i.e., backbone and add-on) was examined for a subset of terminated combination therapies (n=7) with available OS data for both the intervention and the comparator that matched SoC. Cost-effectiveness estimates were extracted as an ICER value from NICE technology appraisals where each component was assessed for the same indication as the combination. These were compared to NICE's £20,000–£30,000/QALY threshold and additional published models were consulted to further understand the cost-effectiveness of the individual treatments



Results

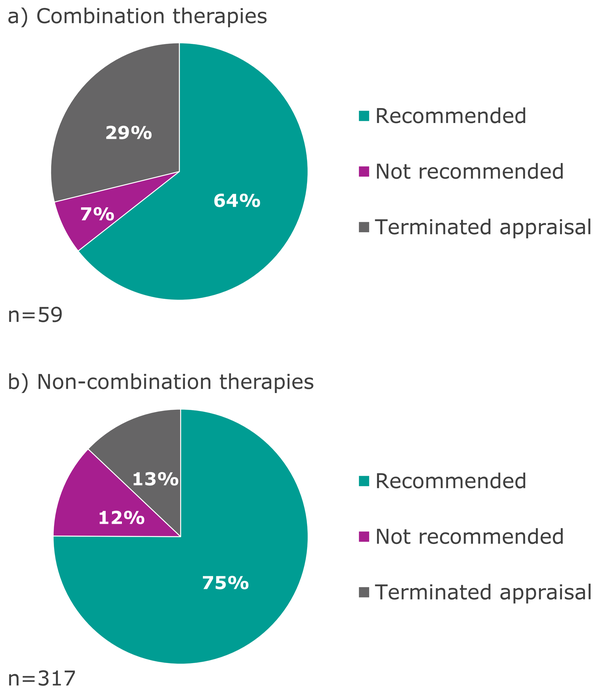
Combination therapies face higher termination risk

- Termination of combination therapies was over twice as high as for non-combinations
- Of 376 NICE oncology appraisals reviewed, 317 were for non-combination therapies and 59 for combinations (Figure 1)
- 75% of non-combination therapies were recommended, compared to only 64% of combinations

29% **Combination** oncology therapies were terminated

13% **Non-combination** oncology therapies were terminated

Figure 1. Oncology therapies appraisal recommendations



Appraisal outcomes for oncology combination (Figure 1a) and non-combination (Figure 1b) therapies published by NICE from 1 April 2014 to 31 March 2024. "Recommended" includes all positive outcomes (recommended, optimised, and recommended for the Cancer Drugs Fund).

Several combination therapies had positive survival data despite HTA appraisal terminations

- Of 17 terminated oncology combination therapies, 9 were for multiple myeloma, 4 for CLL (or small lymphocytic lymphoma), and 2 for NSCLC (Table 1)
- 7 terminated combinations had published OS data versus the SoC at time of submission, which was the combination backbone in 6 cases. These 7 combinations had an average OS gain of 12.7 months

12.7 months **Average OS gain** for 7 terminated **oncology combinations** with OS data versus SoC (range, 4.0–29.1 months). This improvement suggests **termination** is **not due to the lack of demonstrated clinical efficacy.**

Table 1. Summary of the OS and epidemiologic data of the 17 terminated NICE appraisals for oncology combination therapies

NICE TA	Terminated combination	Indication	OS[a]				Number of patients in England[d]
			Median OS intervention	Median OS comparator	Comparator was the SoC[b]	OS difference to SoC[c]	
TA434	Elotuzumab with lenalidomide and dexamethasone	Previously treated multiple myeloma	19.4	14.9	Yes	4.5	17,600[a]
TA454	Daratumumab with lenalidomide and dexamethasone	Relapsed or refractory multiple myeloma	67.6	51.8	Yes	15.8	
TA602	Pomalidomide with bortezomib and dexamethasone	Relapsed or refractory multiple myeloma	35.6	31.6	Yes	4.0	
TA603	Lenalidomide with bortezomib and dexamethasone	Untreated multiple myeloma	75.0	64.0	Yes	11.0	
TA634	Daratumumab with lenalidomide and dexamethasone	Untreated multiple myeloma	NR	N/A	N/A	-	
TA726	Daratumumab with pomalidomide and dexamethasone	Relapsed or refractory multiple myeloma	34.4	23.7	Yes	10.7	
TA727	Isatuximab with carfilzomib and dexamethasone	Relapsed or refractory multiple myeloma	NR	NR	N/A	-	
TA771	Daratumumab with bortezomib, melphalan and prednisone	Untreated multiple myeloma	82.7	53.6	Yes	29.1	
TA841	Carfilzomib with daratumumab and dexamethasone	Relapsed or refractory multiple myeloma	50.8	43.6	No	-	
TA437	Ibrutinib with bendamustine and rituximab	Relapsed or refractory CLL after systemic therapy	NR	NR	N/A	-	20,200[e]
TA469	Idelalisib with ofatumumab	CLL	20.9	19.4	No	-	
TA702	Ibrutinib with obinutuzumab	Untreated CLL and small lymphocytic lymphoma	NR	N/A	N/A	-	
TA703	Ibrutinib with rituximab	Untreated CLL	NR	NR	N/A	-	
TA564	Dabrafenib with trametinib	Advanced metastatic *BRAF* V600E mutation–positive NSCLC	17.3	N/A	N/A	-	250[f]
TA608	Ibrutinib with rituximab	Waldenstrom's macroglobulinaemia	NR	NR	N/A	-	3,200[f]
TA635	Ramucirumab with erlotinib	Untreated *EGFR* mutation–positive NSCLC	NR	NR	N/A	-	20,033[f]
TA785	Nivolumab with cabozantinib	Untreated advanced renal cell carcinoma	49.5	35.5	Yes	14.0	14,378[f]

[a]OS is expressed in months. [b]Comparator SoC status assessed only where OS data were available for both arms; N/A indicates not applicable (OS for intervention and/or comparator was not available or not reached). [c]OS difference versus SoC is the difference in median OS between the intervention and the comparator. [d]Estimated number of UK patients reflects disease prevalence. [e]Observed prevalence for people diagnosed in the UK between 1991 and 2010, based on Cancer Research UK data. [f]Estimate calculated using published incidence, disease subtypes, biomarker prevalence, stage at diagnosis, and median OS, based on data from multiple sources.

Individual components of combination therapies often exceeded or bordered NICE's cost-effectiveness thresholds

- ICERs of the components of the 7 terminated combinations with OS data exceeded or bordered NICE's cost-effectiveness threshold[6] (**Table 2**)
- Independent published models for the individual components showed mixed conclusions regarding the cost-effectiveness of the individual components
- This supports the hypothesis that the combinations are likely to have substantially exceeded payer willingness-to-pay thresholds

These findings suggest that the **barrier to reimbursing combination therapies may lie in demonstrating cost-effectiveness**, despite positive clinical outcomes

Table 2. Cost-effectiveness of components of terminated combinations when assessed as a monotherapy by NICE for the same indication

NICE TA	Individual combination component	Applies to NICE terminated combination(s)	NICE considerations		Published model(s)[c]
			ICER[a]	Relative to cost-effectiveness threshold[b]	
TA129	Bortezomib monotherapy for relapsed MM	TA602	£20,700/QALY	Within	1 ● / 2 ●[7,8]
TA427	Pomalidomide for MM previously treated with lenalidomide and bortezomib	TA726	£48,673/QALY	Below[d]	1 ● / 1 ●[9]
TA542	Cabozantinib for untreated advanced renal cell carcinoma	TA785	<£20,000/QALY	Below	1 ● / 1 ●[10]
TA586	Lenalidomide plus dexamethasone for MM after 1 treatment with bortezomib	TA434 TA454	>£30,000/QALY	Above	1 ●[11]
TA783	Daratumumab monotherapy for treating relapsed or refractory MM	TA454 TA726	<£50,000/QALY	Below[d]	1 ●[12]

The treatment is cost-effective and recommended for reimbursement by NICE ● Cost-effective ● Not cost-effective

The treatment is not cost-effective but is recommended for reimbursement by NICE ● Not mentioned

[a]Cost-effectiveness estimates were given as an ICER value and reflect the lowest estimate when multiple values were reported. Some ICERs were confidential due to patient access schemes. [b]NICE's cost-effectiveness threshold: £20,000-£30,000/QALY. [c]Number of identified cost-effectiveness models and if they explicitly mention if the treatment was or was not cost-effective. [d]NICE's cost-effectiveness threshold if end-of-life criterion was met: £50,000/QALY.