# 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)

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# Disclosures

- 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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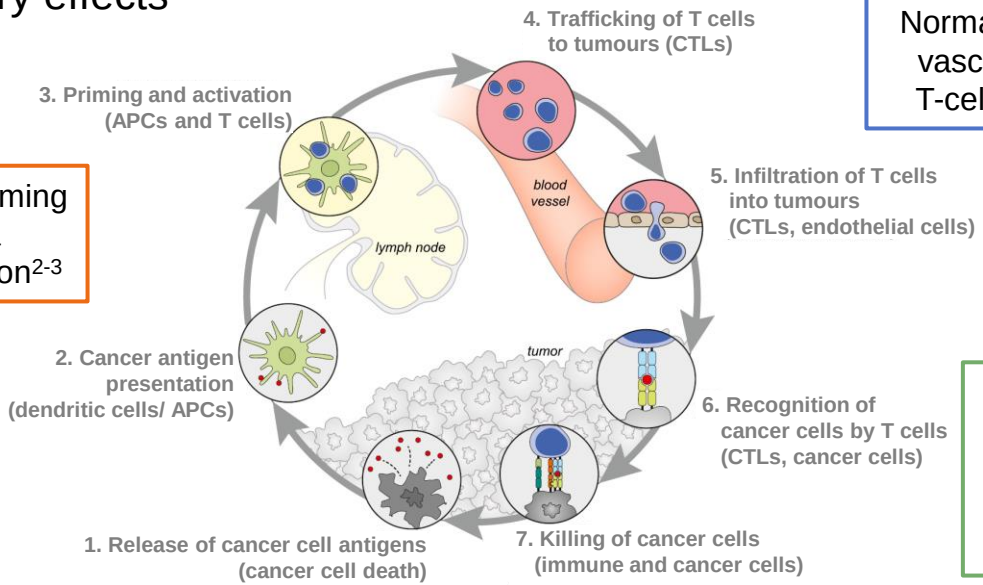
# Rationale for combining atezolizumab + bevacizumab

- 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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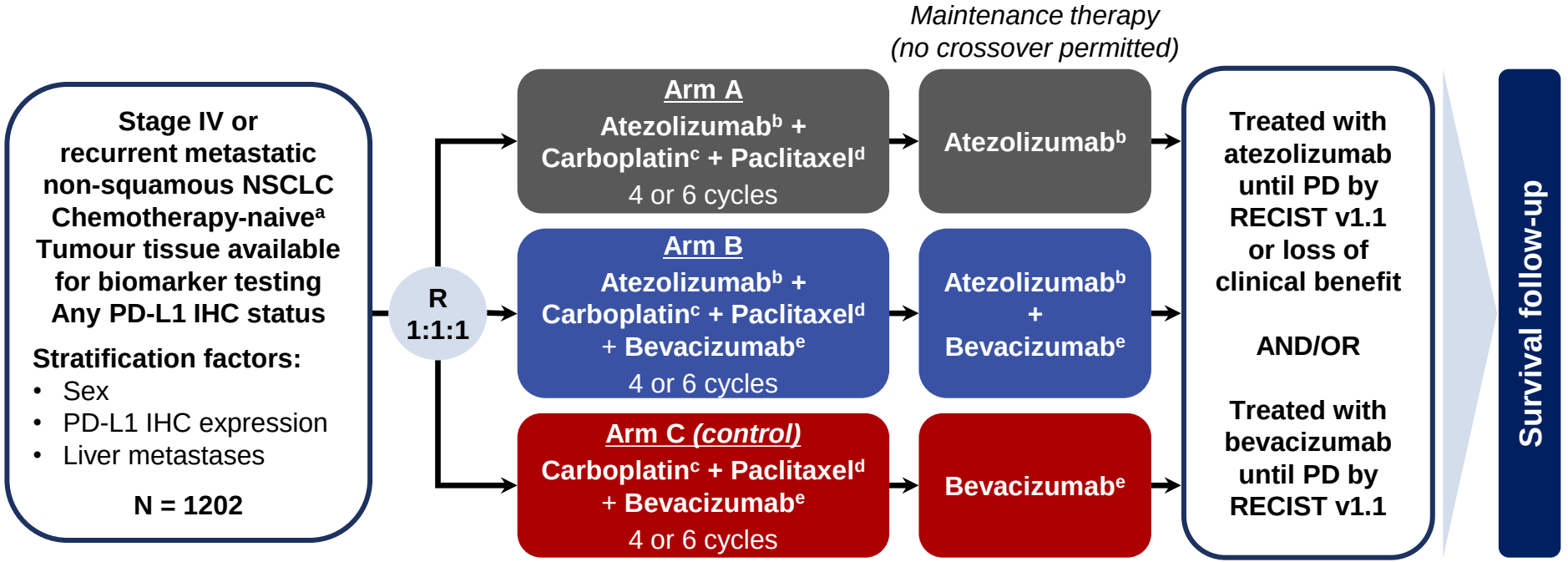
# IMpower150 study design




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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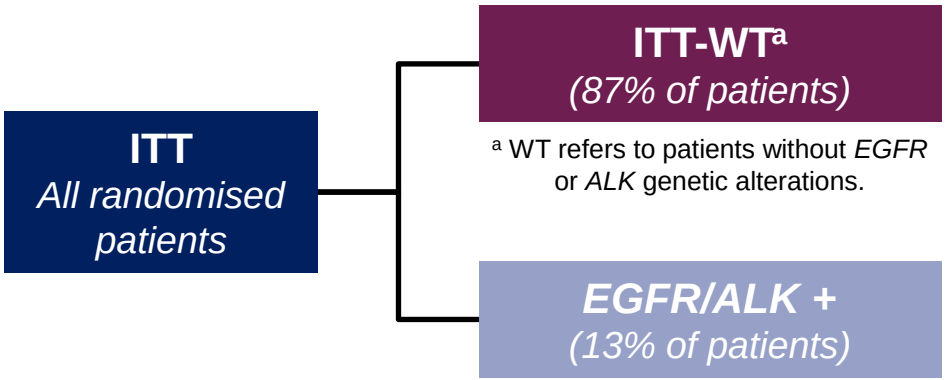
# IMpower150 study populations and objectives




1 **Co-primary objectives**

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



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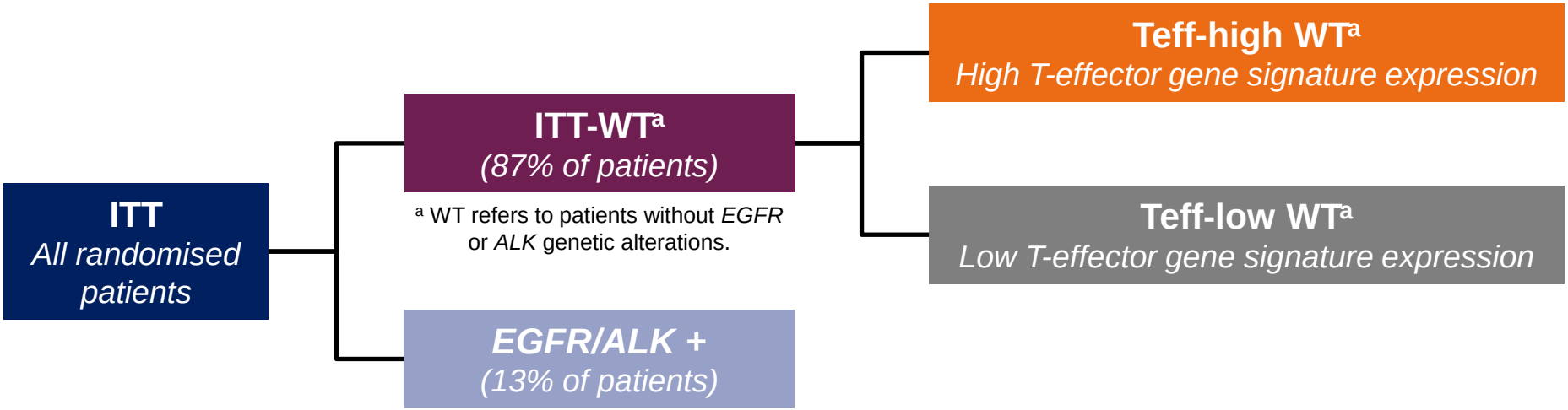
# IMpower150 study populations and objectives




[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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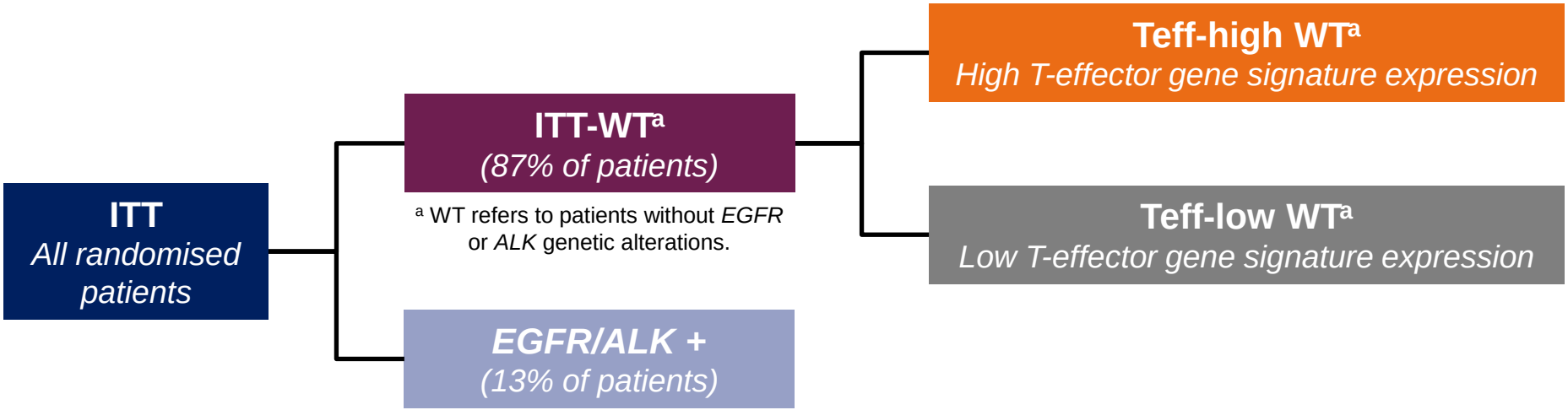
# IMpower150 study populations and objectives

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## Co-primary objectives

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

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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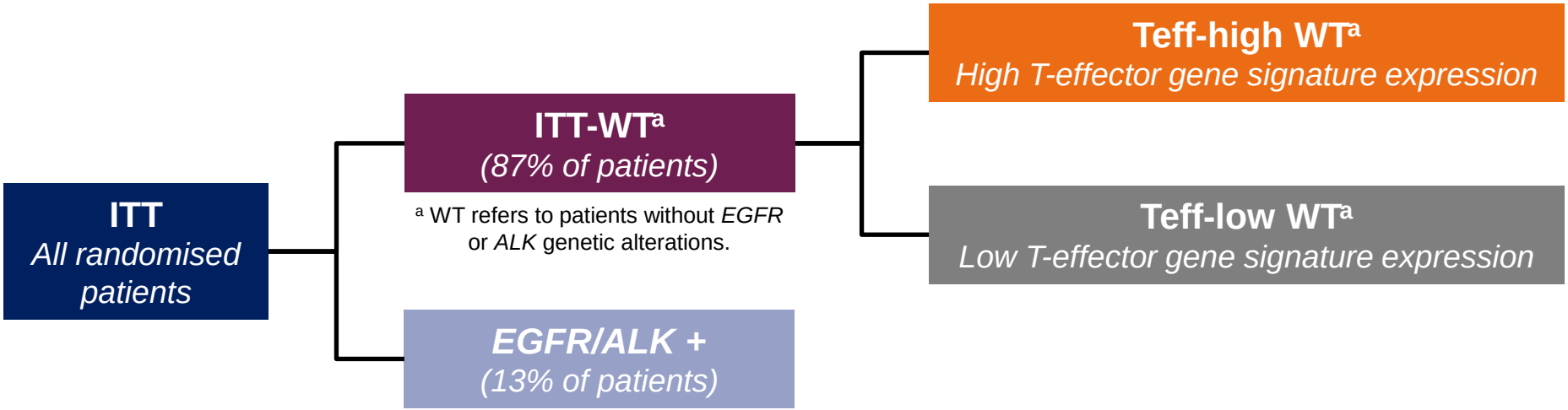
# IMpower150 study populations and objectives




[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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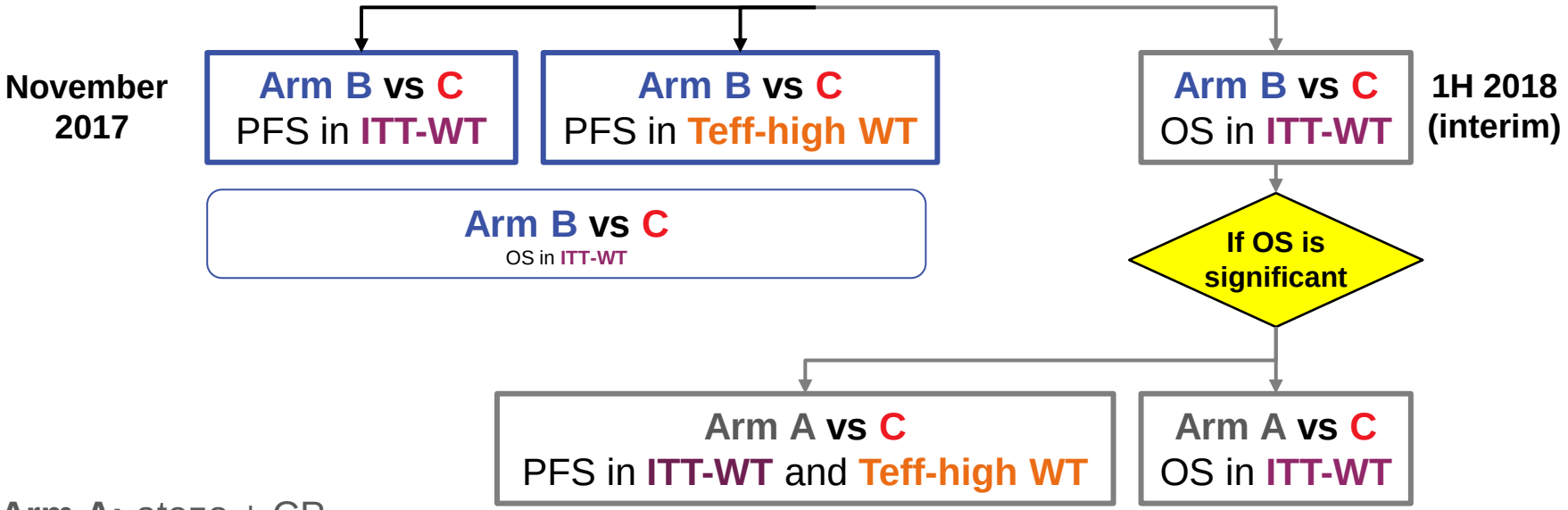
# Statistical testing plan for the co-primary endpoints in IMpower150




**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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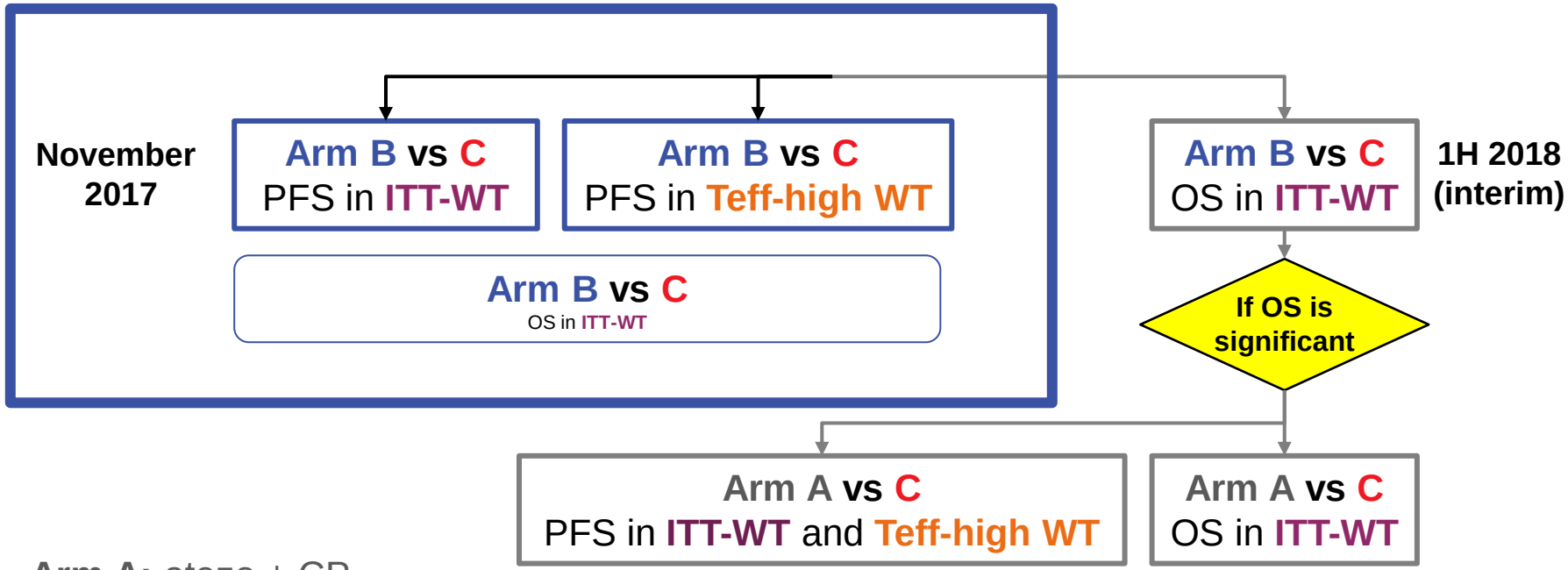
# Statistical testing plan for the co-primary endpoints in IMpower150




**Arm A:** atezo + CP

**Arm B:** atezo + bev + CP

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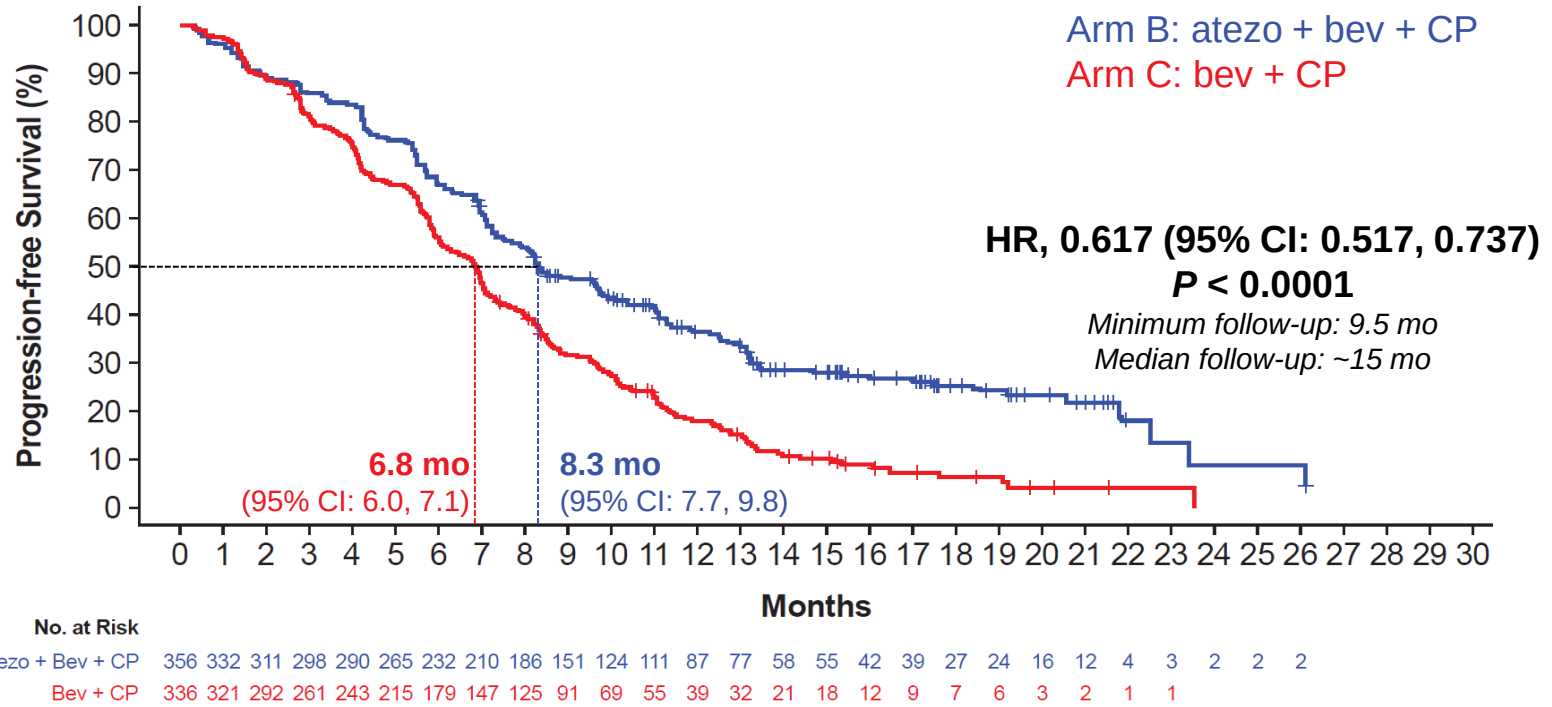
# INV-assessed PFS in ITT-WT (Arm B vs Arm C)




INV, investigator.
Data cutoff: September 15, 2017



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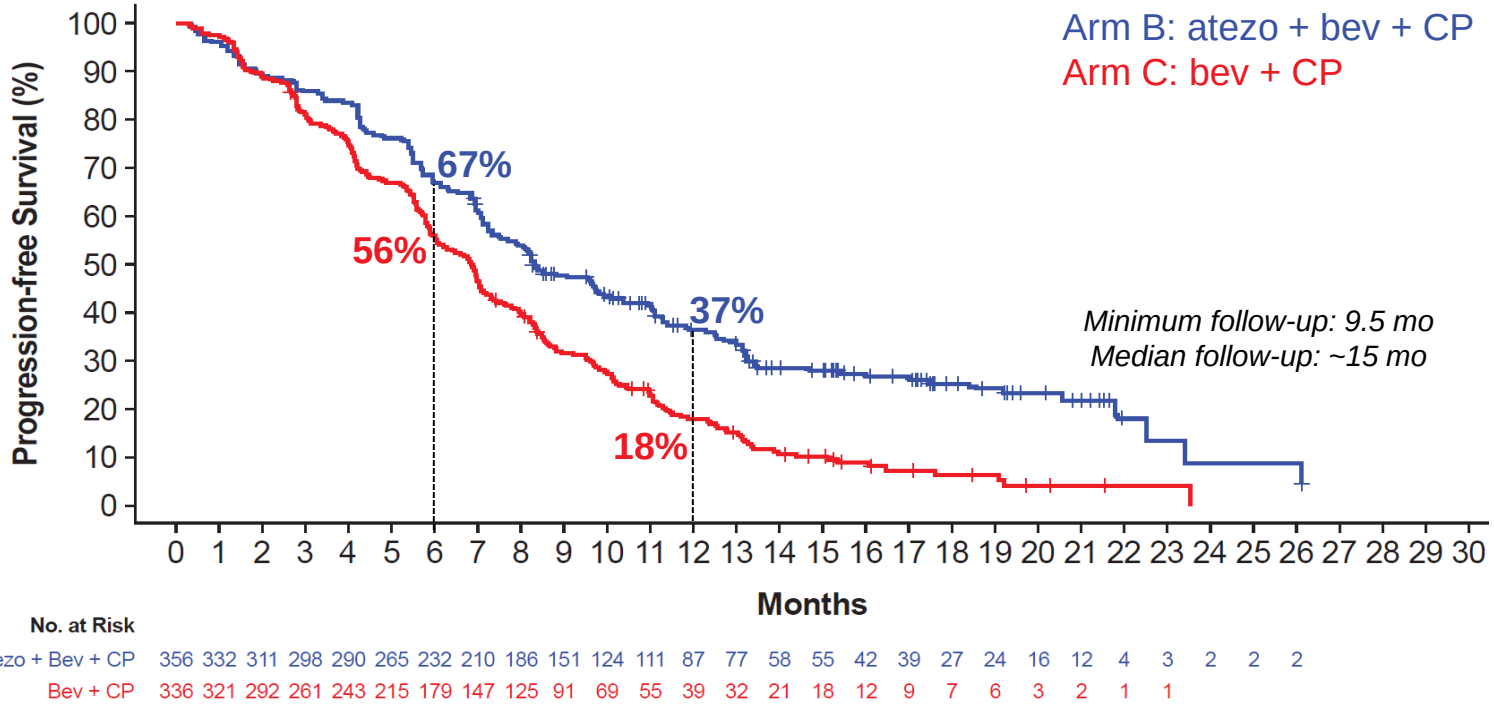
# INV-assessed PFS in ITT-WT (Arm B vs Arm C)




INV, investigator.
Data cutoff: September 15, 2017



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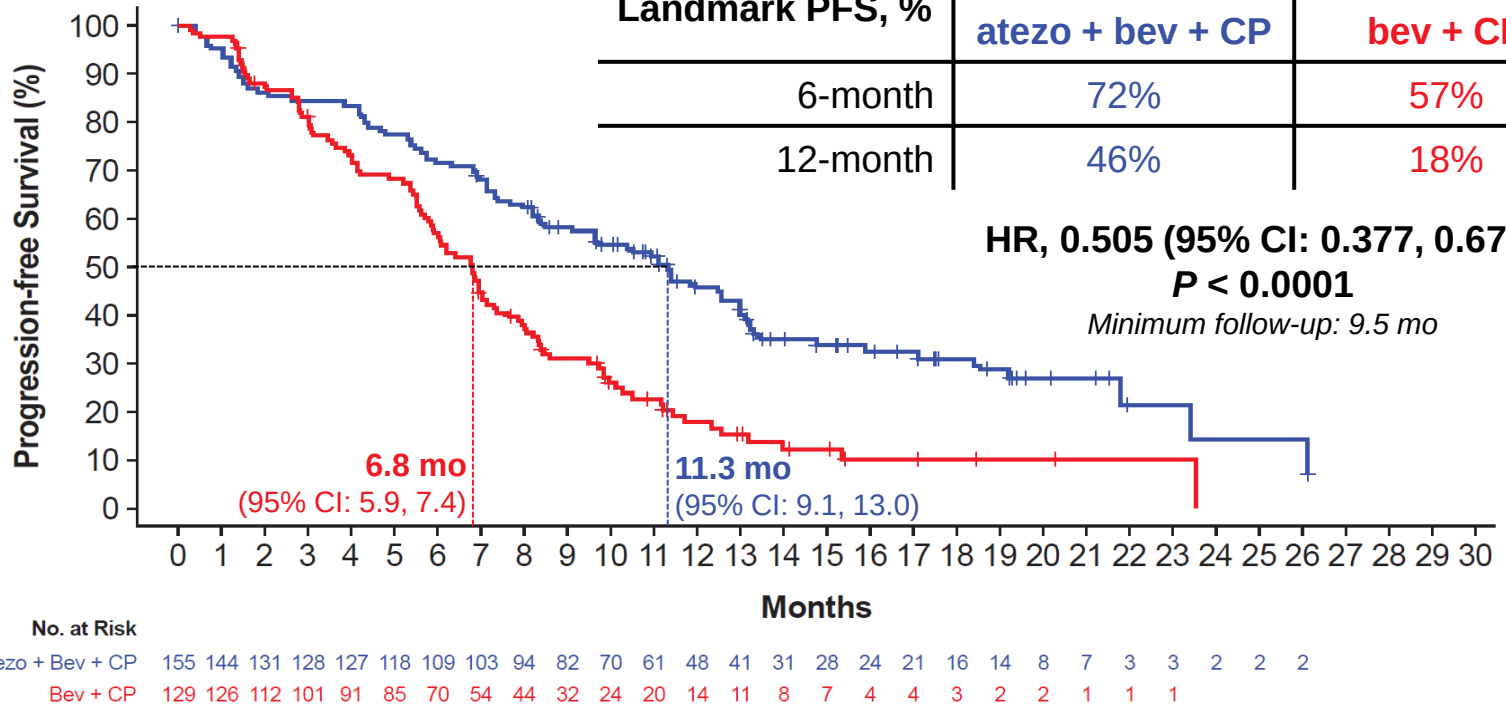
# INV-assessed PFS in Teff-high WT (Arm B vs Arm C)

| 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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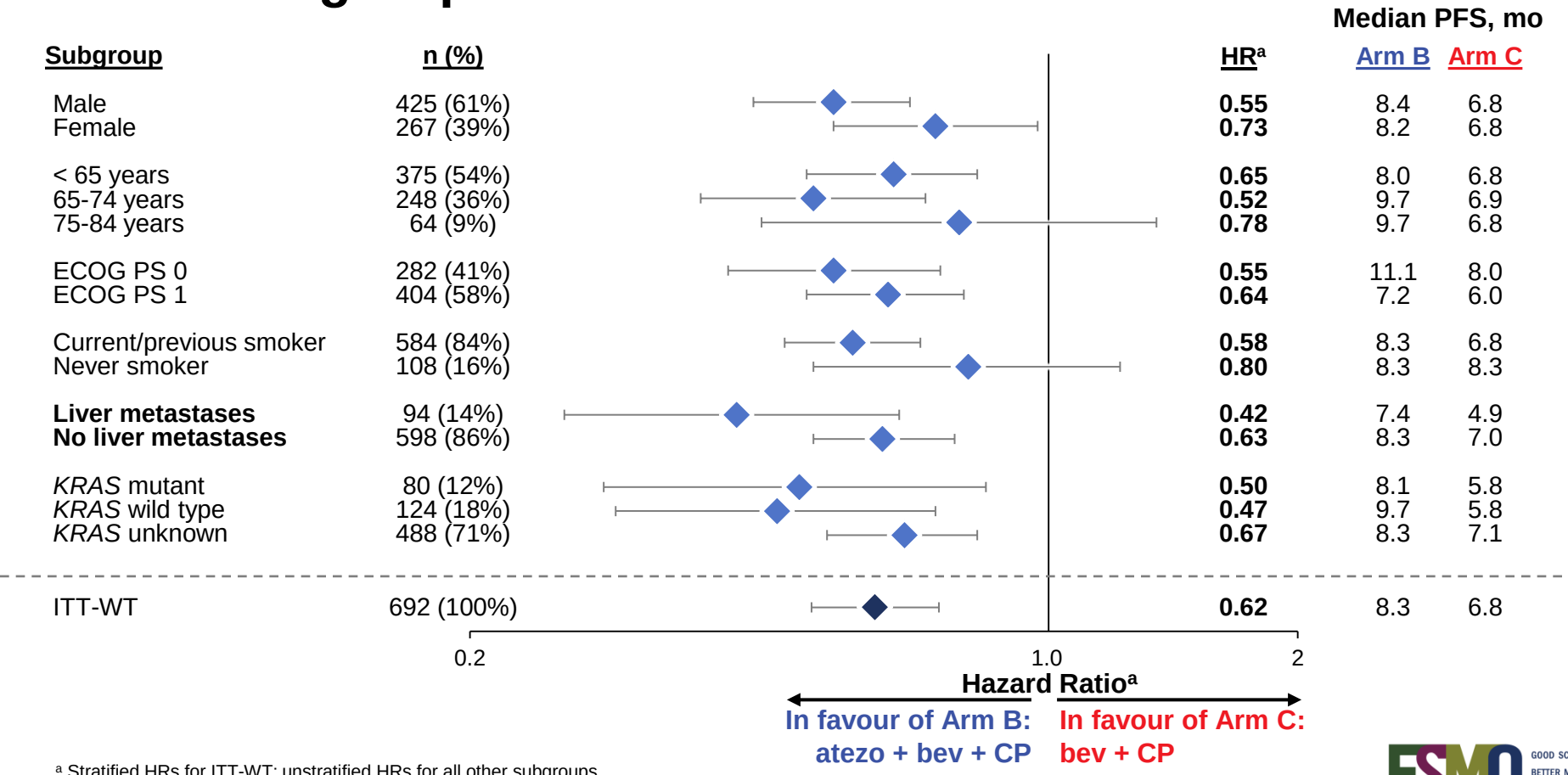
# PFS in subgroups of interest in ITT-WT




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

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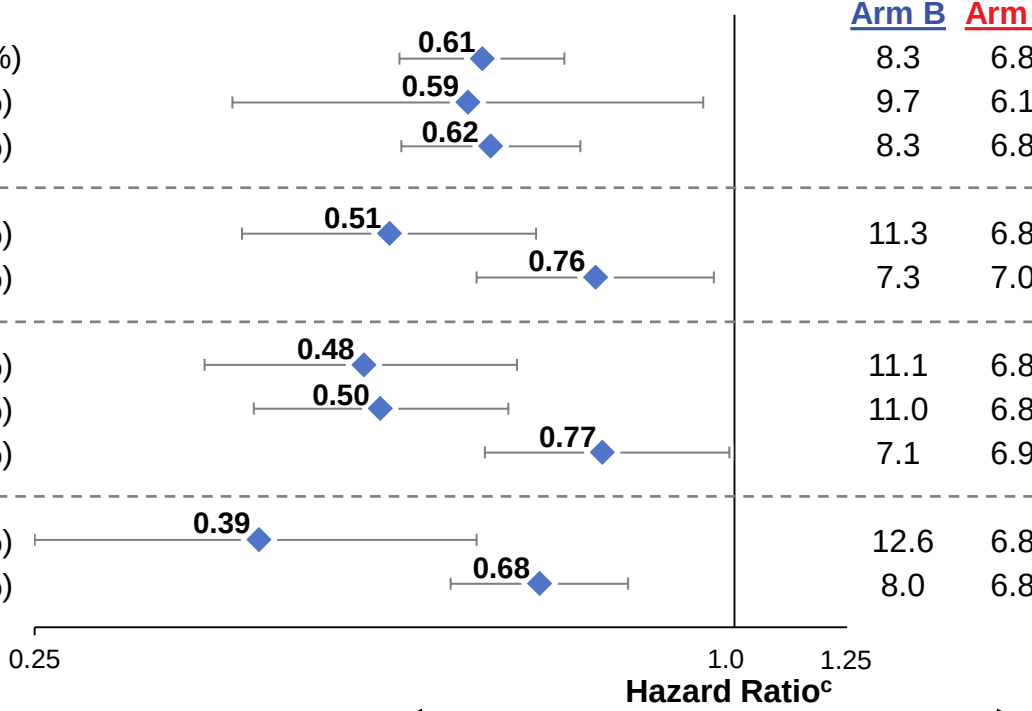
# PFS in key biomarker populations

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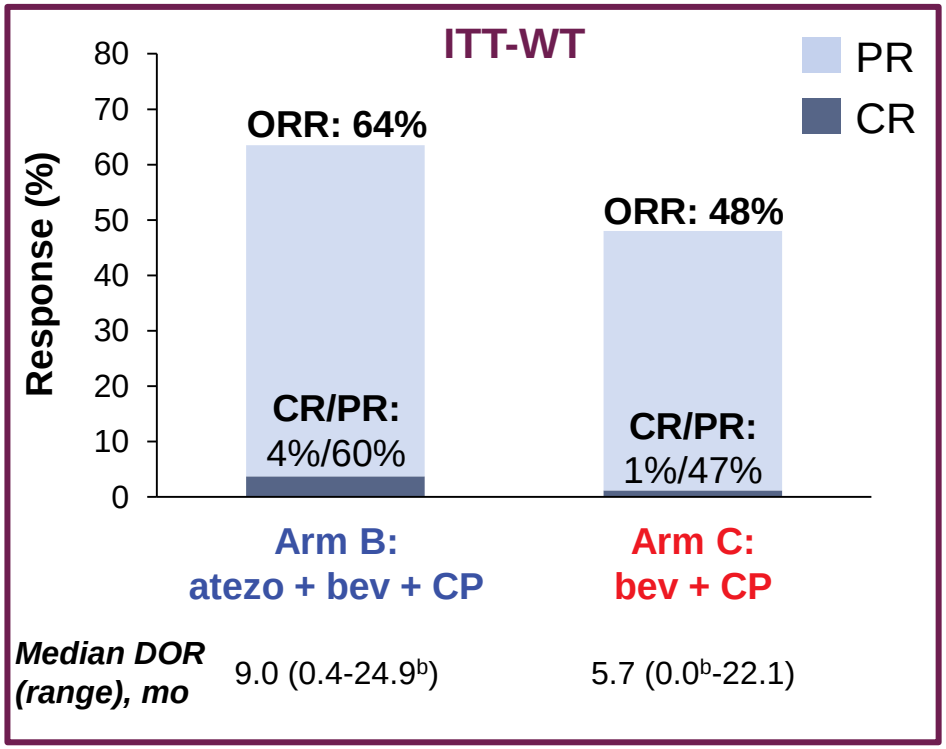
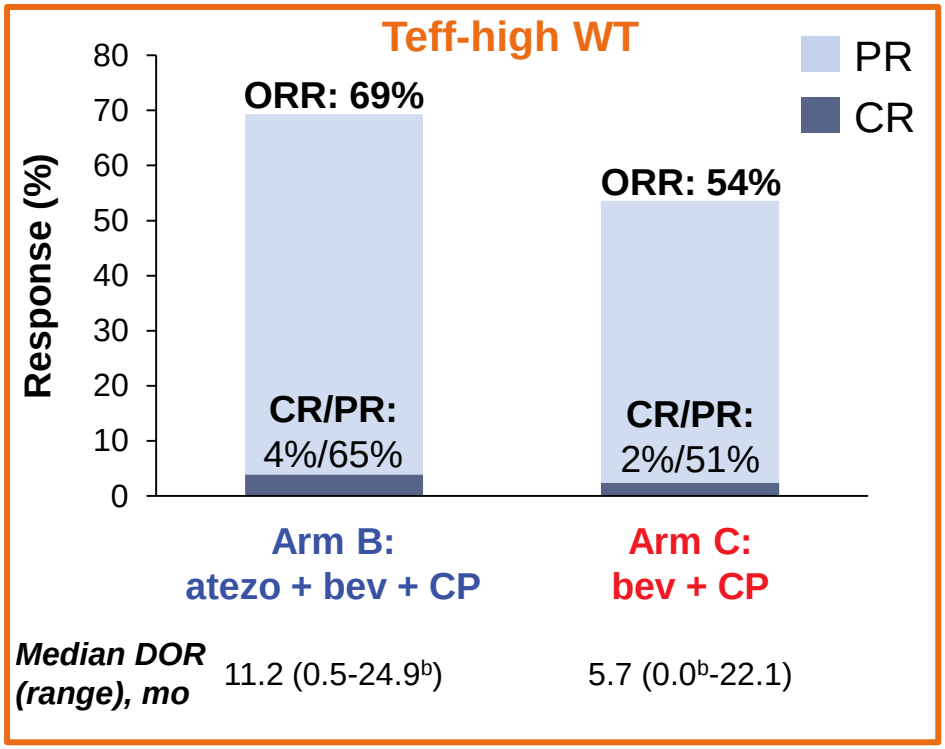
# ORR[a] and DOR in ITT-WT and Teff-high WT




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


Data cutoff: September 15, 2017

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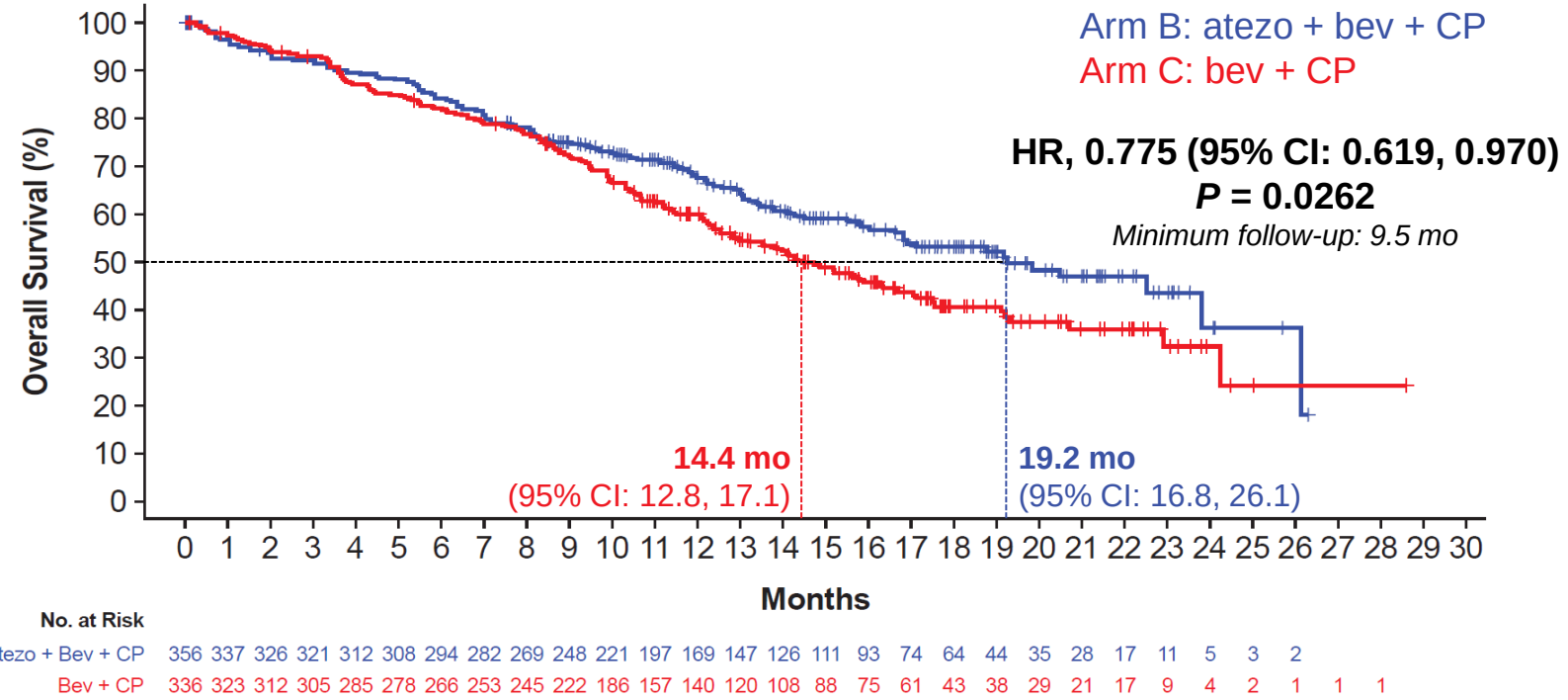
# Preliminary OS in ITT-WT (Arm B vs Arm C)




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

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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


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