IMpower-150

(PD1/PDL1-153)

KEYNOTE-189

IMpower-150 (PD1/PDL1-153)

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(PD1/PDL1-153)

Primary Endpoint: OS, PFS

Secondary Endpoint: ORR, DOR, Safety

Non-Sq

化学療法未治療

非小細胞肺癌患者

（1 次治療）

・EGFR遺伝子変異　陰性

・ALK融合遺伝子　　陰性

・PD-L 1 発現 Any

・Teff testing

R

Arm:B

Atezolizumb

$CBDCA_{(AUC=5,6)}+PTX_{(200mg/m2)}$

±

$Bevacizumab_{(15mg/kg)}$

Up to 4-6 cycles

Arm:C

$CBDCA_{(AUC=5,6)}+PTX_{(200mg/m2)}$

±

$Bevacizumab_{(15mg/kg)}$

Up to 4-6 cycles

	ITT-WT		Teff High-WT	
	PFS	OS	PFS	OS
Arm:B	8.3ヵ月	19.2ヵ月	11.3ヵ月	
	HR=0.617 p<0.0001	HR=0.775 p=0.0262	HR=0.505 p<0.0001	
Arm:C	6.8ヵ月	14.4ヵ月	6.8ヵ月	

※後治療としてPD-1/PD-L1抗体のクロスオーバー許容：Pembro群30/410(7.3%)，化療群87/206(42.2%)

2019/1/14

KEYNOTE-189 (PD1/PDL1-126)

Primary Endpoint: OS, PFS

Secondary Endpoint: ORR, DOR, Safety

Non-Sq

化学療法未治療の非小細胞肺癌患者（1次治療）
- EGFR遺伝子変異　陰性
- ALK融合遺伝子　陰性
- PD-L1発現
  (TPS≧1%, 1%<TPS)

R

Pembrolizumab

CBDCA$_{(AUC=5)}$+Pem$_{(500mg/m2)}$
or
CDDP$_{(75mg/m2)}$+Pem$_{(500mg/m2)}$
（Non-Sq Pem維持療法許容）
Up to 4 cycles

CBDCA$_{(AUC=5)}$+Pem$_{(500mg/m2)}$
or
CDDP$_{(75mg/m2)}$+Pem$_{(500mg/m2)}$
（Non-Sq Pem維持療法許容）
Up to 4 cycles

	全体		TPS<1%		TPS1-49%		TPS≧50%	
	PFS	OS	PFS	OS	PFS	OS	PFS	OS
Pembrolizumab	8.8ヵ月	未達	6.1ヵ月	15.2ヵ月	9.0ヵ月	未達	9.4ヵ月	未達
	HR=0.52 p<0.00001	HR=0.49 p<0.00001	HR=0.75	HR=0.59	HR=0.55	HR=0.55	HR=0.36	HR=0.42
化学療法	4.9ヵ月	11.3ヵ月	5.1ヵ月	12ヵ月	4.9ヵ月	12.9ヵ月	4.7ヵ月	10ヵ月

※後治療としてPD-1/PD-L1抗体のクロスオーバー許容：Pembro群30/410(7.3%)，化療群87/206(42.2%)

Non-Sq

化学療法未治療の
非小細胞肺癌患者（1次治療）
・EGFR遺伝子変異　陰性
・ALK融合遺伝子　陰性
・PD-L1発現
(TPS≧1%, 1%<TPS)

KEYNOTE-189

(PD1/PDL1-126)

Pembrolizumab

CBDCA(AUC=5)+Pem(500mg/m2)
CDDP(75mg/m2)+Pem(500mg/m2)

Up to 4 cycles

全体		TPS<1%		TPS1-49%		TPS≧50%	
PFS	OS	PFS	OS	PFS	OS	PFS	OS
8.8ヵ月	未達	6.1ヵ月	15.2ヵ月	9.0ヵ月	未達	9.4ヵ月	未達
HR=0.52 p<0.00001	HR=0.49 p<0.00001	HR=0.75	HR=0.59	HR=0.55	HR=0.55	HR=0.36	HR=0.42
4.9ヵ月	11.3ヵ月	5.1ヵ月	12ヵ月	4.9ヵ月	12.9ヵ月	4.7ヵ月	10ヵ月

Up to 4 cycles

IMpower-150

(PD1/PDL1-153)

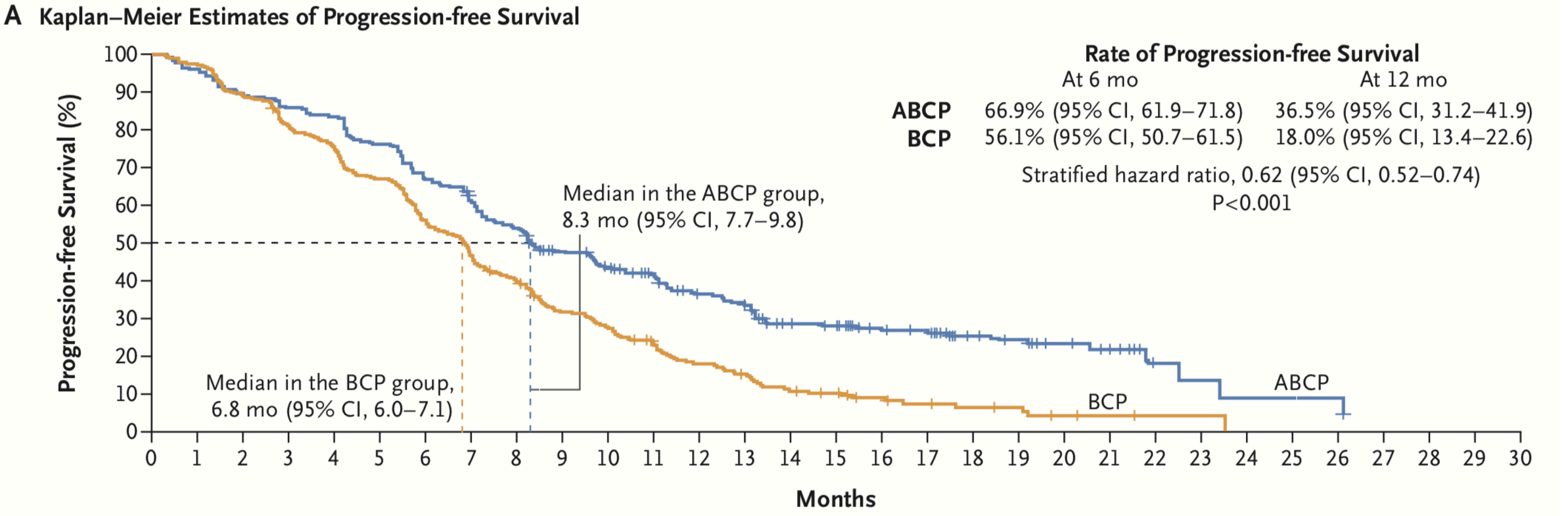
Atezolizumb

CBDCA(AUC=5,6)+PTX(200mg/m2)
±
Bevacizumab(15mg/kg)

Up to 4-6 cycles

ITT-WT		Teff High-WT	
PFS	OS	PFS	OS
8.3ヵ月	19.2ヵ月	11.3ヵ月	
HR=0.617 p<0.0001	HR=0.775 p=0.0262	HR=0.505 p<0.0001	
6.8ヵ月	14.4ヵ月	6.8ヵ月	

IMpower-150



(PD1/PDL1-153)

B Hazard Ratios for Disease Progression or Death in Biomarker Subgroups

Population	No. of Patients (%)	Median Progression-free Survival (mo)		Hazard Ratio (95% CI)
		ABCP	BCP	
ITT population	800 (100)	8.3	6.8	0.61 (0.52–0.72)
Patients with *EGFR* or *ALK* genetic alternations	108 (14)	9.7	6.1	0.59 (0.37–0.94)
WT population	692 (87)	8.3	6.8	0.62 (0.52–0.74)
PD-L1 subgroups (in the WT population)				
TC3 or IC3	135 (20)	12.6	6.8	0.39 (0.25–0.60)
TC1/2/3 or IC1/2/3	354 (51)	11.0	6.8	0.50 (0.39–0.64)
TC1/2 or IC1/2	224 (32)	8.3	6.6	0.56 (0.41–0.77)
TC0/1/2 and IC0/1/2	557 (80)	8.0	6.8	0.68 (0.56–0.82)
TC0 and IC0	338 (49)	7.1	6.9	0.77 (0.61–0.99)
Teff subgroups (in the WT population)				
High gene-signature expression	284 (43)	11.3	6.8	0.51 (0.38–0.68)
Low gene-signature expression	374 (57)	7.3	7.0	0.76 (0.60–0.96)

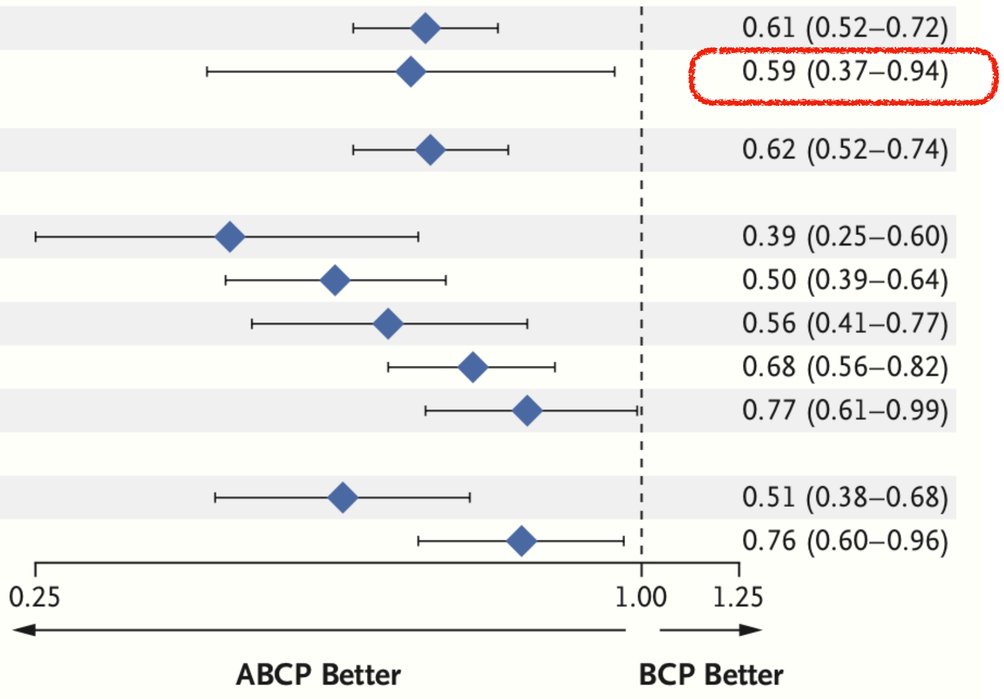
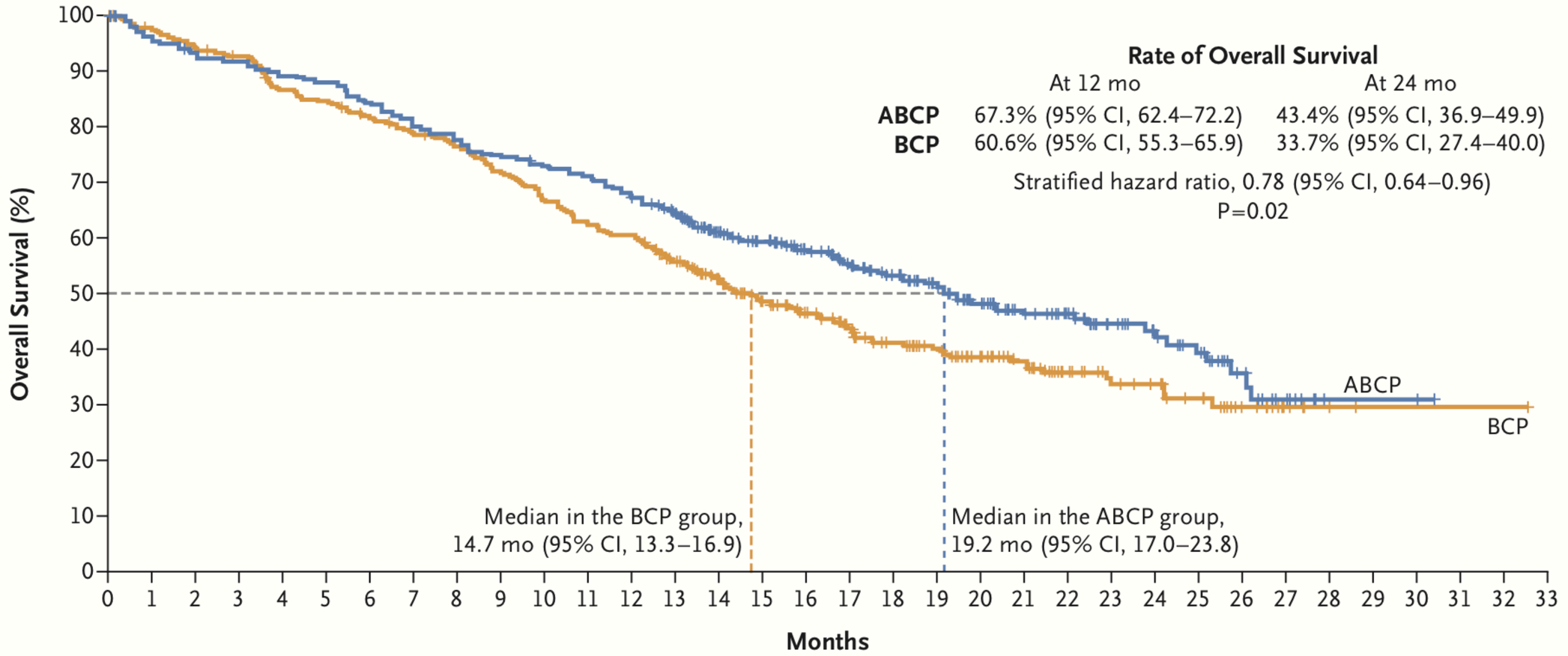


Figure 2. Investigator-Assessed Progression-free Survival in the ABCP Group and the BCP Group.

Panel A shows the Kaplan–Meier estimates of progression-free survival among the patients in the WT population. Panel B shows the hazard ratios (with 95% confidence intervals) for investigator-assessed progression-free survival in biomarker subgroups. Stratified hazard ratios are given for the ITT population (all enrolled patients, including those with *EGFR* or *ALK* genetic alterations), the WT population, and the Teff-high WT population; unstratified hazard ratios are given for the patients with *EGFR* or *ALK* genetic alterations, all programmed death ligand 1 (PD-L1) subgroups, and the subgroup of patients with low Teff gene-signature expression. The PD-L1 subgroups comprised 692 patients, and the Teff subgroups 658 patients; PD-L1 status and Teff gene-signature expression were evaluated among the patients in the WT population. PD-L1 status was determined by immunohistochemical analysis: TC3 or IC3 indicates PD-L1 expression on at least 50% of tumor cells or at least 10% of tumor-infiltrating immune cells (high PD-L1 expression); TC1/2/3 or IC1/2/3, PD-L1 expression on at least 1% of tumor cells or tumor-infiltrating immune cells (PD-L1–positive); TC1/2 or IC1/2, PD-L1 expression on at least 1% of tumor cells or tumor-infiltrating immune cells and less than 50% of tumor cells or less than 10% of tumor-infiltrating immune cells (low PD-L1 expression); TC0/1/2 and IC0/1/2, PD-L1 expression on less than 50% of tumor cells and less than 10% of tumor-infiltrating immune cells (low or negative PD-L1 expression); and TC0 and IC0, PD-L1 expression on less than 1% of tumor cells and tumor-infiltrating immune cells (PD-L1–negative). Patients with a sensitizing *EGFR* mutation or *ALK* translocation were included in the study if they had had disease progression or the occurrence of unacceptable side effects with at least one approved targeted therapy. The date of data cutoff was September 15, 2017.

IMpower-150

IMpower-150



No. at Risk

ABCP	359	339	328	323	314	310	296	284	273	264	256	250	235	218	188	167	147	133	119	103	84	66	57	41	34	28	16	9	2	2	2
BCP	337	326	315	308	287	280	268	255	247	233	216	203	196	174	152	129	115	101	87	77	66	56	40	32	29	22	13	6	3	1	1	1	1

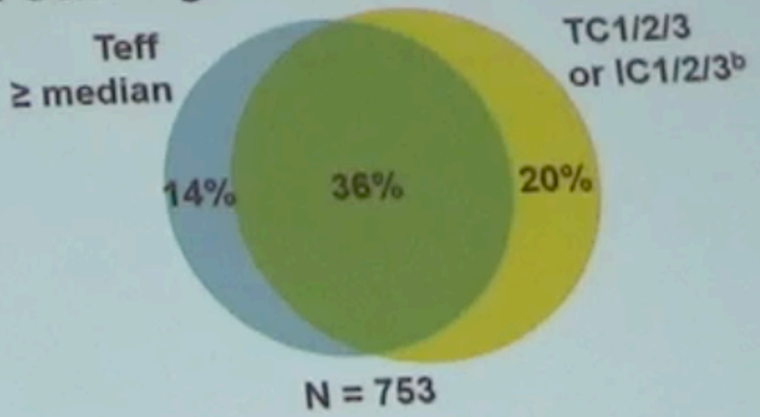
Figure 3. Interim Analysis of Overall Survival in the ABCP Group and the BCP Group.

Shown are Kaplan–Meier estimates of overall survival among the patients in the WT population. The date of data cutoff was January 22, 2018. At the earlier cutoff date of September 15, 2017, four patients were initially reported as having an *EGFR* mutation or an *ALK* translocation and were later confirmed to have WT genotype; this has been corrected in the analysis with the data cutoff at January 22, 2018.

Teff Gene Signature and Overlap With PD-L1 IHC in tumor specimens from study OAK

Teff Gene Signature	
PDL1	PD-L1 expression on TC and IC
IFNG	Pre-existing immunity
CXCL9	Pre-existing immunity

Teff Gene Signature vs PD-L1 IHC (SP142)[a]

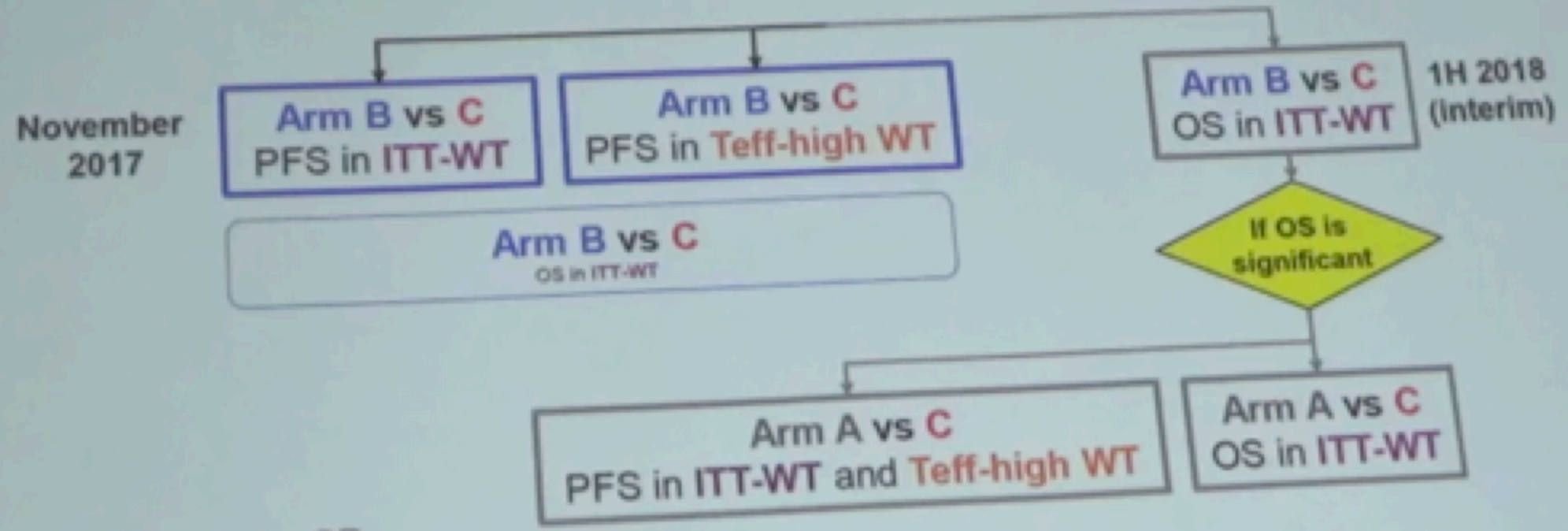


- Teff gene signature is a surrogate for PD-L1 expression and pre-existing immunity
  - Teff signature was defined by mRNA expression of 3 genes (*PDL1*, *CXCL9*, *IFNG*) and derived from a broader 9-gene signature from POPLAR[1]
  - In the OAK study, the Teff signature was associated with PD-L1 expression assessed by IHC ($P = 7.3 \times 10^{-45}$)
- Teff signature partially overlaps with patients identified as PD-L1 positive by IHC and also identifies a unique subset of patients within the PD-L1–negative population

IC, tumor-infiltrating immune cell; IHC, immunohistochemistry; mRNA, messenger RNA; TC, tumor cell
[a] Percentages of the overall NSCLC population (N = 753). [b] TC1/2/3 or IC1/2/3 = TC or IC ≥ 1% PD-L1–expressing cells
1. Fehrenbacher L, et al. *Lancet*. 2016

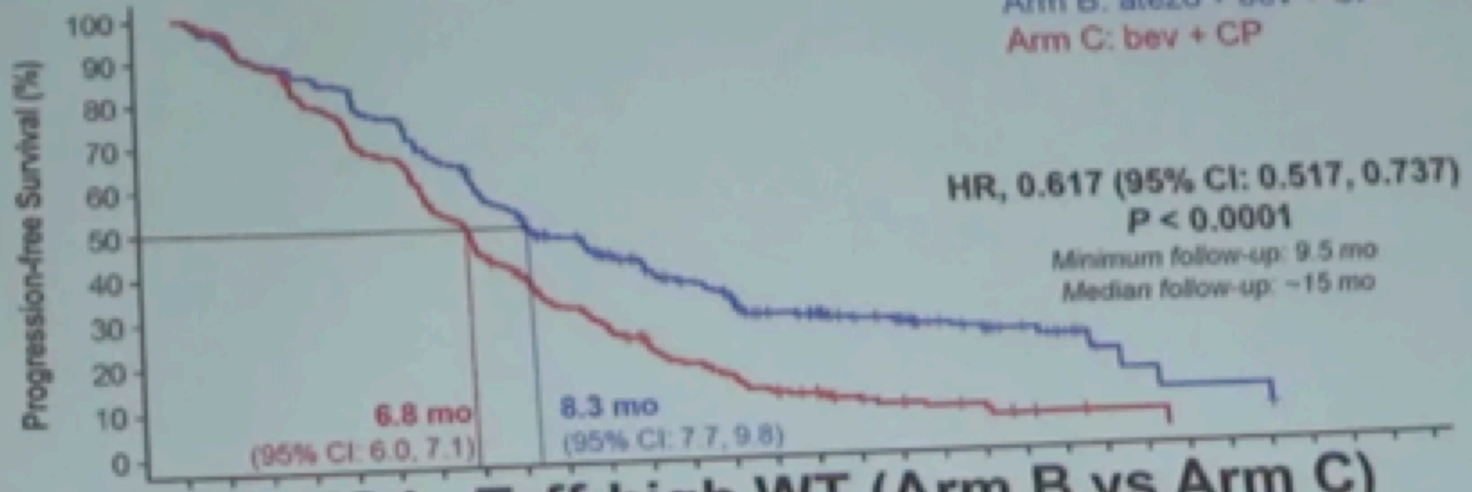
Kowanetz et al. OAK Teff biomarker. WCLC 2017.

Statistical testing plan for the co-primary endpoints in IMpower150



Arm A: atezo + CP
Arm B: atezo + bev + CP
Arm C: bev + CP *(control)*

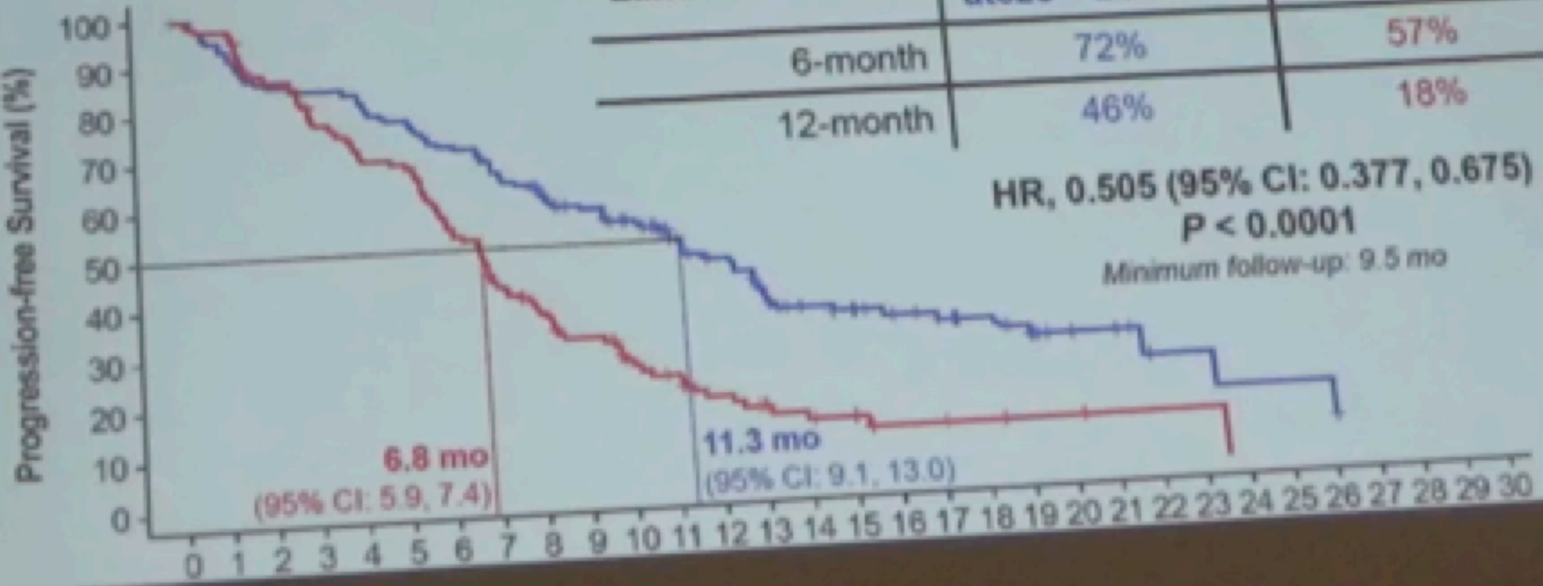
INV-assessed PFS in ITT-WT (Arm B vs Arm C)



HR, 0.617 (95% CI: 0.517, 0.737)
P < 0.0001
Minimum follow-up: 9.5 mo
Median follow-up: ~15 mo

INV-assessed PFS in Teff-high WT (Arm B vs Arm C)

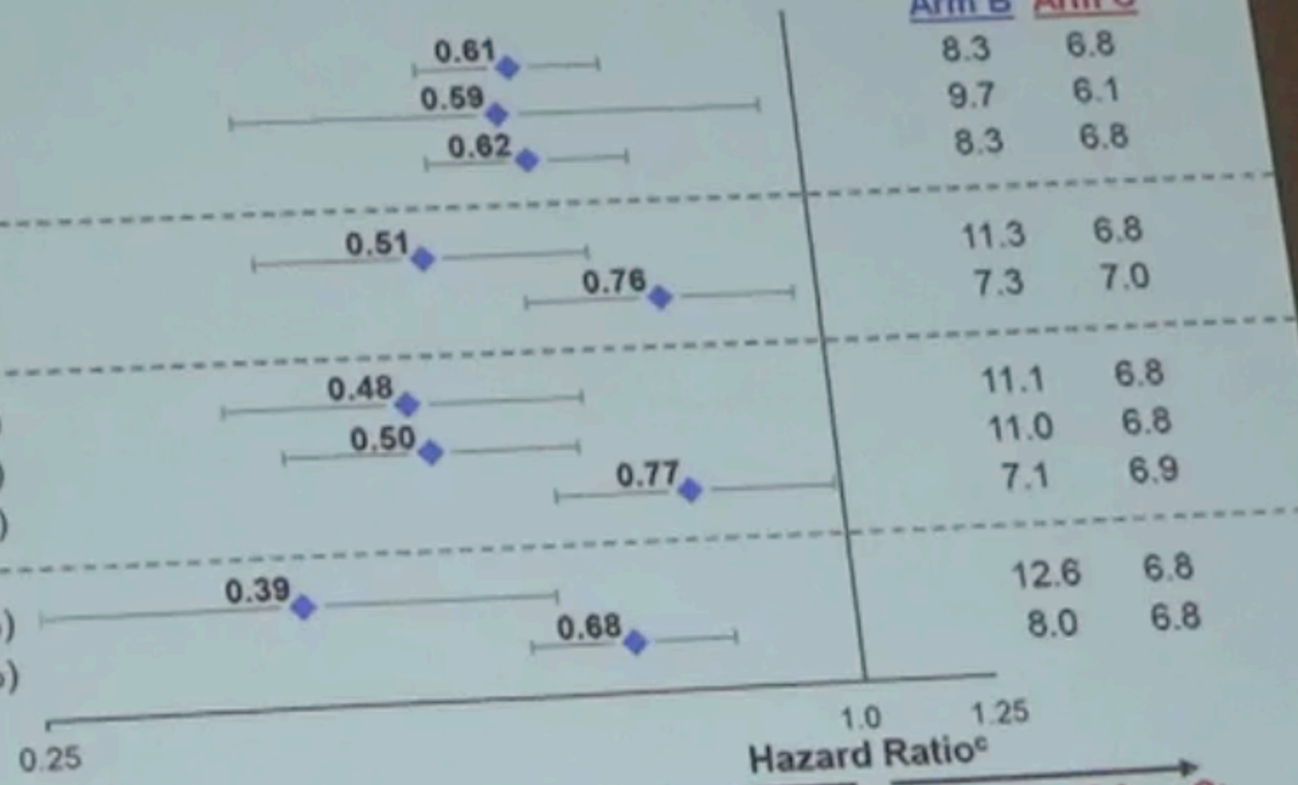
Landmark PFS, %	Arm B: atezo + bev + CP	Arm C: bev + CP
6-month	72%	57%
12-month	46%	18%



HR, 0.505 (95% CI: 0.377, 0.675)
P < 0.0001
Minimum follow-up: 9.5 mo

PFS in key biomarker populations

Population	n (%)[a]	Median PFS, mo Arm B	Arm C
ITT (including *EGFR*/*ALK* mutant +)	800 (100%)	8.3	6.8
***EGFR*/*ALK* mutant + only**[b]	108 (14%)	9.7	6.1
ITT-WT	692 (87%)	8.3	6.8
Teff-high (WT)	284 (43%)	11.3	6.8
Teff-low (WT)	374 (57%)	7.3	7.0
PD-L1 IHC TC2/3 or IC2/3 (WT)	244 (35%)	11.1	6.8
PD-L1 IHC TC1/2/3 or IC1/2/3 (WT)	354 (51%)	11.0	6.8
PD-L1 IHC TC0 and IC0 (WT)	338 (49%)	7.1	6.9
PD-L1 IHC TC3 or IC3 (WT)	135 (20%)	12.6	6.8
PD-L1 IHC TC0/1/2 or IC0/1/2 (WT)	557 (80%)	8.0	6.8

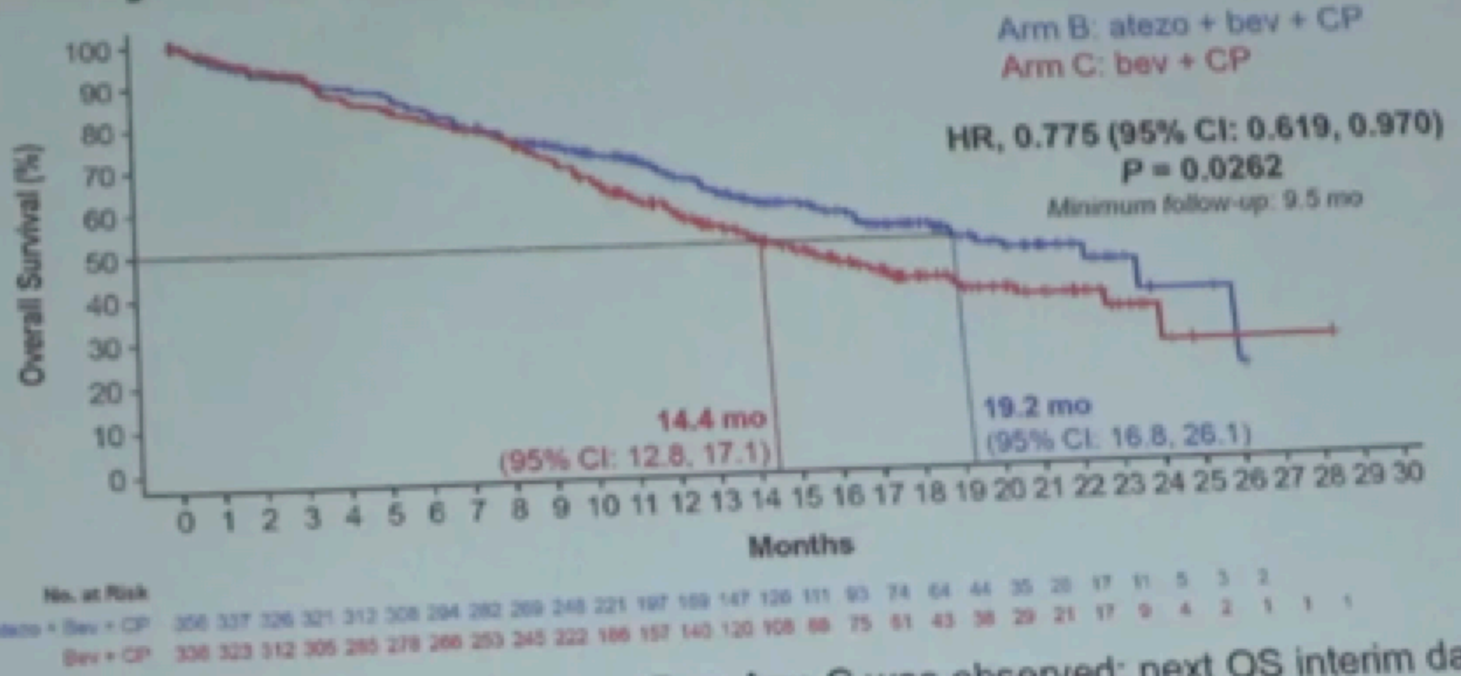


[a] ITT, *EGFR*/*ALK* mutants, and ITT-WT % prevalence out of ITT (n = 800); Teff % prevalence out those tested in ITT-WT (n = 658); PD-L1 IHC % prevalence out of ITT-WT (n = 692).
[b] Patients with a sensitising *EGFR* mutation or *ALK* translocation must have disease progression or intolerance of treatment with one or more approved targeted therapies.
[c] Stratified HRs for ITT, ITT-WT and Teff-high WT populations; unstratified HRs for all other subgroups.

Data cutoff: September 15, 2017

Reck M, et al. IMpower150 PFS analysis.

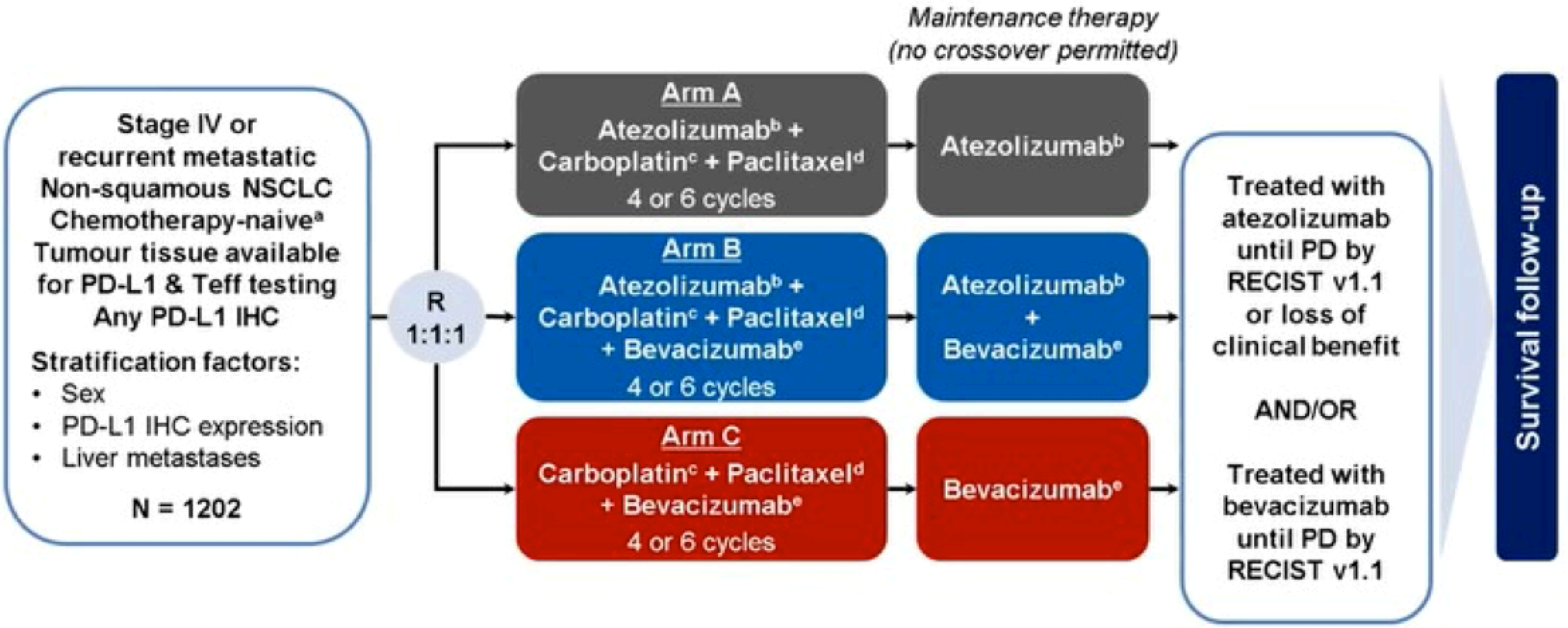
Preliminary OS in ITT-WT (Arm B vs Arm C)



- Promising preliminary OS benefit for Arm B vs Arm C was observed; next OS interim data are anticipated in 1H 2018

	ITT-WT	
	Arm A: atezo + CP (n = 348)	Arm C (control): bev + CP (n = 336)
PFS HR[a] (95% CI)	0.936 (0.787, 1.112)	
ORR,[b] n (%)	171 (49%)	159 (48%)
OS HR[a] (95% CI)	0.884 (0.709, 1.101)	

IMpower150 study design



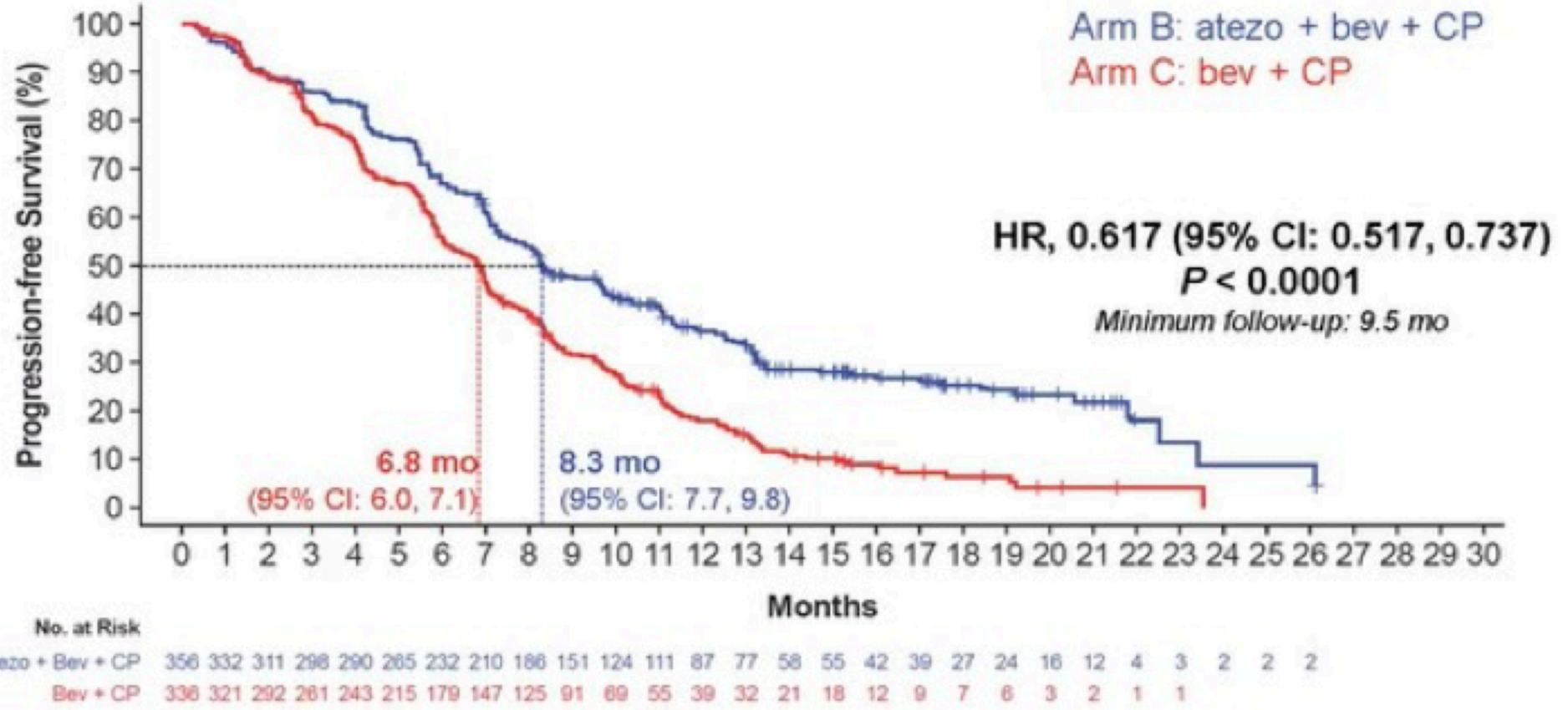
Teff, T-effector; WT, wild-type.

[a] Patients with a sensitizing *EGFR* mutation or *ALK* translocation must have disease progression or intolerance of treatment with one or more approved targeted therapies. [b] Atezolizumab: 1200 mg IV q3w. [c] Carboplatin: AUC 6 IV q3w.

[d] Paclitaxel: 200 mg/m^2 IV q3w. [e] Bevacizumab: 15 mg/kg IV q3w.

Reck M, et al. IMpower150 PFS analysis.

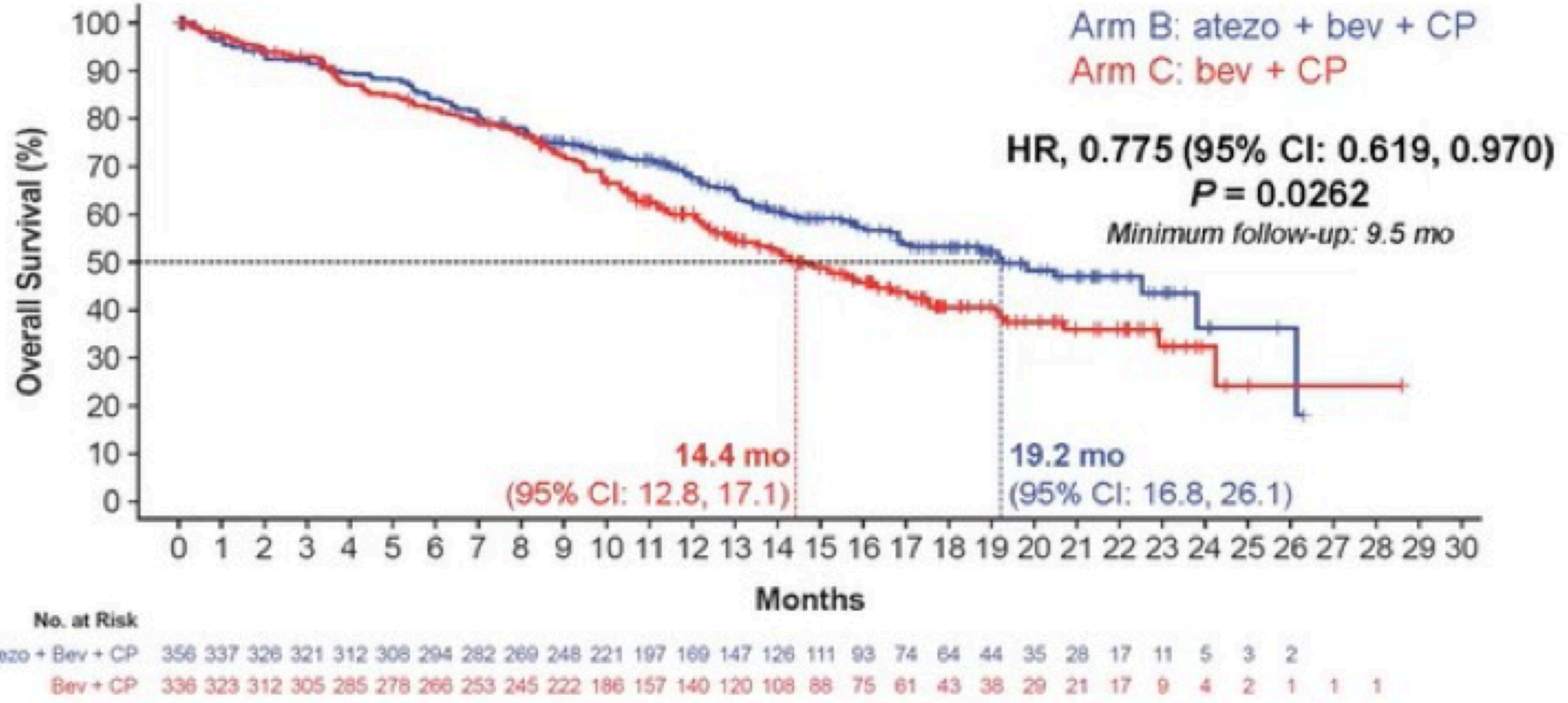
INV-assessed PFS in ITT-WT (Arm B vs Arm C)



INV, investigator.
Data cutoff: September 15, 2017

Reck M, et al. IMpower150 PFS analysis.

Preliminary OS in ITT-WT (Arm B vs Arm C)



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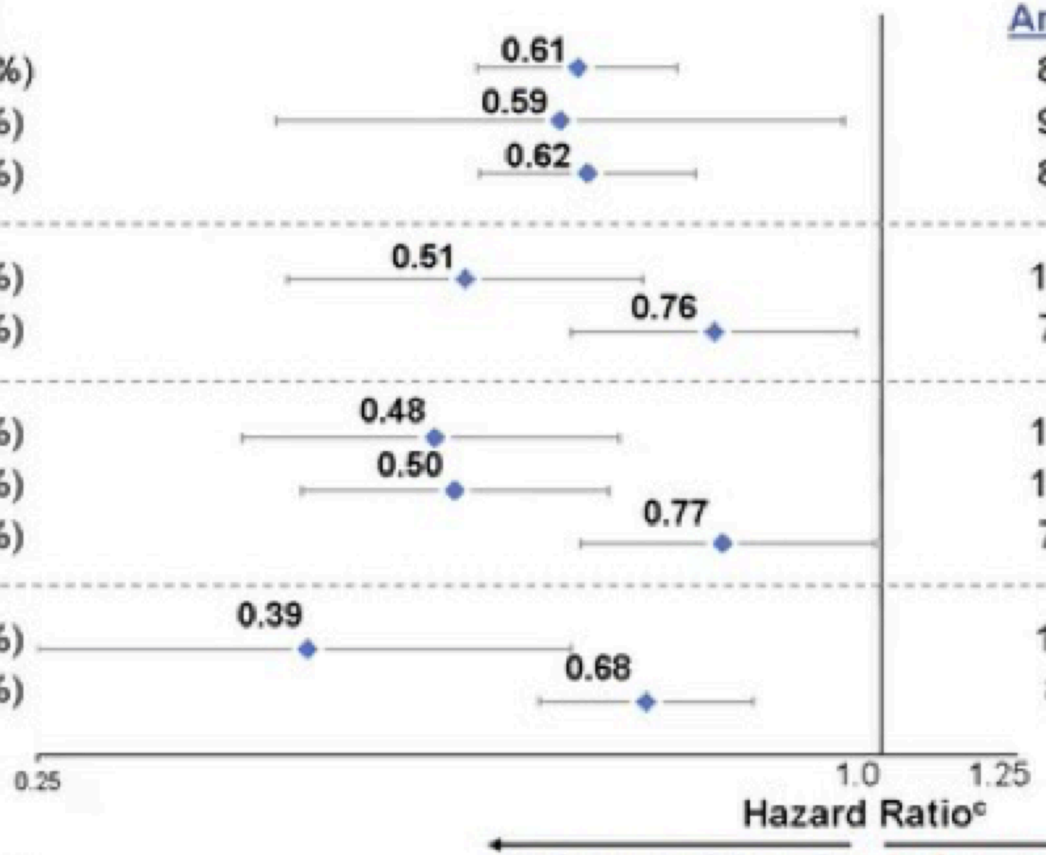

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