AT THE FOREFRONT
UChicago Medicine

The Emerging Role of Immunotherapy for Triple-Negative Breast Cancer: Updates from the 2019 SABCS

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Nebraska Oncology Society
Omaha, Nebraska
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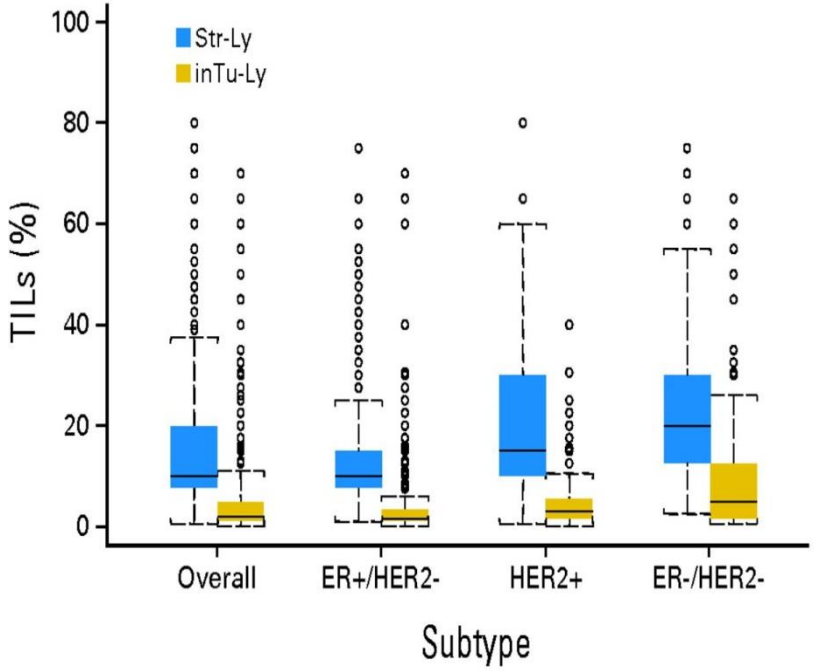
Disclosures

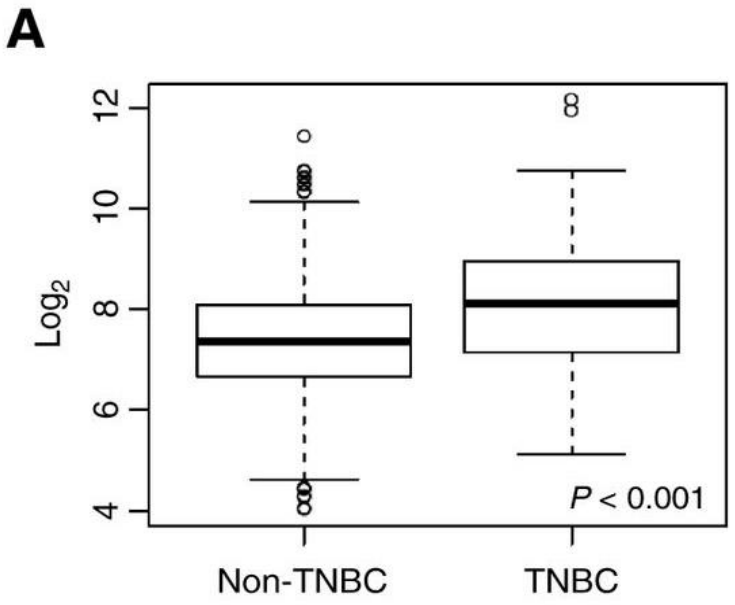
- Consultant or advisory role: AstraZeneca, Celgene, Clovis, Daichii, G1 Therapeutics, Genentech, Macrogenics, Merck, Pfizer, Puma Biotechnology, Syndax
- Data Safety Monitoring Board: G1 Therapeutics
- Research Funding: AstraZeneca, Celgene, Corcept Therapeutics, Genentech, Immunomedics, Merck, Odonate Therapeutics, Pfizer, Seattle Genetics
- **There are no conflicts of interest for this presentation**

Immune Checkpoint Inhibition in TNBC: Rationale

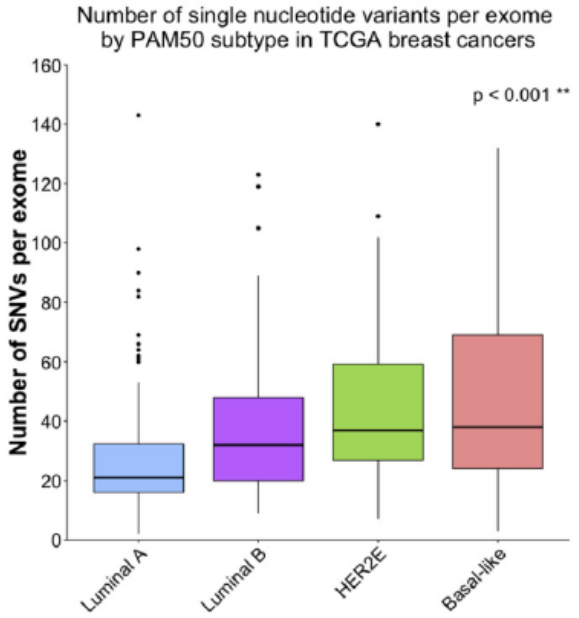
Tumor Infiltrating Lymphocytes



PD-L1 Expression



Nonsynonymous Mutations



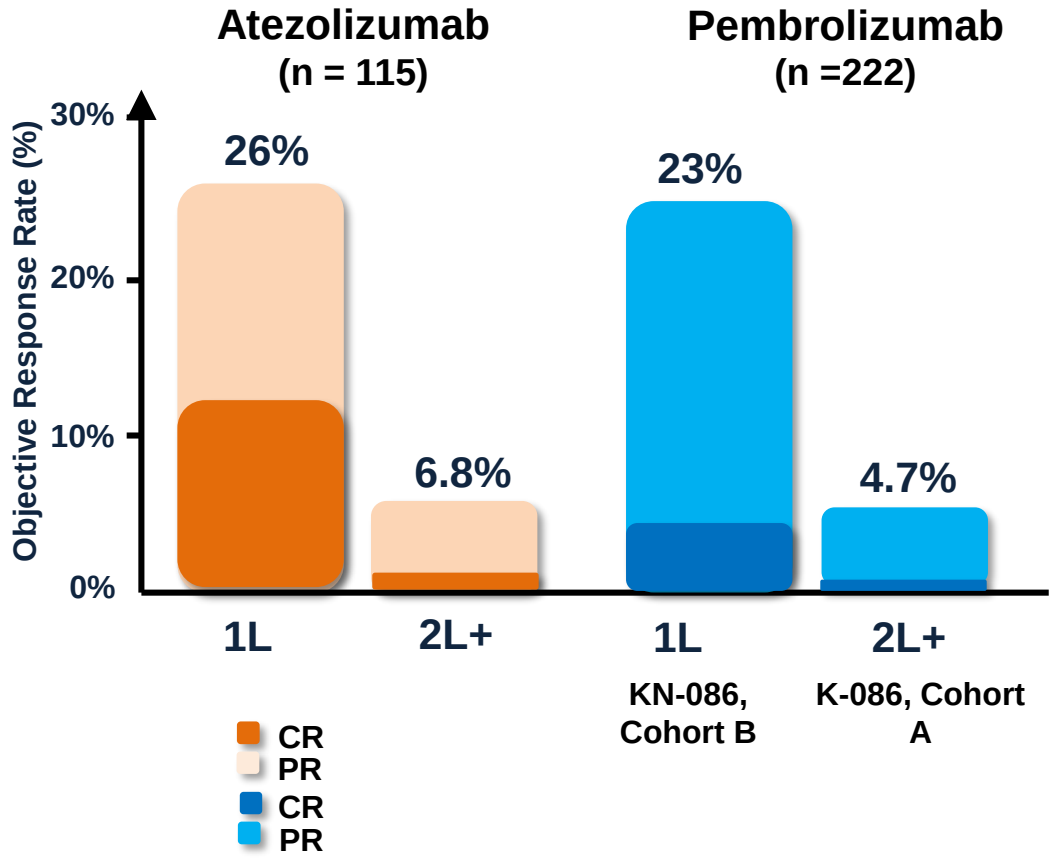
Loi et al, JCO 2013; Mittendorf et al, Cancer Immunol Res 2014; Luen et al, The Breast 2016

Clinical Trials of Immune Checkpoint Inhibitors in Advanced Stage Triple-Negative Breast Cancer

Checkpoint Inhibition in TNBC: Modest Response Rates with Monotherapy

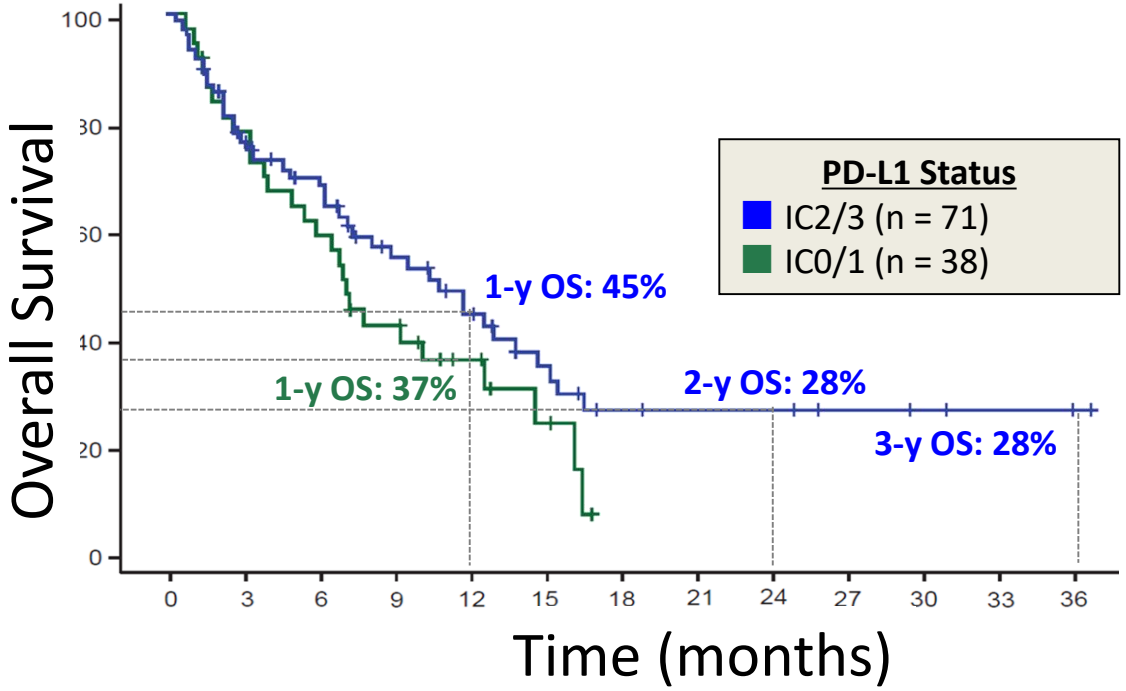
Agent	N	ORR	ORR (PD-L1+)*
Pembrolizumab			
•Single agent (KN-012)	32	18.5%	18.5%
•Single agent (KN-086-A)	170	4.7%	4.8%
•Single agent (KN-086-B)	84	23.0%	23.0%
Atezolizumab			
•Single agent	115	10.0%	13.0%
Avelumab			
•Single agent (Javelin)	58	8.6%	44.4%

*Studies used different antibodies and cutoffs for PD-L1 positivity



Nanda et al, JCO 2016; Dirix et al, BCRT 2017; Emens et al, JAMA Onc 2018; Adams et al, Ann Onc 2018

Atezolizumab Monotherapy: Overall Survival by PD-L1* Status

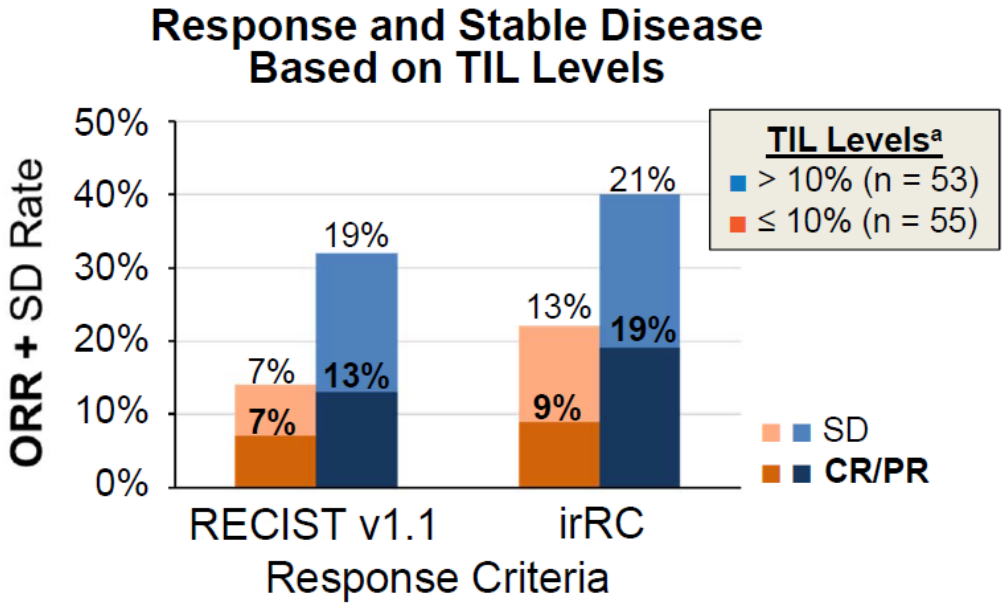


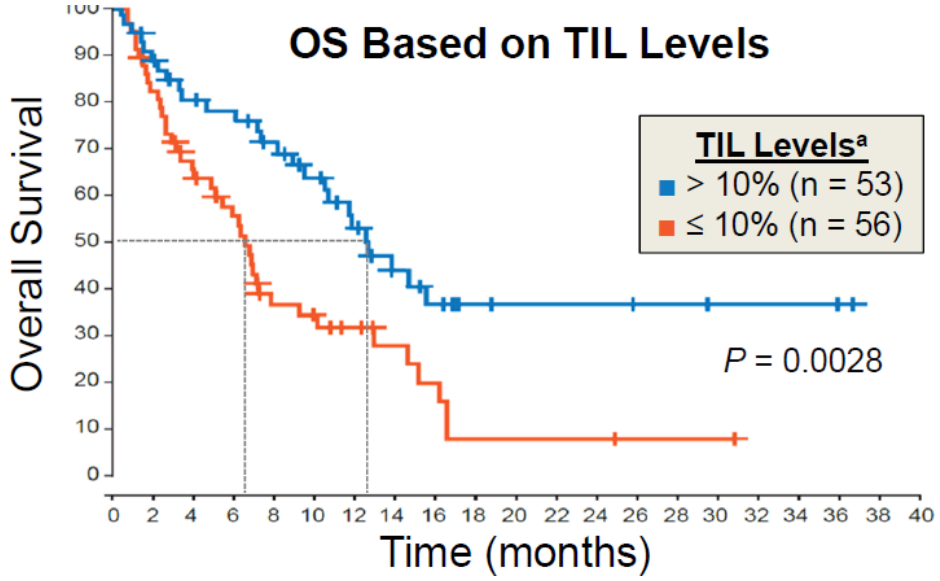
	All Pts (n = 113)	PD-L1 Status	
		IC2/3 (n = 71)	IC0/1 (n = 38)
mOS (95% CI)	9.3 mo (7.0, 12.6)	**10.7 mo** (7.2, 14.7)	7.1 mo (5.1, 12.6)

*Using Ventana SP142 Assay

Schmid et al, AACR 2017; Emens et al, Jama Onc 2018

Higher ORR and OS with Higher TILs with Atezolizumab Monotherapy

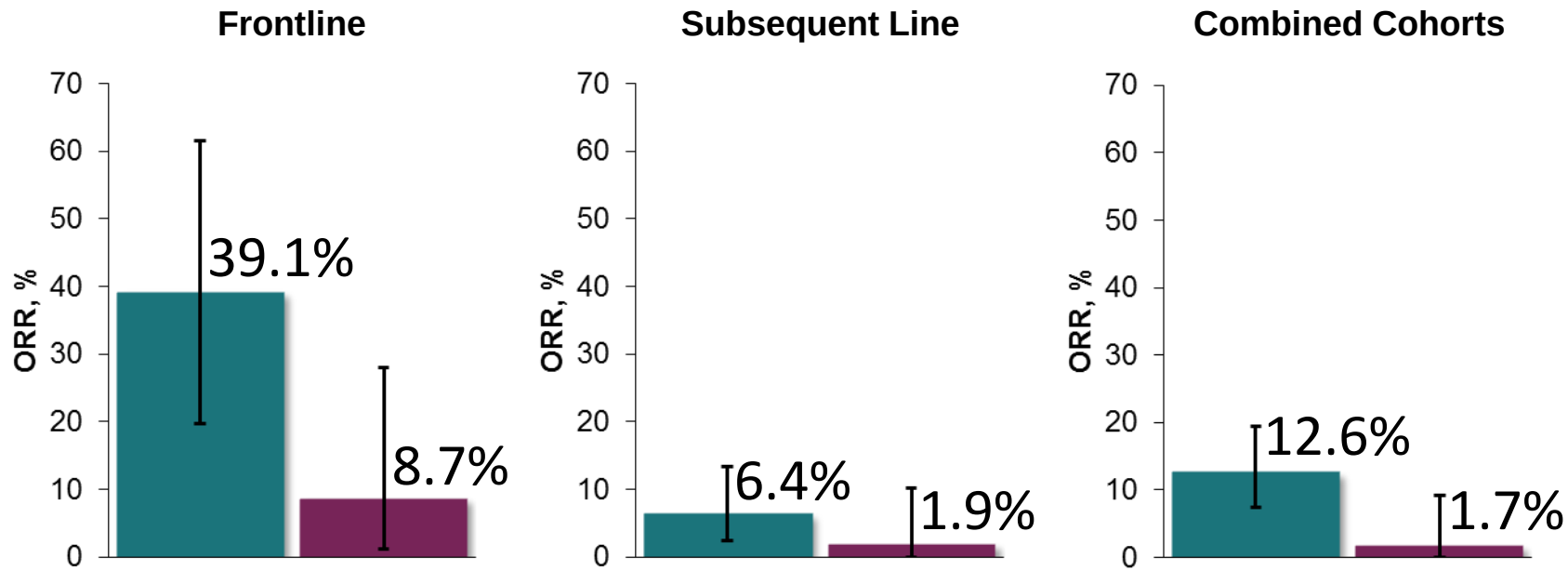




	≤ 10% TILs (n = 53)	> 10% TILs (n = 56)
mOS (95% CI)	6.6 mo (4.9, 10.2)	12.6 mo (10.5, NA)

Schmid et al. AACR 2017; Emens et al, Jama Onc 2018

KEYNOTE 086: Response Rate by Line of Therapy and sTILs with pembrolizumab monotherapy

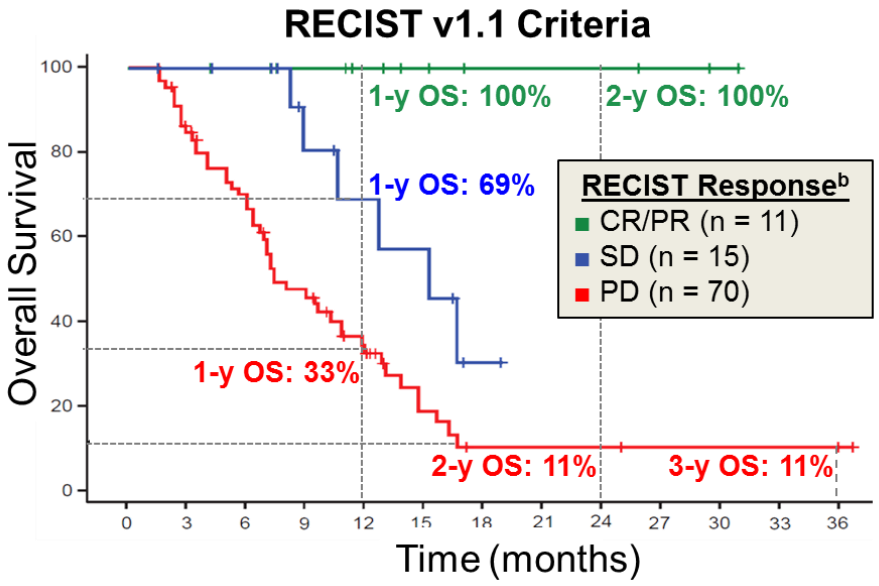


sTIL level	≥17.5%	<17.5%	≥5%	<5%	≥5%	<5%
n	23	23	94	53	135	58
Responders	9	2	6	1	17	1
Ongoing responses	5	2	3	1	10	1

Loi et al. ESMO 2017

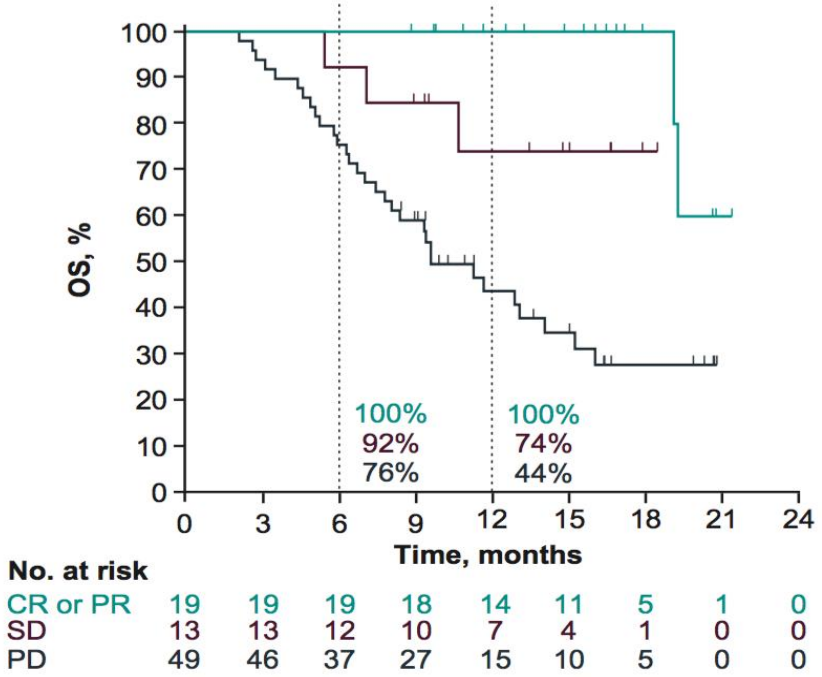
Atezolizumab and Pembrolizumab Monotherapy: Durable Responses

Atezolizumab



N=96
Median OS: 9.3 mo

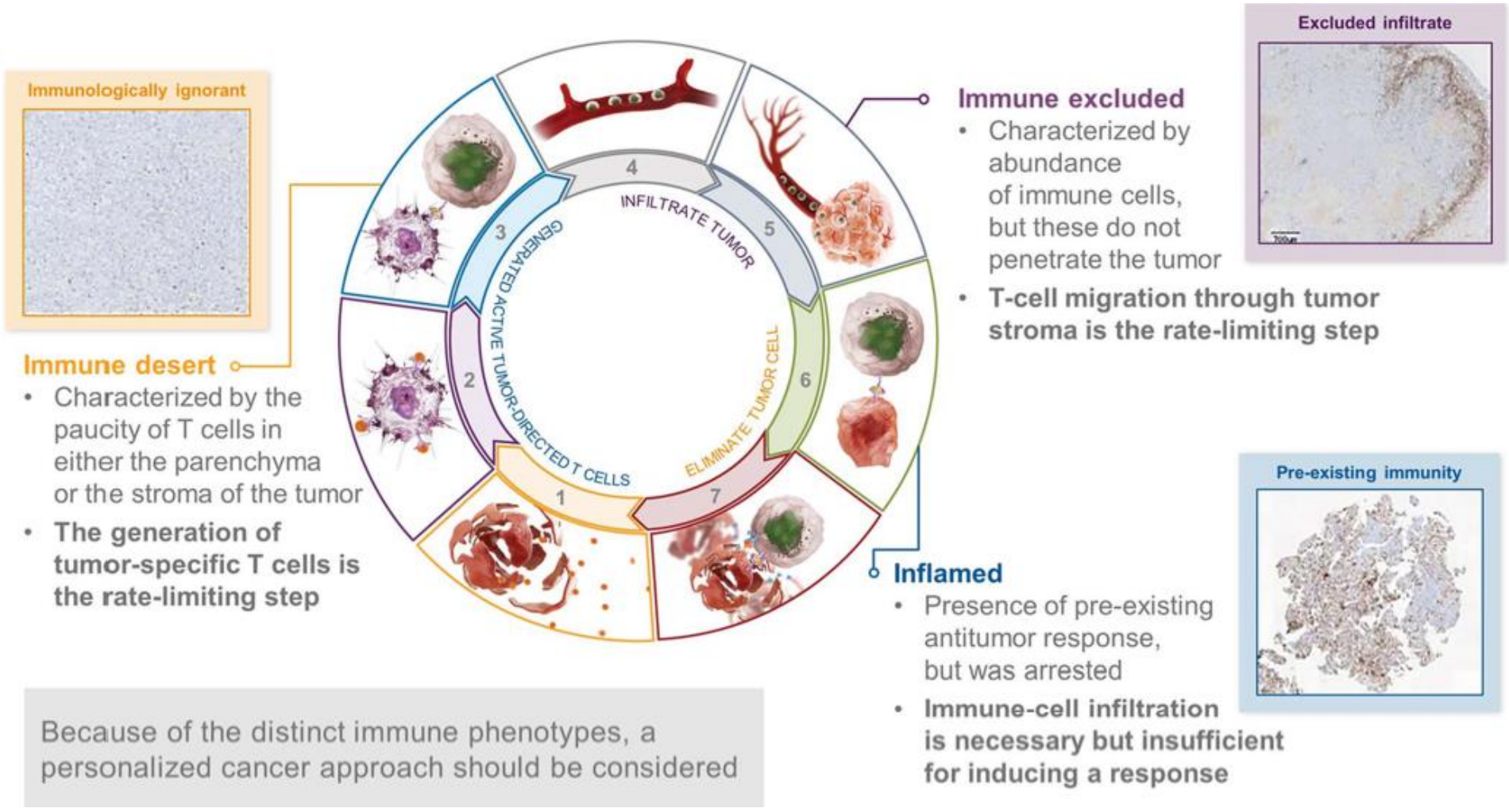
Pembrolizumab



N=81
Median OS: 19.2 mo

Adams et al, Ann Onc 2018; Emens et al, Jama Onc 2018

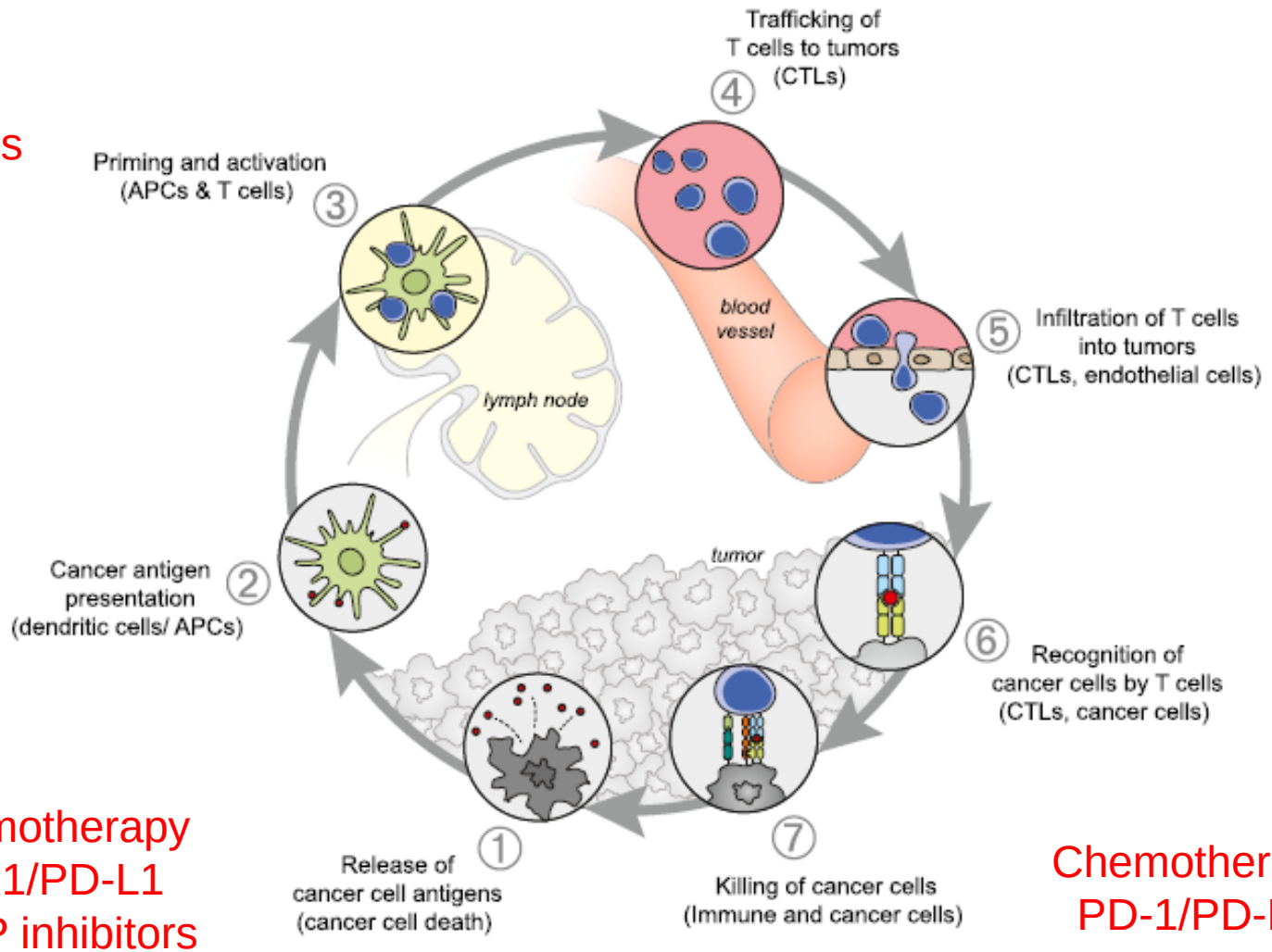
Need for personalized approaches to stimulate T-cell mediated antitumor immunity



Hedge et al, CCR 2016; Chen and Melman, Nature 2017

Cancer-Immunity Cycle: Combinations in Breast Cancer

AKT inhibitors



Chemotherapy
PD-1/PD-L1
VEGF inhibitors
STING
PARP inhibitors

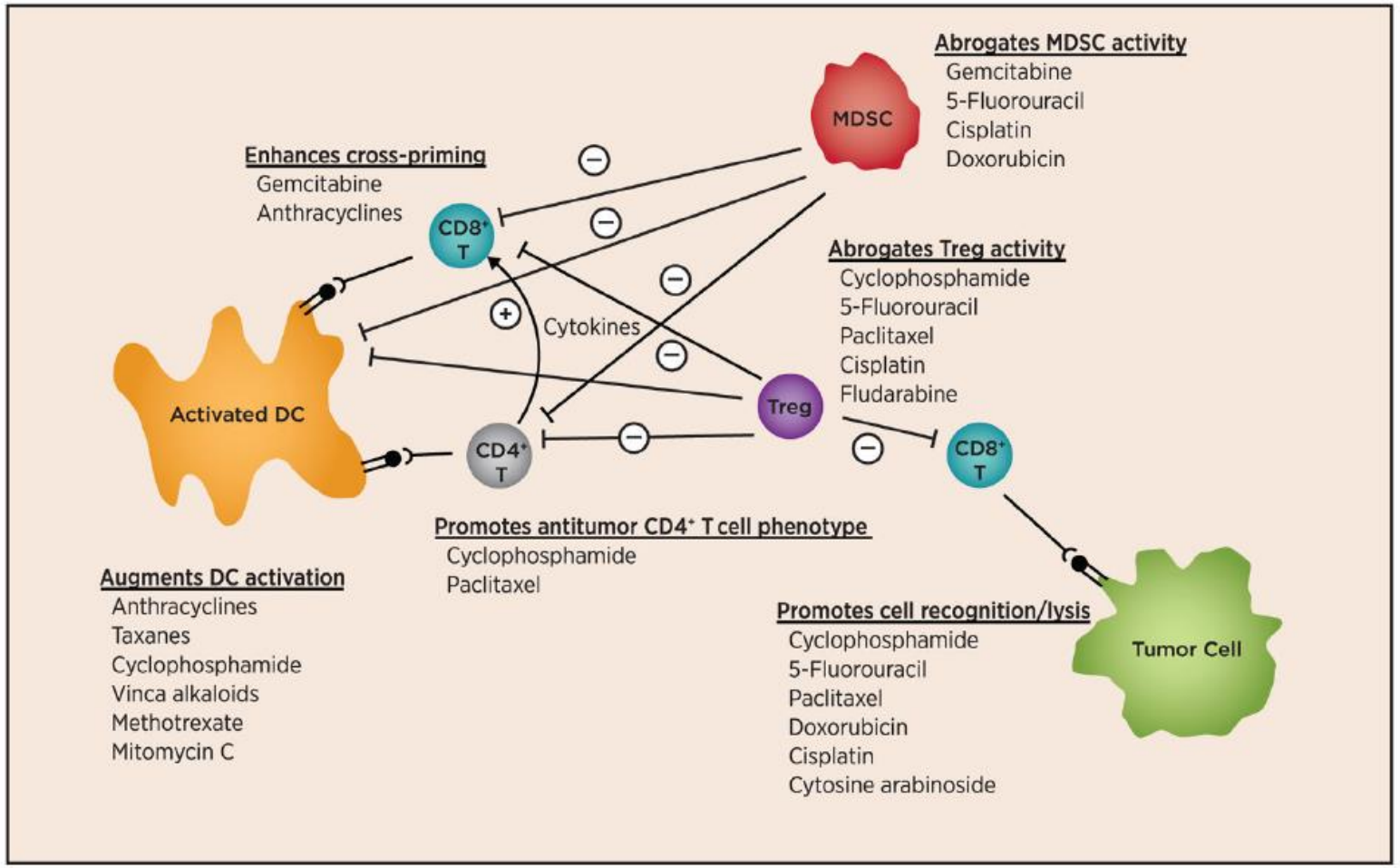
MEK inhibitors

Chemotherapy
PD-1/PD-L1
PARP inhibitors

Chemotherapy
PD-1/PD-L1

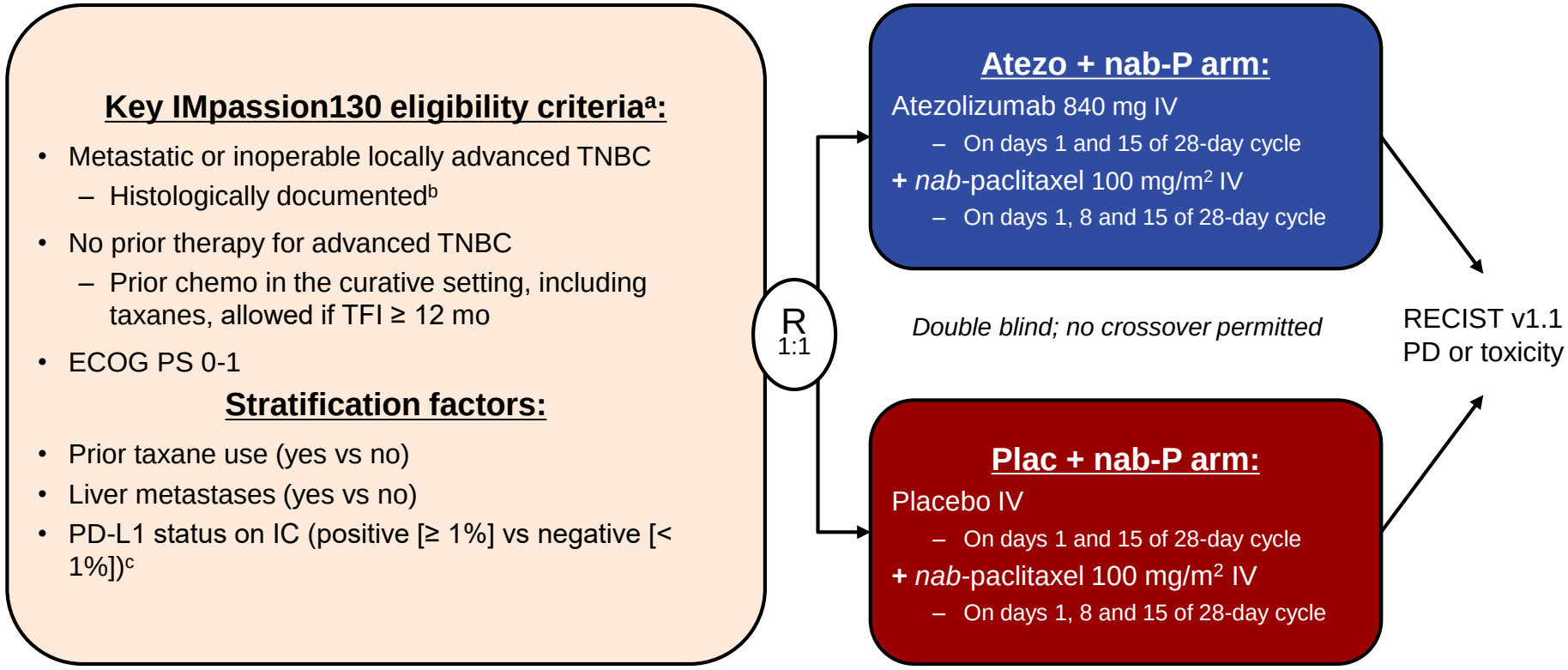
Chen and Mellmen, Immunity, 2013

Combining Checkpoint Inhibitors with Chemotherapy



Emens et al, Cancer Imm Res 2015

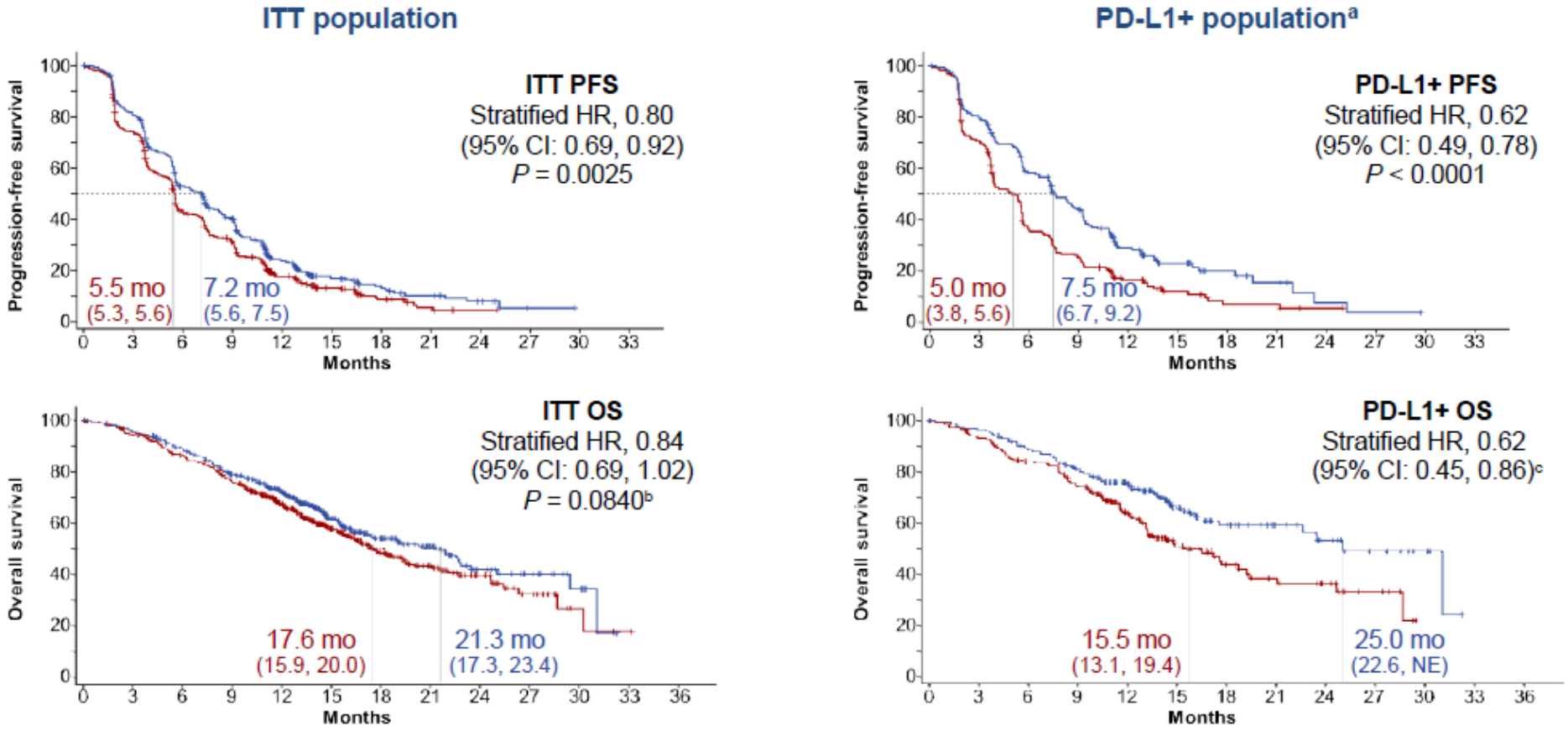
IMpassion130 study design



- Co-primary endpoints were PFS and OS in the ITT and PD-L1+ populations[d]
  - Key secondary efficacy endpoints (ORR and DOR) and safety were also evaluated

Schmid et al, NEJM 2018

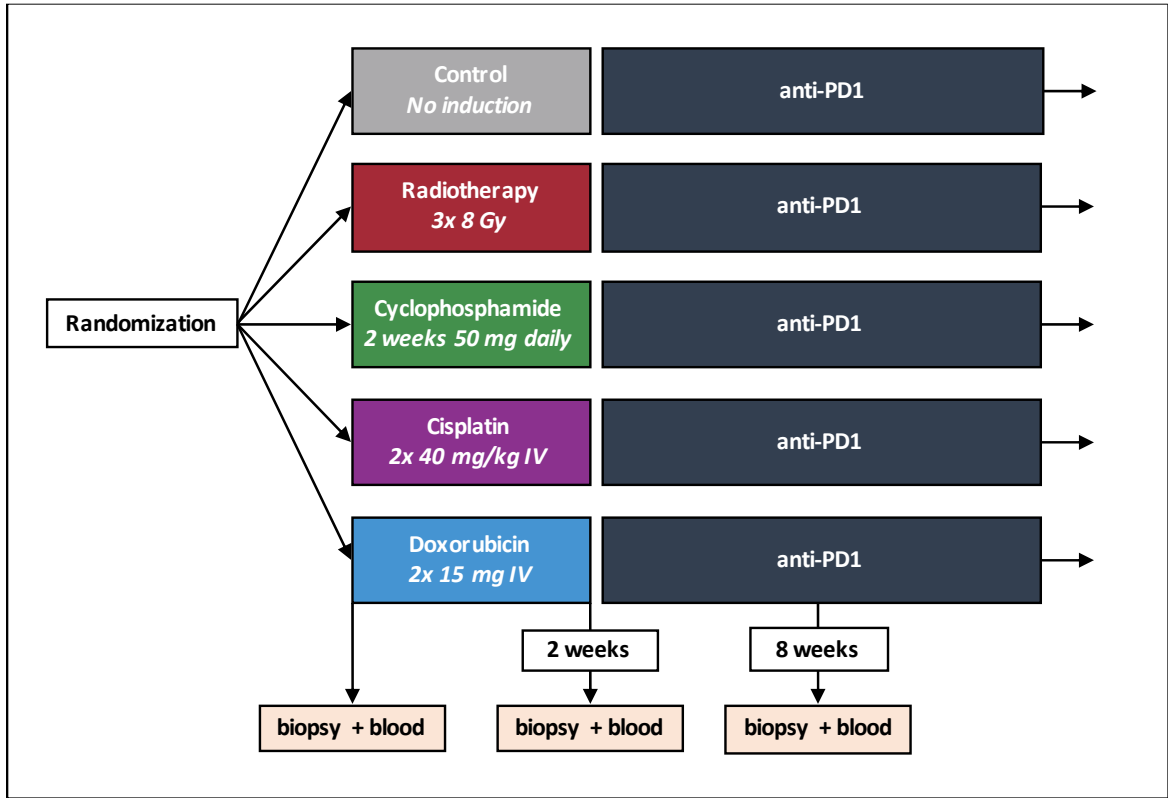
IMpassion 130 PFS/OS in IIT/PD-L1+*

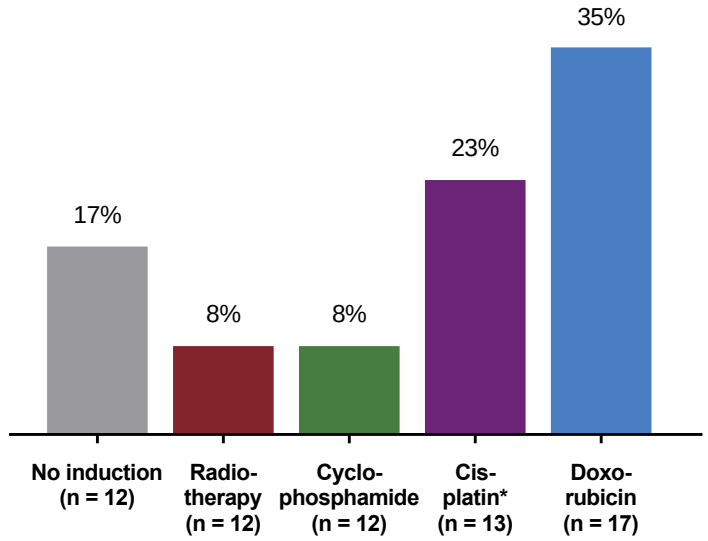


*Using Ventana SP142 Assay

Schmid et al, NEJM 2018

TONIC Trial: Induction followed by Nivolumab Monotherapy in Metastatic Triple-Negative Breast Cancer





Kok et al, ASCO 2018; Voorwerk et al, Nature Medicine 2019

Durvalumab compared to maintenance chemotherapy in patients with metastatic breast cancer : Results from phase II randomized trial SAFIR02-IMMUNO

Florence Dalenc[1], Ingrid Garberis[2], Thomas Filleron[1], Thomas Bachelot[3], Monica Arnedos[2], Mario Campone[4,5] , Marie-Paul Sablin[6], Hervé Bonnefoi[7], Marta Jimenez[8], Alexandra Jacquet[8], Fabrice André[2]

[1]Institut Claudius Regaud, Toulouse, France; [2]Gustave Roussy, Villejuif, France; [3]Centre Léon Bérard, Lyon, France; [4]ICO- Centre René Gauducheau, Nantes, France; [5]ICO- Centre Paul Papin, Angers, France; [6]Institut Curie, Paris, France; [7]Institut Bergonié, Bordeaux, France; [8]UNICANCER R&D, Paris, France.

San Antonio Breast Cancer Symposium, 10-14 december 2019

SAFIR-02 BREAST : Study Design

Metastatic breast cancer or locally advanced disease

HER-2 negative

Resistant to endocrine therapy if ER+

1st line or 2d chemotherapy

n=1462 patients

Frozen or FFPE or ctDNA sample (collected before C3 chemotherapy)

NGS
CGH array

OR/SD after 6-8 CT cycles
(or 4 cycles if stopped for tox)

Targetable molecular alteration ?

YES

R 2:1

Targeted therapy matched to genomics

Maintenance chemo without switch

1ry objective
N=240
Ongoing

NO

R 2:1

Durvalumab

Maintenance chemo without switch

2ry objective
N=199

SABCS 2019:
GS3-02

Patient characteristics

Characteristics	Durvalumab arm A (n=131)	Control arm B (n=68)	p value
Median age	56 (27-79)	56 (24-77)	p = 0.5308
ECOG= 0	72 (59.5%)	37 (56.1%)	p = 0.6481
≥ 3 metastatic sites	55 (42.0%)	30 (44.1%)	p = 0.7730
Liver metastases	61 (46.6%)	34 (50.0%)	p = 0.6454
Lung metastases	35 (26.7%)	20 (29.4%)	p = 0.6869
IHC subtypes defined on primary tumor (n=192) TNBC HR+/HER2- HER2+	 47 (37.6%) 76 (60.8%) 2 (1.0%)	 35 (52.2%) 32 (47.8%) 0 (0.0%)	p = 0.0918
PDL1 expression (≥ 1% IC, S142) (n=133)	28 (32.6%)	16 (34.0%)	
1st Line chemotherapy	118 (90.1%)	61 (89.7%)	
CT regimen in the maintenance arm	NA	No maintenance n=10 Paclitaxel n=16 Capecitabine n=10 (F)EC n=10	
Objective response to induction CT	52 (39.7%)	29 (42.6%)	

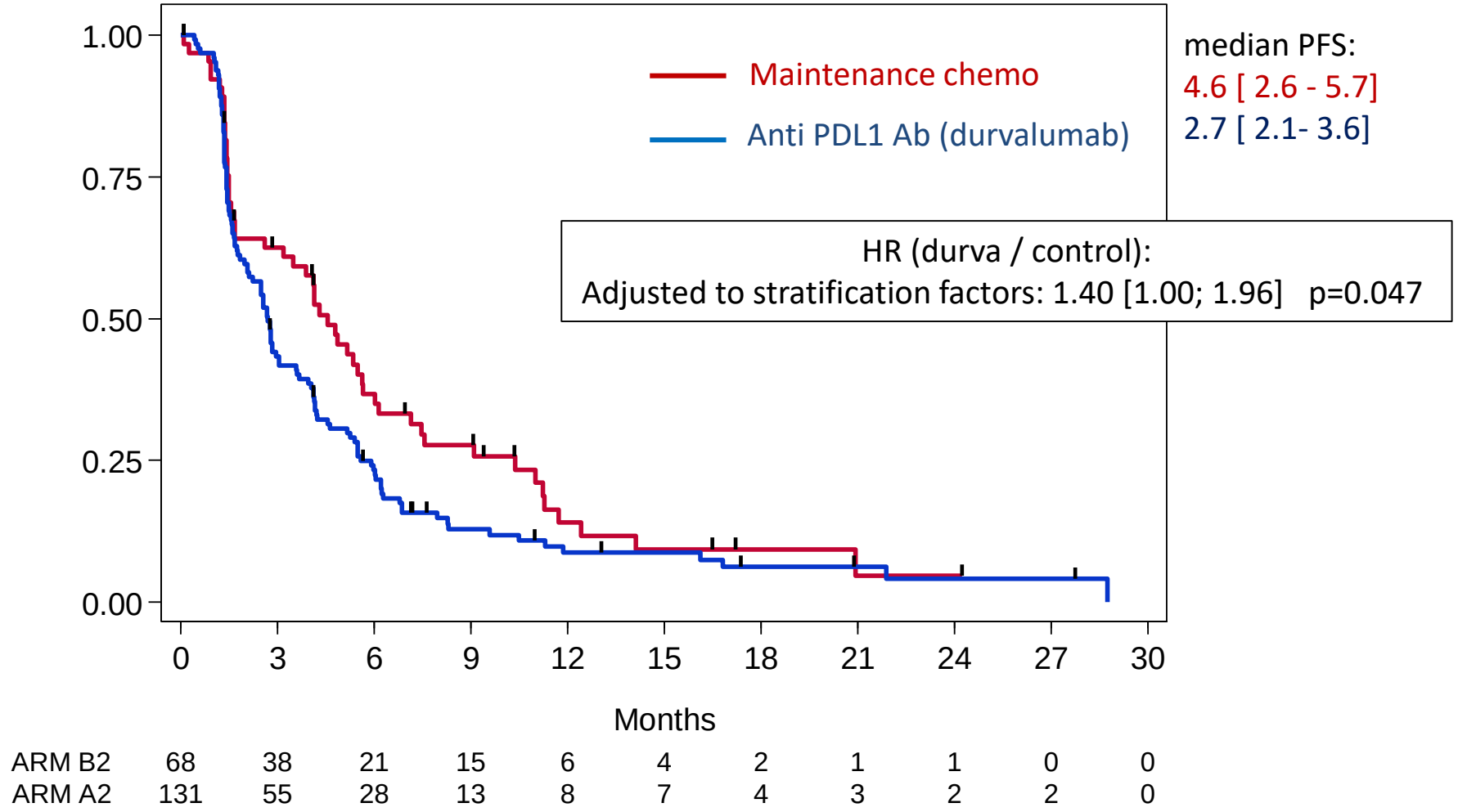
San Antonio Breast Cancer Symposium, 10-14 december 2019

Description of PDL1+ tumors

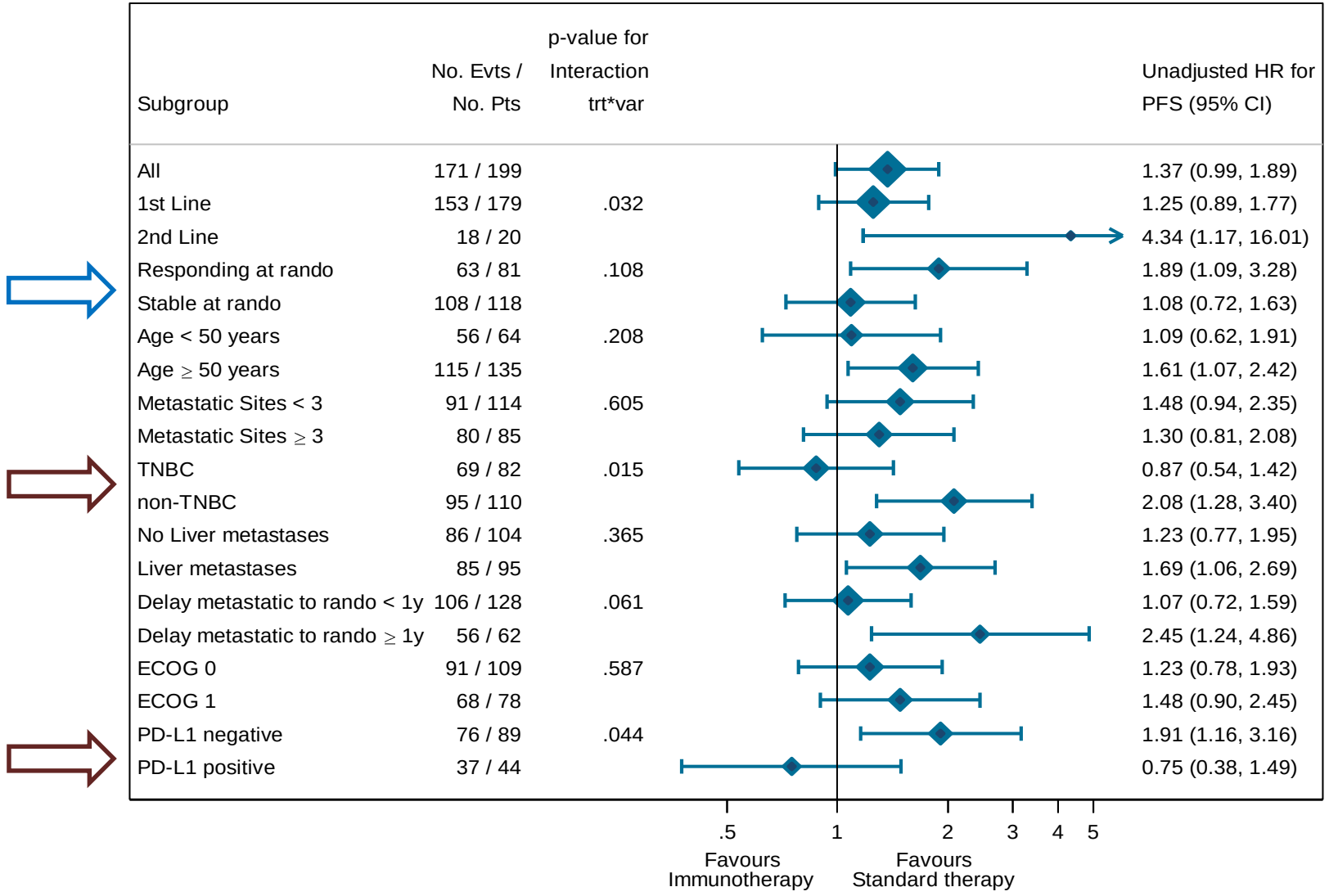
	PDL1+ tumors	PDL1- tumors
TNBC n=61	32 (52.4%)	29 (47.6%)
HR+ n=67	10 (14.9%)	57 (85.1%)

PDL1 status was determined by IHC (≥ 1% IC, S142) (n=133) on metastasis

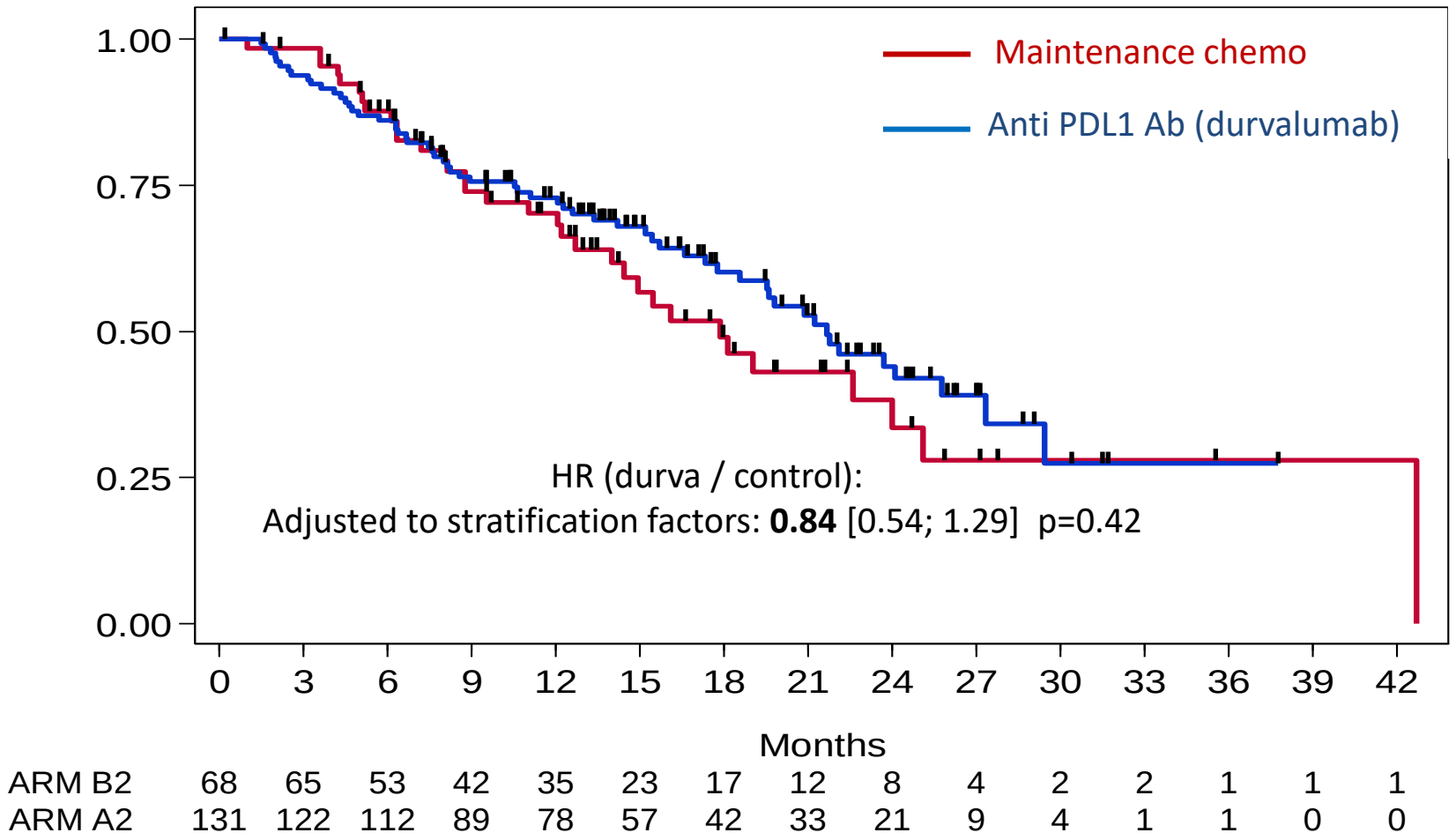
PFS in the overall population (of Immunosubstudy)



PFS in subgroups of interest



OS in the overall population (Immunosubstudy)

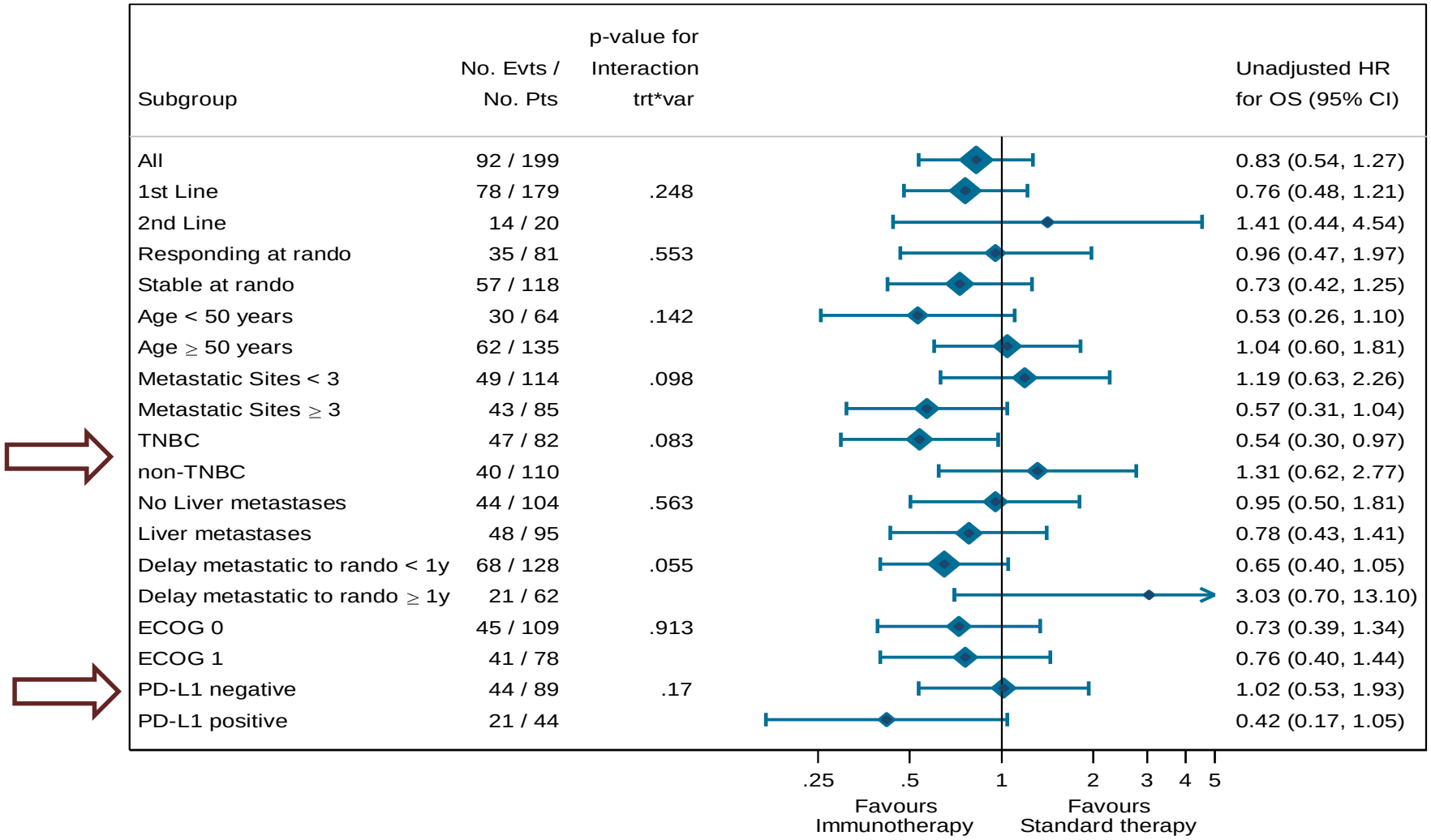


median OS:

17.9 [14.0- 24.0]

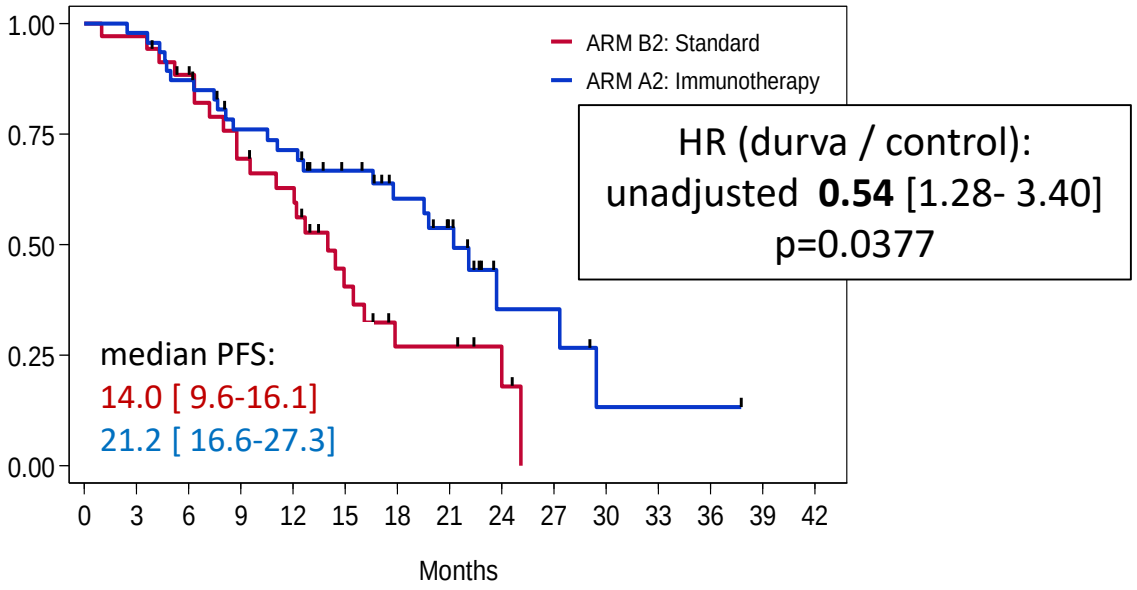
21.7 [18.6- 27.3]

Subgroups of interest



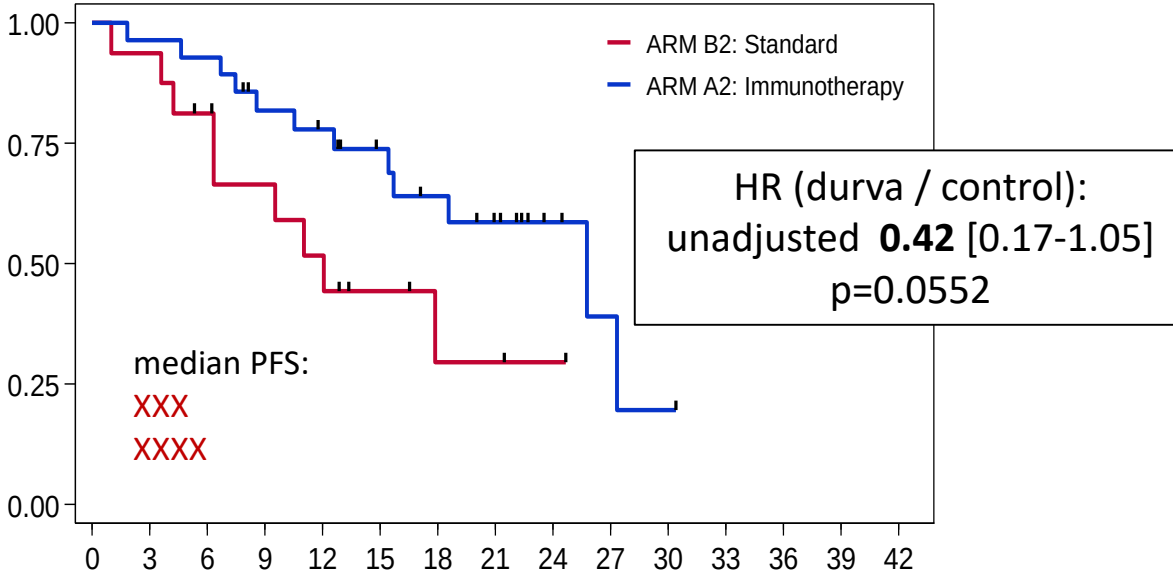
Exploratory analysis :
OS in patients with TN or PDL1+ tumors

TNBC (n=82)



ARM B2	35	34	28	22	19	10	5	5	3	0	0	0	0	0
ARM A2	47	46	41	33	31	24	18	13	4	4	1	1	1	0

PDL1 positive (n=44)



ARM B2	16	15	12	9	7	4	2	2	1	0	0	0
ARM A2	28	27	26	21	19	15	12	9	4	2	1	0

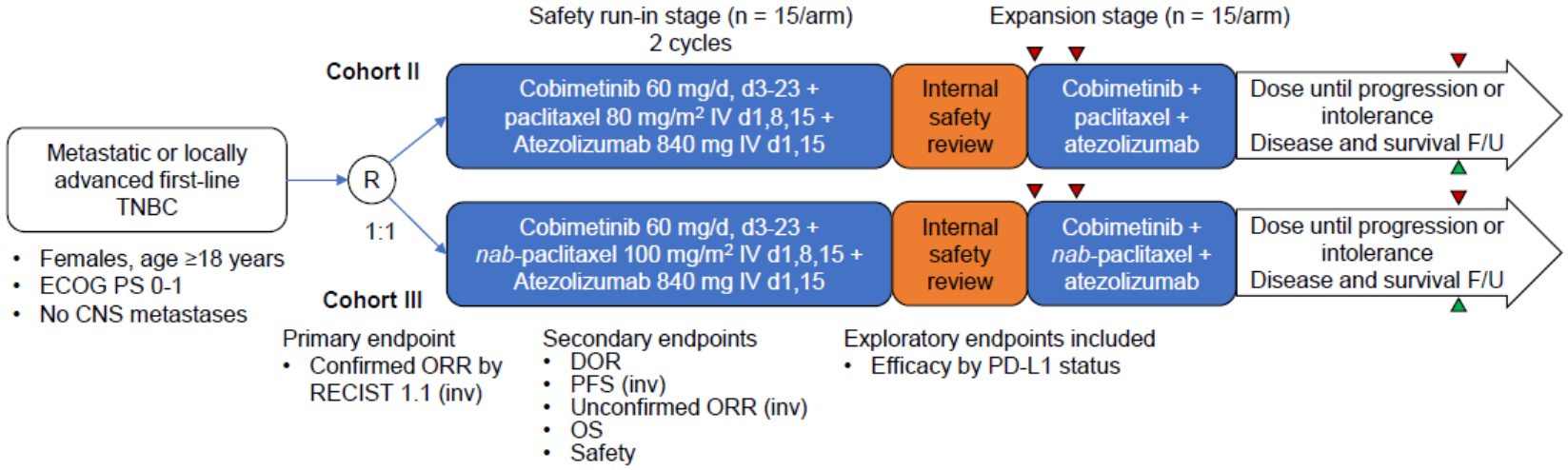
Conclusion

- Durvalumab does not improve outcome in patients with metastatic breast cancer as compared to maintenance chemotherapy

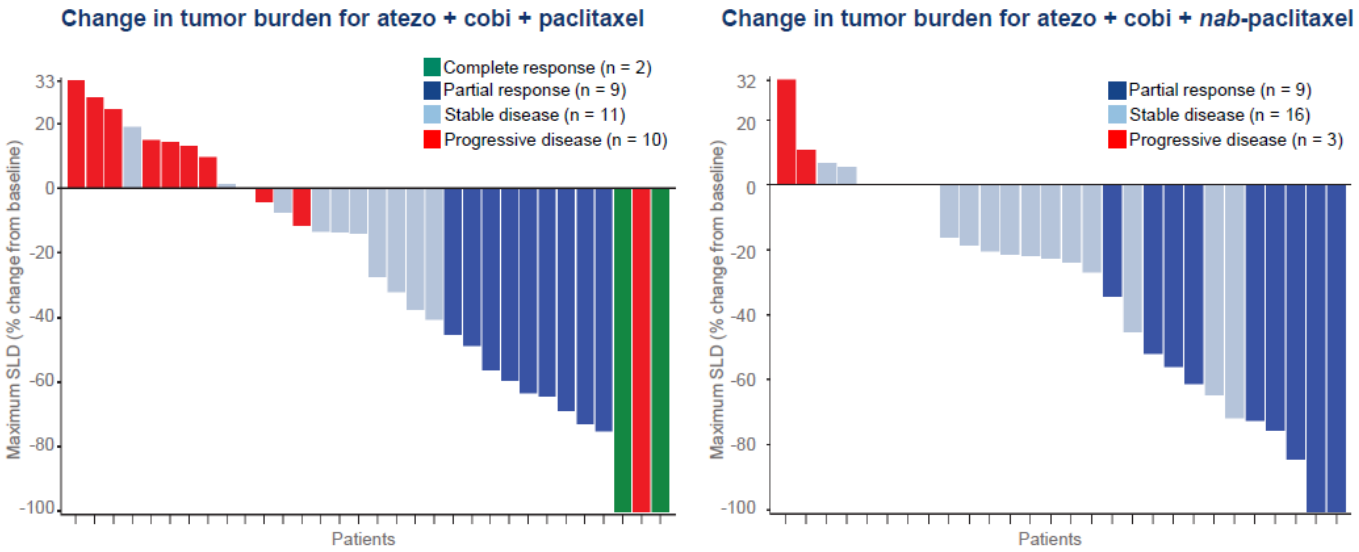
- Unplanned exploratory analyses report a reduction in the hazard of death in patients with TNBC (HR:0.54 , 95%CI: x-X) or PDL1+ tumor (HR: 0.42 95%CI: x-X)

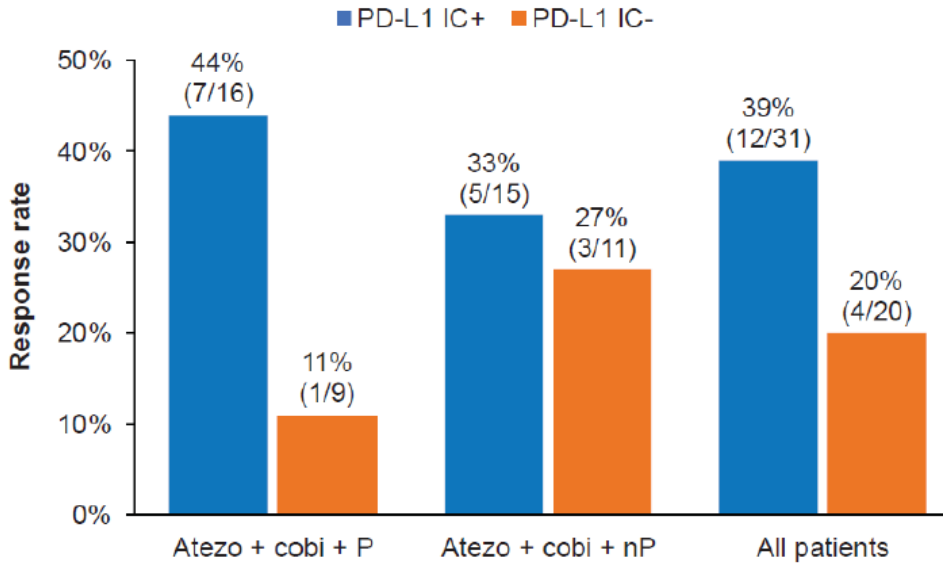
- Unplanned exploratory analyses report that chemotherapy could work better than anti-PDL1 as maintenance therapy in patients with ER+ MBC (HR : 2.08 [1.28- 3.40] p=0.0025)

Phase II COLET Study: Atezolizumab + Cobimetinib + Paclitaxel/Nab-paclitaxel



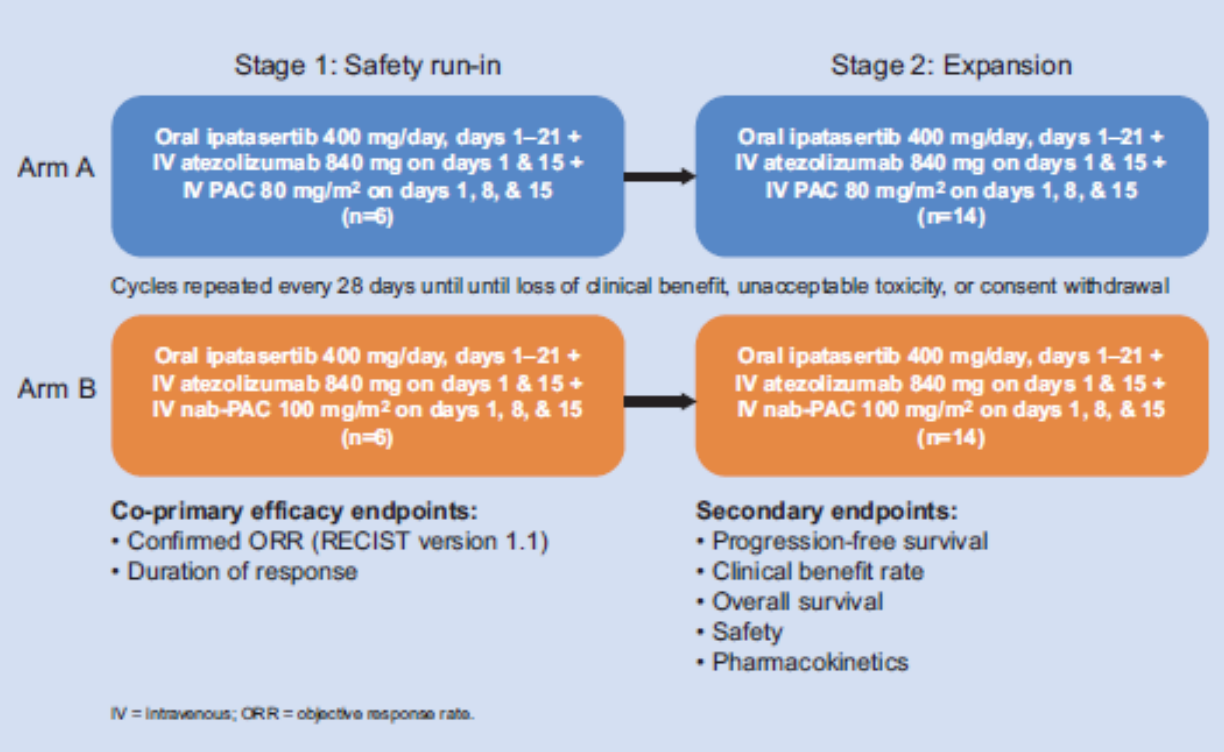
- MEK pathway is active in TNBC
- Suppresses inflammatory response
  - Decreased antigen presentation
  - Decreased PD-L1 expression
- MEKi + anti-PD-L1 improve antigen presentation by blocking PD-L1-mediated suppression

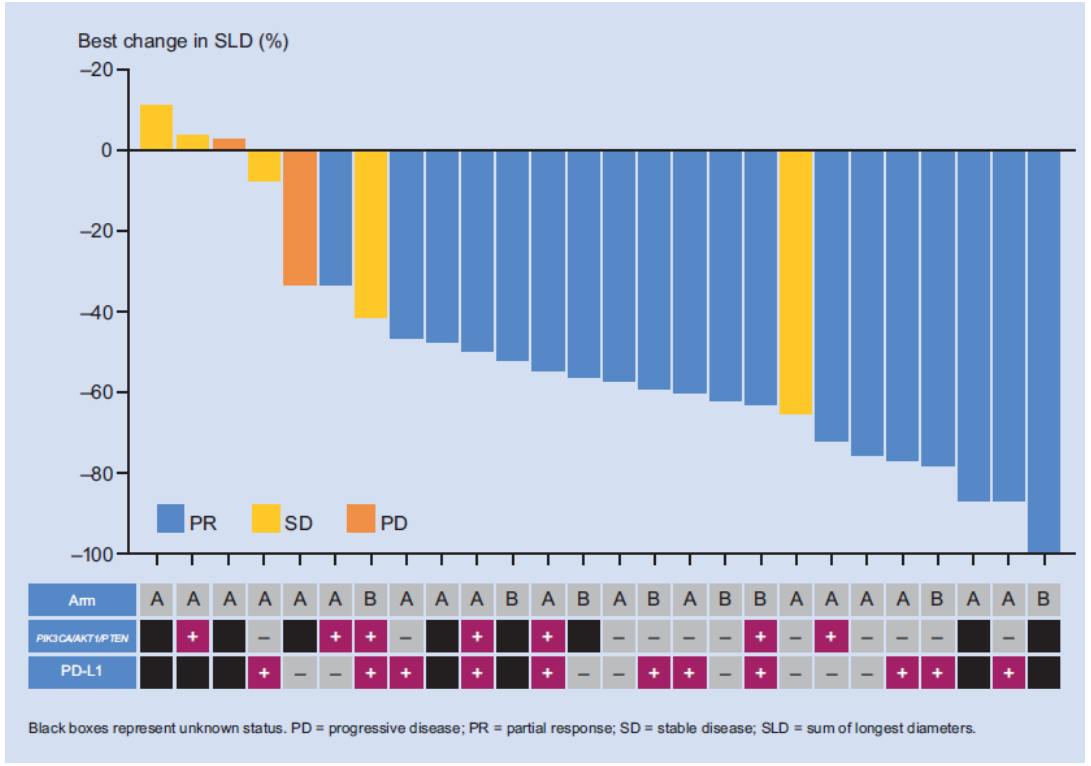




Brufsky et al, ASCO 2019

AKTi: Phase Ib of ipatasertib, atezolizumab and (nab)paclitaxel



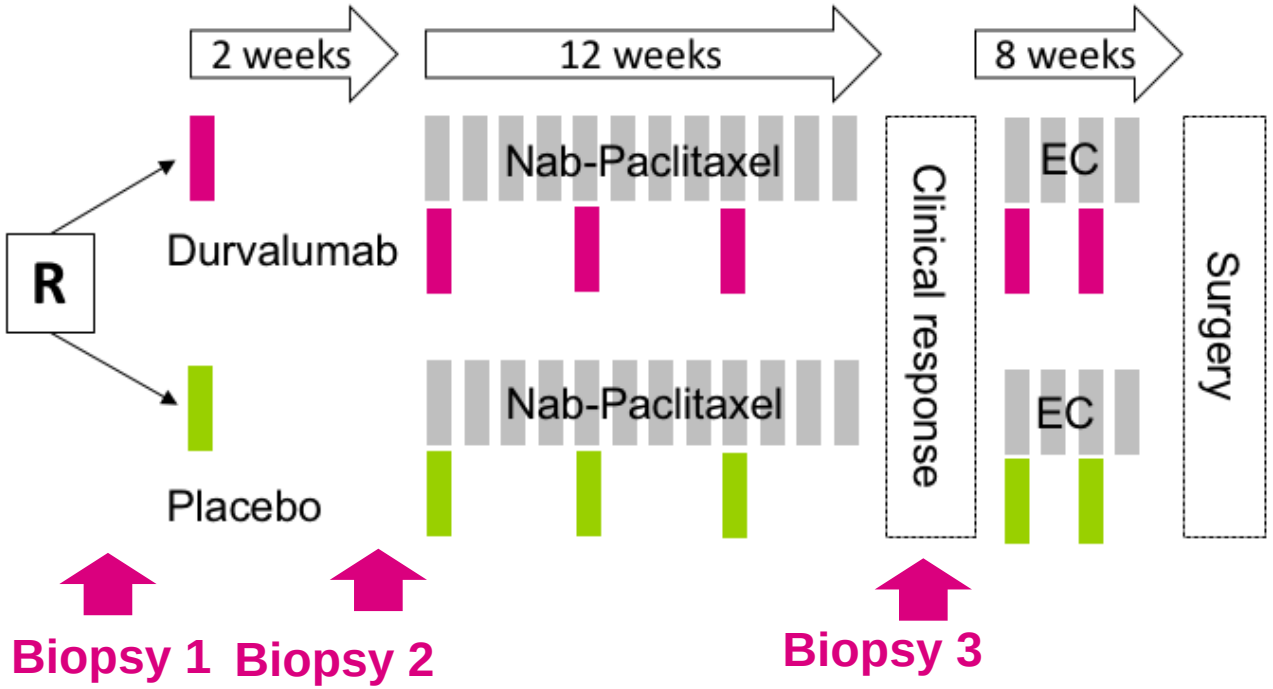


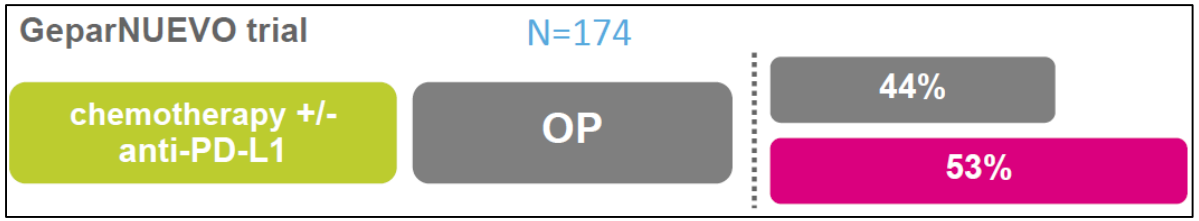
- PI3K/AKT/PTEN alternations linked to immunotherapy resistance
- AKT inhibition can enhance expansion of tumor-specific lymphocytes

Schmid et al, AACR 2019; George et al Immunity 2017; Crompton et al Can Res 2019

Clinical Trials of Immune Checkpoint Inhibitors in Early Stage Breast Cancer

GeparNeuvo: Neoadjuvant Durvalumab

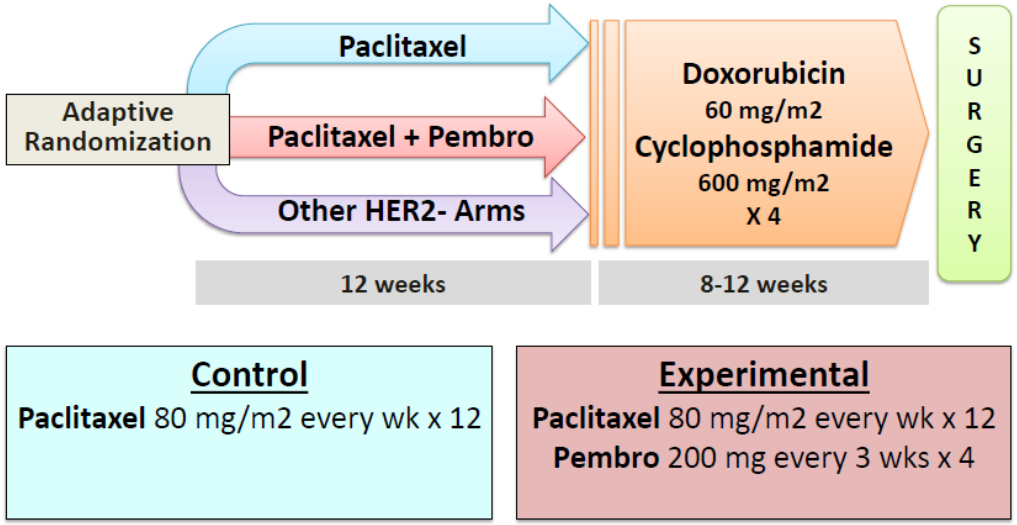




<u>pCR rates</u>:
Window cohort (61 vs 41.4%)
Stage <u>≥</u> IIa (55.5 vs 38.6%)

Loibl et al, ASCO 2018; Loibl et al, Ann Onc 2019

Neoadjuvant Pembrolizumab: Efficacy Results from the I-SPY2 Adaptively Randomized Platform Trial



Signature	Estimated pCR rate (95% probabilty interval)		Probability pembro is superior to control	Predictive probability of success in phase 3
	Pembro	Control		
All HER2-	**0.46** (0.34 – 0.58)	**0.16** (0.06 – 0.27)	**> 99%**	**99%**
TNBC	**0.60** (0.43 – 0.78)	**0.20** (0.06 – 0.33)	**>99%**	**>99%**
HR+/HER2-	**0.34** (0.19 – 0.48)	**0.13** (0.03 – 0.24)	**>99%**	**88%**

Current I-SPY2 Immunotherapy Arms:

- **Pembolizumab/Paclitaxel-> Pembrolizumab (no AC): SABCS 2019 (P3-09-12)**
- Olaparib/Durvalumab/Paclitaxel->AC
- SD-101/Pembrolizumab/Paclitaxel->AC

Nanda et al, ASCO 2017

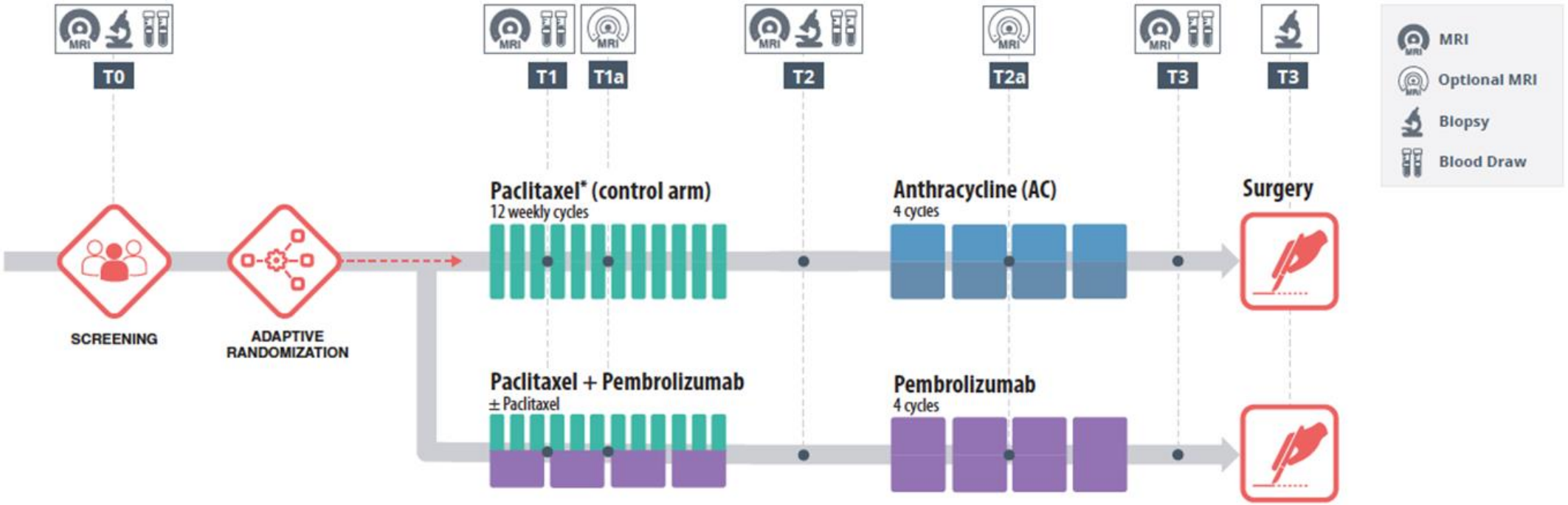
Neoadjuvant Pembrolizumab: Immune-related Adverse Events from the I-SPY2 Adaptively Randomized Platform Trial

	Pembrolizumab (n=69) % (n)		Control (n=180) % (n)	
	All grades	Grade 3-5	All grades	Grade 3-5
Hypothyroidism	8.7 (6)	1.4 (1)	0.6 (1)	0 (0)
Hyperthyroidism	4.3 (3)	0 (0)	0 (0)	0 (0)
Adrenal Insufficiency^	8.7 (6)	7.2 (5)	0 (0)	0 (0)
Hepatitis	2.9 (2)	2.9 (2)	0 (0)	0 (0)
Pneumonitis	2.9 (2)	0 (0)	1.1 (2)	0.6 (1)
Colitis	1.4 (1)	1.4 (1)	0.6 (1)	0.6 (1)
Pruritis	24.6 (17)	0 (0)	11.1 (20)	0.6 (1)

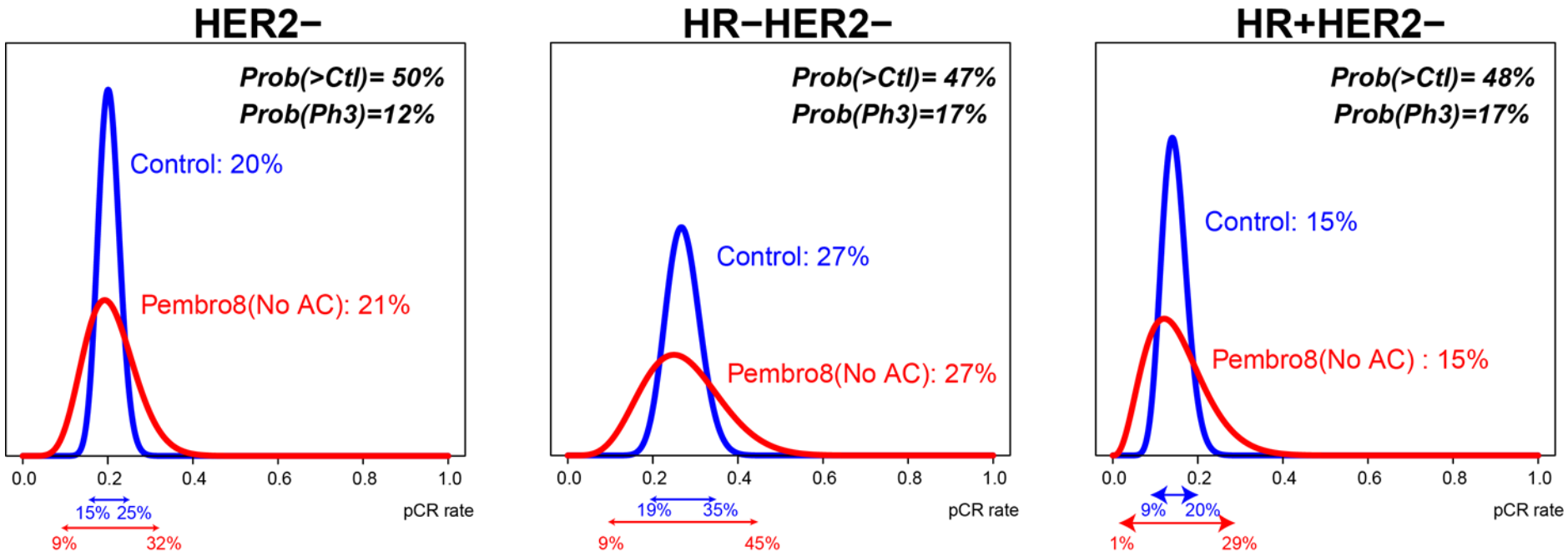
<u>Adrenal insufficiency</u>

- 5/6 presented >10 wks after last pembro dose
- 1/6 presented during pembro (5 wks after 1st pembro dose)
- Rates of primary/secondary AI across studies are 0.8% and 0.6%

Study schema for Pembro 8-no AC and for control



Estimated pCR rates Pembro 8-no AC and for control



Paclitaxel →AC was EQUAL to
Paclitaxel + Pembro x 4 → Pembro x 4

San Antonio Breast Cancer Symposium®, December 10-14, 2019

KEYNOTE-522: Phase 3 Study of Neoadjuvant Pembrolizumab + Chemotherapy versus Placebo + Chemotherapy, Followed by Adjuvant Pembrolizumab versus Placebo for Early Triple-Negative Breast Cancer: Pathologic Complete Response in Key Subgroups and by Treatment Exposure and Residual Cancer Burden

Peter Schmid[1], Yeon Hee Park[2], Marta Ferreira[3], Marie-Ange Mouret-Reynier[4], Seock-Ah Im[5], Jin-Hee Ahn[6], Maria Gion[7], Rina Hui[8], Sally Baron-Hay[9], Jean-Francois Boileau[10], Mei-Ching Liu[11], Nadia Harbeck[12], Masato Takahashi[13], Theodoros Foukakis[14], Peter A. Fasching[15], Fatima Cardoso[16], Jay Andersen[17], Michael Untch[18], Margarita Tokar[19], Florence Dalenc[20], Michael Danso[21], Debra Patt[22], Sherko Kümmel[23], Carsten Denkert[24], Lajos Pusztai[25], Jonas Bergh[14], Heather McArthur[26], Liyi Jia[27], Gursel Aktan[27], Vassiliki Karantza[27], Rebecca Dent[28], Javier Cortes[29], Joyce O'Shaughnessy[30]

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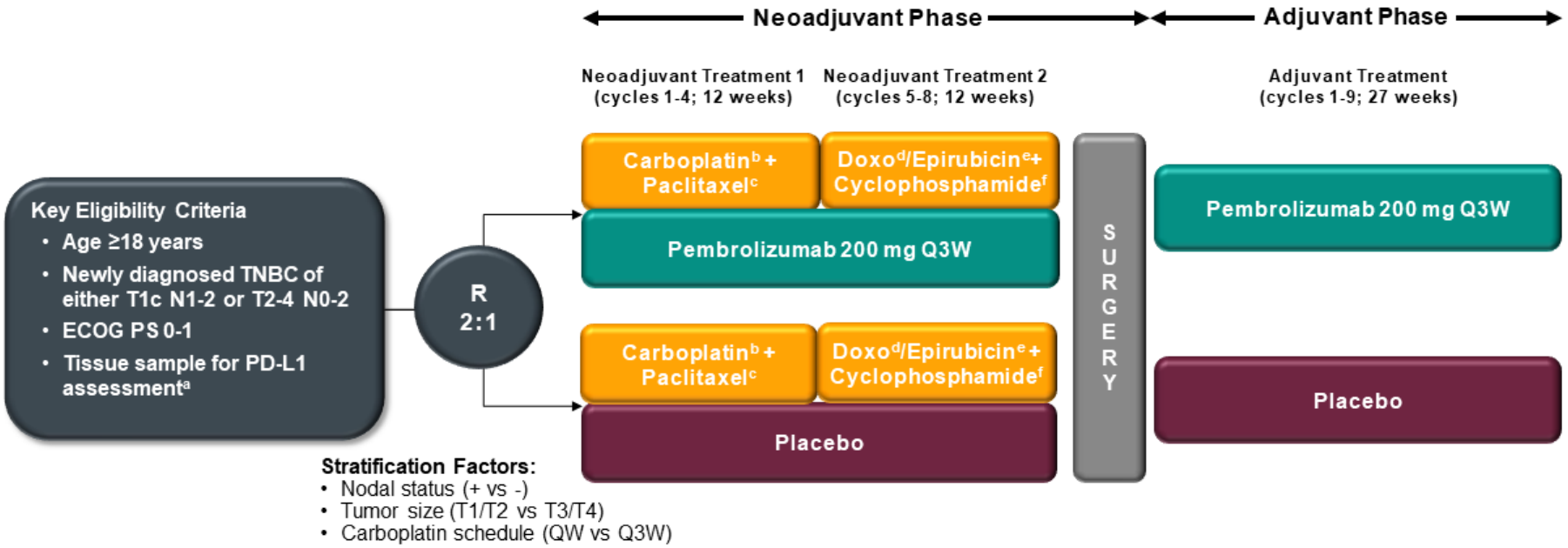
Schmid KN522 ESMO 2019

KEYNOTE-522 Study Design (NCT03036488)



Neoadjuvant phase: starts from the first neoadjuvant treatment and ends after definitive surgery (post treatment included)

Adjuvant phase: starts from the first adjuvant treatment and includes radiation therapy as indicated (post treatment included)

[a]Must consist of at least 2 separate tumor cores from the primary tumor.
[b]Carboplatin dose was AUC 5 Q3W or AUC 1.5 QW.
[c]Paclitaxel dose was 80 mg/m² QW.
[d]Doxorubicin dose was 60 mg/m² Q3W.
[e]Epirubicin dose was 90 mg/m² Q3W.
[f]Cyclophosphamide dose was 600 mg/m² Q3W.

Primary Endpoints:
- pCR
- EFS

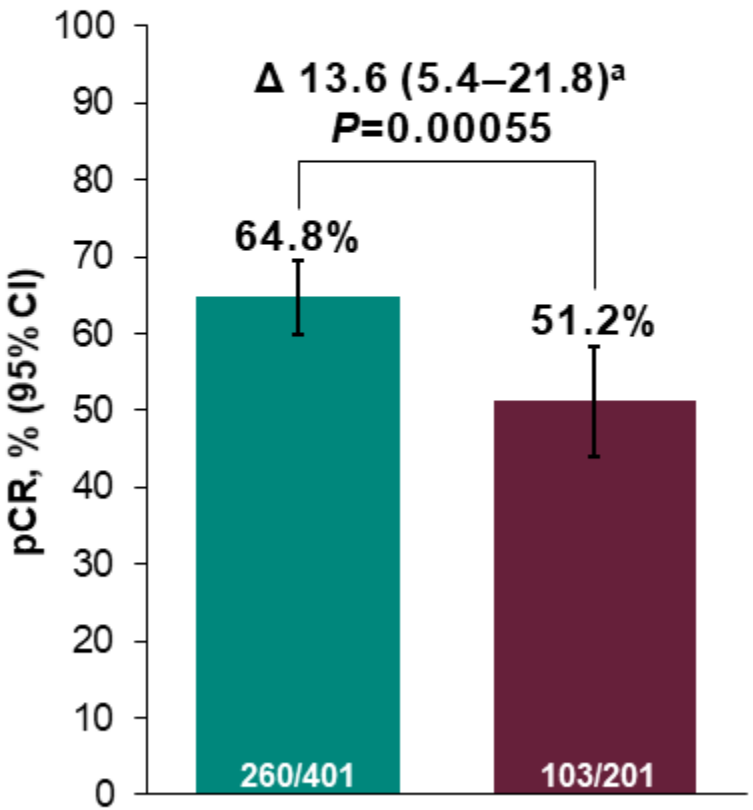
Secondary Endpoints:
- OS
- pCR/EFS/OS in PD-L1+
- Safety

Exploratory Endpoints:
- RCB
- EFS by pCR
- EFS/pCR by TILs

SABCS 2019 (GS3-03)
- **RCB**
- **EFS updates**
- **pCR in subgroups**

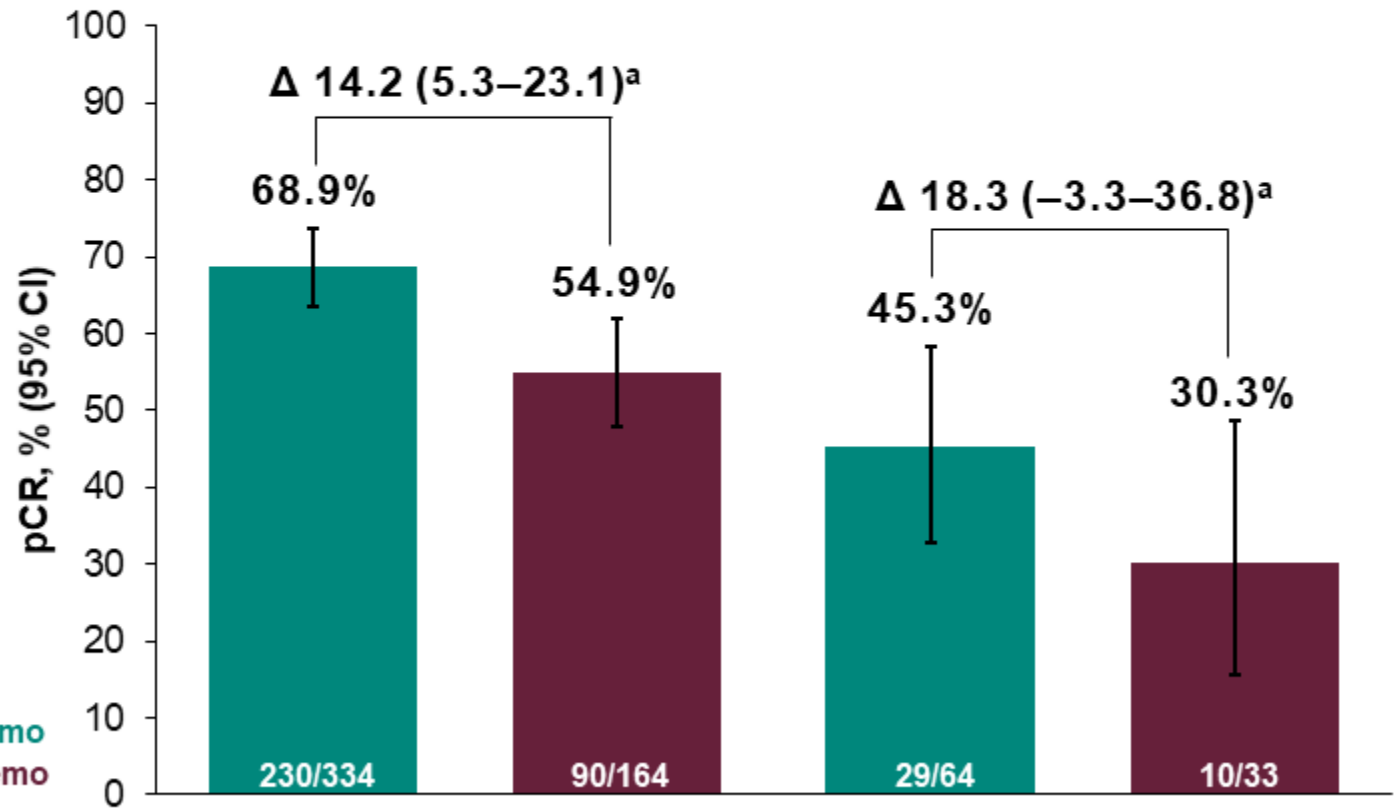
Pathological Complete Response at IA1

Primary Endpoint: ypT0/Tis ypN0



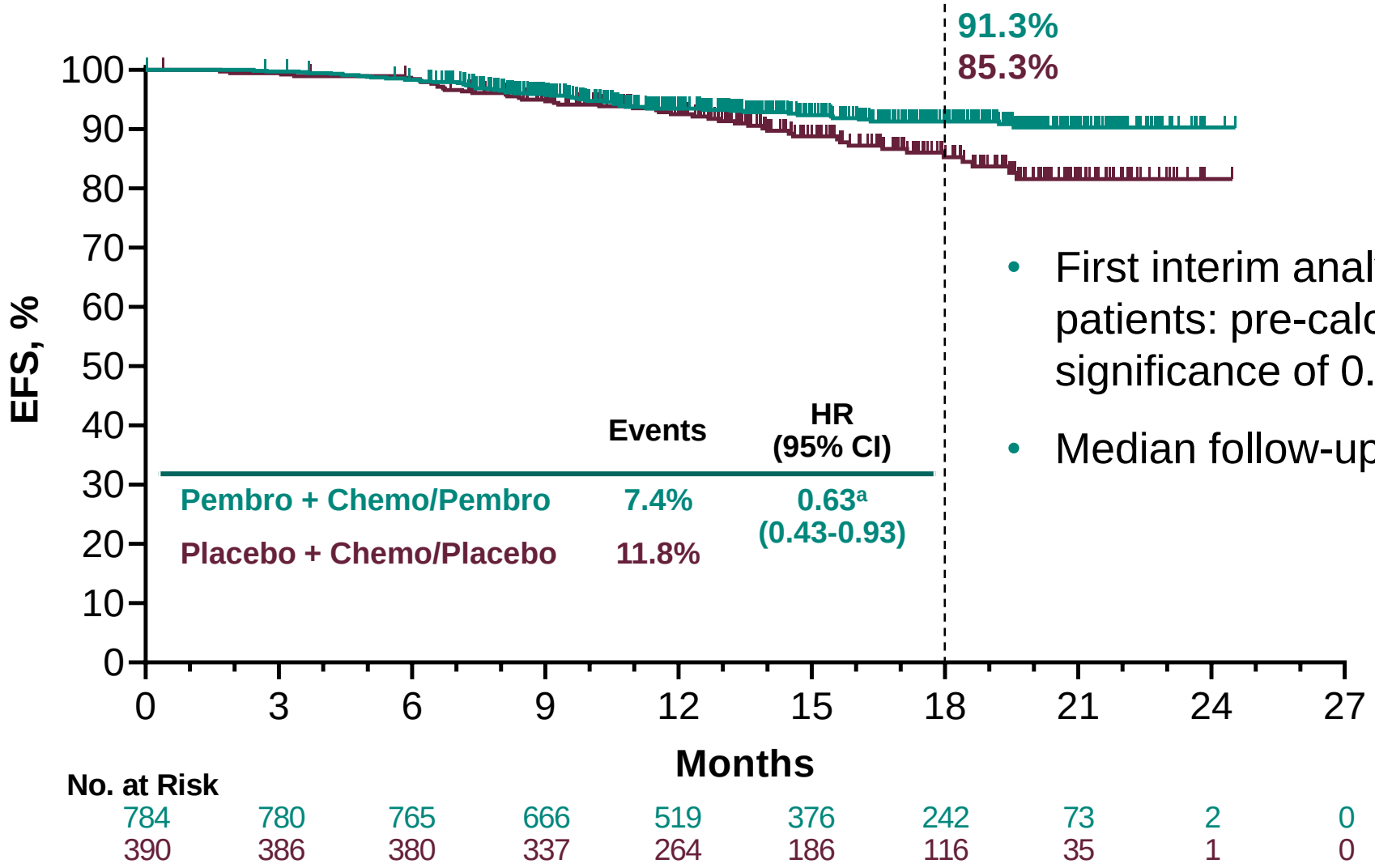
Pembro + Chemo
Placebo + Chemo

By PD-L1 Status[b]: ypT0/Tis ypN0



[a]Estimated treatment difference based on Miettinen & Nurminen method stratified by randomization stratification factors. [b]PD-L1 assessed at a central laboratory using the PD-L1 IHC 22C3 pharmDx assay and measured using the combined positive score (CPS; number of PD-L1–positive tumor cells, lymphocytes, and macrophages divided by total number of tumor cells x 100); PD-L1–positive = CPS ≥1. Data cutoff date: September 24, 2018.

First Pre-planned Interim Analysis for EFS



- First interim analysis of EFS based on 1174 patients: pre-calculated P value boundary for significance of 0.000051 (HR <0.4)
- Median follow-up, 15.5 months

[a]Pre-specified P value boundary of 0.000051 not reached at this analysis (the first interim analysis of EFS). Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. Data cutoff April 24, 2019.

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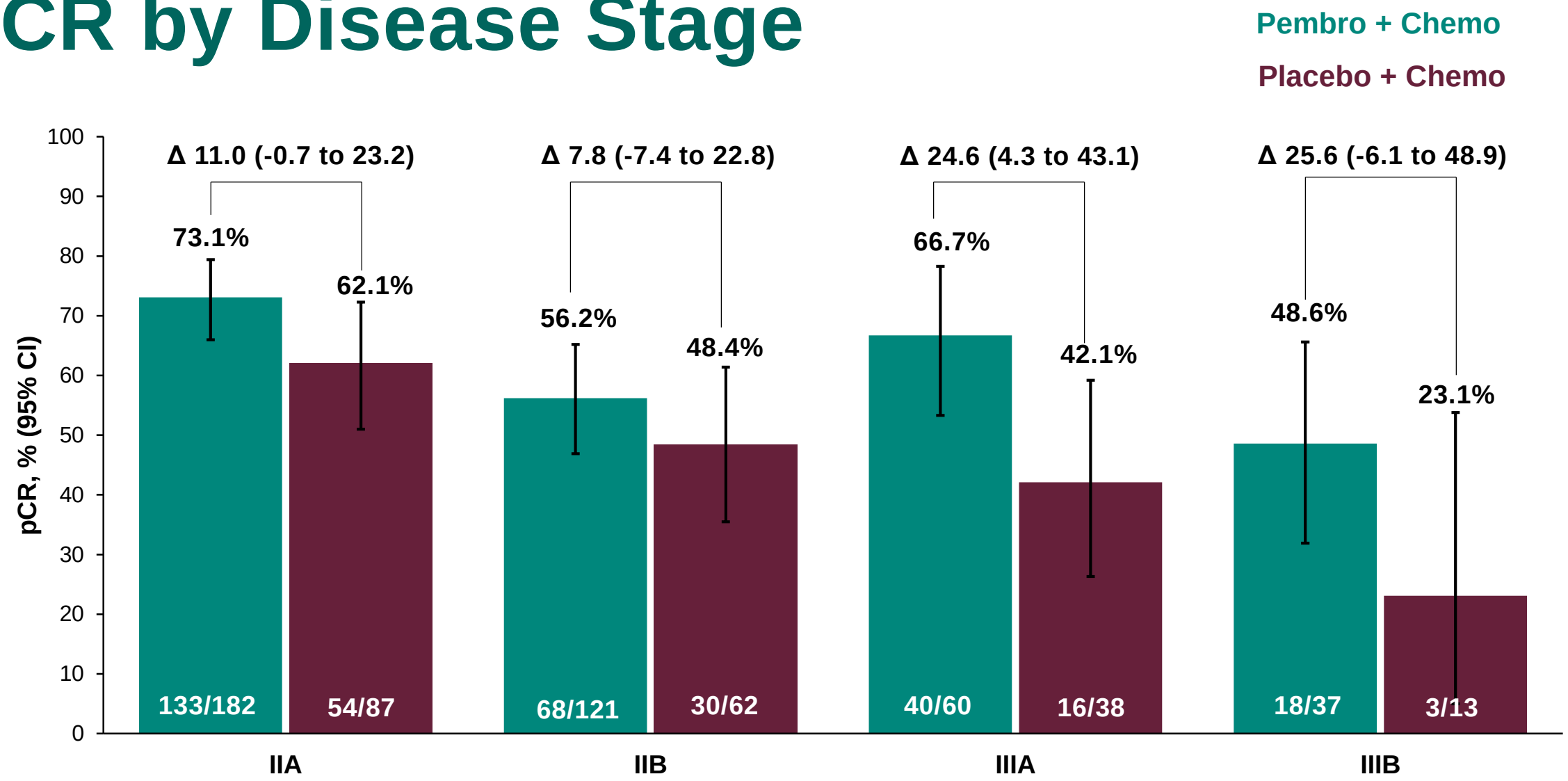
pCR by Disease Stage



Post-hoc analysis. Estimated treatment difference based on unstratified Miettinen & Nurminen method. Data cutoff date: September 24, 2018.

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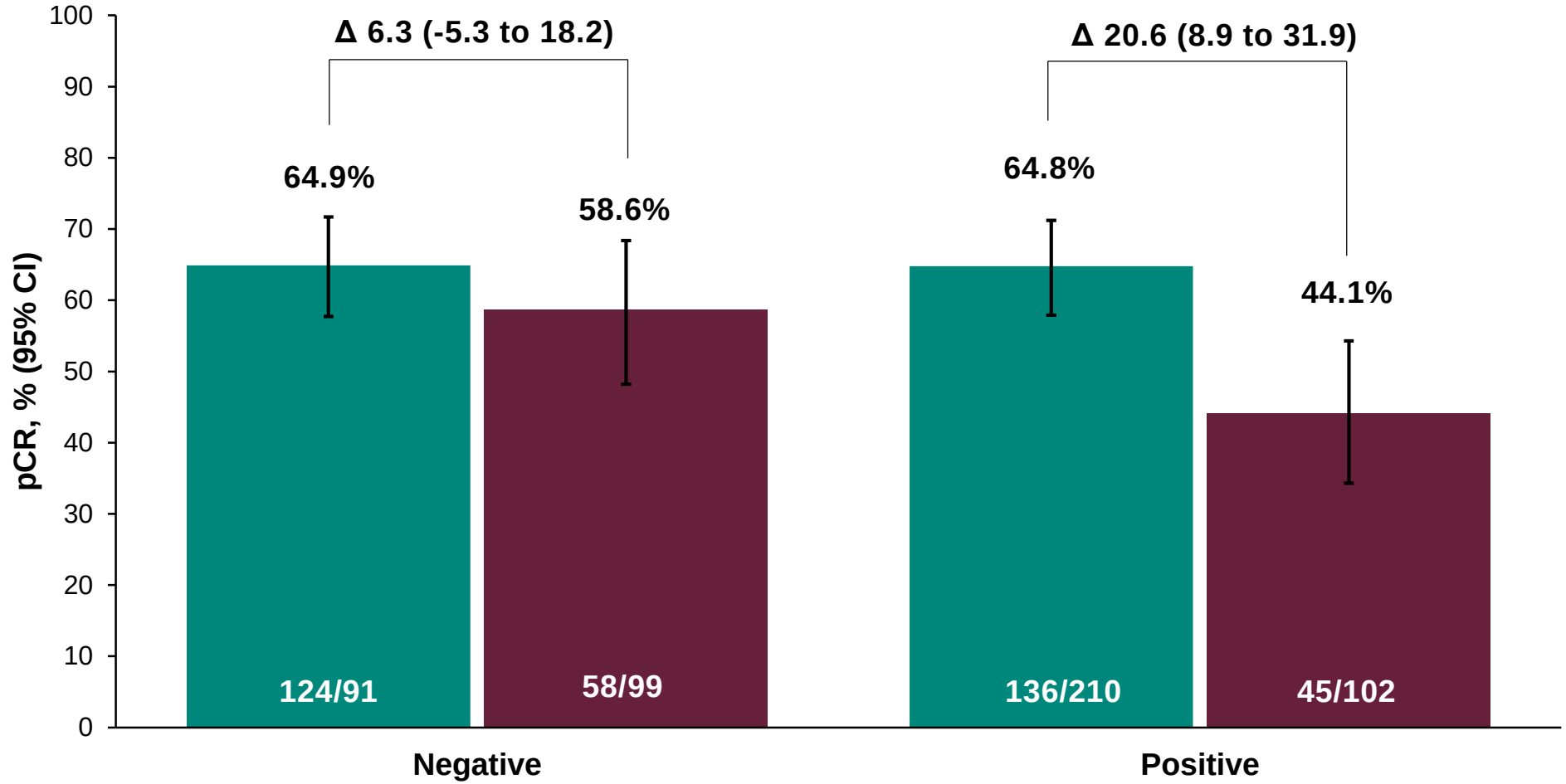
pCR by Lymph Node Involvement

Pembro + Chemo
Placebo + Chemo



Pre-specified analysis. Lymph node involvement was determined by the study investigator by physical exam, sonography/MRI and/or biopsy. Estimated treatment difference based on unstratified Miettinen & Nurminen method. Data cutoff date: September 24, 2018.

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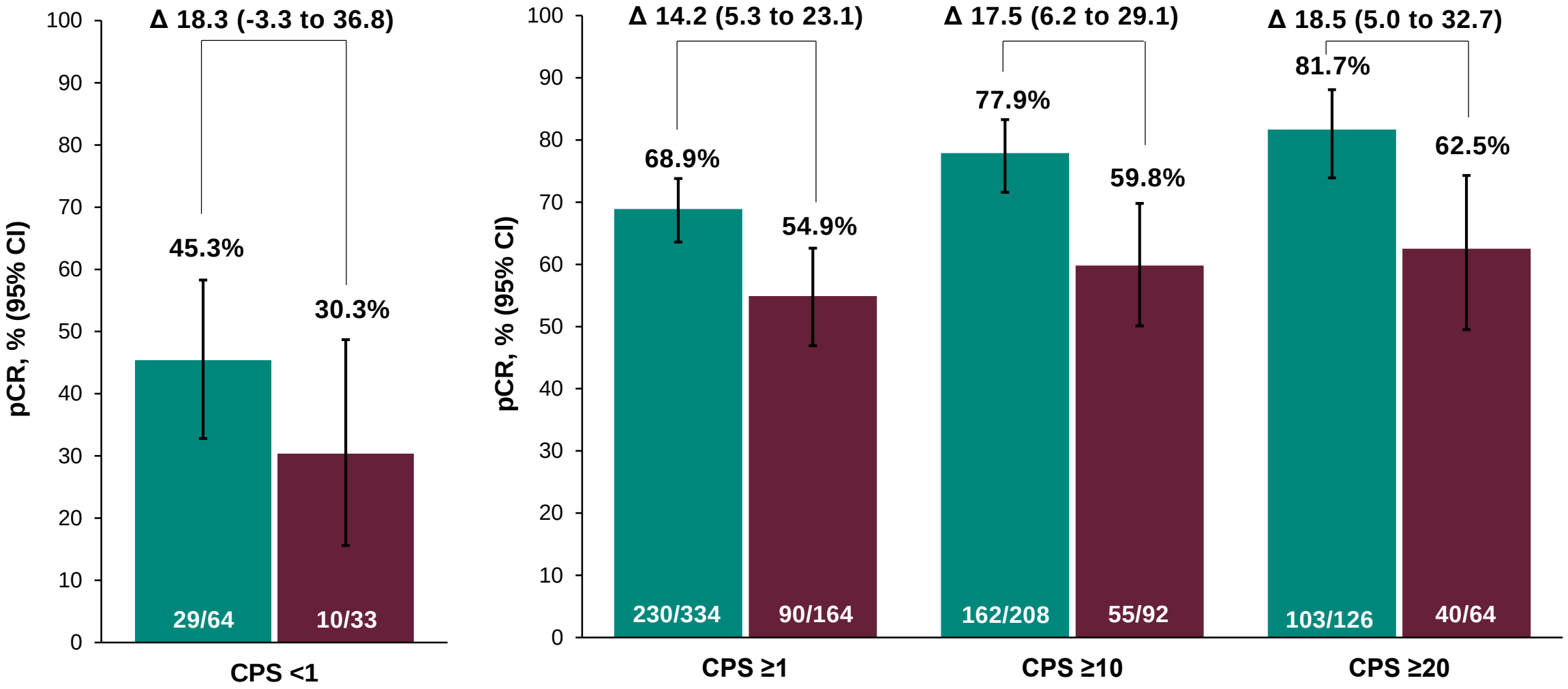
pCR by PD-L1 Expression Level

Pembro + Chemo
Placebo + Chemo



Pre-specified analysis. PD-L1 assessed at a central laboratory using the PD-L1 IHC 22C3 pharmDx assay and measured using CPS; number of PD-L1–positive tumor cells, lymphocytes, and macrophages divided by total number of tumor cells x 100); PD-L1–positive = CPS ≥1. Estimated treatment difference based on Miettinen & Nurminen method stratified by nodal status (positive vs negative), tumor size (T1/T2 vs T3/T4) and choice of carboplatin (Q3W vs QW). Data cutoff date: September 24, 2018.

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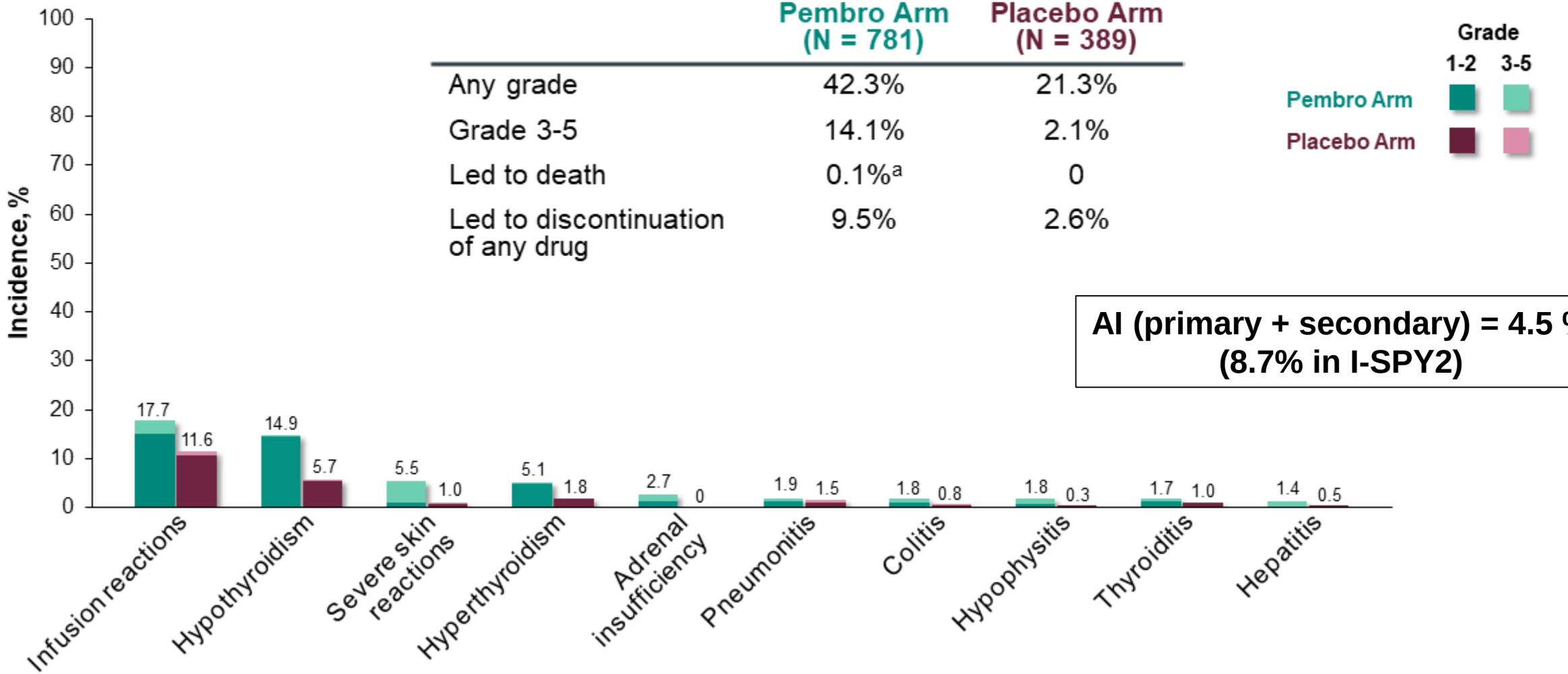
Immune-Mediated AEs and Infusion Reactions in Combined Phases: IA2

	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%



AI (primary + secondary) = 4.5 % (8.7% in I-SPY2)

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

[a]1 patient from pneumonitis.

Considered regardless of attribution to treatment or immune relatedness by the investigator. Related terms included in addition to preferred terms listed. Data cutoff date: April 24, 2019.

Design of the NeoTRIP trial (GS3-04)

HER-2 negative, ER and PgR negative early high-risk (T1cN1; T2N1; T3N0) or locally advanced unilateral breast cancer

R

Carboplatin + *nab*-paclitaxel weekly for 2 wks every 3 for 8 cycles → **S** → **AC/EC/FEC** for 4 cycles

Carboplatin + *nab*-paclitaxel weekly for 2 wks every 3 for 8 cycles **+ Atezolizumab** day 1 every 3 wks for 8 cycles → **S** → **AC/EC/FEC** for 4 cycles

FOLLOW UP

Primary endpoint: EFS (5 years)
Secondary endpoint: pCR, tolerability

Tumour & Blood Banked for Correlative Studies

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Aims of Study

Open-label, randomized phase III trial

- ***Primary aim*:*** event-free survival (**EFS**) at 5 years after randomization of the last patient
- ***Key secondary aim: rate of pCR*** (as absence of invasive cells in breast and lymph nodes).
- The primary population for all efficacy endpoints is the **ITT (intent-to-treat) population**
- Other secondary aims: tolerability of the regimens; studies on putative predictive markers of benefit and/or resistance to the study regimens

**** Sample size calculated for the primary endpoint of EFS***

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Main Characteristics at Randomization - ITT

		No atezo (142)	With atezo (138)	Total (280)
Disease stage	Early high-risk	73 (51%)	69 (50%)	142 (51%)
	Locally advanced	69 (49%)	69 (50%)	138 (49%)
PD-L1	Positive	77 (54%)	79 (57%)	156 (56%)
	Negative	65 (46%)	59 (43%)	124 (44%)
Median age in yr (range)		50 (24-77)	49.5 (25-79)	50 (24-79)
T stage	cT1c	8 (6%)	13 (9%)	21 (7.5%)
	cT2	75 (53%)	61 (44%)	136 (49%)
	cT3	41 (29%)	47 (34%)	88 (31%)
	cT4a-d	18 (13%)	17 (12%)	35 (12.5%)
Nodal status	cN0	19 (13%)	18 (13%)	37 (13%)
	cN1	79 (56%)	85 (62%)	164 (59%)
	cN2	22 (15.5%)	16 (12%)	38 (14%)
	cN3	22 (15.5%)	19 (14%)	41 (15%)

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Primary endpoint: pCR rate

	ITT population	
	With atezo (138)	**No atezo** (142)
% pCR rate	**43.5**	**40.8**
95% CI	35.1-52.2	32.7-49.4
Difference: atezo vs no atezo (95% CI)	**2.63** (14.0-8.8)	
***Odds ratio (95% CI)**	**1.11 (0.69-1.79)**	
***p-value**	**0.66**	

*Cochran-Mantel-Haenszel test, controlling for PD-L1 expression and disease stage and quantified by OR and rate difference

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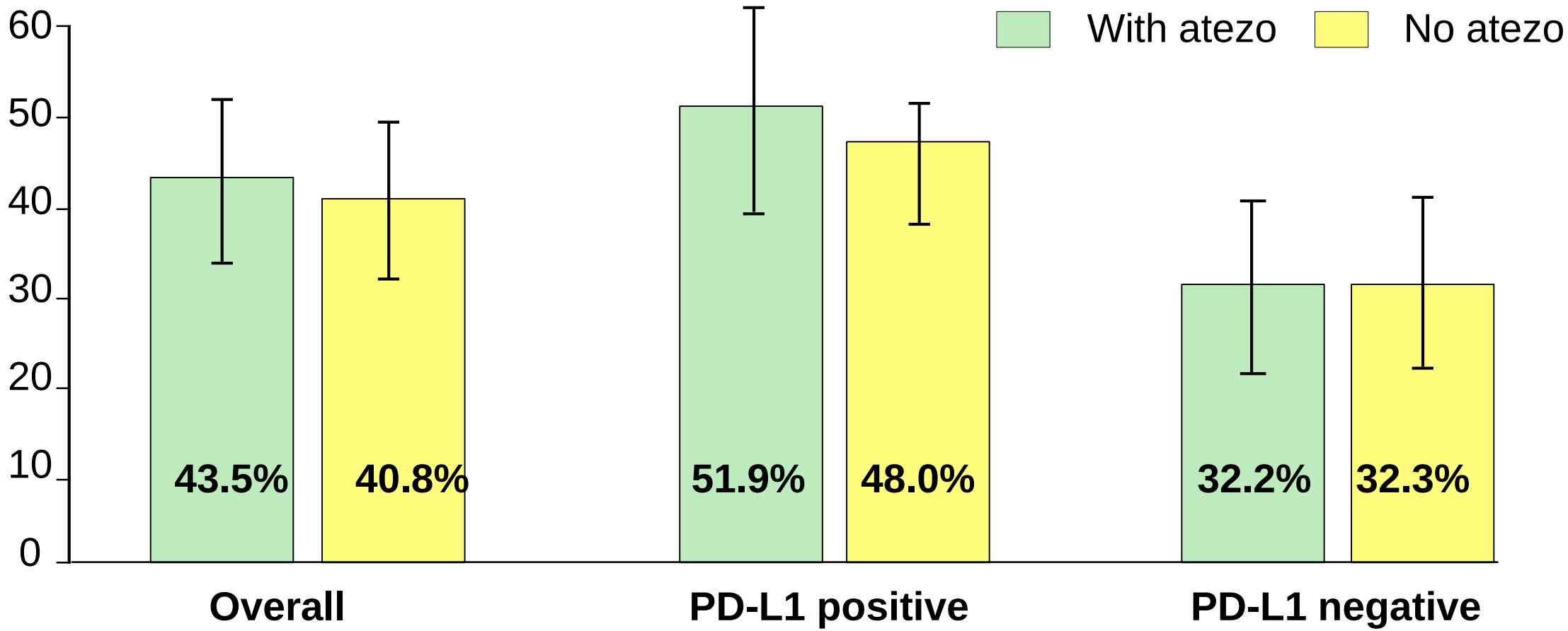
pCR rate and *PD-L1 expression*



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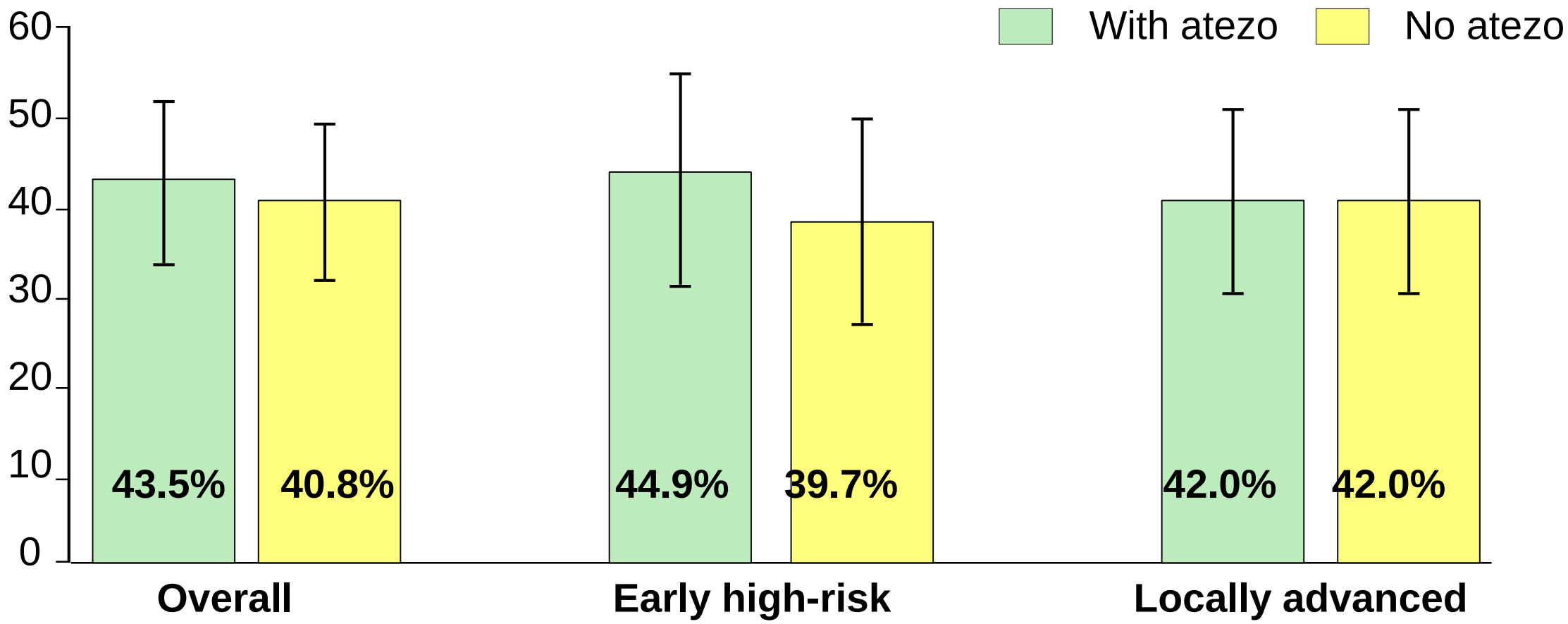
pCR rate and *disease stage*



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Clinical Overall Response (cOR)

	Atezo (n. 138)	No Atezo (n. 142)
Complete Response	29.0%	26.1%
Partial Response	47.1%	42.3%
Stable Disease	3.6%	4.9%
Progressive Disease	5.8%	8.4%
Not assessed	14.5%	18.3%
cOR rate (95% CI)	**76.1%** (68.1 – 82.9)	**68.3%** (60.0 – 75.9)

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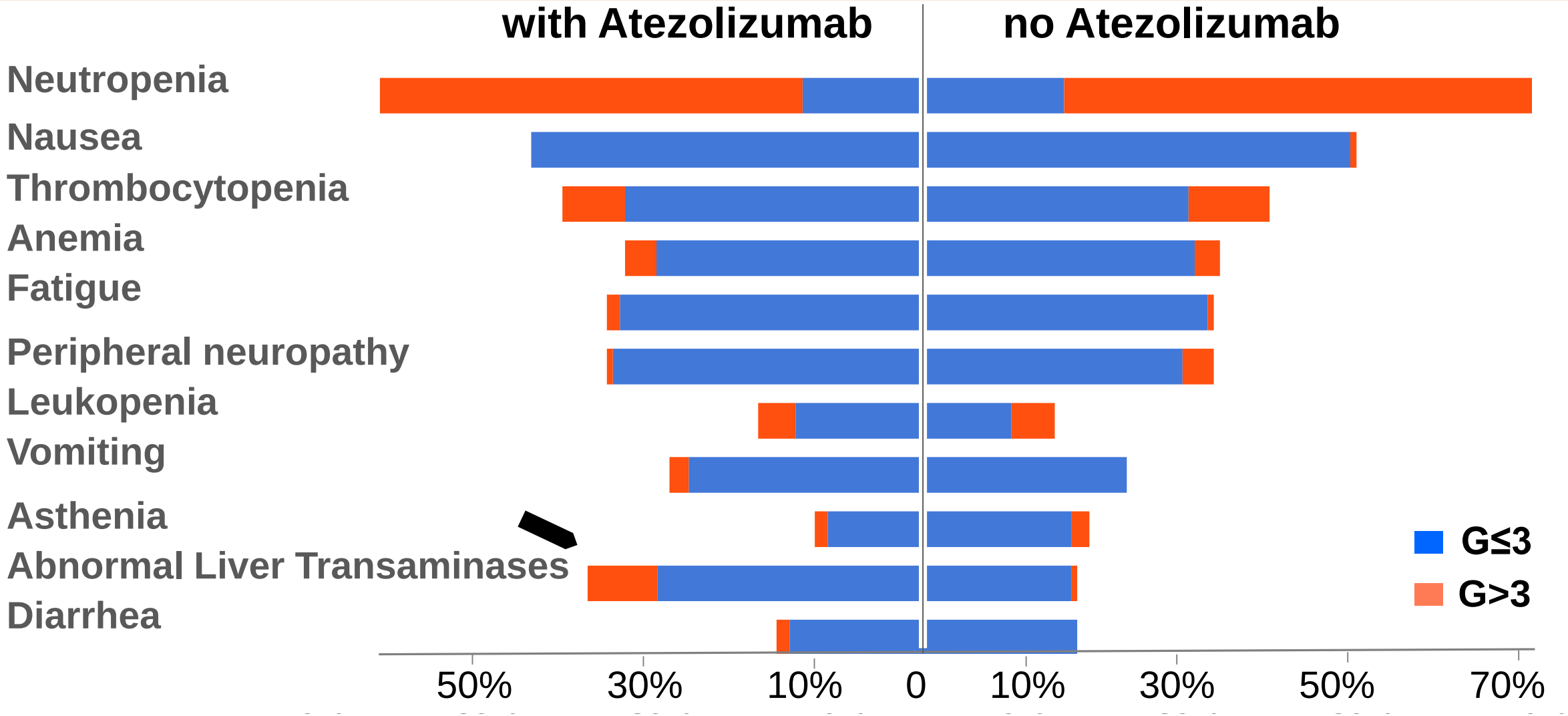
Treatment-related Adverse Events (Incidence ≥ 15%)



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Immune-Mediated Adverse Events and Infusion Reactions

	Any grade		Grade ≥ 3	
	Atezo (138)	No atezo (140)	Atezo (138)	No atezo (140)
Infusion reactions	8.0%	5.7%	1.4%	0.7%
Hypothyroidism	5.8%	1.4%	-	-
Thyroiditis	1.5%	-	-	-
Hyperthyroidism	0.7%	-	-	-
Colitis	1.5%	-	0.7%	-
Pancreatitis	1.5%	-	1.5%	-
Hepatitis	0.7%	-	-	-
Interstitial nephritis	0.7%	-	-	-
Coombs positive hemolytic anemia	0.7%	-	0.7%	-
Thrombotic thrombocytopenic purpura	0.7%	-	0.7%	-

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Conclusions

- The addition of atezolizumab to *nab*-paclitaxel and carboplatin did not significantly increase the rate of pCR in women with TNBC
- In multivariate analysis the presence of PD-L1 expression was the most significant factor influencing treatment outcome (OR 2.08)
- Treatment-related adverse events were similar with either regimen except for a significantly higher overall incidence of SAEs and liver function test abnormalities with atezolizumab.
- Continuous follow up for the primary endpoint of EFS and other efficacy end points is ongoing, and molecular studies are under way

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Summary

- Monotherapy responses in mTNBC are modest
  - Line of therapy, PD-L1, TILs
- Atezolizumab + nab-paclitaxel approved for PD-L1+ advanced TNBC
  - VENTANA SP142, immune cells (concordance among pathologists, antibodies)
- Trials with non-taxane backbones appear promising
  - Induction (TONIC), maintenance (SAFIR)
- Combination of checkpoint blockade and targeted therapies for mTNBC look promising; phase III trials planned/ongoing
- Addition of pembrolizumab to NACT in TNBC significantly improves pCR rates but with immune-related toxicities

Opportunities and Challenges

- Biomarkers, biomarkers, biomarkers
- Sequencing
- Maintenance
- Optimal chemotherapy backbone
- De-escalation of chemotherapy
- Immune-related toxicities

AT THE FOREFRONT
UChicago Medicine

Thank You!

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