

# The current clinical data of IO in

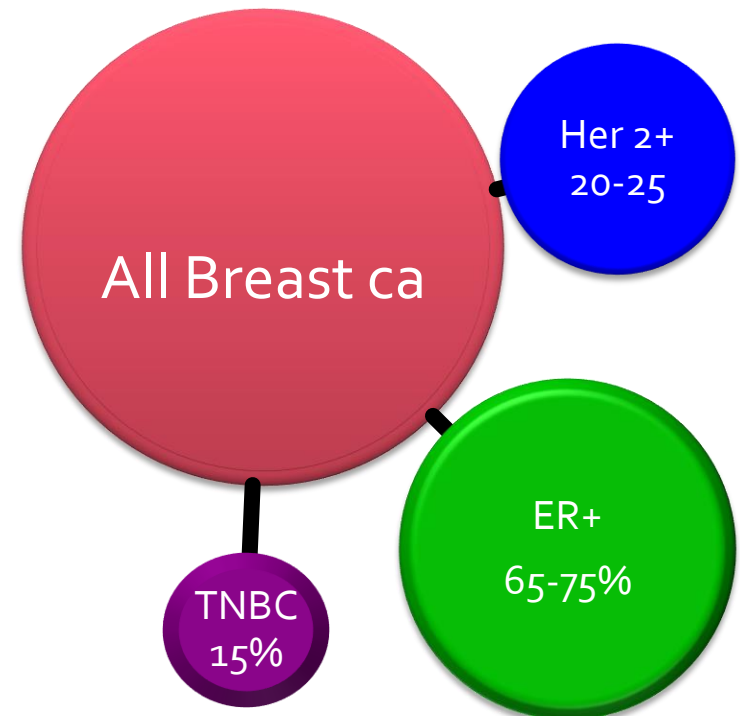


# TNBC

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# What Is TNBC?

- Triple negative = ER negative, PgR negative, HER2 negative
- accounts for 10% - 17% of all BC
- Significantly more aggressive than other subtype of tumors
- Majority G 3 tumors

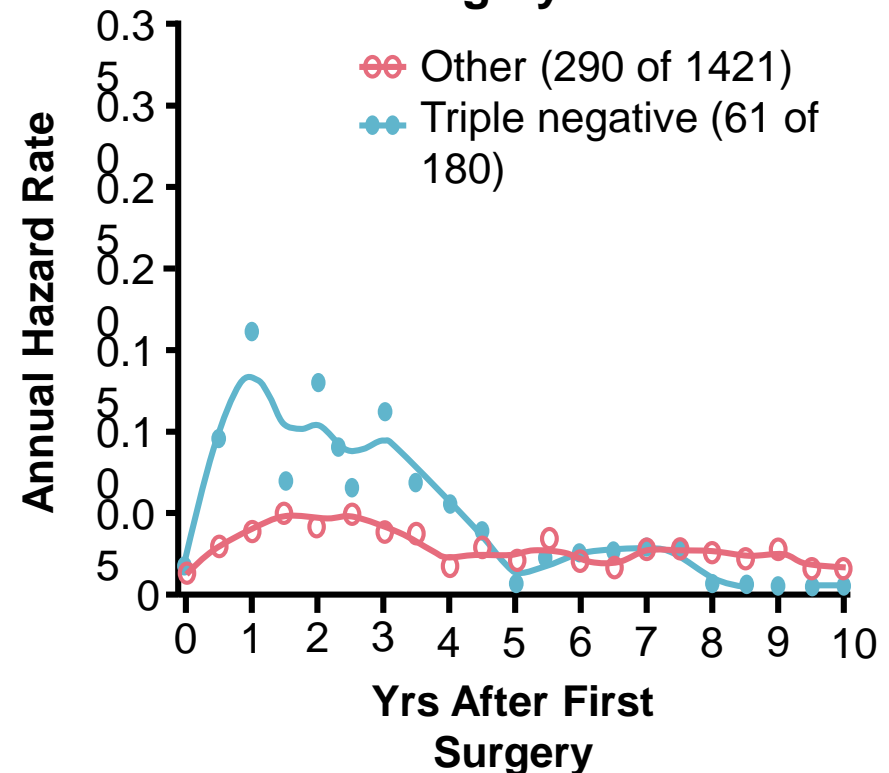


# Clinical Characteristics of Metastatic TNBC

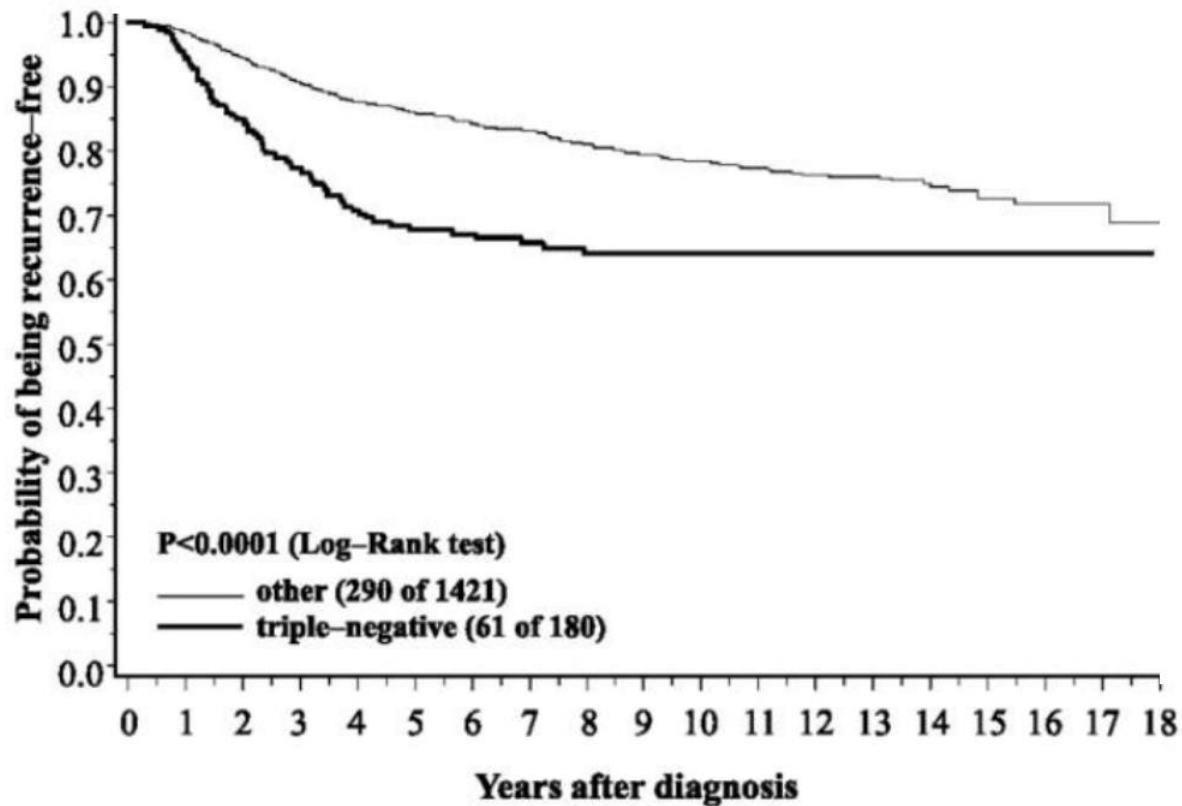
- Relapse pattern<sup>[1]</sup>
  - Short disease-free interval
  - Increase in visceral mets

Rate of Recurrence <sup>[2]</sup>	n	Bone, %	Soft Tissue, %	Viscera, %
TNBC	79	13	13	74
ER+	123	39	7	54
HER2+	78	7	12	81

## Distant Recurrence Following Surgery<sup>[3]</sup>

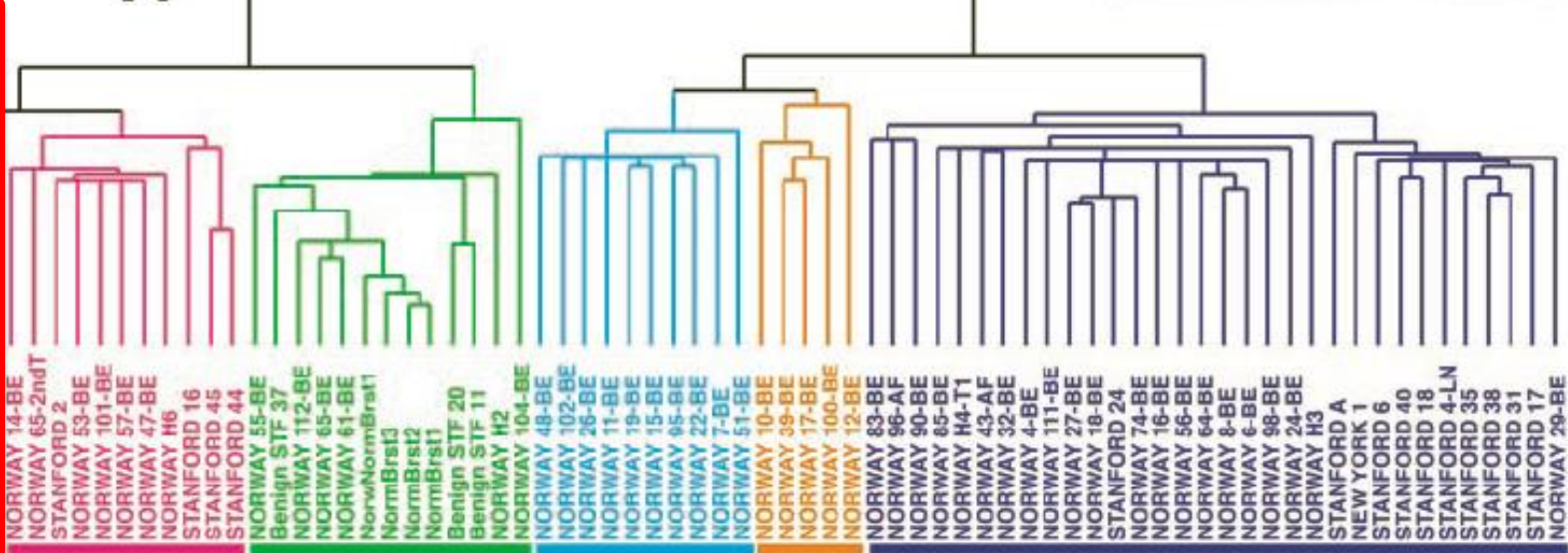


# Rates of Distant recurrences in TNBC & other BC





Basal-like



ERBB2+

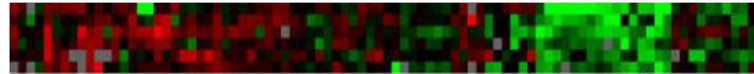
Normal Breast-like

Luminal Subtype C

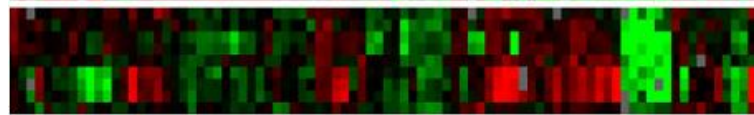
Luminal Subtype B

Luminal Subtype A

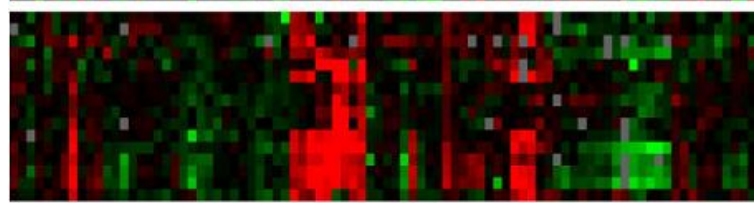
MOLECULAR PROFILING



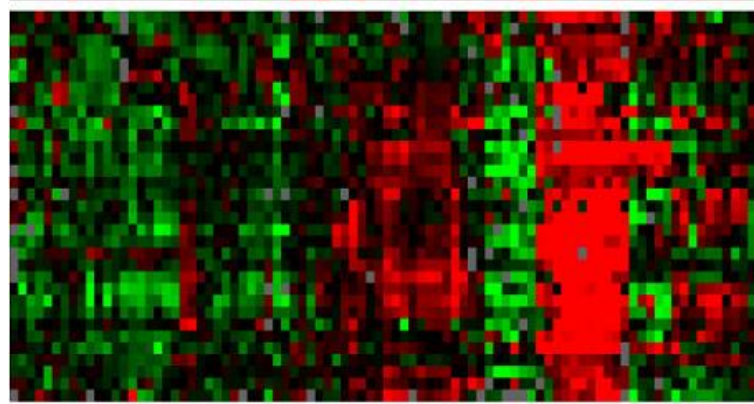
Homo sapiens cDNA FLJ12900 fis, clone NT2RP2004321 R68407  
DKFZ596O1624 protein AA119578  
hepsin transmembrane protease, serine 1 HF2182  
EST similar to transcription elongation factor 1f1B5 RC0960  
trefoil factor 1 breast cancer, estrogen-inducible in R9377  
ESTs W87626



cDNA: FLJ21918 fis, clone HEP04006 T72098  
serine protease inhibitor, Kuritz type, 2 AA031287  
cadherin 1, type 1, E-cadherin epithelial W6659  
cadherin 1, type 1, E-cadherin epithelial H9778  
junction plakoglobin R06417  
creatine kinase, mitochondrial 1 ubiquitous H43515  
nuclear factor 1A AA022462  
creatine kinase, mitochondrial 1 ubiquitous AA019032  
metarctin AA292676



myeloid/lymphoid or mixed-lineage leukemia trithorax homolog AA454610  
zinc finger protein 144 Mel-15 AA468420  
cDNA DKFZp564O2364 from clone DKFZp564O2364 W0240  
matrix metalloproteinase 15 membrane-inserted AA443300  
S/WSN1 related, matrix associated, subfamily e, member 1 W51779  
ESTs L27004  
TNF receptor-associated factor 4 AA596826  
TGFBI-induced anti-apoptotic factor 1 AA446222  
hypothetical protein FLJ10796 W81185  
ficolin 2 R72513  
steroidogenic acute regulatory protein related AA504615  
growth factor receptor-bound protein 7 H53702  
ERBB2 AA025141  
ERBB2 AA443351  
ERBB2 AA480116  
KIAA0130 gene product N54470



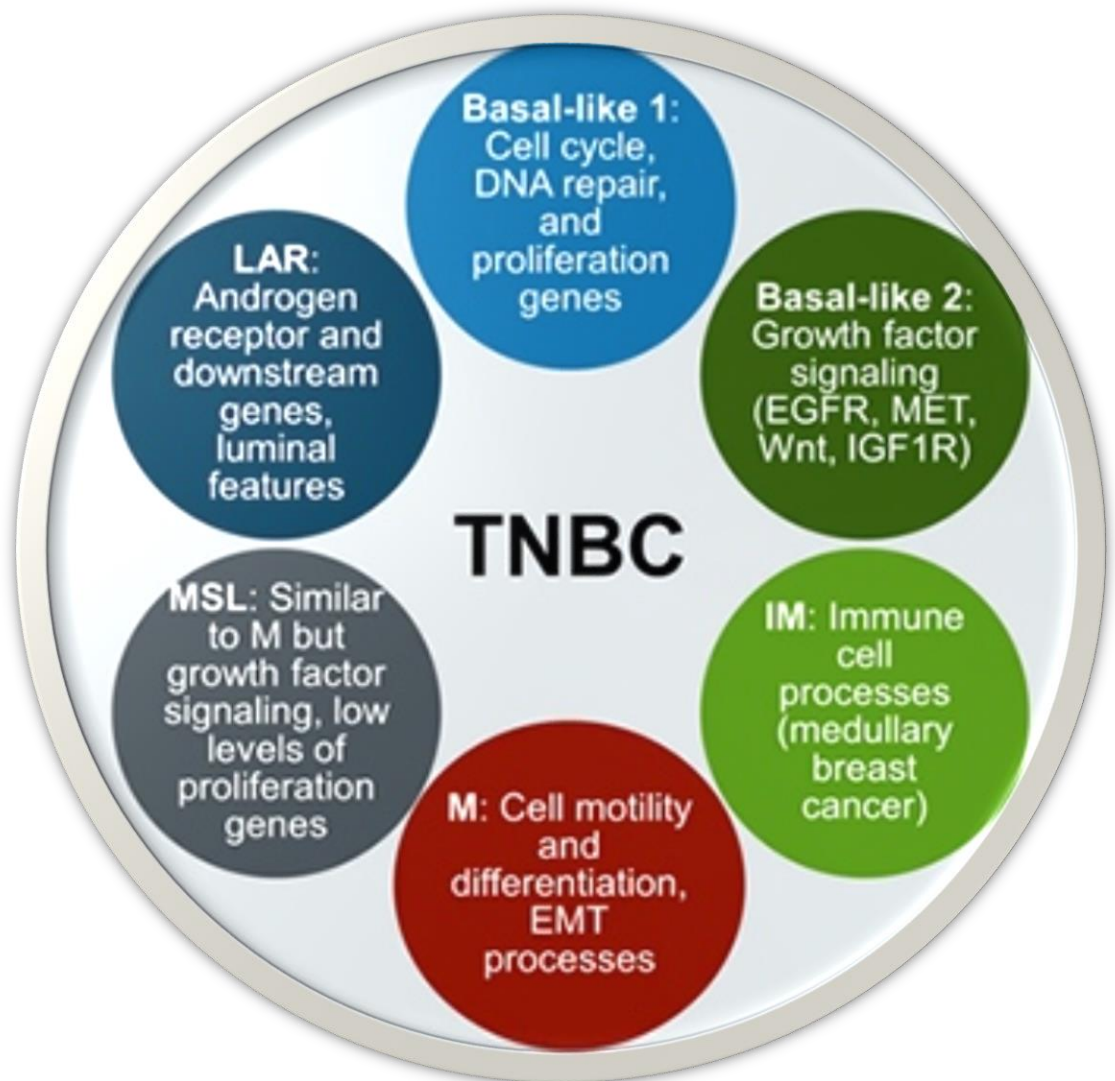
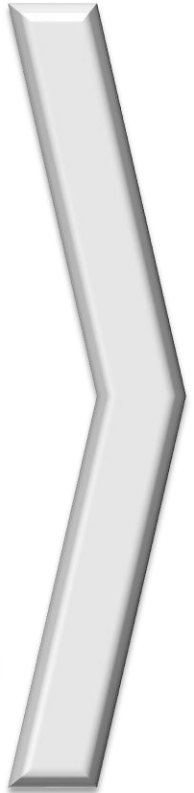
Human proteinase activated receptor-2 AA454652  
pre-B-cell colony-enhancing factor AA291802  
y-myc avian myelocytomatosis viral oncogene homolog AA446400  
ESTs. Highly similar to J52164 frizzled-6 protein T89338  
metallothionein 1L H80129  
metallothionein 1G H53339  
integrin, alpha 2 AA443257  
integrin, alpha 2 AA095027  
GRI1 oncogene, alpha W42723  
secretory leukocyte protease inhibitor antileukoprotease AA026102  
hypothetical protein FLJ20481 N32611  
caveolin 1, caveolin protein, 2KD AA055368  
caveolin 2 T84132  
annexin A1 H63077  
insulin-like growth factor binding protein 6 AA478724  
tropomyosin 1, skeletal, fast AA181354  
ESTs AH79149  
integrin, beta 4 AA078430  
laminin, gamma 2 AA677534  
matrix metalloproteinase 14 membrane-inserted N33214  
laminin, alpha 5 AA001431  
collagen, type XVII, alpha 1 H87335  
bullous pemphigoid antigen 1 230240ND H44794  
ataxia-telangiectasia group D-associated protein AA355485  
keratin 17 AA026100  
keratin 5 W72110  
muscle and heart mammary-derived growth inhibitor H70502  
cadherin 3, type 1, P-cadherin placental AA423217  
epidermal growth factor receptor AA284715  
ESTs. Highly similar to T2EA W37448  
transforming growth factor, beta receptor II AA487034  
Unknown Clone 1  
nonoamine oxidase A AA011095

**TNBC = Basal Like BC**



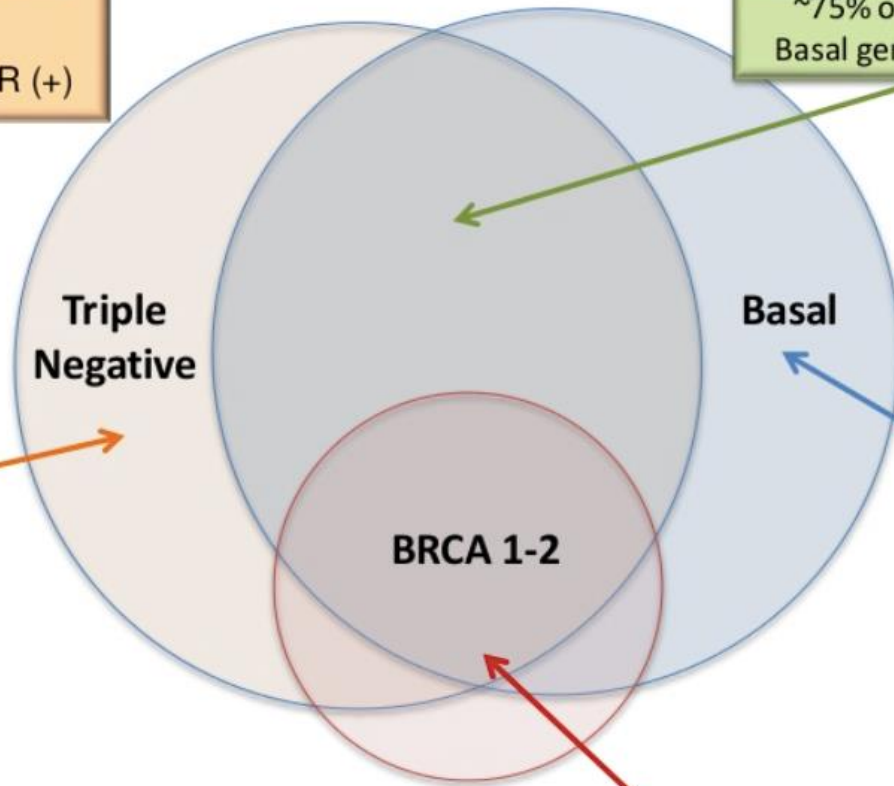


# Lehmann's classification



ER- / PR- / HER2-  
 ~15% of all breast carcinomas  
 Poorly differentiated  
 Express CK 5/6, 17, EGFR (+)

- **Triple negative** but not basal
- Definition by IHC
- Includes other histologies (medullar, adenoid cystic)
- 10-30% can also include "claudin-low," a subtype notable for high expression of stem cell markers
- 90% of TNBC do not have BRCA mutations



~75% of TNBC have Basal gene expression

- **Basal** but not triple negative
- Definition by gene expression
- Includes most BRCA1 mutated tumors
- 15-40% are ER+, PR+ or HER2+

- BRCA1-2 mutated tumors
- ~5% of Breast Cancer
- 50% BRCA-1 carriers are basal-like

1. Pal & Mortimer. *Maturitas* 2009;
2. Gluz et al. *Ann Oncol* 2009;
3. Anders & Carey. *Oncology* 2008.
4. Young et al. *BMC Cancer* 2009
5. Schneider, B. P. et al. *Clin Cancer Res* 2008;14:8010-8018



# Basal like breast ca respond to conventional chemo

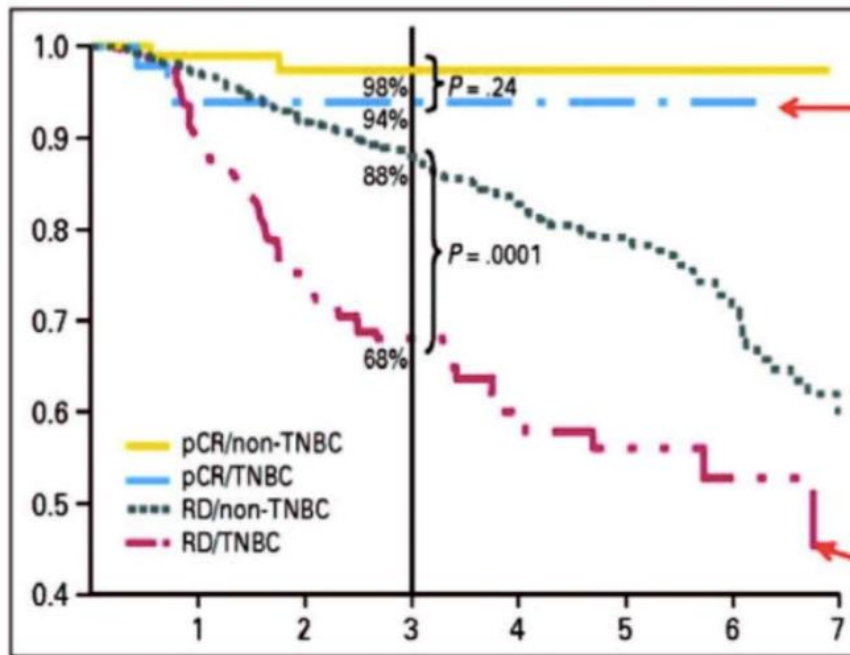
## Pathologic Complete Response:

	T-FAC (N=82)*	AC-T (n=107)*
Luminal A/B	7%	7%
Normal-like	0	NA
HER2+/ER-	45%	36%
Basal-like/triple negative	45%	26%

- Basal-like / triple negative breast cancer responds to primary chemotherapy.

Explanation of higher response but worse outcome?

# Responsiveness to conventional chemotherapy



Basal like / triple negative often responsive

If pCR achieved correlate with good outcome

Nonresponsive = poor outcome

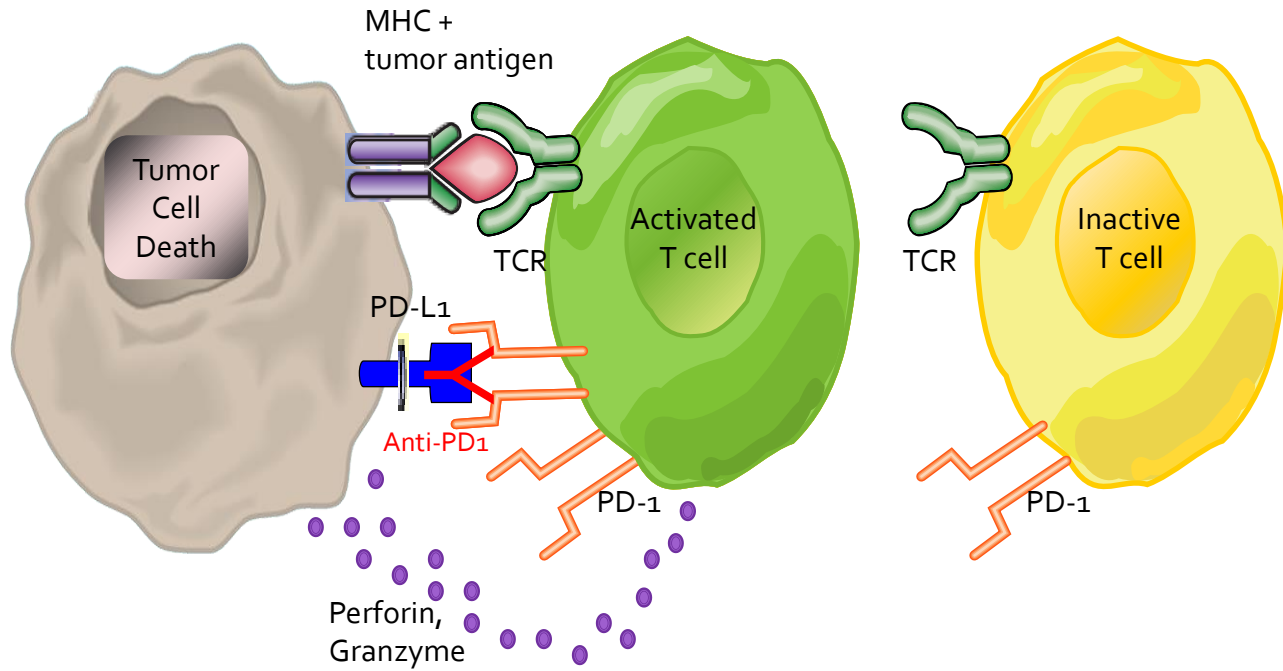
# Overall survival of patients with mBC (2008–2013)

BC subtype	2008	2009	2010	2011	2012	2013
HR+ HER2- (n=9908)	43.7 (40.2–46.6)	42 (38.9–44.6)	40.9 (38.0–43.4)	42 (39.3–45)	44.5 (41.8–47.3)	40.3 (37.8–NR)
HER2 +++ (n=2861)	38.67 (33.6–44.6)	42.3 (38.3–50.8)	40.1 (35.2–45.6)	42.38 (36.5–49.8)	51.1 (46.5–NR)	Median not reached
HR- HER2- (n=2317)	15.1 (12.7–16.4)	15.1 (13.0–17.4)	14.7 (13.2–17.0)	14.0 (11.4–15.9)	13.9 (11.4–15.9)	14.1 (12.5–15.5)

# Immunotherapy

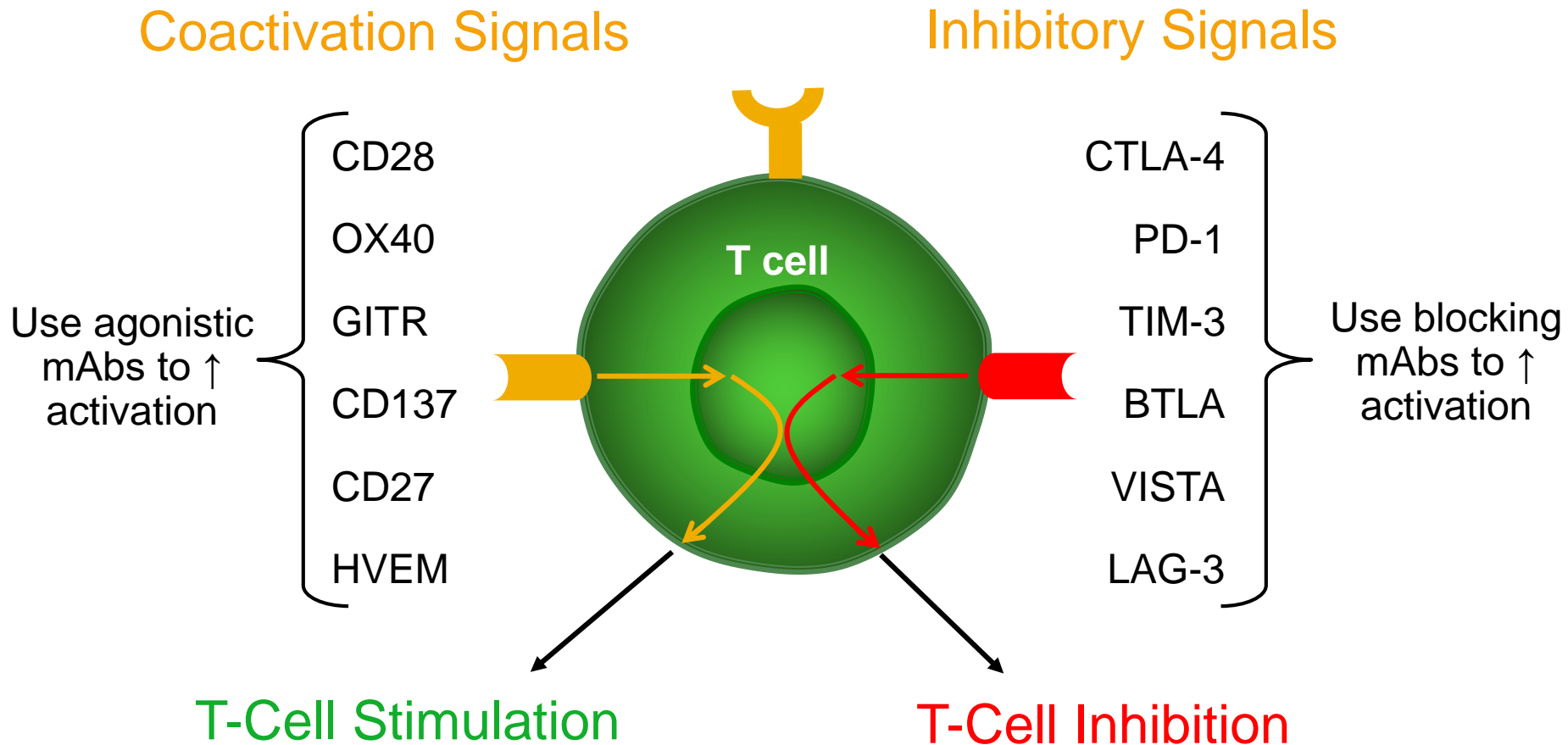


# Role of PD-1 pathway; Mechanism of action





# Regulating the T cell immune response



# KEYNOTE-522: Phase 3 Study of Pembrolizumab + Chemotherapy versus Placebo + Chemotherapy as Neoadjuvant Treatment, Followed by Pembrolizumab versus Placebo as Adjuvant Treatment for Early Triple-Negative Breast Cancer (TNBC)

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1. Barts Cancer Institute, Queen Mary University London, London, UK; 2. IOB Institute of Oncology, Quiron Group; Vall d'Hebron Institute of Oncology (VHIO), Madrid & Barcelona, Spain; 3. University of Toronto, Toronto, Ontario, Canada; 4. Yale School of Medicine, Yale Cancer Center, New Haven, CT, USA; 5. Cedars-Sinai Medical Center, Los Angeles, CA, USA; 6. Breast Unit, Kliniken Essen-Mitte, Essen, Germany; 7. Department of Oncology-Pathology, Karolinska Institutet and Breast Cancer Centre, Cancer theme, Karolinska University Hospital, Solna, Sweden; 8. Institute of Pathology, Philipps-University Marburg and University Hospital Marburg (UKGM), Marburg, Germany; 9. Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; 10. Westmead Breast Cancer Institute, Westmead Hospital and the University of Sydney, Sydney, NSW, Australia; 11. Breast Center, University of Munich (LMU), Munich, Germany; 12. Hokkaido Cancer Center, Sapporo, Japan; 13. University Hospital Erlangen, Comprehensive Cancer Center Erlangen -EMN, Erlangen, Germany; 14. Breast Unit, Champalimaud Clinical Center/Champalimaud Foundation, Lisbon, Portugal; 15. Merck & Co., Inc., Kenilworth, NJ, USA; 16. Baylor University Medical Center, Texas Oncology, US Oncology, Dallas, TX, USA

# Immunotherapy and TNBC

- Neoadjuvant pembrolizumab + chemotherapy showed manageable safety and antitumor activity in early TNBC<sup>5,6</sup>
- Pembrolizumab plus chemotherapy was granted Breakthrough Therapy Designation by the US FDA for the neoadjuvant treatment of patients with high-risk, early-stage TNBC based on data from KEYNOTE-173<sup>5</sup> and I-SPY2<sup>6</sup>

# Pathological Complete Response (pCR)

- Patients with TNBC who achieve pCR after neoadjuvant chemotherapy have sustained clinical benefit<sup>1,2</sup>
- Taxane- and anthracycline-based neoadjuvant regimens produce pCR rates of ~40%<sup>3</sup>; addition of platinum increases pCR rates to ~50-55%<sup>4-7</sup>
- Meta-analysis of individual patient data showed a strong association of pCR after neoadjuvant chemotherapy with improved long-term EFS (HR 0.24) and OS (HR 0.16) benefit<sup>8</sup>
- Regulatory guidance supports pCR as an endpoint for accelerated approval of neoadjuvant treatment in early TNBC with long-term confirmatory EFS<sup>9,10</sup>
- Novel drugs and drug combinations that increase pCR rates and improve long-term EFS are needed

1. Cortazar P et al. *Lancet* 2014;384:164-72.

2. Huang M et al. Poster. ESMO Breast Cancer; May 2-4, 2019; Berlin, Germany.

3. Loibl S et al. *Ann Oncol* 2019;30:1279-88.

4. von Minckwitz G et al. *Lancet Oncol* 2014;15:747-56.

5. Sikov WM et al. *J Clin Oncol* 2015;33:13-21.

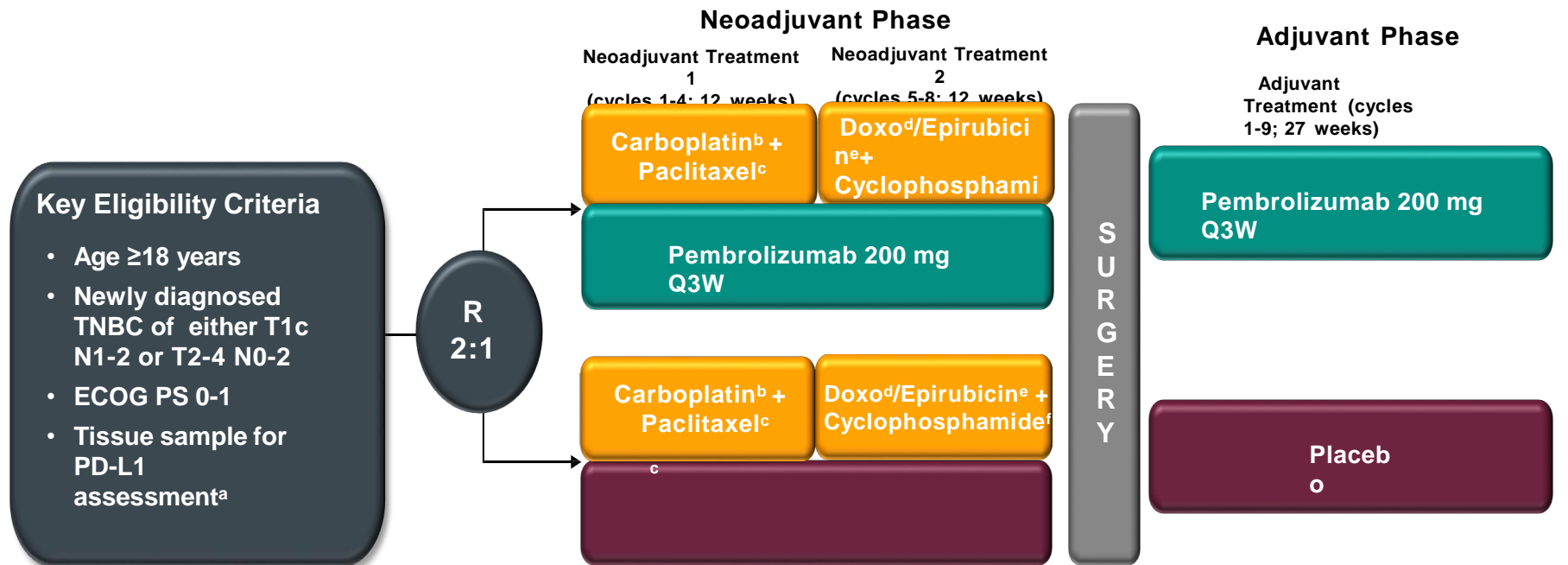
6. Petrelli F et al. *Breast Cancer Res Treat* 2014;14:223-32.

7. Loibl S et al. *Lancet Oncol* 2018;19:497-509.

8. Spring LM et al. *Cancer Research* 2019;79:Abstract GS2-03.

9. Food and Drug Administration (CDER). Silver Spring (MD): U.S. DHHS; 2014.

# KEYNOTE-522 Study Design (NCT03036488)



## Stratification Factors:

- Nodal status (+ vs -)
- Tumor size (T1/T2 vs T3/T4)
- Carboplatin schedule (QW vs Q3W)

**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)

<sup>a</sup>Must consist of at least 2 separate tumor cores from the primary tumor.

<sup>b</sup>Carboplatin dose was AUC 5 Q3W or AUC 1.5 QW. <sup>c</sup>Paclitaxel dose was 80 mg/m<sup>2</sup> QW.

<sup>d</sup>Doxorubicin dose was 60 mg/m<sup>2</sup> Q3W. <sup>e</sup>Epirubicin dose was 90 mg/m<sup>2</sup> Q3W. <sup>f</sup>Cyclophosphamide dose was 600 mg/m<sup>2</sup> Q3W.



# Study Endpoints

- Primary Endpoints
  - pCR (ypT0/Tis ypN0) assessed by local pathologist in ITT population<sup>a</sup>
  - Event-free survival (EFS) assessed by investigator in ITT population
- Secondary Endpoints
  - pCR as per alternative definitions (ypT0 ypN0 and ypT0/Tis)
  - Overall survival (OS)<sup>b</sup>
  - pCR, EFS<sup>a</sup> and OS<sup>b</sup> in the PD-L1–positive population<sup>c</sup>
  - Safety in all treated patients
- Key Exploratory Endpoints
  - Residual cancer burden (RCB)<sup>b</sup>
  - EFS by pCR<sup>b</sup>
  - pCR and EFS by TILs<sup>b</sup>

<sup>a</sup>Subjects without pCR data due to any reason or who received neoadjuvant chemotherapy not specified in the protocol were counted as non -pCR. <sup>b</sup>To be presented at a later date. <sup>c</sup>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

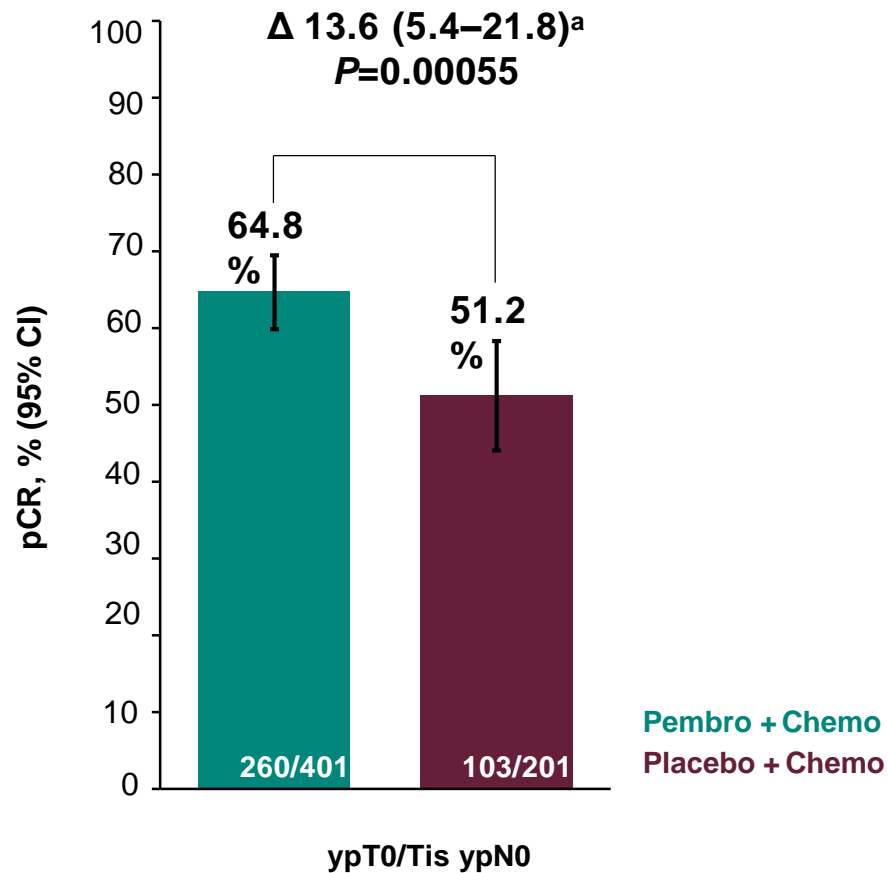
# Baseline Characteristics, ITT Population

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 <sup>a</sup>	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)

<sup>a</sup>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: April 24, 2019.

# Pathological Complete Response at IA<sub>1</sub>

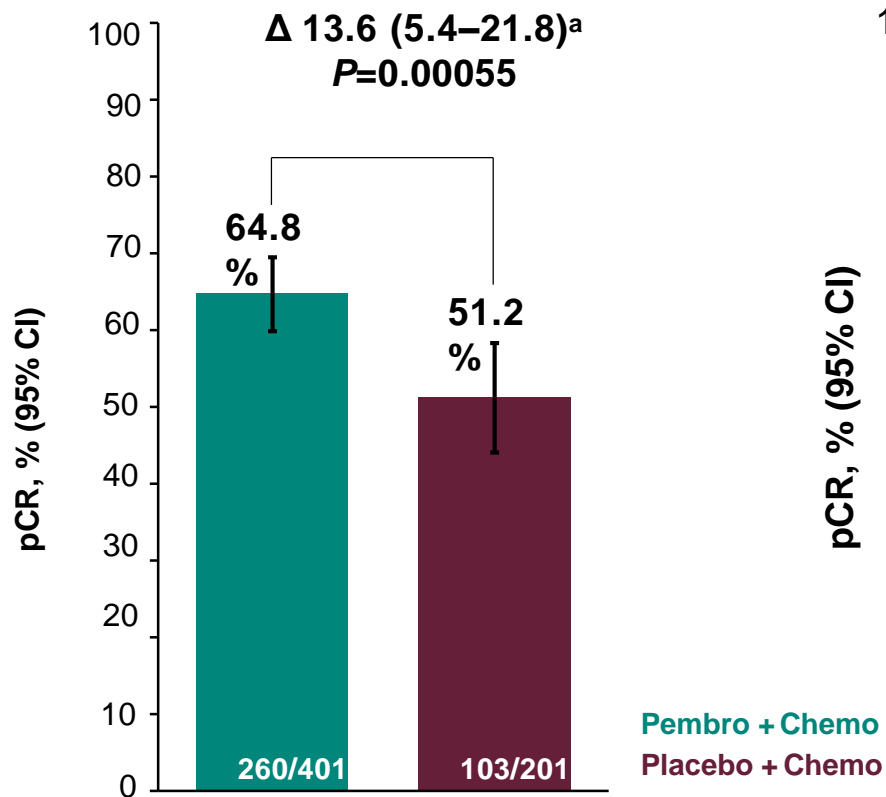
## Primary Endpoint



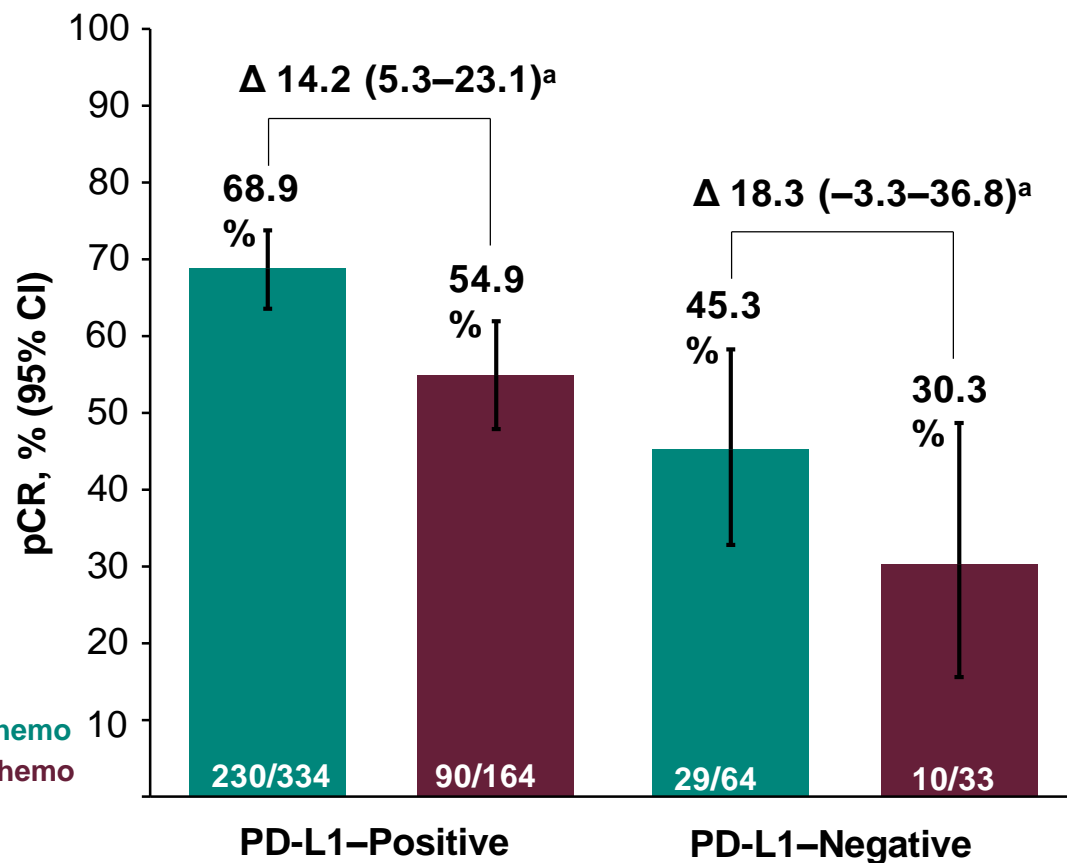
<sup>a</sup>Estimated treatment difference based on Miettinen & Nurminen method stratified by randomization stratification factors. Data cutoff date: September 24, 2018.

# Pathological Complete Response at IA<sub>1</sub>

## Primary Endpoint

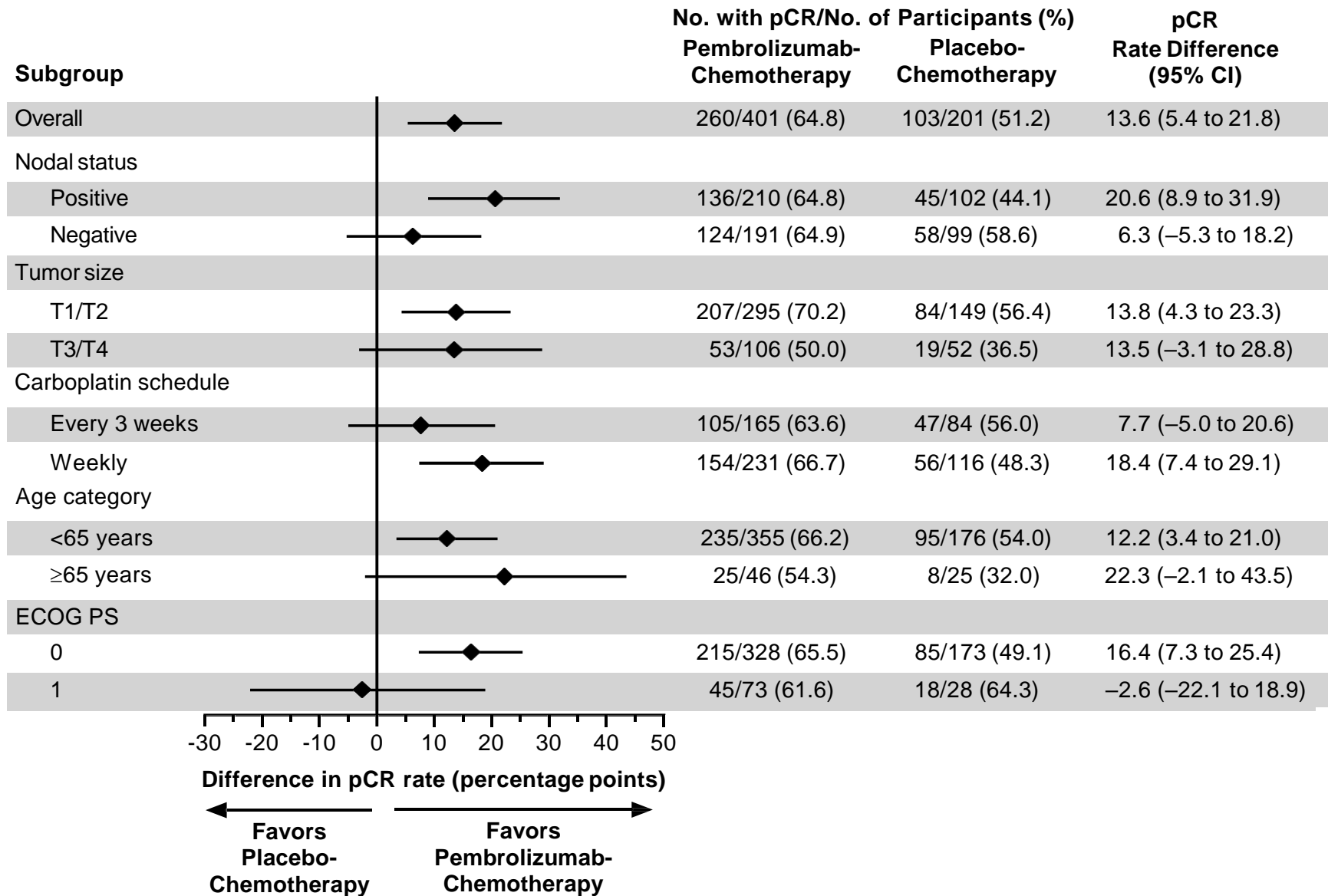


## By PD-L1



<sup>a</sup>Estimated treatment difference based on Miettinen & Nurminen method stratified by randomization stratification factors. <sup>b</sup>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  $\geq$  1. Data cutoff date: September 24, 2018.

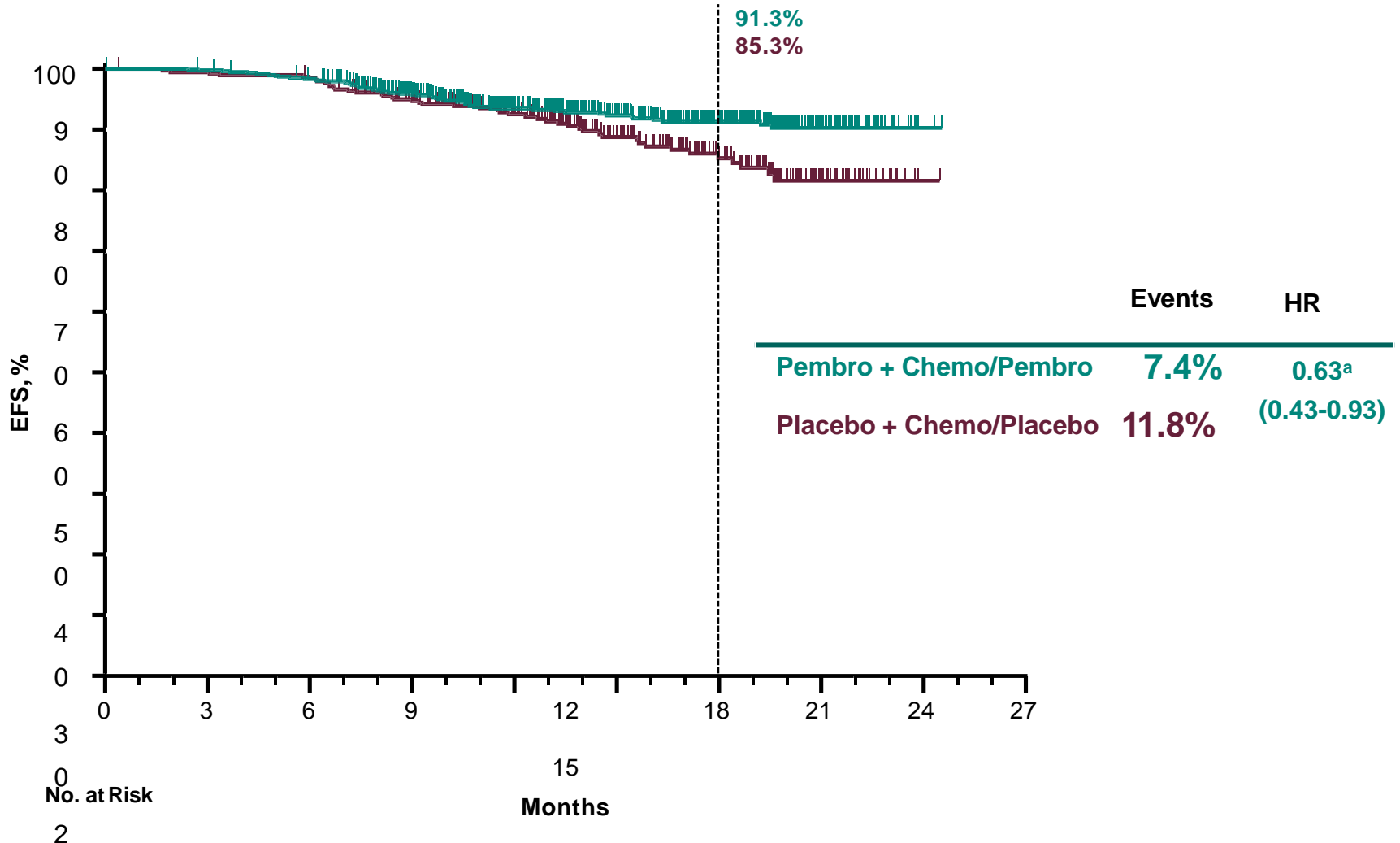
# Pathological Complete Response in Subgroups



For the overall population, analysis is based on Miettinen and Nurminen method stratified by nodal status (positive versus negative), tumor size (T1/T2 versus T3/T4), and frequency of carboplatin administration (once weekly versus once every 3 weeks). For other subgroups, analysis is based on unstratified Miettinen and Nurminen method.









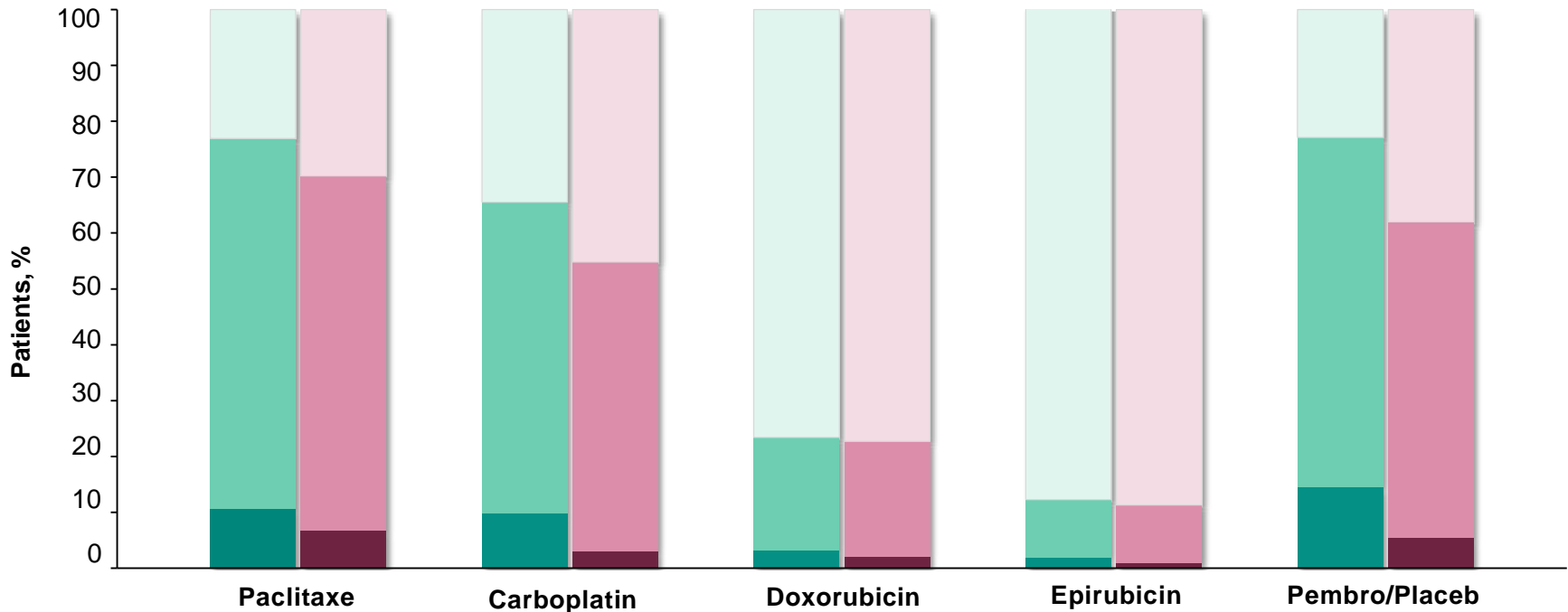
# Event-Free Survival at IA2



<sup>a</sup>Prespecified *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.

# Drug Exposure and Dose Adjustment

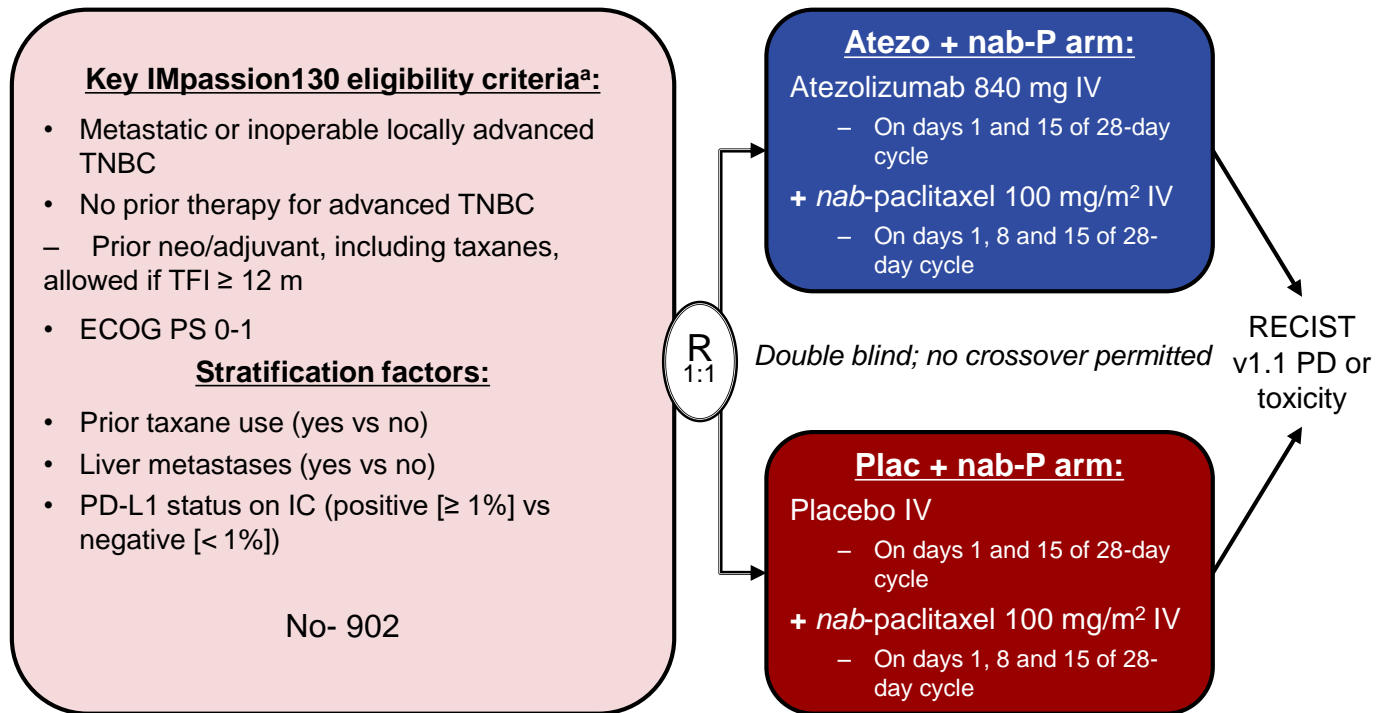
	Discontinuation	Modification	No Change	Mean Treatment Duration (wks)		Mean Number of Doses		
				Pembro	Placebo	Pembro	Placebo	
<b>Pembro</b>				Paclitaxel	11.5	11.5	11.0	11.2
				Carboplatin QW	11.2	11.4	11.0	11.1
<b>Placebo</b>				Carboplatin Q3W	9.7	9.8	3.9	4.0
				Doxorubicin	8.9	9.2	3.8	3.9
				Epirubicin	8.9	8.9	3.8	3.8
				Pembro/Placebo	20.0	21.1	7.1	7.4



# Summary

- KEYNOTE-522 is the first prospective randomized placebo controlled phase 3 trial of pembrolizumab in early TNBC in the neoadjuvant/adjuvant setting
- Addition of pembrolizumab to platinum-containing neoadjuvant chemotherapy resulted in a statistically significant and clinically meaningful increase in pCR (ypT0/Tis ypN0) of 13.6 percentage points (P=0.00055)
  - Consistent benefit seen with pCR defined as ypT0 ypN0 and ypT0/Tis
  - Benefit of pembrolizumab independent of PD-L1 status
- At this early timepoint, there was a favorable trend for EFS in the pembrolizumab arm (HR 0.63)
- Safety was consistent with the known profiles of each regimen; long-term safety follow-up is ongoing

# IMpassion130 study design



Co-primary endpoints were PFS and OS in the ITT and PD-L1+ populations<sup>d</sup>

Key secondary efficacy endpoints (ORR and DOR) and safety were also evaluated

IC, tumour-infiltrating immune cell; TFI, treatment-free interval. <sup>a</sup> ClinicalTrials.gov: NCT02425891. <sup>b</sup> Locally evaluated per ASCO–College of American Pathologists (CAP) guidelines. <sup>c</sup> Centrally evaluated per VENTANA SP142 IHC assay (double blinded for PD-L1 status). <sup>d</sup> Radiological endpoints were investigator assessed (per RECIST v1.1).

Schmid P, et al. IMpassion130 ESMO 2018 (LBA1\_PR) <http://bit.ly/2DMhayg>

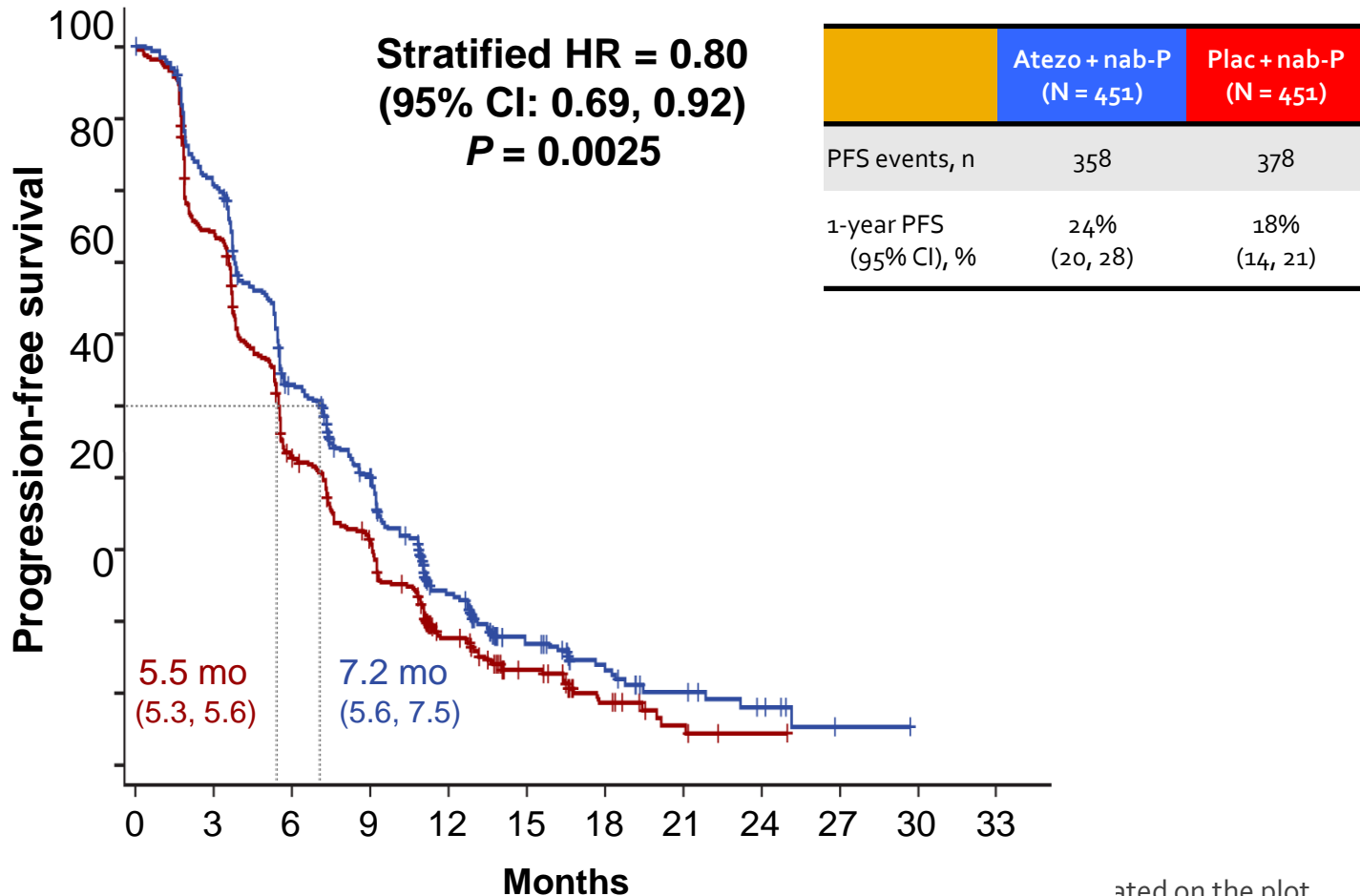
# IMpassion130 baseline characteristics

Characteristic	Atezo + nab-P (N = 451)	Plac + nab-P (N = 451)
Median age (range), y	55 (20-82)	56 (26-86)
Female, n (%)	448 (99%)	450 (100%)
Race, n (%) <sup>a</sup>		
White	308 (68%)	301 (67%)
Asian	85 (19%)	76 (17%)
Black/African American	26 (6%)	33 (7%)
Other/multiple	20 (4%)	26 (6%)
ECOG PS, n (%) <sup>b,c</sup>		
0	256 (57%)	270 (60%)
1	193 (43%)	179 (40%)
Prior (neo)adjuvant treatment, n (%)	284 (63%)	286 (63%)
Prior taxane	231 (51%)	230 (51%)
Prior anthracycline	243 (54%)	242 (54%)

Characteristic	Atezo + nab-P (N = 451)	Plac + nab-P (N = 451)
Metastatic disease, n (%)	404 (90%)	408 (91%)
No. of sites, n (%) <sup>d</sup>		
0-3	332 (74%)	341 (76%)
≥ 4	118 (26%)	108 (24%)
Site of metastatic disease, n (%)		
Lung	226 (50%)	242 (54%)
Bone	145 (32%)	141 (31%)
Liver	126 (28%)	118 (26%)
Brain	30 (7%)	31 (7%)
Lymph node only <sup>d</sup>	33 (7%)	23 (5%)
PD-L1+ (IC), n (%)	185 (41%)	184 (41%)

Data cutoff: 17 April 2018. <sup>a</sup> Race was unknown in 12 patients in the Atezo + nab-P arm and 15 in the Plac + nab-P arm. <sup>b</sup> Of n = 450 in each arm. <sup>c</sup> ECOG PS before start of treatment was 2 in 1 patient per arm. <sup>d</sup> Of n = 450 in the Atezo + nab-P arm and n = 449 in the Plac + nab-P arm.

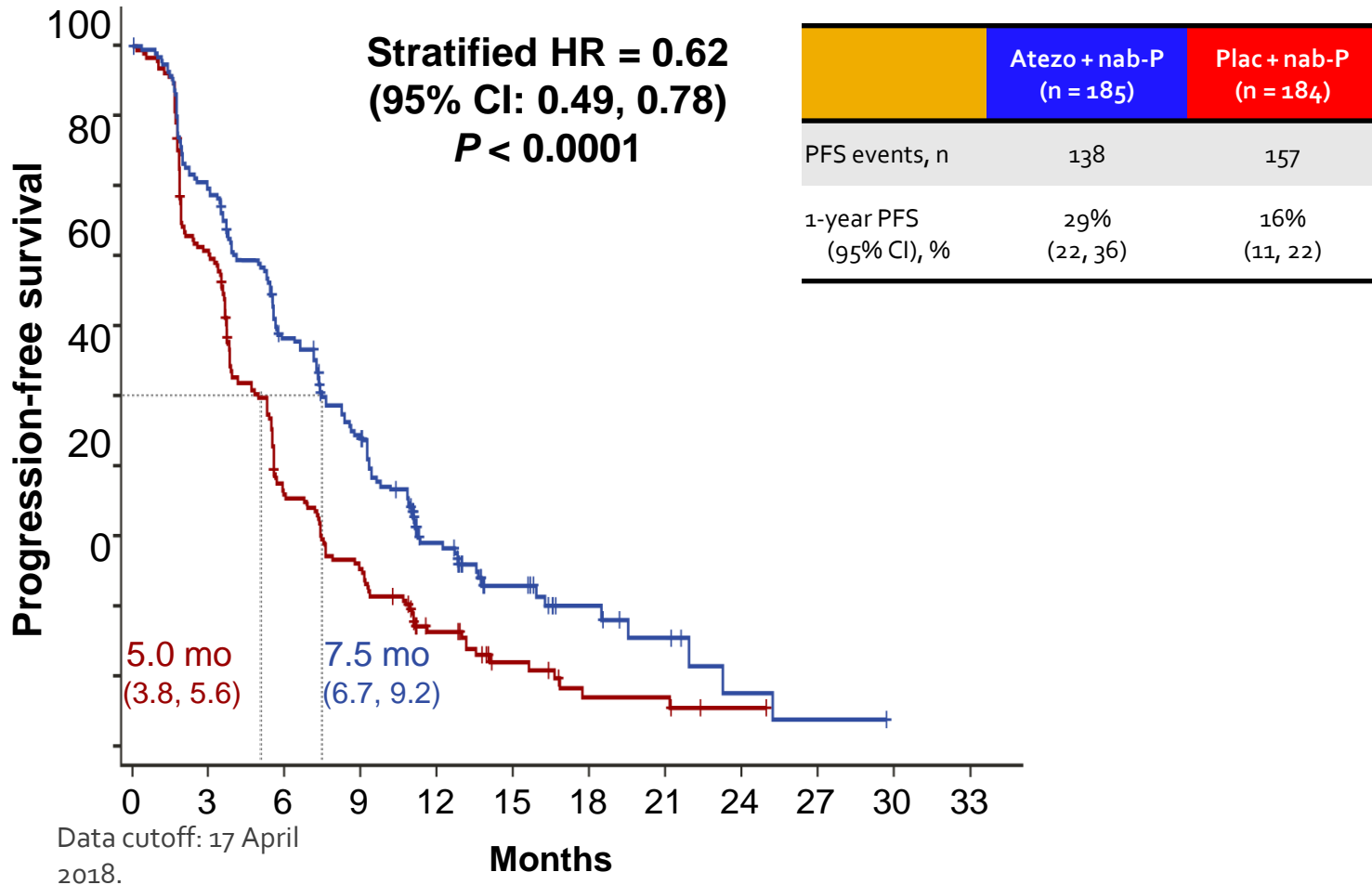
# Primary PFS analysis: ITT population



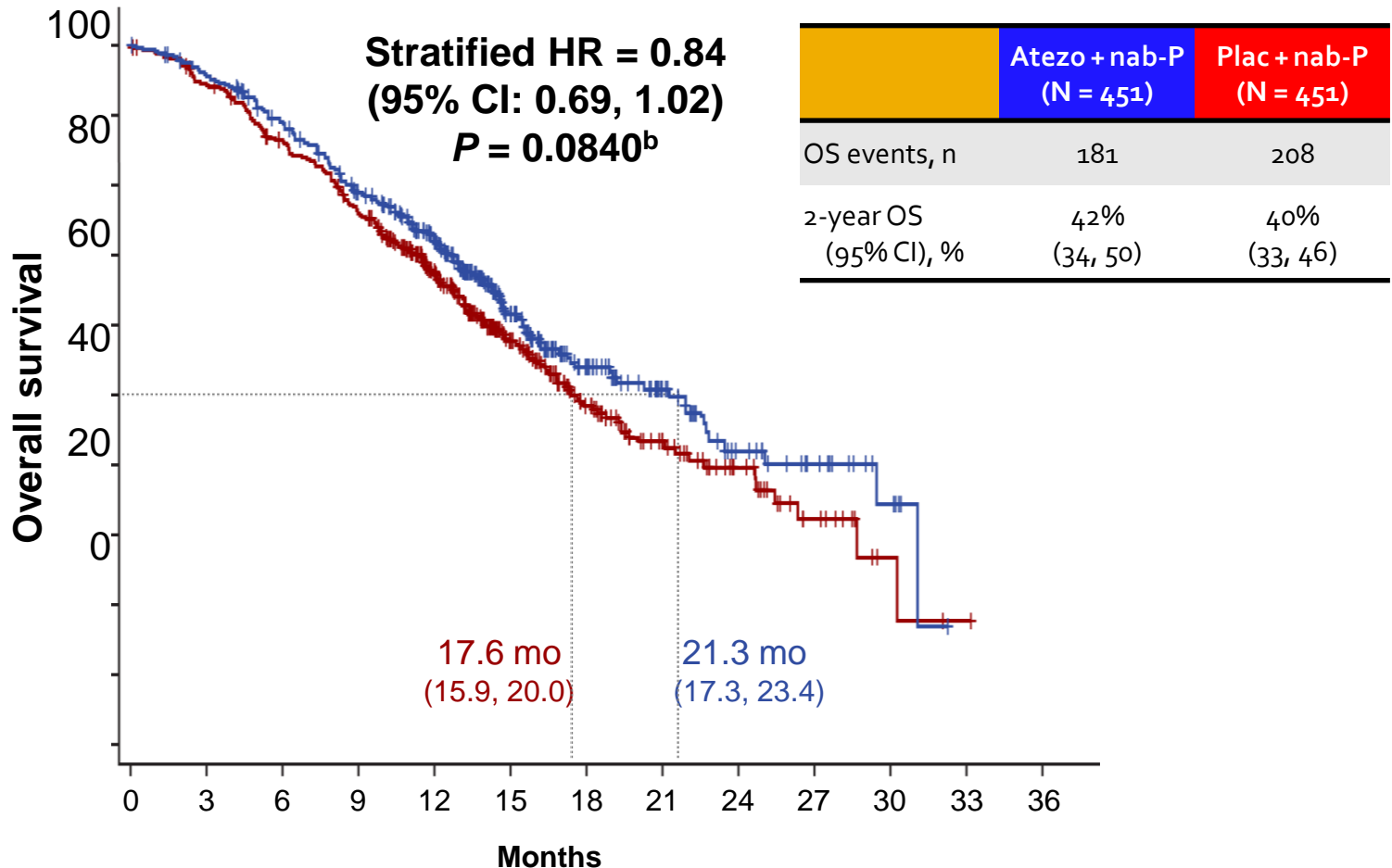
Median follow-up (ITT): 12.9 m.

ated on the plot.

# Primary PFS analysis: PD-L1+ population



# Interim OS analysis: ITT population

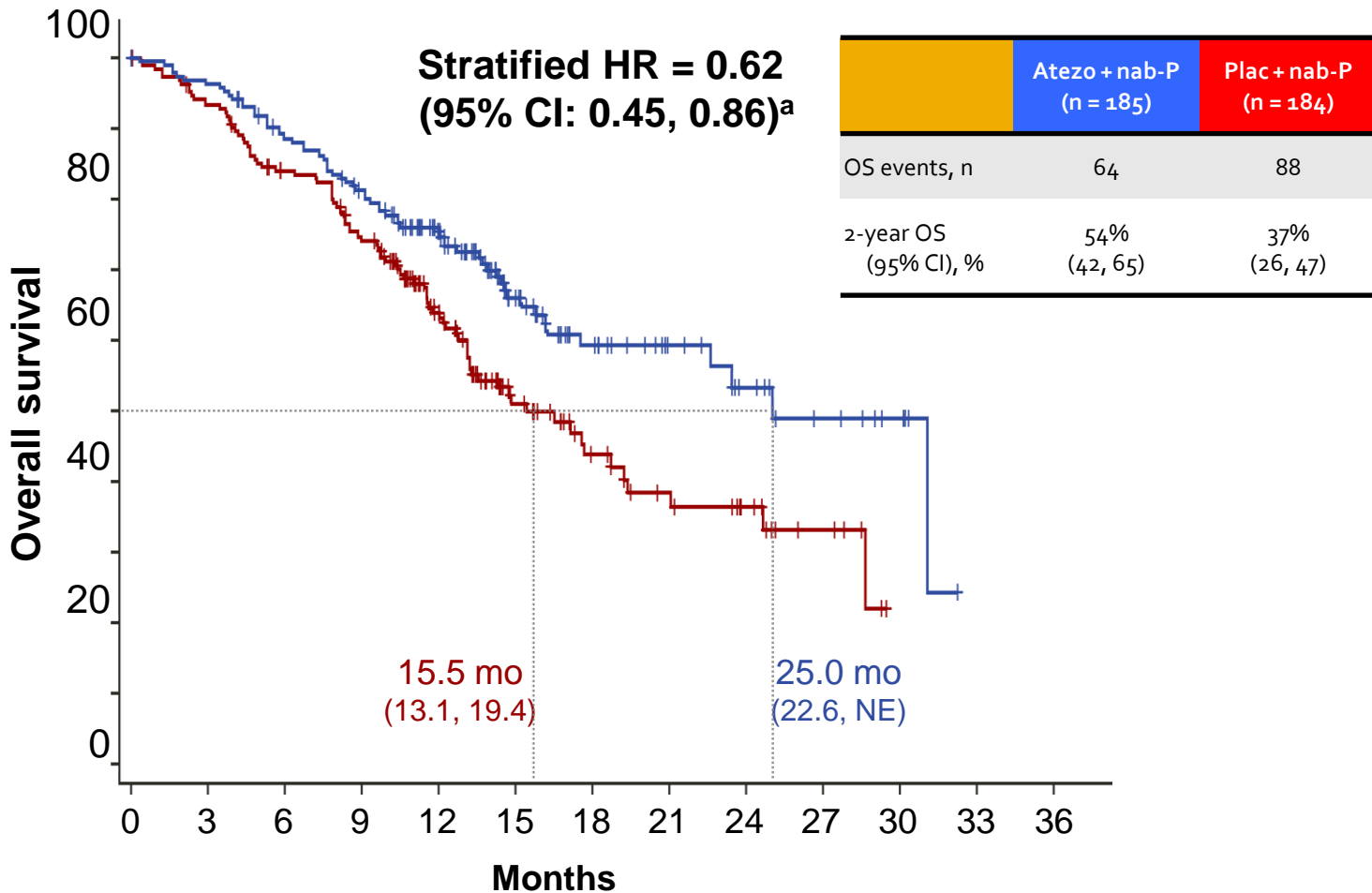


Data cutoff: 17 April 2018. Median OS durations (and 95% CI) are indicated on the plot. Median follow-up (ITT): 12.9 months.

<sup>a</sup> For the interim OS analysis, 59% of events had occurred. <sup>b</sup> Significance boundary was not crossed.

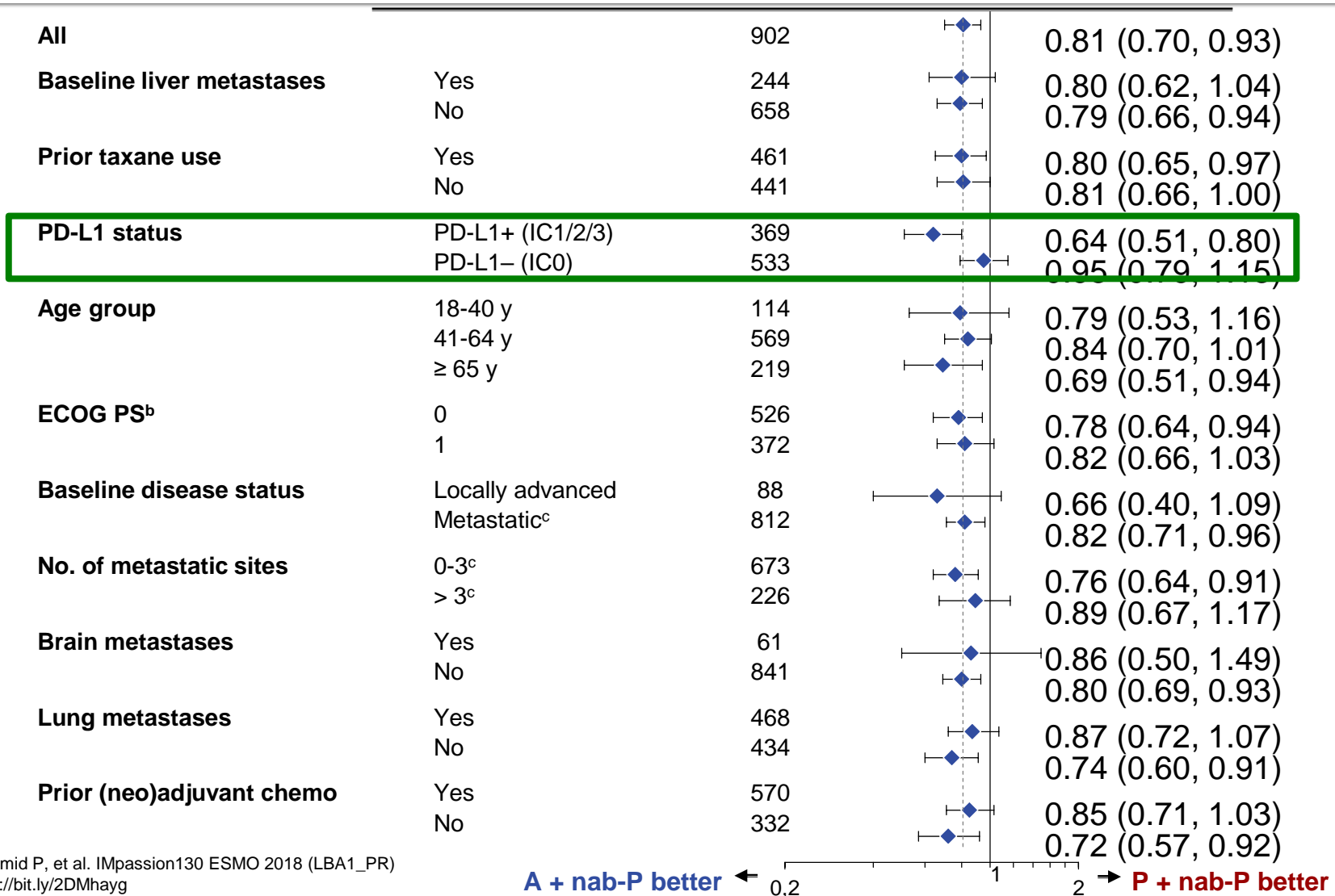


# Interim OS analysis: PD-L1+ population

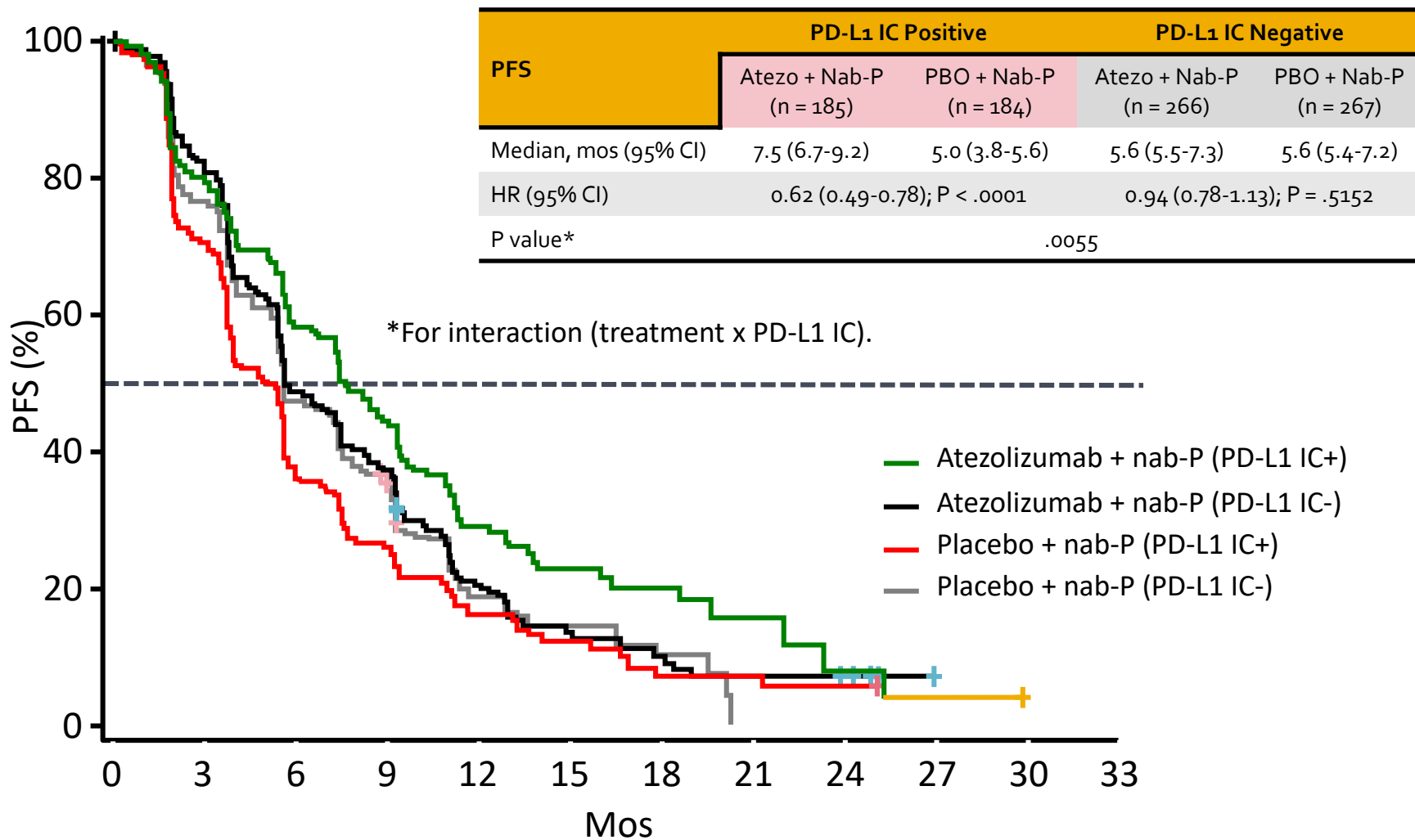


formally tested.

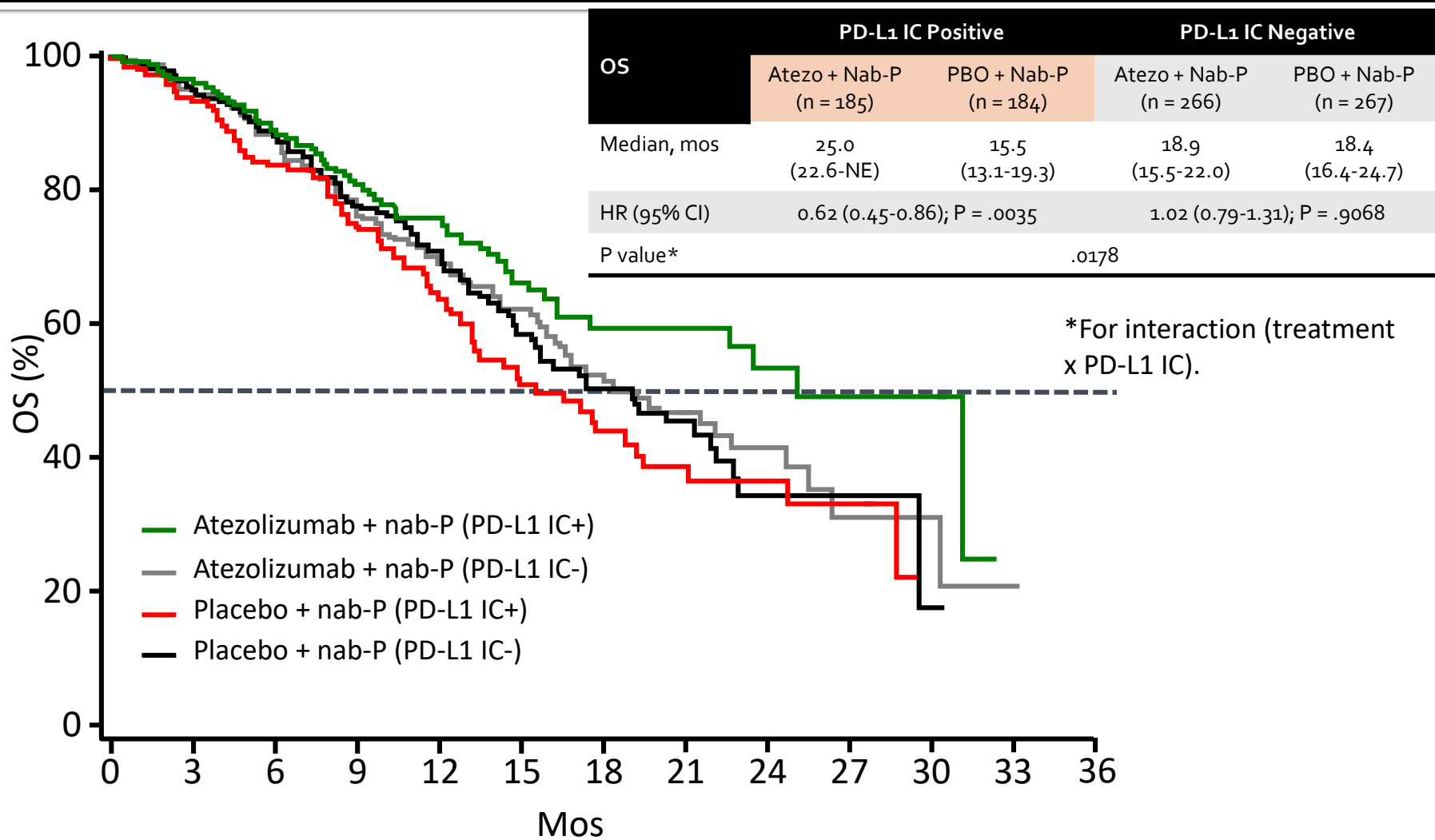
# PFS subgroup analysis: ITT population



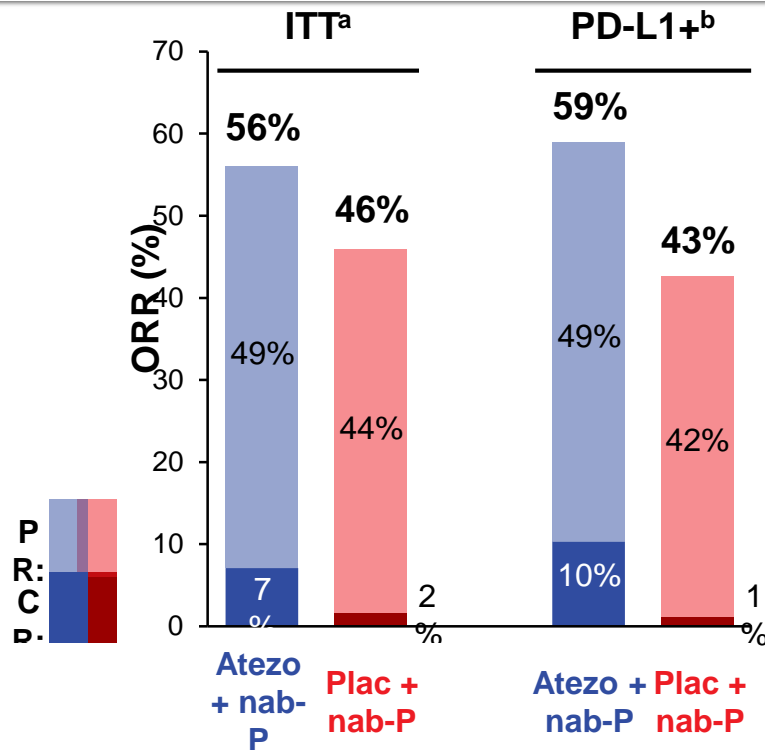
# IMpassion130: PFS by PD-L1 Expression



# IMpassion130: OS by PD-L1 Expression



# Secondary efficacy endpoints



Numerically higher and more durable responses were seen in the Atezo + nab-P arm

ITT:  $P = 0.0021$ ;

PD-L1+:  $P = 0.0016$ )

The CR rate was also higher

ITT population: 7% vs 2% PD-

L1+ patients: 10% vs 1%

DOR, median (95% CI), mo	7.4 (6.9, 9.0)	5.6 (5.5, 6.9)	8.5 (7.3, 9.7)	5.5 (3.7, 7.1)
No. of ongoing responses, n (%) <sup>c</sup>	78 (31%)	52 (25%)	39 (36%)	19 (24%)

# Exposure and dose intensity

	<i>nab</i> -P Exposure		Atezo or Plac Exposure	
	Atezo + <i>nab</i> -P (n = 452)	Plac + <i>nab</i> -P (n = 438)	Atezo + <i>nab</i> -P (n = 452) <sup>a</sup>	Plac + <i>nab</i> -P (n = 438)
<b>Treatment duration, weeks</b>				
Median (range)	22.1 (0-137)	21.8 (0-103)	24.1 (0-139)	22.1 (0-109)
<b>Patients with indicated treatment duration, n (%)</b>				
≤ 16 weeks	361 (80%)	316 (72%)	355 (79%)	316 (72%)
≤ 6 months	315 (70%)	257 (59%)	311 (69%)	259 (59%)
≤ 12 months	100 (22%)	75 (17%)	138 (31%)	108 (25%)
≤ 18 months	53 (12%)	44 (10%)	89 (20%)	63 (14%)
> 18 months	12 (3%)	7 (2%)	25 (6%)	15 (3%)
<b>Dose intensity, %</b>				
Mean (SD)	87.7 (18%)	90.4 (15%)	95.8 (10%)	NE
<b>No. of cycles</b>				
Median (range)	6.0 (1-34)	6.0 (1-26)	7.0 (1-35)	6.0 (1-28)

- A higher proportion of patients in the Atezo + *nab*-P arm compared with the Plac + *nab*-P arm received *nab*-P for
  - at least 6 months (70% vs 59%)
  - at least 12 months (22% vs 17%)
- Atezo did not compromise the dose intensity of *nab*-P

# Safety summary

AE, n (%)	Atezo + nab-P (n = 452)	Plac + nab-P (n = 438)
<b>All-cause AEs</b>		
Any grade	449 (99%)	429 (98%)
Grade 3-4	220 (49%)	185 (42%)
Grade 5	6 (1%)	3 (1%)
<b>Treatment-related AEs</b>		
Any grade	436 (96%)	410 (94%)
Grade 3-4	179 (40%)	132 (30%)
Grade 5 <sup>a</sup>	3 (1%) <sup>a</sup>	1 (< 1%) <sup>a</sup>
<b>Any grade serious AEs</b>		
Serious AEs regardless of attribution	103 (23%)	80 (18%)
Treatment-related serious AEs	56 (12%)	32 (7%)
<b>Any-grade AEs leading to any treatment discontinuation</b>	72 (16%)	36 (8%)
Leading to atezo or plac discontinuation	29 (6%)	6 (1%)
Leading to <i>nab</i> -P discontinuation	72 (16%)	36 (8%)
<b>Any-grade AEs leading to any dose reduction or interruption</b>	212 (47%)	177 (40%)
Leading to atezo or plac dose interruption	139 (31%)	103 (24%)
Leading to <i>nab</i> -P dose reduction or interruption	195 (43%)	172 (39%)

AE, adverse event. Safety-evaluable population. Data cutoff: 17 April 2018. <sup>a</sup>Treatment-related deaths: autoimmune hepatitis, mucosal inflammation/death, septic shock (n = 1 each, Atezo + nab-P arm); hepatic failure (n = 1, Plac + nab-P arm).

# Most common serious AEs

SAEs occurring in  $\geq 1\%$  of patients in either arm (regardless of attribution)

SAE, n (%)	Atezo + nab-P (n = 452)		Plac + nab-P (n = 438)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
All	103 (23%)	78 (17%) <sup>a</sup>	80 (18%)	56 (13%) <sup>b</sup>
Pneumonia	10 (2%)	8 (2%) <sup>c</sup>	5 (1%)	0
Urinary tract infection	5 (1%)	2 (< 1%)	0	0
Dyspnoea	5 (1%)	3 (1%)	2 (< 1%)	2 (< 1%)
Pyrexia	5 (1%)	3 (1%)	3 (1%)	0

- A higher proportion of patients in the Atezo + nab-P arm than in the Plac + nab-P arm reported SAEs (23% vs 18%)
- No SAE was reported with a  $\geq 2\%$  difference between treatment arms

SAE, serious adverse event. Data cutoff: 17 April 2018. <sup>a</sup>Six Grade 5 events occurred. <sup>b</sup>Three Grade 5 events occurred. <sup>c</sup>One Grade 5 event occurred.



# AESIs suggestive of potential immune-related aetiology

AESI, n (%) <sup>a</sup>	Atezo + nab-P (n = 452)		Plac + nab-P (n = 438)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
All	259 (57%)	34 (8%)	183 (42%)	19 (4%)
Important AESIs				
Hepatitis (all)	69 (15%)	23 (5%)	62 (14%)	13 (3%)
Hepatitis (diagnosis)	10 (2%)	6 (1%)	7 (2%)	1 (< 1%)
Hepatitis (lab abnormalities)	62 (14%)	17 (4%)	58 (13%)	12 (3%)
Hypothyroidism	78 (17%)	0	19 (4%)	0
Hyperthyroidism	20 (4%)	1 (< 1%)	6 (1%)	0
Pneumonitis	14 (3%)	1 (< 1%)	1 (< 1%)	0
Meningoencephalitis <sup>b</sup>	5 (1%)	0	2 (< 1%)	0
Colitis	5 (1%)	1 (< 1%)	3 (1%)	1 (< 1%)
Adrenal insufficiency	4 (1%)	1 (< 1%)	0	0
Pancreatitis	2 (< 1%)	1 (< 1%)	0	0
Diabetes mellitus	1 (< 1%)	1 (< 1%)	2 (< 1%)	1 (< 1%)
Nephritis	1 (< 1%)	0	0	0
Other AESIs <sup>c</sup>				
Rash	154 (34%)	4 (1%)	114 (26%)	2 (< 1%)
Infusion-related reactions	5 (1%)	0	5 (1%)	0

- Hepatitis rates were balanced
- 1 grade 5 AESI per arm (both treatment related):
  - Atezo + nab-P: autoimmune hepatitis
  - Plac + nab-P: hepatic failure
- All hypothyroidism AESIs were grade 1-2; none led to discontinuation
  - Atezo + nab-P: 17%
  - Plac + nab-P: 4%
- Pneumonitis was infrequent with only 1 grade 3-4 event in the Atezo + nab-P arm
  - Atezo + nab-P: 3%
  - Plac + nab-P: < 1%

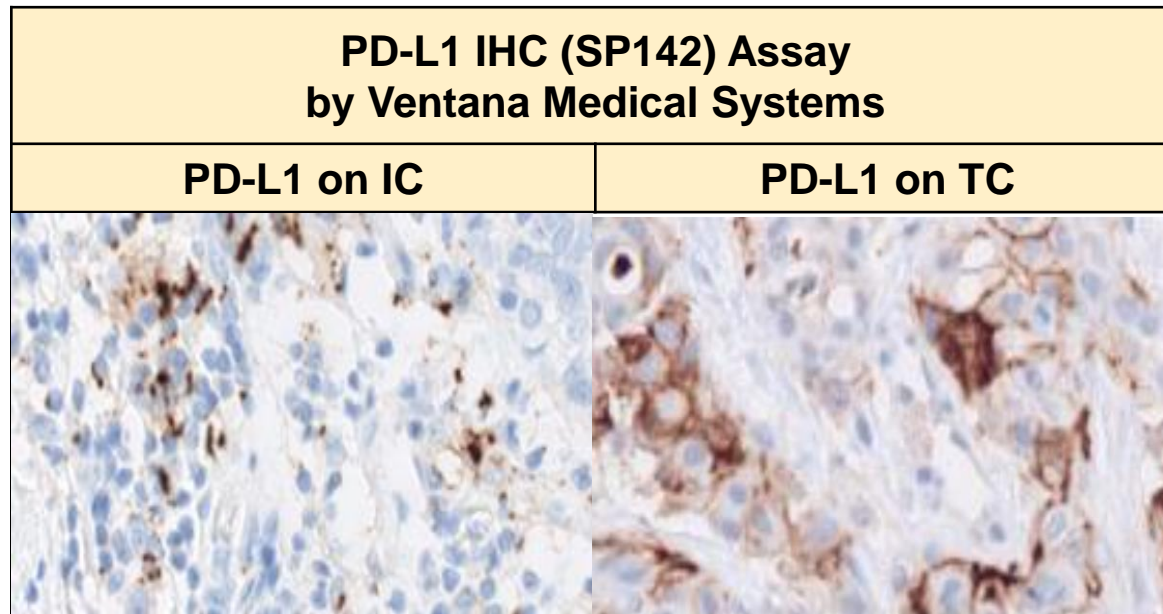
AESI, adverse event of special interest. Data cutoff: 17 April 2018. <sup>a</sup> Baskets of preferred terms according to medical concepts. <sup>b</sup> All events of photophobia.

<sup>c</sup> Includes all AESIs occurring in ≥ 1% of patients in either arm.

# IMpassion130: Efficacy in immune biomarker subgroups from the global, randomized, double-blind, placebo-controlled, Phase III study of atezolizumab + *nab*-paclitaxel in patients with treatment-naive triple negative breast cancer

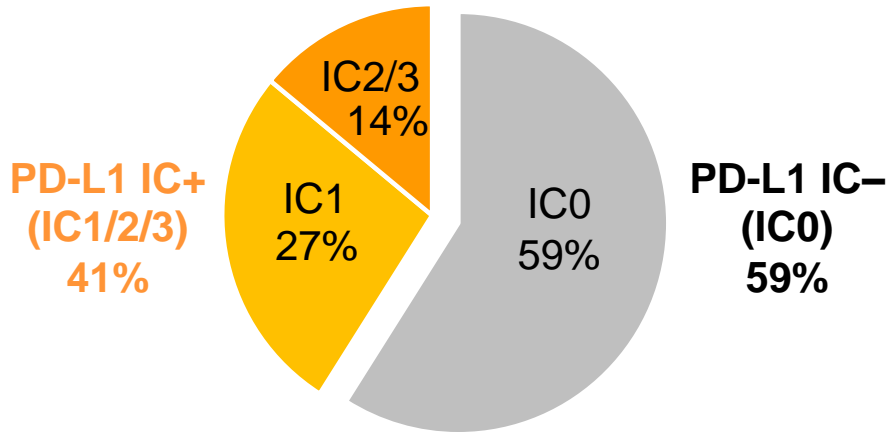
In the IMpassion130 study, ~40% of patients had PD-L1-positive tumours<sup>1</sup>

- Defined as >1% PD-L1 on tumour-infiltrating immune cells



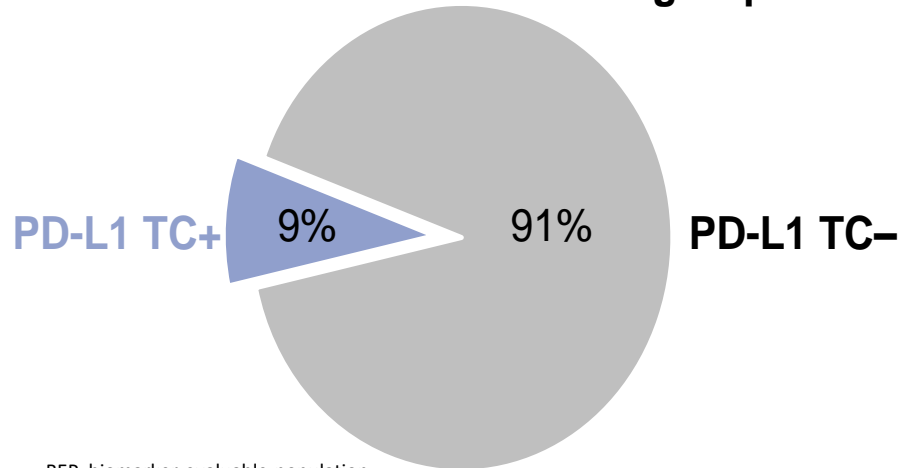
# In IMpassion130, PD-L1 in TNBC is expressed mainly on tumor-infiltrating immune cells

Prevalence of PD-L1 IC subgroups

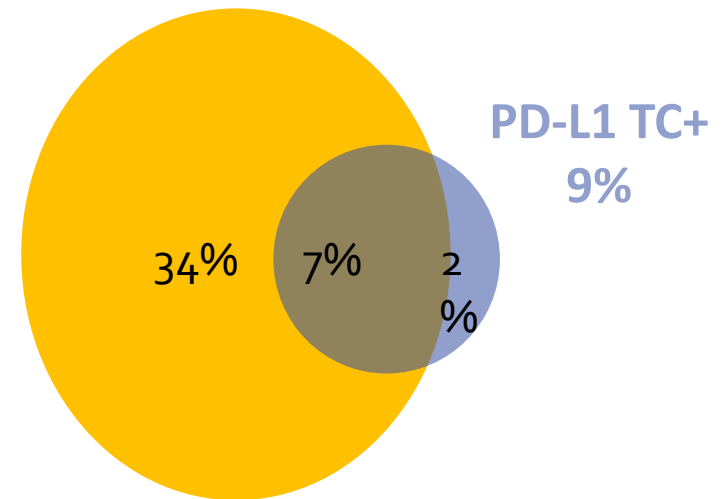


The majority of patients with expression of PD-L1 on TC are included within the PD-L1 IC+ population

Prevalence of PD-L1 TC subgroups



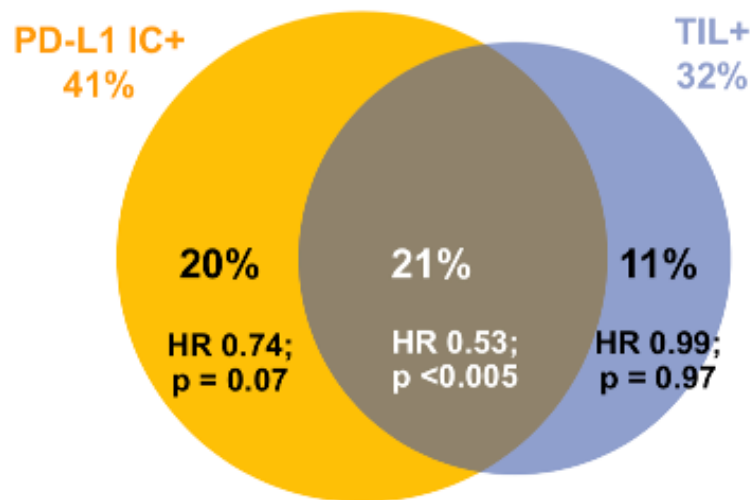
PD-L1 IC+  
41%



■ BEP, biomarker-evaluable population.  
 ■ BEP (TC); n = 900. PD-L1 scoring: IC0: < 1%; IC1: ≥ 1% and < 5%; IC2: ≥ 5% and < 10%; IC3: ≥ 10%; TC-: < 1% PD-L1 on tumor cells; TC+: ≥ 1% PD-L1 on tumor cells.

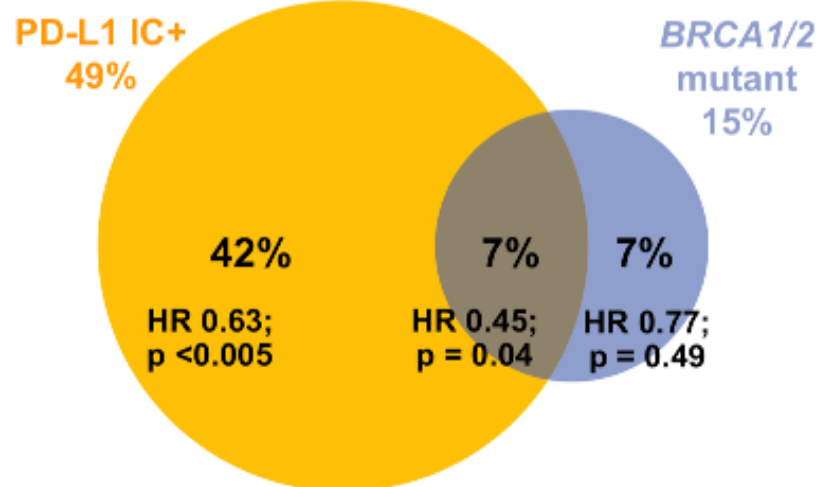
# Stromal TILS & BRCA status & treatment benefit for Atezolizumab

TILs



Stromal TILs has clinical benefit if co-occurring with PD-L1 IC+

BRCA1/2



The clinical benefit derived by PD-L1 IC+ patients was independent of their BRCA1/2 mutation status

# IMpassion130: Survival by PD-L1 Expression and CD8 Expression, sTIL, or BRCA1/2 Mutation Status

HR (95% CI)*	<b>CD8-/PD-L1 IC+</b> (n = 37)	<b>CD8+/PD-L1 IC+</b> (n = 280)	<b>CD8+/PD-L1 IC-</b> (n = 220)
PFS	0.33 (0.13-0.87); P = .03	0.61 (0.46-0.80); P ≤ .005	0.89 (0.66-1.20); P = .45
OS	0.25 (0.06-1.02); P = .05	0.55 (0.38-0.80); P ≤ .005	0.77 (0.50-1.17); P = .21

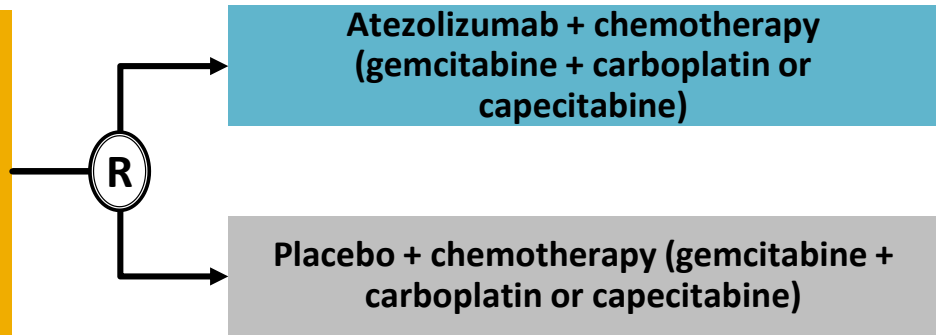
HR (95% CI)†	<b>sTIL-/PD-L1 IC+</b> (n = 176)	<b>sTIL+/PD-L1 IC+</b> (n = 190)	<b>sTIL+/PD-L1 IC-</b> (n = 94)
PFS	0.74 (0.54-1.03); P = .07	0.53 (0.38-0.74); P ≤ .005	0.99 (0.62-1.57); P = .97
OS	0.65 (0.41-1.02); P = .06	0.57 (0.35-0.92); P = .02	1.53 (0.76-3.08); P = .24

HR (95% CI)‡	<b>BRCA1/2 nonmut/PD-L1 IC+</b> (n = 257)	<b>BRCA1/2 mut/PD-L1 IC+</b> (n = 45)	<b>BRCA1/2 mut/PD-L1 IC-</b> (n = 44)
PFS	0.63 (0.48-0.83); P ≤ .005	0.45 (0.21-0.96); P = .04	0.77 (0.37-1.61); P = .49
OS	0.62 (0.43-0.91); P = .01	0.87 (0.26-2.85); P = .82	0.85 (0.29-2.43); P = .76

# Ongoing Cancer Immunotherapy studies

# IMpassion132: phase III atezolizumab study in early relapsing recurrent TNBC

- Locally advanced or mTNBC
- No prior therapy for metastatic or locally advanced disease
- ECOG PS 0–1
- Availability of FFPE tumour sample
- n=350



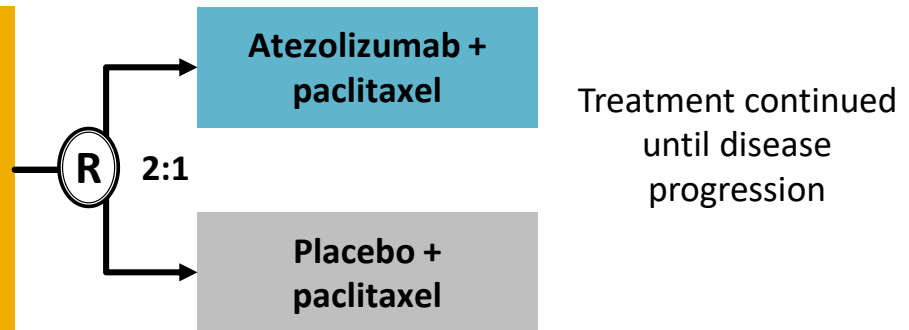
- **Atezolizumab:** 1,200mg given IV on Day 1 q3w
- **Placebo:** given IV on Day 1 q3w
- **Gemcitabine:** 1,000mg / m<sup>2</sup> given IV on Day 1 and Day 8 q3w
- **Carboplatin:** AUC2 given IV on Day 1 and Day 8 q3w
- **Capecitabine:** 1,000mg / m<sup>2</sup> given orally twice daily on Days 1-14 q3w

**Primary endpoint:** OS

**Secondary endpoints:** 12- and 18-month OS rates  
PFS (RECIST 1.1)  
ORR, clinical benefit rate  
DoR (RECIST v1.1)

# IMpassion131: phase III atezolizumab study in mTNBC<sup>1-2</sup>

- Locally advanced or mTNBC
- No prior therapy for metastatic or locally advanced disease
- ECOG PS 0–1
- Selection not based on PD-L1 positivity  
n=540



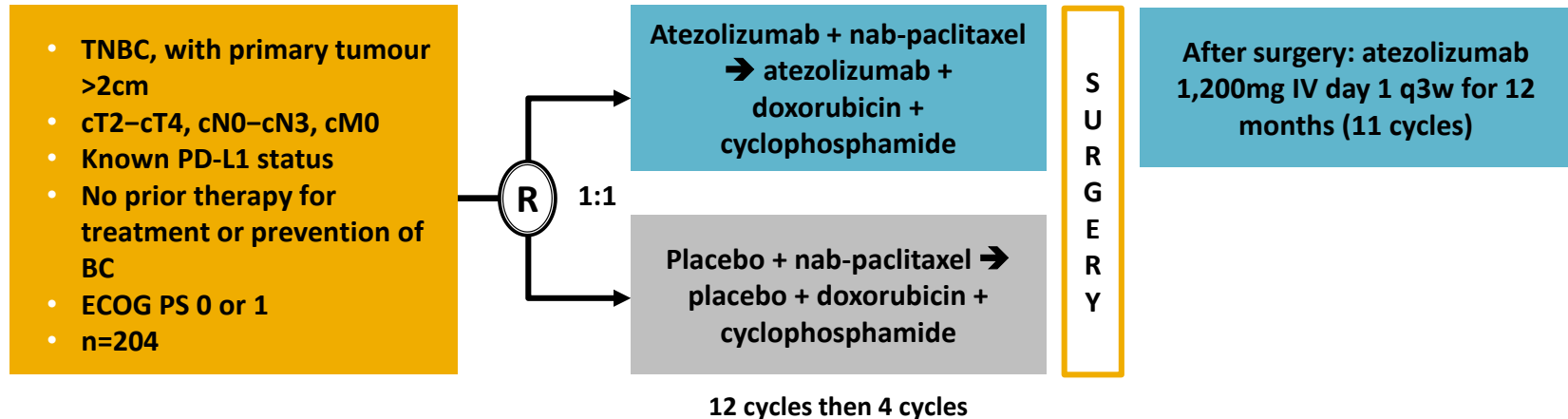
- **Atezolizumab:** 840mg given IV on Day 1 and Day 15 q4w
- **Placebo:** given IV on Day 1 and Day 15 q4w
- **Paclitaxel:** 90mg / m<sup>2</sup> given IV on Days 1, 8 and 15 of every 28-day cycle

**Primary endpoint:** PFS per investigator assessment using RECIST v1.1 criteria

**Secondary endpoints:** OS  
ORR  
DoR (RECIST v1.1)  
QoL



# IMpassion031: phase III atezolizumab neoadjuvant study in early TNBC<sup>1-2</sup>

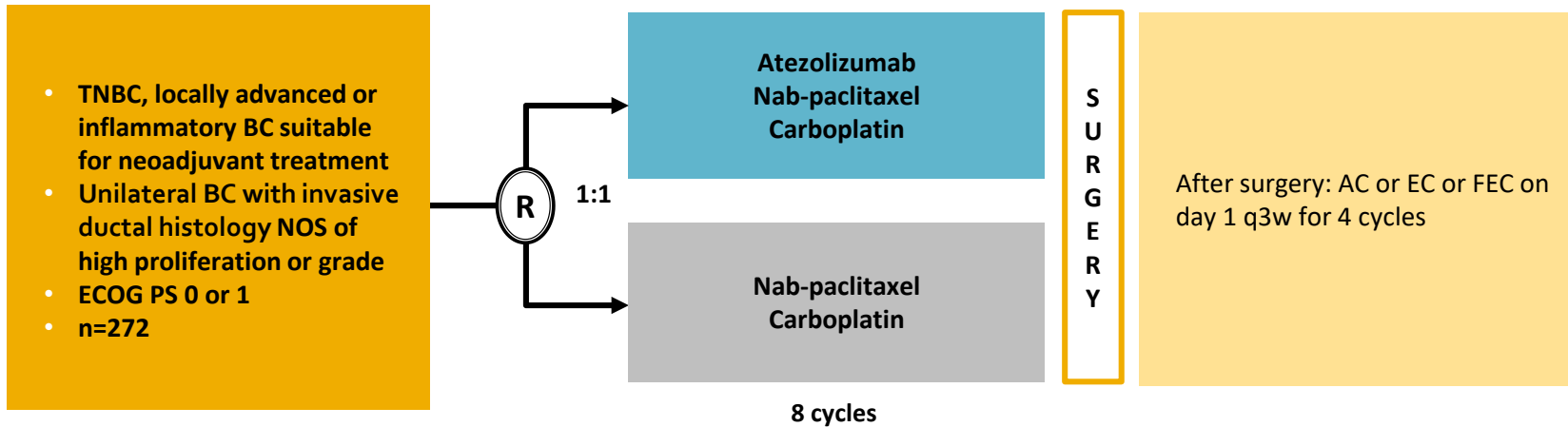


- **Atezolizumab:** 840mg given IV on Day 1 q3w
- **Placebo:** given IV on Day 1 q2w
- **Nab-paclitaxel:** 125mg / m<sup>2</sup> given IV on day 1 and day 8 q2w
- **Doxorubicin:** 60mg / m<sup>2</sup> given IV on day 1 q2w
- **Cyclophosphamide:** 600mg / m<sup>2</sup> given IV on day 1 q2w

**Primary endpoint:** pCR (ypT0 / is ypN0) in the ITT population

**Secondary endpoints:** pCR (ypT0 / is ypN0), EFS, OS in the PD-L1–selected IC1 / 2 / 3 tumour subgroup (PD-L1-positive population) and HRQoL

# NeoTrip: phase III atezolizumab neoadjuvant study\* in TNBC



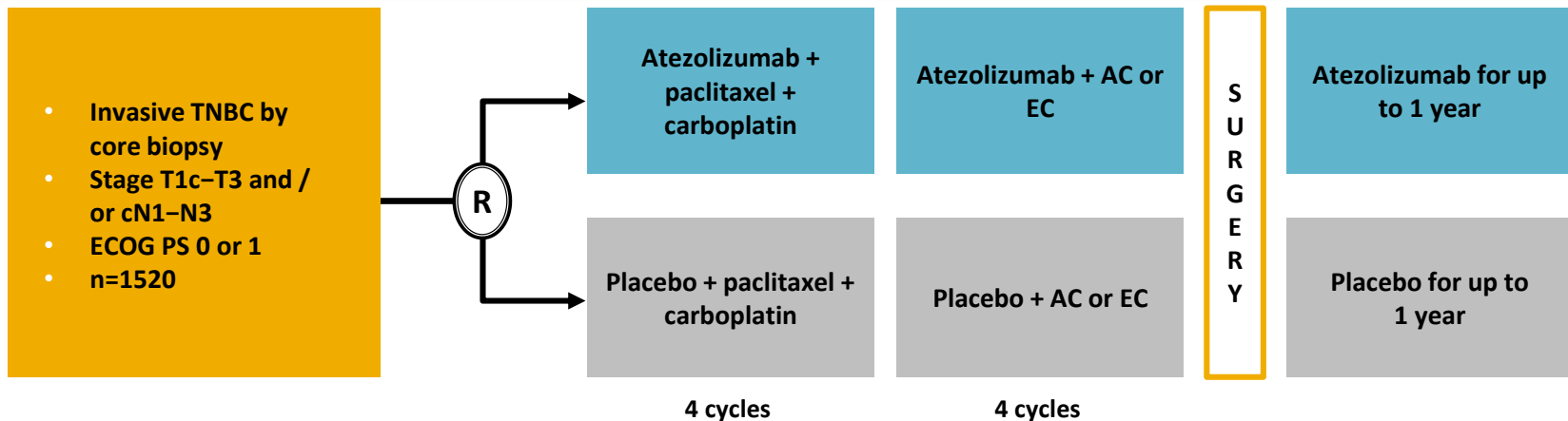
- **Carboplatin:** AUC2 given IV on day 1 and day 8 q3w
- **Nab-paclitaxel:** 125mg / m<sup>2</sup> given IV on day 1 and day 8 q3w
- **Atezolizumab:** 1,200mg IV infusion on day 1 q3w

**Primary endpoint:** 5-year EFS

**Secondary endpoints:** pCR (ypT0 / ypTis ypN0), clinical OR after NACT, and DFS

\*Not a Roche-supported trial - sponsor is Fondazione Michelangelo  
NCT02620280

# NSABP B-59: phase III atezolizumab neoadjuvant study\* in TNBC

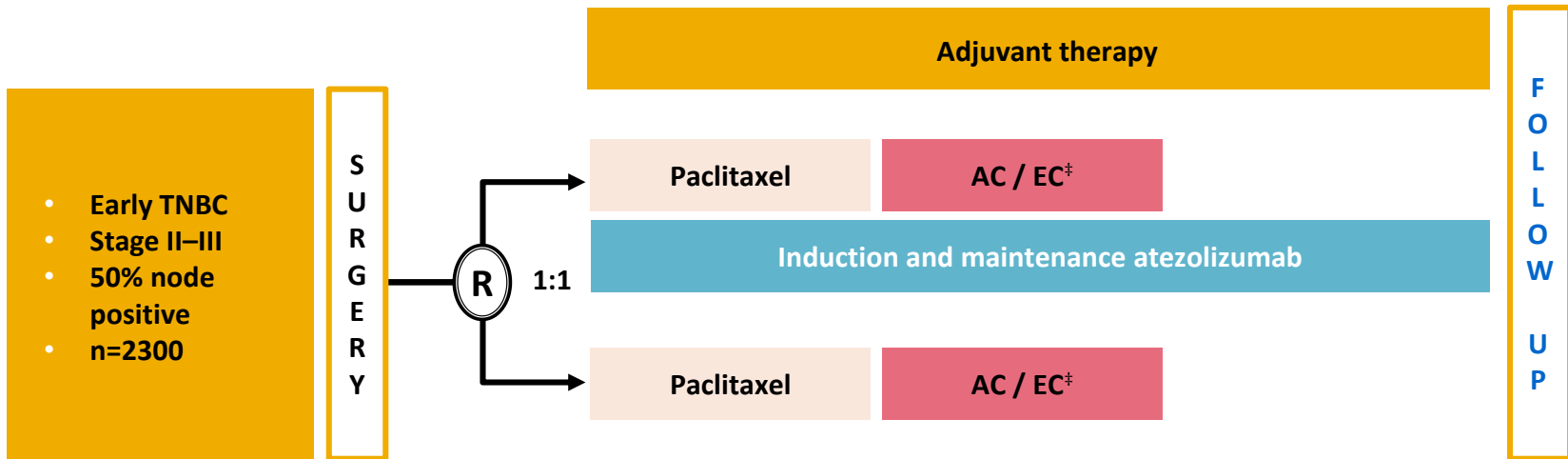


- **Carboplatin:** AUC5 given IV on Day 1 q3w
- **Paclitaxel:** 80mg/m<sup>2</sup> given IV on Days 1, 8 and 15 q3w
- **Atezolizumab:** 1,200mg IV infusion on Day 1 q3w
- **Doxorubicin:** 60mg/m<sup>2</sup> given IV on Day 1 q2w or q3w
- **Cyclophosphamide:** 600mg/m<sup>2</sup> given IV on Day 1 q2w or q3w
- **Epirubicin:** 90mg/m<sup>2</sup> given IV on Day 1 q2w or q3w

**Primary endpoint:** pCR (ypT0 / Tis ypN0), 5-year EFS

**Secondary endpoints:** pCR (ypT0 / Tis and ypT0 ypN0), positive nodal status conversion rate, OS, RFI, DDFS, BMFS, safety

# IMpassion030: phase III atezolizumab study in adjuvant TNBC\*



- **Atezolizumab:** 840mg qw for 10 doses in the induction period and 1,200mg q3w for up to one year in the maintenance period
- **Paclitaxel:** q1w for 12 weeks
- **AC / EC:** q2w for 4 doses<sup>§</sup>

## Rationale for paclitaxel comparator

- Global SoC treatment
- Helps overcome regulatory / payer hurdles to nab-paclitaxel

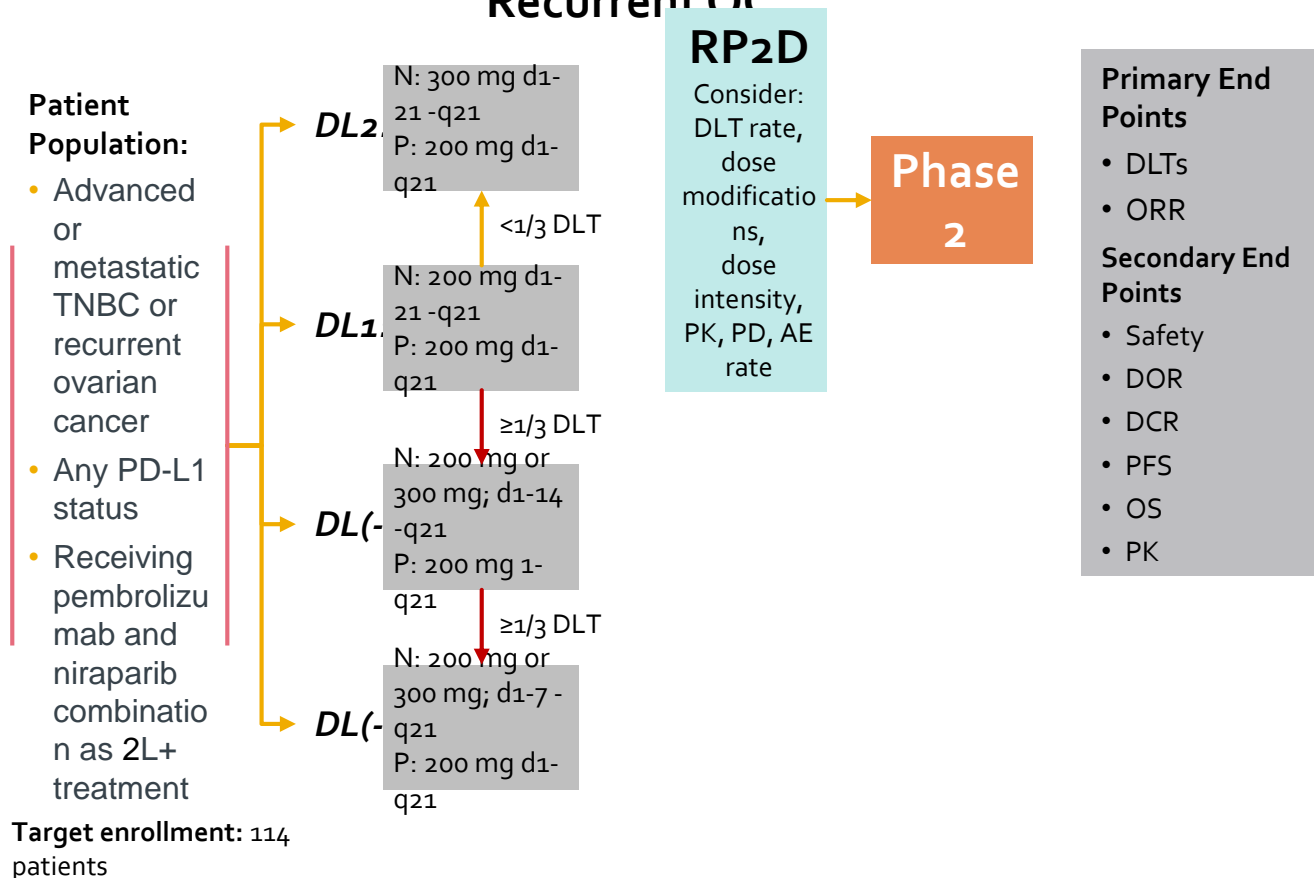
- **Primary endpoint:** iDFS in the ITT population
- **Secondary endpoints:** iDFS in the PD-L1+ IC1 / 2 / 3 subgroups, OS, RFI, distant RFI, safety, health-related QoL

\*Latest design but subject to change; ‡ Dose-dense;

§Supported with G-CSF / GM-CSF

# KEYNOTE-162 (TOPACIO) — Pembrolizumab + Niraparib in Metastatic TNBC: Clinical Trial Design<sup>1,2</sup>

## Phase 1/2 Study of Pembrolizumab + Niraparib as 2L+ Therapy for mTNBC and Recurrent OC



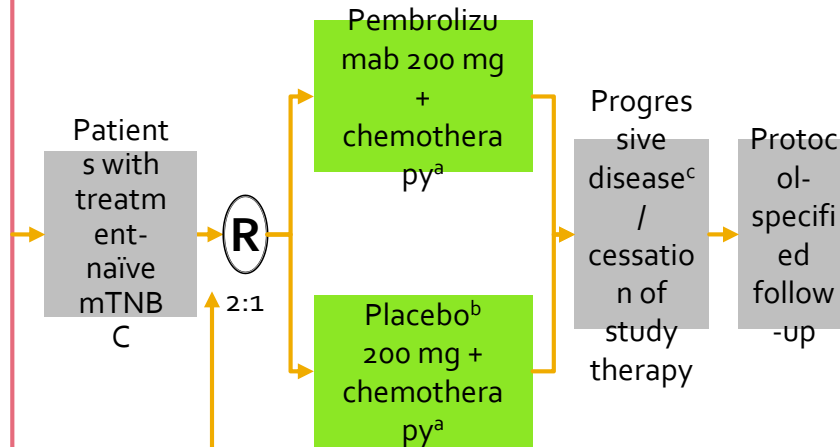
- AE = adverse event; DCR = disease control rate; DL = dose level; DLT = dose-limiting toxicity; DOR = duration of response; ORR = objective response rate; OS = overall survival; PD = progressive disease; PD-L1 = programmed death ligand 1; PK = pharmacokinetics; RP2D = recommended Phase 2 dose; TNBC = triple negative breast cancer.
- 1. ClinicalTrials.gov. <https://clinicaltrials.gov/ct2/show/NCT02657889>. Accessed October 3, 2017. 2. Konstantinopoulos PA et al. Presented at ESMO 2017; September 8–12, 2017; Madrid, Spain. Poster 1143PD.

# KEYNOTE-355: Clinical Trial Design

## Population:

## Part 2: Phase 3 Study of Pembrolizumab + Chemotherapy for Treatment-naïve mTNBC

- Sample size: ~828
- Central determination of TNBC and PD-L1
- Previously untreated recurrent or metastatic ER-/PR-/HER2- breast cancer
- Completion of treatment with curative intent  $\geq 6$  months prior to disease recurrence
- No systemic steroids
- No active autoimmune disease



### Stratification factors:

- Chemotherapy treatment on study (taxane vs gemcitabine/carboplatin)
- PD-L1 tumor status (positive vs negative)
- Prior treatment with same class chemotherapy in the (neo)adjuvant setting (yes vs no)

### Primary End Points

- PFS (in all and PD-L1+ patients)
- OS (in all and

### Secondary End Points

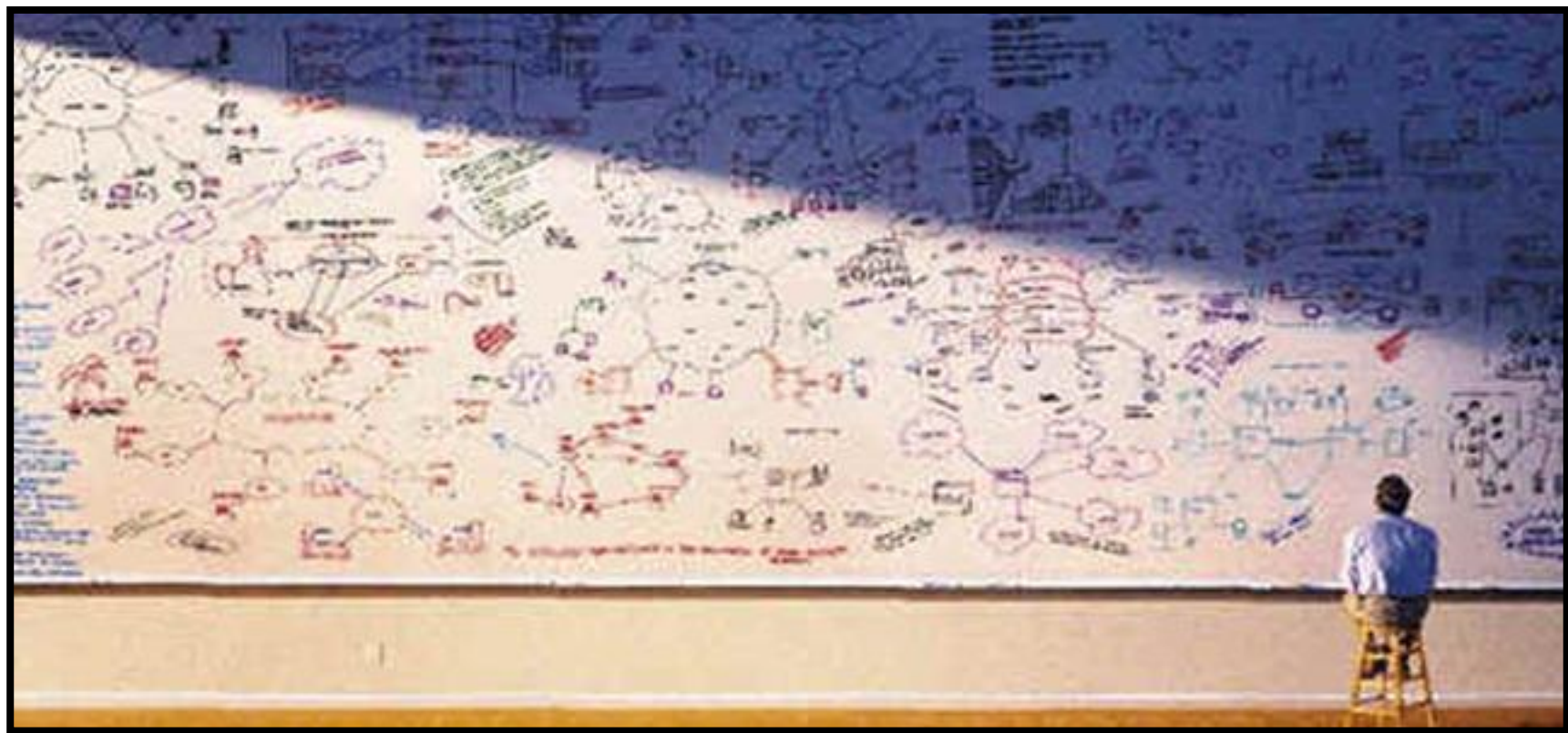
- ORR (in all and PD-L1+ patients)
- DoR (in all and PD-L1+ patients)
- DCR (in all and PD-L1+ patients)
- Safety

• No active CNS metastases

^aTaxane, paclitaxel, or gemcitabine/carboplatin. ^bNormal saline. ^cTreatment may be continued until confirmation of PD. ClinicalTrials.gov. <https://clinicaltrials.gov/ct2/show/NCT02819518>. Accessed March 22, 2017.

# What is Future ?

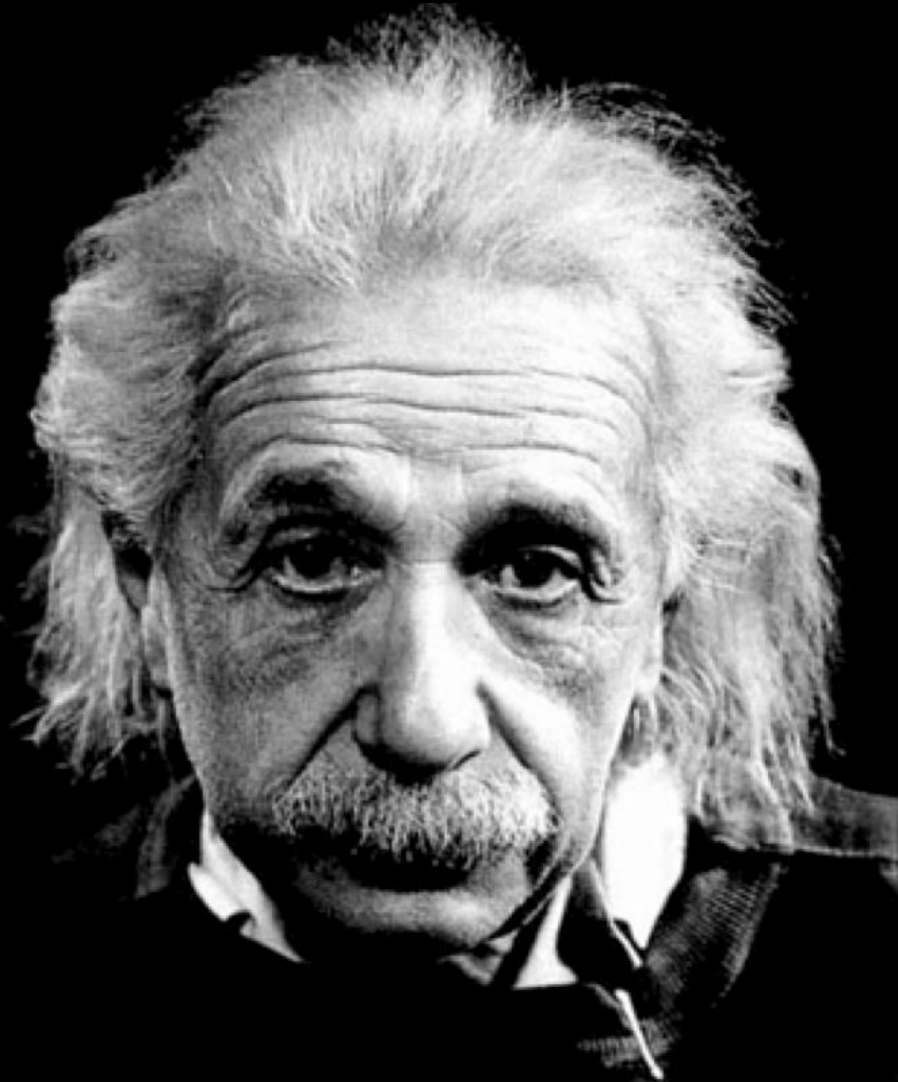






**Everything should be made  
as simple as possible, but  
not simpler.**

**Albert Einstein**



# Thank you

Hassan Jaafar  
Medical Oncology  
SKSH Hospital  
UAE

