

HTA Assessment of Adaptive Trials for Oncology Drugs in Europe



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OBJECTIVES

This study aimed to assess whether adaptive trial designs (i.e., allowing design modifications following trial initiation) have contributed to the regulatory approval of oncology therapies and positive HTA recommendations.



RESULTS

The PubMed search returned 818 results, of which 90 articles were confirmed to report data from either Basket, Umbrella or Platform trials, corresponding to 52 unique adaptive design trials. Further grey literature research identified 12 additional adaptive design clinical trials.

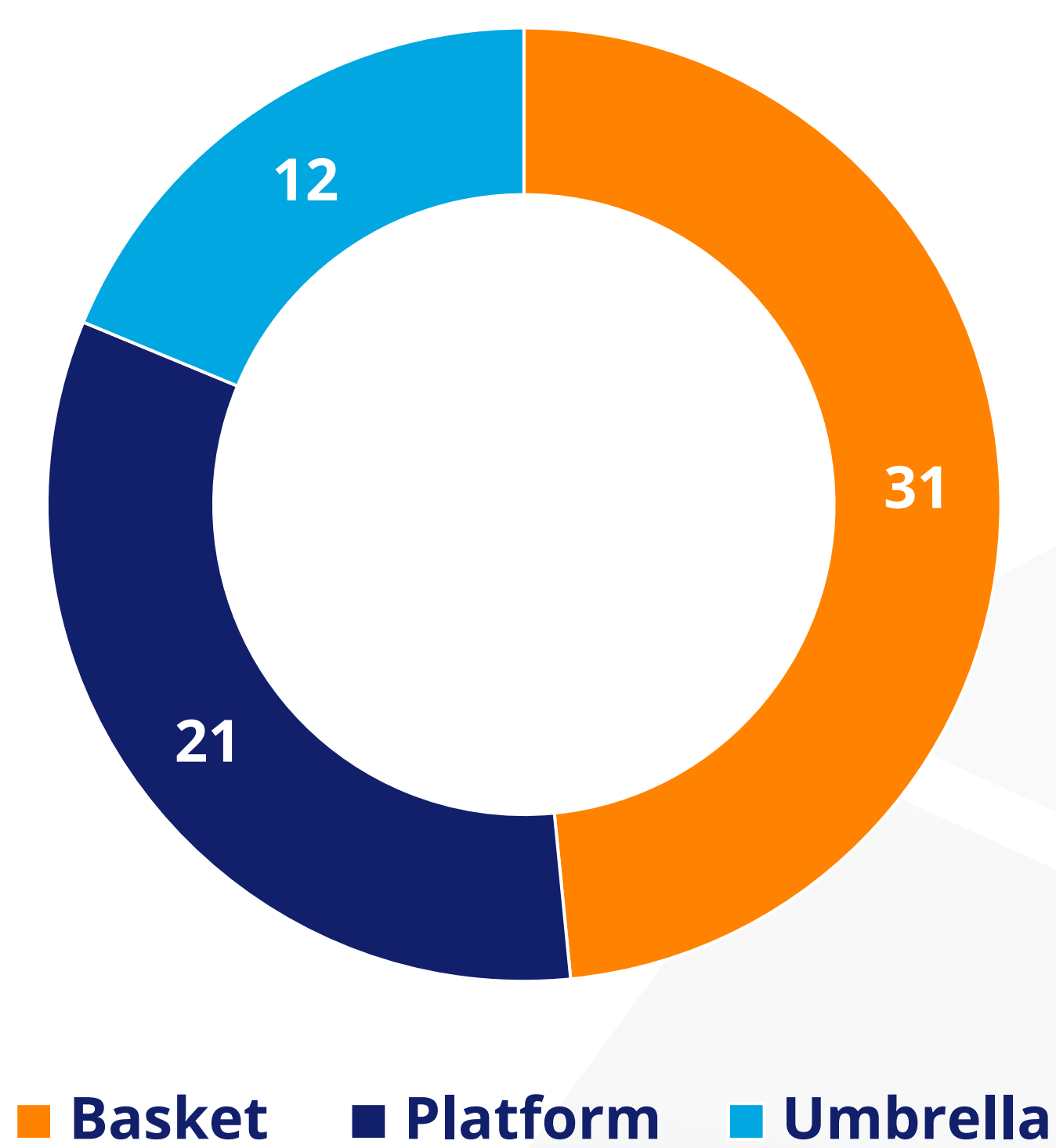
Although RCTs may have adaptive elements and other types of trial may be defined as adaptive trial designs, for the purpose of this study only Platform, Umbrella and Basket trials have been considered¹ (**Table 1**).

Table 1. Description on Adaptive Trial Design Types¹

Trail Design	Description
Platform Trial	Investigates multiple treatments in a single disease in a perpetual and open-ended manner, with treatments leaving the trial when complete and new treatments entering the trial when available
Basket Trial	Investigates a single therapy in multiple diseases or disease subtypes
Umbrella Trial	Investigates multiple treatments administered as monotherapy or drug combinations in a single disease population

The Basket design was the most common adaptive trial design with 31 trials, followed by Platform trials (21) and Umbrella trials (12) (**Figure 1**). There was a balanced distribution between designs investigating one treatment for multiple indications (i.e., Basket trials) and designs investigating multiple treatments in one indication (i.e., Platform and Umbrella trials).

Figure 1. Number of Trials Identified by Type of Adaptive Trial Design



CONCLUSION

The results of this study indicate that adaptive trials have been used, for the most part, in the earlier stages of development of oncology therapies, and to identify the most promising therapies to investigate into Phase III development. This study suggests that clinical trials with an adaptive design are not routinely used to support neither the regulatory approval nor the reimbursement of medical technologies for oncology treatments.



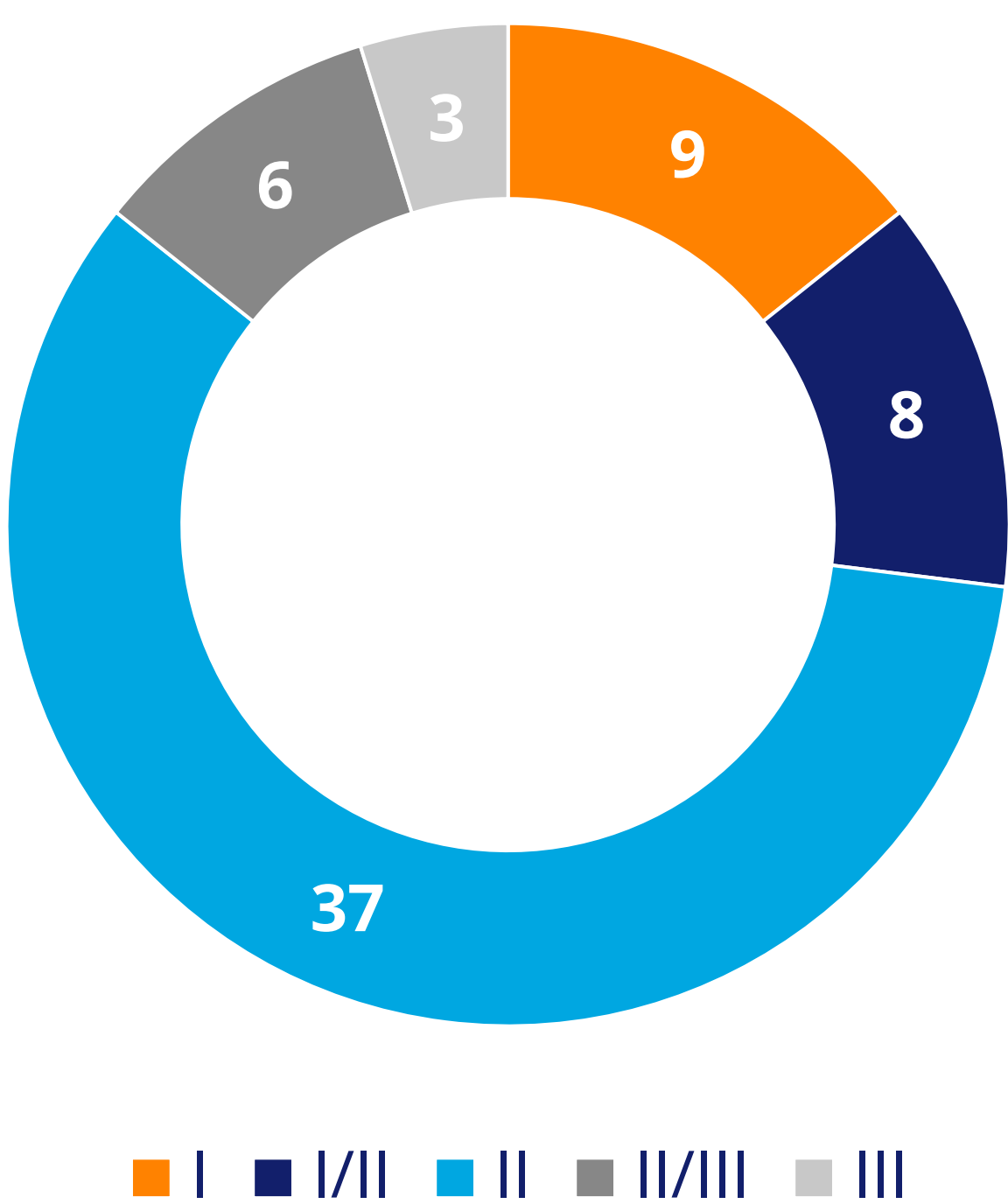
METHODOLOGY

Adaptive trials, investigating oncology treatments, were identified from PubMed* searches and grey literature¹. The regulatory approval by the EMA and the MHRA, as well as HTA reports from 4 European countries were consulted, to assess the impact of adaptive trial designs on regulatory approval and reimbursement of oncology treatments.

*PubMed Search Terms: (((master protocol) OR (Platform trial)) OR (basket trial)) OR (umbrella trial)) / Article Type: Clinical Trials

Most trials identified in this study (~80%) were Phase II, or had a Phase II element (i.e., Phase I/II or Phase II/III) (**Figure 2**).

Figure 2. Number of Adaptive Trials Identified by Development Phase



Only a small number of trials (5) generated data that was reported by regulatory agencies and/or HTA bodies to support the approval and/or reimbursement of oncology drugs, respectively. NICE was the HTA body to report adaptive trial design data more frequently²⁻⁸ (**Table 2**).

Table 2. Treatments Approved by European Regulatory Agencies and/or Receiving a Positive Reimbursement Recommendation Based on Adaptive Trial Data²⁻⁸

Trial	Drug	Indication	EMA	MHRA	HAS (France)	G-BA (Germany)	AIFA (Italy)	NICE (UK)
STAMPEDE Phase II/III	Abiraterone	Prostate Cancer			✓	✓	✓	✓
STAMPEDE Phase II/III	Docetaxel	Prostate Cancer			✓			
STAMPEDE Phase II/III	Enzalutamide	Prostate Cancer						✓
STAMPEDE Phase II/III	Apalutamide	Prostate Cancer						✓
STARTRK-2 Phase II	Entrectinib	NTRK-mut + solid tumors	✓	✓		✓	✓	✓
KEYNOTE-158 Phase II	Pembrolizumab	MSI-H or dMMR non-colorectal	✓	✓				IP
KEYNOTE-001 Phase I	Pembrolizumab	Melanoma	✓	✓				✓
NCT02122913 Phase I	Larotrectinib	NTRK-mut + solid tumors	✓	✓				

Abbreviations: AIFA: Agenzia Italiana del Farmaco; dMMR: Deficient mismatch repair; EMA: European Medicines Agency; G-BA: Gemeinsamer Bundesausschuss; HAS: Haute Autorite de Sante IP: Evaluation in progress; MHRA: Medicines and Healthcare products Regulatory Agency; MSI-H: Microsatellite instability-high; NICE: The National Institute for Health and Care Excellence; NTRK: Neurotrophic tyrosine receptor kinase; TNBC: Triple-negative breast cancer
✓: treatment approved / recommended



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