Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.

eMethods

Study Treatment Regimens, Stratification Factors, and Endpoints

IMpower130: atezolizumab (1200 mg, intravenous [IV], once every 3 weeks [q3w]) combined with chemotherapy (carboplatin: area under the curve [AUC] 6 q3w; nab-paclitaxel: 100 100 mg/m^2 IV every week) or chemotherapy alone, for four or six 21-day cycles. Maintenance treatment was with atezolizumab q3w until loss of clinical benefit in the atezolizumab plus chemotherapy arm and best supportive care or pemetrexed q3w in the chemotherapy arm, until disease progression (PD).

Randomization was stratified by sex, liver metastases, and PD-L1 expression. Coprimary endpoints were investigator-assessed progression-free survival (PFS) and overall survival (OS) in the intention-to-treat (ITT) wildtype (WT; *EGFR*/*ALK* mutation negative) population.

IMpower132: 4 or 6 cycles of either atezolizumab 1200 mg IV q3w combined with chemotherapy IV q3w (cisplatin 75 mg/m^2 or carboplatin AUC 6 mg/mL/min plus pemetrexed 500 mg/m^2) or chemotherapy alone, followed by maintenance therapy with atezolizumab plus pemetrexed (atezolizumab plus chemotherapy arm) or pemetrexed (chemotherapy arm) until PD, unacceptable toxicity, or death.

Stratification was by sex, smoking status, Eastern Cooperative Oncology Group performance status, and chemotherapy regimen. Coprimary endpoints were investigator-assessed PFS per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 and OS in the ITT population.

IMpower150: atezolizumab plus bevacizumab plus carboplatin and paclitaxel, atezolizumab plus carboplatin and paclitaxel or bevacizumab plus carboplatin and

paclitaxel. Study treatments were given by IV injection on day 1 of each 21-day cycle at the following doses: atezolizumab 1200 mg, bevacizumab 15 mg/kg of body weight, carboplatin AUC 6 mg/mL/min, and paclitaxel 200 mg/m² (patients of Asian ethnicity were given 175 mg/m²). Induction treatment comprised of four or six 21-day cycles, with the number of cycles determined by the investigator prior to randomization. Maintenance treatment was with atezolizumab (atezolizumab plus carboplatin and paclitaxel arm), atezolizumab plus bevacizumab (atezolizumab plus bevacizumab plus carboplatin and paclitaxel arm), or bevacizumab (bevacizumab plus carboplatin and paclitaxel arm).

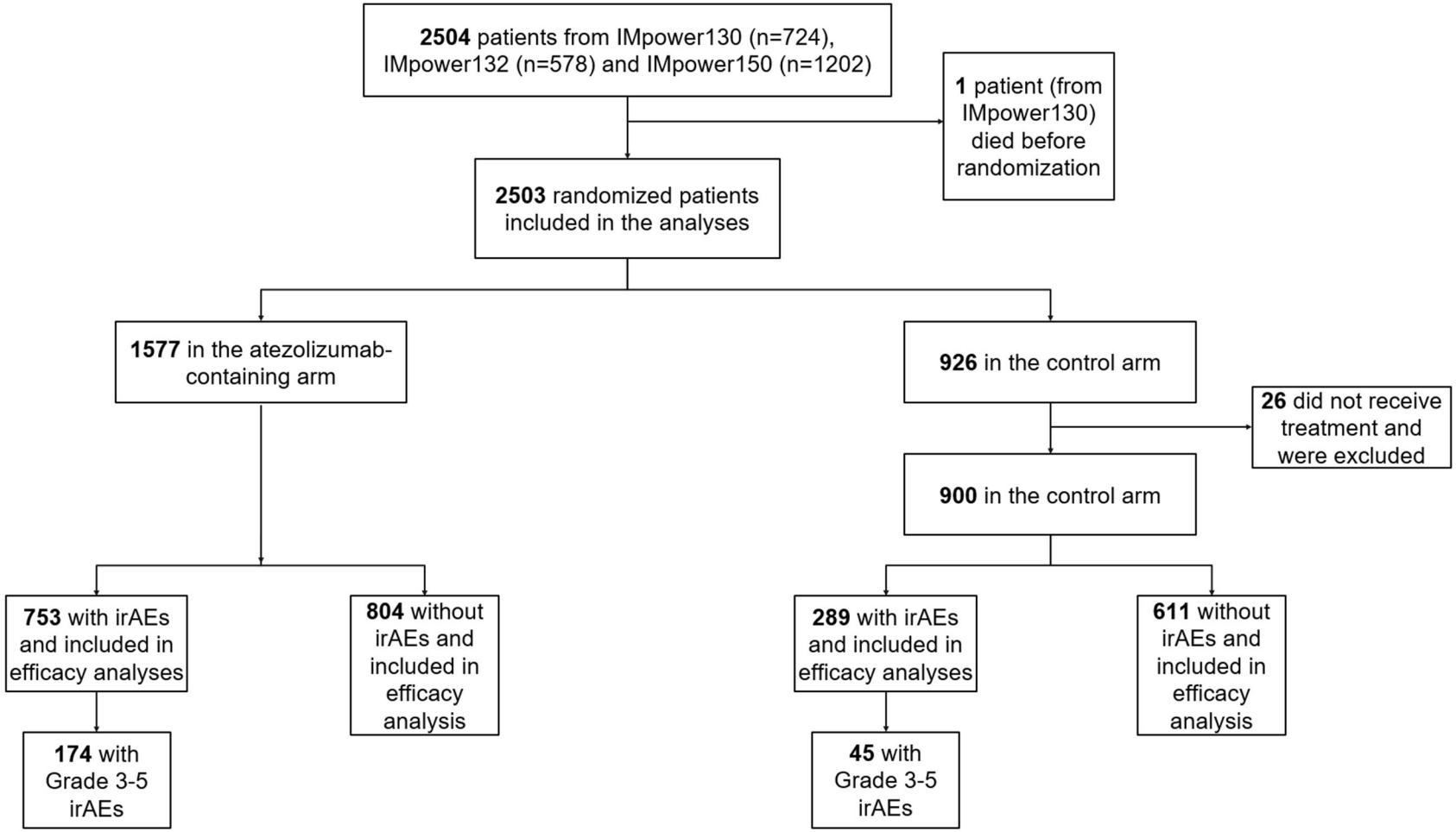
Stratification was by sex, liver metastases, and PD-L1 expression. Coprimary endpoints were investigator-assessed PFS in the ITT-WT population (defined as the ITT population excluding patients with a sensitizing *EGFR* mutation or *ALK* translocation), investigator-assessed PFS in the T-effector–high WT population, and OS in the WT population.

Study Assessments

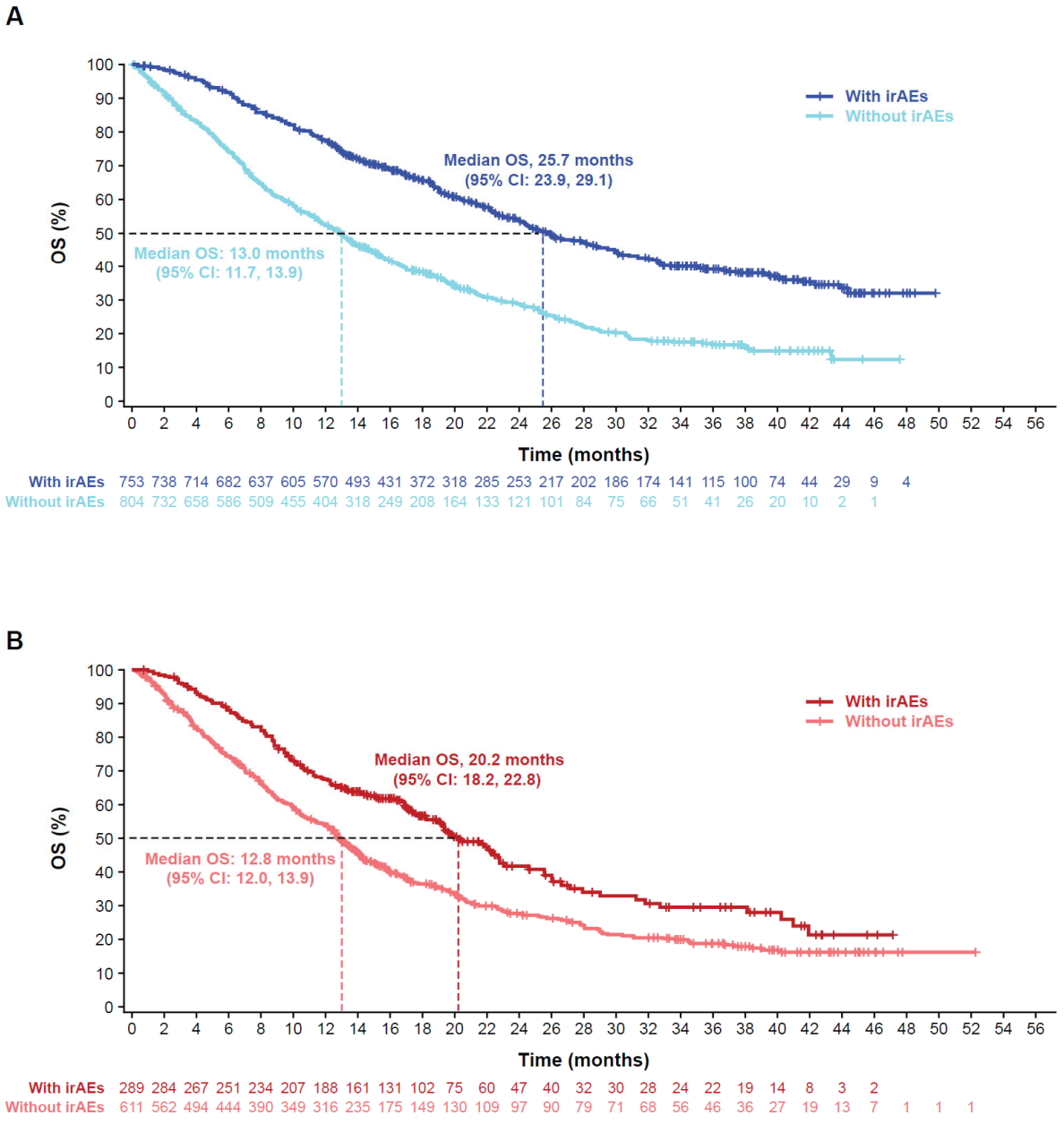
Patients in all studies underwent tumor assessments during screening, every 6 weeks from day 1 of cycle 1 for 48 weeks, and every 9 weeks thereafter until radiographic PD per RECIST 1.1 (or loss of clinical benefit for patients who continued atezolizumab beyond PD), withdrawal of consent, study termination by sponsor, or death, whichever occurred first. In all 3 trials, past and ongoing medical history was assessed at baseline, while AEs were evaluated during the induction and maintenance phases, at treatment discontinuation, and during survival follow-up. The irAEs for atezolizumab were

analyzed by medical concepts/grouped terms in all clinical trials, and the same method was used for this pooled analysis.

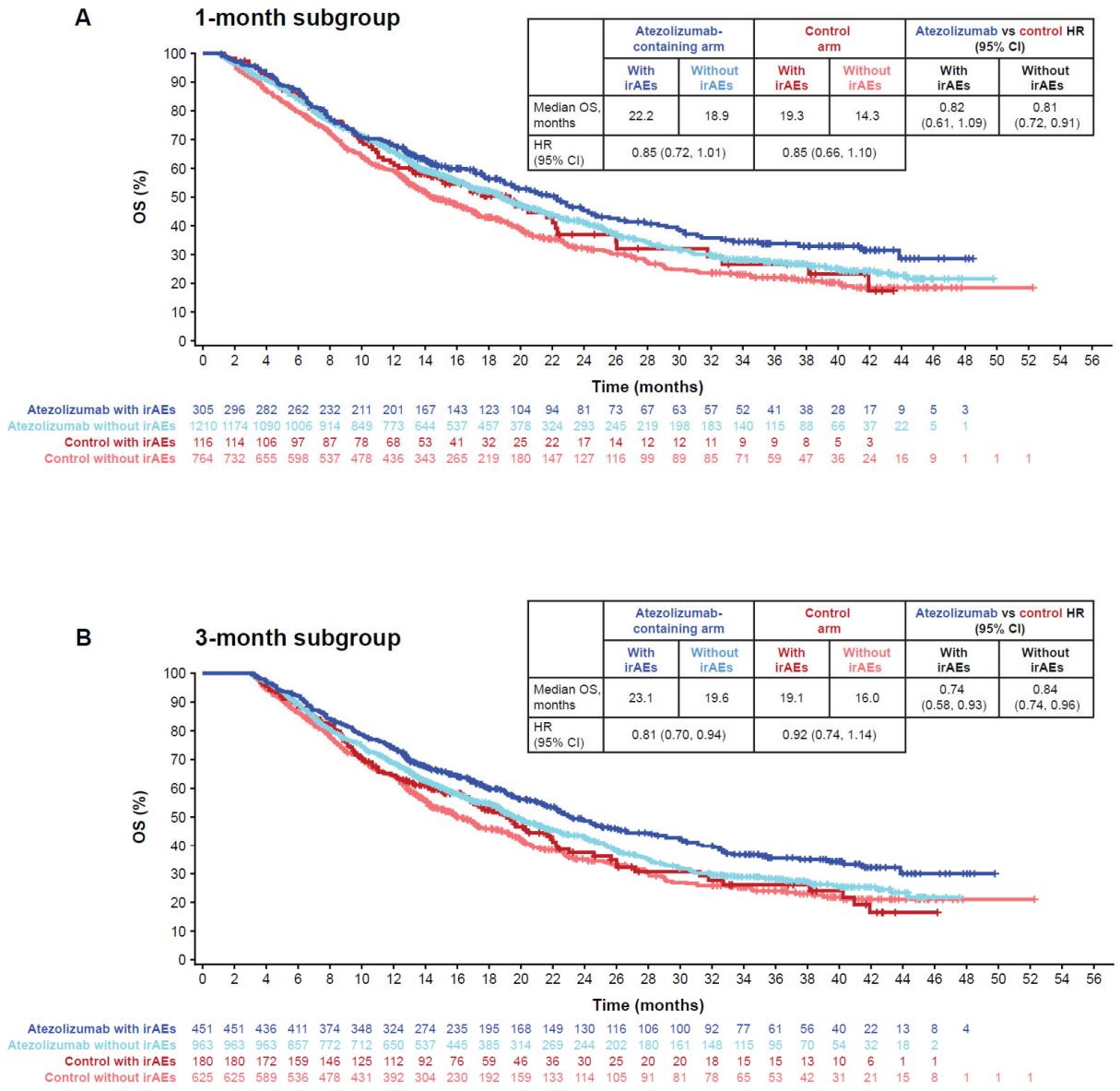
eFigure 1. Patient profile. irAE, immune-related adverse event

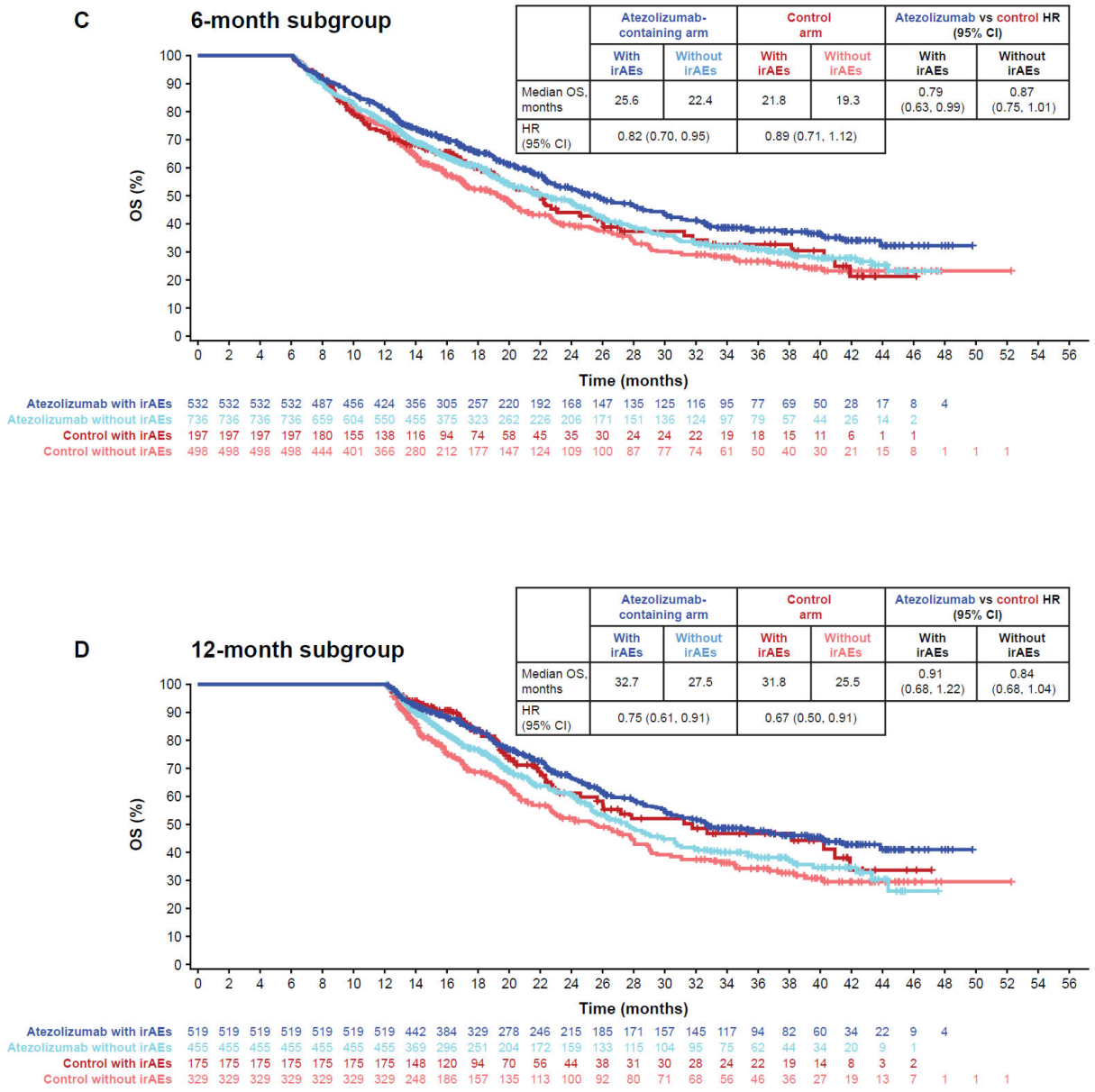


eFigure 2. OS by irAE status in the atezolizumab-containing (A) and control (B) arms. Kaplan-Meier curves are not adjusted for the timing of irAE onset. irAE, immune-related adverse event; OS, overall survival.

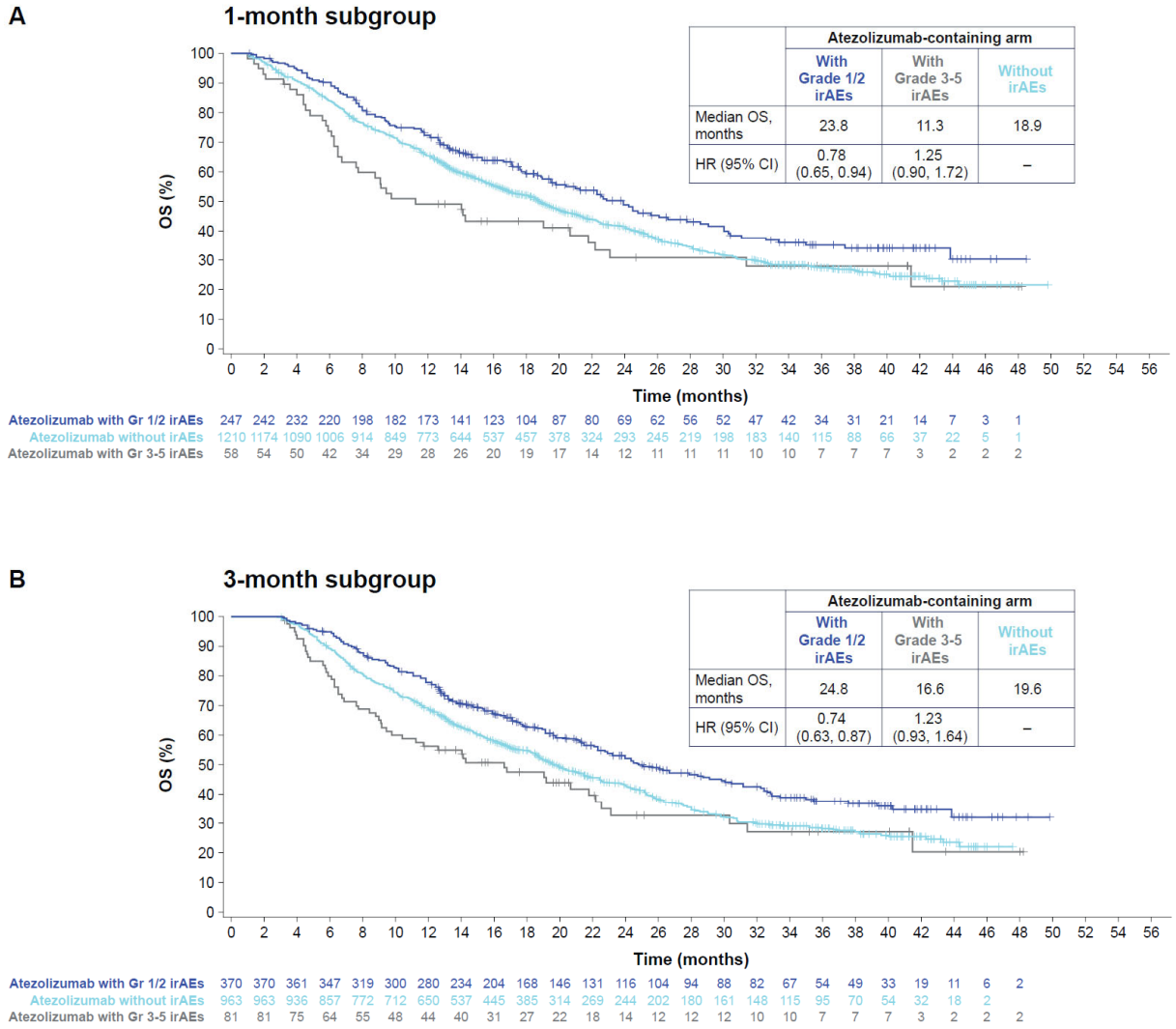


eFigure 3. OS landmark by irAE status in the 1- (A), 3- (B), 6- (C), and 12-month (D) subgroups. HR, hazard ratio; irAE, immune-related adverse event; OS, overall survival.





eFigure 4. OS by irAE grade in the atezolizumab-containing arm in the 1- (A), 3- (B), 6- (C), and 12-month (D) subgroups. HRs are unstratified. Gr, grade; HR, hazard ratio; irAE, immune-related adverse event; OS, overall survival.



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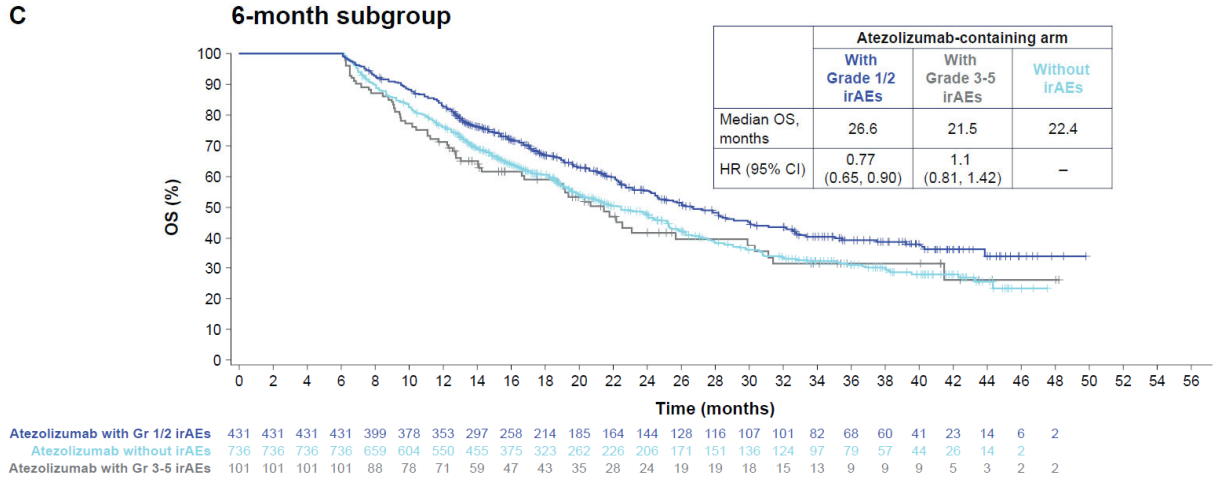

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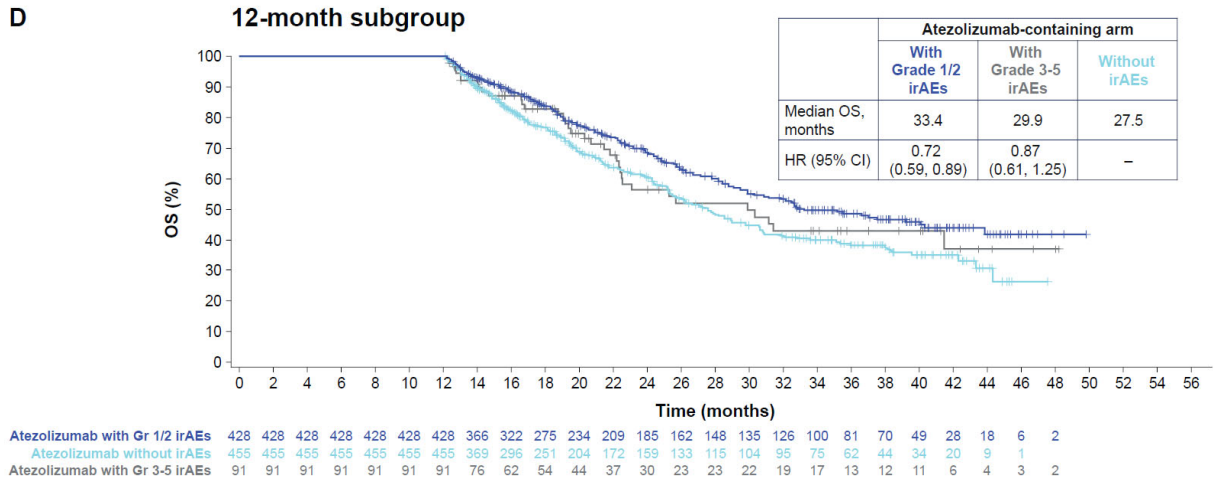

eTable 1. Key demographics and baseline characteristics

	Atezolizumab-containing arm		Control arm	
	With irAEs (n=753)	**Without irAEs (n=824)**	**With irAEs (n=289)**	**Without irAEs (n=637)**
Age, median (range), y	63.0 (19-85)	64.0 (18-89)	64.0 (31-90)	63.0 (33-86)
Sex, n (%)				
Male	447 (59)	503 (61)	173 (60)	396 (62)
Female	306 (41)	321 (39)	116 (40)	241 (38)
Race, n (%)[a]				
American Indian or Alaska Native	0	4(0.5)	1 (0.3)	1 (0.2)
Asian	133 (18)	56 (7)	46 (16)	68 (11)
Black or African American	15 (2)	17 (2)	4 (1)	20 (3)
Multiple	2 (<1)	7 (1)	0	0
Not known	34 (4.5)	35 (4.2)	8 (2.8)	18 (2.8)
White	569 (76)	705 (86)	230 (80)	530 (83)
ECOG PS, n (%)[a]	n=751	n=822	n=288	n=633
0	324 (43)	345 (42)	135 (47)	251 (40)
1	427 (57)	477 (58)	153 (53)	381 (60)
EGFR mutation status, n (%)	n=753	n=824	n=289	n=637
Positive	53 (7)	56 (7)	15 (5)	41 (6)
Negative	691 (92)	760 (92)	272 (94)	591 (93)
Unknown	9 (1)	8 (1)	2 (1)	5 (1)
ALK rearrangement status, n (%)	n=753	n=824	n=289	n=637
Positive	5 (<1)	15 (2)	7 (2)	16 (3)
Negative	743 (99)	806 (98)	280 (97)	617 (97)
Unknown	5 (<1)	3 (<1)	2 (<1)	4 (<1)

PD-L1 status per SP142, n (%)	n=753	n=823	n=289	n=637
TC3 or IC3 (high PD-L1)	142 (19)	117 (14)	41 (14)	95 (15)
TC1/2/3 or IC1/2/3 (any PD-L1)	222 (30)	268 (33)	88 (30)	181 (28)
TC0 and IC0 (PD-L1 negative)	330 (44)	381 (46)	117 (40)	286 (45)
Unknown	59 (8)	57 (7)	43 (15)	75 (12)

Data are n (%) except where otherwise indicated.

IC, tumor-infiltrating immune cell; irAE, immune-related adverse event; ECOG PS, European Cooperative Oncology Group performance status; PD-1, programmed death-1; PD-L1, programmed death-ligand 1; TC, tumor cell.

[a] One patient (0.2%) without irAEs in the control arm had an ECOG PS of 2.

eTable 2. Treatment disposition in patients in the atezolizumab arm with grade 1 or 2 and 3 to 5 irAEs

Disposition of patients, n (%)	Grade 1 or 2 irAEs		Grade 3-5 irAEs			
	With (n=579)	Without (n=804)	1-month subgroup (n=58)	3-month subgroup (n=81)	6-month subgroup (n=101)	12-month subgroup (n=91)
Treatment ongoing	147 (25)	94 (12)	4 (7)	8 (10)	12 (12)	16 (18)
Withdrawn from treatment	432 (75)	710 (88)	54 (93)	73 (90)	89 (88)	75 (82)
AE	60 (14)	80 (11)	27 (50)	33 (45)	42 (47)	37 (49)
PD	278 (64)	423 (60)	22 (41)	31 (43)	37 (42)	28 (37)
Symptomatic deterioration	23 (5)	82 (12)	2 (4)	2 (3)	1 (1)	0
Physician decision (no loss of clinical benefit)	21 (5)	28 (4)	0	3 (4)	4 (5)	4 (5)
Physician decision (loss of clinical benefit)	12 (3)	12 (2)	2 (4)	2 (3)	2 (2)	3 (4)
Other	3 (<1)	6 (<1)	1 (2)	1 (1)	2 (2)	2 (3)
Withdrawal by patient	28 (7)	40 (6)	0	1 (1)	1 (1)	1 (1)
Death	5 (1)	34 (5)	–	–	–	–
Protocol violation	0	1 (<1)	–	–	–	–
Noncompliance	1 (<1)	1 (<1)	–	–	–	–
Lost to follow-up	1 (<1)	3 (<1)	–	–	–	–

AE, adverse event; irAE, immune-related adverse event; PD, disease progression.

eTable 3. Atezolizumab exposure based on grade 3 to 5 irAEs in landmark subgroups in the atezolizumab-containing arm

	Grade 3-5 irAEs			
	1-month subgroup (n=58)	**3-month subgroup (n=81)**	**6-month subgroup (n=101)**	**12-month subgroup (n=91)**
Median treatment duration (range), mo	2.6 (0-48)	3.5 (0-48)	5.4 (0-48)	8.2 (0-48)
Patients with indicated treatment duration, n (%)				
0-3 months	31 (53)	33 (41)	23 (23)	12 (13)
>3-6 months	11 (19)	16 (20)	33 (33)	17 (19)
>6-12 months	10 (17)	16 (20)	23 (23)	32 (35)
>12 months	6 (10)	16 (20)	22 (22)	30 (33)

eTable 4. Confirmed ORR and duration of response by irAE status

	Atezolizumab-containing arm		**Control arm**	
	With irAEs (n=753)	**Without irAEs (n=804)**	**With irAEs (n=289)**	**Without irAEs (n=611)**
Responders (ORR, %)	460 (61)	299 (37)	122 (42)	208 (34)
95% CI, %	58-65	34-41	36-48	30-38
Difference (95% CI), %	23.9 (19-29)		8 (1-15)	
Median time to response (range), mo	1.7 (1.1-29.7)	1.7 (1.0-27.1)	1.6 (1.1-11.3)	1.5 (1.1-13.4)

irAE, immune-related adverse event; ORR, objective response rate.

eTable 5. Sensitivity analyses of OS HR to assess the impact of grade 5 irAEs in landmark analyses

Landmark analysis	OS HR (95% CI) in patients with grade 3-4 irAEs	OS HR (95% CI) in patients with grade 3-5 irAEs
1-month	1.18 (0.85, 1.65)	1.25 (0.90, 1.72)
3-month	1.23 (0.93, 1.64)	1.23 (0.93, 1.64)
6-month	1.04 (0.78, 1.38)	1.1 (0.81, 1.42)
12-month	0.87 (0.61, 1.25)	0.87 (0.61, 1.25)