

ASGO Webinar #63

Translating biomarker data into clinical decision in non-dMMR endometrial cancer

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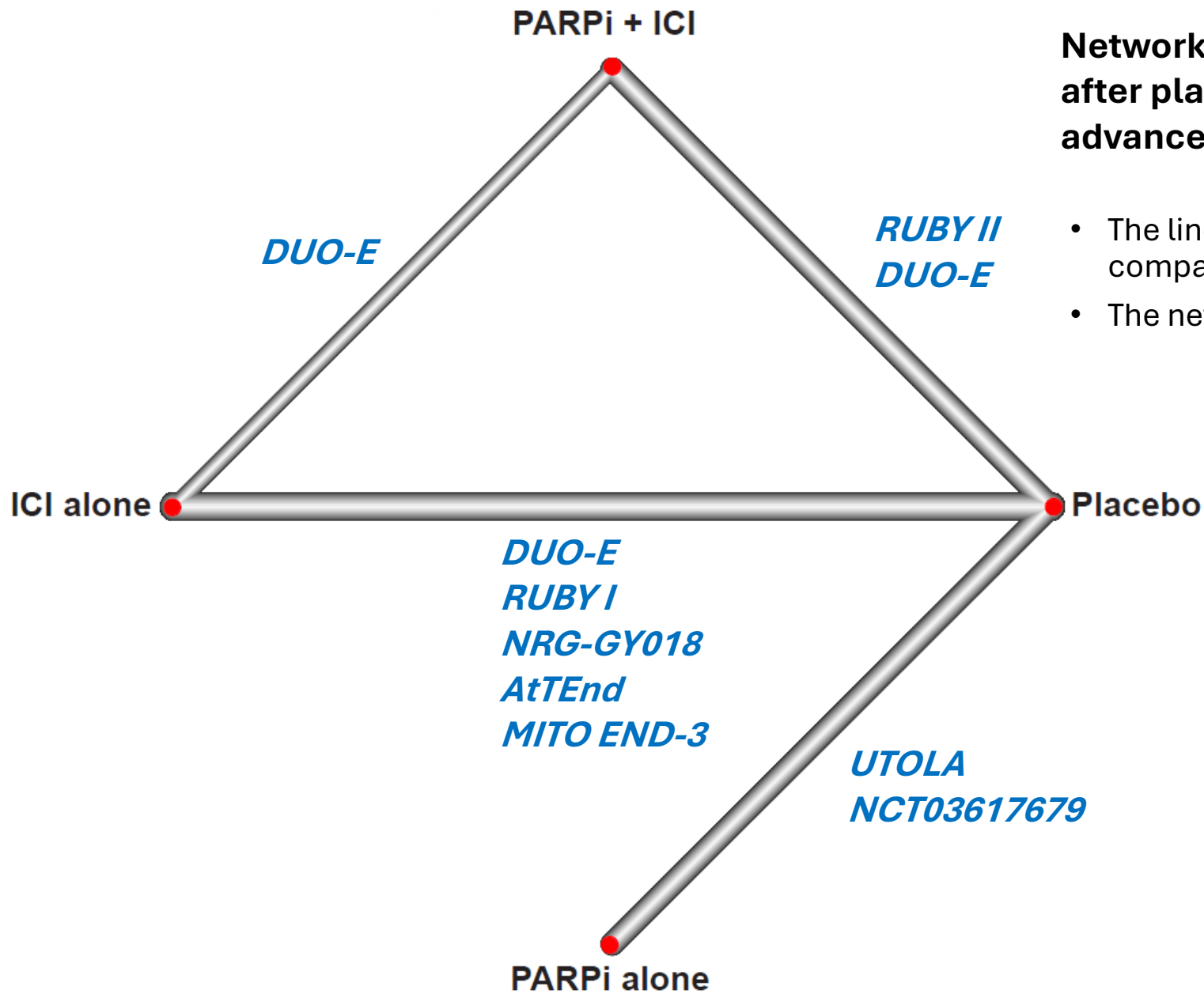
Asian Society of
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Challenges in treating MMRp endometrial cancer

- **Chemo + ICI** shows only marginal benefit in MMRp EC.
- MMRp EC is highly heterogeneous, represents ~70–75% of EC, and includes different molecular subtypes with distinct prognosis.
- **Chemo + ICI + PARPi** appears to enhance the response in MMRp EC, but no robust predictive biomarker has been established to identify which patients may benefit from this combination treatment.
- **p53** and **PD-L1** status are promising predictive markers, but results were inconsistent across different trials.

Main characteristics of RCT studies evaluating immunotherapy and PARP inhibitors as first-line treatment in advanced/recurrent endometrial cancer

Trial	Key inclusion criteria	Experimental treatment	Control treatment	Primary endpoint
RUBY I	Advanced (stage III, IV if IIIC1 high-risk histology and IIIC2 -IV regardless of evaluable or measurable disease) or first recurrent EC ≥ 6 months since last adjuvant platinum Carcinosarcoma allowed	CP + Dostarlimab → Dostarlimab x 3 years	CP + placebo → placebo x 3 years	1) PFS in dMMR/MSI-H 2) PFS in ITT population 3) OS in ITT
RUBY II	Advanced (stage III, IV if IIIC1 high-risk histology and IIIC2 -IV regardless of evaluable or measurable disease) or first recurrent EC ≥ 6 months since last adjuvant platinum Carcinosarcoma allowed	CP + Dostarlimab → Dostarlimab + niraparib x 3 years	CP + placebo → placebo iv + placebo po x 3 years	1) PFS in ITT 2) PFS in pMMR
NRG-GY018	Measurable stage III/IVA or measurable/non-measurable stage IVB or first recurrent EC ≥ 12 months since last adjuvant platinum Carcinosarcoma excluded	CP + Pembrolizumab → Pembrolizumab x 14 cycles (approx. 2 years)	CP + placebo → placebo x 14 cycles (approx 2 years)	1) PFS in pMMR 2) PFS in dMMR
AtTEnd	Advanced, newly diagnosed with residual disease after surgery or first recurrent EC ≥ 6 months since last adjuvant platinum Carcinosarcoma allowed	CP + Atezolizumab → Atezolizumab until PD	CP + Placebo → placebo until PD	1) PFS in dMMR 2) PFS in all comers 3) OS in all comers
MITO-END3	Advanced or first recurrent EC ≥ 6 months since last adjuvant platinum Carcinosarcoma excluded	CP + Avelumab → Avelumab until PD	CP	PFS in the ITT population
DUO-E	Measurable stage III or measurable/non-measurable stage IV or first recurrent EC ≥ 12 months since last adjuvant platinum Carcinosarcoma allowed	CP + Durvalumab → Durvalumab + placebo bid until PD CP + Durvalumab → Durvalumab + olaparib bid until PD	CP + Placebo → placebo + placebo bid until PD	PFS in ITT (Durva vs Control, Durva + Ola vs Control)
NCT03617679	Metastatic or recurrent EC, 1 or 2 previous lines of therapy No residual disease or PR after CT Carcinosarcoma allowed	Cytotoxic therapy → Rucaparib until PD (randomized after CT)	Cytotoxic therapy → placebo until PD (randomized after CT)	PFS in ITT
UTOLA	Advanced or metastatic EC ≥ 12 months since last adjuvant platinum	Platinum-based CT → Olaparib until PD (randomized after CT)	Platinum-based CT → placebo until PD (randomized after CT)	PFS in ITT

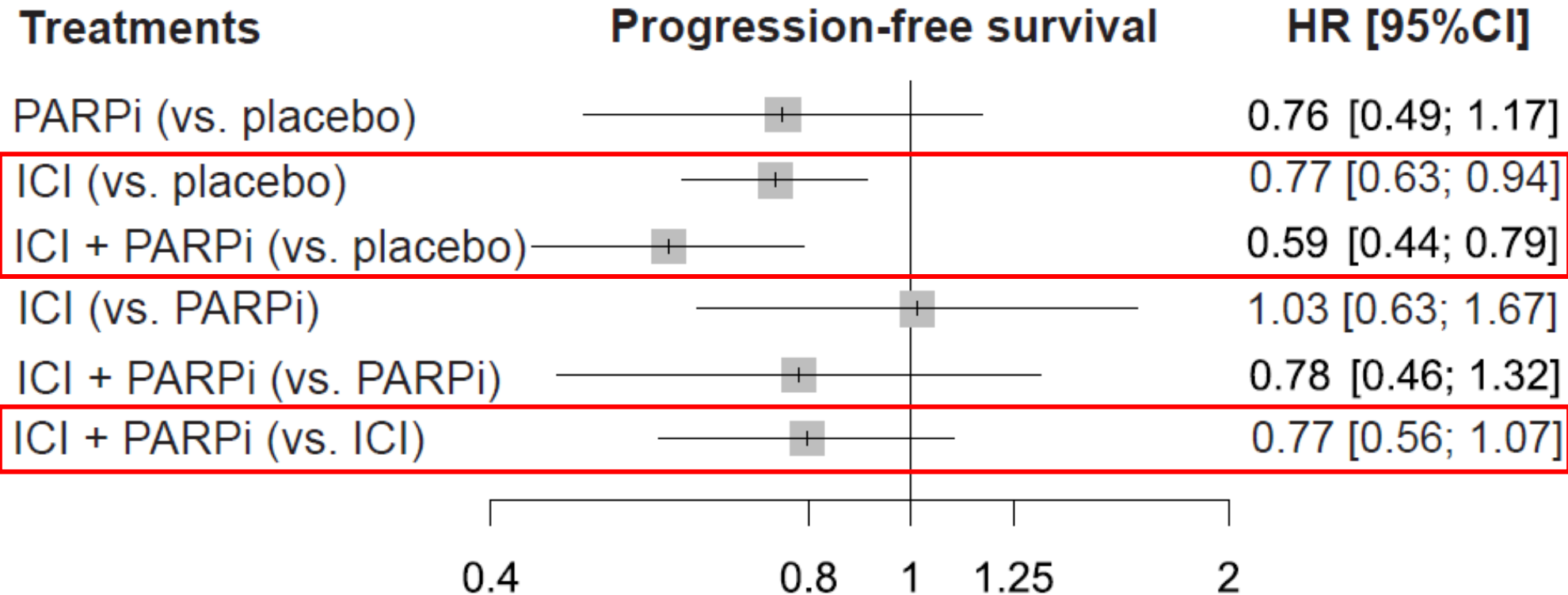


Network graph of the maintenance treatment after platinum-based chemotherapy in advanced or recurrent endometrial cancer

- The lines connect treatments that have been compared head-to-head.
- The network was built for the PFS endpoint.

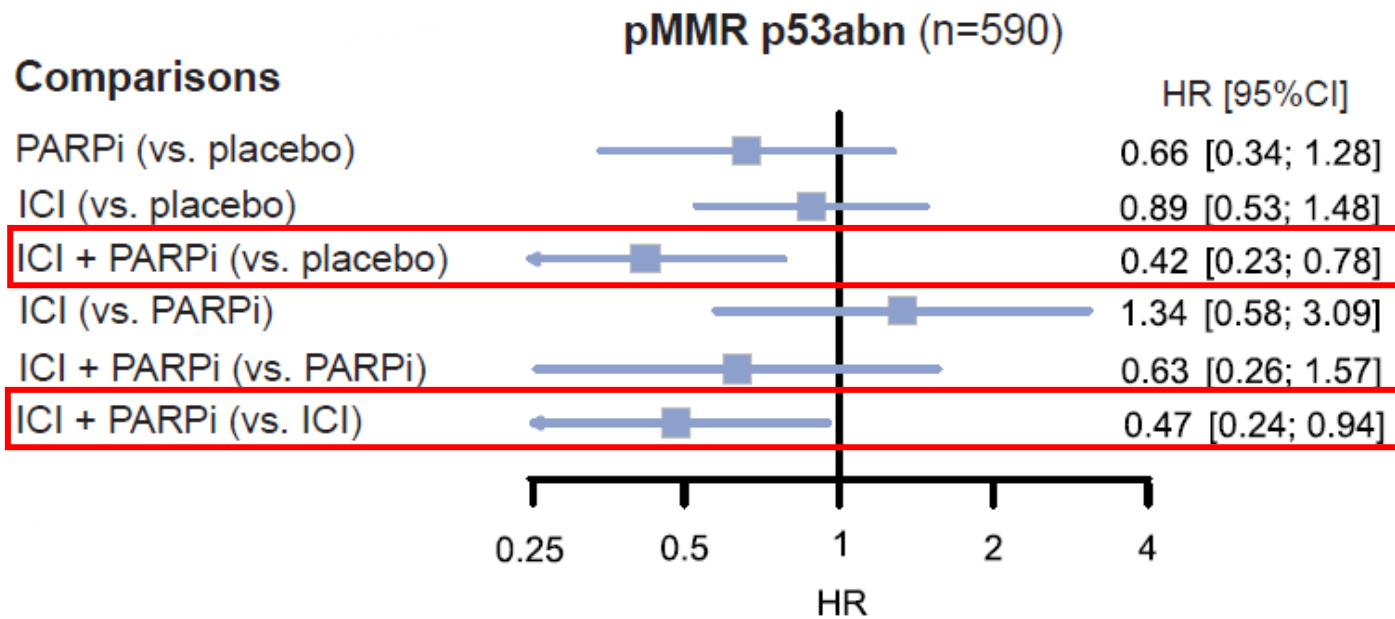
Different treatment comparison: PFS in MMRp population

MMRp population (n=2,427)

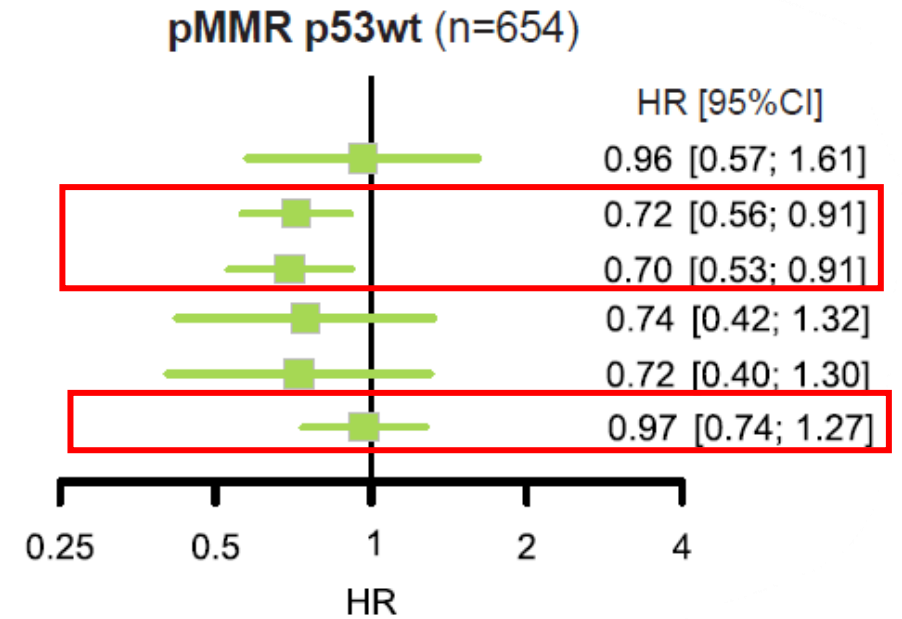


- In MMRp patients, both **ICI** and **ICI + PARPi** improved PFS outcomes.
- **ICI + PARPi** showed numerically better outcomes, although not statistically significant, compared to ICI alone.

Different treatment comparison: PFS by p53 status in MMRp population

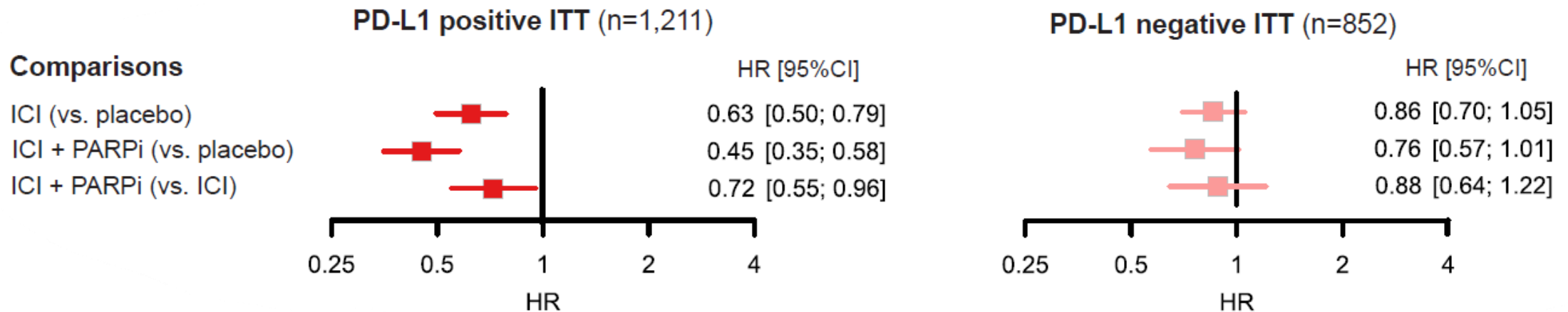


In MMRp patients with p53 mutation, **ICI + PARPi** was associated with improvement in PFS compared to ICI alone.



In MMRp patients with p53wt, ICI + PARPi did not improve outcomes compared to ICI alone.

Different treatment comparison: PFS by PD-L1 status in ITT population

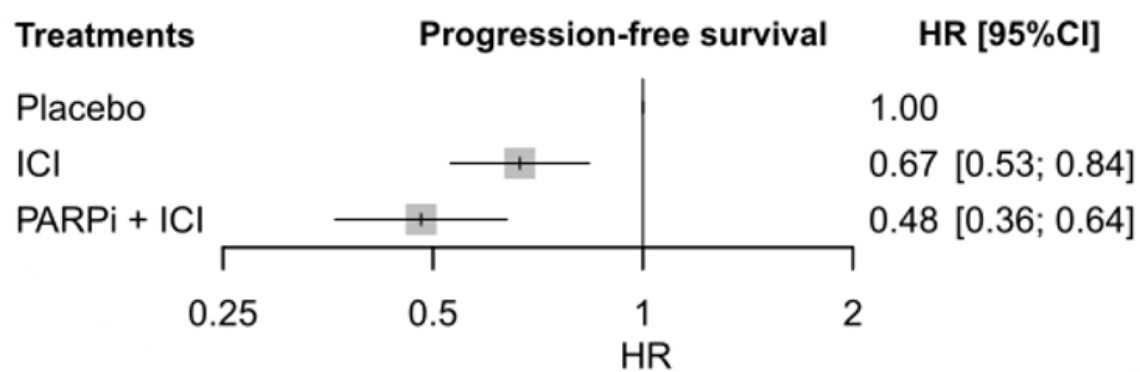


- In PD-L1 positive patients, both **ICI** and **ICI + PARPi** improved PFS outcomes.
- The PFS improvement was greater with ICI + PARPi compared with ICI alone.

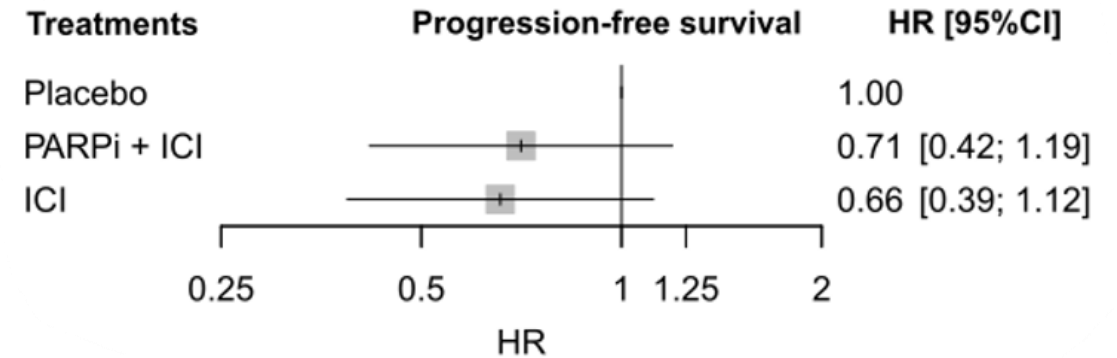
In PD-L1 negative patients, no benefit was observed with ICI, either alone or in combination with PARPi.

Different treatment comparison: PFS by PD-L1 status in MMRp population

PD-L1 positive in the MMRp population (n=872)



PD-L1 negative in the MMRp population (n=393)



In the MMRp patients, the sensitivity analysis showed similar results as in the ITT population.

Conclusions

- These results do not support a general recommendation of the use of ICI + PARPi for all MMRp population.
- Current evidence supports the use of ICI + PARPi in the MMRp p53-abnormal population.
- PD-L1 status is also suggested as a potential biomarker.
- Limitations of using PD-L1 as a predictive marker
 - Variability in detection methods
 - Differences in cut-off values: studies use different definitions of “PD-L1 positivity”
 - Intertumoural and intratumoural heterogeneity
 - PD-L1 expression may differ between primary and metastatic lesions
 - Heterogeneous expression can also occur within the same tumor

Questions-1

- For patients with **MMRp**, **p53 wild-type** EC who has experienced recurrence, given the high temporal and spatial variability of PD-L1 expression, would you recommend re-biopsy of the recurrent tumor for PD-L1 re-testing ?

Questions-2

- **GOG 86P** trial demonstrated that in advanced or recurrent EC with p53 mutation, the addition of bevacizumab to chemotherapy may improve survival.
- For patients with **MMRp, p53mut EC**, what would be your first-line treatment choice: **chemo + bevacizumab** or **chemo + ICI + PARPi**? Beyond economic considerations, what other factors would influence your decision?