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Oncologia D'Or - Hospital do Câncer Aldenora Bello – Clínica Preciore

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Adding atezolizumab to adjuvant chemotherapy for stage II and III triple-negative breast cancer is unlikely to improve efficacy: interim analysis of the ALEXANDRA/IMpassion030 phase 3 trial

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Background

- Triple-negative breast cancer (TNBC) is an aggressive subtype and improving its outcome represents an unmet medical need¹.
- TNBC is considered the more immunogenic breast cancer subtype due to higher level of sTILs, higher expression of immunosuppressive genes and the presence of immune activation signatures^{1,2,3}.
- Initial pivotal studies of cancer immunotherapy for early-stage disease (e.g. melanoma) demonstrated clear benefit when treating micrometastatic disease (adjuvant immunotherapy)⁴.
- At the time the Alexandra/IMpassion030 trial was designed, the optimal timing of when to use PD-(L)1 inhibitor in combination with multi-agent chemotherapy in early TNBC was unknown (neoadjuvant vs. adjuvant).
- Atezolizumab plus nab-paclitaxel has been approved by Health Authorities for PD-L1-positive, metastatic TNBC^{5,6}.
- Alexandra/IMpassion030 was designed to investigate the value of adding the anti-PD-L1 inhibitor atezolizumab as adjuvant treatment in TNBC patients receiving standard anthracycline- and taxane- based adjuvant chemotherapy.

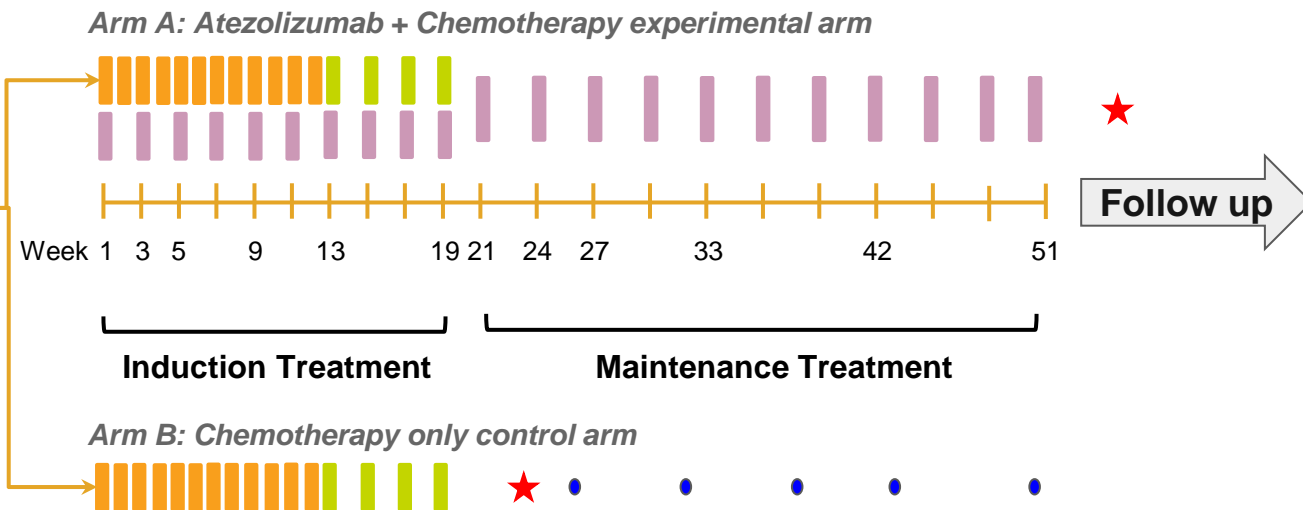
¹Bianchini G et al Nat Rev Clin Oncol 2016, ²Loi S et al J Clin Oncol 2013; 31:860-7. ³Ignatiadis M et al J Clin Oncol 2012; 30:1996-2004. ⁴Weber J et al NEJM 2017;377:1824-1835, ⁵P Schmid et al, NEJM 2018; 379:2108-2121, ⁶Tecentriq® SmPC, Japanese-PI, South Korean Product Information, Brazilian Healthcare Professional Leaflet

Alexandra/IMpassion030 phase 3 open-label study design

SURGERY

- Early TNBC
- Stage II-III
 - At least 50% node-positive
 - N=2300

(R)



Stratification factors:

Axillary nodal status

(0 vs. 1-3 vs. ≥ 4 positive lymph nodes)

Surgery

(breast conserving vs. mastectomy)

Tumor PD-L1 status

(IC0 vs. IC1/2/3)

- Paclitaxel qw for 12 weeks
- ddAC/EC q2w for 4 doses supported with G-CSF/GM-CSF
- Atezolizumab
 - Induction: 840 mg q2w for up to 10 doses
 - Maintenance: 1200 mg q3w to complete 1 year
- Monitoring visit Arm B

★ End of 30-day safety reporting period after last study treatment

Endpoints

- **Primary efficacy endpoint**

Invasive Disease-Free Survival (iDFS) in the intent to treat (ITT) population

- **Secondary efficacy endpoints**

iDFS in the PD-L1-positive subpopulation

iDFS in the node-positive subpopulation

iDFS including second primary non-breast invasive cancer

Overall Survival (OS)

Relapse-Free Interval (RFI)

Distant Relapse-Free Interval (DRFI)

Disease-free survival (DFS)

- **Other endpoints**

Patient reported outcomes (PROs)

Safety

Pharmacokinetics

Immunogenicity

Biomarkers/translational research

Statistical analysis considerations

Health Authority request for additional interim and a futility analysis

Initial Statistical Analysis Plan:

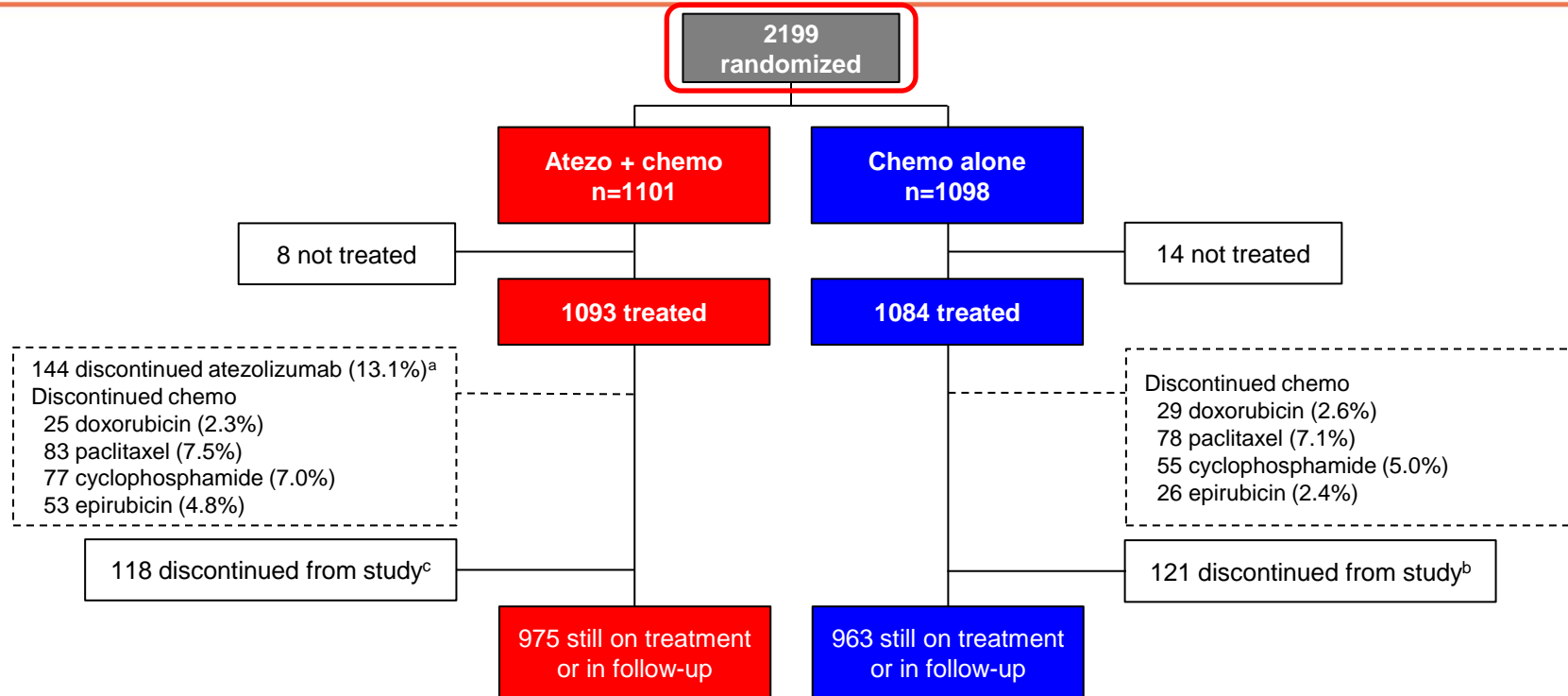
- 2300 patients and primary endpoint invasive Disease-Free Survival (iDFS)
 - One planned interim analysis at 80% information (310 iDFS events)
-
- Final analyses at 388 iDFS events
 - Two-sided, stratified log-rank test with alpha 0.05, power 80%, hazard ratio 0.75, ITT population

Updated Statistical Analysis Plan*:

- At the time of the SAP amendment 2199 patients had been randomized.
 - Two planned interim analyses at 62% and 80% information (242 and 312 iDFS events)
 - Futility boundary added at a Hazard Ratio (HR) > 1
-
- Final analyses at 390 iDFS events
 - Two-sided, stratified log-rank test with alpha 0.05, power 80%, hazard ratio 0.75, ITT population

* Main statistical design considerations, with the addition of one interim and futility analysis, remained the same as for the initial statistical analysis plan. Data which follows is based upon clinical cut-off date of 17 February 2023, extracted from a dataset which was not fully cleaned to meet the Health Authority timeline requirement to perform the interim analysis that followed the iDMC recommendation to halt recruitment (temporarily).

ALEXANDRA/IMpassion030 interim analysis consort diagram



^a5 death, 44 disease relapse, 1 lost to follow-up, 3 non-compliance, 7 physician decision, 56 patient withdrawal, 9 other

^b49 death, 5 lost to follow-up, 4 physician decision, 63 patient withdrawal

^c60 death, 5 lost to follow-up, 3 physician decision, 50 patient withdrawal

Analyses based on all randomized patients per intention-to-treat principle

Baseline characteristics, ITT population (1)

Characteristic, n (%)	Atezo + chemo (n=1101)	Chemo alone (n=1098)	Total (N=2199)
Age (years), median (range)	53 (24–86)	53 (23–79)	53 (23–86)
Age Group (years)			
<65	916 (83.2)	904 (82.3)	1820 (82.8)
≥65	185 (16.8)	194 (17.7)	379 (17.2)
Race			
White	554 (50.3)	564 (51.4)	1118 (50.8)
Asian	423 (38.4)	401 (36.5)	824 (37.5)
American Indian or Alaska Native	28 (2.5)	27 (2.5)	55 (2.5)
Black or African American	8 (0.7%)	2 (0.2)	10 (0.5)
Other ¹	2 (0.2)	6 (0.5)	8 (0.4)
Unknown	86 (7.8)	98 (8.9)	184 (8.4)
ECOG Score at baseline			
0	887 (80.6)	895 (81.5)	1782 (81.0)
1	214 (19.4)	203 (18.5)	417 (19.0)

¹ Race category 'Other' includes 'Native Hawaiian or other pacific islander' and 'Multiple'

Characteristic, n (%)	Atezo + chemo (n=1101)	Chemo alone (n=1098)	Total (N=2199)
Histology			
Ductal, NOS	823 (74.9)	793 (72.2)	1616 (73.6)
Lobular	39 (3.5)	54 (4.9)	93 (4.2)
Metaplastic	50 (4.5)	46 (4.2)	96 (4.4)
Other ¹	211 (19.2)	241 (21.9)	452 (20.6)
Histological Grade at Screening			
Well Differentiated	60 (5.5)	75 (6.8)	135 (6.1)
Moderately Differentiated	205 (18.6)	233 (21.2)	438 (19.9)
Poorly Differentiated	686 (62.4)	653 (59.5)	1339 (60.9)
Anaplastic	3 (0.3)	3 (0.3)	6 (0.3)
Unknown	146 (13.3)	134 (12.2)	280 (12.7)

¹ Histological Subtype category 'Other' includes 'Tubular', 'Mucinous', 'Ductal with medullary features' and 'Other'

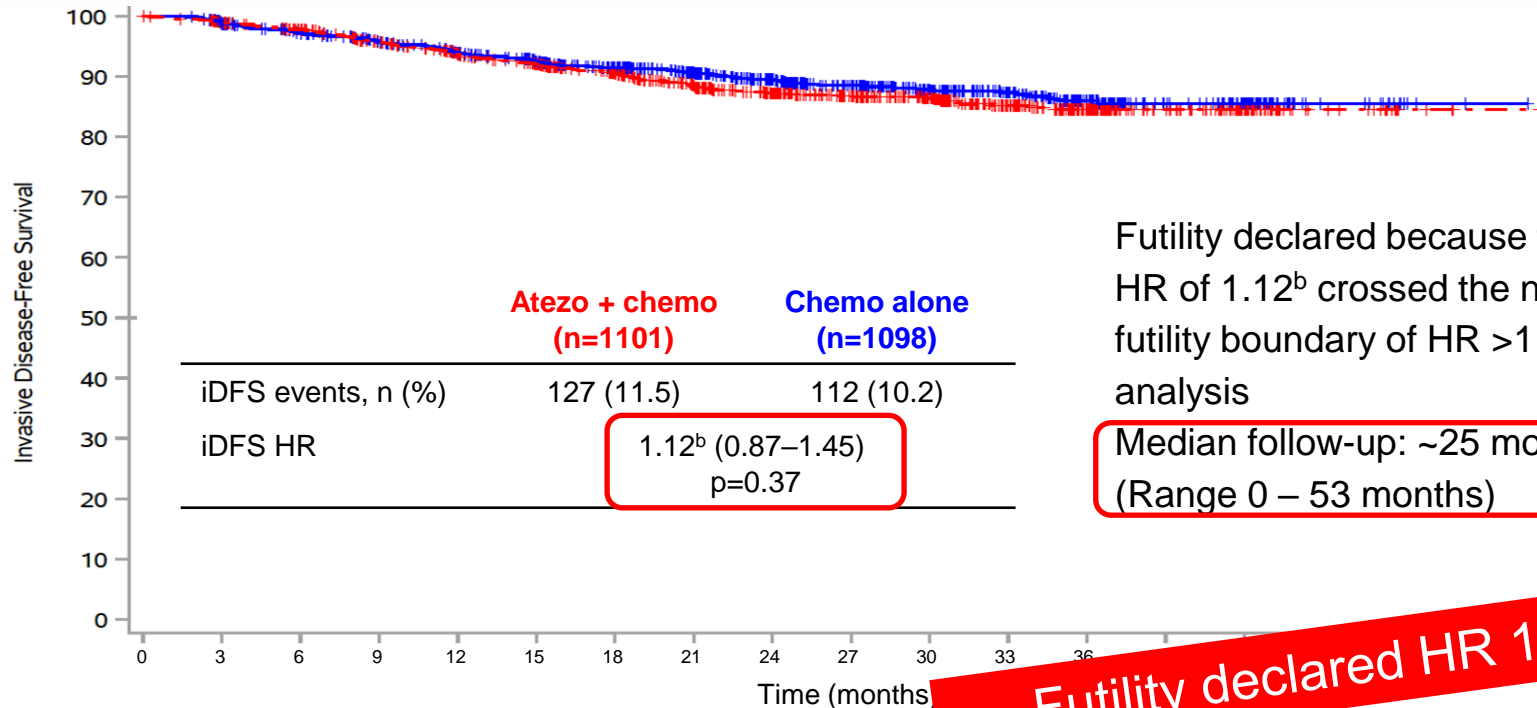
² Primary Tumor Stage category 'Other' includes 'pT0', 'pT1a', 'pT1b', 'pT1c', 'pT1d', 'pT1e', 'pT1f', 'pT1g', 'pT1h', 'pT1i', 'pT1j', 'pT1k', 'pT1l', 'pT1m', 'pT1n', 'pT1o', 'pT1p', 'pT1q', 'pT1r', 'pT1s', 'pT1t', 'pT1u', 'pT1v', 'pT1w', 'pT1x', 'pT1y', 'pT1z', 'pT2', 'pT3', 'pT4', 'pT4b' and missing

Characteristic, n (%)	Atezo + chemo (n=1101)	Chemo alone (n=1098)	Total (N=2199)
Primary Tumor Stage			
pT1-pT2	1024 (93.0)	1045 (95.2)	2069 (94.1)
pT3	71 (6.4)	51 (4.6)	122 (5.5)
Other ²	6 (0.5)	2 (0.2)	8 (0.4)
Axillary Nodal Status (I _x RS)			
0	577 (52.4)	573 (52.2)	1150 (52.3)
1-3	390 (35.4)	390 (35.5)	780 (35.5)
≥4	134 (12.2)	135 (12.3)	269 (12.2)
AJCC Stage at Surgery			
Stage II	935 (84.9)	940 (85.6)	1875 (85.3)
Stage III	161 (14.6)	157 (14.3)	318 (14.5)
Other ¹	5 (0.5)	1 (<0.1)	6 (0.3)

¹ AJCC Stage category 'Other' includes 'Stage I' and missing

Characteristic, n (%)	Atezo + chemo (n=1101)	Chemo alone (n=1098)	Total (N=2199)
PD-L1 Status (I _x RS)			
IC 0	316 (28.7)	316 (28.8)	632 (28.7)
IC 1/2/3	785 (71.3)	782 (71.2)	1567 (71.3)
Surgery (I _x RS)			
Breast conserving	524 (47.6)	523 (47.6)	1047 (47.6)
Mastectomy	577 (52.4)	575 (52.4)	1152 (52.4)

Primary efficacy endpoint: iDFS^a (ITT population)



Futility declared because the observed HR of 1.12^b crossed the non-binding futility boundary of HR >1 at this interim analysis

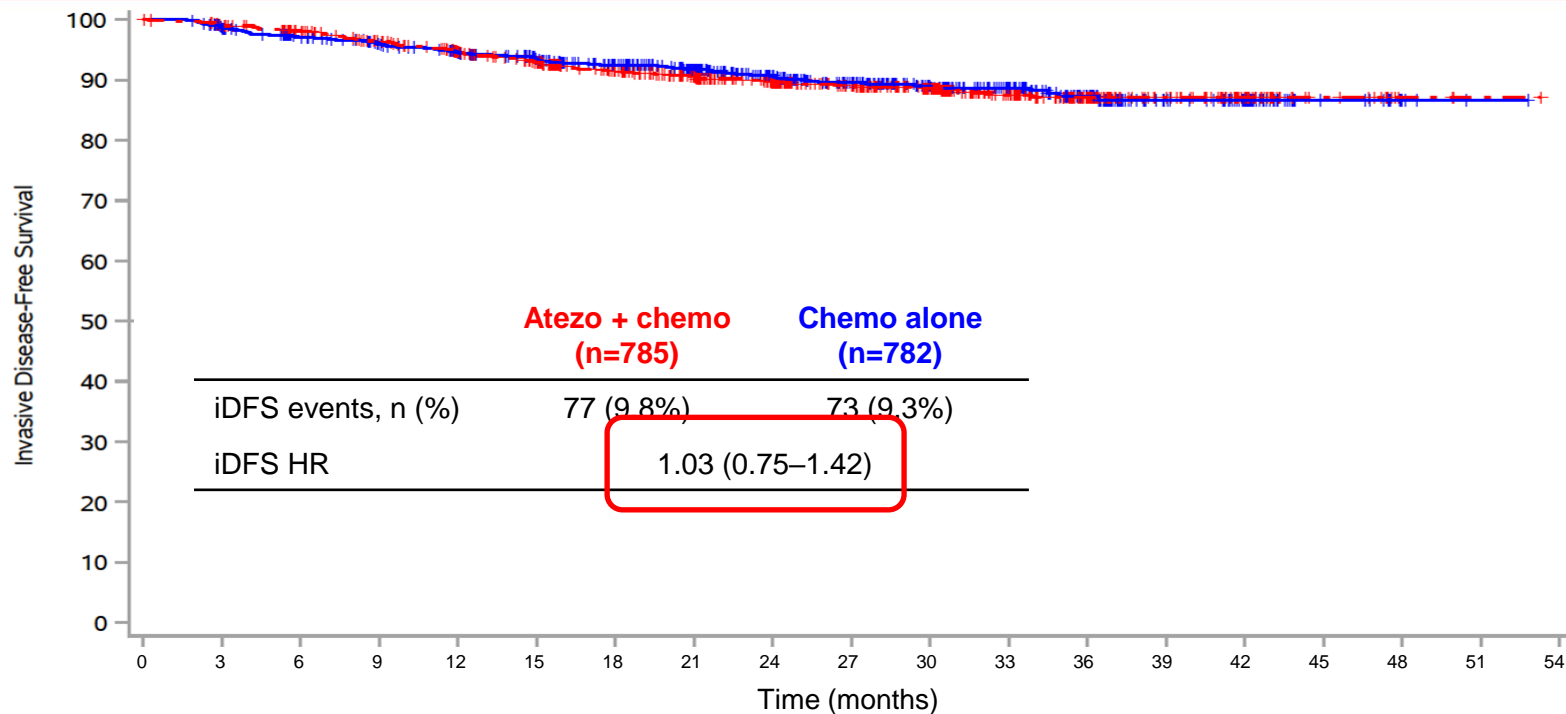
Median follow-up: ~25 months (Range 0 – 53 months)

Futility declared HR 1.12

	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54
Chemo alone	1098	1022	970	923	864	812	731	663	565	471	372	274	175	109	74	17	5	1	0
Atezo + chemo	1101	1042	995	932	869	820	735	648	564	481	391	294	202	120	66	22	5	2	0

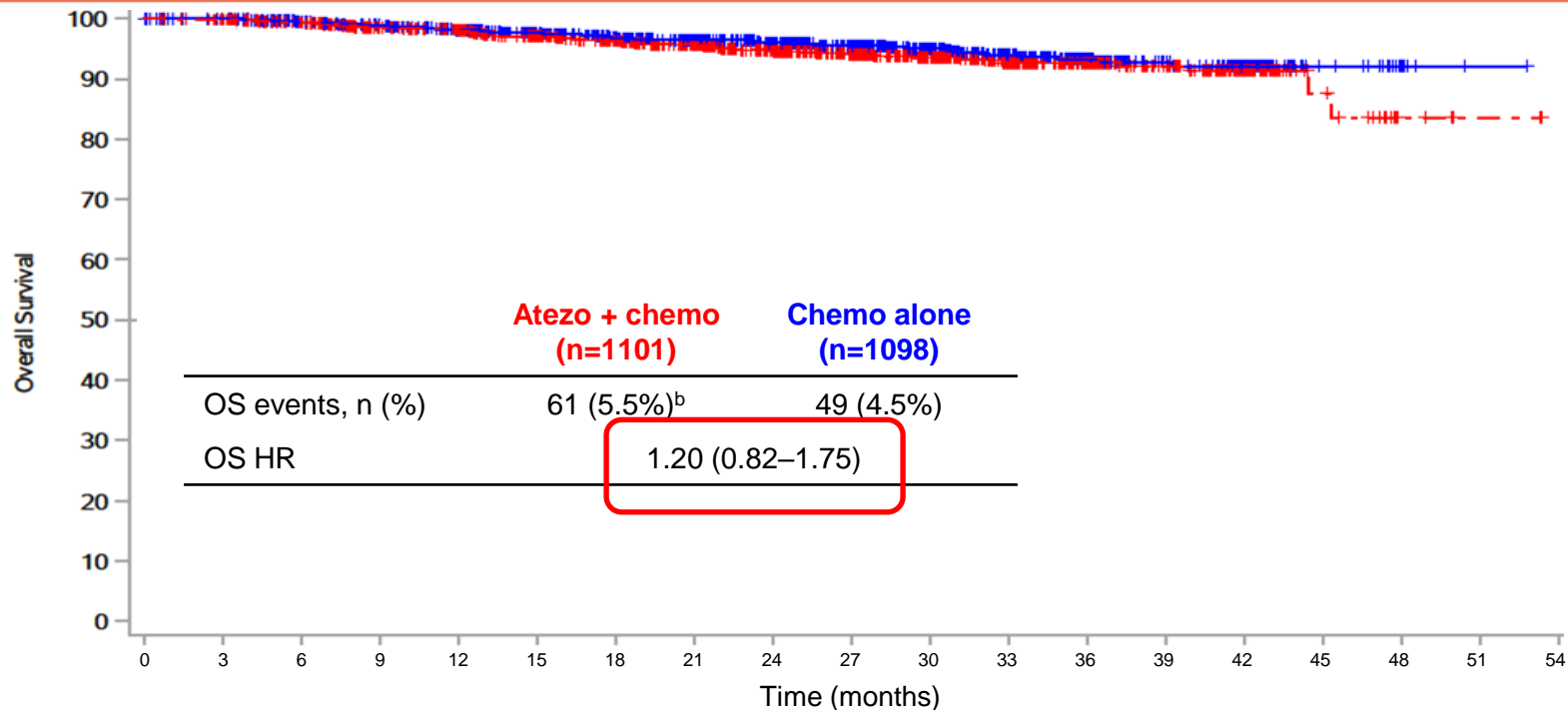
^aDefined as the interval from randomization until date of first occurrence of an iDFS event, ^bstratified by PD-L1 status, Surgery, and Axillary Nodal Status

Key secondary efficacy endpoint: iDFS in the PD-L1+ subgroup (71%)



Chemo alone	782	728	691	660	622	589	534	486	416	350	276	223	154	81	53	14	4	1	0
Atezo + chemo	785	749	718	680	640	601	536	480	425	366	300	230	156	90	48	17	3	1	0

Key secondary efficacy endpoint: OS^a, ITT population



Chemo alone	1098	1072	1026	984	939	862	777	709	608	509	399	313	219	120	79	20	6	1	0
Atezo + chemo	1101	1082	1038	980	948	875	786	706	615	521	422	320	225	135	74	23	5	2	0

^aDefined as the interval between randomization until death from any cause. ^bOne patient in the atezo arm who died 25 Dec 2022 not taken into account (data issue).

Overview of number of patients with at least one AE

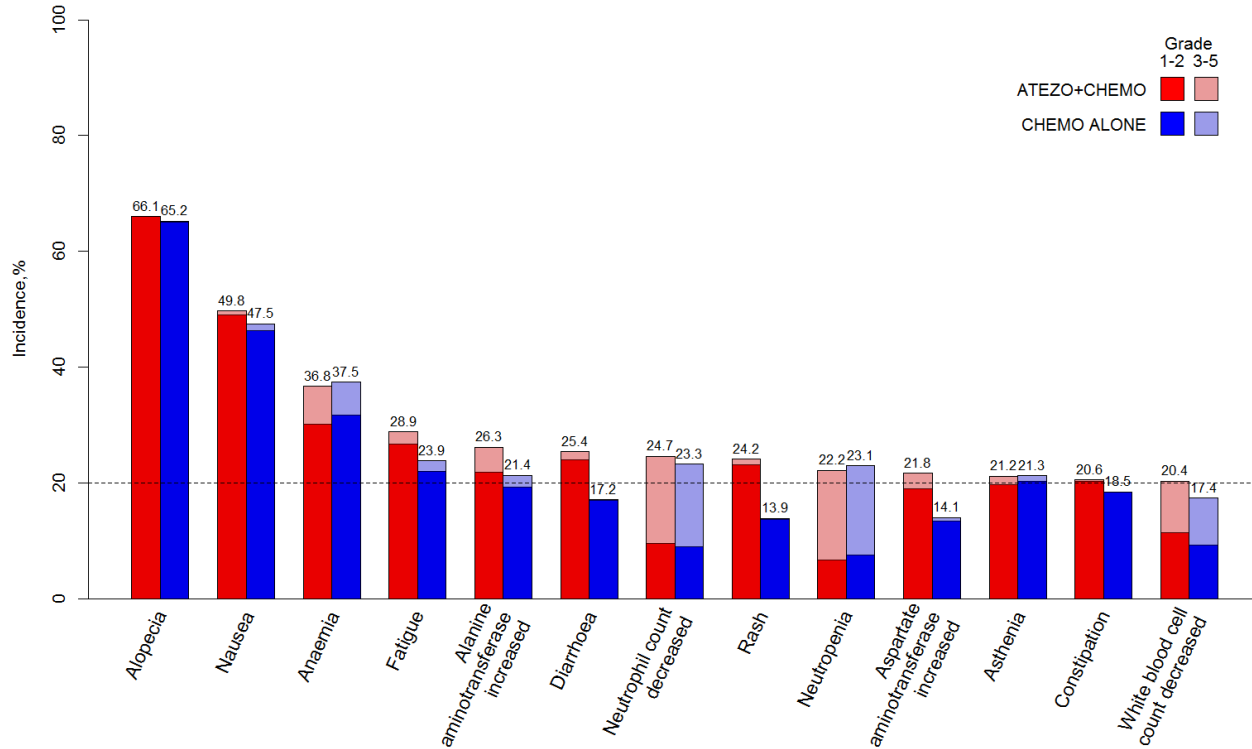
AE Overview*, n (%)	Atezo + chemo (n=1093)	Chemo alone (n=1084)	Total (N=2177)
TEAEs ¹	1090 (99.7)	1073 (99.0)	2163 (99.4)
TRAEs ² All Grade	1083 (99.1)	1066 (98.3)	2149 (98.7)
TRAEs Grade 3 - 4	587 (53.7)	472 (43.5)	1059 (48.6)
TRSAE	198 (18.1)	107 (9.9)	305 (14.0)
Treatment related Deaths	2 (0.2)	1 (<0.1)	3 (0.1)
AE leading to any treatment discontinuation	185 (16.9)	60 (5.5)	245 (11.3)
AEs leading to discontinuation of:			
Atezolizumab	144 (13.2)	0 (0)	144 (6.6)
Epirubicin	30 (2.7)	12 (1.1)	42 (1.9)
Doxorubicin	14 (1.3)	17 (1.6)	31 (1.4)
Cyclophosphamide	43 (3.9)	30 (2.8)	73 (3.4)
Paclitaxel	54 (4.9)	33 (3.0)	87 (4.0)

¹TEAE=Treatment Emergent Adverse Event

²TRAE=Treatment Related Adverse Event

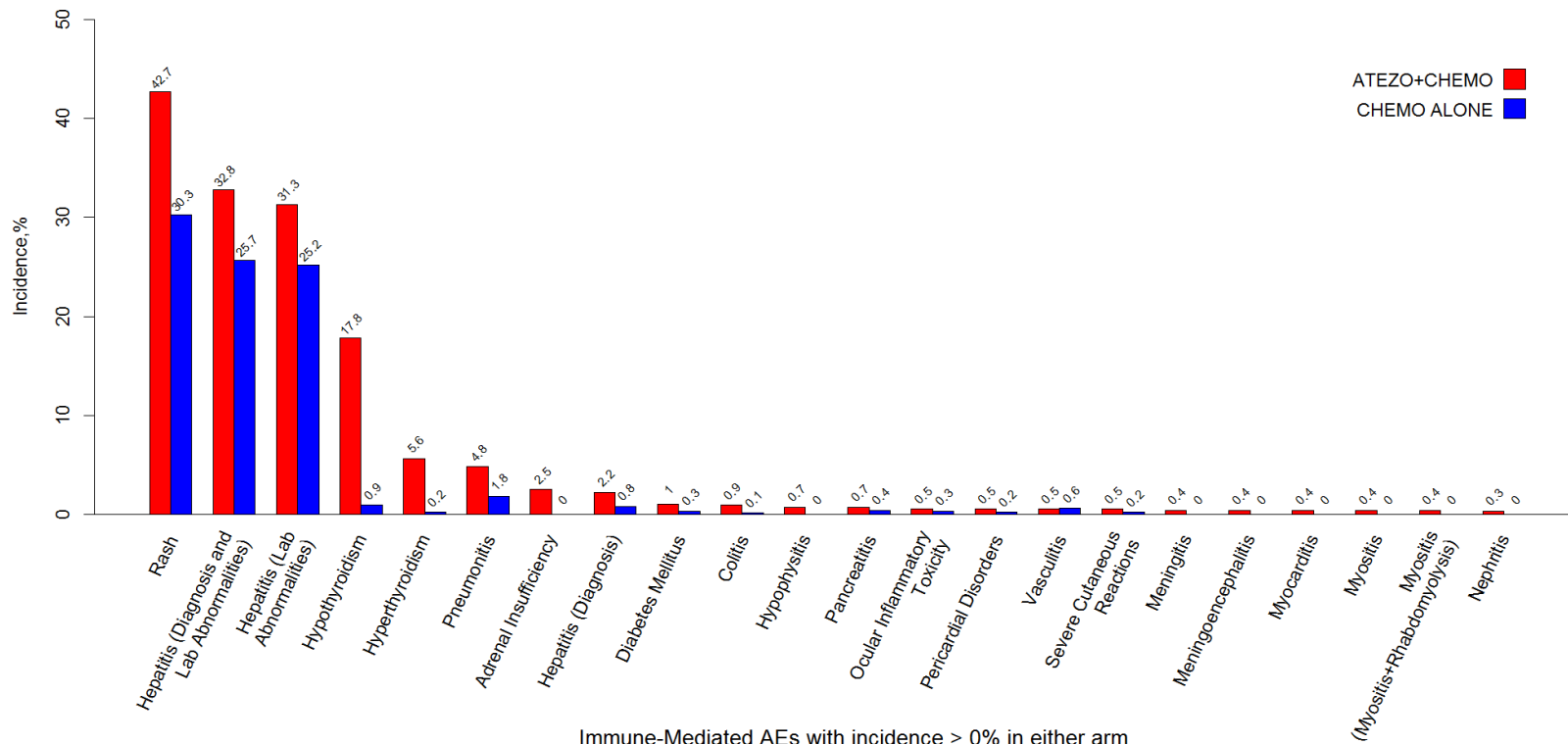
*Safety follow-up period collects all AEs until 30 days after last dose of study treatment therefore atezo + chemo arm had longer safety FU due to the continued atezo dosing during maintenance phase. During the maintenance phase, the chemo arm had ½ the frequency of visits.

TEAEs \geq 20% and Grading by Arm



Treatment-Emergent AEs with incidence \geq 20% in either arm

Immune-Mediated AEs

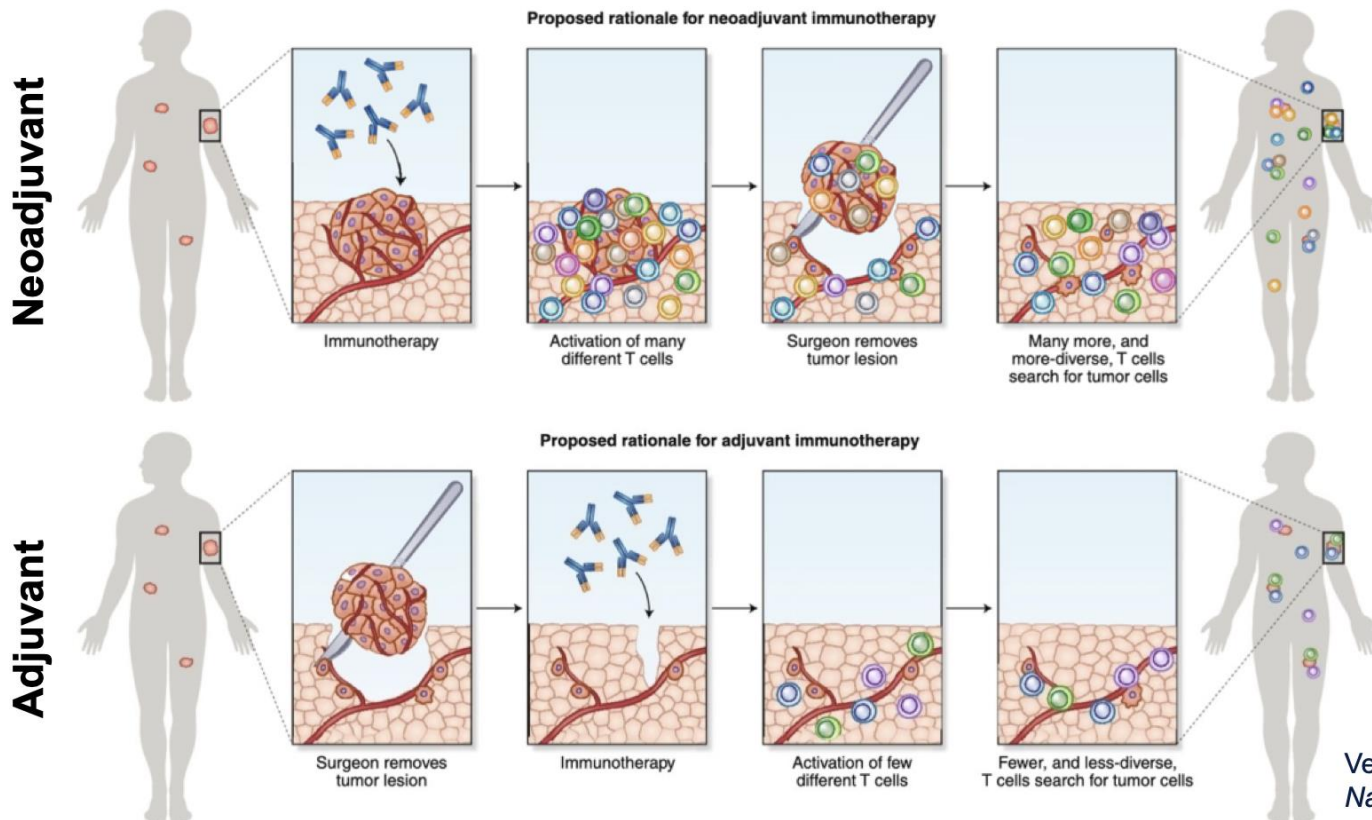


Conclusions

- At the requested interim analysis of the phase 3 ALEXANDRA/IMpassion030 trial, iDFS in ITT population (primary endpoint) crossed the pre-specified futility boundary (HR>1), HR 1.12 [0.87–1.45].
- The primary endpoint together with secondary efficacy endpoints do not support addition of atezolizumab to adjuvant chemotherapy in patients who have undergone primary surgery for early TNBC.
- Safety data were consistent with the known safety profile of atezolizumab in early TNBC (IMpassion031)¹ and across indications with numerically more grade 3/4 AEs, SAEs, and AEs in the atezolizumab compared to chemotherapy alone arm. Addition of atezolizumab did not compromise delivery of the SoC chemotherapy backbone.
- Study data are being updated to a clinical cut-off of 17 November 2023, and results will be published based on the final database. Moreover, the study partners will conduct translational research to address critical questions in this unique dataset.
- The ALEXANDRA/IMpassion030 trial contributes to an improved understanding about the optimal use of immunotherapy in patients with early TNBC.

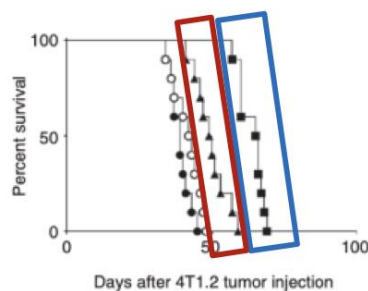
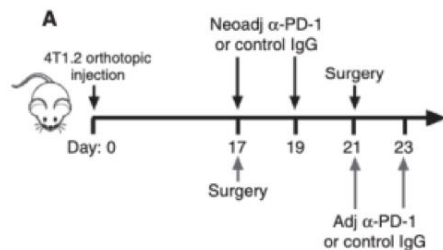
¹ E A Mittendorf et al, The Lancet 2020; 396: 1090–100

Racional da imunoterapia neoadjuvante versus adjuvante



Maior eficácia da imunoterapia neoadjuvante versus adjuvante para erradicar doença micrometástática em modelo murino de câncer de mama

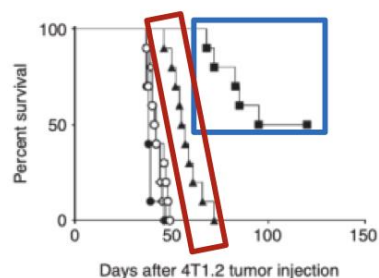
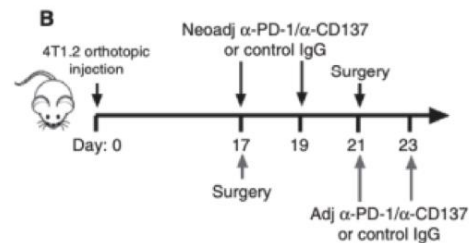
Anti-PD1



○ Neoadj control IgG
● Adj control IgG
■ Neoadj α-PD-1
▲ Adj α-PD-1

$P < 0.0001$

Anti-PD1 + anti-CD137



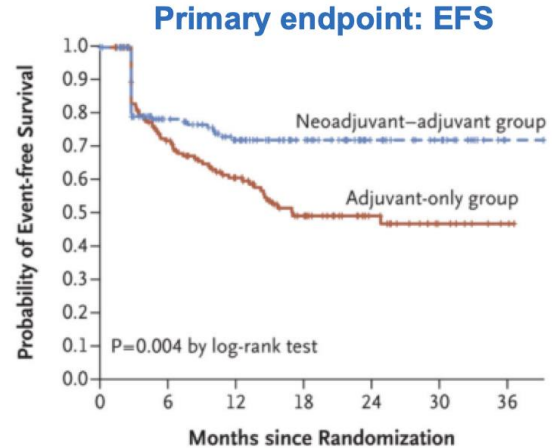
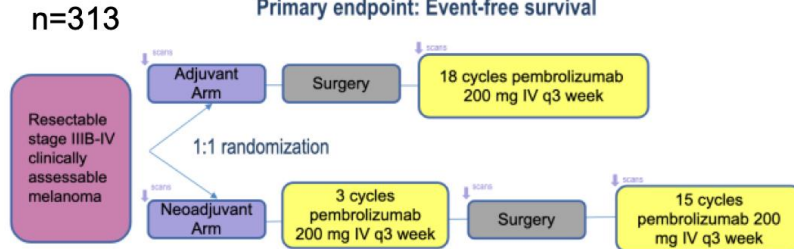
○ Neoadj control IgG
● Adj control IgG
■ Neoadj α-PD-1/α-CD137
▲ Adj α-PD-1/α-CD137
◇ α-PD-1/α-CD137 - No surgery

$P < 0.0001$

Melhor timing da imunoterapia em melanoma estágio II-III

What about timing of IO administration in other tumor types?
Neoadjuvant + adjuvant vs. adjuvant IO in stage II-III melanoma

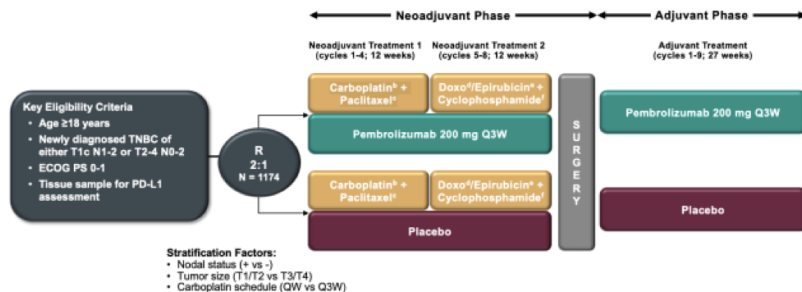
S1801 Study Schema



** Based on these data, neoadjuvant + adjuvant PD1 inhibitors is becoming a standard approach for stage IIIB-IV resectable melanoma

Estudos fase III imunoterapia neo/adj no CMTN inicial

KEYNOTE-522



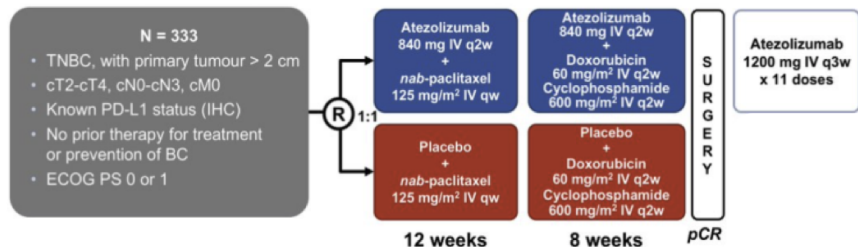
pCR rates

- Pembro arm: 64.8%
 - Placebo arm: 51.2%
- Δ13.6
p<0.001

EFS rates

- Pembro arm: 81.3%
 - Placebo arm: 72.3%
- Δ9.0%
HR 0.63

Impassion031



pCR rates

- Atezo arm: 57.6%
 - Placebo arm: 41.1%
- Δ16.5%
p=0.0044

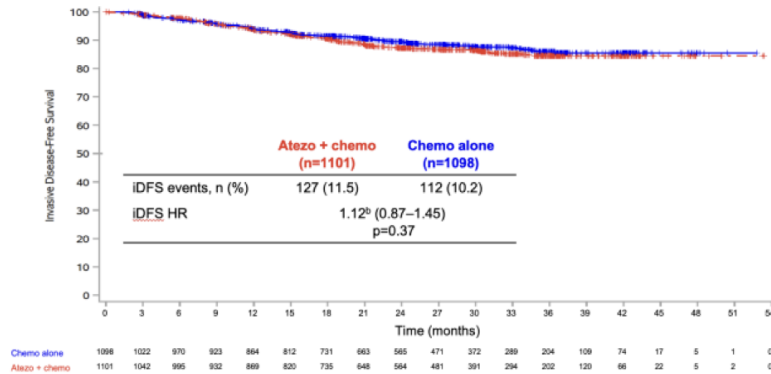
EFS rates

Not reported

Schmid et. al. *NEJM* 2020, ESMO 2023
Mittendorf et. al. *Lancet* 2020

IMpassion030: Adjuvant AC/T +/- atezolizumab for stage II-III TNBC

Primary efficacy endpoint: iDFS (ITT population)



** Median f/u 25 months: Futility declared because the observed HR of 1.12 in the ITT population crossed the non-binding futility boundary of HR >1 at this interim analysis.

Secondary efficacy endpoints:

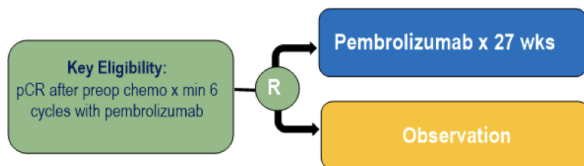
- iDFS in PD-L1+ subgroup – No difference
- OS (ITT population) – No difference

- Dados **NÃO** favorecem uso do atezolizumab adjuvante em pacientes submetidas à cirurgia inicial
- Racional:
 - Ausência do tumor primário?
 - Agente anti-PD-L1 inferior?
 - Outras variáveis?
- Aguardando dados de outros estudos (S1418 – pembro adj em doença residual pós NACT)

Questões práticas

- Precisamos de IO neoadjuvante e adjuvante nas pacientes com TNBC inicial que atingem pCR após NACT?

OptimICE-pCR (NCT05812807)



Stratification Factors:

- Baseline nodal status
- Receipt of anthracycline chemotherapy: yes vs. no

- Podemos melhorar os resultados das pacientes que não atingem pCR com combinação CT + IO neoadjuvante? Melhores tratamentos adjuvantes?

- **SASCIA** (ER+/HER2- and TNBC): Sacituzumab govitecan x 8 vs. TPC (NCT04595565)
- **Optimize RD/ASCENT-05**: Sacituzumab govitecan + pembrolizumab x 8 vs. pembrolizumab +/- capecitabine (NCT05633654)
- **Tropion Breast03**: Dato-DXd +/- durvalumab vs. capecitabine and/or pembrolizumab (NCT05629585)



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