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Post Hoc Analysis of Objective Response Rate by Mismatch Repair Protein Dimer Loss/Mutation Status in Patients with Mismatch Repair Deficient Endometrial Cancer Treated with Dostarlimab

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*Affiliated with GSK when this study was conducted.

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Disclosure (Anna V. Tinker)

	No, nothing to disclose
X	Yes, please specify:

Company Name	*Honoraria/ Expenses*	*Consulting/ Advisory Board*	*Funded Research*	*Royalties/ Patent*	*Stock Options*	*Ownership/ Equity Position*	*Employee*	*Other (please specify)*
AstraZeneca	X		X					
Eisai	X							
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Background

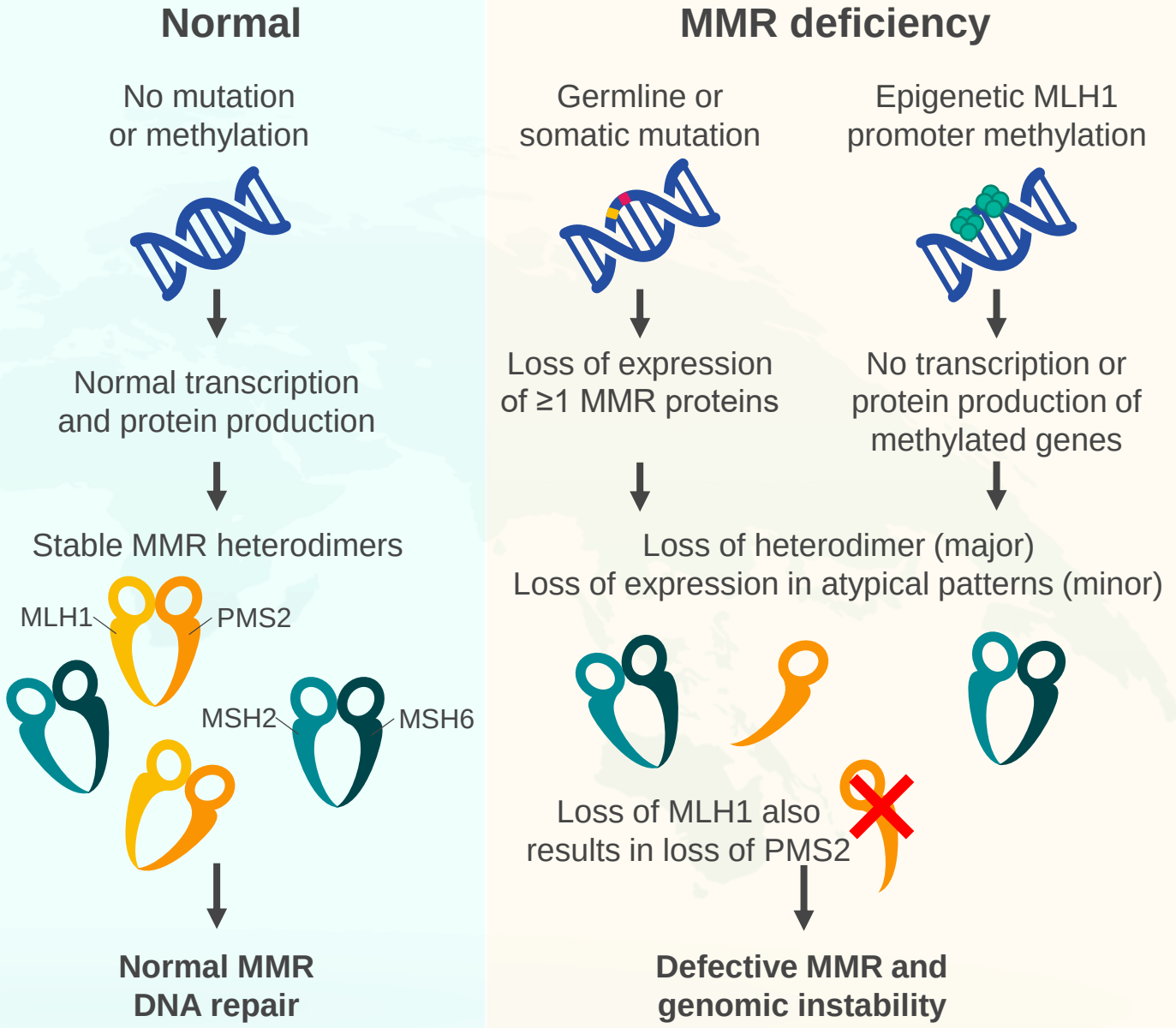
- Endometrial cancer is the most common gynecological malignant neoplasm in the US and EU, with an incidence that is rising globally[1–3]
- Endometrial cancer is reported to have a high prevalence of dMMR/MSI-H, at 25%–30%[4,5]
- dMMR/MSI-H tumors have shown high response rates to anti–PD-1 therapy

dMMR, mismatch repair deficient; MSI-H, microsatellite instability–high; PD-1, programmed death 1.

1. Siegel RL, et al. *CA Cancer J Clin.* 2022;72:7–33. 2. Lortet-Tieulent J, et al. *J Natl Cancer Inst.* 2018;110(4):354–361. 3. Guo F, et al. *J Clin Oncol.* 2021;39(suppl 15):abstr 5578. 4. Lorenzi M, et al. *J Oncol.* 2020;2020:1807929. 5. Bonneville R, et al. *JCO Precis Oncol*. 2017;2017:PO.17.00073.

Background

- MMR deficiency is caused by loss of expression of the MMR proteins MLH1, PMS2, MSH2, and/or MSH6[1]
  - These proteins function as heterodimers (MLH1–PMS2 and MSH2–MSH6) to mediate DNA repair
- Loss of expression is caused primarily by 2 mechanisms
  1. Germline (Lynch syndrome) or somatic mutation of MLH1, PMS2, MSH2, and/or MSH6
  2. Epigenetic methylation of the MLH1 promoter



dMMR, MMR deficient; MMR, mismatch repair.

1. Pecina-Slaus N, et al. *Front Mol Biosci.* 2020:7:122.

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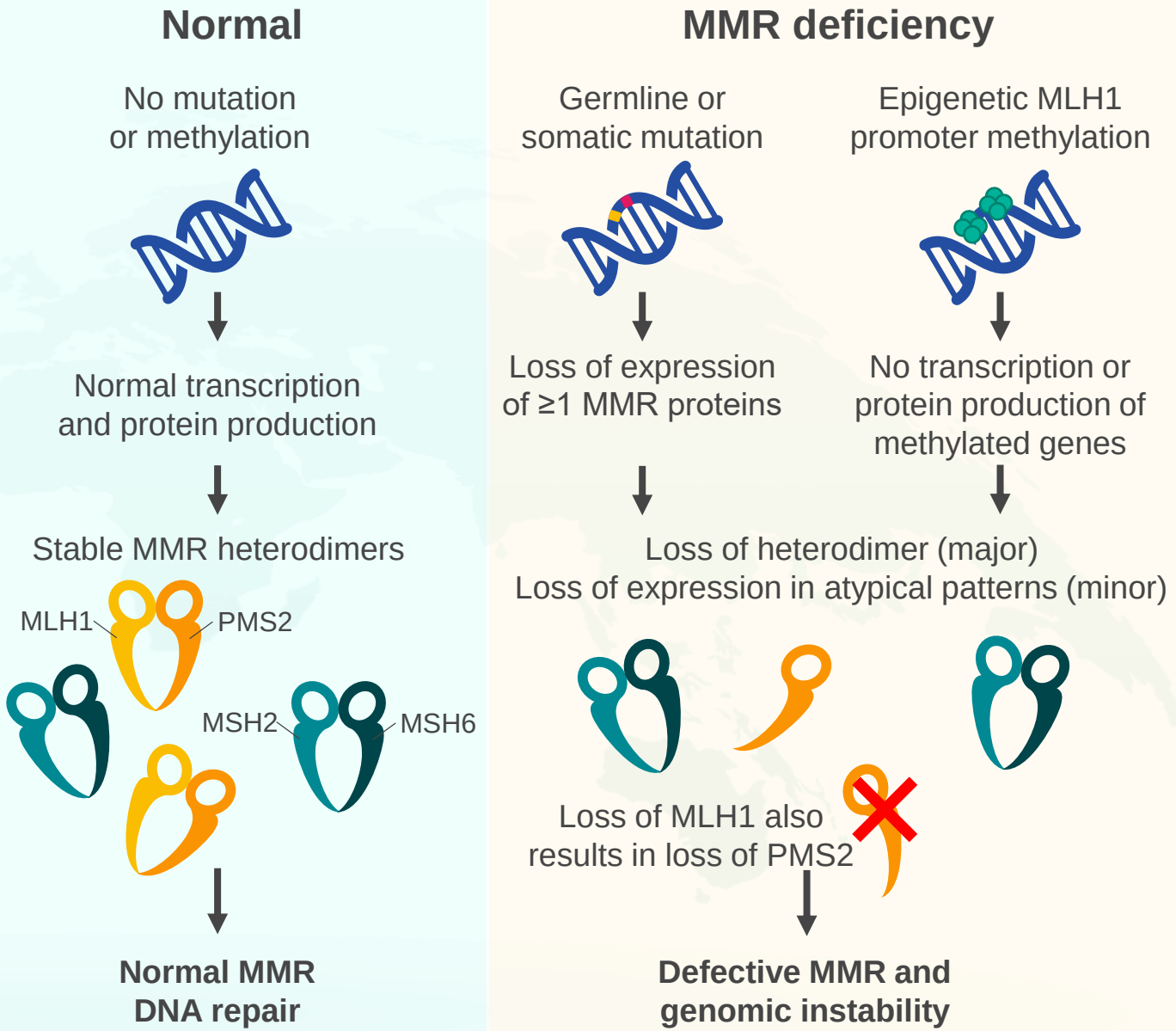
Background

- Gene mutation or epigenetic silencing of 1 gene typically leads to loss of expression of the heterodimer (most common dMMR staining pattern) and results in defective MMR and genomic instability[1]
  - Other patterns of loss are possible (loss of only 1 protein; loss of 3 proteins; or loss of atypical combinations of 2 proteins, eg, PMS2 and MSH6, etc)

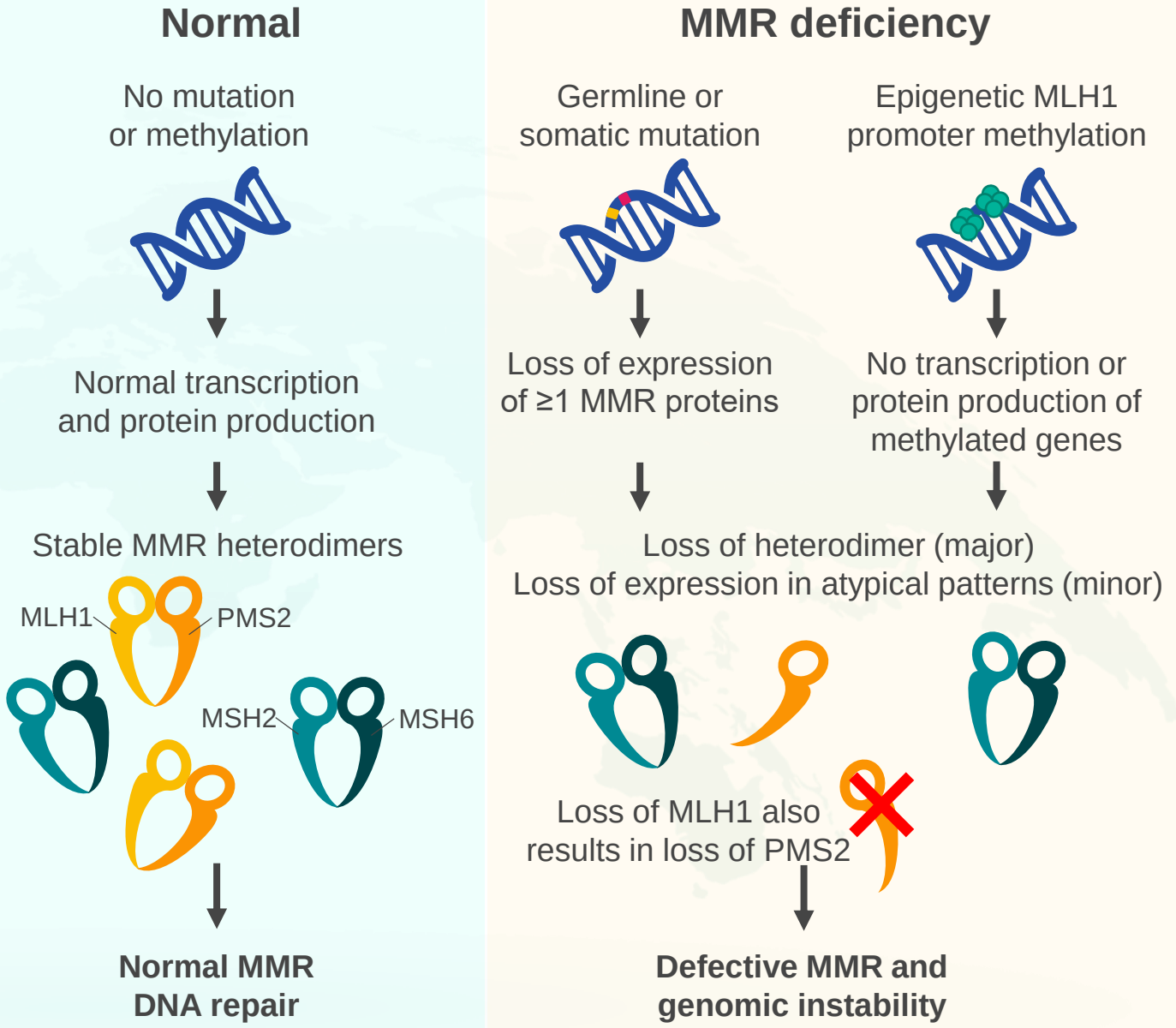


dMMR, MMR deficient; EC, endometrial cancer; MMR, mismatch repair.

1. Pecina-Slaus N, et al. *Front Mol Biosci.* 2020:7:122.

Background

- MLH1 promoter methylation accounts for approximately 75%–80% of cases with MMR deficiency in EC[1-4]
  - Somatic or germline mutation in an MMR gene is estimated to account for 10-20% of MMR deficiency in EC[1-4]
- The relationship between mechanism of MMR deficiency and outcomes is not well understood



dMMR, MMR deficient; EC, endometrial cancer; MMR, mismatch repair.

1. Pasanen, A, et al. *Mod Pathol* **33**, 1443–1452 (2020). 2. Kurpiel, B, et al. *Int J of Gyn Path* 41:1:1-11 (2022).
3. Buchanan, D, et al. *JCO* 2014 32:2, 90-100, 4. Kahn, RM et al. *Cancer*, 125: 3172-3183.

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Objective

- Here, we report on a post hoc analysis of objective response rate in patients with dMMR advanced or recurrent endometrial cancer treated with dostarlimab per the following subgroups:
  - MMR heterodimer loss pattern
  - Mutation status of the *MLH1* gene

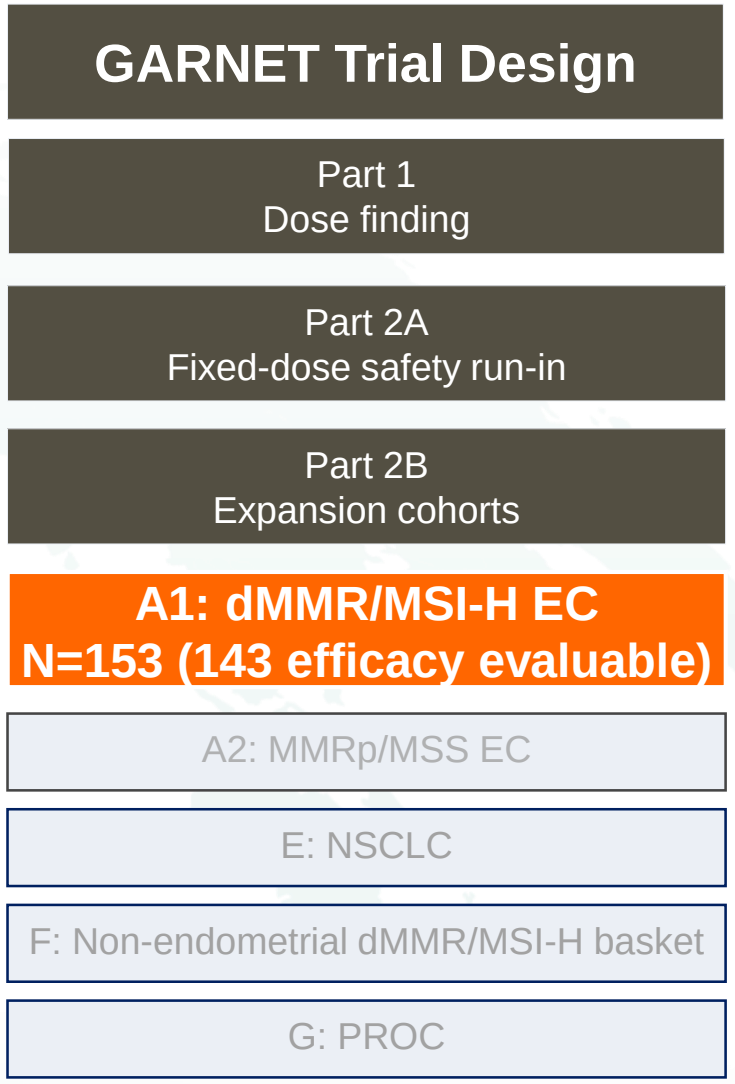
Topline efficacy and safety on this cohort have been previously reported[1]

dMMR, MMR deficient; MMR, mismatch repair.

1. Dostarlimab in advanced/recurrent (AR) mismatch repair deficient/microsatellite instability–high or proficient/stable (dMMR/MSI-H or MMRp/MSS) endometrial cancer (EC): The GARNET study. Ana Oaknin, et al. Journal of Clinical Oncology 2022 40:16_suppl, 5509-5509

Methods

- GARNET is a multicenter, open-label, single-arm phase 1 study
  - Patients received 500 mg of dostarlimab intravenously Q3W for 4 cycles, then 1000 mg Q6W until disease progression, discontinuation, or withdrawal
- Cohort A1 enrolled patients with dMMR advanced or recurrent EC
- MMR protein status (presence or loss of expression) was determined by local or central IHC
- MMR gene mutation status was determined by central testing with Foundation One



dMMR, MMR deficient; EC, endometrial cancer; IHC, immunohistochemistry; MMR, mismatch repair; MSI-H, microsatellite instability–high; NSCLC, non–small cell lung cancer; PROC, platinum-resistant ovarian cancer.
Data cutoff 01 Nov 2021

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Demographics and Baseline Characteristics

Characteristic	dMMR/MSI-H EC N=143
Age, median (range), years	65.0 (39–85)
FIGO disease stage at diagnosis, n (%)	
Stage I or II	62 (43.4)
Stage III or IV	81 (56.6)
Histology, n (%)	
Grade 1 or 2 endometrioid carcinoma	92 (64.3)
Serous	7 (4.9)
Grade 3 endometrioid	21 (14.7)
Clear cell	1 (0.7)
Squamous	1 (0.7)
Undifferentiated	4 (2.8)
Mixed carcinoma	7 (4.9)
Other[a]	10 (7.0)
Prior anticancer treatment, n (%)	143 (100)
Prior lines of therapy, n (%)[b]	
1	90 (62.9)
2	35 (24.5)
≥3	18 (12.6)
Prior radiation, n (%)	101 (70.6)

[a]Other includes dedifferentiated, endometrial adenocarcinoma, unspecified, unknown, and undifferentiated clear cell carcinoma. [b]Includes lines of therapy in the adjuvant setting.
dMMR, mismatch repair deficient; EC, endometrial cancer; FIGO, International Federation of Gynecology and Obstetrics; MSI-H, microsatellite instability–high.

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No difference in ORR or DOR by pattern of MMR protein loss

- MMR protein loss is similar to the estimated ratios in the dMMR EC population[1-4]

MMR protein staining pattern (IHC)	Patients, N	Responders, n	ORR, % (95% exact CI)	DOR median (95% CI), mo
Cohort A1 (dMMR/MSI-H EC)	143	65	45.5 (37.1–54.0)	NR (38.9–NR)
MLH1–PMS2 dimer loss	94 (66%)	46	48.9 (38.5–59.5)	NR (34.7–NR)
MSH2–MSH6 dimer loss	16 (11%)	9	56.3 (29.9–80.2)	NR (13.9–NR)
Other[a]	33 (23%)	10	30.3 (15.6–48.7)	NR (13.7–NR)

1. Pasanen, A, et al. *Mod Pathol* **33**, 1443–1452 (2020). 2. Kurpiel, B, et al. *Int J of Gyn Path* 41:1:1-11 (2022). 3. Buchanan, D, et al. *JCO* 2014 32:2, 90-100, 4. Kahn, RM et al. *Cancer*, 125: 3172-3183.

[a]Other: any other pattern of loss that is not exclusively MLH1–PMS2 or MSH2–MSH6 dimer loss. This group includes 17 patients with loss of expression of 1 MMR protein, 13 with loss of 3 proteins, 1 with loss of 2 proteins that are not a canonical dimer, and 2 with MMR unknown/MSI-H status.
dMMR, MMR deficient; DOR, duration of response; EC, endometrial cancer; IHC, immunohistochemistry; MMR, mismatch repair; MSI-H, microsatellite instability–high; ORR, objective response rate.

No difference in ORR or DOR in those with MLH1 loss by mutation status

- Most MLH1 loss was not accompanied by mutations, consistent with the estimated rate in the dMMR population[1-4]

	Patients, N	Responders, n	ORR, % (95% exact CI)	DOR median (95% CI), mo
Cohort A1 (dMMR/MSI-H EC)	143	65	45.5 (37.1–54.0)	NR (38.9–NR)
Cohort A1 patients with available mutation data	101	—	—	—
MLH1 loss by IHC (any pattern)[a]	78	31	39.7 (28.8–51.5)	NR (38.9–NR)
MLH1 loss by IHC (any pattern) and mutation in *MLH1* or *PMS2* genes	7 (9%)	3	42.9 (9.9–81.6)	NR (NR–NR)
MLH1 loss by IHC (any pattern) and no mutation in *MLH1* or *PMS2* genes	71 (91%)	28	39.4 (28.0–51.7)	NR (38.9–NR)

1. Pasanen, A, et al. *Mod Pathol* **33**, 1443–1452 (2020). 2. Kurpiel, B, et al. *Int J of Gyn Path* 41:1:1-11 (2022). 3. Buchanan, D, et al. *JCO* 2014 32:2, 90-100, 4. Kahn, RM et al. *Cancer*, 125: 3172-3183.

[a]This group includes 66 patients with loss of the MLH1–PMS2 dimer and 12 with another pattern.
dMMR, MMR deficient; DOR, duration of response; EC, endometrial cancer; IHC, immunohistochemistry; MMR, mismatch repair; MSI-H, microsatellite instability–high; ORR, objective response rate.

Conclusions

- Patients with dMMR/MSI-H advanced/recurrent EC benefitted from dostarlimab (ORR of 45.5%)
- Consistent with the literature, the most common pattern of MMR protein loss was the MLH1–PMS2 heterodimer (66% of patients in the GARNET cohort A1 vs ≈75% in the general EC population)[1-4]
- Tumors with loss of MLH1 and no mutation identified in *MLH1* or *PMS2* are likely to have MLH1 promoter methylation; however, direct testing of methylation would be the most accurate means to identify these patients
  - There were no noticeable differences observed in ORR by pattern of MMR protein loss or MMR gene methylation/mutation status
  - This data set is the largest to explore the response rate by mechanism leading to MMR deficiency
- These data are hypothesis generating
  - GARNET was not powered to study the effect of MMR protein pattern or mutation status on response to dostarlimab
- **The data suggest the route to MMR deficiency does not influence response to dostarlimab (ORR of 39.4% in patients with presumed MLH1 promoter methylation)**

1. Pasanen, A, et al. *Mod Pathol* **33**: 1443–1452 (2020). 2. Kurpiel, B, et al. *Int J of Gyn Path* **41(1):** 1-11 (2022). 3. Buchanan, D, et al. *JCO* 2014 **32(2)**, 90-100, 4. Kahn, RM et al. *Cancer*, **125**: 3172-3183.

dMMR, MMR deficient; EC, endometrial cancer; MMR, mismatch repair; ORR, objective response rate.

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