AT THE FOREFRONT
UChicago Medicine

Optimal Integration of Immune Checkpoint Inhibitors into the Management of Triple-Negative Breast Cancer

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Research To Practice
Triple-Negative Breast Cancer Satellite Symposium
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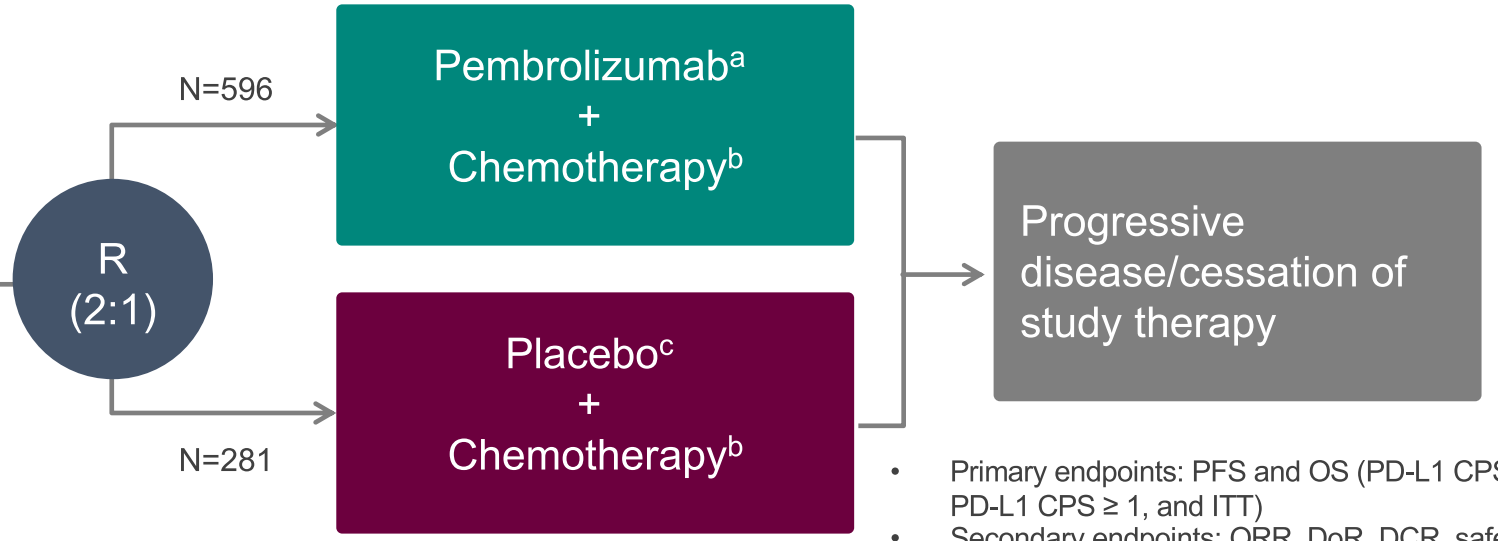
KEYNOTE-355: Study Design

Key Eligibility Criteria

- Age≥ 18 years
- Central determination of TNBC and PD-L1 expression
- Previously untreated locally recurrent inoperable or metastatic TNBC
- Completion of treatment with curative intent ≥ 6 months prior to first disease recurrence
- ECOG performance status 0 or 1
- Life expectancy ≥ 12 weeks from randomization
- Adequate organ function
- No systemic steroids
- No active CNS metastases
- No active autoimmune disease



- Primary endpoints: PFS and OS (PD-L1 CPS ≥ 10, PD-L1 CPS ≥ 1, and ITT)
- Secondary endpoints: ORR, DoR, DCR, safety

Stratification Factors:

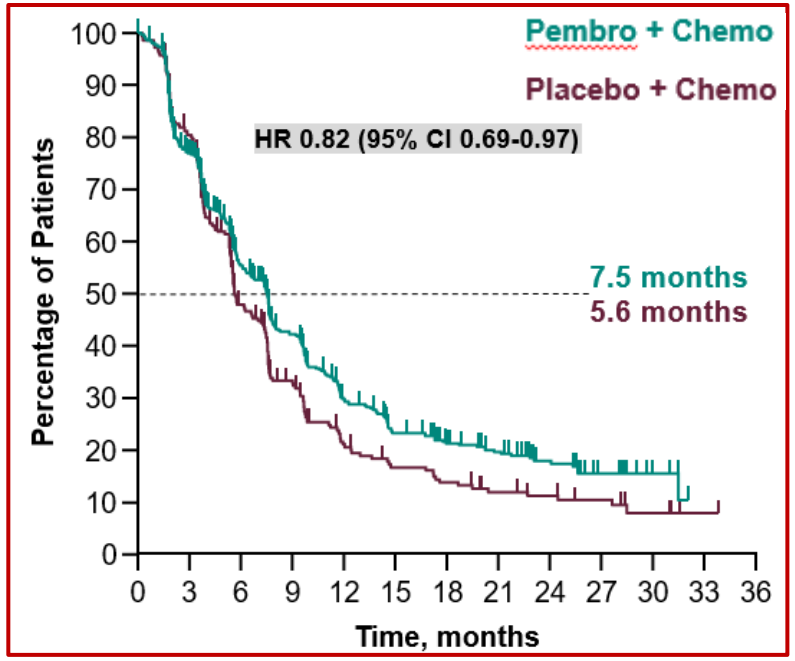
- Chemotherapy on study (taxane vs gemcitabine/carboplatin)
- PD-L1 tumor expression (CPS ≥ 1 vs CPS < 1)
- Prior treatment with same class chemotherapy in the neoadjuvant or adjuvant setting (yes vs no)

a Pembrolizumab: 200 mg intravenously (IV) every 3 weeks (Q3W)
b Chemotherapy:
- Nab-paclitaxel: 100 mg/m2 IV on Days 1, 8, and 15 every 28 days or
- Paclitaxel: 90 mg/m2 on Days 1, 8, and 15 every 28 days or
- Gemcitabine and carboplatin: 1000 mg/m2 and AUC 2, respectively, on Days 1 and 8 every 21 days

Cortes. ASCO 2020. Abstr 1000.

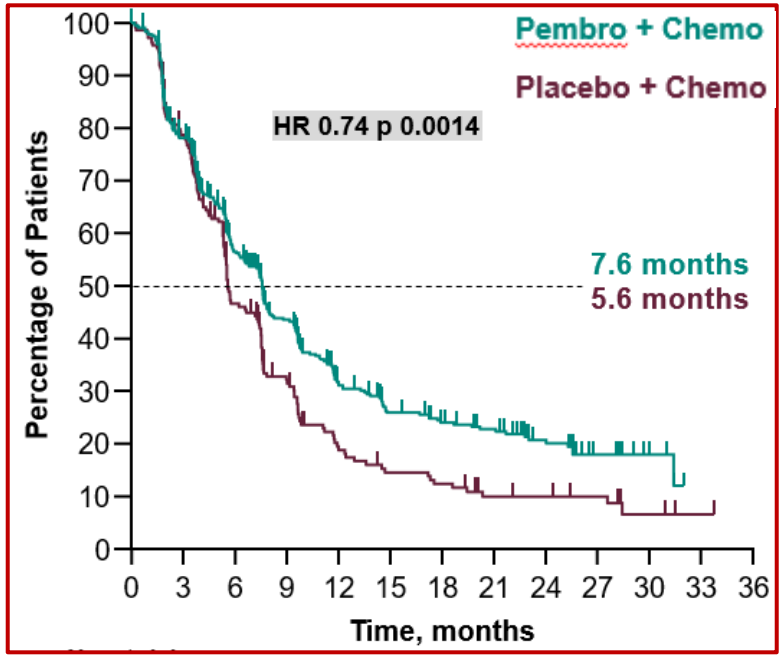
KEYNOTE-355: PFS

ITT



Statistical significance was not tested due to the prespecified hierarchical testing strategy

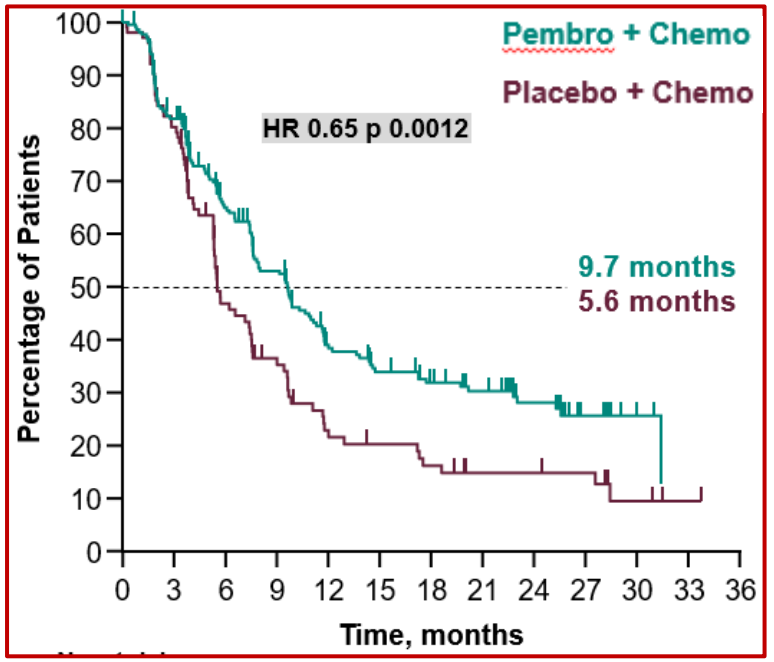
PD-L1 CPS ≥1



Prespecified *P* value boundary of 0.00111 **not** met

75% of pts

PD-L1 CPS ≥10

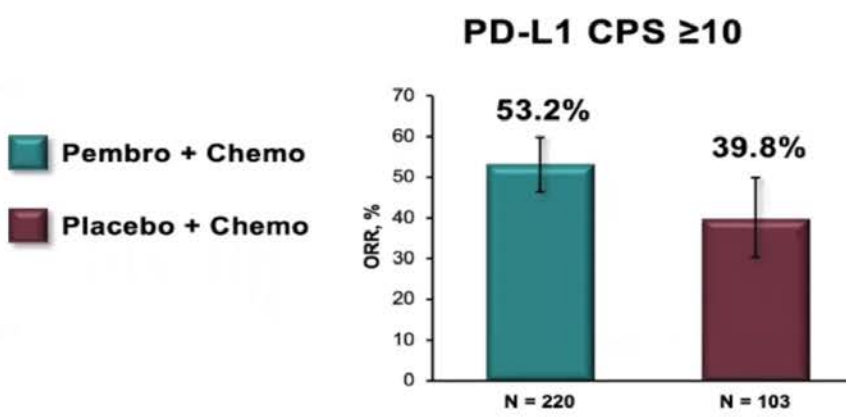


Prespecified *P* value boundary of 0.00411 met

38% of pts

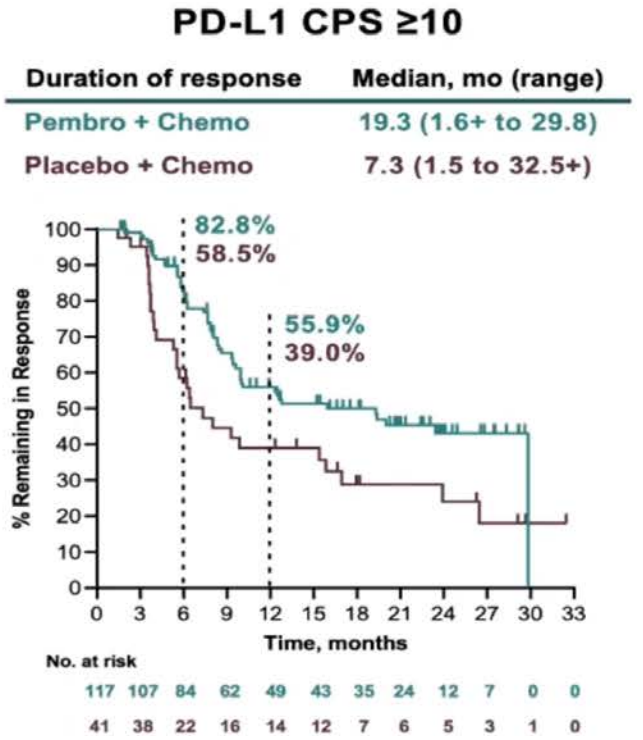
Cortes et al, Abst 1000, ASCO 2020

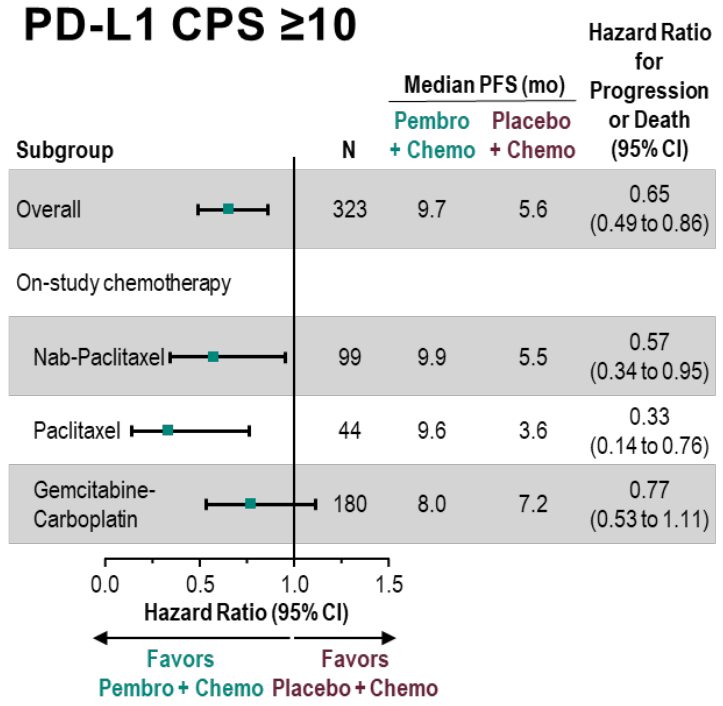
Response Rate and Duration of Response for PD-L1 CPS ≥ 10



PD-L1 CPS ≥10

	Pembro + Chemo (N = 220)	Placebo + Chemo (N = 103)
ORR, % (95% CI)	53.2 (46.4–59.9)	39.8 (30.3–49.9)
DCR,[a] % (95% CI)	65.0 (58.3–71.3)	54.4 (44.3–64.2)

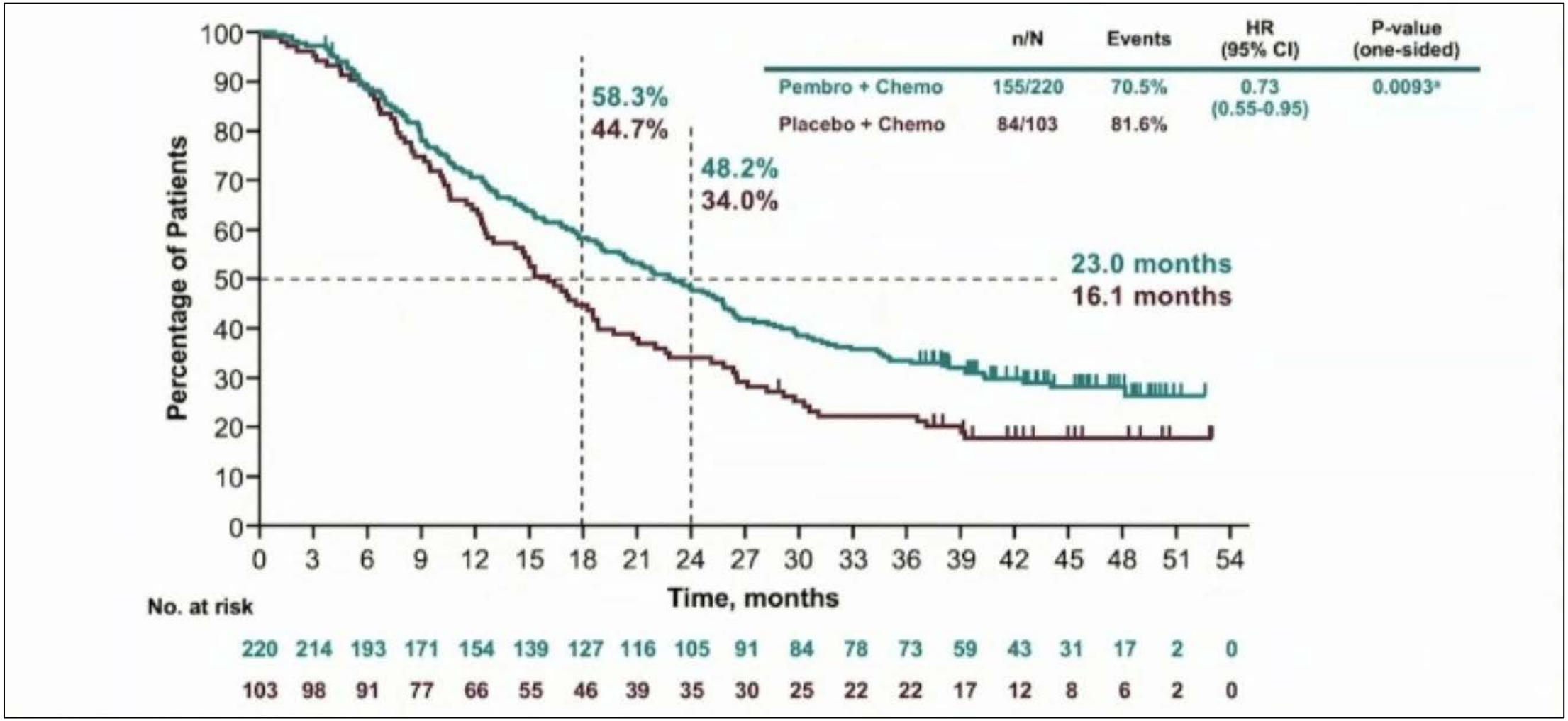




- Treatment benefit limited to PD-L1+ tumors (CPS ≥ 10 using DAKO 22C3)
- Granted accelerated approval by US FDA on 13NOV2020; Full approval on 26JUL2021

Rugo et al, Abstract GS3-01, SABCS 2020

KEYNOTE-355: Significant Improvement in OS for CPS ≥ 10



Rugo H, et al. ESMO 2021. LBA 16.

IMpassion130: Study Design

- Randomized, double-blind, placebo-controlled phase III trial

Stratified by prior taxane use in curative setting (yes vs no), liver metastases (yes vs no), PD-L1 IC status (≥ 1% vs < 1%)

Patients with metastatic or inoperable, locally advanced TNBC; no prior therapy for advanced setting (prior RT or CT in curative setting allowed if ≥ 12-mo DFI); RECIST v1.1 measurable disease; ECOG PS 0/1; tumor evaluable for PD-L1* (N = 902)

Atezolizumab 840 mg IV Q2W **+** **nab-Paclitaxel** 100 mg/m^2 IV on D1, 8, 15 28-day cycles (n = 451)

Placebo IV Q2W **+** **nab-Paclitaxel** 100 mg/m^2 IV on D1, 8, 15 28-day cycles (n = 451)

Treatment until PD per RECIST v1.1 or intolerable toxicity

No crossover Allowed

Survival follow-up

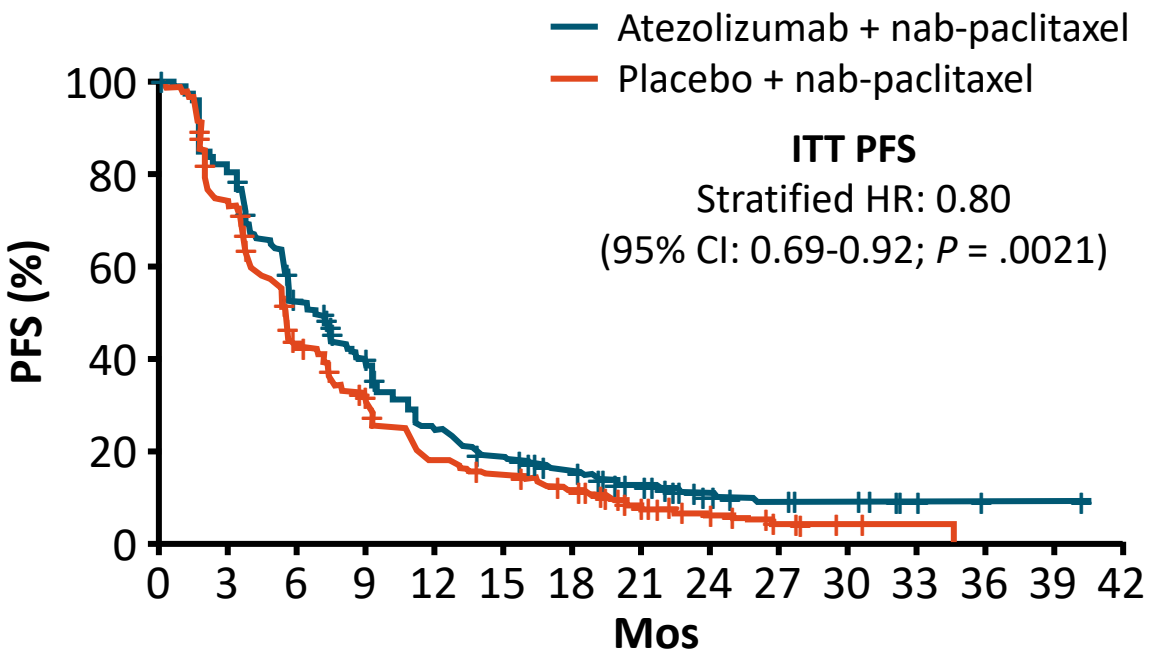
- Coprimary endpoints: PFS and OS (ITT population and PD-L1+ subgroup)
  - Prespecified hierarchical OS testing in ITT population; if significant, then PD-L1+ population

***By prospective central testing with SP142 PD-L1 IHC assay. 41% of patients in each arm were PD-L1+ (≥ 1 % IC).**

Schmid. ASCO 2019. Abstr 1003. Schmid. NEJM. 2018;379:2108.

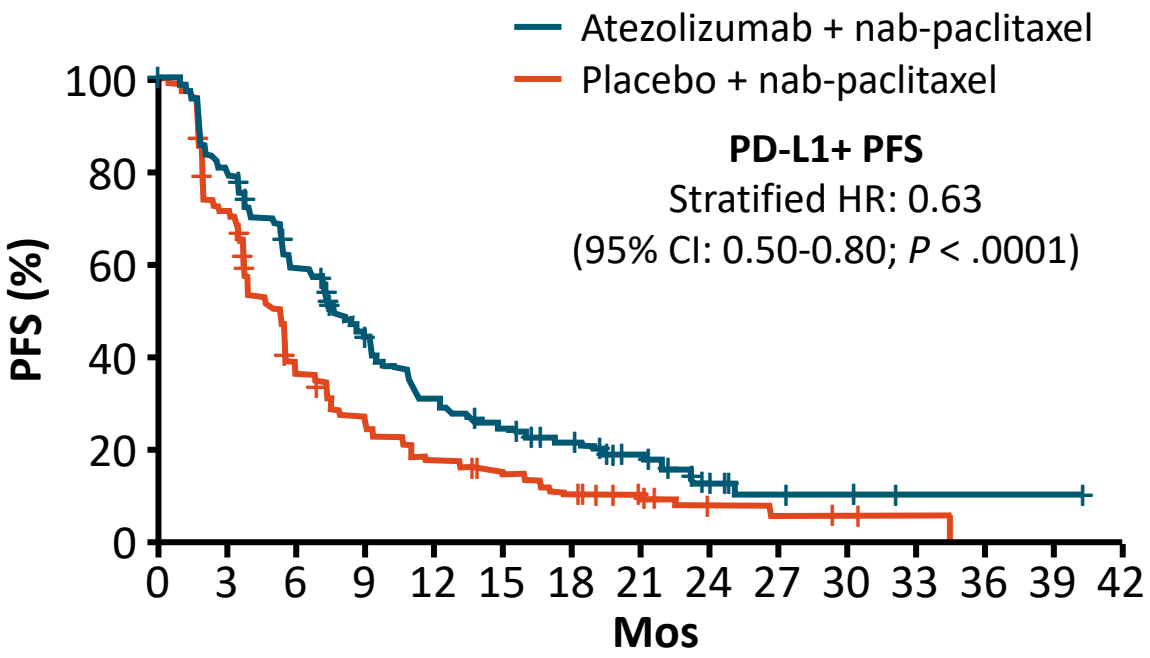
IMpassion130: PFS in ITT/PD-L1+*

ITT Population



Patients at Risk, n (Number Censored)													
Atezolizumab + nab-paclitaxel	361 (3)	227 (13)	165 (22)	100 (25)	73 (26)	58 (30)	37 (42)	17 (56)	11 (61)	8 (64)	3 (69)	1 (71)	1 (71)
Placebo + nab-paclitaxel	329 (7)	186 (13)	134 (17)	78 (18)	62 (20)	46 (23)	24 (33)	13 (39)	5 (43)	2 (46)	1 (47)		

PD-L1+ Population

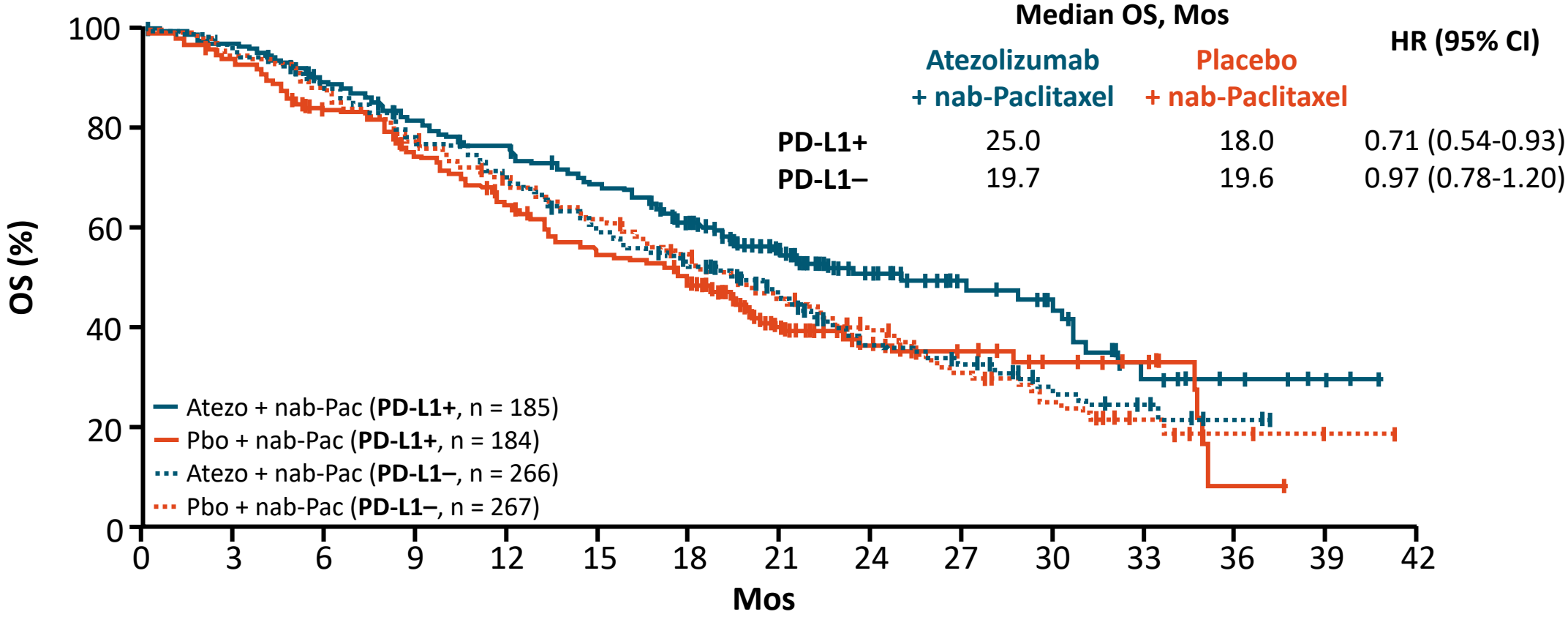


Patients at Risk, n (Number Censored)													
Atezolizumab + nab-paclitaxel	146 (1)	104 (5)	75 (9)	51 (10)	40 (11)	32 (14)	19 (23)	8 (29)	4 (32)	3 (33)	1 (35)	1 (35)	1 (35)
Placebo + nab-paclitaxel	128 (3)	63 (7)	45 (7)	30 (7)	23 (9)	16 (9)	9 (16)	4 (19)	3 (19)	2 (20)	1 (21)		

*Using Ventana SP142 Assay.

Schmid. Lancet Oncol. 2020;21:44.

IMpassion130: OS by PD-L1 Status



- Treatment benefit limited to PD-L1+ tumors (IC ≥ 1% using VENTANA SP142)
- Accelerated approval granted by US FDA on 8MAR2019; Voluntary withdrawl by Roche announced on 27AUG2021

Schmid. Lancet Oncol. 2020;21:44.

IMpassion131: Study Design

- Randomized, double-blind, placebo-controlled phase III trial

Stratified by prior taxane use in curative setting (yes vs no), geography, liver metastases (yes vs no), PD-L1 IC status (≥ 1% vs < 1%)

Patients with metastatic or unresectable locally advanced TNBC; no prior therapy for advanced setting (prior RT or CT in curative setting allowed if ≥ 12-mo DFI); RECIST v1.1 measurable disease; ECOG PS 0/1; tumor evaluable for PD-L1* (N = 902)

Atezolizumab 840 mg IV Q2W **+**
Paclitaxel 90 mg/m^2 IV on Days 1, 8, 15
28-day cycles
(n = 451)

Placebo IV Q2W **+**
Paclitaxel 90 mg/m^2 IV on Days 1, 8, 15
28-day cycles
(n = 451)

Treatment until PD per RECIST v1.1 or intolerable toxicity

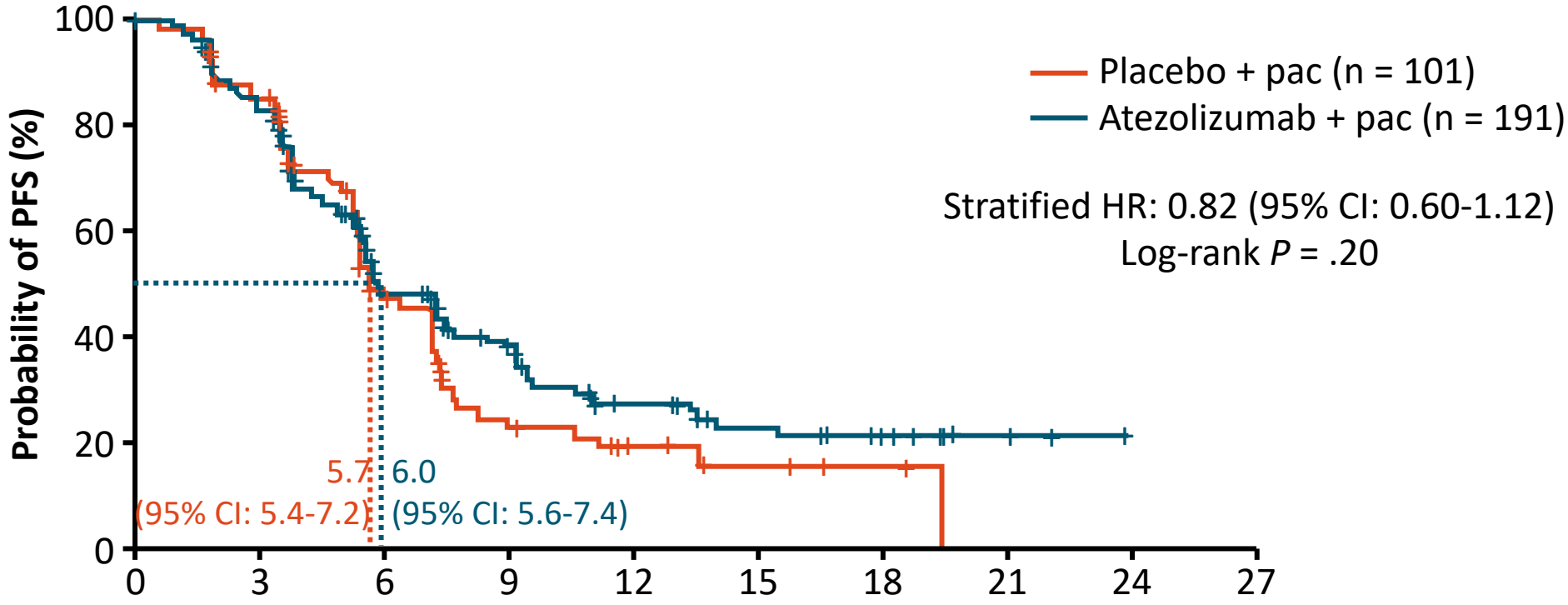
- Primary endpoint: PFS (Investigator assessed)
- Secondary endpoints: OS, ORR, PFS (by IRC), PROs, safety

*By prospective central testing with SP142 PD-L1 IHC assay. 41% of patients in each arm were PD-L1+ (≥ 1 % IC).

Miles. ESMO 2020. Abstr LBA15.

IMpassion131: Primary Analysis of PFS in PD-L1+ Population

- PFS events occurred in 61% of patients (data cutoff: Nov 15, 2019)

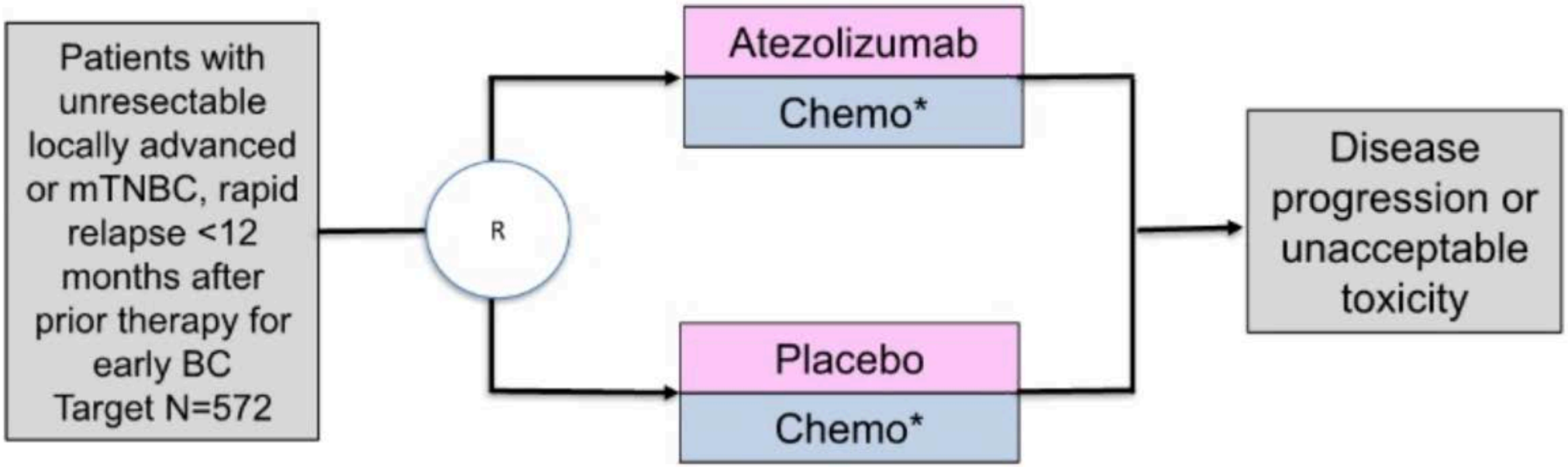


Patients at Risk, n

Placebo + pac	101	81	33	14	7	4	2	0	0	0
Atezolizumab + pac	191	152	69	44	22	15	8	3	0	0

Miles. ESMO 2020. Abstr LBA15.

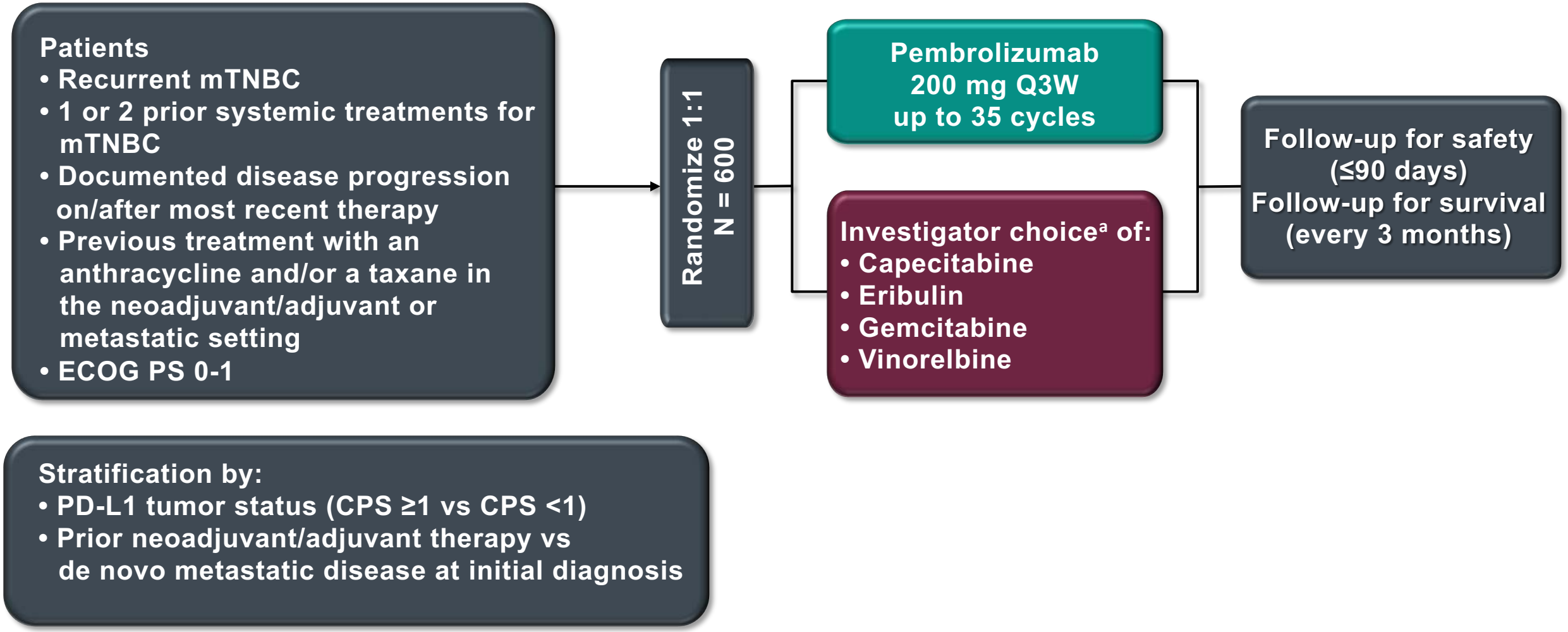
IMpassion132-Metastatic



Primary endpoints: OS (PD-L1+), expected Q1 2023
Secondary endpoints: 12-month and 18-month OS rates, PFS, ORR

*Chemo: Gemcitabine/carboplatin or capecitabine

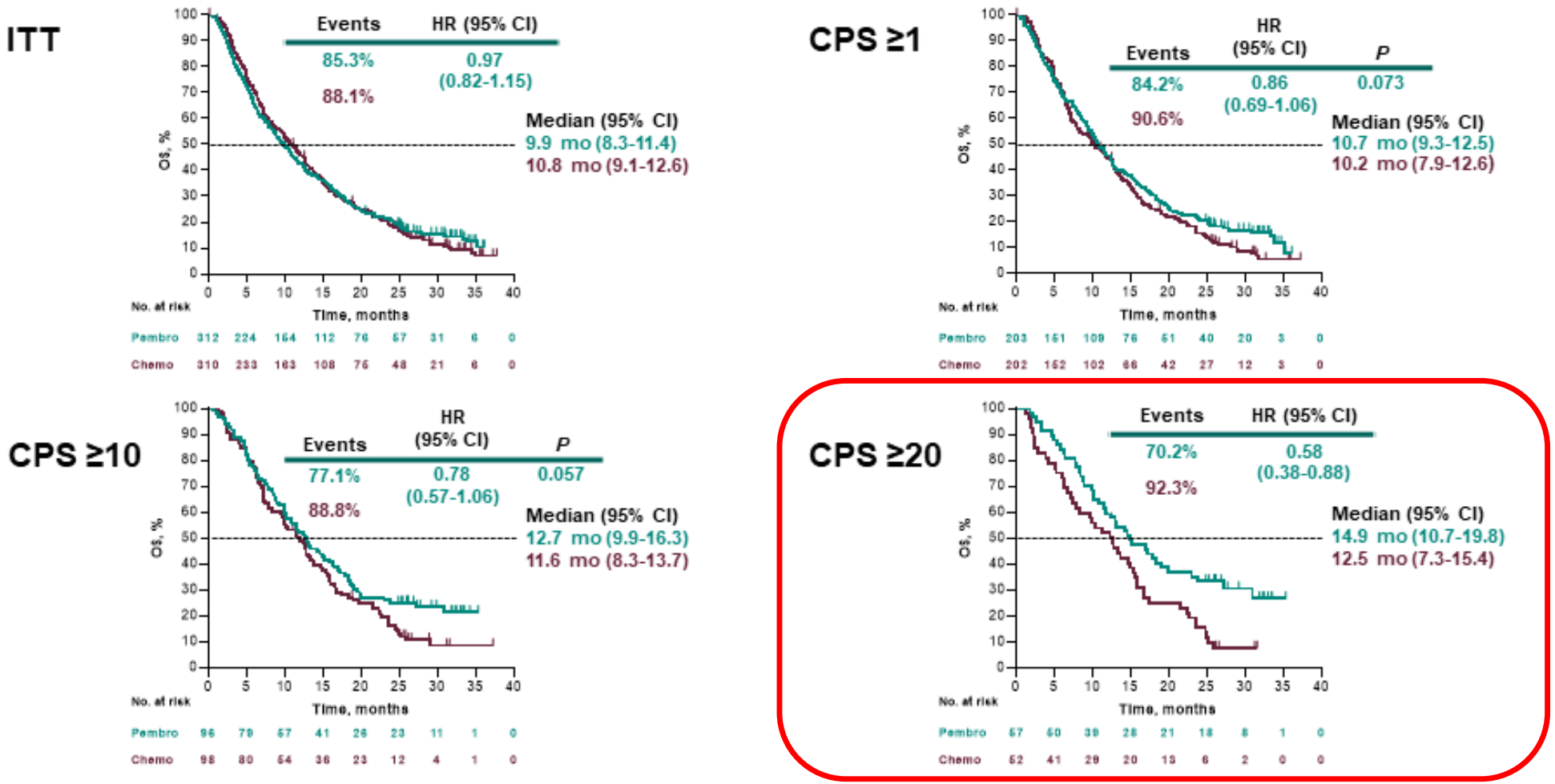
KEYNOTE-119 Study Design



Cortes et al, ESMO 2019
Winer EP et al, Lancet Oncol 2021

KN119: Benefit of pembrolizumab increases with greater PD-L1 expression

Keynote 119: Benefit of pembrolizumab over chemotherapy only in CPS≥20



OS in the ITT, CPS ≥1 and CPS ≥10 populations were primary endpoints; OS in the CPS ≥20 population was an exploratory endpoint. Data cutoff date: April 11, 2019

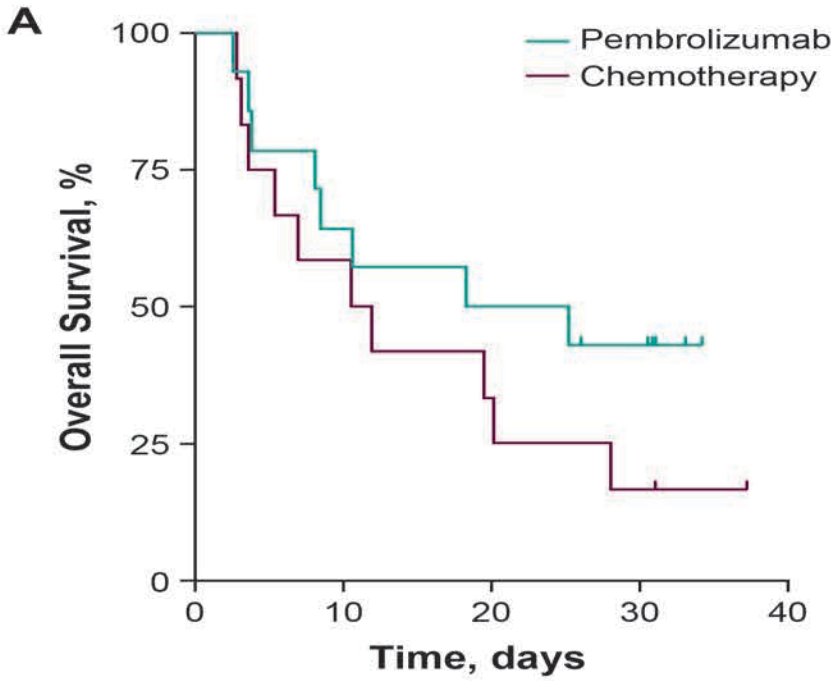
Cortes et al, ESMO 2019
Winer EP et al, Lancet Oncol 2021

KEYNOTE-119: Association of TMB and Clinical Outcomes by Treatment

	TMB ≥10 mut/Mb n = 26		TMB <10 mut/Mb n = 227	
	Pembrolizumab n = 14	Chemotherapy n = 12	Pembrolizumab n = 118	Chemotherapy n = 109
ORR, % (95% CI)	14.3 (4.0-39.9)	8.3 (0.4-35.4)	12.7 (7.9-19.9)	12.8 (7.8-20.4)
PFS, HR (95% CI)	1.14 (0.42-3.07)		1.24 (0.92-1.67)	
OS, HR (95% CI)	0.58 (0.21-1.57)		0.81 (0.61-1.07)	

- Trend to improvement in ORR and OS in those with TMB ≥ 10 mut/Mb
- Minority (10.2%) had TMB ≥ 10 mut/Mb

≥10 mut/Mb

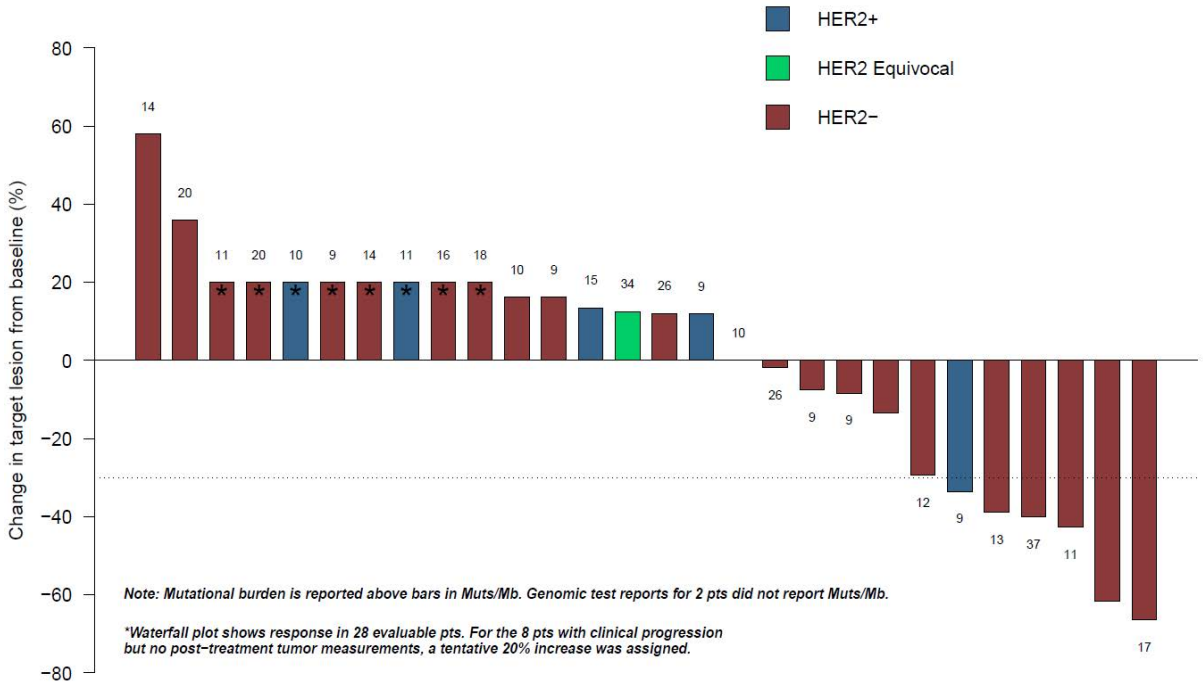


Winer EP et al, Abst 1013, ASCO 2020

Pembrolizumab in Patients with Metastatic Breast Cancer with reported High TMB (TAPUR)

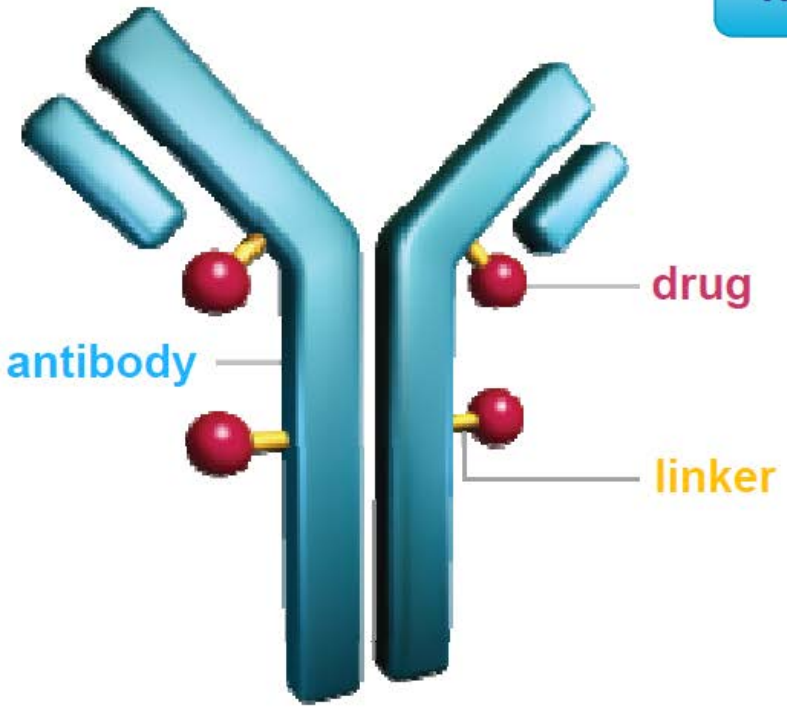
- ~10% of mBC with high TMB
- ORR 21%
- Consistent with data from KN-158 that led to tumor agnostic approval of pembrolizumab for H-TMB cancers

Clinical Outcomes	
DC (OR or SD 16+wks) N (%), [90% CI]	10 (37%), [24%, 46%]
OR (CR or PR) N (%), [95% CI]	6 (21%), [8%, 41%]
mPFS, wks, (95% CI)	10.6 (7.7, 21.1)
mOS, wks, (95% CI)	31.6 (11.9, inf)



Alva A et al, ASCO 2019
Alva A et al, JCO 2021

Antibody Drug Conjugates

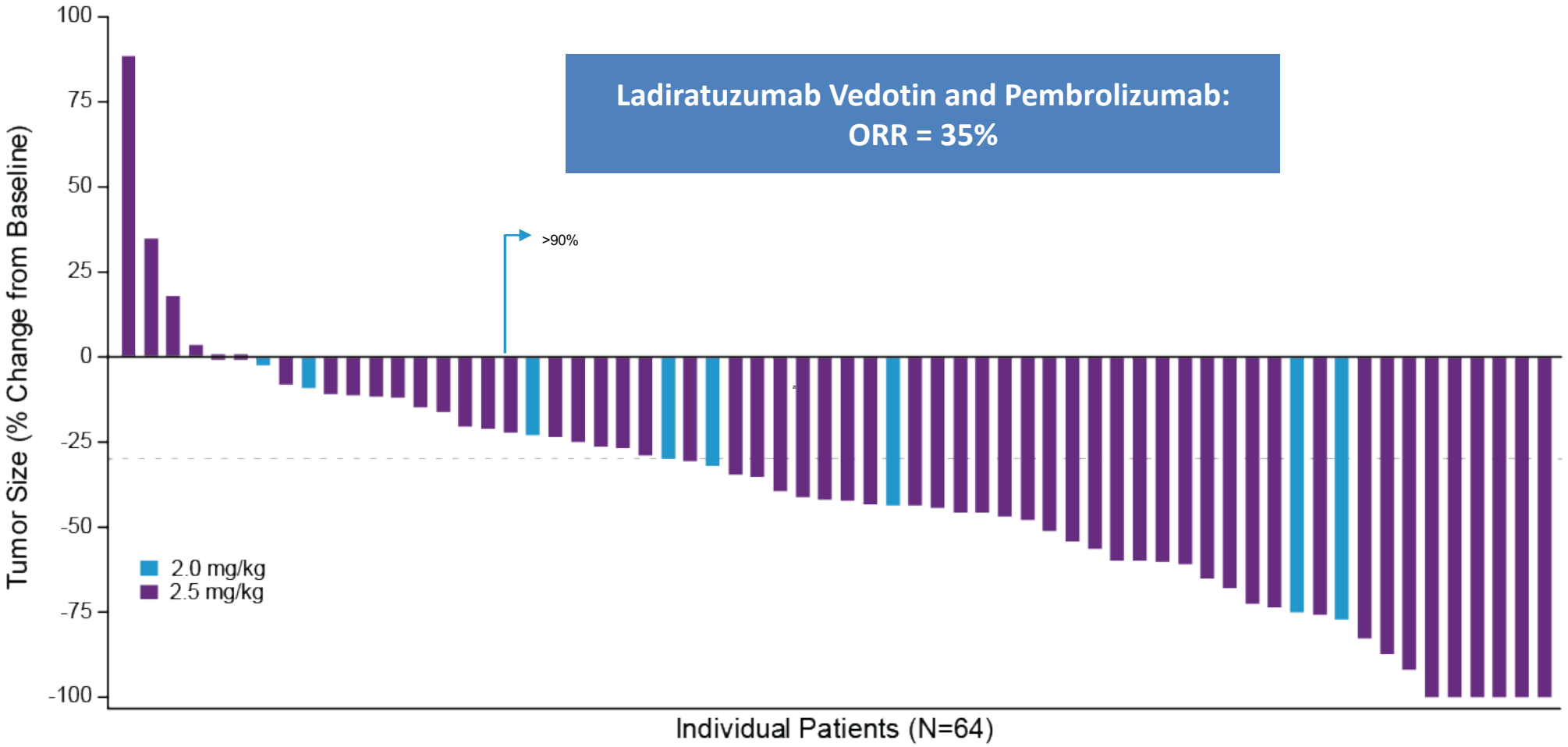


1. Monoclonal antibody specific for a tumor antigen with little/no expression on normal cells

2. Linker that is stable in circulation but releases the cytotoxic agent in target cells

3. Potent cytotoxic agent designed to induce target cell death when internalized and released

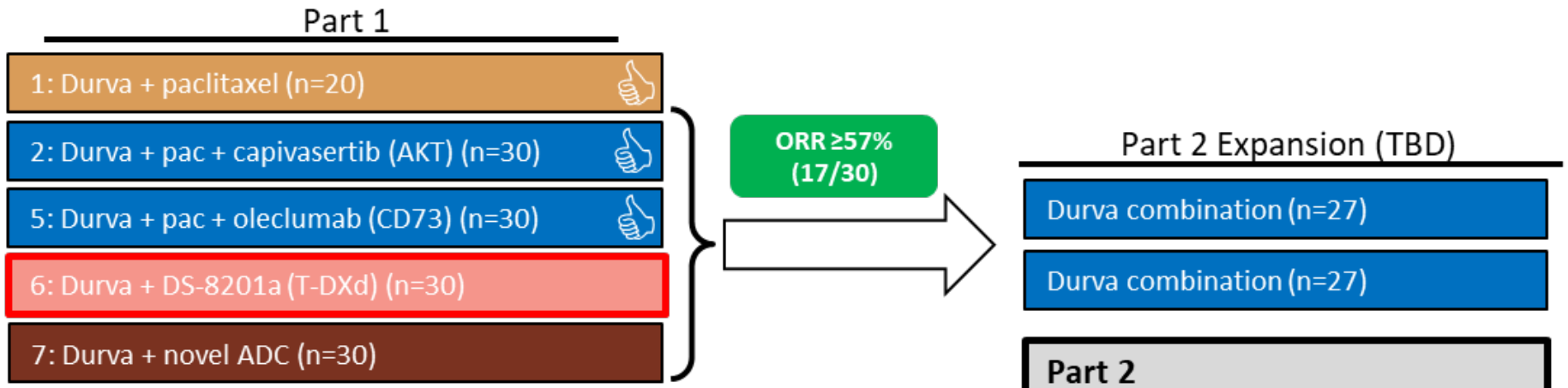
Combination of Ladiratuzumab (ADC targeting LIV1 linked to MMAE) and Immunotherapy



Han H, et al. SABCS 2019.

BEGONIA Study Design: T-DXd + Durvalumab for HER2 low TNBC

- Metastatic TNBC
- No prior treatment for stage IV disease
- ECOG PS 0–1
- RECIST evaluable
- Patients may have relapsed from earlier stage disease but must be ≥12 months since prior taxane treatment
- **Arm 6: locally confirmed HER2 IHC 1–2+ (ISH-)**



Arms 2–6
Safety run-in: 6 DLT evaluable patients for 28 days (arms 2–5) or 21 days (arms 6–7) with ≤1 DLT

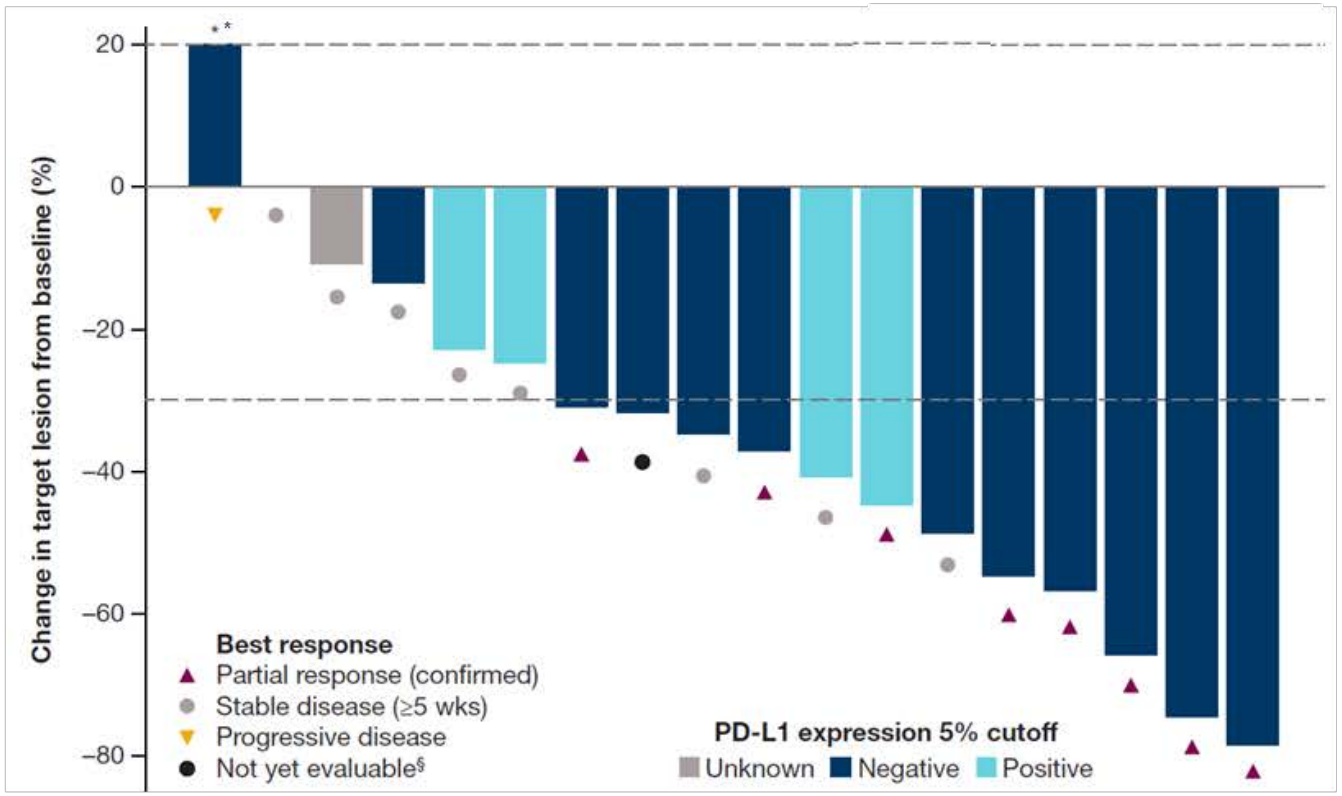
Part 1
Primary endpoint: safety and tolerability
Secondary endpoints: ORR, PFS, DoR, OS, PK/ADA

Part 2
Primary endpoint: ORR
Secondary endpoints: safety and tolerability, PFS, DoR, OS, PFS6m

BEGONIA: Efficacy

- Responses were observed in both PD-L1–positive (confirmed ORR 1/1 [100%]) and PD-L1–negative (confirmed ORR 7/10 [70.0%]) groups

Parameter	D+T-DXd
Patients who completed at least 1 on-treatment assessment, n	18
Response evaluable analysis set, n‡	12
Confirmed ORR, n (%)‡ 95% CI Complete response, n Partial response, n	8/12 (66.7) 41.0, 86.7 0 8
Stable disease, n	8
Progressive disease, n	1



Schmid P, et al. ASCO 2021.

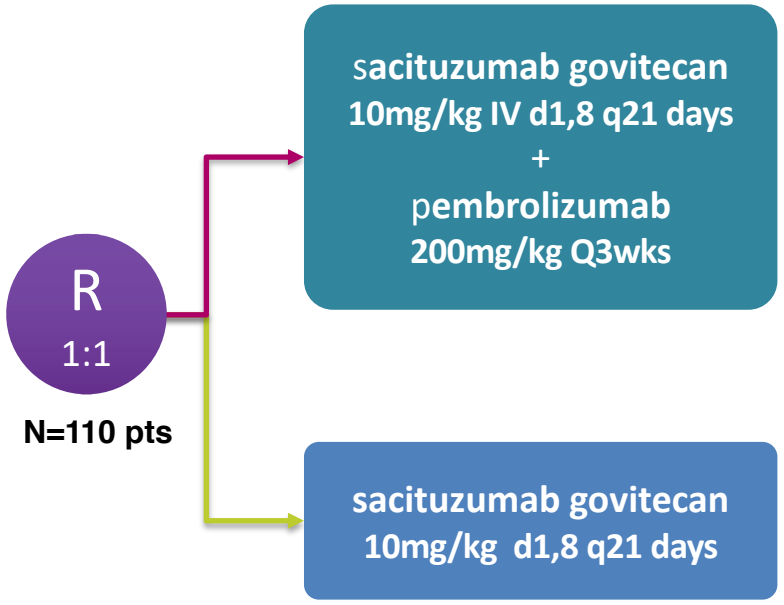
SACI-IO TNBC: Sacituzumab Govitecan +/- pembrolizumab in 1st line PD-L1- TNBC

mTNBC:
No Prior Chemo
No Prior PD-1/L1

PD-L1 <1% by SP-142
ER ≤ 5%
PR ≤ 5%
HER2-

Stable brain mets
Strata: Neo/adjuvant progression <12m

Exclude prior: PD-1/L1, SG, Irinotecan



80% power to detect PFS improvement from 5.5 months (Arm B) to 8.5 months (Arm A)

Primary Endpoint
- PFS

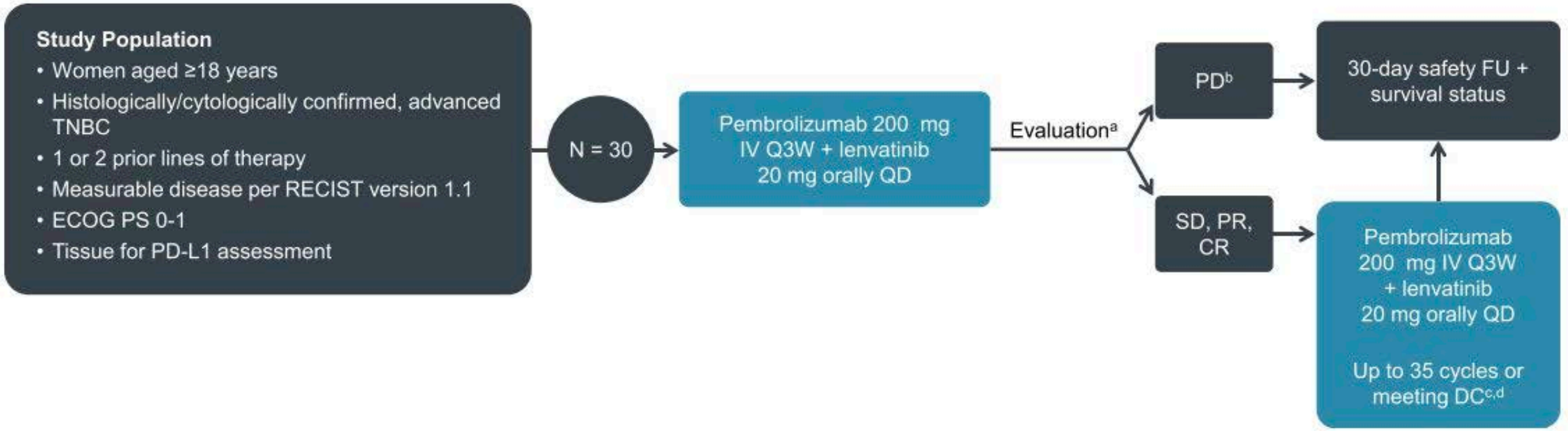
Secondary Endpoints
- OS, ORR
- DOR, CBR

Dana-Farber Cancer Institute

PI: Ana Garrido-Castro/Sara Tolaney

LEAP-005 Study Design: Lenvatinib plus Pembrolizumab

Figure 1. LEAP-005 Study Design



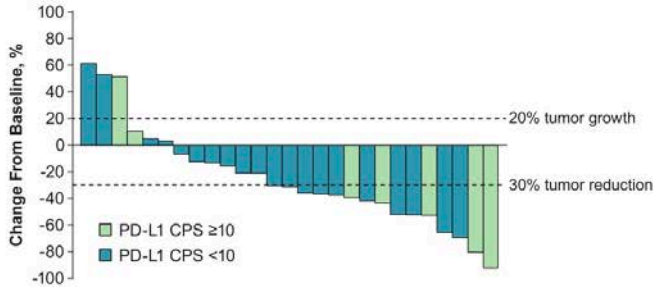
LEAP-005: Safety and Efficacy

Table 3. Summary of Safety and Tolerability

	Lenvatinib + Pembrolizumab N = 31	
	Any Grade	Grade 3-5
Treatment-related AEs	30 (97)	17 (55)
Led to death	1 (3)[a]	1 (3)[a]
Led to discontinuation	3 (10)	3 (10)
Treatment-related AEs occurring in ≥20% of study population		
Hypertension	13 (42)	4 (13)
Fatigue	9 (29)	1 (3)
Diarrhea	7 (23)	1 (3)
Decreased appetite	8 (26)	2 (6)
Hypothyroidism	8 (26)	0
Nausea	8 (26)	0
Clinically significant treatment-related AEs for lenvatinib	24 (77)	6 (19)
Any immune-mediated AE	15 (48)	1 (3)
Hypothyroidism	11 (35)	0
Hyperthyroidism	3 (10)	0
Adrenal insufficiency	1 (3)	1 (3)
Hypophysitis	1 (3)	0
Pneumonitis	1 (3)	0
Infusion reaction	1 (3)	0

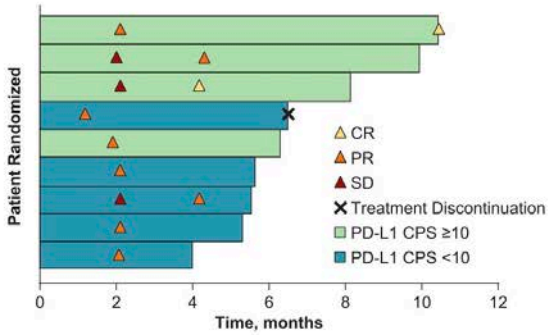
Data are presented as n (%).
[a]Subarachnoid hemorrhage.

Figure 3. Best Percentage Change From Baseline in Target Lesion Size (RECIST v1.1, BICR)



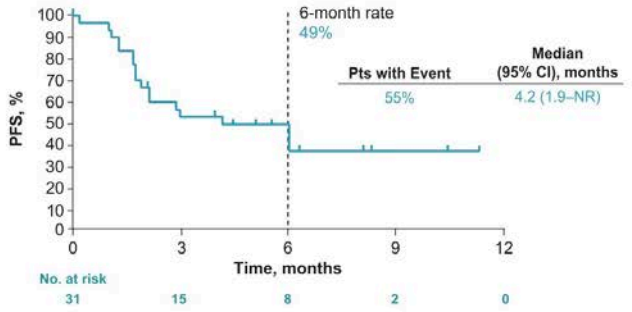
Includes patients with one or more evaluable post-baseline imaging assessment (n = 27).

Figure 4. Treatment Duration and Response Evaluation (RECIST v1.1, BICR)



Includes patients whose best overall response was complete or partial response.
The length of the bars represents the time since treatment initiation.
x = treatment discontinuation was due to initiation of new anticancer therapy.

Figure 5. Progression-Free Survival (RECIST v1.1, BICR)



Chung et al, Abstract PS 12-07, SABCS 2020

Summary

- Pembrolizumab plus chemotherapy with full regulatory approval in US for PD-L1+ (CPS ≥ 10) TNBC
- Atezolizumab plus nab-paclitaxel voluntarily withdrawn in US, but remains available outside of US for PD-L1+ (IC ≥ 1%) TNBC
- Trials of novel combination strategies ongoing

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Thank You!

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