MSD
INVENTING FOR LIFE

Managed access Consultee & Commentator engagement meeting:
Terminated guidance development for pembrolizumab for advanced, unresectable or metastatic urothelial cancer (CDF review of TA522) ID1634

Overview of clinical data and the decision to proceed with a termination

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10th February 2021

KEYNOTE-052 Phase 2 Study Evaluating First-Line Pembrolizumab in Cisplatin-Ineligible Advanced Urothelial Cancer: Updated Response and Survival Results

P. H. O'Donnell[1]; A. V. Balar[2]; J. Vuky[3]; D. E. Castellano[4]; J. Bellmunt[5]; T. Powles[6]; D. F. Bajorin[7]; P. Grivas[8]; N. M. Hahn[9]; E. R. Plimack[10]; M. J. Savage[11]; X. Fang[11]; J. L.Godwin[11]; T. L. Frenkl[11]; R. de Wit[12]

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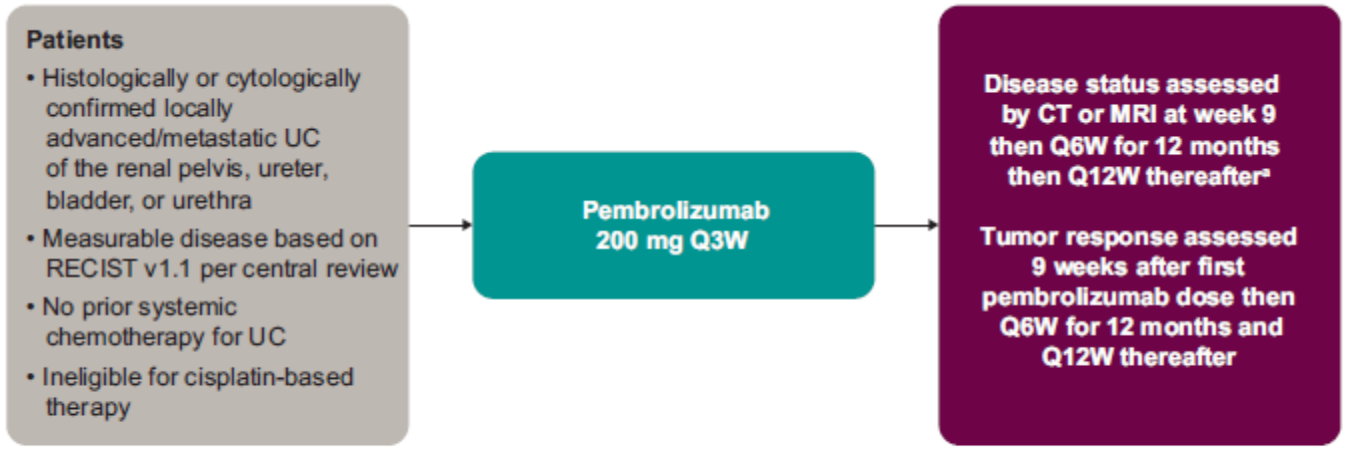
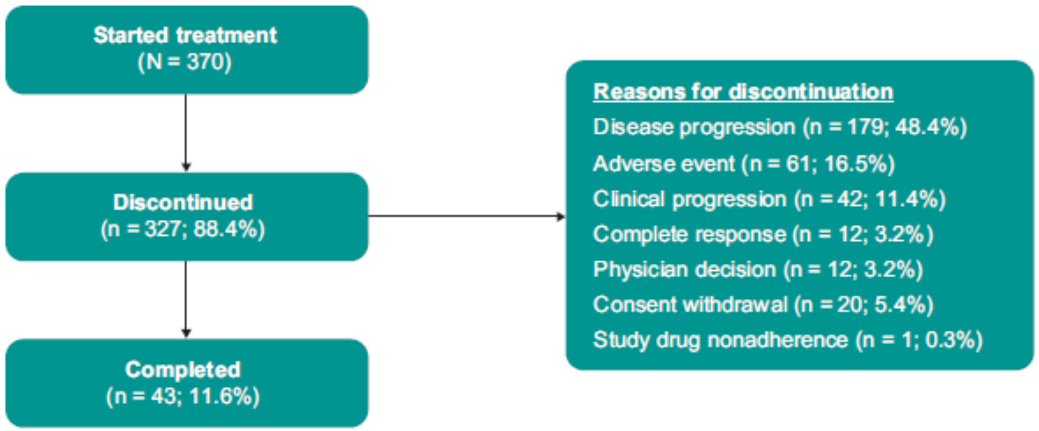


CT, computed tomography; MRI, magnetic resonance imaging; Q3W, every 3 weeks; Q6W, every 6 weeks; Q12W, every 12 weeks; UC, urothelial carcinoma.
[a]Until disease progression, start of new anticancer treatment, withdrawal of consent, or death.

Statistical Analysis

- Primary end point
  - Objective response rate (ORR) per RECIST v1.1 (independent radiologic review)
- Secondary end points
  - Duration of response (DOR) per RECIST v1.1 (independent radiologic review)
  - Progression-free survival (PFS) per RECIST v1.1 (independent radiologic review)
  - Overall survival (OS)
  - Safety and tolerability
- Primary and secondary efficacy end points were evaluated in all patients and by PD-L1 expression status
  - PD-L1 positive was defined as a CPS ≥10
    - CPS ≥10 was chosen to represent positive PD-L1 expression based on validation data reported in the primary analysis[5]
    - CPS was computed as the ratio of the number of tumor cells, lymphocytes, and macrophages expressing PD-L1 (numerator) to the total number of viable tumor cells in the biopsy specimen (denominator) × 100
- The all-patients-as-treated population (all enrolled patients who received ≥1 dose of pembrolizumab) served as the analysis population for efficacy and safety
- The Clopper-Pearson exact binomial method was used to assess point estimates and 95% CIs for ORR
- The Kaplan-Meier method was used to assess DOR, PFS, and OS
- Database cutoff was September 26, 2018

Figure 2. Patient Disposition



Patient Disposition and Baseline Demographics

- Mean follow-up (standard deviation [SD]) was 15.3 (12.1) months
  - 178 (48.1%) patients stopped study treatment within 3 months; 77 (20.8%) patients remained on study for ≥12 months
  - The last patient was enrolled 24.9 months before the data cutoff date
- Mean follow-up (SD) for responders was 28.1 (8.1) months

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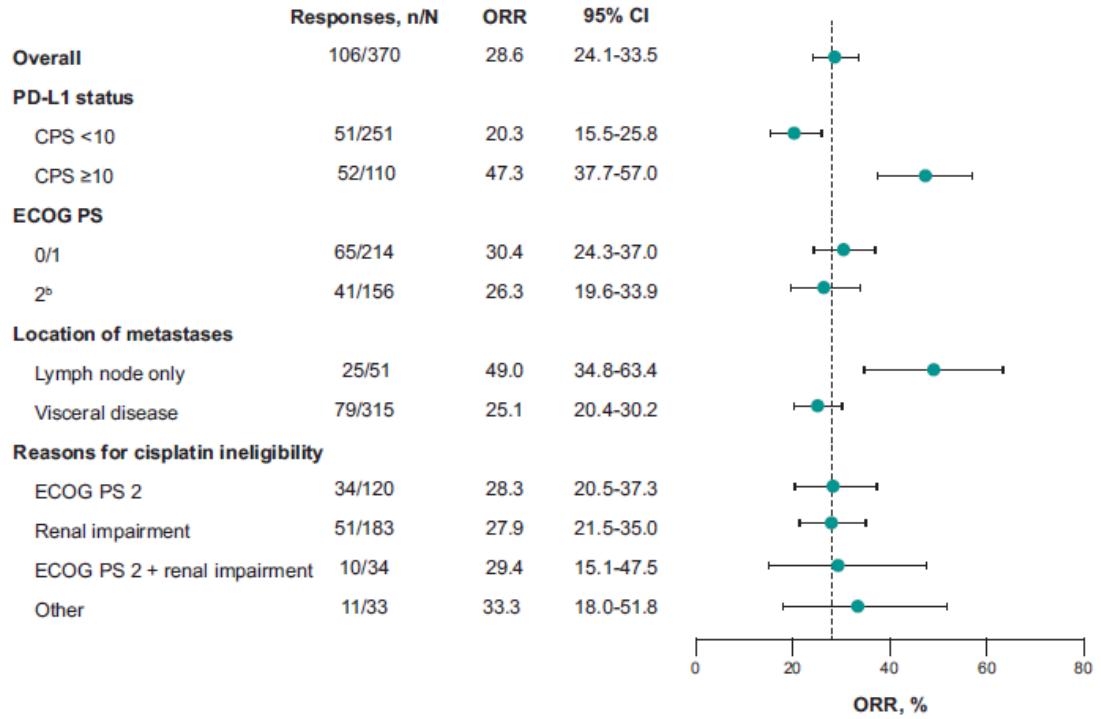
Table 2. Objective Response Rate in All Patients and Those With CPS ≥10 per Independent Radiologic Review

	All Patients N = 370		CPS ≥10 N = 110	
Response	n (%)	95% CI	n (%)	95% CI
Objective response rate	106 (28.6)	24.1-33.5	52 (47.3)	37.7-57.0
CR	33 (8.9)	6.2-12.3	22 (20.0)	13.0-28.7
PR	73 (19.7)	15.8-24.2	30 (27.3)	19.2-36.6
Stable disease	67 (18.1)	14.3-22.4	22 (20.0)	13.0-28.7
PD	157 (42.4)	37.3-47.6	30 (27.3)	19.2-36.6
No assessment[a]	31 (8.4)	5.8-11.7	6 (5.5)	2.0-11.5
NE[b]	9 (2.4)	1.1-4.6	0 (0)	0.0-3.3

CPS, combined positive score; CR, complete response; NE, nonevaluable; PD, progressive disease; PR, partial response.
[a]No available postbaseline imaging data.
[b]Had a postbaseline scan, and best objective response was determined to be NE by RECIST v1.1.

Figure 3. Objective Response Rates[a] by Patient Subgroups



CPS, combined positive score; ECOG PS, Eastern Cooperative Oncology Group performance status; ORR, objective response rate; PD-L1, programmed death ligand 1.
[a]Per RECIST v1.1 by independent radiologic review.
[b]Includes 1 patient with ECOG PS of 3.

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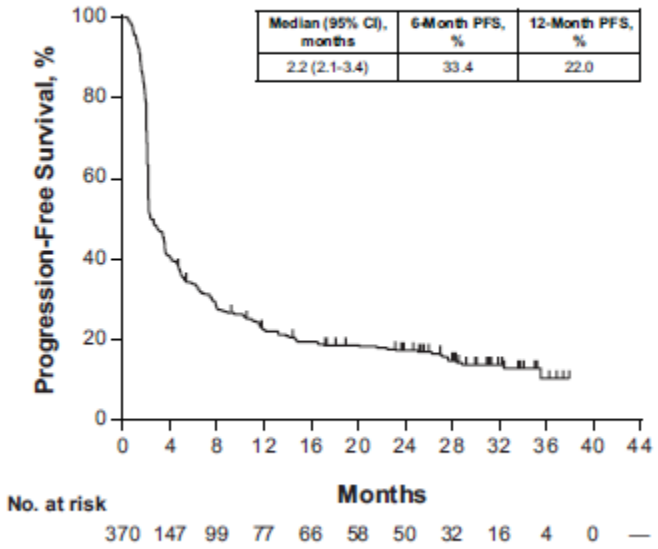
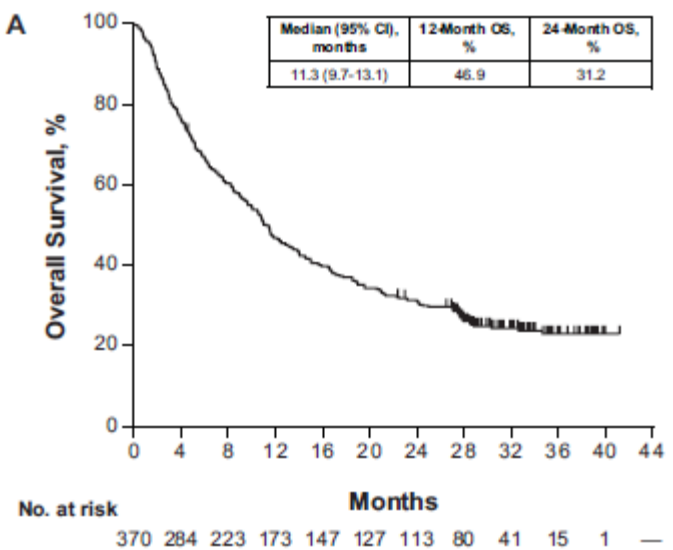
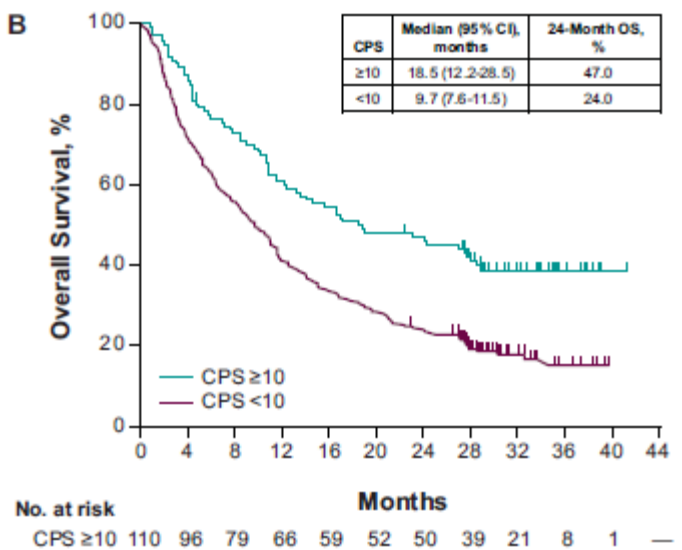
Figure 5. Kaplan-Meier Estimate of Progression-Free Survival



PFS, progression-free survival.

Figure 6. Kaplan-Meier Estimates of OS in (A) the Overall Population and (B) in Relation to PD-L1 Expression CPS ≥10 or CPS <10





CPS, combined positive score; OS, overall survival; PD-L1, programmed death ligand 1.

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Safety

- Grade 3-5 treatment-related adverse events (AEs) were reported in 20.8% of patients, most frequently fatigue (2.4%), colitis (1.9%), increased blood alkaline phosphatase level (1.6%), muscle weakness (1.4%), and hepatitis (1.4%)
- 34 (9.2%) patients discontinued because of treatment-related AEs
  - 16 (4.3%) of those were serious treatment-related AEs
- 1 patient died because of a treatment-related AE (myositis)

Table 3. Treatment-Related Adverse Events Occurring in ≥3% of Patients

Treatment-Related Adverse Event, n (%)	N = 370
Any	249 (67.3)
Fatigue	67 (18.1)
Pruritus	66 (17.8)
Rash	43 (11.6)
Decreased appetite	40 (10.8)
Hypothyroidism	37 (10.0)
Diarrhea	34 (9.2)
Nausea	32 (8.6)
Asthenia	15 (4.1)
Maculopapular rash	15 (4.1)
Pneumonitis	15 (4.1)
Increased AST	14 (3.8)
Pyrexia	14 (3.8)
Increased ALT	13 (3.5)
Dysgeusia	13 (3.5)
Vomiting	13 (3.5)
Cough	12 (3.2)
Constipation	11 (3.0)
Dry mouth	11 (3.0)
Influenzalike illness	11 (3.0)
Peripheral edema	11 (3.0)

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

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Pembrolizumab Alone or Combined With Chemotherapy vs Chemotherapy Alone as First-Line Therapy for Advanced Urothelial Carcinoma: KEYNOTE-361

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KEYNOTE-361 Study Design (NCT02853305)

Key Eligibility Criteria

- UC of renal pelvis, ureter, bladder or urethra
- Locally advanced unresectable or metastatic disease
- No prior systemic therapy for advanced disease
- ECOG PS 0, 1 or 2
- Tissue sample for PD-L1 assessment[a]

Stratification Factors

- PD-L1 expression[a] (CPS ≥10 vs <10)
- Choice of platinum

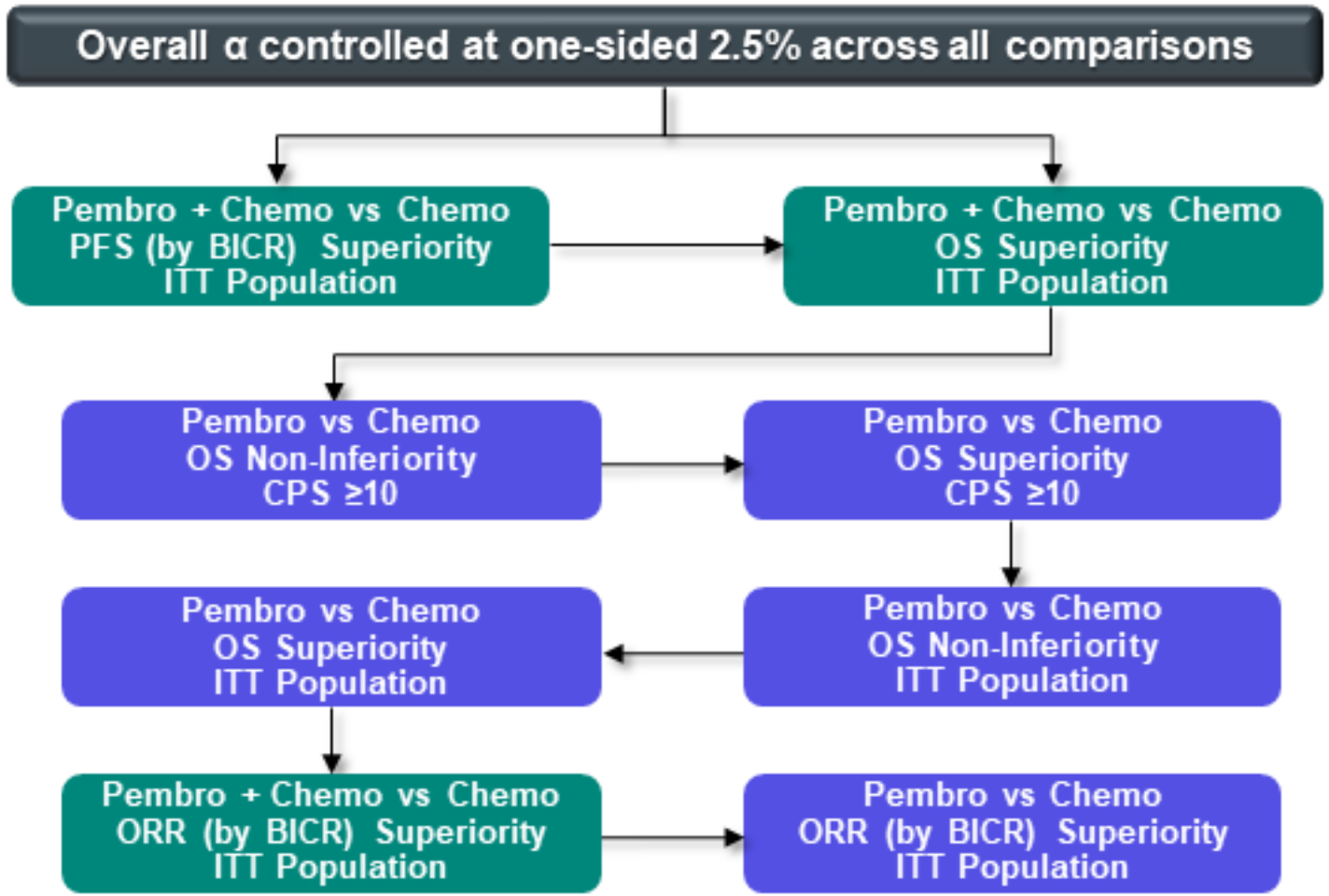
R (1:1:1)

- Pembrolizumab 200 mg Q3W + Gemcitabine 1000 mg/m^2 + Cisplatin 70 mg/m^2 *OR* Carboplatin AUC 5 for ≤6 cycles → Pembrolizumab 200 mg Q3W for ≤29 cycles
- Pembrolizumab 200 mg Q3W for ≤35 cycles
- Gemcitabine 1000 mg/m^2 on days 1 and 8 Q3W + Cisplatin 70 mg/m^2 *OR* Carboplatin AUC 5 on day 1 Q3W for ≤6 cycles

- Dual primary endpoints: PFS per RECIST v1.1 by BICR and OS
- Secondary endpoints: ORR, DCR, and DOR by BICR per RECIST v1.1, safety

[a]Assessed using the PD-L1 IHC 22C3 pharmDx assay. CPS (combined positive score) is the number of PD-L1–staining cells (tumor cells, lymphocytes, and macrophages) divided by the total number of viable tumor cells, multiplied by 100.
BICR, blinded independent central review.

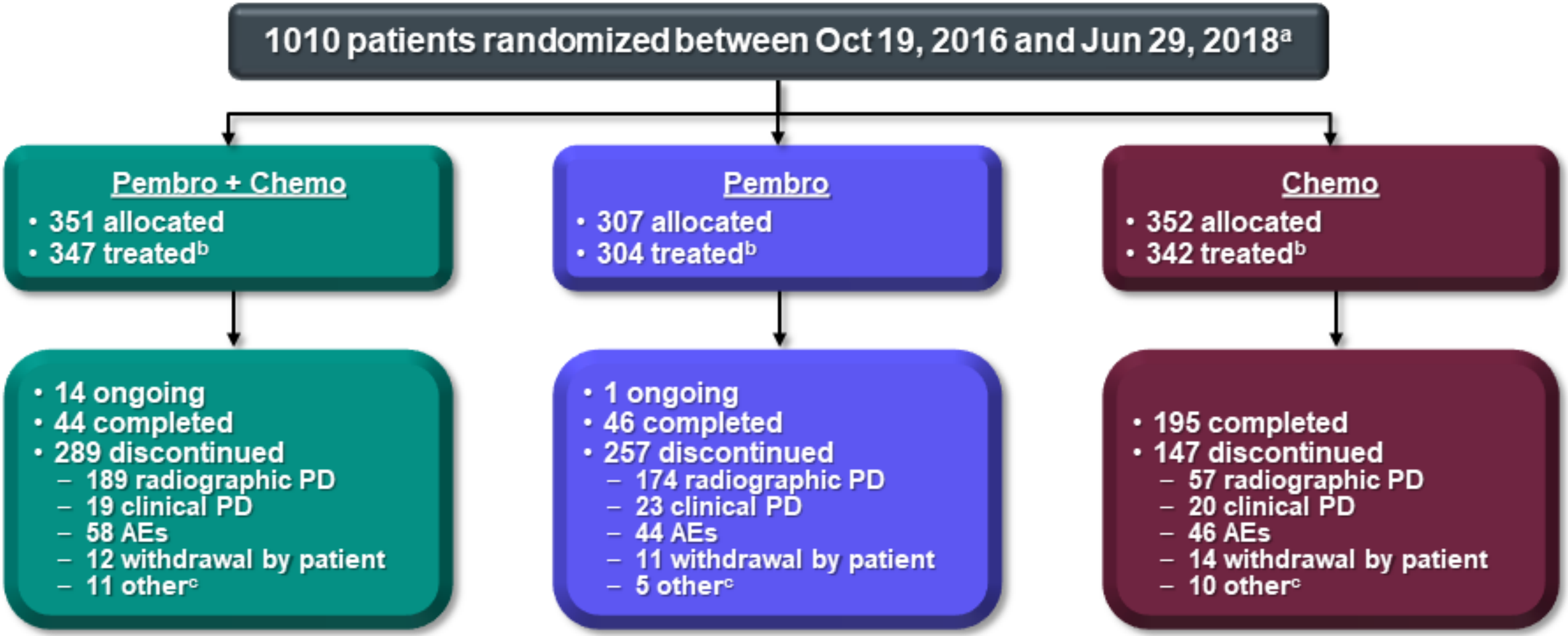
Statistical Considerations



- Hypotheses in top row tested first and in parallel

- Remaining hypotheses tested only if the hypothesis immediately before was statistically significant

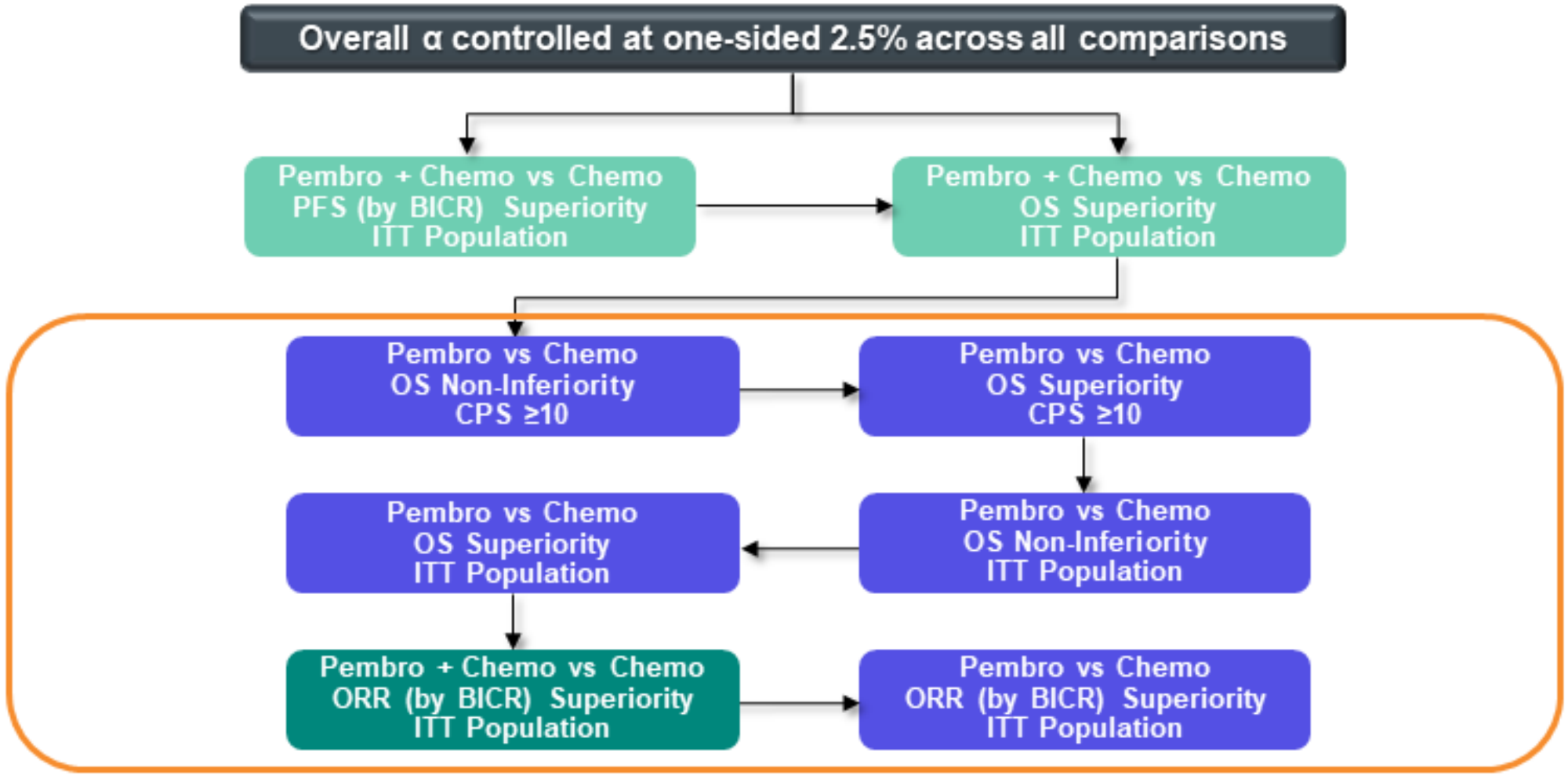
Patient Disposition



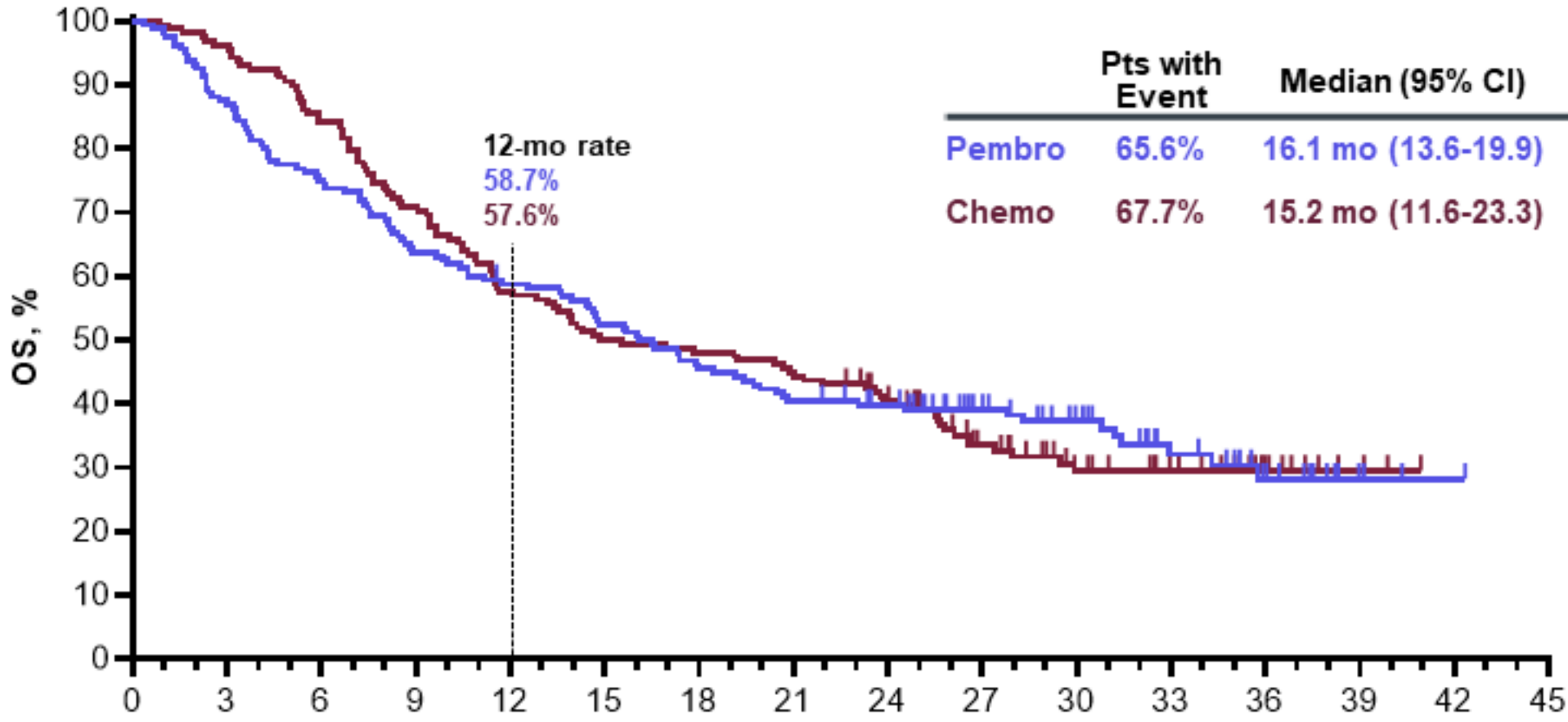
Median (range) time from randomization to cutoff: 31.7 (22.0-42.3) mo

[a]On or after Feb 21, 2018, a protocol amendment limited accrual to the pembro arm to patients with CPS≥10 tumors. 82% of patients were already randomized prior to Feb 21, 2018.
[b]Defined as patients who started study medication in the trial.
[c]Includes complete response, non-compliance with study drug, non-study anticancer therapy, physician decision, and use of excluded medication.
Data cutoff date: April 29, 2020.

Analysis Plan



OS: Pembro vs Chemo, Patients With CPS≥10 Tumors



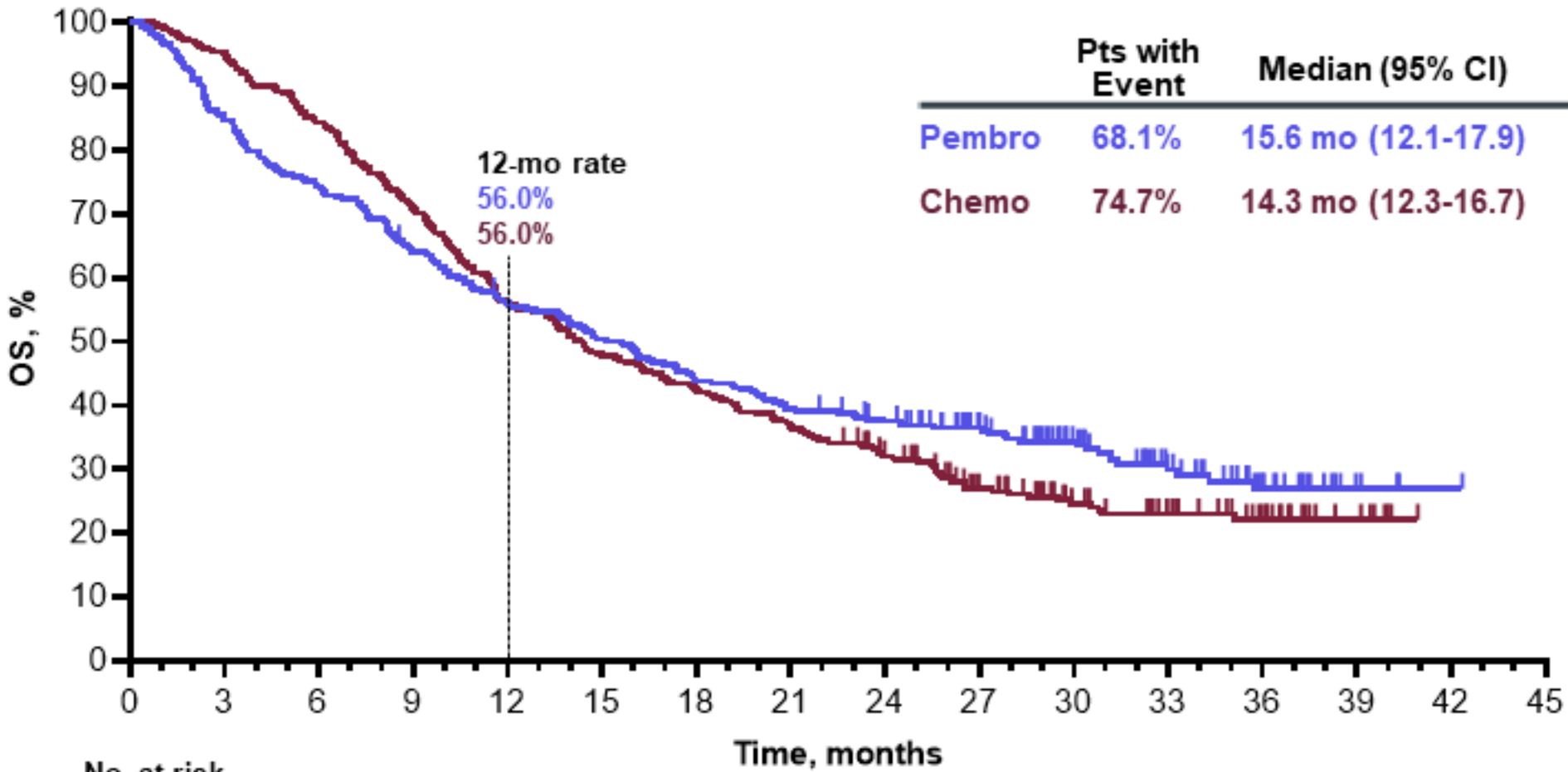
	Pts with Event	Median (95% CI)	HR (95% CI)
Pembro	65.6%	16.1 mo (13.6-19.9)	1.01 (0.77-1.32)
Chemo	67.7%	15.2 mo (11.6-23.3)	

No. at risk

160	139	120	102	93	83	72	64	59	46	34	20	12	3	1	0
158	152	133	112	91	79	76	71	60	40	25	17	9	3	0	0

Data cutoff date: April 29, 2020.

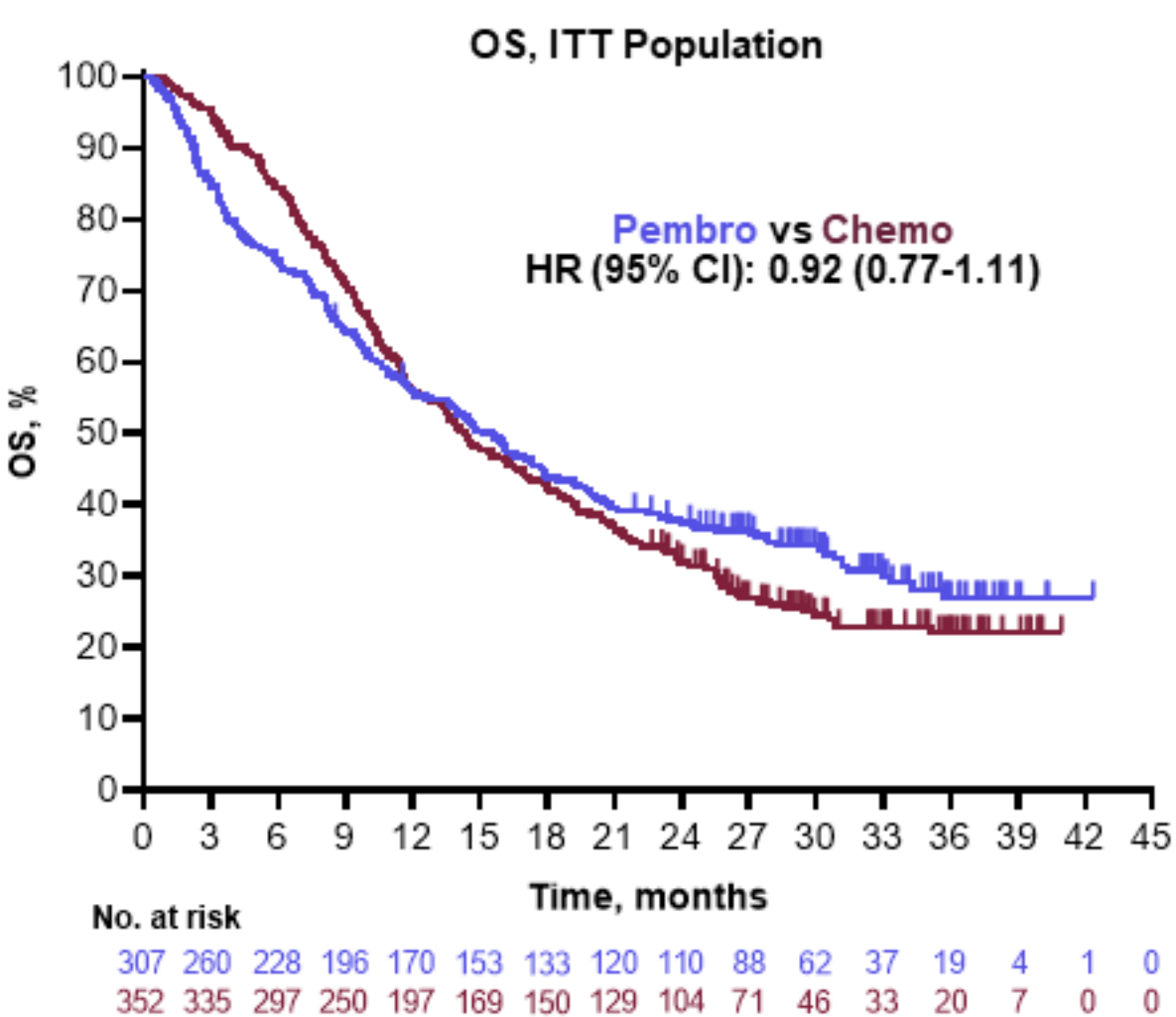
OS: Pembro vs Chemo, ITT Population

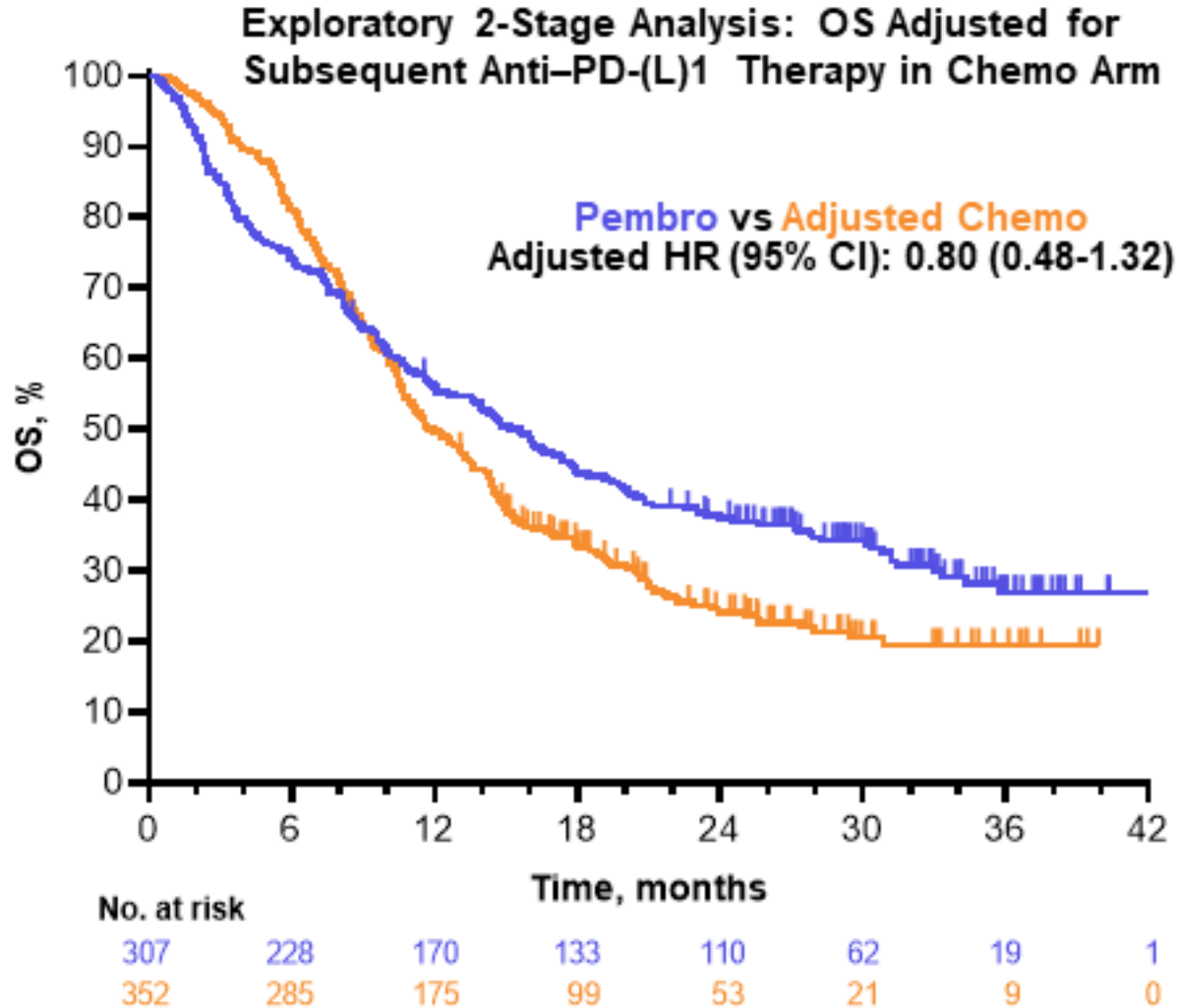


	Pts with Event	Median (95% CI)	HR (95% CI)
Pembro	68.1%	15.6 mo (12.1-17.9)	0.92 (0.77-1.11)
Chemo	74.7%	14.3 mo (12.3-16.7)	

Data cutoff date: April 29, 2020.

OS: Effect of Subsequent Anti–PD-(L)1 Therapy, ITT Population (Exploratory Analysis)



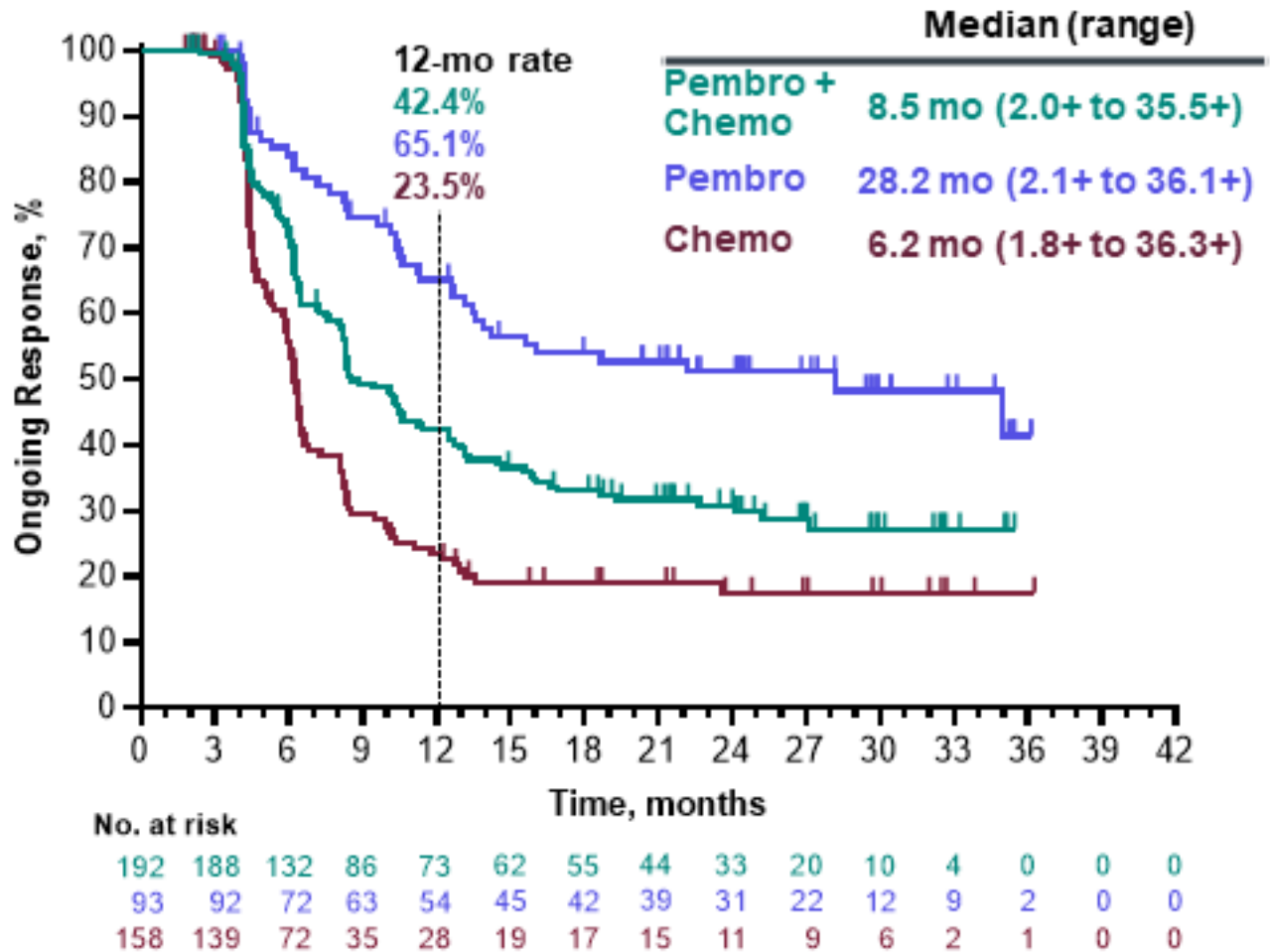


Data cutoff date: April 29, 2020.

ORR and DOR by BICR, ITT Population

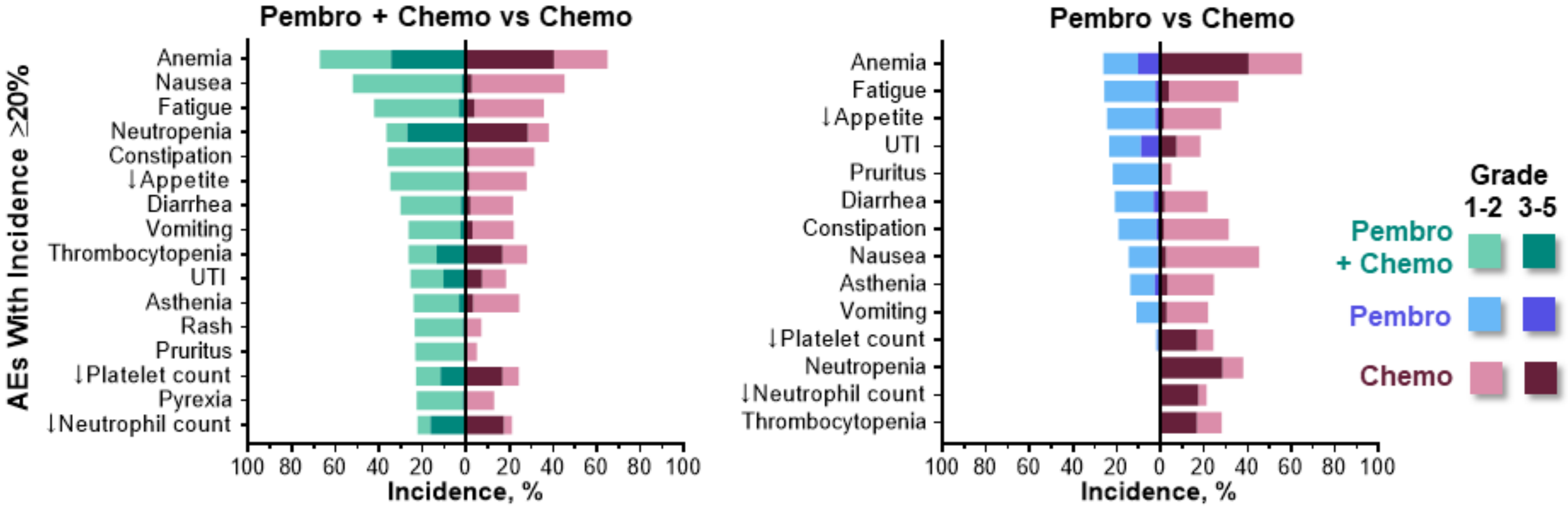
Confirmed Response, n (%)	Pembro + Chemo N = 351	Pembro N = 307	Chemo N = 352
ORR	**192 (54.7)**	**93 (30.3)**	**158 (44.9)**
DCR	**282 (80.3)**	**145 (47.2)**	**267 (75.9)**
CR	53 (15.1)	34 (11.1)	43 (12.2)
PR	139 (39.6)	59 (19.2)	115 (32.7)
SD	90 (25.6)	52 (16.9)	109 (31.0)
PD	39 (11.1)	118 (38.4)	39 (11.1)
Non-CR/non-PD[a]	10 (2.8)	8 (2.6)	16 (4.5)
Not evaluable or assessed[b]	20 (5.7)	36 (11.7)	30 (8.5)

Duration of Response[a]



[a]Includes patients with confirmed CR or PR.
Responses based on BICR per RECIST v1.1. Data cutoff date: April 29, 2020.

All-Cause AEs, As-Treated Population



All AEs	Pembro + Chemo	Chemo
Any grade	99.7%	99.7%
Grade 3-5	87.4%	81.9%
Led to death	9.2%	2.6%
Led to discontinuation	30.9%	18.1%

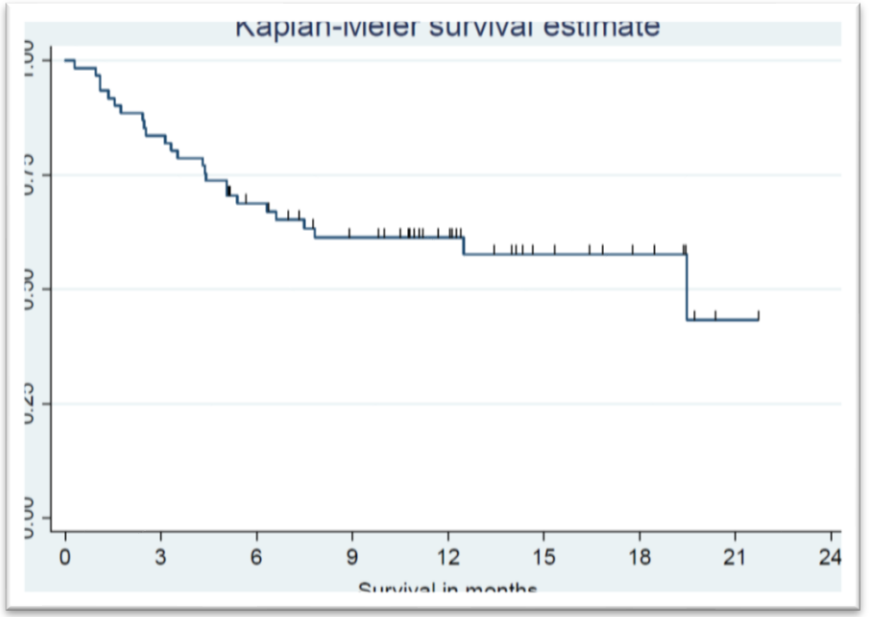
All AEs	Pembro	Chemo
Any grade	95.7%	99.7%
Grade 3-5	62.9%	81.9%
Led to death	8.6%	2.6%
Led to discontinuation	15.9%	18.1%

Median (range) duration of treatment was 7.7 (0-27.8) months for pembro + chemo, 4.2 (0-28.1) months for pembro, and 3.7 (0-7.2) months for chemo. As-treated population includes all patients who received ≥1 dose of trial treatment. Data cutoff date: April 29, 2020.

SACT Data – Analysis of overall survival (OS)

- **Treatment records for 61 patients were available in SACT, the minimum follow-up was 5 months from the last CDF application.**
- **Patients were traced for their vital status on 22-MAY-2020. The median follow-up time in SACT was 8.8 months.**
- **Median OS based on SACT data was 19.5 months**
  - **OS at 6 months was 69%; at 12 months was 61%**
- **Median OS with pembrolizumab (PD-L1 CPS≥10; cisplatin-ineligible):**
  - **KEYNOTE-052 = 18.5 months (n = 110 patients)**

Kaplan-Meier plot (N=61), SACT OS data.



Number of patients at risk, those that have died (events) and those that are still alive (censored) by quarterly breakpoints, SACT OS data.

Time intervals (months)	0-24	3-24	6-24	9-24	12-24	15-24	18-24	24
Number at risk	61	51	39	30	19	11	7	1
Censored	36	36	33	28	17	10	6	1
Events	25	15	6	2	2	1	1	0

MSD decision to terminate CDF Review

- **At the time of CDF recommendation based on data from KEYNOTE-052, MSD were optimistic that KEYNOTE-361, which provided direct comparative evidence vs standard chemotherapy, would demonstrate a statistically significant benefit in PFS and OS for Pembrolizumab in the subgroup of patients with PD-L1 CPS≥10**
- **However, no statistically significant differences in OS nor PFS were found in KEYNOTE-361 between pembrolizumab and standard chemotherapy in the subgroup of interest**
- **Given the absence of clinical benefit versus standard chemotherapy, there was no plausible case for pembrolizumab to be cost effective in this patient population, therefore it was agreed with NICE to proceed with a termination of the CDF Review**
- **In light of the data MSD have presented today, it appears clear that the outcome of a formal CDF Review would have arrived at the same conclusion as a full CDF Review**
- **Patients with UC continue to have access to an immunotherapy in the first-line setting and promising treatment options for UC are currently undergoing NICE appraisal. MSD and other companies continue to investigate promising treatments in ongoing clinical trials in UC.**