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Combination Policy – Value of Combination Treatments and the Future in Cancer Management

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BACKGROUND

- Combination regimens are becoming the mainstay of cancer treatment[1]
- There are more than 300 active clinical trials evaluating combination products in oncology in the UK alone[2], and the number of combination treatments in oncology is expected to grow significantly
- Amongst these combinations, a significant proportion include two or more branded products[2]

OBJECTIVE

- The aim of this project is to contextualise the value of combination therapies against the background of National Institute for Health and Care Excellence (NICE) frameworks relying on cost effectiveness modelling in their decision-making processes

METHODS

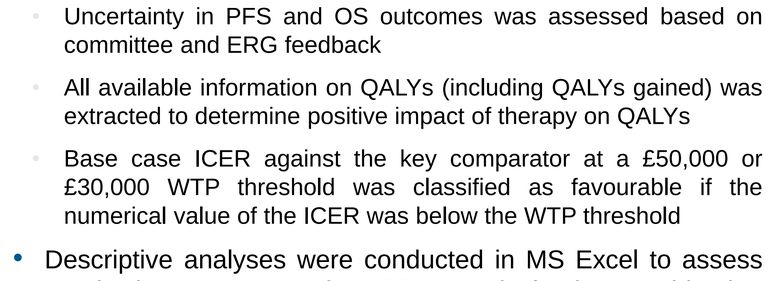
- A review of publicly available NICE health technology assessments (HTAs) involving combination oncology therapies was conducted
- All published HTAs for combination therapies between January 2017 – June 2022 were included
- The outcome of the HTA was classified using the NICE definitions a) recommended (cancer drugs fund (CDF)), b) only in Research, c) optimised, d) optimised (CDF), e) not recommended, and f) terminated appraisal
  - Optimised outcomes (optimised for license, and optimised (CDF)) are categorised as optimised
- Data was extracted from committee papers, and the final appraisal document for the following parameters:
  - Significant difference in progression free survival (PFS) and overall survival (OS), base case results vs. key comparators for quality adjusted life years (QALYs), incremental cost-effectiveness ratio (ICER) and probabilistic result from the cost-effectiveness acceptability curve (CEAC) at the pre-specified willingness to pay (WTP) threshold
  - Uncertainty in PFS and OS outcomes was assessed based on committee and ERG feedback
  - All available information on QALYs (including QALYs gained) was extracted to determine positive impact of therapy on QALYs
  - Base case ICER against the key comparator at a £50,000 or £30,000 WTP threshold was classified as favourable if the numerical value of the ICER was below the WTP threshold
- Descriptive analyses were conducted in MS Excel to assess trends in outcomes of NICE appraisals for combination therapies

RESULTS

Descriptive summary

- Between January 2017 and June 2022, a total of 195 appraisals in oncology were identified. Of these, 21.5% (n = 42) appraisals were terminated
- A third (n = 65) of all oncology appraisals were for combination therapies, of which close to a third (n = 21) were identified as terminated appraisals
- Overall, 27.7% (n = 17) appraisals received an optimised recommendation for license, and 65.6% (n = 42) received a recommendation restricted by commercial agreements.
- Over half (n = 23) of the submissions had more than 1 appraisal committee meeting
- A pattern of increasing appraisals for combination therapies in oncology was observed between 2017- 2020

Figure 1. Number of oncology appraisals for combination therapies by year



Distribution of appraisal outcomes by tumour type

- Majority (70%) of the appraisals were for solid tumour indications
- A majority (74%) of appraisals for solid tumours resulted in optimised recommendations
- Half of the appraisals for non-solid tumours resulted in terminated appraisals, whereas the other half received optimised recommendations

Figure 2. NICE outcomes for combination therapies indicated in solid tumours between January 2017-June 2022

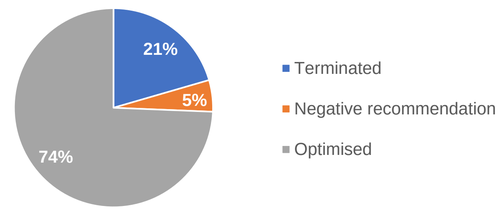
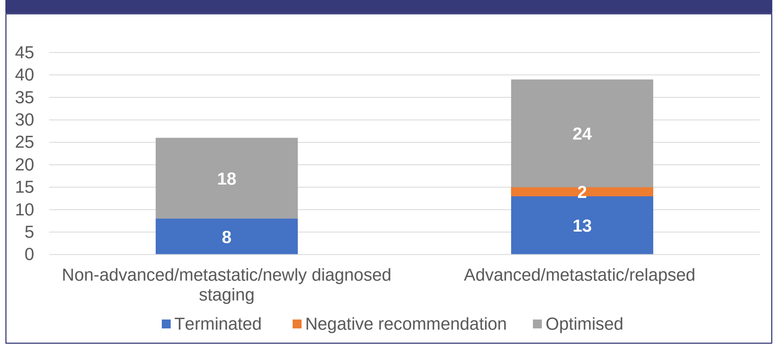


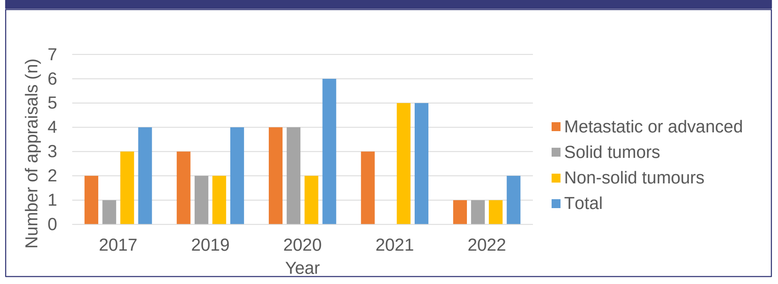
Figure 3. Appraisal outcome by advanced or metastatic disease staging



Distribution of appraisal outcomes by tumour type

- An increasing trend was observed in the terminated appraisals for combination therapies in oncology overall, solid tumours, and for the metastatic or advanced indications between 2017-2020, with the exception of 2018 where no appraisals were terminated

Figure 4. Classification of indications for terminated appraisals between January 2017-June 2022



No terminated appraisals were identified for the year 2018. As such, data for 2018 are not presented.
Metastatic or advanced category includes cancers defined as such in the title. Additionally included are cancers defined as relapsed and/or remitting.
Cancer types were classified as solid and non-solid per the definitions of solid and liquid tumours from the National Cancer Institute (NCI)

Number of appraisal committee meetings

- Over half (n = 23) of the submissions had more than 1 appraisal committee meeting
- OS, uncertainty, unfavourable base case ICERs, and probability of cost-effectiveness <75% was more frequently associated with more than 1 appraisal committee meeting
- Data immaturity was the most common reason for OS uncertainty
- More appraisals at the £50,000 WTP threshold, meeting the end-of-life criteria, were associated with more than 1 appraisal committee meeting

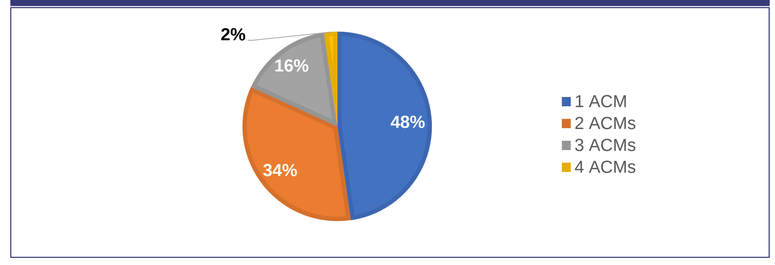
Table 1. Relationship between number of appraisal committee meetings, and uncertainty in key cost-effectiveness parameters

Parameter ‡ (n)		Number of appraisal committee meetings	
		ACM =1	ACM ≥2
Overall survival uncertainty [a]		7	15
Quality adjusted life year (QALY) [a,b]		1	1
Base case ICER	Favourable	16	5
	Unfavourable	-	8
Probability of cost-effectiveness	≤25%	-	4
	Between 25%-75%	4	4
	>75%	17	15
Willingness to pay threshold	£50,000	4	7
	£30,000	15	15

‡PFS uncertainty was not identified in the submissions, and as such the data are not included in the table
[a]Number of appraisals where the related outcome was determined uncertain
[b]QALY data was not available in 18 appraisals, the base case ICERs were not available for 15 appraisals; the probability of cost-effectiveness was not available for 24 appraisals
Probability of cost-effectiveness at a WTP threshold is included from the probabilistic sensitivity analyses results

ACM, appraisal committee meeting; PFS, progression free survival; QALY, quality adjusted life year; pCE, probability of cost effectiveness at a pre-specified WTP threshold; WTP, willingness to pay threshold

Figure 5. Frequency of multiple appraisal committee meetings (ACM) between January 2017- June 2022



Discussion

- There is evidence of a steady increase in the number of NICE appraisals for combination therapies overall. The slight decline observed in 2021 and 2022 for combinations is aligned with overall oncology appraisals
- While combination therapies make up one third of all oncology appraisals to NICE, half of the terminated oncology appraisals are made up of combination therapies
- Despite OS uncertainty, the benefit of combination therapies was clearly captured in the measure of QALYs
- A higher proportion of appraisals where cost-effectiveness thresholds are not met underwent multiple appraisal committee meetings

LIMITATIONS

- We anticipate there may be historical bias in trends seen pre- and post- the COVID pandemic. As the study captures data over a short time horizon an impact on trends is expected
- Publicly available data on terminated appraisals is limited and thus limits the scope of analyses for these appraisals
- Data on QALYs, ICERs and probability of cost effectiveness is limited, and is expected to have an impact on the generalisability of results

FUTURE RESEARCH

- To mitigate the limitations of this study, we recommend an increase in geographical scope and time horizon for these analyses as future research
- Assessment of HTA outcomes for innovative products in combinations for non-oncology indications can provide further insights into the extent of the issue

CONCLUSIONS

- **Greater flexibility is needed within existing reimbursement frameworks to assess the value of combination therapies in oncology**
- **Furthermore, the recent changes in the methods for evaluation of therapies for reimbursement in the NICE methods, brings into question the adaptability of existing frameworks to make innovative technologies for often severe and advanced cancer accessible to patients in an efficient way.**

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DISCLOSURES

This study was conducted and funded by Sanofi. PS, IG, AS,NM, AK, NJ, and RA are employees of Sanofi.

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