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# Primary results from IMpassion131, a double-blind placebo-controlled randomised phase 3 trial of first-line paclitaxel ± atezolizumab for unresectable locally advanced/metastatic triple-negative breast cancer

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# Disclosure information

Dr Miles has received honoraria for consultancy/advisory boards from Roche/Genentech, Eisai and Genomic Health

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# Rationale for IMpassion131 and status of immunotherapy in TNBC

- TNBC is a heterogeneous disease entity with high unmet need
- Some TNBC tumours have immune infiltrate and high PD-L1 expression, providing the rationale for immunotherapy in TNBC[1,2]
- IMpassion130 established the anti-PD-L1 monoclonal antibody atezolizumab as a new standard of care in PD-L1+ metastatic TNBC
  - Combining atezolizumab with nab-paclitaxel as first-line therapy showed significantly improved PFS and clinically meaningful OS effect in PD-L1+ metastatic TNBC[3–5]
- Subsequent trials in metastatic TNBC have assessed different immunotherapy agents, alternative chemotherapy backbones and additional patient populations
  - IMpassion131 (NCT03125902) evaluated atezolizumab in combination with first-line paclitaxel

nab = nanoparticle albumin-bound; OS = overall survival; PD-L1 = programmed cell death ligand-1; PFS = progression-free survival; TNBC = triple-negative breast cancer

[1]Loi S et al. Ann Oncol 2014. [2]Mittendorf EA et al. Cancer Immunol Res 2014; [3]Schmid P et al. NEJM 2018; [4]Schmid P et al. Lancet 2020; [5]Emens LA et al. ESMO 2020

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# IMpassion131 trial design

## Double-blind placebo-controlled randomised phase 3 trial

- Metastatic or unresectable locally advanced TNBC
- No prior chemotherapy or targeted therapy for advanced TNBC
- Previous eBC treatment completed ≥12 months before randomisation
- Taxane eligible
- Measurable disease
- ECOG PS 0/1

R
2:1

**Atezolizumab 840 mg d1 & 15 + paclitaxel 90 mg/m$^2$ d1, 8 & 15**

8–10 mg dexamethasone or equivalent for at least the first 2 infusions, cycles repeated q28d

**Placebo d1 & 15 + paclitaxel 90 mg/m$^2$ d1, 8 & 15**

Stratification:

- Prior taxane (yes vs no)
- Tumour PD-L1 status (IC <1% vs ≥1%)[a]
- Liver metastases (yes vs no)
- Geographical region (N America vs W Europe/Australia vs E Europe/Asia Pacific vs S America)

**Primary endpoint:** PFS (investigator assessed)
**Secondary endpoints** include:

- OS, ORR, PFS (IRC assessed)
- PROs
- Safety
- Translational research

[a]PD-L1 IC: area of PD-L1-stained tumour-infiltrating ICs as a percentage of tumour area by VENTANA SP142 immunohistochemistry assay. eBC = early breast cancer; ECOG PS = Eastern Cooperative Oncology Group performance status; IC = immune cell; IRC = independent review committee; ORR = objective response rate; PRO = patient-reported outcome; q28d = every 28 days; R = randomisation

# Statistical design and study conduct

- Hierarchical testing informed by results from IMpassion130[1]
- Primary endpoint: Investigator-assessed PFS
  - Tested first in PD-L1+ population (defined as IC ≥1%)
  - Target HR 0.62 (median PFS 5.0 → 8.0 months); 5% 2-sided alpha and 80% power; 155 PFS events in PD-L1+ population
  - If significant in PD-L1+, PFS tested in the ITT population
- Data cut-off for primary PFS and first planned interim OS analysis: 15 November 2019
- Secondary endpoints tested only if all previous tests are significant:
  - OS (PD-L1+ then ITT population)
  - ORR (PD-L1+ then ITT population)
- Data cut-off for updated interim OS analysis: 19 August 2020
- Final OS analysis planned after deaths in 122 (51%) of anticipated 240 patients with PD-L1+ TNBC

HR = hazard ratio; ITT = intent-to-treat

[1]Schmid P et al. NEJM 2018

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# Patient population

## Baseline characteristics well balanced between treatment arms, 45% PD-L1+ (IC ≥1%)

| Characteristic, n (%) | | PD-L1+ population | | ITT population | |
|---|---|---|---|---|---|
| | | Placebo + PAC (n=101) | Atezo + PAC (n=191) | Placebo + PAC (n=220) | Atezo + PAC (n=431) |
| Median (range) age, years | | 53 (25–78) | 55 (23–83) | 53 (25–81) | 54 (22–85) |
| ECOG PS | 0 | 59 (58) | 118 (62) | 130 (59) | 262 (61) |
| | 1 | 42 (42) | 73 (38) | 90 (41) | 169 (39) |
| Liver metastases | | 24 (24) | 37 (19) | 61 (28) | 118 (27) |
| >3 metastatic sites | | 13 (13) | 35 (18) | 48 (22) | 105 (24) |
| PD-L1+[a] | | 101 (100) | 191 (100) | 101 (46) | 191 (44) |
| Prior taxane | | 54 (53) | 97 (51) | 107 (49) | 208 (48) |
| Prior anthracycline | | 50 (50) | 98 (51) | 110 (50) | 212 (49) |
| de novo mBC | | 30 (30) | 53 (28) | 69 (31) | 131 (30) |

[a]As reported on interactive web-response system (for stratification). Atezo = atezolizumab; mBC = metastatic breast cancer; PAC = paclitaxel

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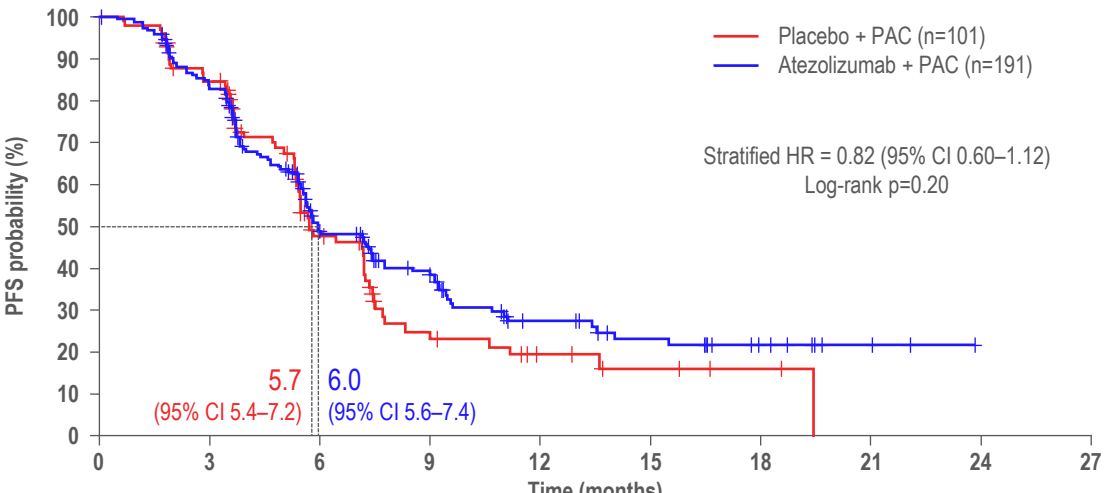
# Primary analysis: PFS in the PD-L1+ population

## Events in 61% of patients (data cut-off: 15 Nov 2019)




| Number at risk | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Placebo + PAC | 101 | 81 | 33 | 14 | 7 | 4 | 2 | 0 | 0 | 0 |
| Atezolizumab + PAC | 191 | 152 | 69 | 44 | 22 | 15 | 8 | 3 | 0 | 0 |

Median duration of follow-up: 8.6 months (placebo + PAC) vs 9.0 months (atezolizumab + PAC). CI = confidence interval

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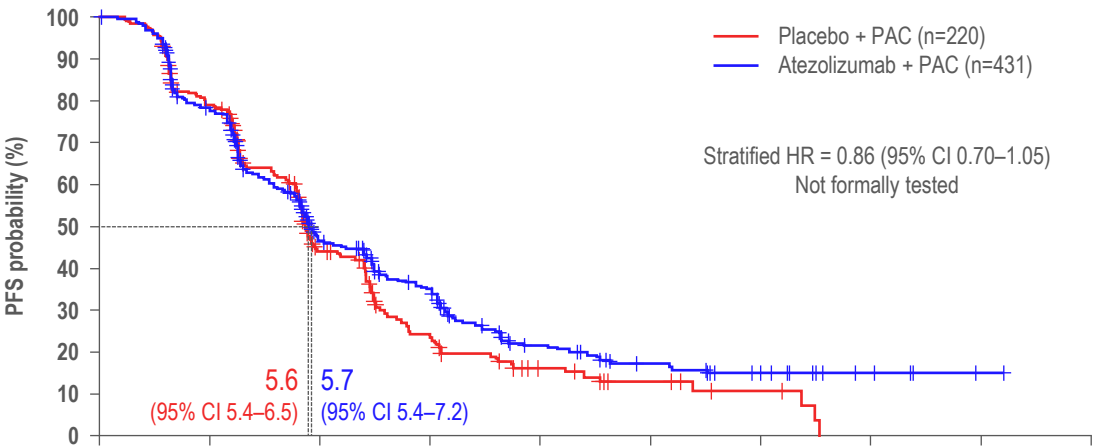
# PFS in the ITT population

## Events in 67% of patients (data cut-off: 15 Nov 2019)

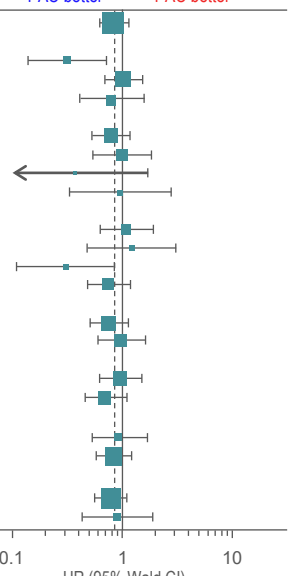



| Number at risk | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Placebo + PAC | 220 | 162 | 72 | 32 | 15 | 8 | 4 | 0 | 0 | 0 |
| Atezolizumab + PAC | 431 | 312 | 146 | 94 | 40 | 25 | 15 | 7 | 1 | 0 |

Median duration of follow-up: 8.5 months (placebo + PAC) vs 8.8 months (atezolizumab + PAC)

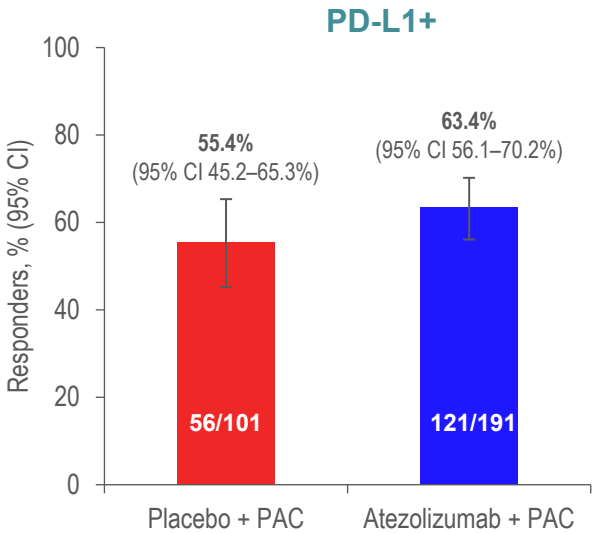
# PFS by subgroup (PD-L1+ population)

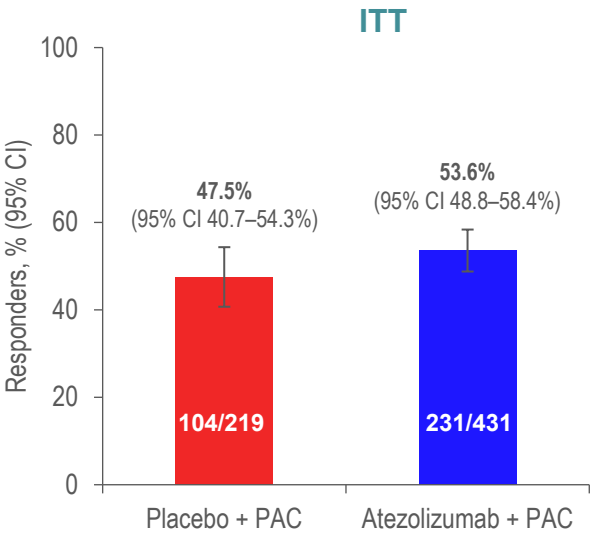
| Baseline risk factors | Total n | Placebo + PAC (n=101) n | Placebo + PAC (n=101) Median, months | Atezolizumab + PAC (n=191) n | Atezolizumab + PAC (n=191) Median, months | HR (95% Wald CI) |
|---|---|---|---|---|---|---|
| All patients | 292 | 101 | 5.7 | 191 | 5.9 | 0.84 (0.62–1.14) |
| Age group | | | | | | |
| 18–40 years | 38 | 16 | 3.4 | 22 | 5.5 | 0.32 (0.14–0.72) |
| 41–64 years | 182 | 62 | 6.4 | 120 | 5.6 | 1.03 (0.70–1.53) |
| ≥65 years | 72 | 23 | 7.7 | 49 | 9.4 | 0.80 (0.41–1.58) |
| Race | | | | | | |
| White | 170 | 59 | 5.7 | 111 | 5.9 | 0.79 (0.53–1.17) |
| Asian | 87 | 30 | 7.2 | 57 | 7.3 | 1.00 (0.54–1.84) |
| Black/African American | 12 | 4 | 3.6 | 8 | 7.1 | 0.38 (0.08–1.71) |
| Other | 23 | 8 | 5.5 | 15 | 5.6 | 0.96 (0.33–2.78) |
| Geographical region | | | | | | |
| Eastern Europe/Asia Pacific | 109 | 35 | 7.2 | 74 | 7.3 | 1.10 (0.63–1.92) |
| North America | 29 | 11 | 7.4 | 18 | 5.4 | 1.21 (0.48–3.06) |
| South America | 25 | 10 | 3.6 | 15 | 4.9 | 0.31 (0.11–0.84) |
| Western Europe/Australia | 129 | 45 | 5.7 | 84 | 5.9 | 0.76 (0.48–1.19) |
| ECOG PS | | | | | | |
| 0 | 177 | 59 | 7.1 | 118 | 7.2 | 0.76 (0.51–1.13) |
| 1 | 115 | 42 | 5.5 | 73 | 5.6 | 0.99 (0.60–1.62) |
| Prior taxane therapy | | | | | | |
| Yes | 151 | 54 | 7.2 | 97 | 7.4 | 0.97 (0.62–1.50) |
| No | 141 | 47 | 5.5 | 94 | 5.8 | 0.71 (0.46–1.10) |
| Presence of liver metastases | | | | | | |
| Yes | 61 | 24 | 5.3 | 37 | 3.9 | 0.94 (0.53–1.69) |
| No | 231 | 77 | 7.2 | 154 | 7.4 | 0.84 (0.58–1.21) |
| Number of sites | | | | | | |
| 0–3 | 244 | 88 | 6.4 | 156 | 7.2 | 0.78 (0.56–1.10) |
| >3 | 48 | 13 | 5.4 | 35 | 5.2 | 0.90 (0.43–1.89) |



# Investigator-assessed unconfirmed best ORR

## Response-evaluable population



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# OS analysis

| OS | PD-L1+ population | | ITT population | |
|---|---|---|---|---|
| | Placebo + PAC (n=101) | Atezo + PAC (n=191) | Placebo + PAC (n=220) | Atezo + PAC (n=431) |
| **First interim OS analysis (data cut-off: 15 Nov 2019), events in 27% of the ITT population** | | | | |
| Deaths, n (%) | 15 (15) | 45 (24) | 52 (24) | 126 (29) |
| Median OS, months (95% CI) | NE (19.1–NE) | NE (22.1–NE) | 22.8 (19.1–NE) | 18.1 (15.9–NE) |
| Stratified HR (95% CI) | 1.55 (0.86–2.80) | | 1.31 (0.94–1.82) | |

NE = not estimable

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# OS analysis

| OS | PD-L1+ population | | ITT population | |
|---|---|---|---|---|
| | Placebo + PAC (n=101) | Atezo + PAC (n=191) | Placebo + PAC (n=220) | Atezo + PAC (n=431) |
| **First interim OS analysis (data cut-off: 15 Nov 2019), events in 27% of the ITT population** | | | | |
| Deaths, n (%) | 15 (15) | 45 (24) | 52 (24) | 126 (29) |
| Median OS, months (95% CI) | NE (19.1–NE) | NE (22.1–NE) | 22.8 (19.1–NE) | 18.1 (15.9–NE) |
| Stratified HR (95% CI) | 1.55 (0.86–2.80) | | 1.31 (0.94–1.82) | |
| **Updated interim OS analysis (data cut-off: 19 Aug 2020), events in 47% of the ITT population** | | | | |
| Deaths, n (%) | 38 (38) | 82 (43) | 97 (44) | 207 (48) |
| Median OS, months (95% CI) | 28.3 (19.1–NE) | 22.1 (19.2–30.5) | 22.8 (17.1–28.3) | 19.2 (16.8–22.5) |
| Stratified HR (95% CI) | 1.12 (0.76–1.65) | | 1.11 (0.87–1.42) | |
| 2-year OS rate, % (95% CI) | 51 (38–65) | 49 (40–58) | 45 (36–54) | 42 (36–48) |

NE = not estimable

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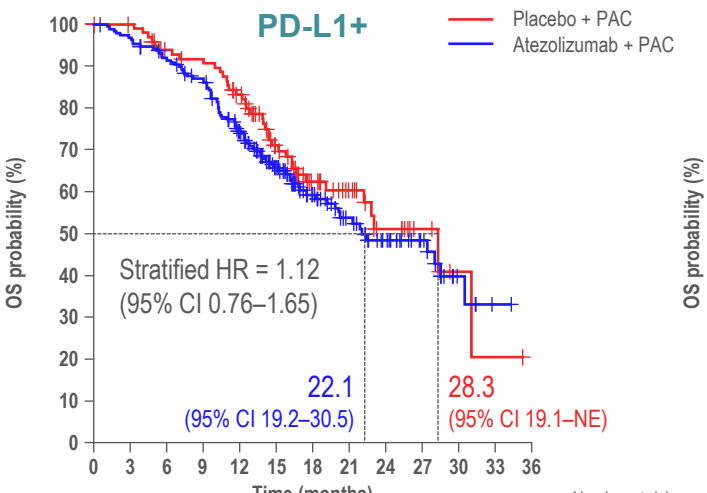
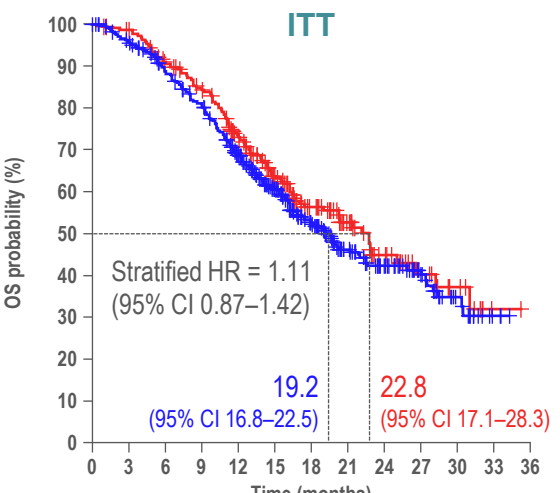
# Updated OS

## Data cut-off 19 Aug 2020




Median duration of follow-up: 14.5 months (placebo + PAC) vs 14.1 months (atezolizumab + PAC) in the ITT population

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# Summary of treatment exposure (safety population)

| Exposure | Placebo + PAC (n=218) | | Atezo + PAC (n=431) | |
|---|---|---|---|---|
| | Placebo | PAC | Atezo | PAC |
| Median (range) No. of cycles | 6 (1–22) | 6 (1–21) | 5 (1–28) | 5 (1–28) |
| Median (range) treatment duration, months | 5.0 (0–20) | 4.6 (0–19) | 4.2 (0–25) | 4.2 (0–25) |
| Mean (SD) dose intensity, %[a] | – | 93.9 (9.5) | 96.8 (8.0) | 92.5 (10.9) |
| Median (range) dose intensity, %[a] | – | 100.0 (48.9–100.0) | 100.0 (33.3–100.5) | 98.8 (50.0–113.9) |
| Median total cumulative dose | – | 1350 mg/m$^2$ | 8400 mg | 1252 mg/m$^2$ |

[a]Overall dose intensity (%) = (total number of actual doses/total number of planned doses) × 100%, calculated over the treatment duration. Treatment duration (days) = last dose date – first dose date + 1 day. SD = standard deviation

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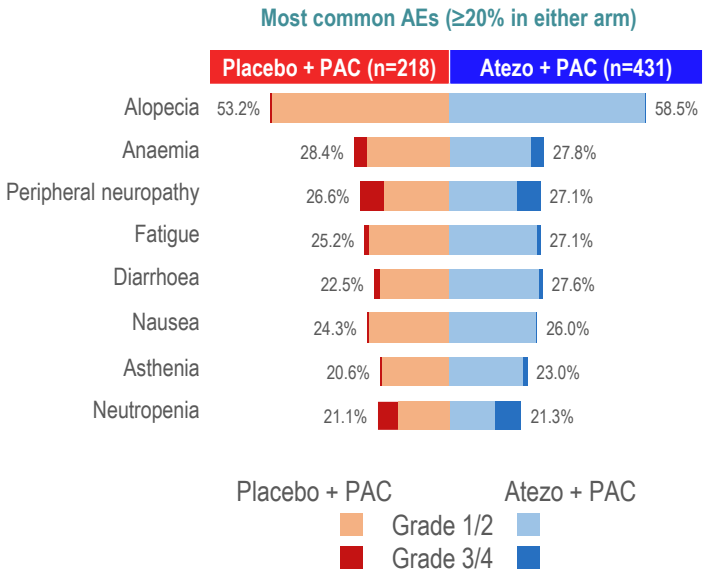
# Overview of safety (safety population)

| AEs, n (%) | Placebo + PAC (n=218) | Atezo + PAC (n=431) |
|---|---|---|
| Any grade AE | 213 (98) | 427 (99) |
| AE with fatal outcome | 4 (2) | 9 (2) |
| Treatment-related AE with fatal outcome | 0 | 4 (0.9) |
| Serious AE | 35 (16) | 98 (23) |
| Treatment-related serious AE | 17 (8) | 55 (13) |
| Grade 3/4 AE | 94 (43) | 213 (49) |
| Treatment-related grade 3/4 AE | 74 (34) | 162 (38) |
| AE leading to any treatment discontinuation | 32 (15) | 85 (20) |
| AE leading to atezo/placebo discontinuation | 10 (5) | 29 (7) |
| AE leading to PAC discontinuation | 31 (14) | 76 (18) |
| AESI | 116 (53) | 259 (60) |
| AESI with fatal outcome[a] | 0 | 1 (0.2) |
| Grade 3/4 AESI | 11 (5) | 42 (10) |

[a]The fatal AESI polymyositis was considered by the investigator as related to atezolizumab
AE = adverse event; AESI = adverse event of special interest

# Summary of safety (safety population)



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# AEs of special interest for atezolizumab (≥2 patients in either arm)

| Immune-mediated AEs by medical concept, n (%) | Placebo + PAC (n=218) | | Atezo + PAC (n=431) | |
|---|---|---|---|---|
| | Any grade | Grade 3/4[a] | Any grade | Grade 3/4[a] |
| Hepatitis (diagnosis)[b] | 1 (0.5) | 0 | 7 (1.6) | 2 (0.5) |
| Pneumonitis | 2 (0.9) | 0 | 16 (3.7) | 3 (0.7) |
| Hypothyroidism | 9 (4.1) | 0 | 55 (12.8) | 0 |
| Hyperthyroidism | 0 | 0 | 22 (5.1) | 0 |
| Diabetes mellitus | 2 (0.9) | 2 (0.9) | 4 (0.9) | 3 (0.7) |
| Adrenal insufficiency | 0 | 0 | 2 (0.5) | 0 |
| Infusion-related reactions | 8 (3.7) | 0 | 14 (3.2) | 2 (0.5) |
| Pancreatitis | 1 (0.5) | 1 (0.5) | 6 (1.4) | 6 (1.4) |
| Colitis | 2 (0.9) | 2 (0.9) | 3 (0.7) | 1 (0.2) |
| Rash | 67 (30.7) | 2 (0.9) | 137 (31.8) | 4 (0.9) |
| Ocular inflammatory toxicity | 1 (0.5) | 0 | 4 (0.9) | 0 |
| Severe cutaneous reactions | 3 (1.4) | 0 | 1 (0.2) | 0 |
| Myositis | 0 | 0 | 2 (0.5)[c] | 0 |

[a]Grade 3/4 AE refers to highest grade observed. [b]Sponsor-defined group of terms that represent events suggestive of a hepatitis diagnosis (as opposed to events associated with liver function test abnormalities only). [c]Includes 1 fatal case of polymyositis.
In the atezo arm there was 1 case each of myasthenia gravis, Guillain–Barré syndrome and nephritis (grade 3/4) and meningitis and hypophysitis (grade 1/2). In the placebo arm there was 1 case each of hypophysitis (grade 3/4) and nephritis (grade 1/2) There were no cases of rhabdomyolysis, encephalitis, vasculitis, myocarditis, haemolytic anaemia or haemophagocytic lymphohistiocytosis

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# Conclusions

- The primary objective of IMpassion131 was not met: addition of atezolizumab to paclitaxel did not significantly improve PFS in patients with PD-L1-positive metastatic TNBC
- There was no evidence of an OS benefit (secondary endpoint) with the addition of atezolizumab to paclitaxel
- The safety profile of the atezolizumab + paclitaxel combination was consistent with the known effects of the individual study drugs
- Potential reasons for the contrast with the benefit seen in IMpassion130 (atezolizumab + nab-paclitaxel) require further exploration

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