Quali novità nel setting (neo)-adiuvante?

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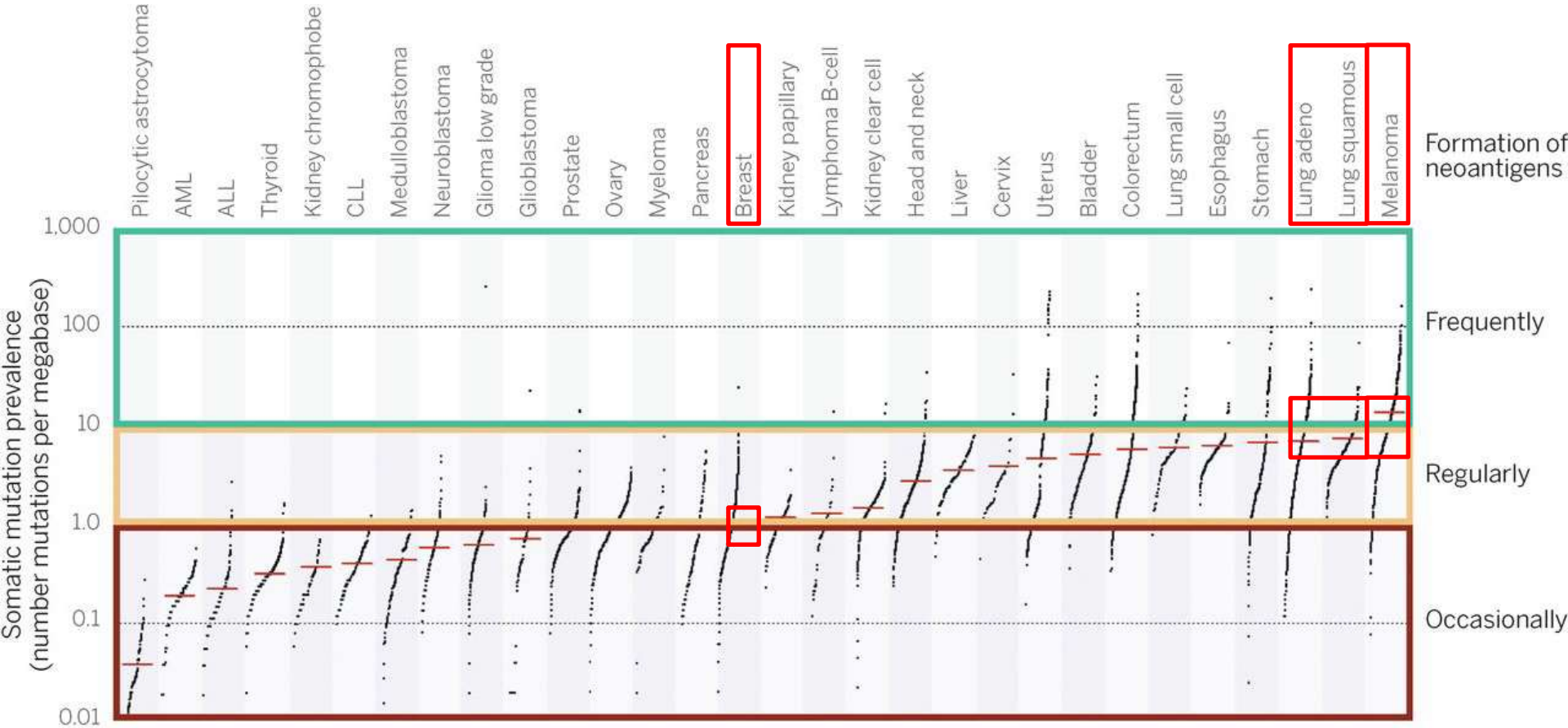
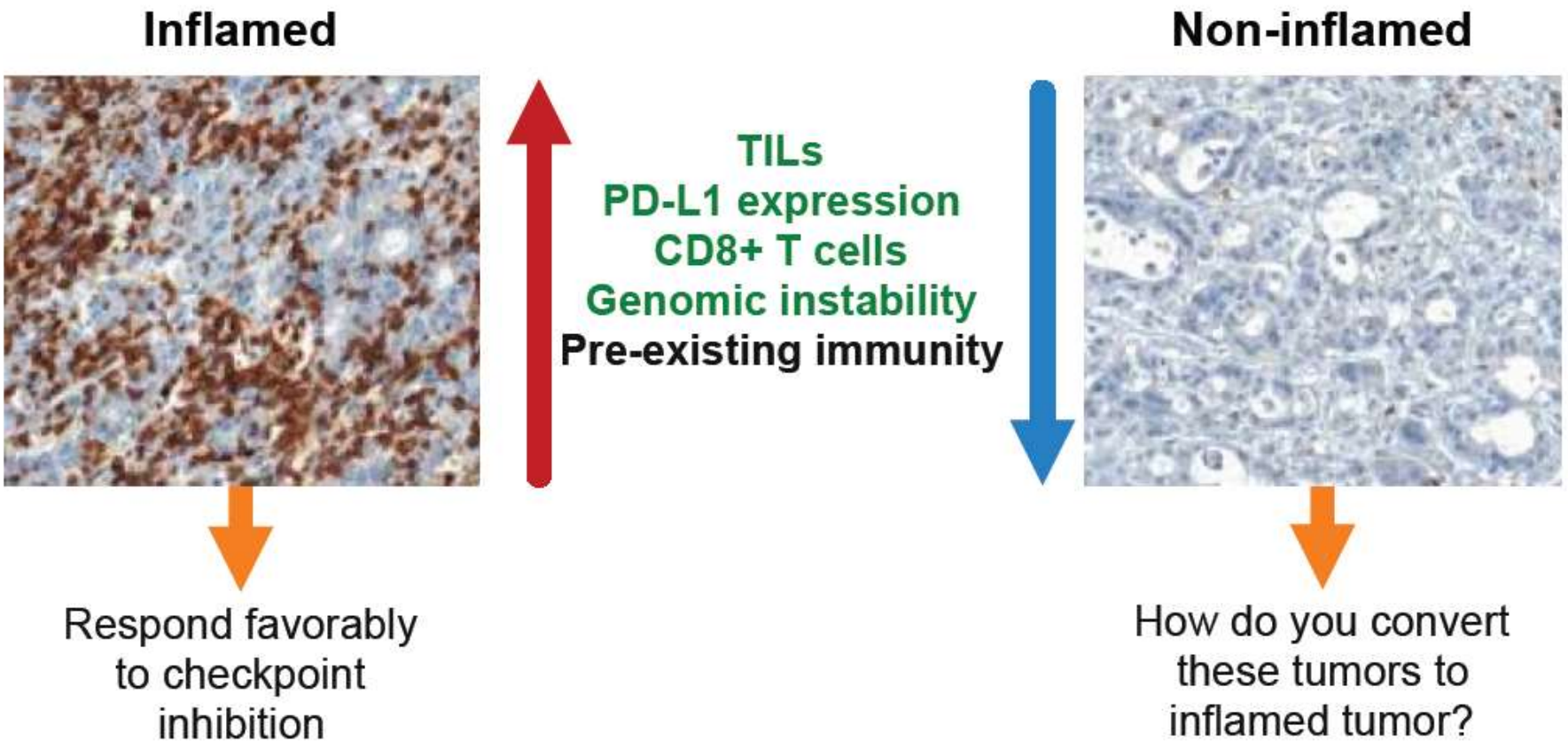
Immunogenic vs. Non-immunogenic Tumors

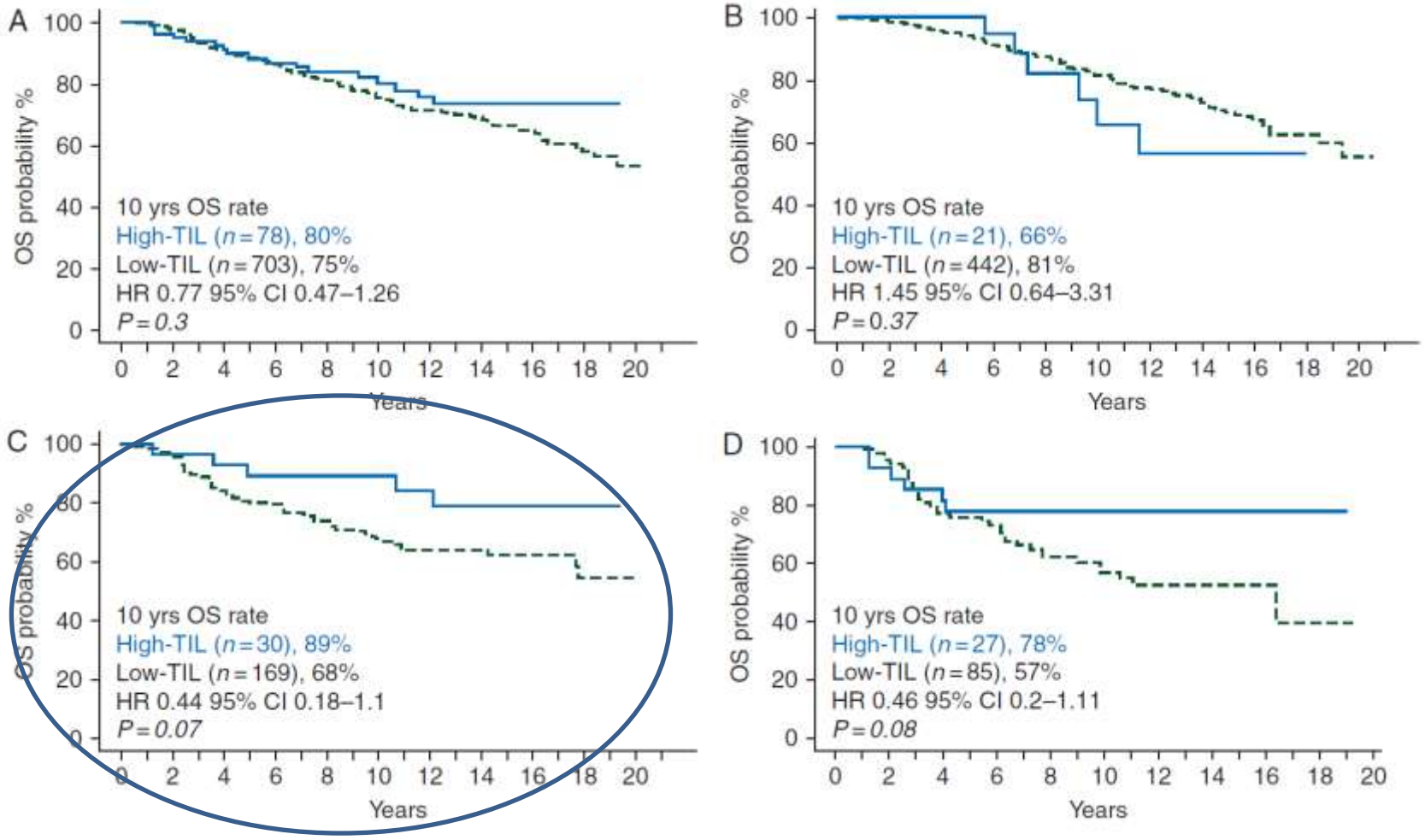


Alexandrov et al., 2013

Immunogenic vs. Non-immunogenic Tumors



Prognostic value of TILs in different BC subgroups



all patients (A) ER+/HER2 (B) ER−/HER2− (C) HER2+ (d).

Dieci MV et al. Ann Oncol 2015

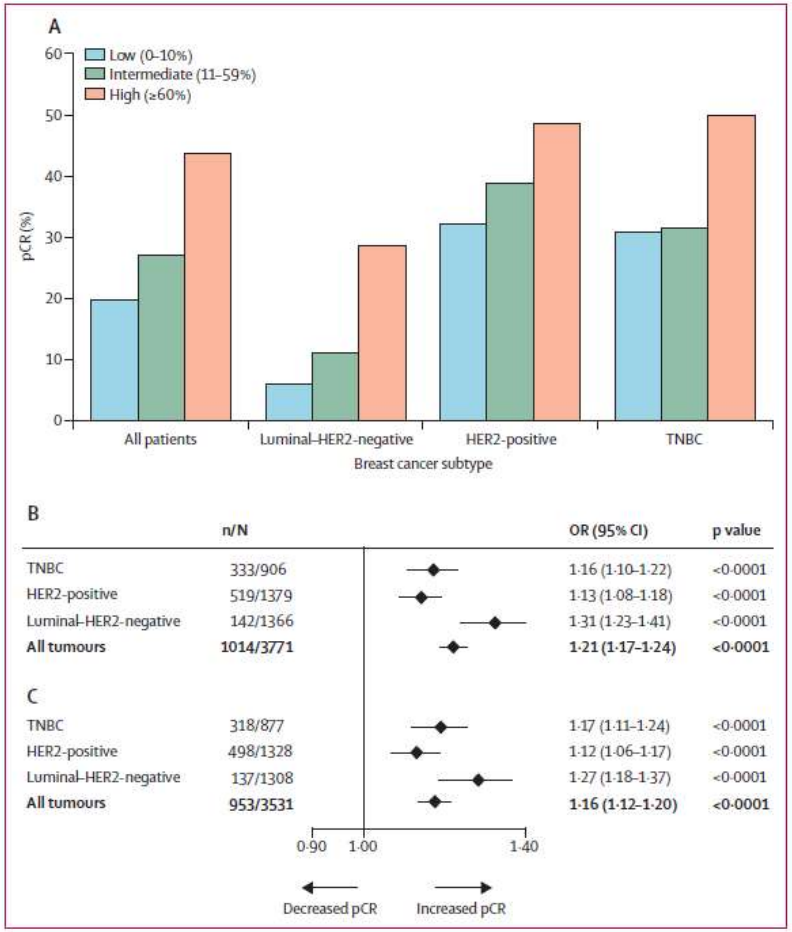
Predictive value of TILs in neoadjuvant trials

Combined data from 6 neoadjuvant trials

In the TNBC subtype, pCR was achieved in

- **31%:** low TILs (0-10%)
- **31%:** intermediate TILs (11-59%)
- **50%:** high TILs (>60%)

(p<0.001)



Denkert, Lancet Oncology 2018

Predictive value of PDL-1 in advanced BC trials

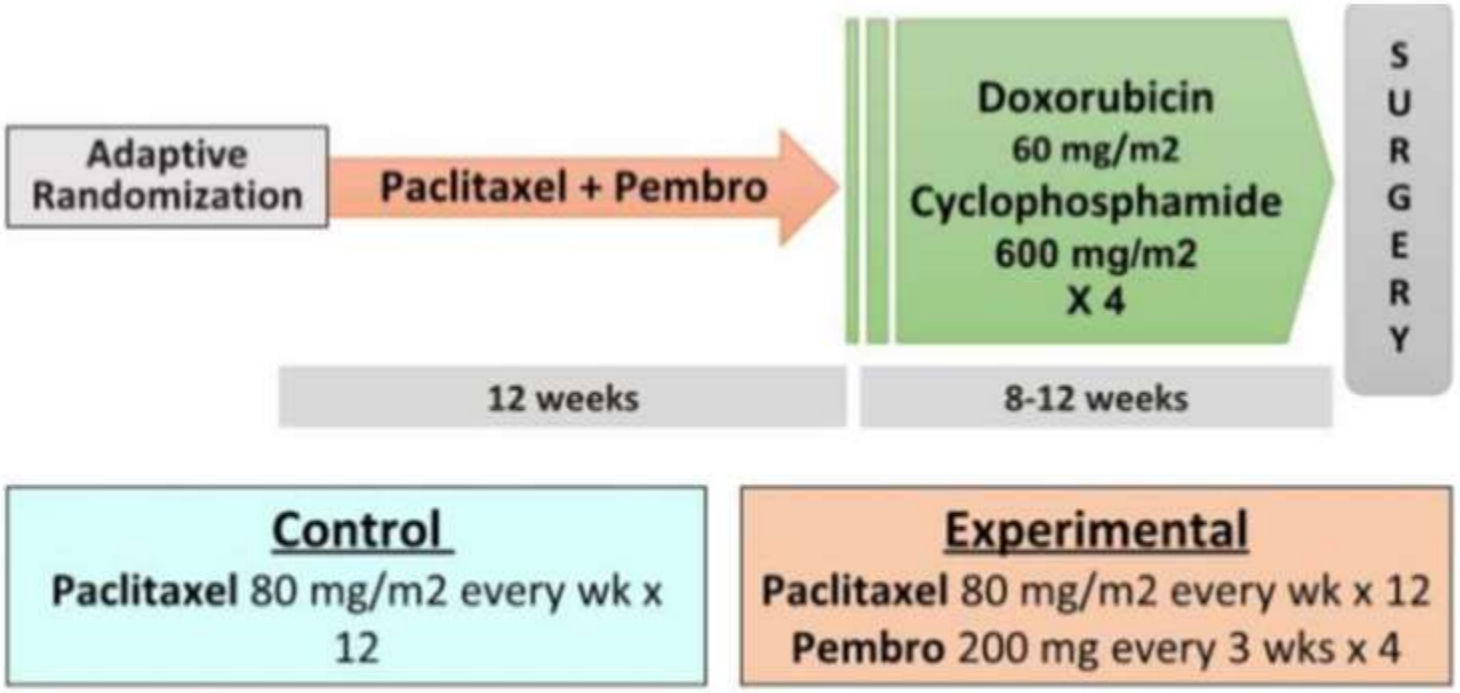
Study	Population	Treatment	PD-L1	Main finding
Nanda 2016 Keynote-012 (phase Ib)	111 (TN MBC) PDL1 positive	Pembrolizumab (ORR)	protein (prototype IHC assay: clone 22C3)	Increased ORR with increasing expression of PD-L1
Schmid 2017 (expansion cohort phase Ia study)	112 (TN MBC) initially limited to PDL1 positive, then opened also to PDL1 negative	Atezolizumab (ORR)	protein (IHC: clone SP142)	ORR for PDL1 2/3 vs PDL1 0/1 17% vs 8%
Dirix 2017 Javelin (expansion cohort phase I trial)	168 (MBC) regardless PDL1 status	Avelumab (ORR)	protein (IHC: clone 73-10)	TC PDL1: no efficacy trends in subgroups defined by PD-L1 expression in tumor cells at different thresholds IC PDL1: ORR for PD-L1+ vs PD-L1− 16.7% vs 1.6% in the overall group, and 22.2% vs 2.6% in TNBC
Loi 2017 Keynote 086 (phase II)	193 (TN MBC) cohort A: regardless PDL1 status cohort B: PDL1 positive	Pembrolizumab (ORR)	protein (IHC: clone 22C3)	No efficacy trends according to PDL1 status
Tolaney 2017 Keynote 150-Enhance 1 (phase Ib/II)	106 (TN MBC) regardless PDL1 status	Pembrolizumab + eribulin (ORR)	protein (IHC: clone 22C3)	No association between response and PDL1 status
Loi 2018 Panacea (phase Ib/II)	58 (HER2+ MBC) phase Ib: PDL1 positive phase II: regardless PDL1 status	Pembrolizumab + Trastuzumab (ORR)	protein (IHC: clone 22C3)	ORR for PDL1+ vs PDL1-: 15.2% vs 0% 1y-OS for PDL1+ vs PDL1-: 65% vs 12%
Adams 2016; Pohlmann 2018 (phase Ib; 2-years update)	32 (TN MBC) regardless PDL1 status	Atezolizumab + nab-paclitaxel(ORR)	protein (IHC: clone SP142)	ORR for PDL1+ (PDL1 1/2/3) vs PDL1- (PDL1 0): 42% vs 33% Secondary endpoints: longer PFS and OS with higher PDL1
Schmid 2018 Impassion130 (phase III)	**902 (mTNBC) regardless PDL1 status (PDL1 status was a stratification factor)**	**nab-paclitaxel + atezolizumab /placebo (PFS, OS)**	**protein (IHC: clone SP142)**	**PFS for PDL1+ in control vs experimental arm: 7.5 vs 5.0 months OS for PDL1+ in control vs experimental arm: 55 vs 15.5 months**

Adapted from Miglietta The Oncologist 2019 – in press

PDL-1in Breast Cancer: not a ideal Biomarker?

- biologic implications and associations of PD-L1 expression,
- dynamic changes in expression,
- heterogeneity in expression on tumor cells and on immune cells,
- prognostic and/or predictive implications

I-SPY 2 TRIAL: Pembro 4 Arm Schema



I-SPY 2 TRIAL: Estimated pCR Rate

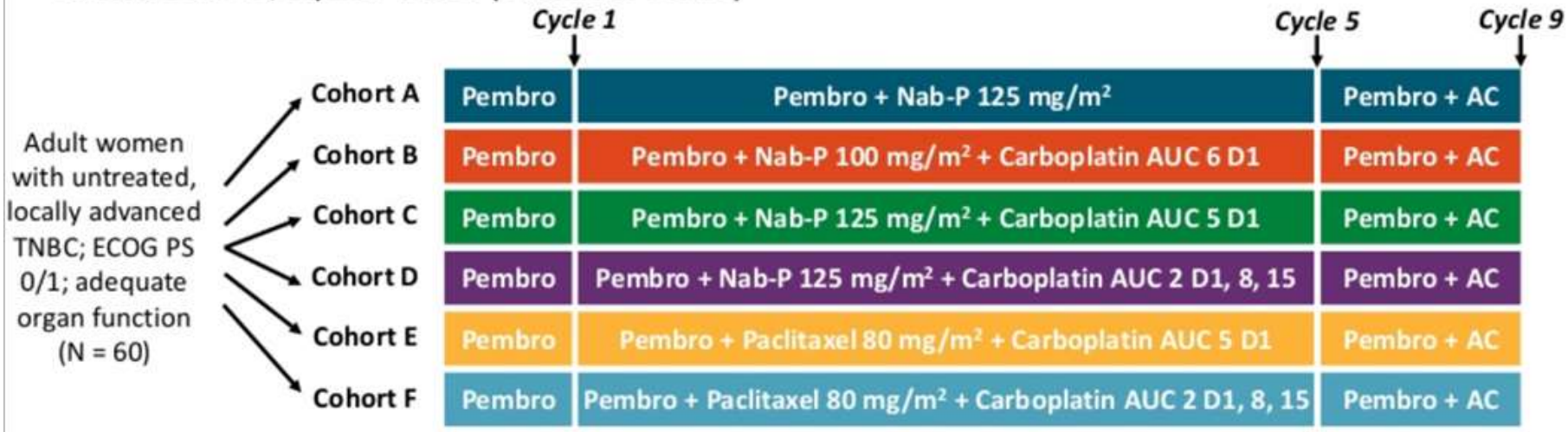
Signature	Estimated pCR Rate (95% Probability Interval)		Probability Pembro Superior to Control	Predictive Probability of Success in Phase 3
	Pembro	Control		
HER2-	0.44 (0.33 – 0.55)	0.17 (0.11 – 0.23)	>0.999	0.985
HR-HER2-	0.60 (0.44 – 0.75)	0.22 (0.13 – 0.30)	>0.999	0.996
HR+HER2-	0.30 (0.17 – 0.43)	0.13 (0.07 – 0.19)	0.996	0.834

The Bayesian model estimated pCR rates appropriately adjust to characteristics of the I-SPY 2 population.
The raw pCR rates (not shown) ar higher than the model estimate of 0.604 in TNBC.

Nanda, ASCO, 2017

KEYNOTE-173: Pembro + CT as Neoadj Trial for TNBC:

- Multicohort, open-label phase Ib study



All tx given IV. Cyclophosphamide: 600 mg/m² Q3W. Doxorubicin: 60 mg/m² Q3W. Nab-P, Pac: Days 1, 8, 15 Q3W. Pembro: 200 mg Day 1 in cycle 1, then Q3W. Definitive surgery per local standards and tissue collection for pCR 3-6 wks following completion of neoadjuvant therapy.

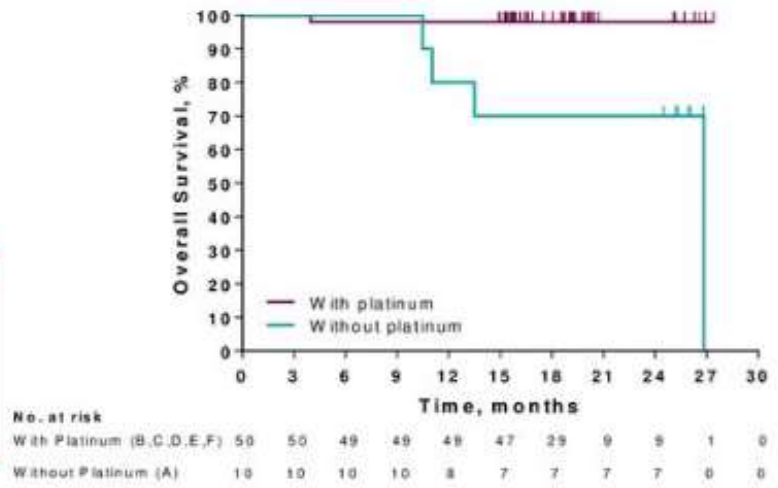
- Primary endpoint: safety/tolerability
- Secondary endpoints including: pCR rate, ORR, EFS, OS

KEYNOTE-173: Efficacy

Arm	Node neg	DLT	pCR
nab 125/no carbo	**1**	**2***	**6**
nab 100/carbo AUC 6	4	4	8
nab 125/carbo AUC 5	4	6	8
nab 100/carbo AUC 2	4	6	6
pac 80/carbo AUC 5	**3**	**0***	**3**
pac 80/carbo AUC 2	3	4	5

*Met threshold for RP2D

pCR rate with platinum 60%



Schmid et al, PD5-01, SABCS 2018

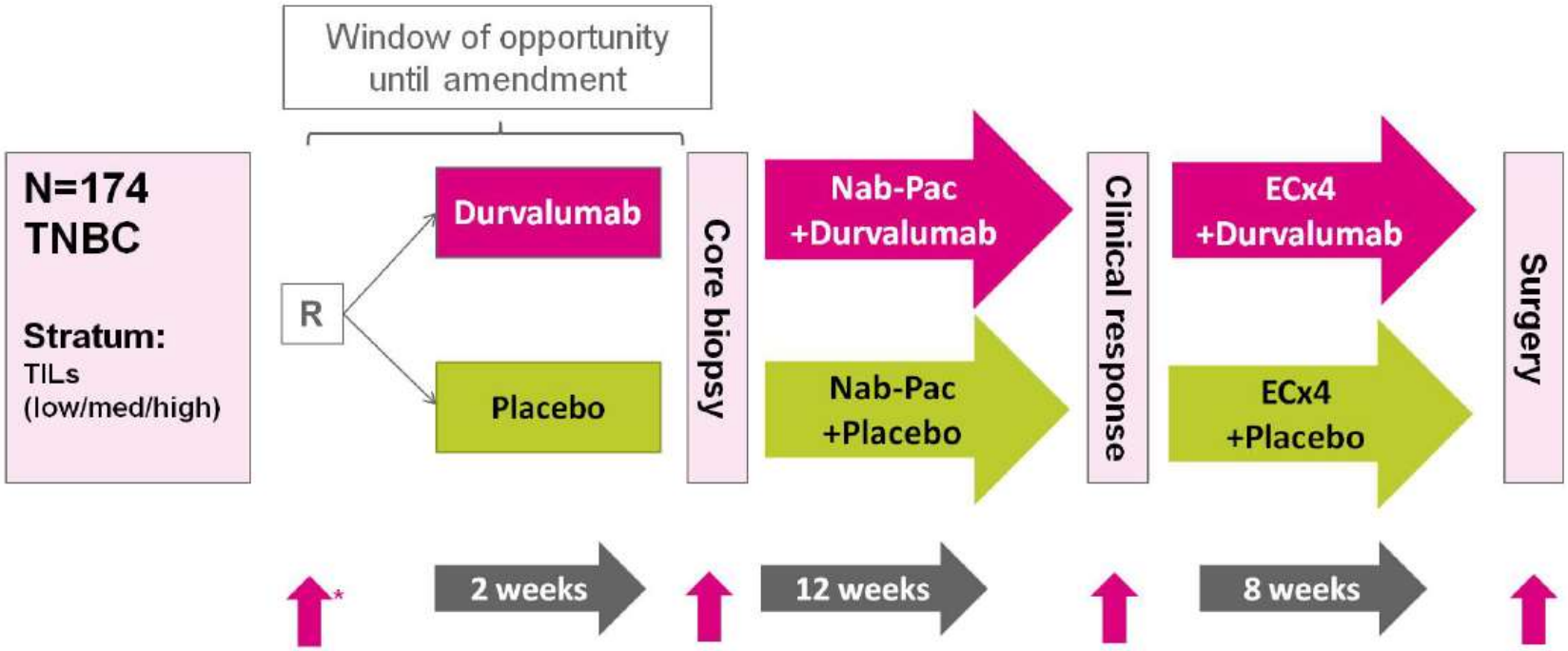
Loi S, Ann Oncol 2019 (Suppl)
Schimd P, AACR 2019 (Suppl)

KEYNOTE-173: Adverse Events

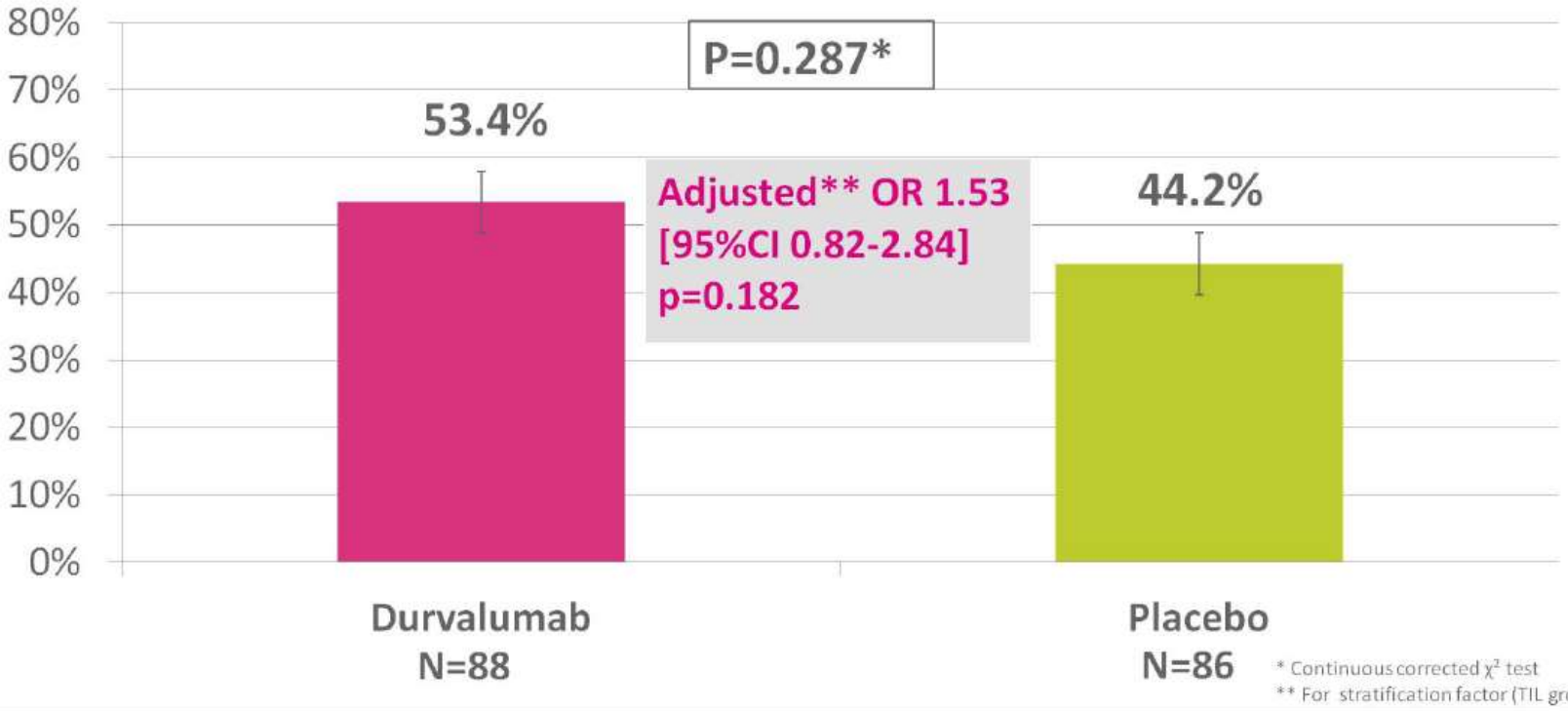
- 100% of patients experienced treatment-related AEs
  - Grade ≥ 3 events reported in 90%
  - Led to pembrolizumab discontinuation in 18%
- 30% of patients experienced immune-related AEs

Treatment-Related AEs, %	All Patients (N = 60)
Any	100
Grade ≥ 3	90
▪ Neutropenia	73
▪ Febrile neutropenia	22
▪ Anemia	20
▪ Thrombocytopenia	8
Immune-related	30
▪ Hypothyroidism	8
▪ Hyperthyroidism	5

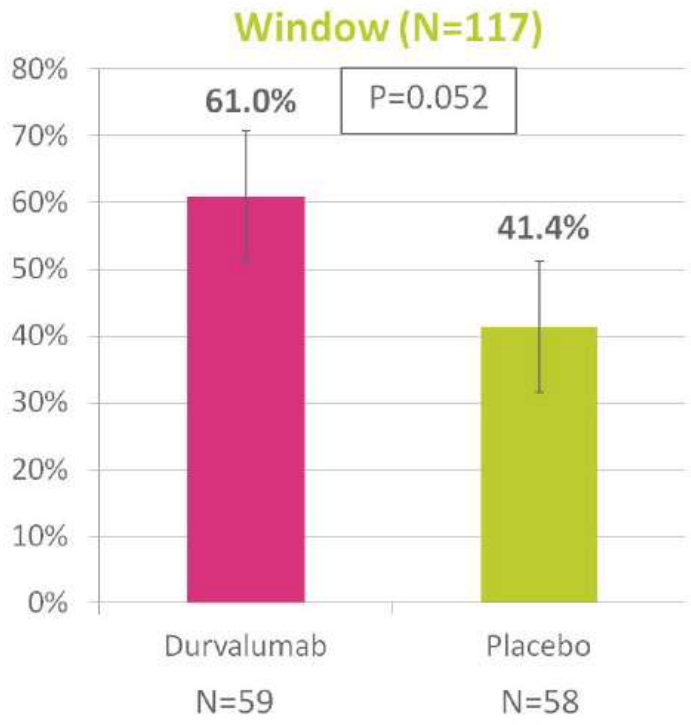
GeparNUEVO Study Design

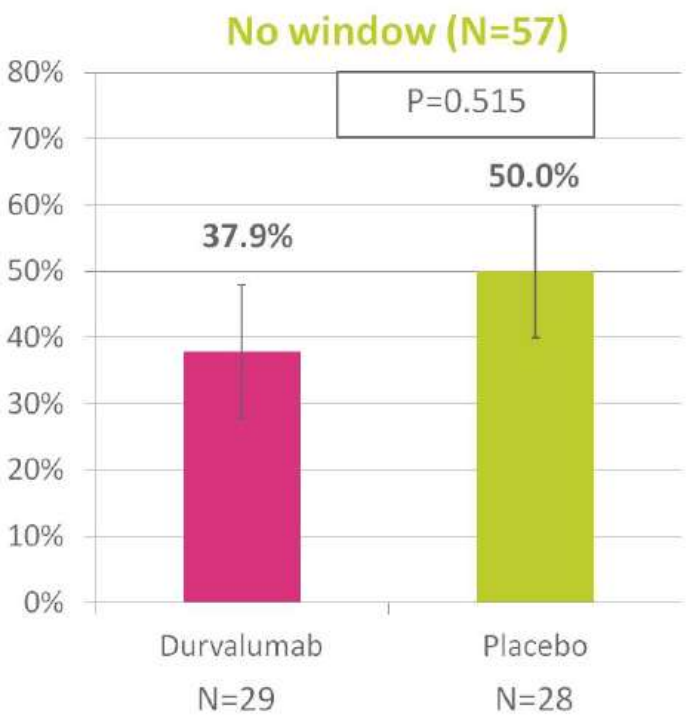


Primary endpoint – pCR (ypT0 ypN0)



Subgroup analysis of the window cohort



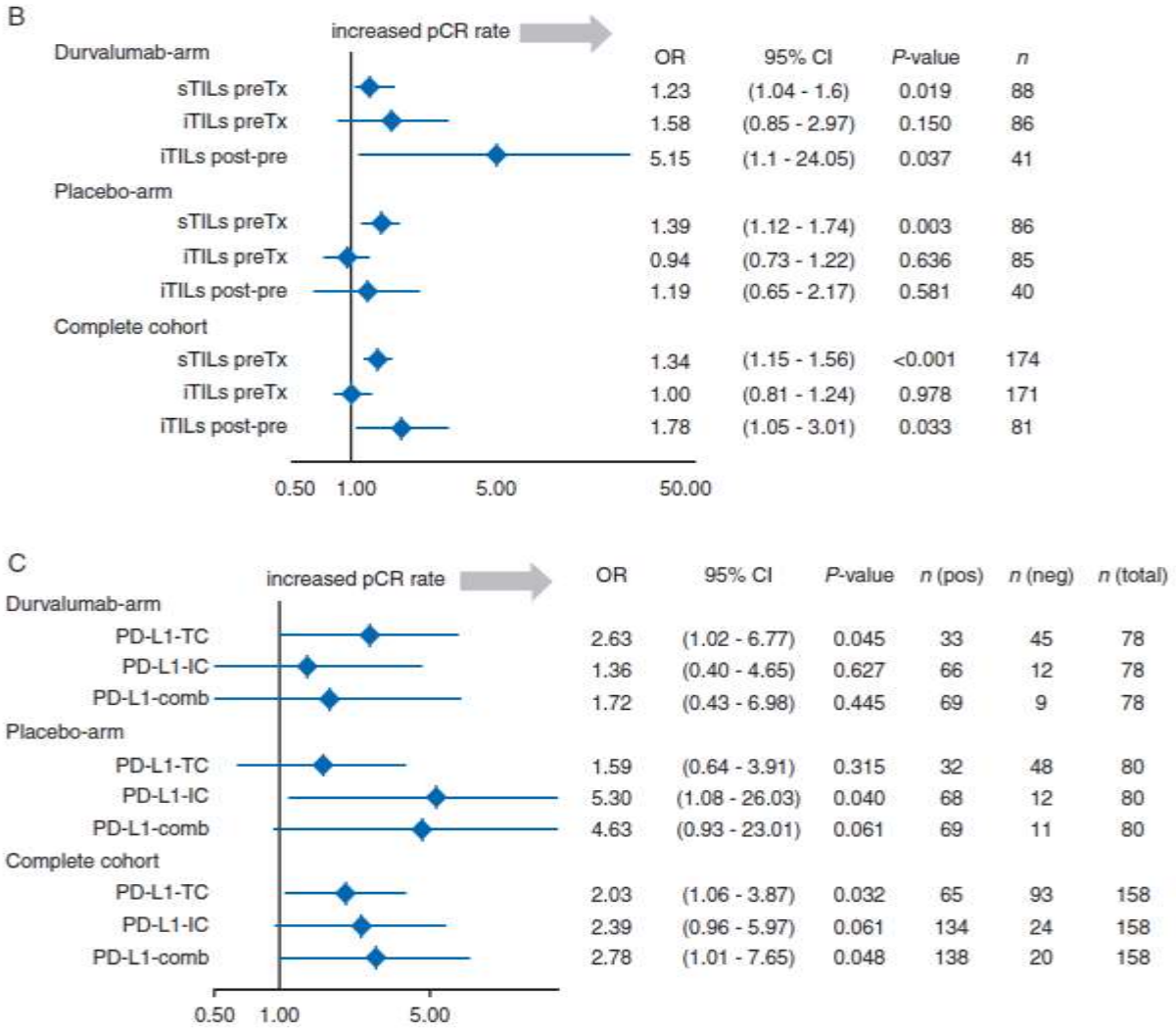


Immune Related Toxicities (Any Grade)

	Durvalumab N=92* N(%)	Placebo N= 82* N(%)	Overall N=174 N(%)
Hepatotoxicity	7 (7.6)	6 (7.3)	13 (7.5)
Dermatitis	13 (14.1)	12 (14.6)	25 (14.4)
Hypophysitis	1 (1.1)	0 (0.0)	1 (0.6)
Pneumonitis	1 (1.1)	1 (1.2)	2 (1.1)
Hypothyroidism	6 (6.5)	2 (2.4)	8 (4.6)
Hyperthyroidism	7 (7.6)	0 (0.0)	7 (4.0)
Neuropathy	5 (5.4)	7 (8.5)	12 (6.9)
Neuropathy, high grade	3 (3.3)	4 (4.9)	7 (4.0)

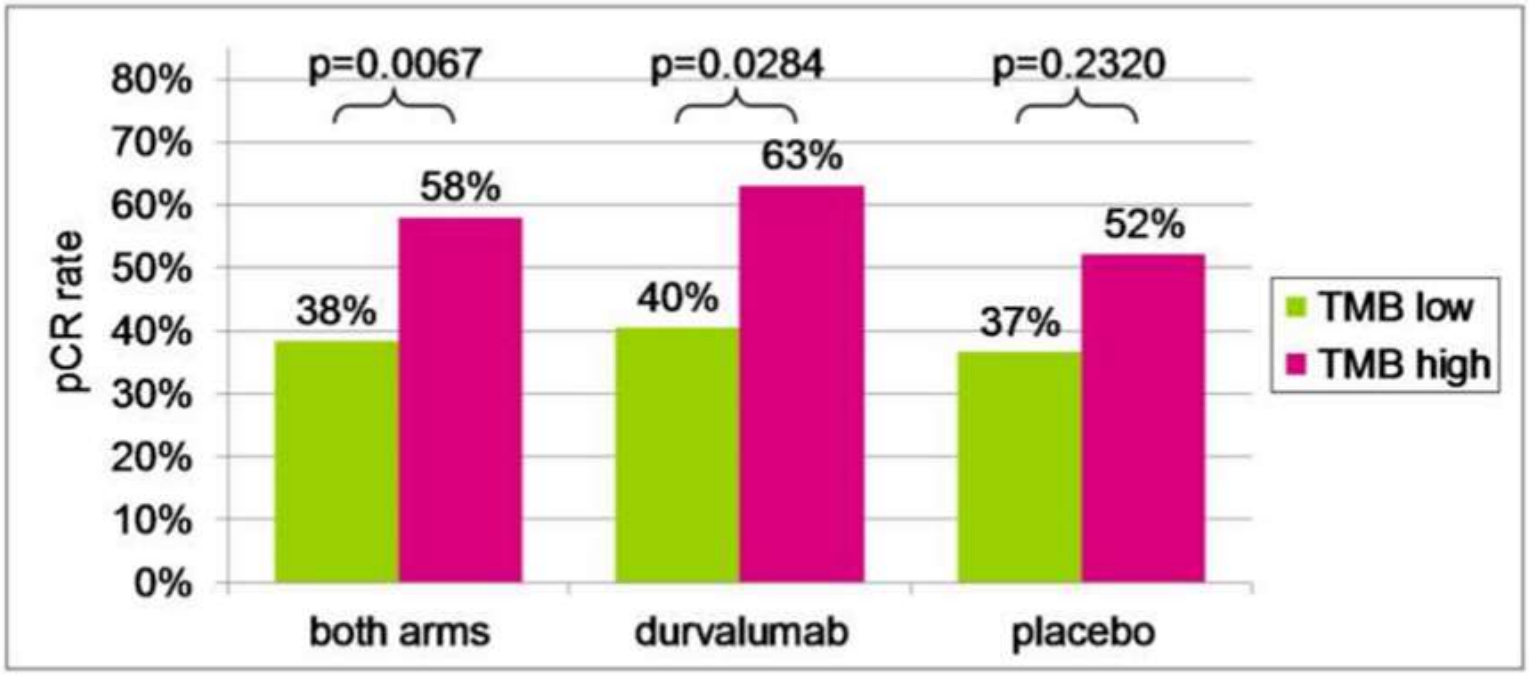
*safety population differs because 4 patients received durvalumab instead of placebo at least once

TILs and PDL-1 in GeparNUEVO



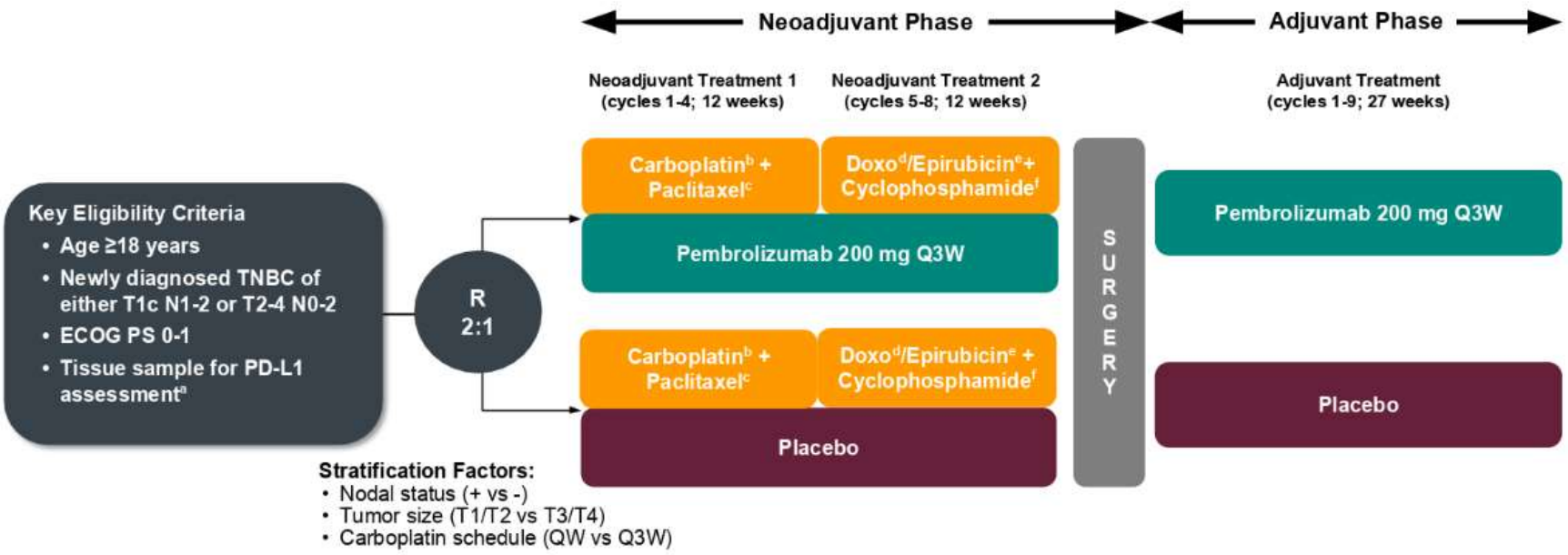
Loibl et al. Ann Oncol 2019

GeparNuevo: Response based on TMB (Seliger et al, abstract 588)



Median TMB: 1.52 mutations/MB
TMB low: below 66.7% percentile; TMB high: above 66.7% percentile
Top TMB tertile PCR 58% versus low TMB tertile 38%

KEYNOTE 522 – Study design

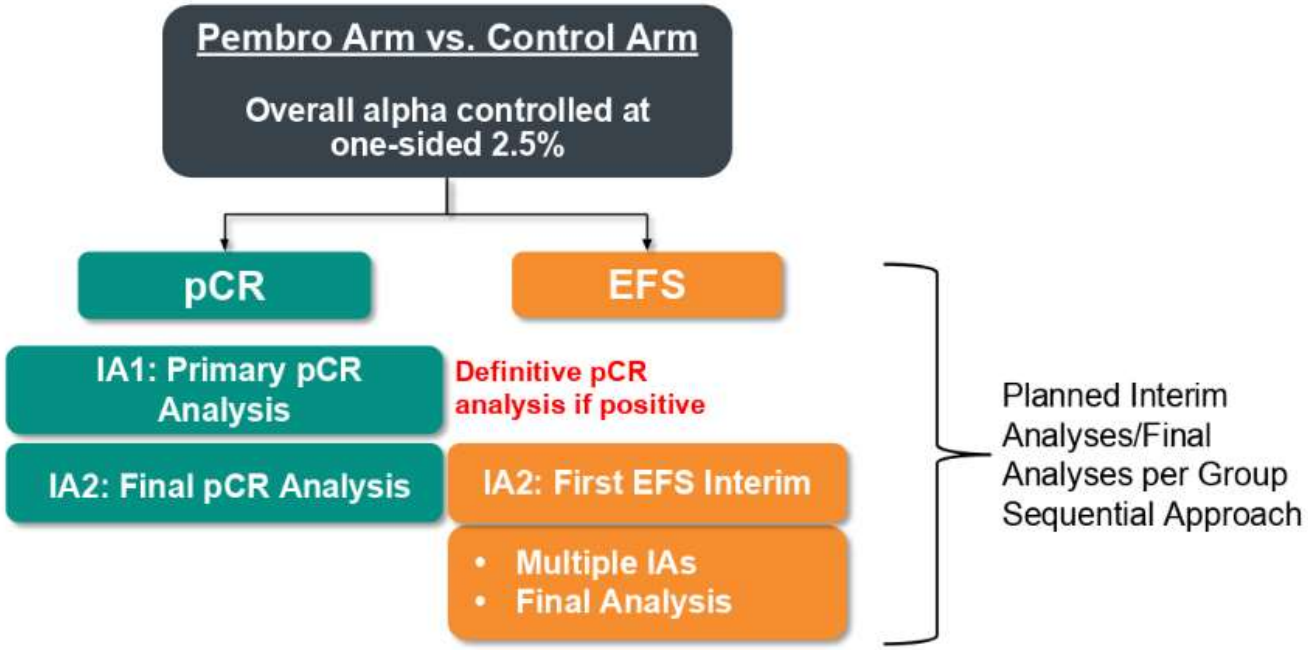


KEYNOTE 522 – Study endpoints

Interims Completed:

✔First IA (IA1) performed after last subject enrolled; Data Cutoff: Sep 24, 2018

✔Second IA (IA2) performed ~24 mo after first subject enrolled; Data Cutoff: Apr 24, 2019



- **IA1:** Primary pCR analysis to test primary hypothesis of pCR based on prespecified first 602 subjects (pre-calculated *P* value boundary for significance of 0.003)
- **IA2:** If pCR hypothesis successful at IA1 (thus definitive), pCR will not be formally tested at IA2
- EFS at IA2 (first interim of EFS): precalculated *P* value boundary for significance of 0.000051 (HR <0.4)

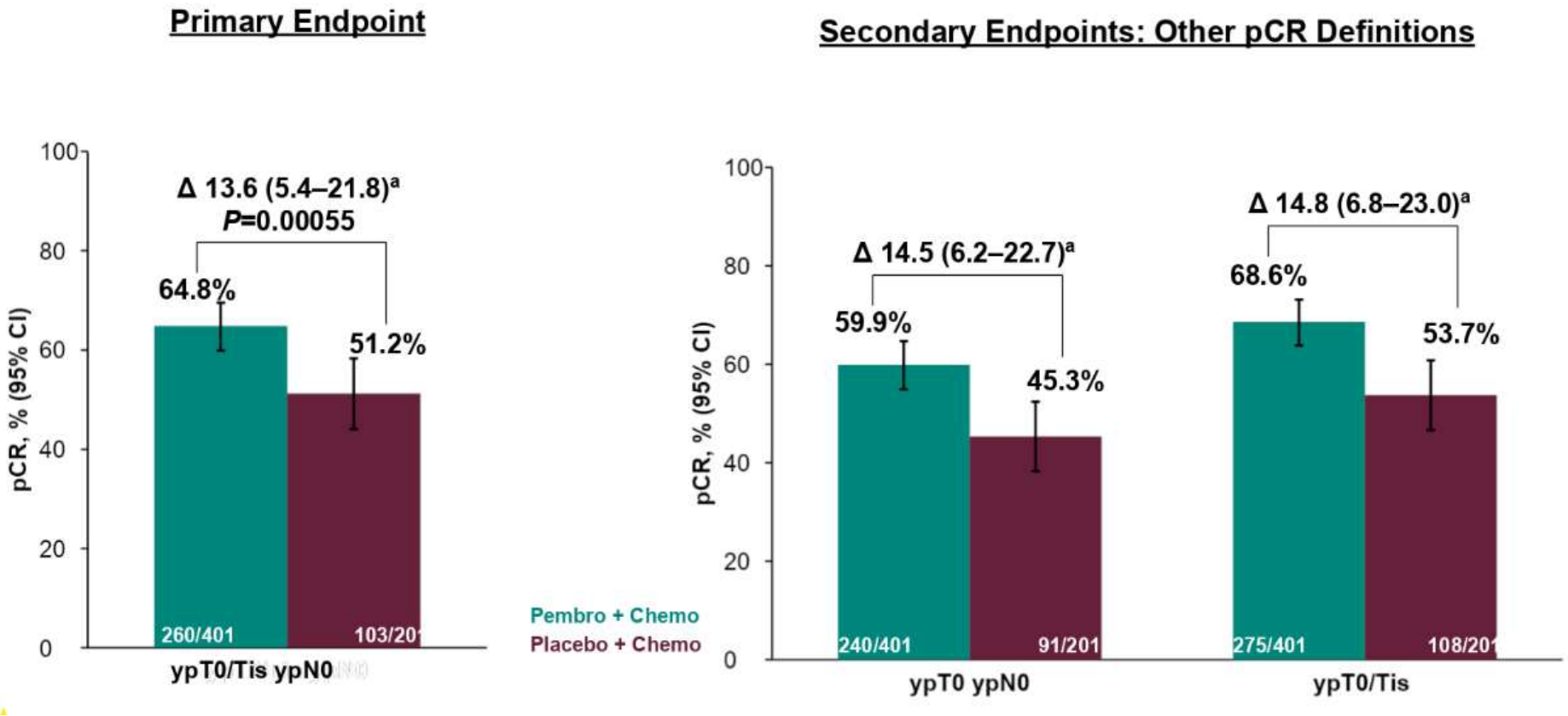
ESMO 2019

Baseline Characteristics

Characteristic, n (%)	All Subjects, N = 1174	
	Pembro + Chemo N = 784	Placebo + Chemo N = 390
Age, median (range), yrs	49 (22-80)	48 (24-79)
ECOG PS 1	106 (13.5)	49 (12.6)
PD-L1–positive[a]	656 (83.7)	317 (81.3)
Carboplatin schedule		
QW	449 (57.3)	223 (57.2)
Q3W	335 (42.7)	167 (42.8)
Tumor size		
T1/T2	580 (74.0)	290 (74.4)
T3/T4	204 (26.0)	100 (25.6)
Nodal involvement		
Positive	405 (51.7)	200 (51.3)
Negative	379 (48.3)	190 (48.7)

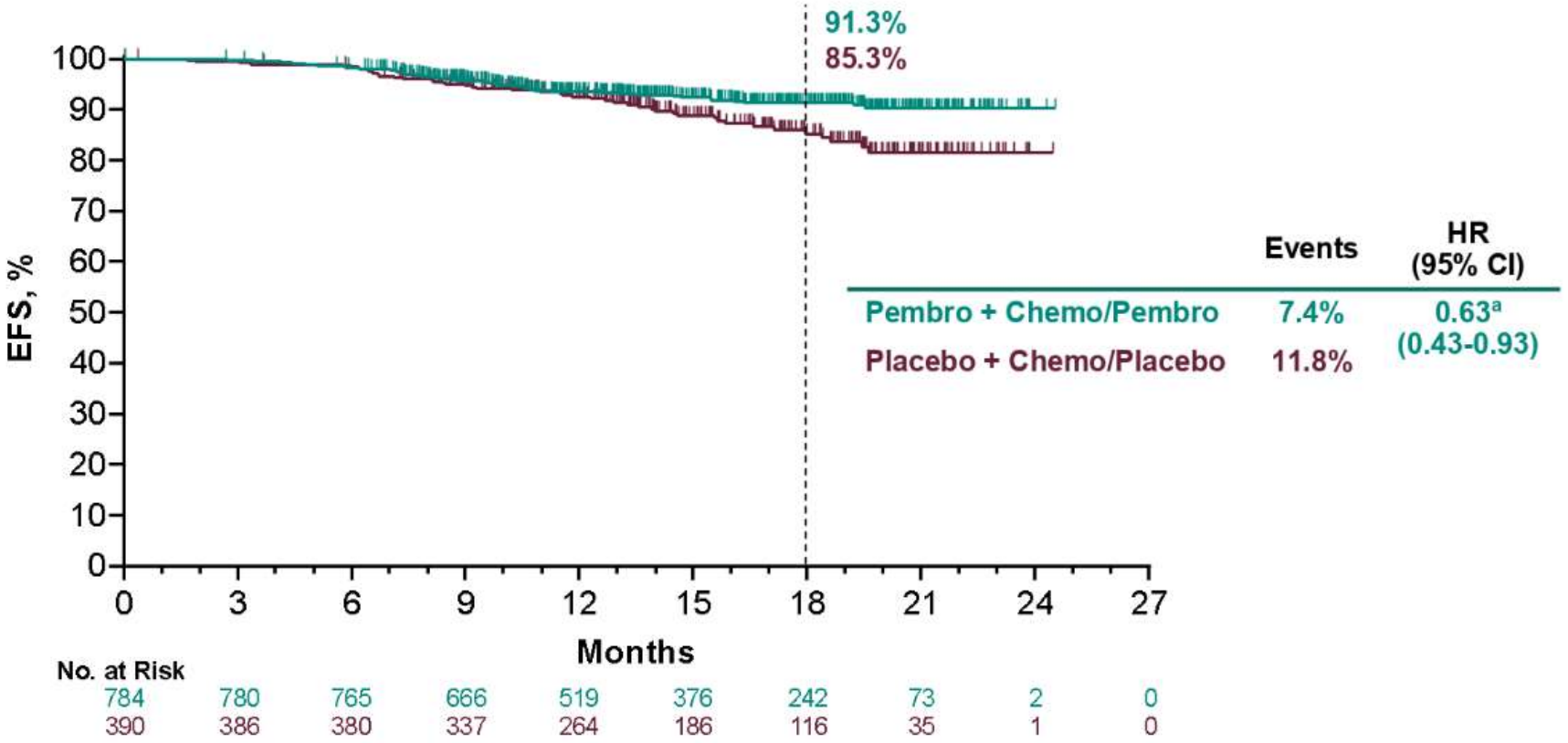
ESMO 2019

Pathological Complete Response at AI2



ESMO 2019

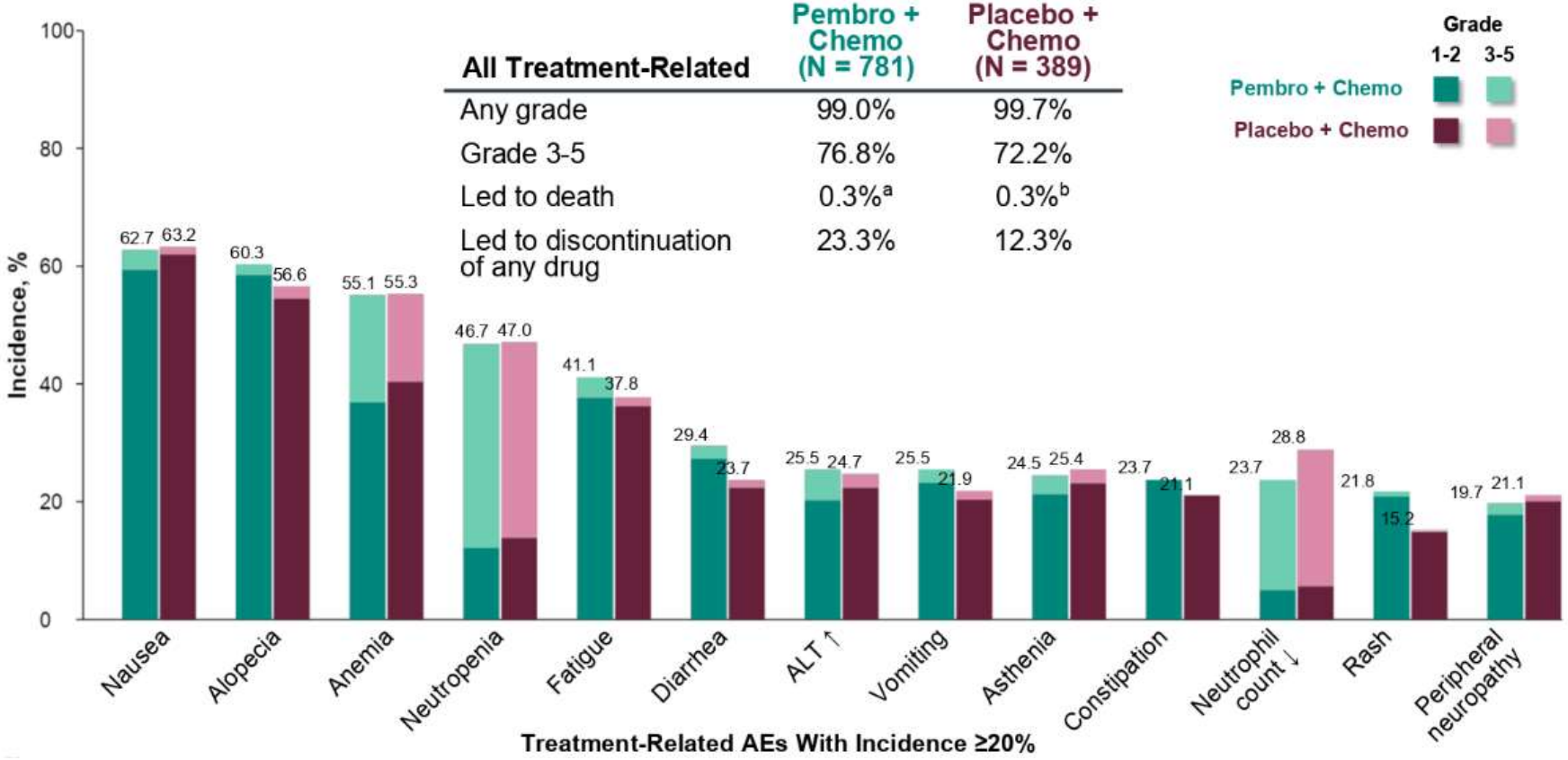
Event free survival at AI2



ESMO 2019

Treatment related AEs in Neoadjuvant Phase

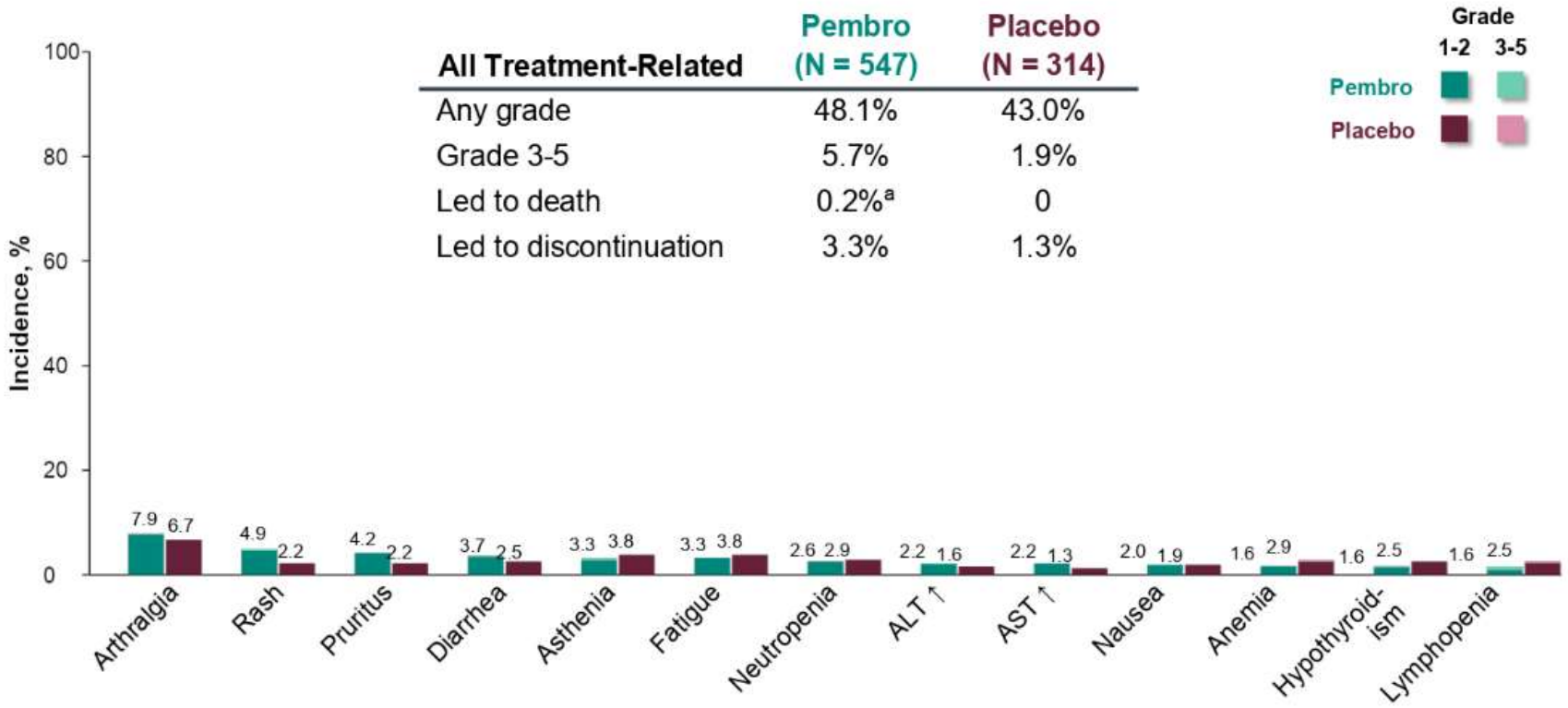
All Treatment-Related	Pembro + Chemo (N = 781)	Placebo + Chemo (N = 389)
Any grade	99.0%	99.7%
Grade 3-5	76.8%	72.2%
Led to death	0.3%[a]	0.3%[b]
Led to discontinuation of any drug	23.3%	12.3%



ESMO 2019

Treatment related AEs in Adjuvant Phase

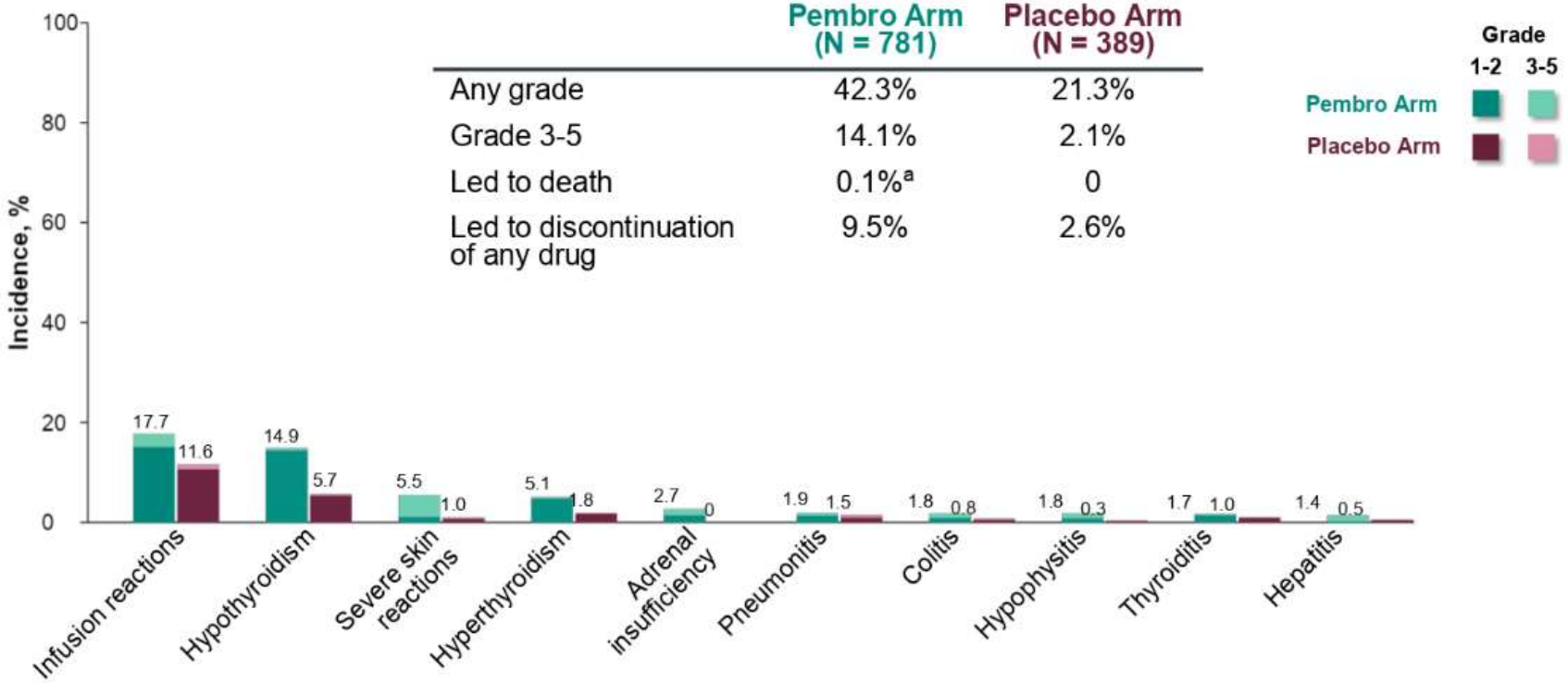
All Treatment-Related	Pembro (N = 547)	Placebo (N = 314)
Any grade	48.1%	43.0%
Grade 3-5	5.7%	1.9%
Led to death	0.2%[a]	0
Led to discontinuation	3.3%	1.3%



ESMO 2019

Immune mediated AEs In Combined Phase

	Pembro Arm (N = 781)	Placebo Arm (N = 389)
Any grade	42.3%	21.3%
Grade 3-5	14.1%	2.1%
Led to death	0.1%[a]	0
Led to discontinuation of any drug	9.5%	2.6%



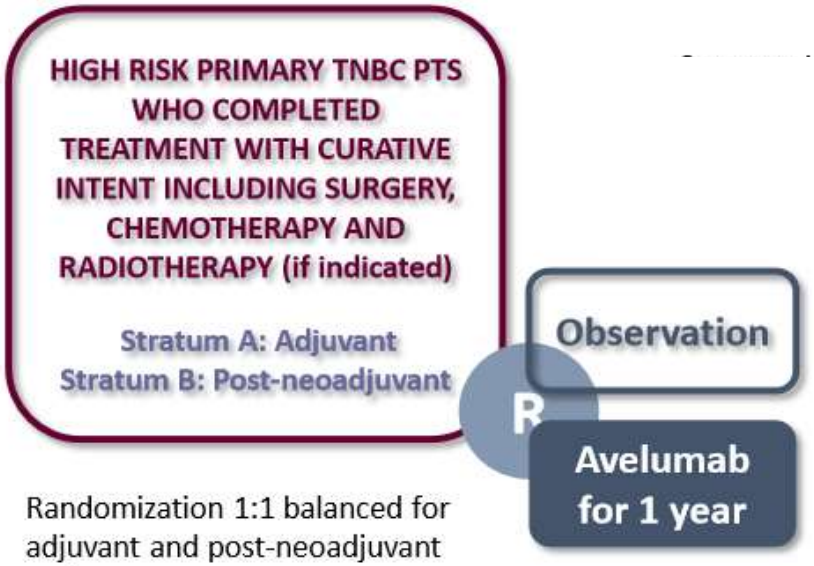
Immune-Mediated AEs and Infusion Reactions With Incidence ≥10 Patients

ESMO 2019

Phase III anti PD-1/PDL-1 neoadjuvant TNBC Trials

Trial	Trial Description	Primary Endpoint(s)	Date Open (Study End)
IMpassion031	Status: Recruiting N=204 Treatment Arms: 1) Atezolizumab+nab-paclitaxel→Atezo+ddAC→Surgery→Atezox1yrs 2) Placebo+nab-paclitaxel→placebo+ddAC→Surgery	pCR	Jul 2017 (Sept 2021)
KeyNote-522	Status: Recruiting N=1150 Treatment Arms: 1) Pembrolizumab+paclitaxel+carbo→Pembro+AC→Surgery→Pembro x9 cycles 2) Placebo+paclitaxel+carbo→placebo+AC→Surgery→placebo	pCR EFS	Mar 2017 (Mar 2025)
NeoTRIP	Status: Closed N=272 Treatment Arms: 1) Atezolizumab+nab-paclitaxel+carbo→Surgery→EC/AC 2) nab-paclitaxel+carbo→Surgery→EC/AC	EFS	Apr 2016 (Oct 2022)
NSABP B-59 GeparDouze	Status: Active N=1520 Treatment Arms: 1) paclitaxel+carbo+placebo→AC→Surgery→placebox1yrs 2) paclitaxel+carbo+Atezolizumab→AC→Surgery→Atezox1yrs	pCR EFS	Dec 2017 (Jun 2024)

Future Perspective



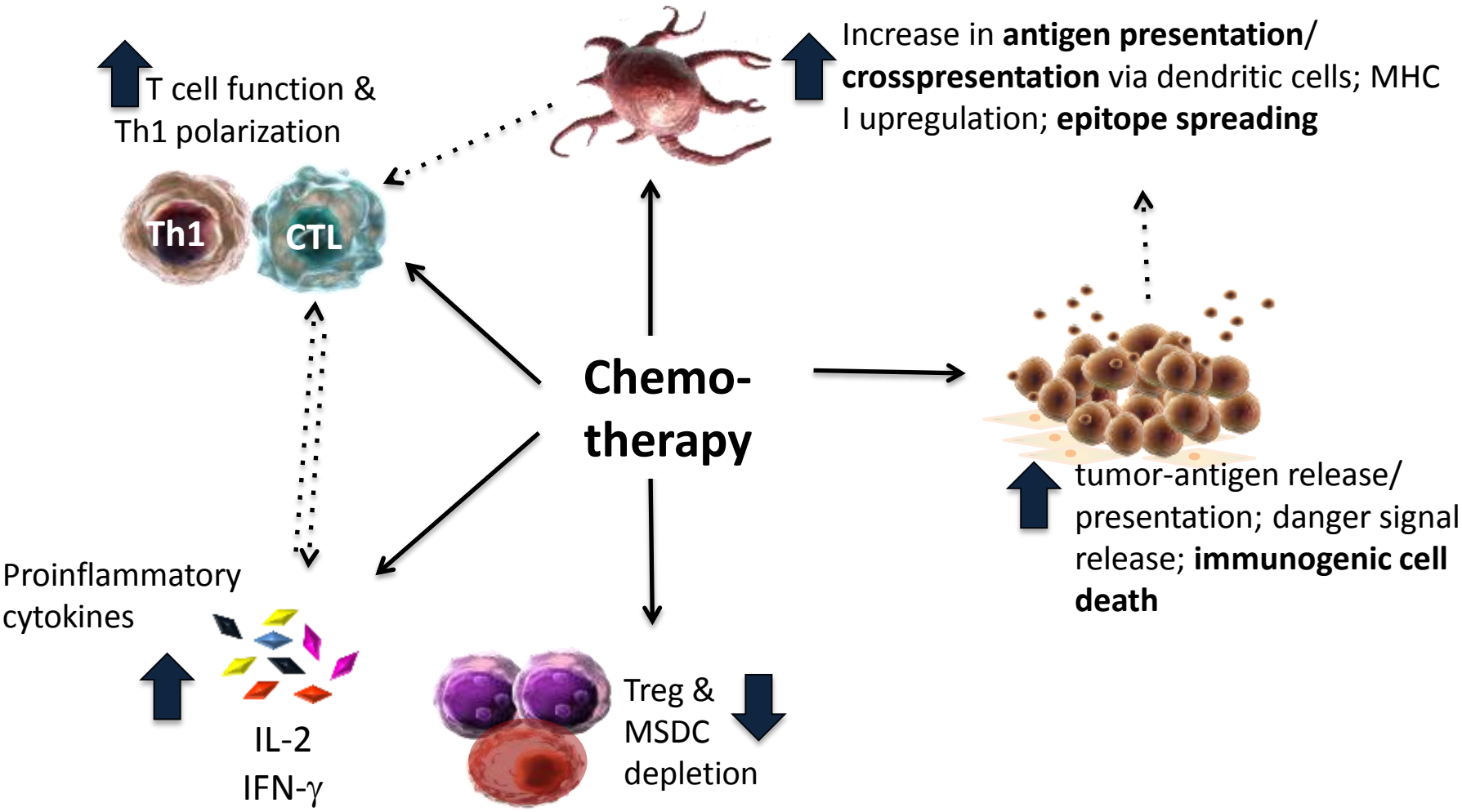
Randomization 1:1 balanced for adjuvant and post-neoadjuvant patients.

Co-primary endpoints: 1. DFS in all-comers; 2. DFS in PD-L1+ patients
Secondary endpoints: OS, Safety, Biomarkers

n=335 (for the 1st co-primary endpoint)

A-BRAVE-TRIAL

Chemotherapy: Pleiotropic stimulatory effects on the immune system



Refining immunotherapy strategies: which is the best CT partner?

Drug	Effect on immune system
Taxanes	• Enhances T cell and NK cell function • Increases recruitment of TIL • Increase efficacy of immuno-stimulatory agents
Doxorubicin	• Induces immunogenic cell death • Increases proliferation of CD8 T cells • Stimulates antigen presentation by DCs • Stimulates MCP1 and M6PR
Cyclophosphamide	• Induces immunogenic cell death • Suppresses Treg inhibitory functions and restores the proliferative capacity of effector T cells and NK cell cytotoxicity
Gemcitabine	• Reduces the number of myeloid suppressor cells • Increases the antitumor activity of CD8(+) T cells and activated NK cells
Oxaliplatin	• Induces immunogenic cell death • Increases MHC I complex • Inhibits PD-L2

Kono et al. Cell Death and Disease 2013

Immunotherapy in (neo)-adj Breast Cancer

- Is there a role for improving response to immune checkpoint inhibitors by selecting the best chemotherapeutic partner?
- Need for better biomarkers and for an understanding of their relationship to one another
- Re-thinking targeted therapies in combination with immune checkpoint inhibitors
- Need for selection of adequate endpoints for future clinical trials testing immunotherapy in TNBC.

GRAZIE