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Original Article

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Phase III double-blind randomized placebo controlled trial of atezolizumab in combination with carboplatin and paclitaxel in women with advanced/recurrent endometrial carcinoma: the Asian cohort of the AtTEnd/ENGOT-EN7 trial

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Trial Registration
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ABSTRACT

Objective: This post-hoc analysis of the AtTEnd trial explored differences in the prognostic characteristics and in the efficacy of atezolizumab between Asians and non-Asians.
Methods: The role of Asian race was evaluated on progression-free survival (PFS) using Cox-models and on time to appearance of new lesions using Fine and Gray models.
Results: From October 2018 to February 2022, 549 patients were randomized, of whom, 20.4% were Asian. Asians showed a better prognostic profile in terms of age, body mass index, Eastern Cooperative Oncology Group performance status, disease status and previous treatments. The prognostic impact of Asian race on PFS was confirmed in the placebo arm (adjusted hazard ratio [HR]=0.41; 95% confidence interval [CI]=0.24–0.70). In proficient mismatch repair (pMMR) tumors, the HRs for PFS comparing atezolizumab versus placebo were 0.82 (95% CI=0.63–1.05) in non-Asians, and 1.42 (95% CI=0.80–2.50) in Asians. In the pMMR population randomized to atezolizumab, the subdistribution HRs comparing Asians to non-Asians were 0.68 (95% CI=0.43–1.09) for progression with new lesions and 1.21 (95% CI=0.73–2.03) for progression without new lesions. Asians showed a higher occurrence of severe adverse events in atezolizumab compared to placebo arm (Asians: 82.1% vs. 64.3%, p=0.036; non-Asian: 63.3% vs. 63.6%, p=0.949).
Conclusion: Race seems to affect the safety of the addition of atezolizumab and, in pMMR tumors, also its efficacy. In the atezolizumab arm, Asian patients seem to have a lower cumulative incidence of new lesions when primary tumor regrowth was considered a competing risk, and a higher cumulative incidence of primary tumor regrowth when new lesions appearance was the competing risk.

Trial Registration: ClinicalTrials.gov Identifier: NCT03603184

Keywords: Endometrial Carcinoma; Atezolizumab; Mismatch Repair; Asian

Synopsis
An analysis of the AtTEnd trial in proficient mismatch repair tumors showed no benefit from atezolizumab in Asians. The clinical profile of these populations seems quite different. Asian patients on atezolizumab have a lower cumulative incidence of new lesions but a higher cumulative incidence of primary tumor regrowth than non-Asians.

INTRODUCTION

Endometrial cancer is one of the most common cancers in women, and its incidence and mortality rates are rising worldwide [1]. Notably, in Japan, the incidence of uterine corpus cancer (mainly endometrial cancer) has increased eightfold compared to 40 years ago [2]. Until recently the standard treatment for advanced or recurrent endometrial cancer was the combination chemotherapy of carboplatin and paclitaxel, which had limited efficacy with a progression-free survival (PFS) of 10–13 months [3,4]. Therefore, there was an urgent need to improve the treatment of endometrial cancer.

Immune checkpoint inhibitors (ICIs) have shown to be effective as a single agent especially in patients with deficient mismatch repair (dMMR) endometrial cancer [5-7], and recent phase III clinical trials have shown that the addition of ICIs to chemotherapy improves PFS in patients with advanced or recurrent endometrial cancer [8-10].

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Conflict of Interest
KH reports personal fees and grants/research support from AstraZeneca from AstraZeneca, Chugai, MSD/Merck, Taiho, Takeda, and Daiichi-Sankyo.

RF, FG, EB and SU report grants from Roche to their institution to support the conduct of the study.

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AtTEnd trial is the first international phase III trial investigating the addition of atezolizumab, an anti-programmed death ligand 1 (PD-L1) antibody, to standard platinum-based chemotherapy for advanced/recurrent endometrial carcinoma [11]. The addition of atezolizumab to chemotherapy significantly improved PFS in the dMMR population (hazard ratio [HR]=0.36; 95% confidence interval [CI]=0.23–0.57; p=0.001; median not reached with atezolizumab vs. 6.9 months with placebo) and in the all-comer population (HR=0.74; 95% CI=0.61–0.91; p=0.022; median 10.1 vs. 8.9 months, respectively). In this study, subgroup analyses suggested that Asian race may be a negative predictive factor of atezolizumab efficacy in terms of PFS.

The association between race and ICI efficacy is poorly understood. In the DUO-E trial, the efficacy of durvalumab was reduced in Asian compared with White cohort. However, in cervical cancer, the efficacy of ICIs was similar in Asian and non-Asian race subgroups [12,13].

In this post-hoc analysis, we investigated patient and tumor characteristics in Asian and non-Asian cohorts that may impact on immunotherapy efficacy and toxicity profile.

MATERIALS AND METHODS

AtTEnd trial (NCT03603184; 2018-001072-37) is a multicenter double-blind placebo-controlled randomized phase III trial conducted at 89 hospitals in 11 countries across Europe, Australia, New Zealand, and Asia (**Data S1**). Full details of methods have been previously published [11]. Briefly, patients with newly diagnosed endometrial cancer, or recurrent disease were randomly assigned in a 2:1 ratio to receive atezolizumab or placebo combined with chemotherapy and continued as maintenance therapy.

Atezolizumab (or placebo) was administered at 1,200 mg combined with carboplatin and paclitaxel intravenously on day 1 every 21 days for 6–8 cycles, followed by atezolizumab 1,200 mg or placebo every 21 days until objective radiological disease progression, unacceptable toxicity, or consent withdrawal.

The study had two independent co-primary endpoints: PFS (in the dMMR and all-comer populations) and overall survival (OS) (in the all-comer population). PFS was defined as the time from randomization to the date of first progression, as assessed by investigators, or death from any cause, whichever occurred first.

The Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 was used to evaluate the radiological assessments. If a patient continued treatment after progression, progression was to be confirmed 4–8 weeks later according to immune RECIST. Adverse events (AEs) were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0.

The analysis according to Asian race was not prespecified and therefore no a-priori clinical hypothesis was stated, and no alpha was allocated to this analysis. Race was defined as reported by the patients.

The analyses were performed separately in patients with a dMMR and proficient mismatch repair (pMMR) tumor due to the predictive effect of the mismatch repair (MMR) status emerging from the pre-planned PFS subgroup analysis [11].

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This clinical trial update is an original submission; however, some results were presented in an oral presentation at the European Society of Gynecological Oncology (ESGO) Annual Meeting 2024 (Nishio et al. Int J Gynecol Cancer 2024;34:A20-A21). The Mario Negri Institute for Pharmacological Research of Milan, Italy is the legal entity responsible for the governance, coordination, and execution of the study on behalf of Mario Negri Gynecologic Oncology (MaNGO) group.

Data Availability

In accordance with the journal's guidelines, we will provide our data for independent analysis by a selected team by the Editorial Team for the purposes of additional data analysis or for the reproducibility of this study in other centers if such is requested.

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Author Contributions

Conceptualization: H.K., F.R., B.E., C.N.; Data curation: P.B., H.E., A.Y., L.C., R.M., H.F., K.V., L.C.H., N.S.[1], M.L., A.K., L.Y.C., U.S., R.A., N.S.[2], A.E., L.J., G.A., T.K., B.E.E., P.I., C.C., A.A., B.A., B.M.P.; Formal analysis: G.F.; Investigation: H.K., P.B., H.E., A.Y., L.C., R.M., H.F., K.V., L.C.H., N.S.[1], M.L., A.K., L.Y.C., R.A., N.S.[2], A.E., L.J., G.A., T.K., B.E.E., P.I., C.C., A.A., B.A., B.M.P., C.N.; Writing - original draft: H.K., F.R., B.E.; Writing - review & editing: P.B., G.F., H.E., A.Y., L.C., R.M., H.F., K.V., L.C.H., N.S.[1], M.L., A.K., L.Y.C., U.S., R.A., N.S.[2], A.E., L.J., G.A., T.K., B.E.E., P.I., C.C., A.A., B.A., B.M.P., C.N.

N.S.[1], Shin Nishio; N.S.[2], Satoshi Nakagawa.

Continuous variables were expressed as mean ± standard deviation or median (first quartile to third quartile). Categorical variables were expressed as frequency and proportion of each subject in each category. To compare the Asian and non-Asian cohorts the χ^2 test (or Fisher's exact test) and the Wilcoxon test were performed for categorical and continuous variable, respectively. The prognostic effect on PFS of variables detected as statistically different between the 2 cohorts was evaluated in patients randomized to placebo by means of univariable and multivariable Cox proportional hazards models. Results are provided as HRs and 95% CIs. The Kaplan-Meier (KM) method and the log-rank test were used to estimate and compare the survival curves. The χ^2 test was used to evaluate the proportion of severe toxicities in the atezolizumab arm compared to placebo arm.

PFS is a composite outcome measure combining three distinct events: tumor regrowth, appearance of new lesions and death without progression [14]. The clinical significance of each event varies, and the appearance of metastases, i.e. new lesions rather than tumor regrowth is the hallmark of tumor aggressiveness [15]. The role of Asian race on the time to appearance of metastases was assessed with a competing risks analysis in patients with a pMMR tumor according to randomization arm. The event of interest was the appearance of new lesions (with or without the synchronous appearance of tumor regrowth) or clinical progression. The cause-specific cumulative incidence function curves of Asian and non-Asian cohorts were compared using the Gray's test and the prognostic effect of race on the time to appearance of metastases was evaluated by means of the Fine and Gray model. Results are provided as subdistribution HRs (SHRs) and 95% CI [16]. Safety was assessed in all patients who received at least 1 dose of any study drug and described according to treatment arm and race. p-value threshold was set at 0.05, 2-sided. Statistical analyses were performed with SAS version 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

1. Patients

Between October 3, 2018 and February 7, 2022, 549 patients were randomized and included in the intention-to-treat population of the AtTEnd study (atezolizumab, n=360; placebo, n=189). Of those patients, 112 were Asian (Japan, n=80; Republic of Korea, n=21; Australia/New Zealand, n=4; UK, n=4; Taiwan, n=2; Germany, n=1). **Fig. 1** shows the study flow chart with Asian and non-Asian cohorts distribution.

Baseline characteristics that were differently distributed between Asian and non-Asian cohorts are presented in **Table 1**. A more comprehensive description of all variables tested is reported in **Table S1**. Notably, Asian patients, compared to non-Asian, appeared to be younger (median age: 63 vs. 67 years, p<0.001), leaner (median body mass index: 23.1 vs. 28.7 kg/m^2, p<0.001), fitter (Eastern Cooperative Oncology Group performance status equal to 0: 82.0% vs. 65.5%, p=0.001) and more frequently with a positive PD-L1 expression (50.0% vs. 26.6%, p<0.001). Other differences emerged in terms of status of disease (55.4% in Asian vs. 70.3% in non-Asian cohort, p=0.003, were enrolled in the recurrent setting), and on previous treatments. In particular more Asian patients underwent surgery in the newly-diagnosed group, (82.0% in Asian vs. 42.3% in non-Asian cohort, p<0.001) and Asian patients enrolled at relapse were more frequently treated with adjuvant chemotherapy (67.7% in Asian vs. 40.7% in non-Asian cohort, p<0.001) whereas previous radiotherapy was more frequently administered in non-Asian (16.1% in Asian vs. 49.8% in non-Asian cohort, p<0.001).

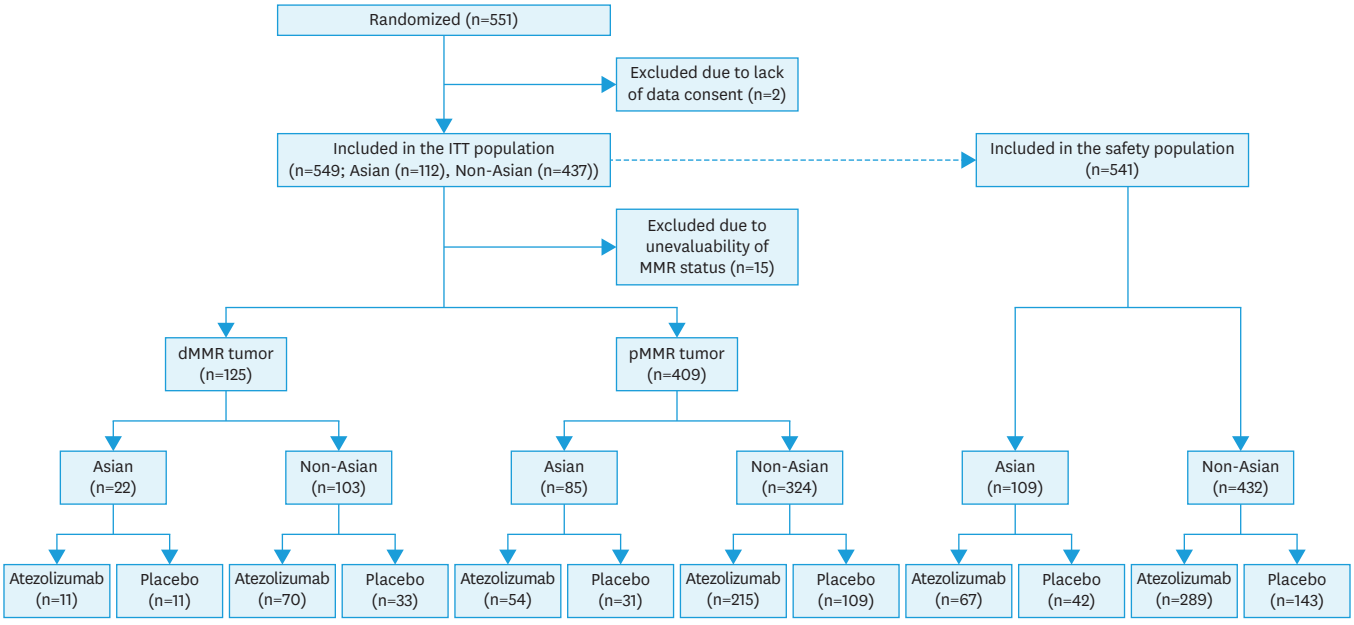

Fig. 1. Flow chart of the study population.
dMMR, deficient mismatch repair; ITT, intention-to-treat; MMR, mismatch repair; pMMR, proficient mismatch repair.

Conversely, there was no difference in the mismatch profile between the cohorts (19.6% dMMR tumor in Asian vs. 23.6% in non-Asian cohort, p=0.335).

The median number of chemotherapy cycles was 6 in both cohorts but the proportion of Asian patients who received up to 8 cycles was higher both in placebo (35.7% in Asian vs. 17.5% in non-Asian cohort, p=0.012) and atezolizumab arm (25.4% in Asian vs. 13.8% in non-Asian cohort, p=0.020). The distribution of reasons for chemotherapy discontinuation was similar in the two cohorts (**Table S2**).

2. PFS

The data cutoff set for the primary analysis on PFS was the same set for this analysis, i.e. May 31, 2023. The median duration of follow-up was 28.3 (interquartile range, 21.2–37.6) months.

Fig. S1 shows the KM curves of PFS comparing the Asian to non-Asian cohort in all comers receiving placebo (median PFS: 11.8 months in Asian, 8.5 months in non-Asian; log-rank p<0.001). The results of multivariable models in placebo arm adjusted for the variables differently distributed between Asian and non-Asian cohorts to evaluate the prognostic effect of Asian race are shown in **Tables S3-S5**. The positive prognostic role of Asian race was confirmed in all the models.

Fig. 2A shows the PFS KM curves of atezolizumab and placebo arms in the dMMR subgroup for the Asian (p=0.270) and non-Asian (p<0.001) cohorts. The beneficial impact of atezolizumab was statistically confirmed in the non-Asian cohort (HR=0.31; 95% CI=0.19–0.51; p<0.001), but not in the Asian cohort (HR=0.46; 95% CI=0.11–1.88; p=0.281).

PFS comparisons between atezolizumab and placebo in patients with a pMMR tumor for the Asian (p=0.224) and non-Asian cohorts (p=0.117) are shown in **Fig. 2B**. Although no interaction of treatment and race (p=0.071) was found, the estimate of HR was 0.82 (95%

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Table 1. Baseline demographic and clinical characteristics of Asian and non-Asian cohorts - ITT analysis set

Characteristics	Patients with dMMR tumor			Patients with pMMR tumor			Overall		
	Asian (n=22)	Non-Asian (n=103)	p-value*	Asian (n=85)	Non-Asian (n=324)	p-value*	Asian (n=112)	Non-Asian (n=437)	p-value*
Age (yr)			<0.001			<0.001			<0.001
Mean ± SD	56.5±7.8	65.8±9.3		62.8±10.7	67.3±8.1		61.6±10.4	67.0±8.4	
Median (Q1–Q3)	56.5 (53.0–59.0)	66.0 (60.0–73.0)		64.0 (57.0–68.0)	68.0 (62.0–73.0)		63.0 (56.0–68.0)	67.0 (62.0–73.0)	
BMI (kg/m^2)			<0.001			<0.001			<0.001
Mean ± SD	23.3±6.0	30.2±8.3		24.6±5.3	29.9±7.3		24.3±5.5	30.0±7.5	
Median (Q1–Q3)	21.9 (19.9–26.4)	28.9 (23.4–34.7)		23.3 (21.0–28.1)	28.6 (24.3–34.4)		23.1 (20.8–27.3)	28.7 (24.2–34.5)	
Missing	0	0		3	7				
Obesity	3 (13.6)	48 (46.6)	0.004	14 (17.1)	131 (41.3)	<0.001	18 (16.5)	185 (43.0)	<0.001
Missing	0	0		3	7		3	7	
ECOG performance status			0.025			0.013			0.001
0	19 (86.4)	62 (61.4)		68 (81.0)	215 (67.0)		91 (82.0)	283 (65.5)	
1–2	3 (13.6)	39 (38.6)		16 (19.0)	106 (33.0)		20 (18.0)	149 (34.5)	
Missing	0	2		1	3		1	5	
PD-L1 (IC) expression			0.039			<0.001			<0.001
Negative	6 (27.3)	53 (51.5)		49 (57.6)	265 (82.0)		56 (50.0)	320 (73.4)	
Positive	16 (72.7)	50 (48.5)		36 (42.4)	58 (18.0)		56 (50.0)	116 (26.6)	
Not evaluable	0	0		0	1		0	1	
Status of disease			0.306			0.054†			0.013†
Newly diagnosed - stage I	0 (0.0)	0 (0.0)		0 (0.0)	1 (0.3)		0 (0.0)	1 (0.2)	
Newly diagnosed - stage III	2 (9.1)	5 (4.9)		7 (8.2)	16 (4.6)		10 (8.9)	21 (4.8)	
Newly diagnosed - stage IV	9 (40.9)	29 (28.2)		30 (35.3)	79 (24.4)		40 (35.7)	108 (24.7)	
Recurrent	11 (50.0)	69 (67.0)		48 (56.5)	229 (70.7)		62 (55.4)	307 (70.3)	
Patients with newly diagnosed disease	11 (50.0)	34 (33.0)	0.132	37 (43.5)	95 (29.3)	0.013	50 (44.6)	130 (29.7)	0.003
Previous surgery	10 (90.9)	13 (38.2)	0.002	29 (78.4)	41 (43.2)	<0.001	41 (82.0)	55 (42.3)	<0.001
Patients with recurrent disease	11 (50.0)	69 (67.0)		48 (56.5)	229 (70.7)		62 (55.4)	307 (70.3)	
Previous chemotherapy and radio therapy			<0.001†			<0.001			<0.001
No	0 (0.0)	24 (34.8)		12 (25.0)	66 (28.8)		13 (21.0)	91 (29.6)	
Only chemotherapy	8 (72.7)	6 (8.7)		29 (60.4)	56 (24.5)		39 (62.9)	63 (20.6)	
Only radiation therapy	3 (27.3)	28 (40.6)		4 (8.3)	58 (25.3)		7 (11.3)	91 (29.6)	
Both chemotherapy and radiation therapy	0 (0.0)	11 (15.9)		3 (6.3)	49 (21.4)		3 (4.8)	62 (20.2)	

Data shown are number (%) not otherwise specified.
BMI, body mass index; dMMR, deficient mismatch repair; ECOG, Eastern Cooperative Oncology Group; ITT, intention-to-treat; PD-L1, programmed death ligand 1; pMMR, proficient mismatch repair; Q, quartile; SD, standard deviation.
*The χ^2 test or Wilcoxon test; †Fisher exact test.

CI=0.63–1.05; p=0.119) in the non-Asian cohort, and 1.42 (95% CI=0.80–2.50; p=0.227) in the Asian cohort.

3. Tumor progression with or without new lesions

In further characterization of the pMMR population, **Table S6** illustrates the number of distinct PFS events by race, separately in patients treated with placebo and atezolizumab.

In patients with a pMMR tumor treated with placebo, the SHR estimates for Asian compared to non-Asian population were 0.73 (95% CI=0.38–1.39; p=0.334, Gray's test p=0.341) for progression due to the appearance of new lesion and 0.46 (95% CI=0.20–1.05; p=0.066, Gray's test p=0.076) for tumor progression without new lesions (**Fig. 3A and B**). In patients with a pMMR tumor and treated with atezolizumab, the SHRs for Asian compared to non-Asian cohorts were 0.68 (95% CI=0.43–1.09; p=0.106, Gray's test, p=0.115) for progression due to the appearance of new lesion and 1.21 (95% CI=0.73–2.03; p=0.459, Gray's test, p=0.472) for tumor progression without new lesions (**Fig. 3C and D**). None of these comparisons reached the statistical significance.

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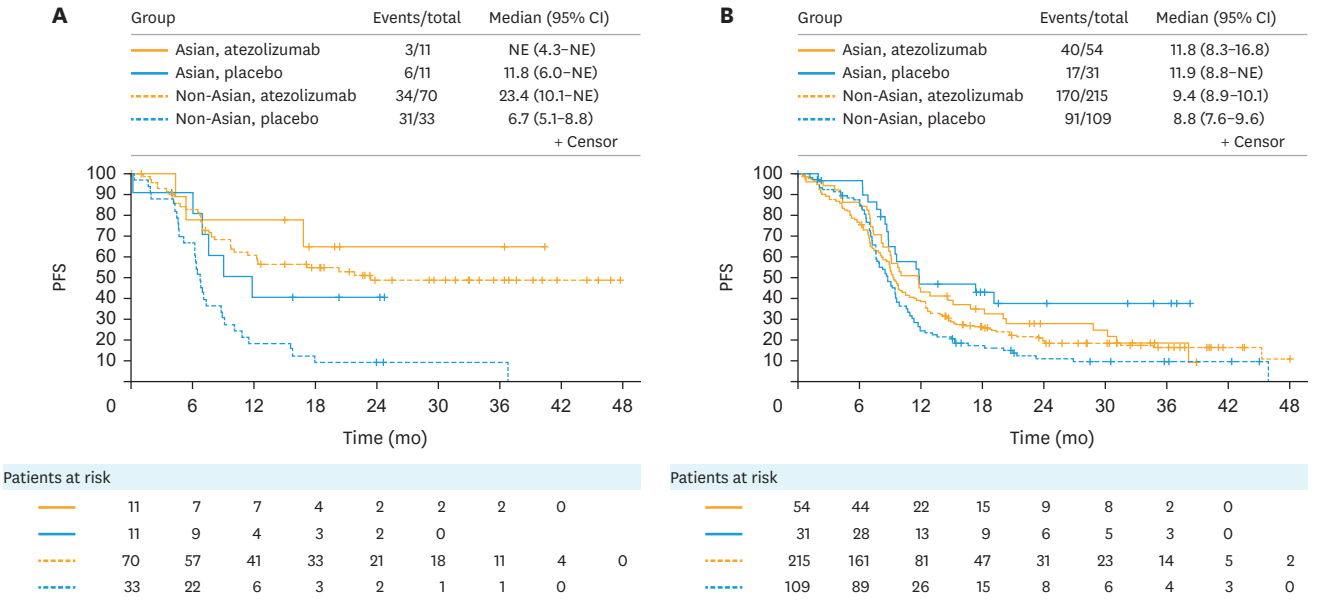

Fig. 2. Kaplan-Meier curves of PFS according to treatment arm and race. (A) dMMR subgroup and (B) pMMR subgroup.
CI, confidence interval; dMMR, deficient mismatch repair; PFS, progression-free survival; pMMR, proficient mismatch repair.

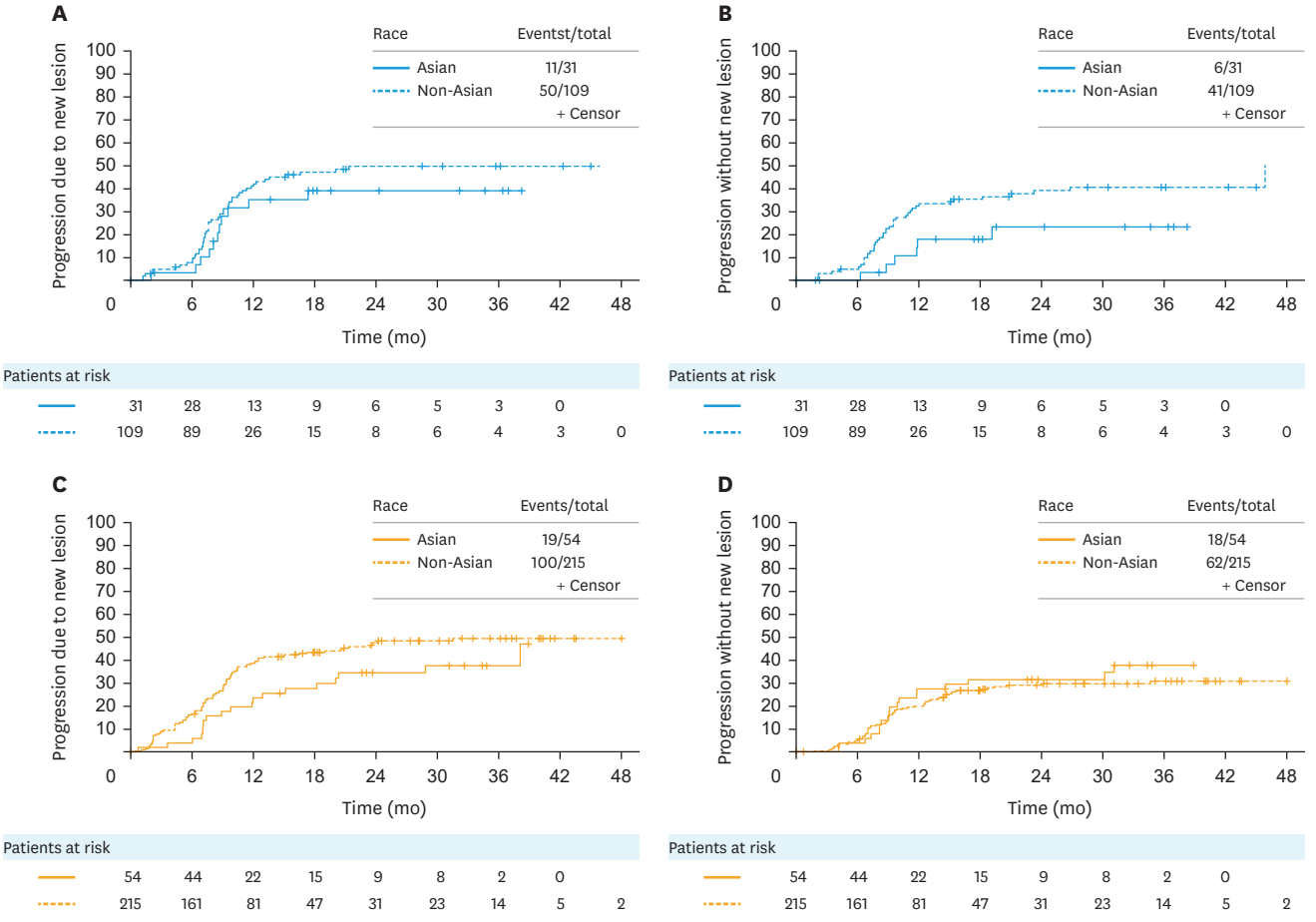

Fig. 3. Cumulative incidence curves of progression.
Cumulative incidence curves of progression for (A) new lesions, (B) tumor regrowth in placebo arm according to race; cumulative incidence curves of progression for (C) new lesions, (D) tumor regrowth in atezolizumab arm according to race.

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4. Safety profile

Treatment-emergent AEs occurring in at least 20% of patients in any of the 2 study arms by race are listed in **Table 2**. In the Asian cohort, the frequency of severe AEs was higher in the atezolizumab (82.1%) than in the placebo arm (64.3%, p=0.036), while it seemed to be similar in the non-Asian cohort (63.3% in atezolizumab vs. 63.6% in placebo arm, p=0.949). A statistically significant differences was detected in leukopenia events for which a higher frequency was observed in non-Asian patients treated with atezolizumab than in those treated with placebo (20 patients, 6.9% vs. 3 patients, 2.1%, p=0.036). As expected, the frequency of severe immune-related AEs was higher in atezolizumab arm for both race cohorts but interestingly the relative increase versus placebo was more pronounced in the Asian cohort (16 patients, 23.9% vs. 2 patients, 4.8%, p=0.009) than in non-Asian (35 patients, 12.1% vs. 8 patients, 5.6%, p=0.033) (**Table S7**).

Table 2. Maximum grade of adverse events occurred in at least 20% of patients - safety analysis set (n=541)

Variables	G0	G1	G2	G3	G4	G5	G3+G4+G5	χ^2 test, p-value†
Overall								
Non-Asian, placebo	0 (0.0)	5 (3.5)	47 (32.9)	67 (46.9)	20 (14.0)	4 (2.8)	91 (63.6)	0.949
Non-Asian, atezolizumab	4 (1.4)	16 (5.5)	86 (29.8)	120 (41.5)	54 (18.7)	9 (3.1)	183 (63.3)	
Asian, placebo	0 (0.0)	5 (11.9)	10 (23.8)	19 (45.2)	8 (19.0)	0 (0.0)	27 (64.3)	0.036
Asian, atezolizumab	1 (1.5)	0 (0.0)	11 (16.4)	37 (55.2)	17 (25.4)	1 (1.5)	55 (82.1)	
Blood and lymphatic system disorders								
Anaemia								
Non-Asian, placebo	88 (61.5)	11 (7.7)	25 (17.5)	18 (12.6)	1 (0.7)	0 (0.0)	19 (13.3)	0.728
Non-Asian, atezolizumab	170 (58.8)	23 (8.0)	61 (21.1)	34 (11.8)	1 (0.3)	0 (0.0)	35 (12.1)	
Asian, placebo	32 (76.2)	1 (2.4)	4 (9.5)	5 (11.9)	0 (0.0)	0 (0.0)	5 (11.9)	0.229
Asian, atezolizumab	41 (61.2)	2 (3.0)	10 (14.9)	14 (20.9)	0 (0.0)	0 (0.0)	14 (20.9)	
Leukopenia								
Non-Asian, placebo	138 (96.5)	0 (0.0)	2 (1.4)	3 (2.1)	0 (0.0)	0 (0.0)	3 (2.1)	0.036
Non-Asian, atezolizumab	257 (88.9)	4 (1.4)	8 (2.8)	17 (5.9)	3 (1.0)	0 (0.0)	20 (6.9)	
Asian, placebo	34 (81.0)	0 (0.0)	5 (11.9)	3 (7.1)	0 (0.0)	0 (0.0)	3 (7.1)	0.112
Asian, atezolizumab	49 (73.1)	0 (0.0)	6 (9.0)	10 (14.9)	2 (3.0)	0 (0.0)	12 (17.9)	
Neutropenia								
Non-Asian, placebo	91 (63.6)	2 (1.4)	16 (11.2)	22 (15.4)	12 (8.4)	0 (0.0)	34 (23.8)	0.765
Non-Asian, atezolizumab	185 (64.0)	10 (3.5)	29 (10.0)	31 (10.7)	34 (11.8)	0 (0.0)	65 (22.5)	
Asian, placebo	22 (52.4)	0 (0.0)	3 (7.1)	10 (23.8)	7 (16.7)	0 (0.0)	17 (40.5)	0.457
Asian, atezolizumab	29 (43.3)	1 (1.5)	5 (7.5)	18 (26.9)	14 (20.9)	0 (0.0)	32 (47.8)	
Thrombocytopenia								
Non-Asian, placebo	100 (69.9)	13 (9.1)	20 (14.0)	9 (6.3)	1 (0.7)	0 (0.0)	10 (7.0)	0.870
Non-Asian, atezolizumab	213 (73.7)	28 (9.7)	29 (10.0)	16 (5.5)	3 (1.0)	0 (0.0)	19 (6.6)	
Asian, placebo	35 (83.3)	1 (2.4)	2 (4.8)	4 (9.5)	0 (0.0)	0 (0.0)	4 (9.5)	0.309
Asian, atezolizumab	42 (62.7)	8 (11.9)	6 (9.0)	9 (13.4)	2 (3.0)	0 (0.0)	11 (16.4)	
Gastrointestinal disorders								
Constipation								
Non-Asian, placebo	105 (73.4)	26 (18.2)	12 (8.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	-
Non-Asian, atezolizumab	211 (73.0)	56 (19.4)	22 (7.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Asian, placebo	30 (71.4)	6 (14.3)	6 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	-
Asian, atezolizumab	47 (70.1)	13 (19.4)	7 (10.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Diarrhea								
Non-Asian, placebo	112 (78.3)	21 (14.7)	10 (7.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.061
Non-Asian, atezolizumab	220 (76.1)	48 (16.6)	14 (4.8)	7 (2.4)	0 (0.0)	0 (0.0)	7 (2.4)	
Asian, placebo	38 (90.5)	4 (9.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.426
Asian, atezolizumab	60 (89.6)	6 (9.0)	0 (0.0)	1 (1.5)	0 (0.0)	0 (0.0)	1 (1.5)	
Nausea								
Non-Asian, placebo	91 (63.6)	37 (25.9)	13 (9.1)	2 (1.4)	0 (0.0)	0 (0.0)	2 (1.4)	0.990
Non-Asian, atezolizumab	197 (68.2)	70 (24.2)	18 (6.2)	4 (1.4)	0 (0.0)	0 (0.0)	4 (1.4)	
Asian, placebo	25 (59.5)	12 (28.6)	5 (11.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	-
Asian, atezolizumab	39 (58.2)	16 (23.9)	12 (17.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	

(continued to the next page)

Table 2. (Continued) Maximum grade of adverse events occurred in at least 20% of patients - safety analysis set (n=541)

Variables	G0	G1	G2	G3	G4	G5	G3+G4+G5	χ^2 test, p-value†
Stomatitis								
Non-Asian, placebo	130 (90.9)	11 (7.7)	2 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.319
Non-Asian, atezolizumab	267 (92.4)	18 (6.2)	2 (0.7)	2 (0.7)	0 (0.0)	0 (0.0)	2 (0.7)	
Asian, placebo	38 (90.5)	0 (0.0)	4 (9.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	-
Asian, atezolizumab	53 (79.1)	6 (9.0)	8 (11.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
General disorders and administration site conditions								
Fatigue								
Non-Asian, placebo	75 (52.4)	40 (28.0)	24 (16.8)	4 (2.8)	0 (0.0)	0 (0.0)	4 (2.8)	0.856
Non-Asian, atezolizumab	154 (53.3)	81 (28.0)	45 (15.6)	9 (3.1)	0 (0.0)	0 (0.0)	9 (3.1)	
Asian, placebo	35 (83.3)	6 (14.3)	1 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.426
Asian, atezolizumab	64 (95.5)	0 (0.0)	2 (3.0)	1 (1.5)	0 (0.0)	0 (0.0)	1 (1.5)	
Pyrexia								
Non-Asian, placebo	128 (89.5)	10 (7.0)	4 (2.8)	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.7)	0.993
Non-Asian, atezolizumab	256 (88.6)	26 (9.0)	5 (1.7)	2 (0.7)	0 (0.0)	0 (0.0)	2 (0.7)	
Asian, placebo	38 (90.5)	4 (9.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.258
Asian, atezolizumab	45 (67.2)	15 (22.4)	5 (7.5)	2 (3.0)	0 (0.0)	0 (0.0)	2 (3.0)	
Musculoskeletal and connective tissue disorders								
Arthralgia								
Non-Asian, placebo*	102 (71.8)	21 (14.8)	16 (11.3)	3 (2.1)	0 (0.0)	0 (0.0)	3 (2.1)	0.196
Non-Asian, atezolizumab	223 (77.2)	42 (14.5)	22 (7.6)	2 (0.7)	0 (0.0)	0 (0.0)	2 (0.7)	
Asian, placebo	33 (78.6)	5 (11.9)	4 (9.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.426
Asian, atezolizumab	43 (64.2)	17 (25.4)	6 (9.0)	1 (1.5)	0 (0.0)	0 (0.0)	1 (1.5)	
Myalgia								
Non-Asian, placebo	132 (92.3)	8 (5.6)	2 (1.4)	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.7)	0.993
Non-Asian, atezolizumab	255 (88.2)	18 (6.2)	14 (4.8)	2 (0.7)	0 (0.0)	0 (0.0)	2 (0.7)	
Asian, placebo	37 (88.1)	2 (4.8)	3 (7.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.426
Asian, atezolizumab	53 (79.1)	8 (11.9)	5 (7.5)	1 (1.5)	0 (0.0)	0 (0.0)	1 (1.5)	
Nervous system disorders								
Peripheral sensory neuropathy								
Non-Asian, placebo	96 (67.1)	31 (21.7)	11 (7.7)	5 (3.5)	0 (0.0)	0 (0.0)	5 (3.5)	0.873
Non-Asian, atezolizumab	195 (67.5)	50 (17.3)	33 (11.4)	11 (3.8)	0 (0.0)	0 (0.0)	11 (3.8)	
Asian, placebo	16 (38.1)	17 (40.5)	9 (21.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.426
Asian, atezolizumab	26 (38.8)	24 (35.8)	16 (23.9)	1 (1.5)	0 (0.0)	0 (0.0)	1 (1.5)	
Psychiatric disorders								
Insomnia								
Non-Asian, placebo	136 (95.1)	5 (3.5)	2 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	-
Non-Asian, atezolizumab	275 (95.2)	13 (4.5)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Asian, placebo	38 (90.5)	4 (9.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	-
Asian, atezolizumab	51 (76.1)	12 (17.9)	4 (6.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Skin and subcutaneous tissue disorders								
Alopecia								
Non-Asian, placebo	95 (66.4)	5 (3.5)	43 (30.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	-
Non-Asian, atezolizumab	200 (69.2)	21 (7.3)	68 (23.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Asian, placebo	23 (54.8)	5 (11.9)	14 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	-
Asian, atezolizumab	43 (64.2)	8 (11.9)	16 (23.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	

Values are presented as number of subjects (%).
G, grade.
*For one event no grade was reported; †The proportion of patients with severe adverse events was compared between the placebo and atezolizumab arms in Asian and non-Asian subgroups.

DISCUSSION

This exploratory analysis aimed to assess whether the addition of atezolizumab to chemotherapy in advanced or recurrent endometrial cancer patients impacts PFS differently among Asian and non-Asian patients, and to elucidate potential causes for these differences.

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The findings revealed that Asian patients in the study were generally younger, non-obese, more likely to have undergone surgical intervention, less likely to have received prior radiotherapy and more likely to have received adjuvant chemotherapy for recurrent disease. Interestingly, within the placebo group, Asian patients exhibited longer PFS compared to their non-Asian counterparts, regardless of MMR status. Though inconclusive, the literature is rife with reports about differences in OS in Asian women with endometrial cancer while information about differences in disease-free survival is sparse [17,18].

The addition of atezolizumab to standard chemotherapy appears to improve the efficacy in both Asian and non-Asian patients with dMMR, but its benefit in those with pMMR appears to be notably reduced among Asians. In order to add granularity and transparence to the analysis we explored possible differences in the efficacy of atezolizumab regarding the specific components of PFS with a competing risk analysis. This analysis suggests that in the atezolizumab arm, Asian patients could have a lower cumulative incidence of new lesions appearance when primary tumor regrowth was considered a competing risk, and a higher cumulative incidence of primary tumor regrowth when new lesions appearance was the competing risk.

Since the appearance of new lesions rather than primary tumor growth seems to be the most important determinant of a poor survival, we will evaluate the impact of these differences on OS as soon as the data are mature [15].

Previous clinical trials have identified microsatellite instability/MMR status, PD-L1 expression, tumor mutational burden, and ARID1A mutations as key biomarkers for predicting the efficacy of ICIs. In the present study, we hypothesized that race is a factor associated with the efficacy of atezolizumab in the pMMR population. Consistent findings have been reported in other clinical trials involving uterine cancer. For instance, the DUO-E trial revealed that durvalumab was less effective in Asian patients compared to non-Asians. Although the influence of race on the efficacy of ICIs has been infrequently reported, a study in lung cancer indicated no significant difference in treatment efficacy between Asian and non-Asian cohorts [19]. This study suggests a pronounced disparity in the efficacy of atezolizumab between Asian and non-Asian patients within the pMMR population, though the precise reasons for this variation remain unclear. ARID1A expression was consistent across both groups, and although PD-L1 positivity was more prevalent among Asians, this would not account for the diminished efficacy of atezolizumab observed in this cohort. In our study, non-Asian patients exhibited a higher incidence of serous carcinoma, a histological subtype commonly linked to p53 abnormalities. Exploratory analyses from the RUBY trial revealed that patients with p53 abnormalities are more likely to benefit from ICIs [8]. It is possible that the variation in the prevalence of p53 abnormalities among the study populations influenced the outcomes observed in this investigation. Furthermore, distinct differences exist between Asian and non-Asian patients concerning prior treatment modalities. Asian patients were more likely to have undergone surgical intervention during their initial presentation and were also more likely to have received prior chemotherapy, while being less likely to have received prior radiation therapy in the recurrent setting. The potential impact of prior radiotherapy on the efficacy of ICIs warrants consideration. Notably, the KEYNOTE-001 trial, revealed that patients with a history of radiation therapy exhibited prolonged PFS and OS compared to those without such treatment [20]. A retrospective study demonstrated that nivolumab was more effective in patients who had received prior radiation compared to those who had not [21]. The lower incidence of prior radiotherapy among Asian patients

compared to non-Asians may justify a reduced efficacy of atezolizumab in the pMMR population among Asians.

Safety outcomes were also impacted by a higher incidence of anemia and thrombocytopenia in Asian patients, particularly for grade 3 or higher events. Such toxicities were higher in the atezolizumab but not in the placebo arm suggesting an association between immunotherapy toxicity and Asian race. Other toxicities (i.e. neutropenia and peripheral sensory neuropathy) had higher incidence in Asian patients in both arms and this effect may be attributed to the fact that a greater number of Asian patients received more than 6 cycles of chemotherapy. Regarding neutropenia, it has been reported that the frequency of leukopenia induced by taxane and platinum-based chemotherapy is higher in Asian populations [22,23] and our findings are aligned with these. The influence of race on the frequency of peripheral neuropathy has been documented in African-American populations, but there are no similar reports for Asian patients [24], leaving the underlying cause of this adverse event in Asians uncertain. However, factors related to pharmacogenomics and pharmaco-ethnicity may have played a role in the safety. Adverse events are unlikely to be associated with differences in the efficacy of atezolizumab between Asian and non-Asian populations in this pMMR cohort.

This analysis has certain limitations. First, comparisons between Asian and non-Asian cohorts were not pre-specified, and the statistical power was limited due to the underrepresentation of Asians (20%). Therefore, this analysis should be evaluated using a hypothesis-generating approach and the statistically non-significant results should be interpreted with caution. Second, we did not collected data about the patients' microbiome which has intricate interactions with the efficacy of immunotherapy and whose composition can be shaped by host genetics and diet [25]. Similarly, no data allowed us to explore the intra-tumoral microbiota which has recently emerged as a potent modulator of tumor microenvironment including its potential leveraging the immunogenic response [26]. Furthermore, this study did not include a comparative analysis of pharmacogenetics.

In conclusion, Asian race could influence the efficacy and safety profile of atezolizumab. In the pMMR population, atezolizumab did not confer a PFS benefit in Asian patients, whereas a trend of better PFS in non-Asian patients was confirmed. Future clinical studies should carefully consider racial differences in treatment efficacy.

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SUPPLEMENTARY MATERIALS

Data S1
AtTEnd study groups

Table S1
Baseline demographic and clinical characteristics of Asian and non-Asian cohorts - ITT analysis set

Table S2
Chemotherapy compliance - safety analysis set

Table S3
Prognostic effect of baseline demographic and clinical characteristics on PFS: univariable and multivariable Cox proportional hazards models - ITT population, in patients treated with placebo

Table S4
Prognostic effect of baseline demographic and clinical characteristics on PFS: univariable and multivariable Cox proportional hazards models - ITT population, in patients with newly diagnosed disease treated with placebo

Table S5
Prognostic effect of baseline demographic and clinical characteristics on PFS: univariable and multivariable Cox proportional hazards models - ITT population, in patients with recurrent disease treated with placebo

Table S6
Component events of PFS according to race and treatment arm - ITT population, in patients with pMMR tumor

Table S7
Maximum grade of immune-related adverse events - safety analysis set (n=541)

Fig. S1
Kaplan-Meier curves of PFS in all comers receiving placebo according to race.

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