Use of External Control Arm to Support Regulatory Approval → Case study : Pembrolizumab and Lenvatinib Combination

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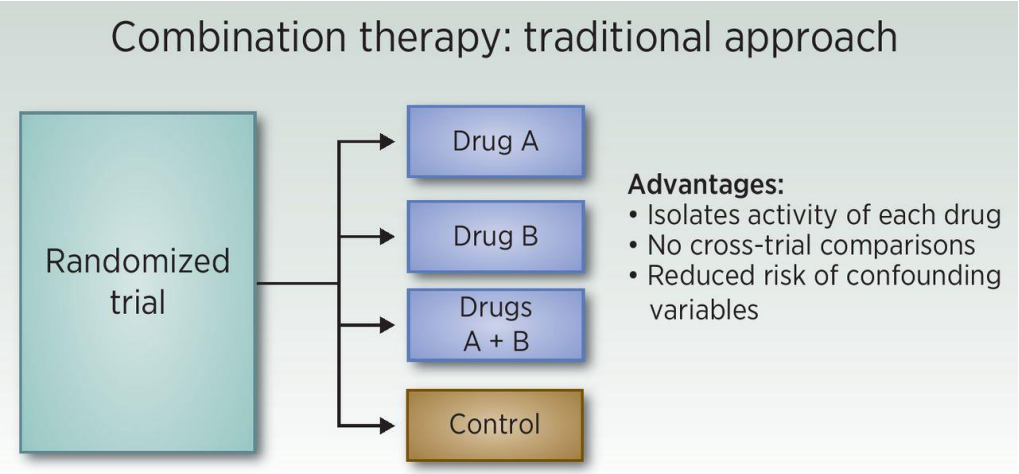
Agenda

1. Use of external control arms in oncology trials
2. General principles for combination therapy
3. FDA evaluation
4. EMA evaluation
5. Key take aways

Use of External Control Arms (ECA) in Oncology trials

- A randomized controlled trial (RCT) is the gold standard for evaluating efficacy and safety of a medicinal product
- Oncology drug development increasingly relies on the use of single-arm clinical trials, especially in certain settings where there are ethical or feasibility challenges with using a concurrent control arm
- While single-arm trials alone may yield important safety and efficacy signals and can be relied on for regulatory decision making in certain clinical and regulatory contexts, external controls may provide additional context and supplementary evidence
- Key considerations for use of ECA:
  - ❑ Relevance and quality of data sources
  - ❑ Well-defined patient populations
  - ❑ Robust pre-specified statistical analysis plans to mitigate biases

General Principles for Combination Therapy



- Standard approach when developing combination drug regimens consists of a RCT design including:
  - Treatment arm for the combination,
  - Treatment arms for each monotherapy component in the combination regimen, and
  - Control arm (if one of the drugs is not a standard-of-care option)
- To evaluate the safety and efficacy of each agent individually, and in combination, compared with standard of care while also providing a clear understanding of the contribution of each component in the combination

→ **To promote cancer drug development, some flexibility in trial design may be needed and alternative approaches to combination drug trials should be considered**

FDA Evaluation – Clinical Context

- Combination of KEYTRUDA® (pembrolizumab) and LENVIMA® (lenvatinib) for endometrial cancer (EC)
- Use of Project Orbis for expedited oncology drug approval in 2019

	Evidence and uncertainties	Conclusions and reasons
Analysis of condition	• Endometrial cancer is a common gynecologic malignancy worldwide with an increasing prevalence • Most patients present with early-stage disease, typically curable with surgery • 20%–30% of EC present with a high frequency of somatic mutations that can be attributed to dMMR, leading to the MSI-H phenotype (remaining patients being pMMR)	• Advanced EC is a serious and life-threatening disease with a **significant unmet medical** need for more effective therapies
Current treatment options	• Single-agent chemotherapy is the mainstay of treatment for women with advanced EC that progresses following initial curative therapy, where response rates and response durations are generally low	• Patients with advanced EC that is not MSI-H/dMMR could benefit from treatment that provides a more favorable response rate and prolonged DOR compared with available therapies

Unmet medical need in EC → need for effective treatments beyond single agent chemotherapy

dMMR: mismatch repair deficient, pMMR: mismatch repair proficient, MSI-H: microsatellite instability high

FDA Evaluation – Submission Package Content

1 combination study to support the efficacy and safety of the combination:		
Study 111/ KEYNOTE-146	Single-arm trial - Phase 1b/2 trial of **lenvatinib plus pembrolizumab** in subjects with selected solid tumors – Endometrial cohort to support efficacy and all cohorts to support safety	108 EC participants (previously treated): 94 pMMR/not MSI-H, 11 dMMR/MSI-H and 3 unknown

3 monotherapy studies to support the contribution of lenvatinib and pembrolizumab to the efficacy and safety profile of the combination:		
Study 204	Phase 2 study of **lenvatinib monotherapy** in participants with advanced endometrial carcinoma and PD following first line platinum-based chemotherapy	133 EC participants (MMR status not specified)
KEYNOTE-158	Phase 2 study of **pembrolizumab monotherapy** in participants with multiple types of advanced solid tumors, including endometrial carcinoma regardless of PD-L1 expression, which had progressed after standard of care therapy.	**Cohort D**: 107 EC participants: 90 pMMR/not MSI-H, 11 dMMR/MSI-H and 6 unknown **Cohort K**: 79 EC participants: all dMMR/MSI-H
KEYNOTE-028	Phase 1b study of **pembrolizumab monotherapy** in participants with PD-L1 positive advanced solid tumors, including endometrial carcinoma	24 EC participants: 18 pMMR/not MSI-H, 1 dMMR/MSI-H and 5 unknown

Combination Showed Greater Efficacy Compared with Monotherapies

Parameter	LENVIMA 20 mg + KEYTRUDA 200 mg	LENVIMA Monotherapy	KEYTRUDA Monotherapy	
	Study 111/KEYNOTE-146 (n = 94)	Study 204 (N = 133)	KEYNOTE-158 (n = 90)	KEYNOTE-028 (n = 21)
MSI status	Not MSI-H or dMMR	Not specified	Not MSI-H or dMMR	Not specified
ORR (CR + PR), n (%) (95% CI)	36 (38.3) (28.5–48.9)	19 (14.3) (8.8–21.4)	7 (7.8) (3.2–15.4)	2 (9.5) (1.2–30.4)
Best overall response, n (%)				
CR	10 (10.6)	1 (0.8)	0	1 (4.8)
PR	26 (27.7)	18 (13.5)	7 (7.8)	1 (4.8)
Duration of response, months				
Median (95% CI)	NE (6.3–NE)	7.2 (4.5–NE)	Not reached	Not reached
Range (minimum, maximum)	(1.2+, 33.1+)	(1.02+, 9.76+)	(8.4+, 27.6+)	(49.8+, 51.0+)

NE: not estimable

Tumor assessments for Study 111/KENOTE-146 and Study 204 are based on IIR per RECIST 1.1; tumor assessments for KEYNOTE-158 and KEYNOTE-028 are based on IIR per RECIST 1.1

Makker V et al. *J Clin Oncol*. LENVIMA and KEYTRUDA prescribing information 2019; Woodcliff Lake, NJ: Eisai Inc; Vergote I et al. *Gynecol Oncol.* 2020;156:575-82; Marabelle A., et al. *J Clin Oncol.* 2020;38(1):1-10; Ott PA et al. *J Clin Oncol.* 2016;34(no. 15_suppl)5581.

FDA Evaluation Approach [1/2]

Overview of the FDA's approach to evaluating the KEYNOTE-146 data:

- Trial design limitations as KEYNOTE-146 was a single-arm trial:
  - ❑ No statistical inferential procedures for result evaluation
  - ❑ Effectiveness assessed by improvement over existing therapies based on higher response rate and duration of response (DOR)

- Monotherapy support:
  - ❑ Monotherapy data from 3 previous trials (Study 204, KEYNOTE-158, KEYNOTE-028) used for supportive information
  - ❑ KEYNOTE-028 excluded from comparisons due to differences in dosing and small sample size (n=24)

- Population variability:
  - ❑ Considerable differences in patient baseline characteristics across studies affecting treatment effect assessment (prior therapies, ECOG performance, age, gender, geography, and histology)

FDA Evaluation Approach [2/2]

- Challenges in cross-trial comparison:
  - ❑ Non-randomized studies may introduce treatment-selection bias
  - ❑ Patient populations not directly comparable across trials

- Analytical approaches to ensure comparability:
  - ❑ FDA conducted exploratory analyses (propensity score matching and weighting) to adjust for covariates
  - ❑ Post-hoc comparisons indicated numerically higher overall response rate (ORR) for the combination treatment compared to monotherapies

- Ongoing phase 3 trials:
  - ❑ Study E7080-G000-309/KEYNOTE-775 and Study E7080-G000-313/MK-7902-001 evaluating combination therapy versus standard treatment in advanced endometrial carcinoma
  - ❑ Ongoing trials aimed to confirm clinical benefits and enhance application robustness

FDA Evaluation – Benefit/Risk Conclusions

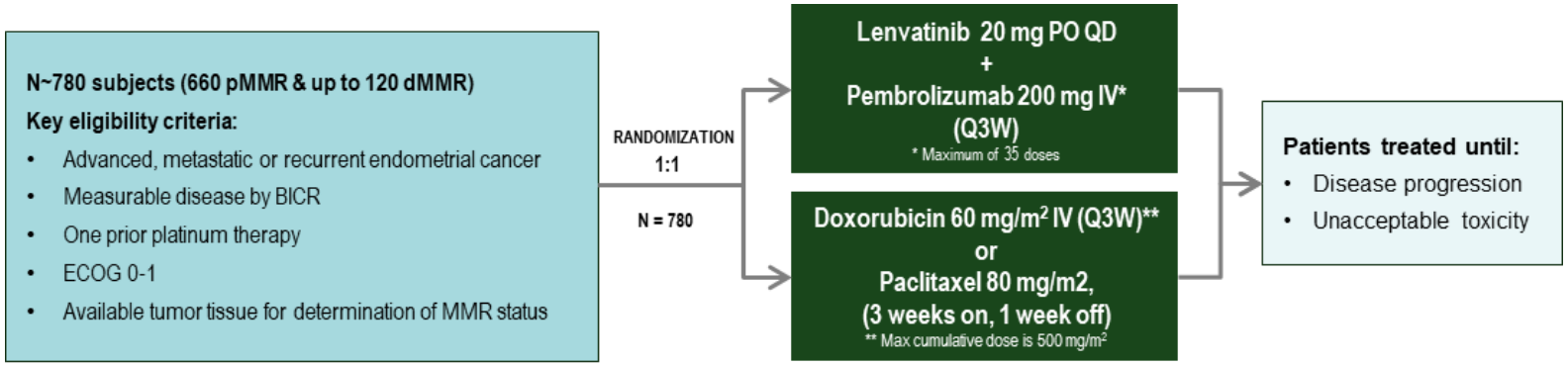
	Conclusions
Benefit	• ORR of 38.3% greater than typically seen with cytotoxic chemotherapy in this disease setting and longer DOR • A postmarketing requirement is required to verify clinical benefit in a randomized study
Risk	• Overall safety profile of lenvatinib and pembrolizumab combination for the treatment of patients with advanced endometrial cancer is consistent with the known safety profile of lenvatinib and pembrolizumab and acceptable for the intended population, and current risk mitigation strategies are sufficient • The safe use of lenvatinib and pembrolizumab can be managed through accurate labeling and routine oncology care

On September 17, 2019, FDA granted accelerated approval to:
Pembrolizumab plus lenvatinib for the treatment of patients with advanced endometrial carcinoma that is not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) and who have disease progression following prior systemic therapy

EMA Evaluation [1/2]

Overview of the EMA's approach to evaluating same combination with Type II variation based on KEYNOTE-775:

Phase 3 Randomized, Open-label Trial to Compare the Efficacy and Safety of Lenvatinib in Combination With Pembrolizumab Versus Treatment of Physician's Choice in Participants With Advanced Endometrial Cancer



Stratification by:

MMR Status (pMMR vs dMMR) & further stratification within pMMR by:

- **Geographic region** (Region 1: Europe, USA, Canada, Australia, New Zealand, and Israel vs Region 2: rest of the world)
- **ECOG** (0 vs 1)
- **Prior history of pelvic radiation** (Y vs N)

Primary Objectives:

- Progression-free survival (PFS)
- Overall survival (OS)

Secondary Objectives:

- Objective response rate (ORR)
- Health related quality of life (HRQoL)
- PK
- Safety and tolerability

Success achieved for all Primary and key Secondary endpoints in pMMR and all comer population (dMMR not formally tested)

Makker V et al. *N Engl J Med.* 2022;386:437-448

EMA Evaluation [2/2]

European Public Assessment Report (EPAR)*:

- KEYNOTE-775 phase 3 study design is lacking monotherapy arms which hampers the assessment of the contribution of each component to the combination

- Results from 3 supportive studies are provided to provide evidence of the contribution of lenvatinib and pembrolizumab monotherapies to the efficacy of the combination:
  - ❑ KEYNOTE-158 and KEYNOTE-028 studies for the pembrolizumab component
  - ❑ Study 204 for the lenvatinib component

- Based on this indirect comparison, it is suggested that :
  - ❑ Both pembrolizumab and lenvatinib, each having a limited activity separately, are contributing to the treatment effect in the combination regimen in pMMR population
  - ❑ In the dMMR subgroup the activity of the pembrolizumab + lenvatinib does not appear significantly different as compared to pembrolizumab alone, while lenvatinib adds toxicity

* keytruda-h-c-003820-ii-0105-epar-assessment-report-variation_en.pdf

EMA Evaluation – Benefit/Risk Conclusions

	Conclusions
Benefit	• KEYNOTE-775 study showed a statistically significant and clinically meaningful advantage in OS and PFS of the combination pembrolizumab + lenvatinib as compared to standard chemotherapy • The benefit of the combination over chemotherapy was shown in the all comers as well as in the pMMR population (populations for the primary analyses), and was evident also in the dMMR subgroup
Risk	• The safety profile of lenvatinib+pembrolizumab is different compared to chemotherapy, as expected, and consistent with the known safety profile of both drugs, with no new safety concern identified

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On November 15, 2021, EC approval was granted for the extension of indication: *Pembrolizumab in combination with lenvatinib for the treatment of advanced or recurrent endometrial carcinoma in adults who have disease progression on or following prior treatment with a platinum-containing therapy in any setting and who are not candidates for curative surgery or radiation.*

Key Take Aways

Regulatory interest

- ECAs are increasingly recognized as valuable, especially in contexts where RCTs are difficult to implement or high unmet need
- Not yet accepted as primary evidence for treatment effectiveness in drug labeling → could become pivotal for regulatory approval in oncology

Methodology

- Incorporating external control data involves a structured approach focusing on defining study purpose and ensuring data quality, completeness, and comparability to experimental arms

Challenges

- Non-comparable endpoints may undermine analysis
- Consistent detail in data measurement is crucial for valid comparisons
- Focused design and statistical methods can mitigate bias, although serious data validity issues may compromise findings

Future

- Developing robust methodologies for ECAs will improve their credibility and utility, paving the way for their broader acceptance in regulatory submissions