COMBINATION THERAPIES: TWO IS COMPANY BUT IS THREE (OR MORE) A CONCERN?

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Summary

- Despite the concern that triplet and quadruplet IO therapies may be associated with increased safety events, improved efficacy outcomes appear to outweigh the added safety concerns associated with the addition of another IO agent
- While the key drivers for HTA assessments vary across markets, efficacy and trial design are the most consistent drivers having a large influence on outcomes
- When comparing triplet/quadruplet regimens to their respective doublet/triplet comparators, failure to demonstrate favorable safety and tolerability results in worsened HTA outcomes across all markets, depending on the extent of improved efficacy
- For some markets (e.g., DEU and FRA), improved QoL may ease concerns around worsened safety outcomes, given the markets' emphasis on patient-related outcomes
- Efficacy continues to be the main driver for positive HTA outcomes, as demonstrated in FRA, DEU, and GBR; however, safety and QoL profiles play a larger role as combination therapies expand to include additional agents in certain markets (e.g., DEU and FRA)

Introduction & Objectives

Combination therapies are becoming increasingly common in clinical practice, including triplet and quadruplet regimens, and there are many more currently in development. These multi-therapy combinations have the potential to improve efficacy and clinical outcomes for patients. However, they also raise potential toxicity concerns. The objective of this analysis is to understand how safety criteria are being weighed throughout the HTA assessment process and determine whether payers and HTA bodies believe the added clinical benefits of triplet / quadruplet regimens outweigh the risks, using Non-Small Cell Lung Cancer (NSCLC) and Multiple Myeloma (MM) as case studies.

Methods

HTA reports were analyzed in FRA, DEU, and GBR to compare outcome rationales of doublet/triplet regimens (Pd vs. IsaPd and Pd vs. DPd in MM | PC vs. PEM-PCb in NSCLC) as well as triplet/quadruplet regimens (VTd vs. DVTd in MM | NICb vs. ABCP in NSCLC). The assessments were compared by analyzing changes in efficacy outcomes, such as OS, PFS, and safety/tolerability, including AE occurrences and QoL, to understand how decision-making committees prioritize various criteria when determining HTA outcomes and evaluate whether the safety criteria is prioritized more in triplet/quadruplet combination assessments. Across all markets in scope, the same methodology was used for evaluating these factors, while also accounting for expected differences in their evaluation policies (i.e., DEU's lack of PFS acceptance). Efficacy outcomes (i.e., OS, PFS, MRD) across therapies were evaluated to assess the clinical significance (if achieved) vs. the trial comparator and how they differentiated across various HTA markets. The safety profiles were similarly evaluated to assess impact on the ultimate HTA outcome. AEs were assessed based on severity, type, and frequency, which varied by treatment and differentially influenced the overall safety profile. The QoL outcomes (e.g., EQ-5D VAS, EORTC QLQ C30, future perspective scale, emotional functioning deterioration, C30 symptom scores) were recorded, if specifically analyzed in HTA reports, to evaluate potential impact on outcome. Finally, CE was analyzed in GBR, given its importance in this market.

Country	Regimen	HTA Outcomes	NSCLC: HTA Perception of Clinical Evidence Package vs. Trial Comparator	
			HTA-Assessed Trial Design and Efficacy	HTA-Assessed Trial Safety
FRA	PEM-PCb	SMR Important ASMR III	Superior PFS of +3.9 mo. and ORR of +28.7% vs. the trial comparator drove the ASMR III	Discontinuation due to AEs 27.7% vs. 14.9% for PC; Increased rates of TRAEs and SAEs noted as unfavorable by the TC
	PC	SMR Important ASMR V	No additional OS benefit as PC and GEM-C both had mOS of 10.3 mo.; efficacy considered only non-inferior versus GEM-C	PC had lower rates of discontinuation due to SAEs vs. GEM-C (1.8% vs. 2.8%); TC considered safety of PC non-inferior vs. GEM-C
	NICb	SMR Moderate ASMR IV	Superior, clinically relevant OS gain of +3.4 months; however, trial comparator was not deemed appropriate	Unfavorable safety (47% grade 3-4 SAEs in patients receiving NICb vs. 32% in chemotherapy) was a key value detractor leading to modest HAS outcome
	ABCP	SMR Moderate ASMR IV	Modest OS improvement of 4.8 mo. and PFS improvement of 1.5 mo. vs. BCP; IMpower150 study had methodological limitations (i.e., open-label design)	The TC highlighted significant toxicities with the quadruplet [more grade 3 or 4 AEs vs. BCP (65% vs. 60%), AEs leading to discontinuation of treatment (41% vs. 26 %) and AE leading to death (6.6% vs. 5.6%)]
DEU	PEM-PCb	Non-Quantifiable Added Benefit (PD-L1 <50%)	OS benefit with the pembrolizumab combination could not be quantified due to a high risk of bias noted by the G-BA due to the open-label study design	Analysis of SAEs were inconclusive due to patient cross-over, resulting in variable follow-up periods
	NICb	Minor added benefit (PD-L1 <50%)	Survival was significantly improved (mOS benefit of +3.4 months); comparator chosen was determined the sole appropriate comparator	Negative side effects do not call into question the additional benefit through OS improvement but led to a downgrade in the extent of added benefit
	ABCP	No Added Benefit (PD-L1 <50%)	Comparator does not correspond to relevant comparator specified by the G-BA, therefore efficacy data submitted versus the trial comparator not assessed	Comparator does not correspond to relevant comparator specified by the G-BA, therefore safety data not assessed; MNF-submitted ITC was not accepted
GBR	PEM-PCb	Recommended (Within the CDF*)	PEM-PCb demonstrated statistically significant improvement in OS vs. PEM in ITT population and was recommended assuming price meets CE	The available NICE assessment did not mention safety outcomes in the decision to recommend PEM-PCb
	PC	Recommended	No additional OS benefit as PC and GEM-C both had mOS of 10.3 mo. No statistically significant difference in mPFS (4.8 mo vs. 5.1 mo. In GEM-C)	Marginally improved safety outcomes vs. GEM-C [lower frequency of grade 3 and 4 AEs (i.e., neutropenia, febrile neutropenia, thrombocytopenia, anemia and alopecia]
	NICb	Not Recommended (Preliminary)	OS benefit of +4.7 mo. vs. standard chemotherapy; NICE did not consider the comparator to be appropriate and therefore accepted ITCs from the manufacturer	NICE noted unpleasant and serious AEs were more common in NICb vs. other chemo-immunotherapies, particularly immune-related toxicities; limiting treatment to 2 cycles of chemotherapy was recommended to reduce renal toxicity
	ABCP	Recommended (PD-L1<50%)	The committee concluded that the quadruplet was superior to the triplet given improvements in OS and PFS	Quadruplet was only recommended for patients who are well enough (ECOG 0-1). AE profile was comparable with triplet

Figure 1 | NSCLC: HTA Perception of Clinical Evidence Package vs. Trial Comparator

Country	Regimen	HTA Outcomes	MM: HTA Perception of Clinical Evidence Package vs. Trial Comparator		
			HTA-Assessed Trial Design and Efficacy	HTA Assessed Safety	HTA Assessed QoL Data
FRA	Pd	SMR Important ASMR III	Modest mPFS gain of +2 months vs. dex.	Safety outcomes comparable to high-dose dex	No impact of QoL due to insufficient data collected at the time of assessment
	IsaPd	SMR Important ASMR IV *(no liste en sus)*	Moderate PFS improvement of +5 months vs. Pd	Safety profile consistent with anti-CD38 antibodies, particularly in terms of infections and febrile neutropenia	Lack of demonstrated impact on QoL
	DPd	SMR Important ASMR IV *(3L+ Only) (pending liste en sus)*	PFS improvement of +5.5 months vs. Pd	The adverse event profile consistent with other indications for daratumumab & with other anti-CD38 antibodies	Lack of robust QoL data
	DVTd	SMR Important ASMR IV	Although not considered a substitution criterion for OS, undetectable MRD (64% versus 44%) was a value driver for moderate HTA outcome	Increased grade 3-4 AEs, severe neutropenia (28% versus 15%), severe lymphopenia (17% versus 10%) and serious pneumonia (3.5% versus 1.7%)	Lack of demonstrated impact on QoL
DEU	Pd	Hint of Considerable Added Benefit *(Patients eligible to high-dose D)*	Improved mOS benefit in patients eligible for high-dose Dex vs. Dex monotherapy	Side effects and frequencies of AEs comparable between both treatment groups	Improved outcomes in "physical function", "emotional function" & "role function" seen as key value drivers
	IsaPd	Hint of Minor Added Benefit	Unsuitable efficacy endpoints (i.e., no mOS data at launch)	Increased side effects vs. comparator, notably for severe AEs (90.8% vs. 75.2%)	Improved global health status deterioration (28.6% vs. 35.9%) and role functioning deterioration (24.0% vs. 39.2%)
	DPd	Hint of Minor Added Benefit	G-BA noted no OS data shown for DPd vs. Pd (not reached vs. 20.27 months)	Increased safety events vs. Pd in specific AEs (CTCAE grade ≥3) including lymphopenia (13.5% vs. 2.0%) and febrile neutropenia (8.07% vs. 1.0%)	Statistically significant advantages for emotional functioning deterioration (16.0% vs. 29.5%) and future perspective scale (22.6% vs. 31.4%)
	DVTd	Hint of Non-Quantifiable Added Benefit	Significant uncertainty in trial design resulted in the extent of positive effect of OS being non-quantified	Comparable safety event outcome to trial comparator for serious AEs, severe AEs (CTCAE grade ≥ 3), and discontinuation due to AEs	A statistically significant advantage regarding disease symptoms in the "pain" scale and in the functional scale "global health status"
GBR	Pd	Partial / Conditional Reimbursement *(Based on commercial arrangement for P)*	Statistically significant improvement in mOS and mPFS	The NICE found Pd to be a well tolerated treatment option in this disease space	QoL not assessed
	IsaPd	Partial / Conditional Reimbursement *(3L Only)*	Improved mPFS (11.53 vs. 6.47 months) and ORR (60.4% vs. 35.3%) outcomes vs. Pd in the ITT population	Trend towards lower deterioration in renal function for IsaPd vs. Pd (22.6% vs. 34.8%)	QoL as measured by EORTC-QLQ-C30 GHS score was sustained over time and similar to comparator (Pd)
	DPd	Terminated Appraisal	The combination did not receive a recommendation decision from NICE given JANSSEN withdrew the evidence submission for appraisal and NICE considers the combination regimen to not be a cost-effective use of NHS resources		
	DVTd	Recommended *(Based on commercial arrangement for D)*	Improved PFS and OS outcomes were primary value drivers for positive NICE assessment	Acceptable AE profile with limited and manageable adverse effects demonstrated by daratumumab	No additional gains in HR-QoL

Figure 2 | MM: HTA Perception of Clinical Evidence Package vs. Trial Comparator

LEGEND	
	Demonstrated and considered relevant / appropriate to the local HTA body therefore was not seen as a detractor from HTA outcome
	Was not considered appropriate / relevant and was mentioned in report but was not seen as a detractor from HTA outcome
	Was not considered appropriate / relevant, was mentioned in the report as a detractor from HTA outcome
N / A	Was not evaluated by HTA assessment

HTA outcomes for PEM-PCb were comparable or superior to the outcomes for the PC doublet across all markets within scope. The addition of pembrolizumab to the doublet results in a worse safety profile versus the trial comparator, noted by the TC in FRA, but not flagged as cause of concern for the G-BA. In GBR, it led to NICE limiting it to 2 cycles of chemotherapy to reduce renal toxicity. In DEU, the efficacy of NICb was considered by the G-BA to be clinically relevant; conversely, HAS and NICE did not consider the trial comparator to be appropriate, and consequently, did not consider the survival benefit of the triplet in the trial to be accurately assessable. Across all markets, the ACBP quadruplet faced trial design challenges. These rendered a negative HTA outcome by the G-BA as they could not conduct the benefit assessment. In FRA, while they did evaluate the quadruplet, the safety profile was highlighted as a main deteriorator. NICE accepted ITCs and experts' opinions to mitigate safety profile concerns, resulting in a final recommendation for patients who are considered fit enough (ECOG 0-1).

Both IsaPd and DPd triplets received inferior HTA outcomes versus the Pd doublet in FRA and DEU. While the addition of Isa/D to Pd demonstrated incremental benefits in efficacy, the triplets both demonstrated increased safety concerns. The TC decisions were primarily driven by the improved PFS outcomes, while the G-BA focused on patient-related outcomes (i.e., QoL) in the absence of OS benefit. Both of the HTA bodies reduced the extent of the favorable benefit citing safety concerns. DVTd HTA outcomes were primarily limited by the lack of OS data rather than poor safety. However, the TC did emphasize safety concerns for DVTd beyond other HTA bodies, suggesting increased safety-related scrutiny in FRA compared to DEU, where QoL benefit can offset safety concerns. In GBR, IsaPd received the same HTA outcome as Pd despite increased safety concerns, driven by favorable survival and QoL benefit in the trial. For DPd, JNJ withdrew the evidence submission, and NICE terminated the appraisal as the combination was not considered to be cost-effective. For DVTd, JNJ provided robust clinical expert opinions to mitigate potential safety concerns due to the AE profile which were accepted by NICE.

Conclusions

Due to the familiarity of HTA bodies with oncologist management of AEs from chemotherapies, there was limited concern around the management of associated toxicities for doublet/triplet regimens with chemotherapy backbones. Although, HTA bodies did tend to scrutinize the safety and QoL profiles more for regimens containing multiple novel agents, whose safety profile was often comparable or inferior to the clinical trial comparator. However, poor safety alone was not a consistent driver of poor HTA outcomes. Poorly perceived safety profiles were often supplemented by a lack of clear efficacy benefit, inappropriate trial design, or both, which led to a less favorable HTA outcome. In addition, GBR safety concerns were associated with non-acceptable CE analyses contributing to less favorable HTA outcomes.

Moreover, combination therapies do not always translate to deteriorated QoL with safety concerns eased for multi-component regimens associated with improved QoL (e.g., IsaPd and DPd for MM; NICb for NSCLC in DEU) or significantly improved efficacy (e.g., PEM-PCb for NSCLC in FRA and GBR; NICb for NSCLC in FRA; DPd for MM in FRA; IsaPd for MM in DEU). The safety profile of the NSCLC quadruplet was scrutinized the most across markets. The combination's moderate efficacy improvement was overshadowed by its poor safety profile, so access was limited based on patient fitness.

Superior efficacy compared to trial comparators appears to remain the predominant driver of positive HTA outcomes, and safety and patient related outcomes, such as QoL, are further emphasized across triplet/quadruplet regimens. While this likely indicates HTA bodies will continue to closely scrutinize the safety and QoL profiles of new IO combinations, particularly as more triplets and quadruplets launch, the scrutiny may not heavily impact the prospects of multi-combination therapies with progressively weaker safety profiles unless it is accompanied by trial design or efficacy issues.

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Abbreviations

ABCP: atezolizumab-bevacizumab-carboplatin-paclitaxel; **AE:** Adverse Event; **CE:** Cost Effectiveness; **D:** Daratumumab; **DPd:** daratumumab, pomalidomide and dexamethasone; **DVTd:** daratumumab-bortezomib-thalidomide-dexamethasone; **ECOG:** Eastern Cooperative Oncology Group; **HTA:** Health Technology Assessment; **IO:** Immuno-oncology; **IsaPd:** isatuximab, pomalidomide and dexamethasone; **ITC:** Indirect Treatment Comparison; **NICb:** nivolumab-ipilimumab-carboplatin; **OS:** Overall Survival; **P:** Pomalidomide; **PC:** pemetrexed-cisplatin; **Pd:** Pomalidomide and dexamethasone; **PEM-PCb:** pembrolizumab-pemetrexed-carboplatin; **QoL**: Quality of Life; **SAE:** Serious Adverse Events; **TC:** Transparency Committee

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