Primary PFS and safety analyses of a randomised Phase III study of carboplatin + paclitaxel +/− bevacizumab, with or without atezolizumab in 1L non-squamous metastatic NSCLC (IMpower150)

Martin Reck,[1] Mark A. Socinski,[2] Federico Cappuzzo,[3] Francisco Orlandi,[4] Daniil Stroyakovskii,[5] Naoyuki Nogami,[6] Delvys Rodríguez-Abreu,[7] Denis Moro-Sibilot,[8] Christian A. Thomas,[9] Fabrice Barlesi,[10] Gene Finley,[11] Claudia Kelsch,[12] Anthony Lee,[12] Shelley Coleman,[12] Yijing Shen,[12] Marcin Kowanetz,[12] Ariel Lopez-Chavez,[12] Alan Sandler,[12] Robert Jotte[13]

[1]Lung Clinic Grosshansdorf, Airway Research Center North, German Center of Lung Research, Grosshansdorf, Germany; [2]Florida Hospital Cancer Institute, Orlando, FL, USA; [3]Azienda Unità Sanitaria Locale della Romagna, Ravenna, Italy; [4]Instituto Nacional del Torax, Santiago, Chile; [5]Moscow City Oncology Hospital, Moscow, Russia; [6]National Hospital Organization Shikoku Cancer Center, Matsuyama, Japan; [7]Hospital Universitario Insular de Gran Canaria, Las Palmas, Spain; [8]Centre Hospitalier Universitaire de Grenoble Alpes, Grenoble, France; [9]New England Cancer Specialists, Scarborough, ME, USA; [10]Aix Marseille University, Assistance Publique Hôpitaux de Marseille, Marseille, France; [11]Allegheny Cancer Center, Pittsburgh, PA, USA; [12]Genentech, Inc., South San Francisco, CA, USA; [13]Rocky Mountain Cancer Centers, Denver, CO, USA

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- Dr Martin Reck has the following to disclose:
  - Consulting or advisory role for AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Eli Lilly, F. Hoffmann-La Roche, MSD, Novartis and Pfizer
  - Speakers' bureau for AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Eli Lilly, F. Hoffmann-La Roche, MSD, Novartis and Pfizer
- This study is sponsored by F. Hoffmann-La Roche, Ltd

Background: NSCLC landscape

- Standards of care for patients with advanced 1L NSCLC include[1,2]:
  - Targeted therapies (patients with *EGFR* mutation or *ALK* rearrangement)
  - Pembrolizumab (anti–PD-1) in patients with PD-L1 expressing tumours with TPS ≥ 50% (≈ 25%-30% prevalence)
  - Platinum-based chemotherapy +/- bevacizumab[3]

- Atezolizumab (anti–PD-L1) has demonstrated overall survival benefit[4] and is approved in the US[5] and EU[6] for the treatment of 2L+ NSCLC regardless of PD-L1 expression

- Phase Ib data of atezolizumab + platinum-doublet chemotherapy in patients with 1L NSCLC demonstrated promising efficacy and tolerable safety[7]

NSCLC; non-small cell lung cancer; PD-1, programmed death-1;
PD-L1, programmed death-ligand 1; TPS, tumour proportion score.

1. Novello S, et al. *Ann Oncol*, 2016. 2. NCCN Clinical Practice Guidelines in Oncology. NSCLC. V7.2017.
3. Sandler A, et al. *N Engl J Med*, 2006. 4. Rittmeyer A, et al. *Lancet*, 2017. 5. TECENTRIQ [USPI]. Genentech Inc, 2017.
6. TECENTRIQ [SmPC]. Roche Registration Ltd, 2017. 7. Liu SV, et al. ASCO 2017.

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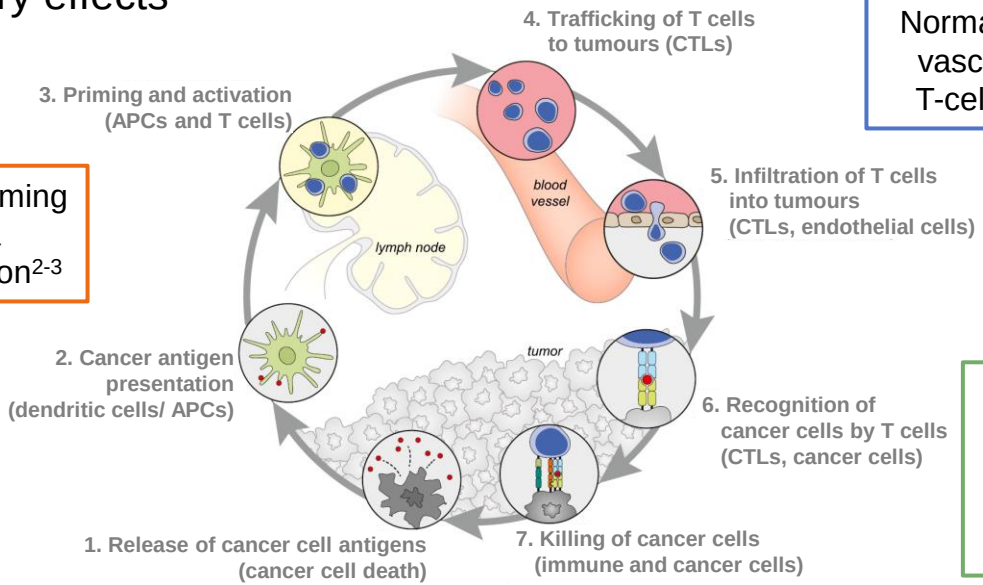
Rationale for combining atezolizumab + bevacizumab

- In addition to its known anti-angiogenic effects[1], bevacizumab's inhibition of VEGF has immune modulatory effects

Promotion of T-cell priming and activation via dendritic cell maturation[2-3]



Normalisation of the tumour vasculature for increased T-cell tumour infiltration[4-7]

Establishing an immune-permissive tumour microenvironment by decreasing MDSC and Treg populations[7-11]

- Atezolizumab's T-cell mediated cancer cell killing may be enhanced through bevacizumab's reversal of VEGF-mediated immunosuppression

1. Ferrara N, et al. *Nat Rev Drug Discov*, 2004. 2. Gabrilovich DI, et al. *Nat Med*, 1996. 3. Oyama T, et al. *J Immunol*, 1998. 4. Goel S, et al. *Physiol Rev*, 2011. 5. Motz GT, et al. *Nat Med*, 2014. 6. Hodi FS, et al. *Cancer Immunol Res*, 2014. 7. Wallin JJ, et al. *Nat Commun*, 2016. 8. Gabrilovich DI, Nagaraj S. *Nat Rev Immunol*, 2009. 9. Roland CL, et al. *PLoS One*, 2009. 10. Facciabene A, et al. *Nature*, 2011. 11. Voron T, et al. *J Exp Med*, 2015.
Figure adapted from Chen DS, Mellman I. *Immunity*, 2013.

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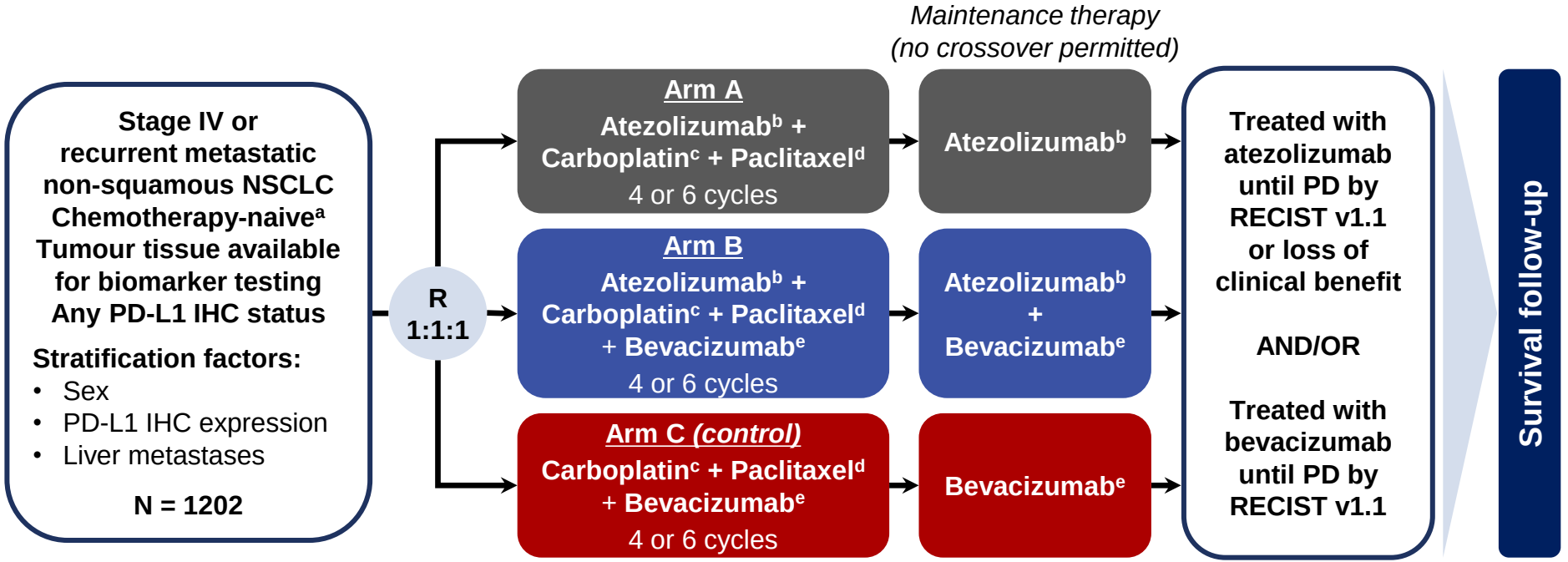
IMpower150 study design



The principal question is to assess whether the addition of atezolizumab to Arm C provides clinical benefit

[a] Patients with a sensitising *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.

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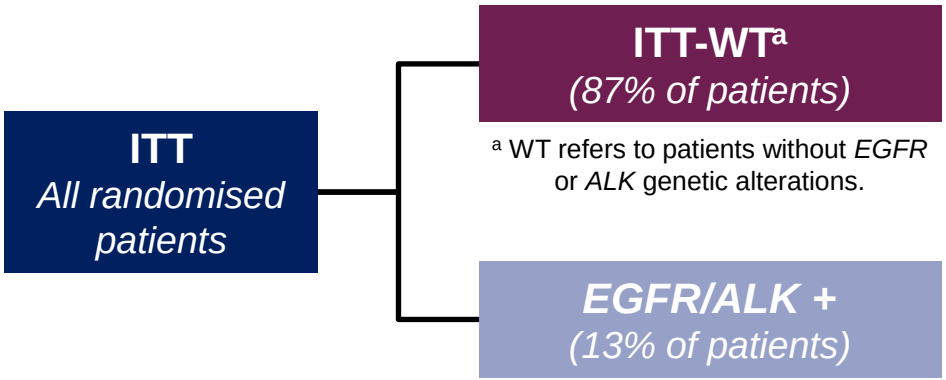
IMpower150 study populations and objectives



1 **Co-primary objectives**

- Investigator-assessed **PFS** in **ITT-WT**

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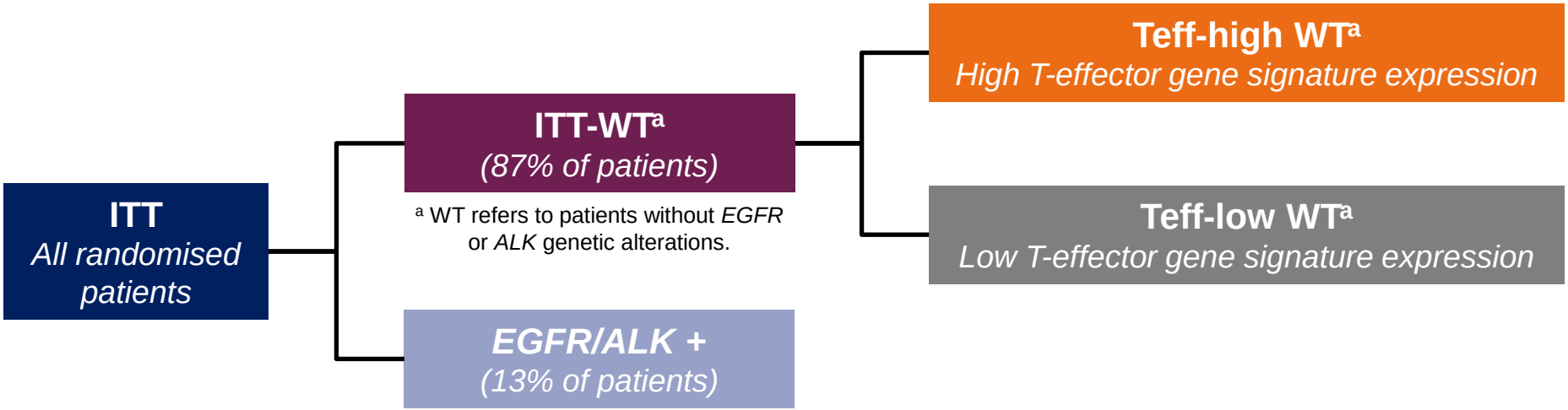
IMpower150 study populations and objectives



[a] WT refers to patients without *EGFR* or *ALK* genetic alterations.

1 **Co-primary objectives**

- Investigator-assessed **PFS** in **ITT-WT**
- Investigator-assessed **PFS** in **Teff-high WT**

The T-effector (Teff) gene signature is defined by expression of *PD-L1*, *CXCL9* and *IFNγ* and is a surrogate of both PD-L1 IHC expression and pre-existing immunity (Kowanetz M, et al. WCLC, 2017).

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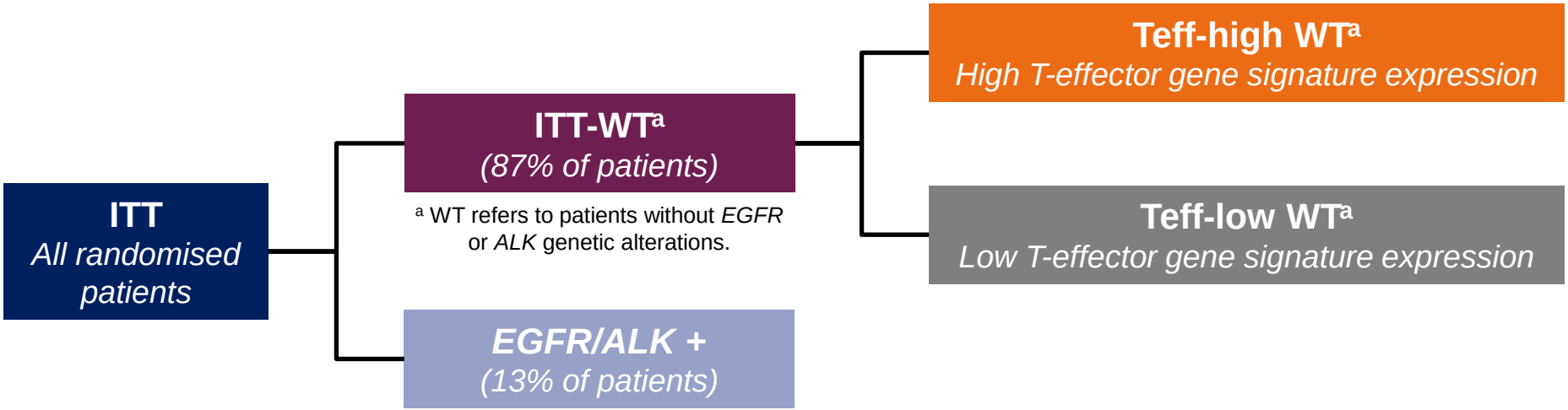
IMpower150 study populations and objectives



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Co-primary objectives

- Investigator-assessed **PFS** in **ITT-WT**
- Investigator-assessed **PFS** in **Teff-high WT**
- **OS** in **ITT-WT**

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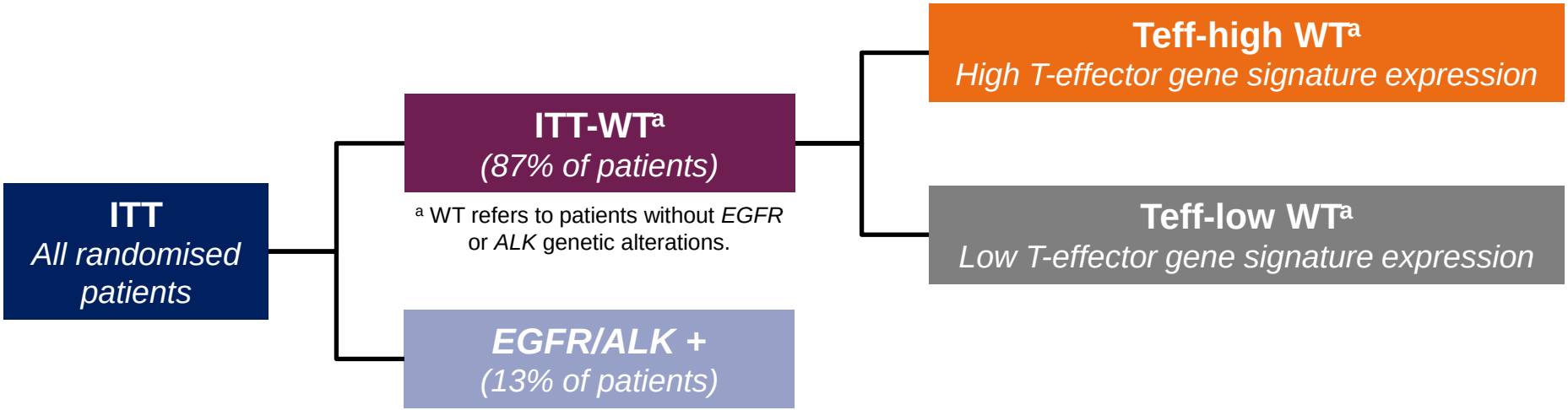
IMpower150 study populations and objectives



[a] WT refers to patients without *EGFR* or *ALK* genetic alterations.

1 Co-primary objectives

- Investigator-assessed **PFS** in **ITT-WT**
- Investigator-assessed **PFS** in **Teff-high WT**
- **OS** in **ITT-WT**

2 Key secondary objectives

- Investigator-assessed **PFS** and **OS** in **ITT**
- Investigator-assessed **PFS** in PD-L1 IHC subgroups
- Independent review facility (IRF)-assessed **PFS**
- **ORR** and **DOR** per RECIST v1.1
- **Safety** in **ITT**

The T-effector (Teff) gene signature is defined by expression of *PD-L1*, *CXCL9* and *IFNγ* and is a surrogate of both PD-L1 IHC expression and pre-existing immunity (Kowanetz M, et al. WCLC, 2017).

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Biomarkers in IMpower150

- IMpower150 provided the opportunity to evaluate multiple strategies to enrich for PFS, including T-effector (Teff) gene signature expression and PD-L1 IHC
- The Teff gene signature is defined by mRNA expression of 3 genes (*PD-L1*, *CXCL9* and *IFNγ*) and is a surrogate for both PD-L1 expression and pre-existing immunity
  - In the OAK study, the Teff gene signature appeared to be a more sensitive biomarker of PFS benefit for monotherapy atezolizumab vs docetaxel than PD-L1 IHC expression[1]
- PD-L1 expression was evaluated using the SP142 IHC assay, as defined in the Phase III OAK study of atezolizumab vs docetaxel[2]

1. Kowanetz M, et al. WCLC 2017 [abstract MA 05.09]. 2. Rittmeyer A, et al. Lancet, 2017.

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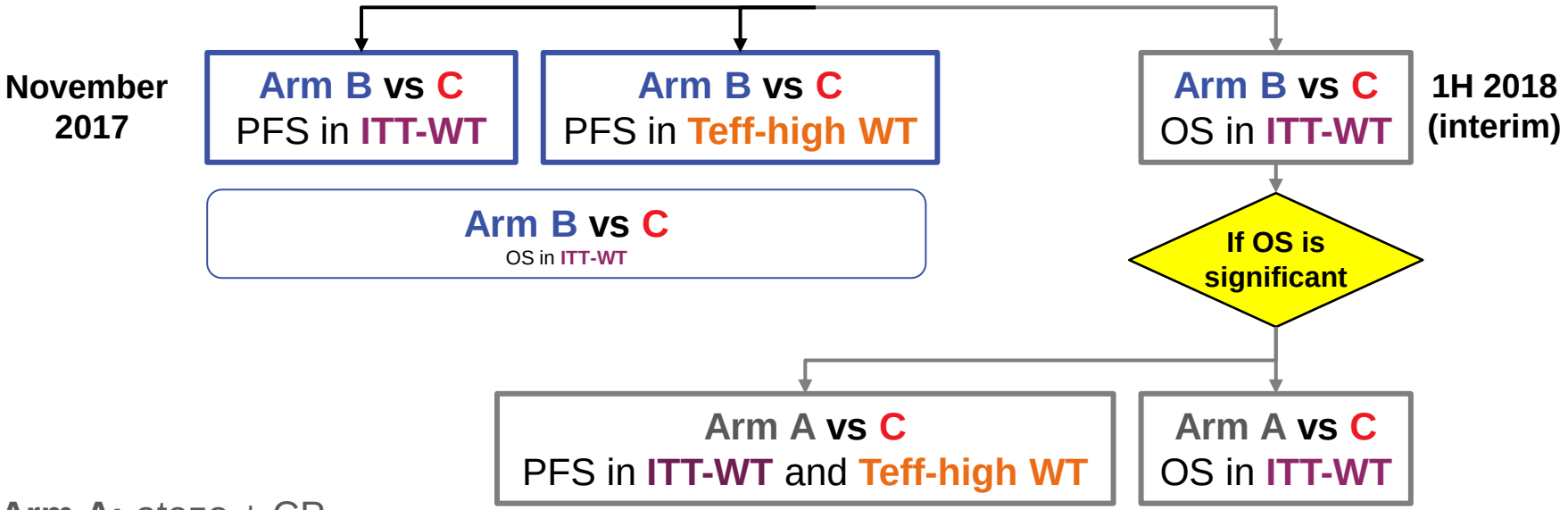
Statistical testing plan for the co-primary endpoints in IMpower150



Arm A: atezo + CP

Arm B: atezo + bev + CP

Arm C: bev + CP *(control)*

atezo, atezolizumab; bev, bevacizumab; CP, carboplatin + paclitaxel.

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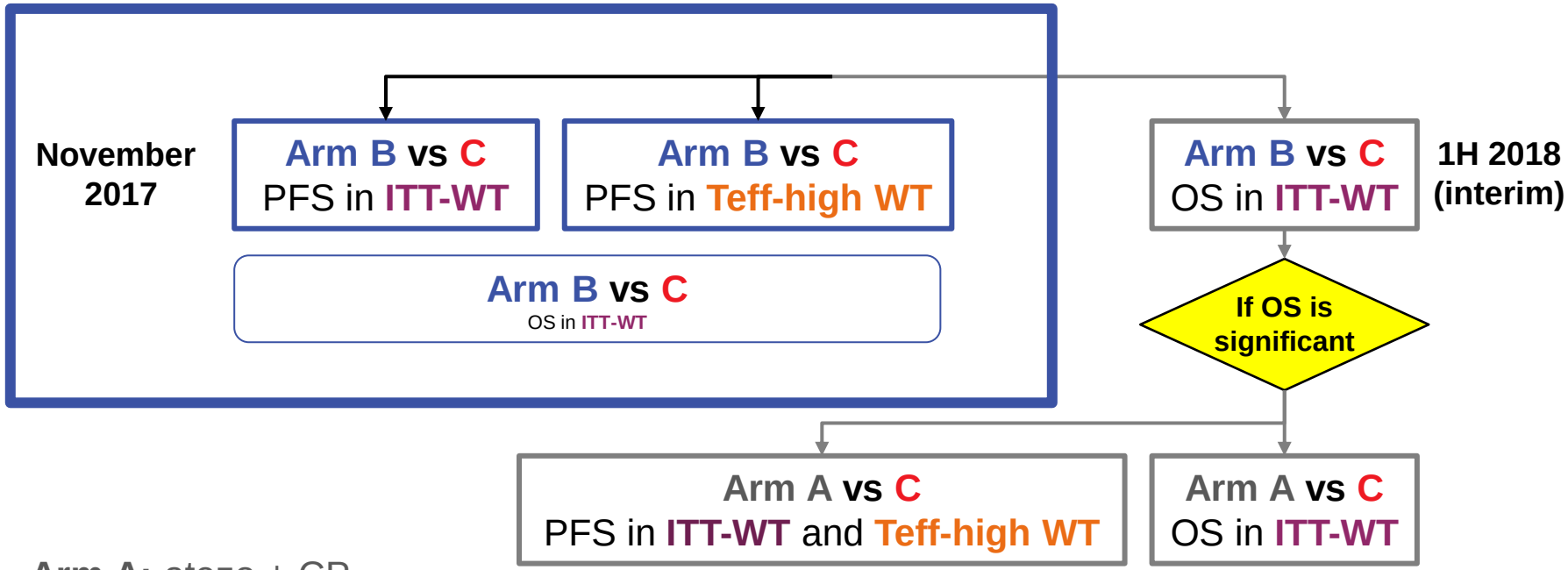
Statistical testing plan for the co-primary endpoints in IMpower150



Arm A: atezo + CP

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Arm C: bev + CP *(control)*

atezo, atezolizumab; bev, bevacizumab; CP, carboplatin + paclitaxel.

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Baseline characteristics in ITT

Baseline characteristics	Arm A: atezo + CP (N = 402)	Arm B: atezo + bev + CP (N = 400)	Arm C (*control*): bev + CP (N = 400)
Median age (range), years	63 (32-85)	63 (31-89)	63 (31-90)
Sex, male, n (%)	241 (60%)	240 (60%)	239 (60%)
ECOG PS, 0, n (%)	180 (45%)	159 (40%)	179 (45%)
Tobacco use history, n (%)			
Current smoker | Previous smoker	98 (24%) | 227 (57%)	90 (23%) | 228 (57%)	92 (23%) | 231 (58%)
Never smoker	77 (19%)	82 (21%)	77 (19%)
Liver metastases, yes, n (%)	53 (13%)	53 (13%)	57 (14%)
EGFR mutation, positive, n (%)	46 (11%)	35 (9%)	45 (11%)
ALK rearrangement, positive, n (%)	9 (2%)	13 (3%)	21 (5%)
Teff gene signature expression, high, n (%)[a]	177 (44%)	166 (42%)	148 (37%)
Of those tested	124	106	115
KRAS mutation, positive, n (%)	36 (29%)	47 (44%)	38 (33%)
PD-L1 expression, n (%)[b]			
TC2/3 or IC2/3	137 (34%)	140 (35%)	133 (33%)
TC1/2/3 or IC1/2/3	213 (53%)	209 (52%)	195 (49%)
TC0 and IC0	188 (47%)	191 (48%)	205 (51%)

IC, tumour-infiltrating immune cells; TC, tumour cells.

[a] The Teff gene signature high cut-off ≥ –1.91 was used. [b] 1 patient in Arm A had unknown PD-L1 IHC expression.

TC2/3 or IC2/3 = TC or IC ≥ 5% PD-L1+; TC1/2/3 or IC1/2/3 = TC or IC ≥ 1% PD-L1+; TC0 and IC0 = TC and IC < 1% PD-L1+.

Data cutoff: September 15, 2017

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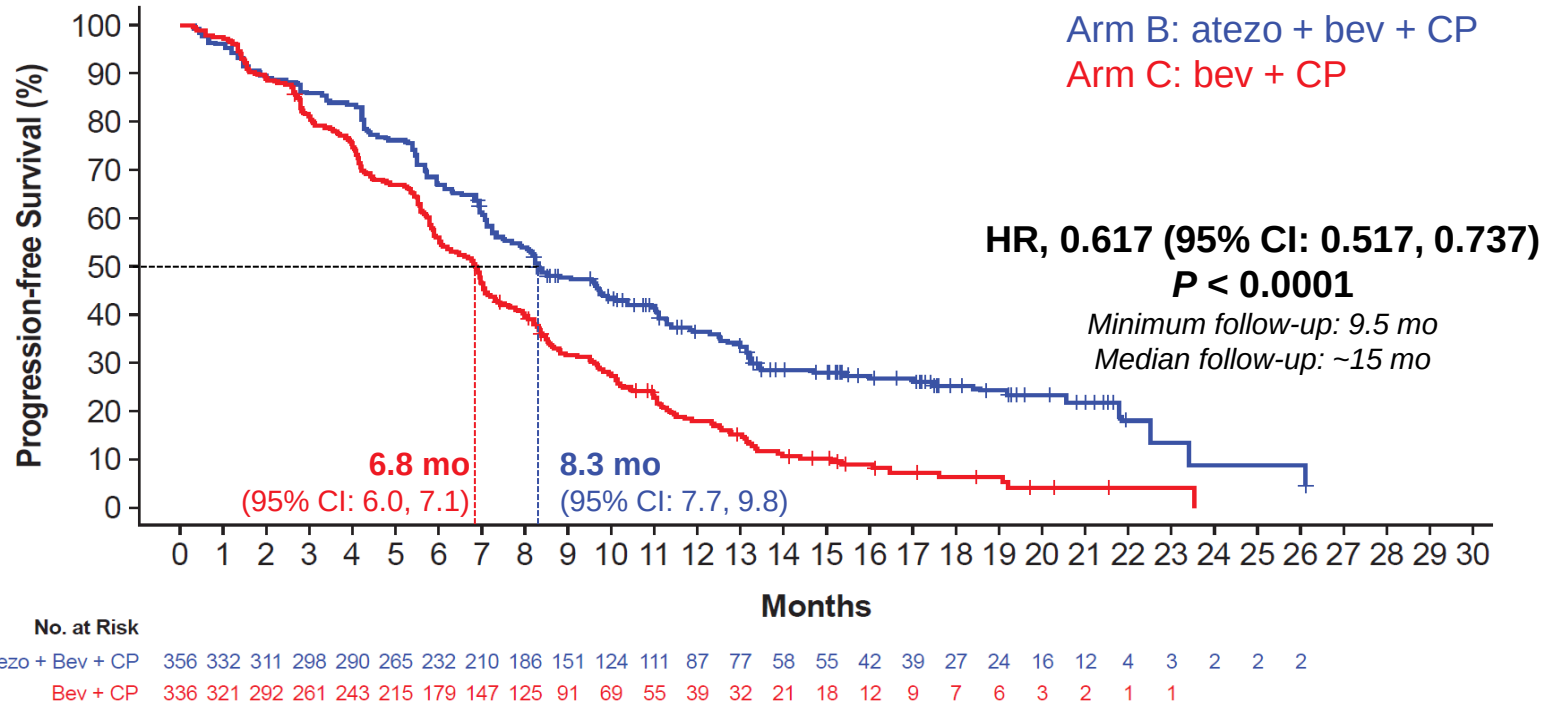
INV-assessed PFS in ITT-WT (Arm B vs Arm C)



INV, investigator.
Data cutoff: September 15, 2017

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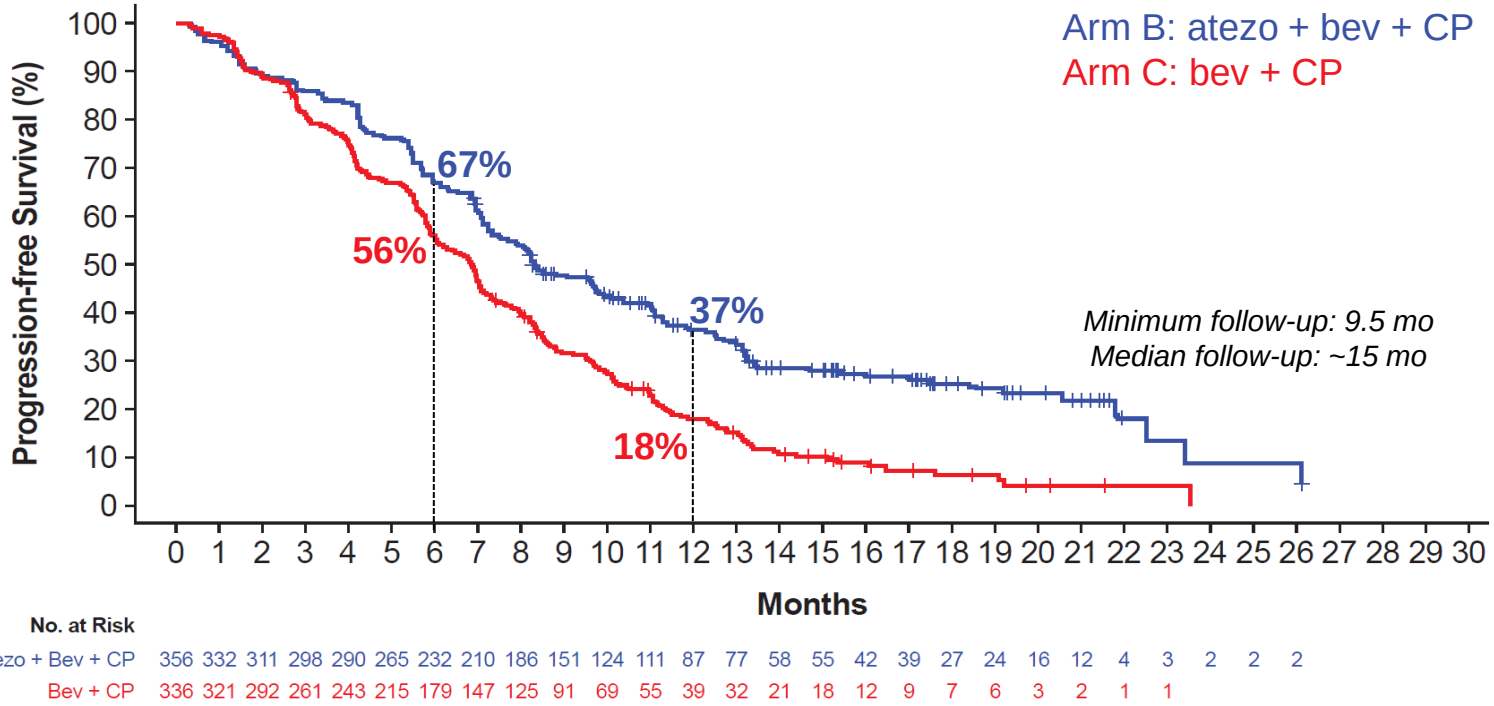
INV-assessed PFS in ITT-WT (Arm B vs Arm C)



INV, investigator.
Data cutoff: September 15, 2017

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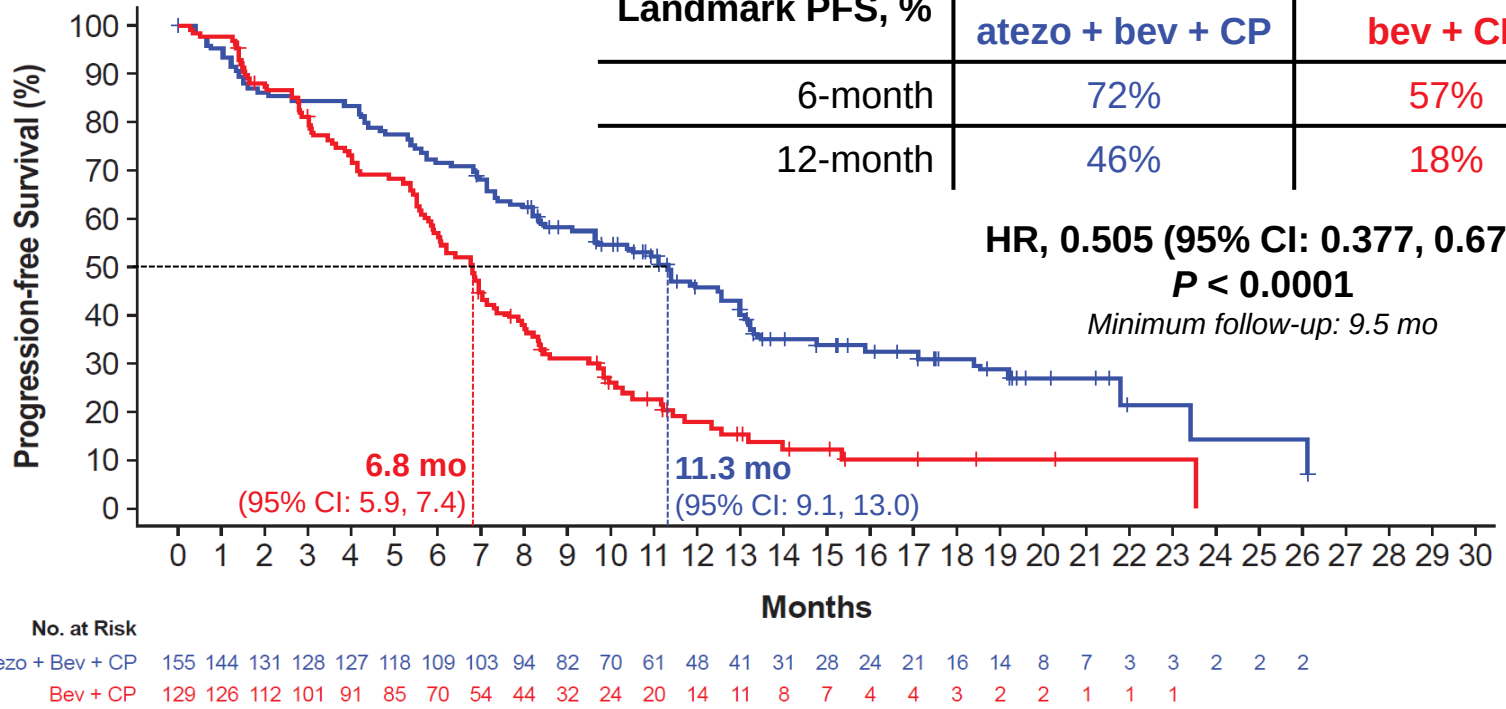
INV-assessed PFS in Teff-high WT (Arm B vs Arm C)

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



INV, investigator.

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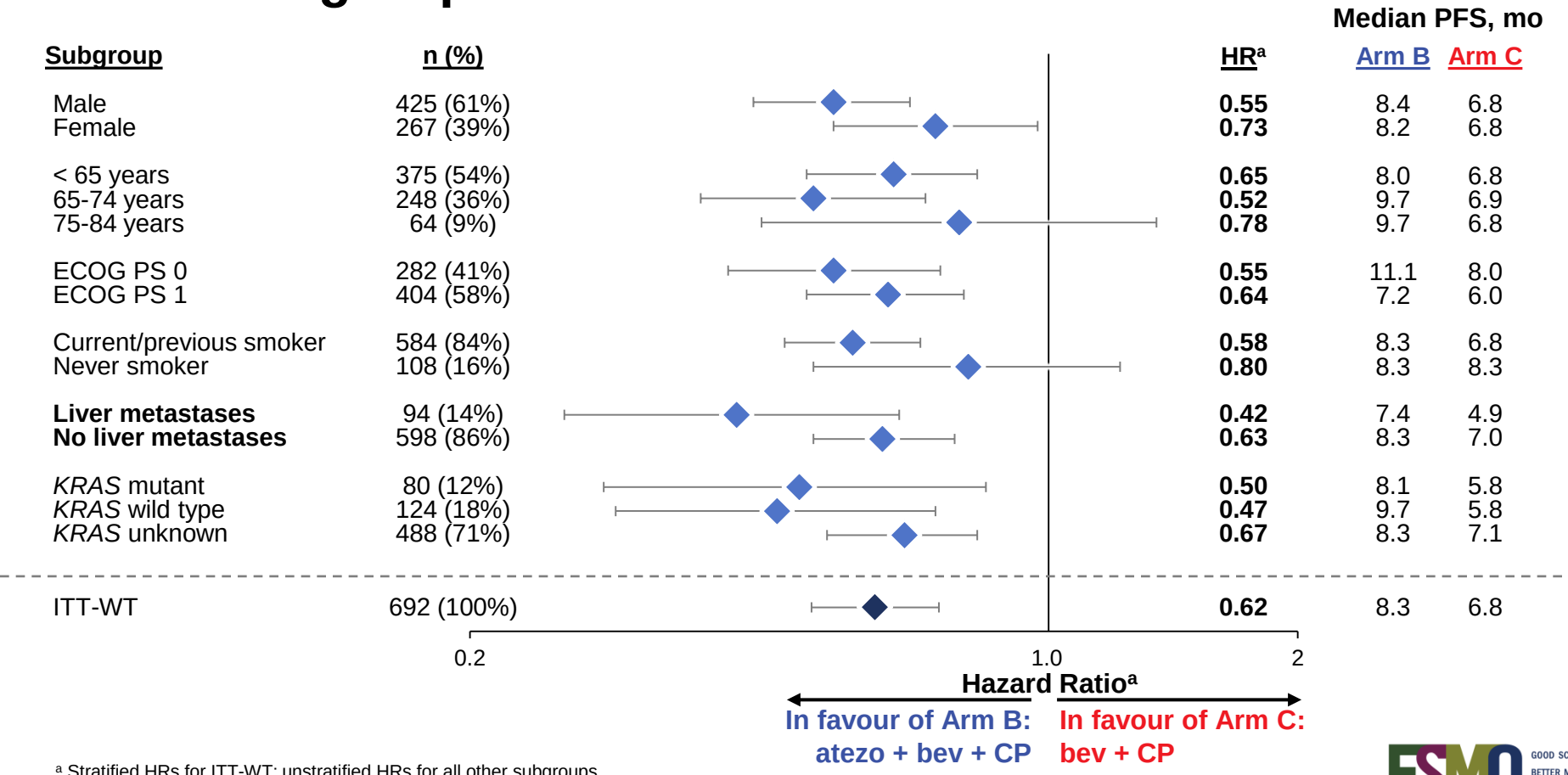
PFS in subgroups of interest in ITT-WT



[a] Stratified HRs for ITT-WT; unstratified HRs for all other subgroups.
Data cutoff: September 15, 2017

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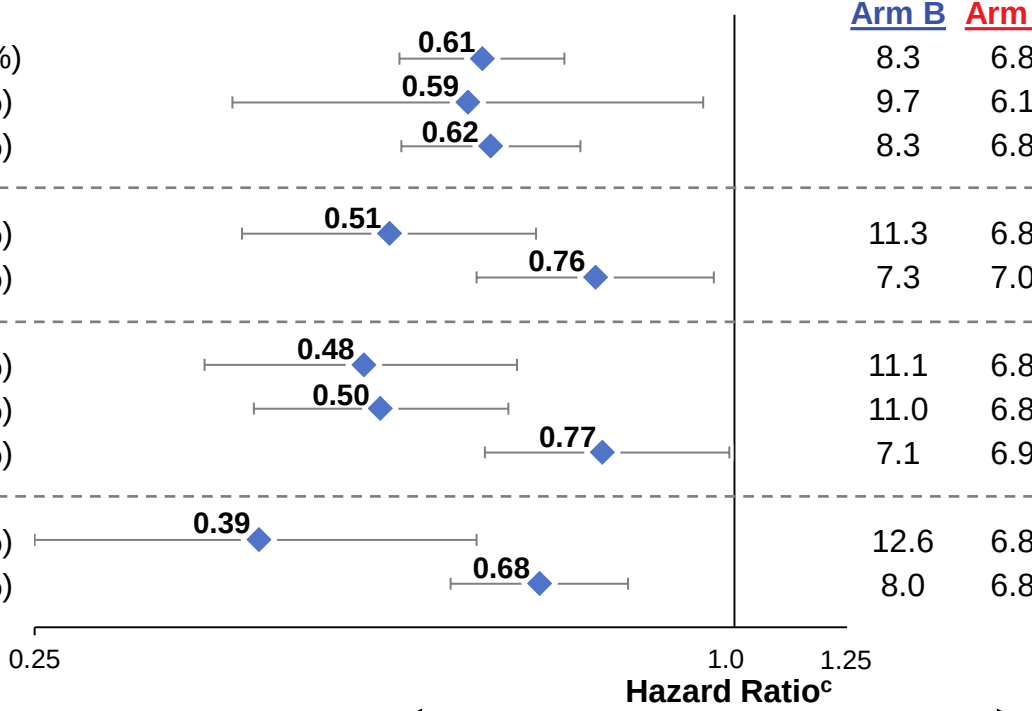
PFS in key biomarker populations

Population	n (%)[a]	Median PFS, mo: Arm B	Median PFS, mo: 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

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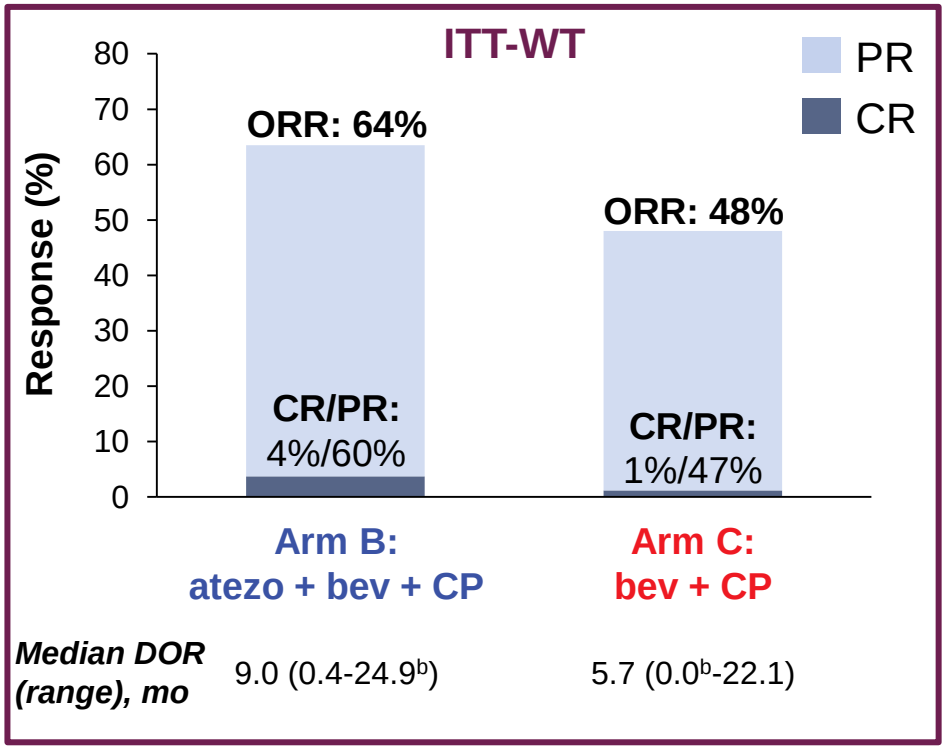
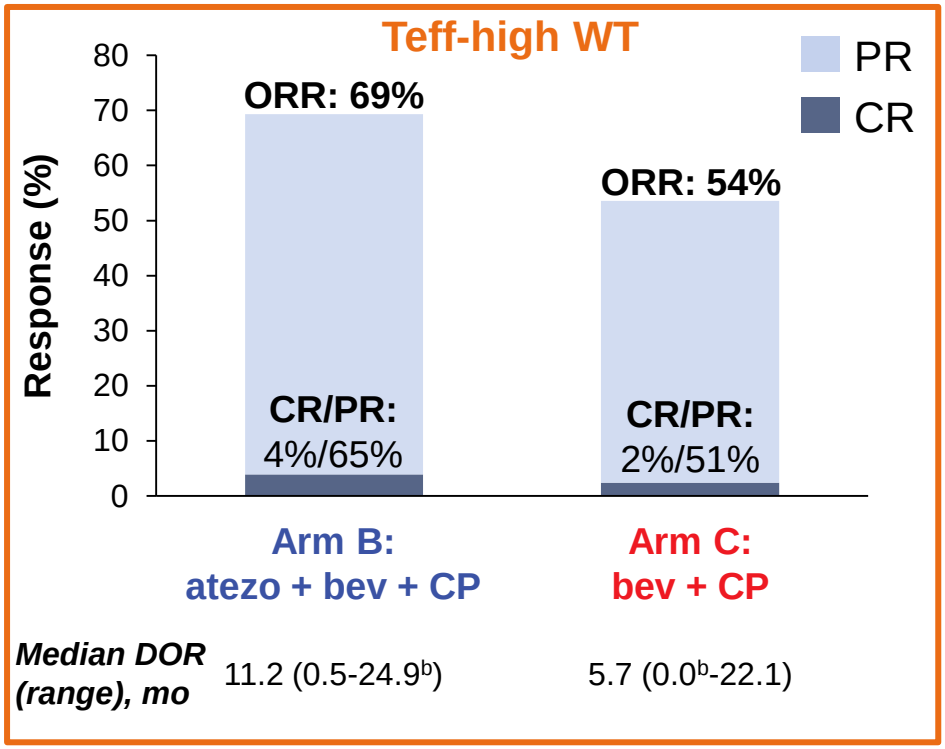
ORR[a] and DOR in ITT-WT and Teff-high WT





[a] Investigator-assessed ORR.
[b] Censored value.

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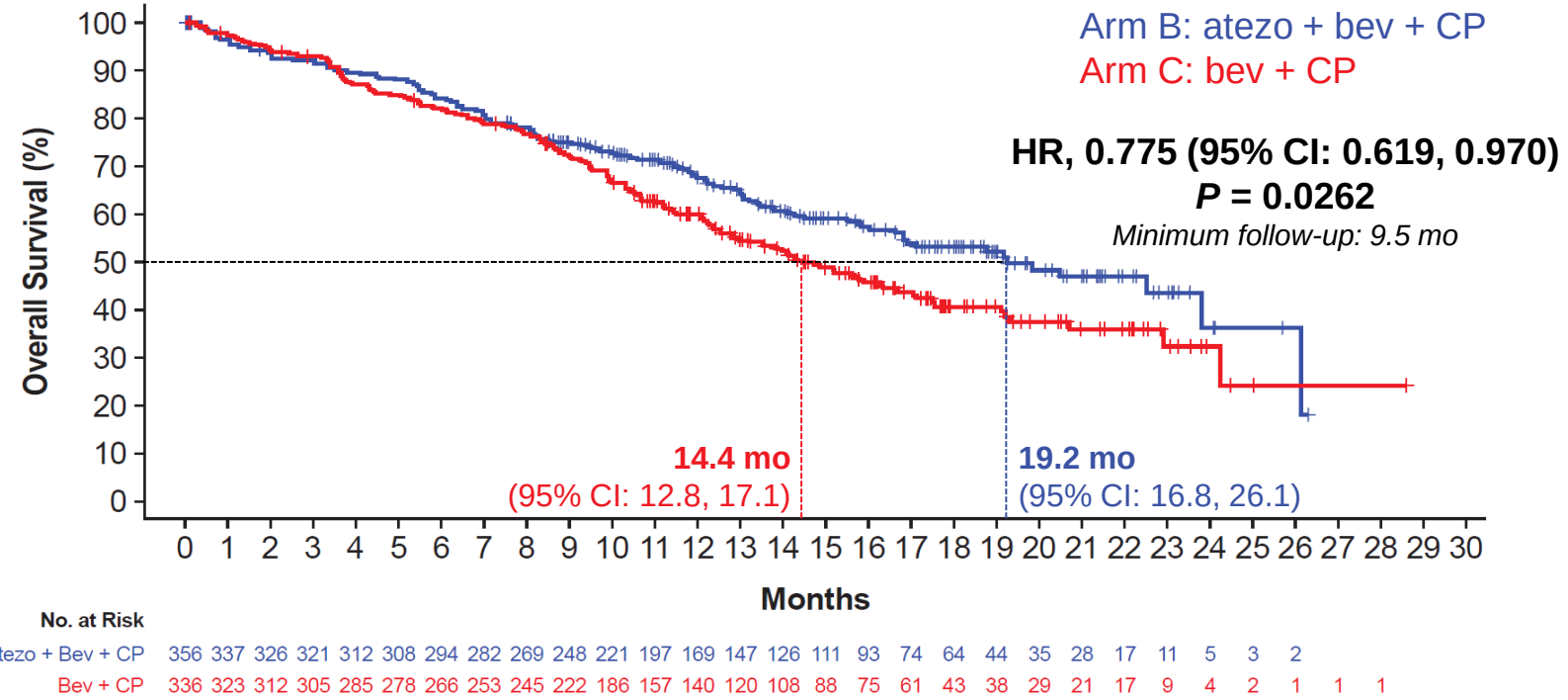
Preliminary OS in ITT-WT (Arm B vs Arm C)



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

 Data cutoff: September 15, 2017

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Preliminary efficacy in ITT-WT (Arm A vs Arm C)

	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%)

- Formal statistical testing for Arm A vs Arm C will be conducted only after the OS boundary for Arm B vs Arm C is crossed

[a] Stratified HR.
[b] n = 347 (Arm A) and n = 331 (Arm C).
Data cutoff: September 15, 2017

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Preliminary efficacy in ITT-WT (Arm A vs Arm C)

	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)	

- Formal statistical testing for Arm A vs Arm C will be conducted only after the OS boundary for Arm B vs Arm C is crossed

[a] Stratified HR.
[b] n = 347 (Arm A) and n = 331 (Arm C).
Data cutoff: September 15, 2017

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Safety summary

	Arm A: atezo + CP (n = 400)	Arm B: atezo + bev + CP (n = 393)	Arm C (*control*): bev + CP (n = 394)
Median doses received (range), n			
Atezolizumab	10 (1-37)	12 (1-38)	NA
Bevacizumab	NA	10 (1-38)	8 (1-33)
All cause AE, n (%)	389 (97%)	385 (98%)	390 (99%)
Grade 3-4	226 (57%)	242 (62%)	230 (58%)
Grade 5	10 (3%)	23 (6%)	21 (5%)
Treatment-related AE, n (%)	372 (93%)	371 (94%)	376 (95%)
Grade 3-4	170 (43%)	219 (56%)	188 (48%)
Grade 5[a]	3 (1%)	11 (3%)	9 (2%)
Serious AE, n (%)	155 (39%)	165 (42%)	134 (34%)
Treatment-related serious AE	77 (19%)	100 (25%)	76 (19%)
AEs of special interest, n (%)[b]	184 (46%)	199 (51%)	108 (27%)
Grade 3-4	37 (9%)	45 (11%)	13 (3%)
Grade 5	2 (1%)	0	0
AE leading to withdrawal from any treatment	56 (14%)	128 (33%)	98 (25%)
AE leading to dose interruption or modification	203 (51%)	235 (60%)	189 (48%)

[a] Including fatal haemorrhagic AEs: Arm C: haemoptysis n = 1, pulmonary haemorrhage n = 2; Arm B haemoptysis n = 3, pulmonary haemorrhage n = 2, haemorrhage intracranial n = 1; Arm A: haemoptysis n = 1, haemorrhage intracranial n = 1.
[b] Investigator text for AEs encoded using MedDRA v20.1.
Data cutoff: September 15, 2017

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Immune-related AEs of special interest in ≥ 5 patients across arms

	Arm A: atezo + CP (n = 400)		Arm B: atezo + bev + CP (n = 393)		Arm C (*control*): bev + CP (n = 394)	
AEs of special interest, n (%)	**All grade**	**Grade 3-4**	**All grade**	**Grade 3-4**	**All grade**	**Grade 3-4**
Rash	114 (29%)	14 (4%)	113 (29%)	9 (2%)	52 (13%)	2 (1%)
Hepatitis	39 (10%)	12 (3%)	54 (14%)	19 (5%)	29 (7%)	3 (1%)
Laboratory abnormalities	34 (9%)	10 (3%)	47 (12%)	16 (4%)	29 (7%)	3 (1%)
Hypothyroidism	30 (8%)	1 (<1%)	50 (13%)	1 (<1%)	15 (4%)	0
Infusion-related reactions	16 (4%)	3 (1%)	13 (3%)	2 (1%)	11 (3%)	3 (1%)
Pneumonitis	21 (5%)	7 (2%)	11 (3%)	6 (2%)	5 (1%)	2 (1%)
Hyperthyroidism	11 (3%)	0	16 (4%)	1 (<1%)	5 (1%)	0
Colitis	3 (1%)	2 (1%)	9 (2%)	5 (1%)	2 (1%)	2 (1%)
Severe cutaneous reaction	3 (1%)	3 (1%)	4 (1%)	0	1 (<1%)	0
Adrenal insufficiency	2 (1%)	0	2 (1%)	1 (<1%)	3 (1%)	1 (<1%)
Pancreatitis	2 (1%)	2 (1%)	5 (1%)	2 (1%)	0	0

Data cutoff: September 15, 2017

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Summary

- IMpower150 is the first phase III immunotherapy-based combination study to demonstrate a statistically significant and clinically meaningful improvement in PFS in all-comer 1L NSQ mNSCLC, providing a potential new standard of care for patients
- PFS benefit was demonstrated with the addition of atezolizumab to bevacizumab + CP (Arm B) vs bevacizumab + CP (Arm C) in all populations tested, including patients with sensitising *EGFR* or *ALK* genetic alterations, Teff-low tumours, PD-L1–negative tumours and liver metastases
- Atezolizumab in combination with chemotherapy ± bevacizumab appears to be well tolerated and its safety profile is consistent with known safety risks
- OS data, while not mature, are promising in Arm B vs Arm C; next interim analysis for all arms is anticipated in 1H 2018

mNSCLC, metastatic NSCLC; NSQ, non-squamous.

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Acknowledgements

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- Participating study investigators and clinical sites
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- Medical writing assistance for this presentation was provided by Emily C. Casey, PhD, of Health Interactions and funded by F. Hoffmann-La Roche, Ltd