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MD Anderson Cancer Center
Making Cancer History®

Immunotherapy Developments and TNBC

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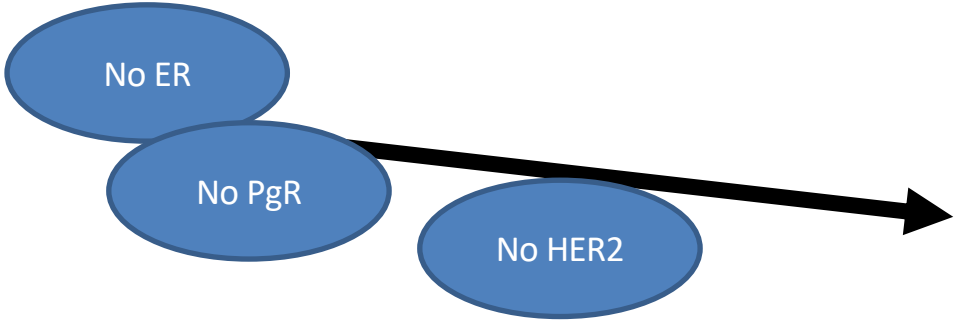
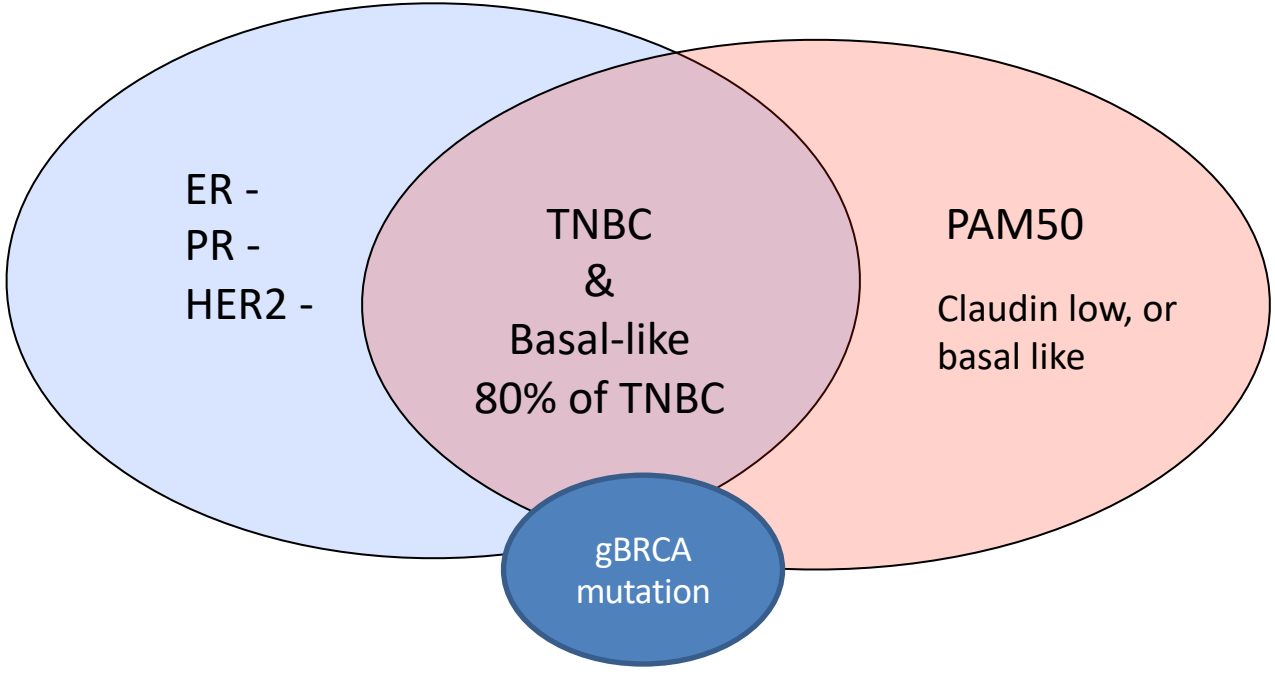
Triple negative Breast Cancer

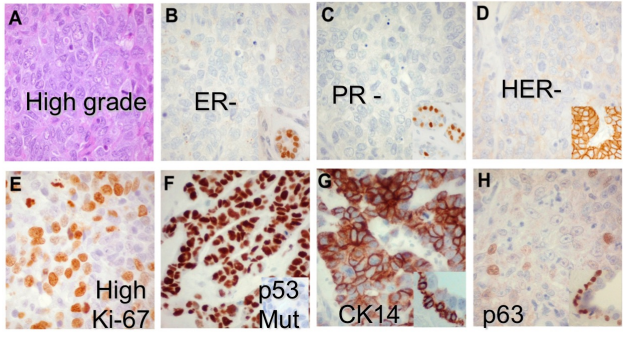
- About 15-20 percent of breast cancers are triple negative (diagnosis of exclusion)
- These tumors tend to occur more often in younger women and African-American, Hispanic heritage
- High proportion of *BRCA1*-related breast cancers are both triple negative and basal-like

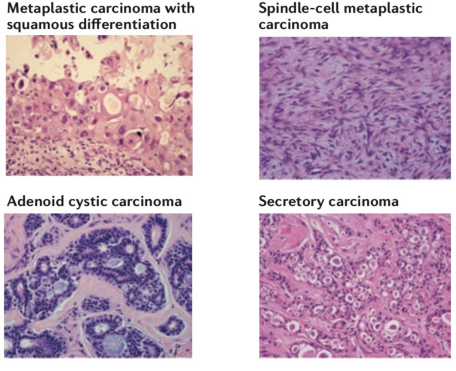


"Triple negative breast cancer"



Triple Negative Breast Cancer





Heterogenous basket of tumors that lack ER, PR, HER2

- Invasive ductal carcinoma (95%)
- Invasive lobular carcinoma (1–2%)
- Metaplastic carcinoma with squamous differentiation (<1%)
- Spindle-cell metaplastic carcinoma (<1%)
- Adenoid cystic carcinoma (<1%)
- Secretory carcinoma (<1%)
- Typical medullary carcinoma (<1%)
- Atypical medullary carcinoma (<1%)
- Apocrine carcinoma (<1%)

Bianchini et al. 2016

A lot of heterogeneity…

Basal-like 1: cell cycle, DNA repair and proliferation genes

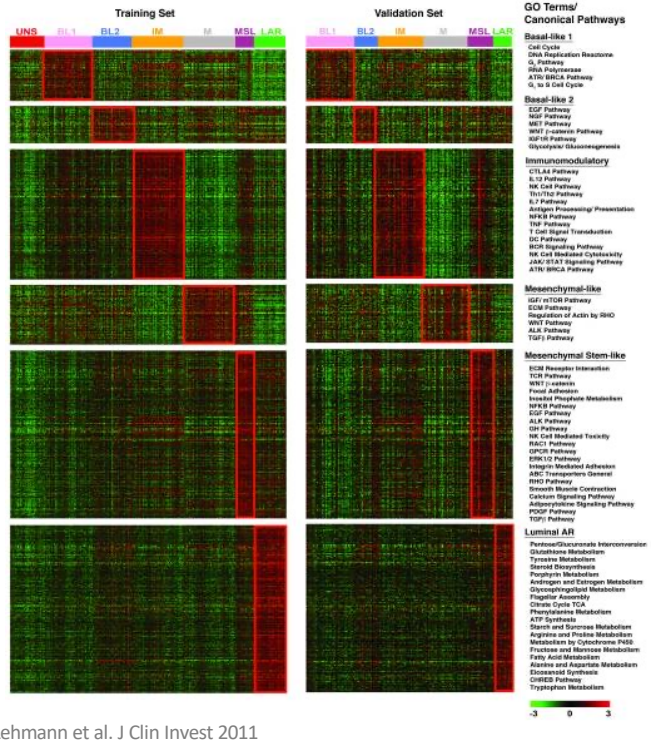
Basal-like 2: Growth factor signaling (EGFR, MET, Wnt, IGF1R)

IM: immune cell processes (medullary breast cancer)

M: Cell motility and differentiation, EMT processes

MSL: similar to M but growth factor signaling, low levels of proliferation genes (metaplastic cancers)

LAR: Androgen receptor and downstream genes, luminal features



Lehmann et al. J Clin Invest 2011

METASTATIC DISEASE

TNBC- Chemotherapy

- **Taxanes**
  - Paclitaxel, Docetaxel, nab-paclitaxel
- **Anthacyclines**
  - Liposomal Doxorubicin, AC
- Ixabepilone (+/- capecitabine)
- Eribulin
- Platinums (Gem+carbo)

TNBC-Other agents

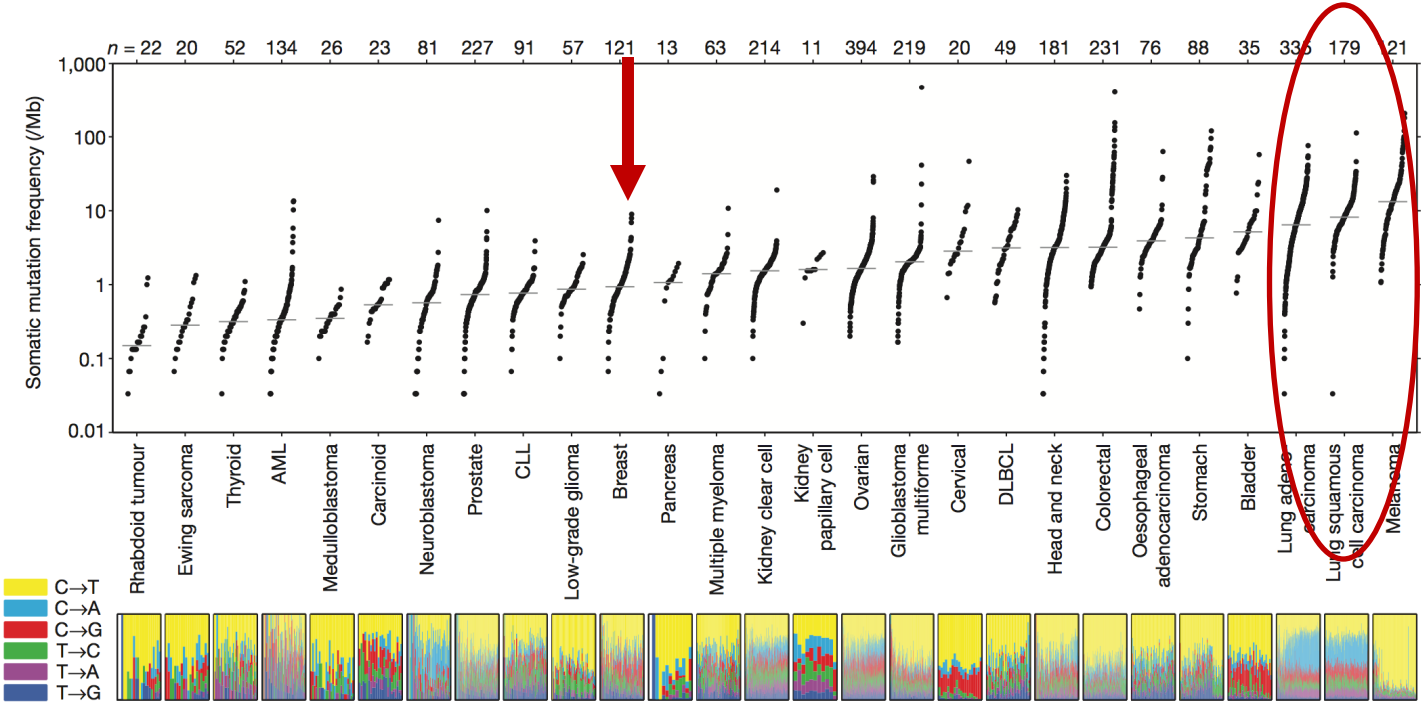
- **Immunotherapy**
  - Atezolizumab
  - Pembrolizumab
- **PARPi**
  - Olaparib
  - Talazoparib
- **ADG**
  - Sacituzumab Govotecan
  - Trastuzumab Deruxtecan

TNBC-Other agents: Specific subpopulations

- **Immunotherapy**
  - Atezolizumab
  - Pembrolizumab **PDL-1 +**
- **PARPi**
  - Olaparib **BRCA 1,2 mutations**
  - Talazoparib
- **ADG**
  - Sacituzumab Govotecan
  - Trastuzumab Deruxtecan **Her2-Low**

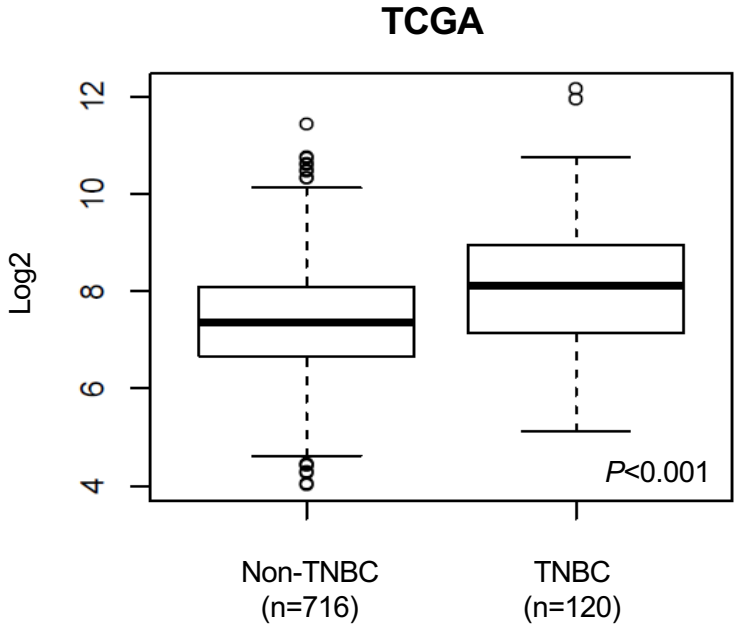
IMMUNOTHERAPY-PDL1

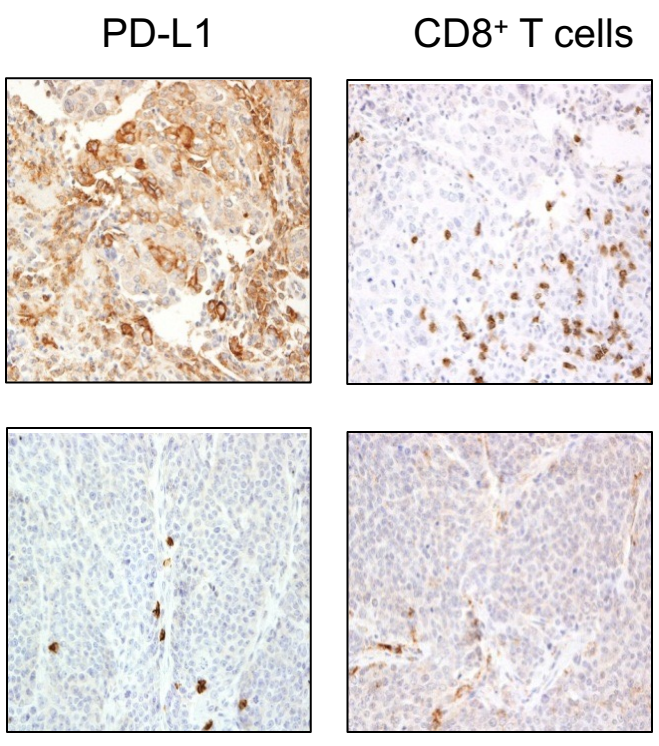
Mutational Load



Lawrence MS et al. *Nature* 2013;499:214-218

PD-L1 in TNBC

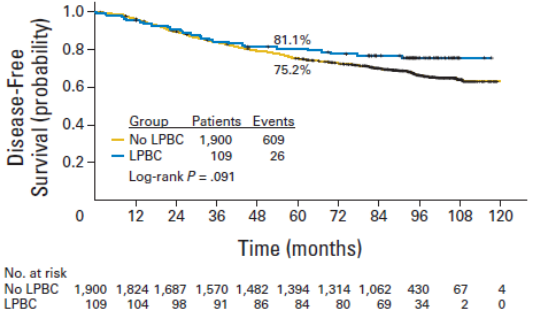




Mittendorf EA, et al. *Cancer Immunol Res*, 2014;2:361-370

Prognostic Value of TIL

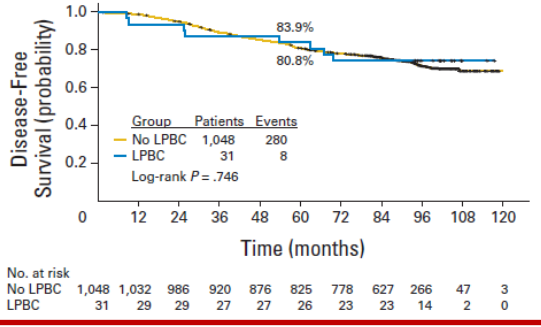
All Patients



No. at risk

No LPBC	1,900	1,824	1,687	1,570	1,482	1,394	1,314	1,062	430	67	4
LPBC	109	104	98	91	86	84	80	69	34	2	0

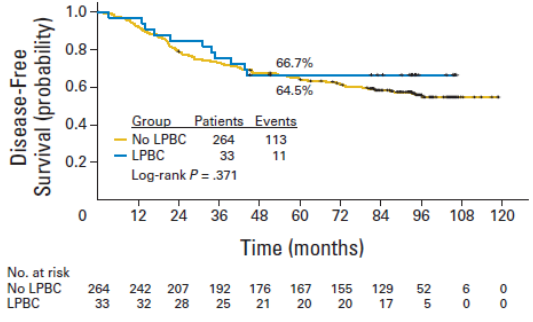
ER+/HER2-



No. at risk

No LPBC	1,048	1,032	986	920	876	825	778	627	266	47	3
LPBC	31	29	29	27	27	26	23	23	14	2	0

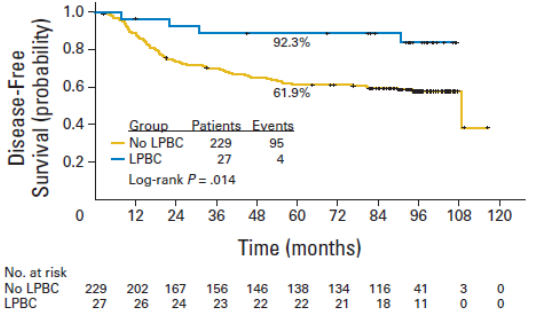
HER2+



No. at risk

No LPBC	264	242	207	192	176	167	155	129	52	6	0
LPBC	33	32	28	25	21	20	20	17	5	0	0

TNBC

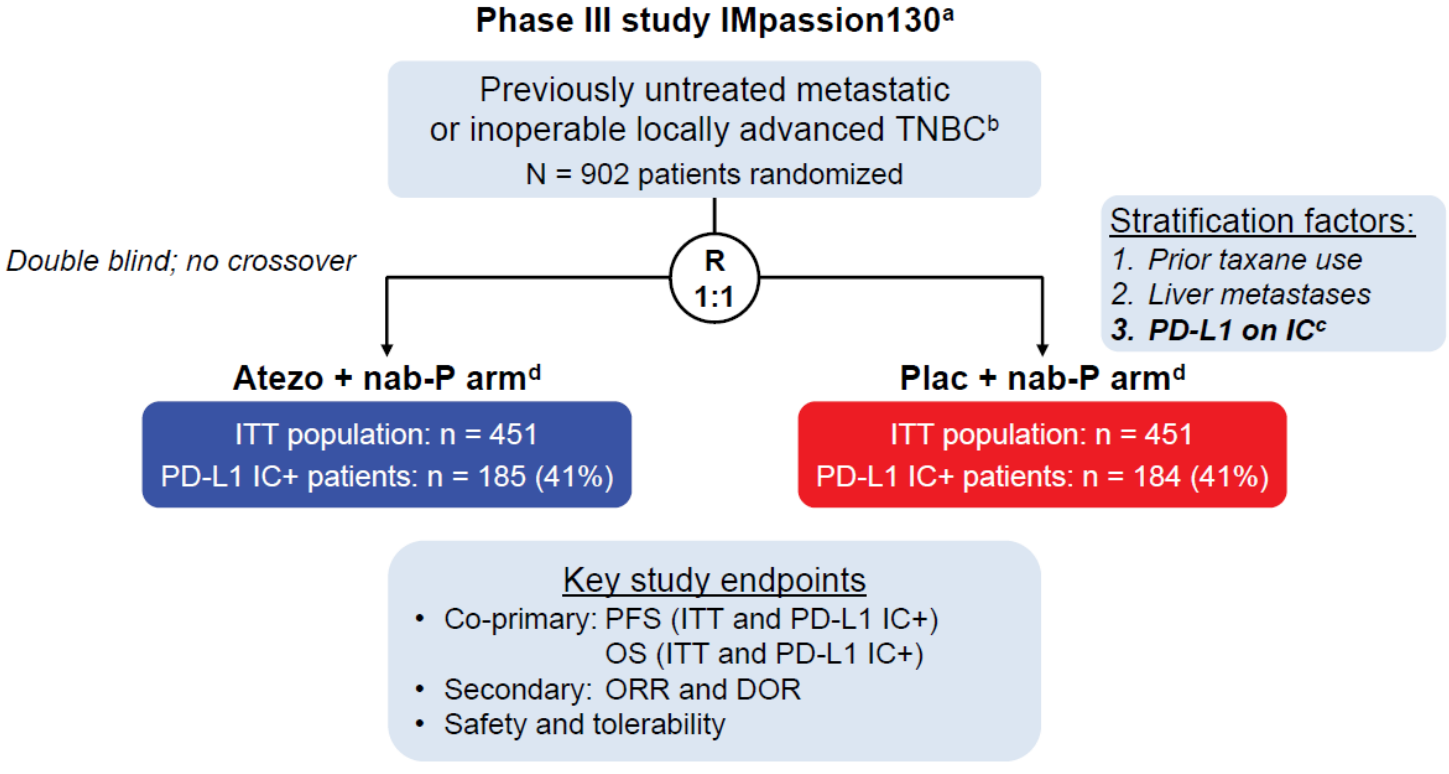


No. at risk

No LPBC	229	202	167	156	146	138	134	116	41	3	0
LPBC	27	26	24	23	22	22	21	18	11	0	0

Loi S, et al. *J Clin Onc* 2013; 31:860-867

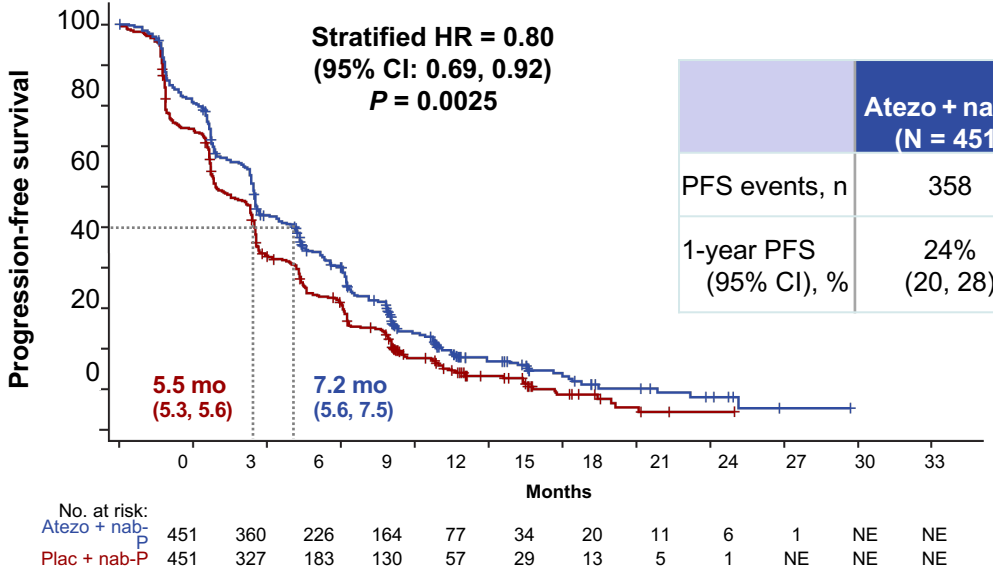
IMpassion 130



[a] NCT02425891. [b] Locally evaluated per ASCO-CAP guidelines. Prior chemotherapy in the curative setting, including taxanes, allowed if treatment-free interval ≥ 12 mo.
[c] Centrally evaluated per VENTANA SP142 IHC assay (double blinded for PD-L1 status, PD-L1+: PD-L1 on ≥ 1% of IC). [d] Atezolizumab or placebo 840 mg IV on days 1 and 15 + *nab*-paclitaxel 100 mg/m^2 IV on days 1, 8 and 15 of 28-day cycle until RECIST v1.1 PD. 1. Schmid *N Engl J Med* 2018.

Schmid P, et al. *NEJM* 2018;379:2108-2121

Primary PFS Analysis: ITT Population

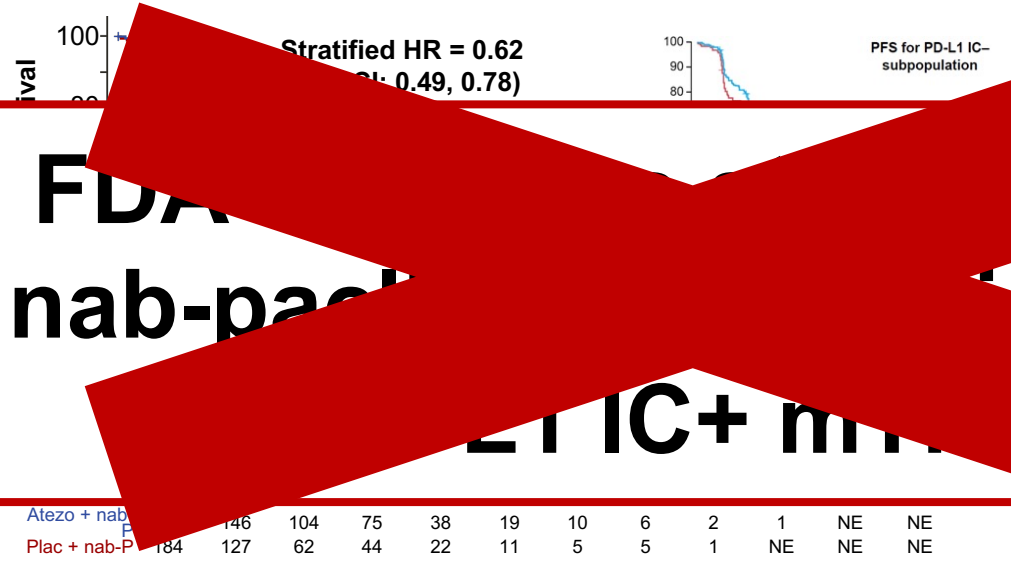


	Atezo + nab-P (N = 451)	Plac + nab-P (N = 451)
PFS events, n	358	378
1-year PFS (95% CI), %	24% (20, 28)	18% (14, 21)

NE, not estimable. Data cutoff: 17 April 2018. Median PFS durations (and 95% CI) are indicated on the plot. Median follow-up (ITT): 12.9 months.

Schmid P, et al. *NEJM* 2018;379:2108-2121

Primary PFS Analysis: PD-L1+ Population

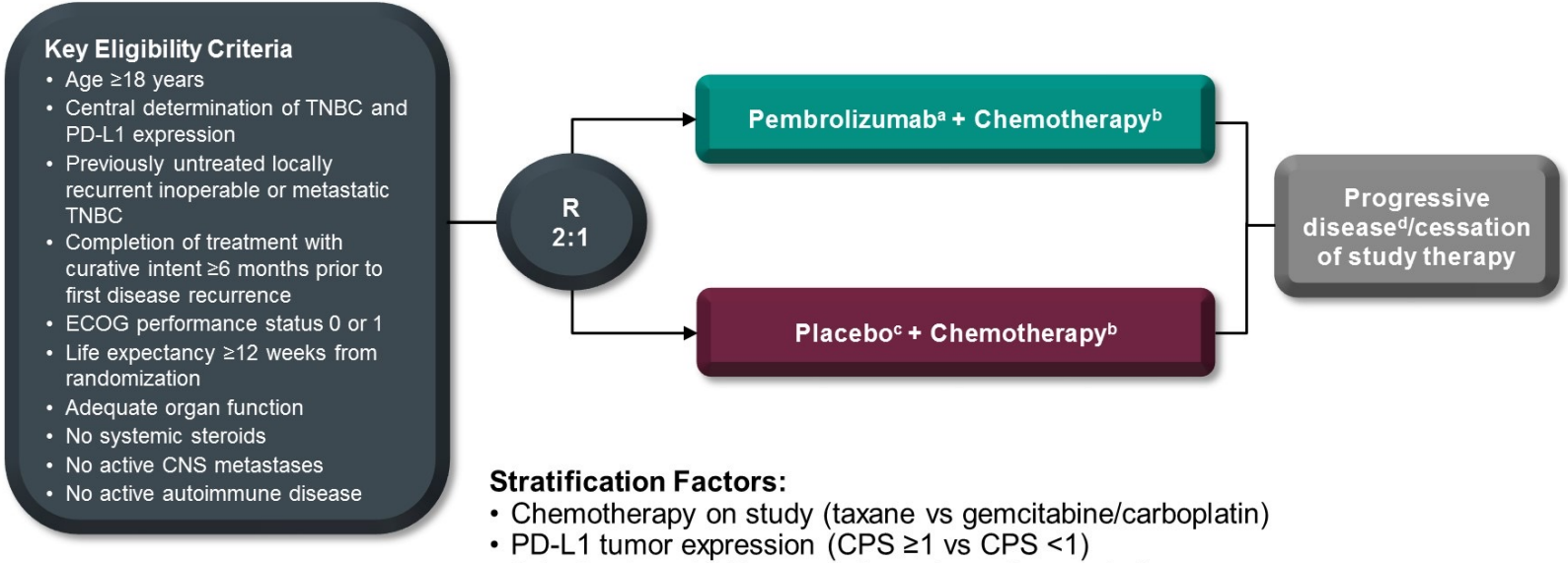


FDA [illegible] nab + nab-pac[illegible]nts with [illegible]L1 IC+ mTNBC

	Atezo + nab-P (N = 185)	Plac + nab-P (N = 184)
PFS events, n	138	157
1-year PFS (95% CI), %	29% (22, 36)	16% (11, 22)

Schmid P, et al. *NEJM* 2018;379:2108-2121

KEYNOTE-355 Study Design (NCT02819518)



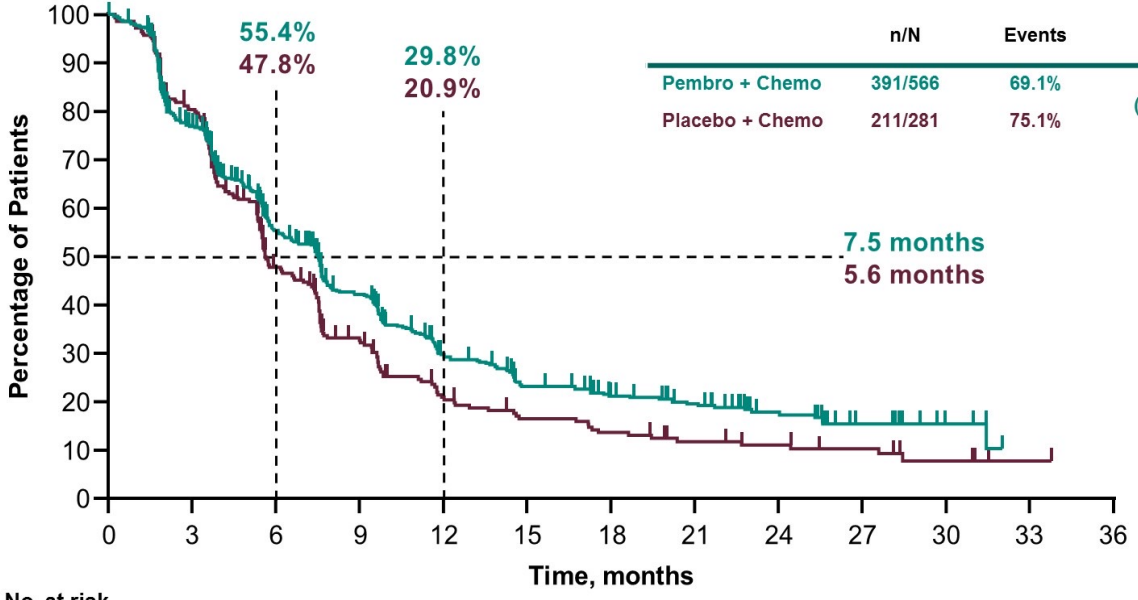
Stratification Factors:
- Chemotherapy on study (taxane vs gemcitabine/carboplatin)
- PD-L1 tumor expression (CPS ≥1 vs CPS <1)
- Prior treatment with same class chemotherapy in the neoadjuvant or adjuvant setting (yes vs no)

[a]Pembrolizumab 200 mg intravenous (IV) every 3 weeks (Q3W)
[b]Chemotherapy dosing regimens are as follows:
Nab-paclitaxel 100 mg/m^2 IV on days 1, 8, and 15 every 28 days
Paclitaxel 90 mg/m^2 IV on days 1, 8, and 15 every 28 days
Gemcitabine 1000 mg/m^2/carboplatin AUC 2 on days 1 and 8 every 21 days

[c]Normal saline
[d]Treatment may be continued until confirmation of progressive disease
CNS=central nervous system; ECOG=Eastern Cooperative Oncology Group; PD-L1=programmed death ligand 1; R=randomized; TNBC=triple-negative breast cancer

Cortes J et al, Lancet 2020

Progression-Free Survival: ITT



	n/N	Events	HR (95% CI)
Pembro + Chemo	391/566	69.1%	0.82 (0.69-0.97)
Placebo + Chemo	211/281	75.1%	

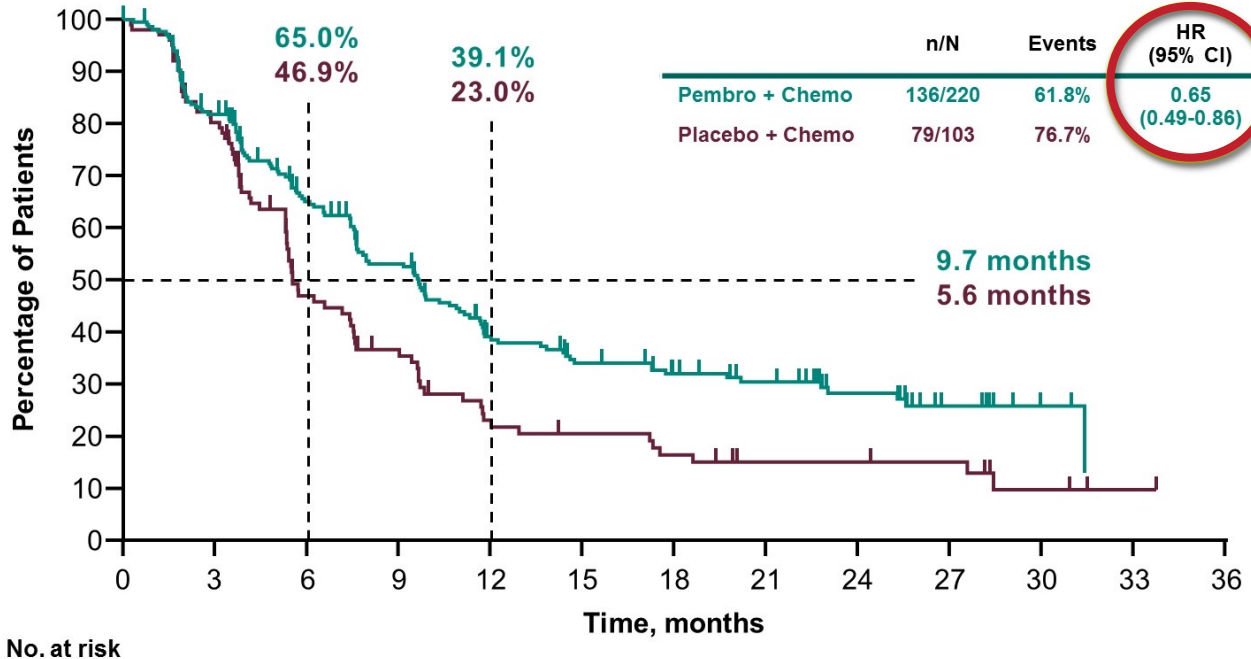
No. at risk

566	408	260	184	118	86	70	57	32	16	6	0	0
281	214	108	68	39	29	24	17	14	11	5	1	0

Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. Statistical significance was not tested due to the prespecified hierarchical testing strategy. Data cutoff December 11, 2019.

Cortes J et al, Lancet 2020

Progression-Free Survival: PD-L1 CPS ≥10



	n/N	Events	HR (95% CI)	P-value (one-sided)
Pembro + Chemo	136/220	61.8%	0.65 (0.49-0.86)	0.0012[a]
Placebo + Chemo	79/103	76.7%		

No. at risk

220	173	122	96	63	52	44	37	25	12	5	0	0
103	80	41	30	18	15	12	8	8	7	3	1	0

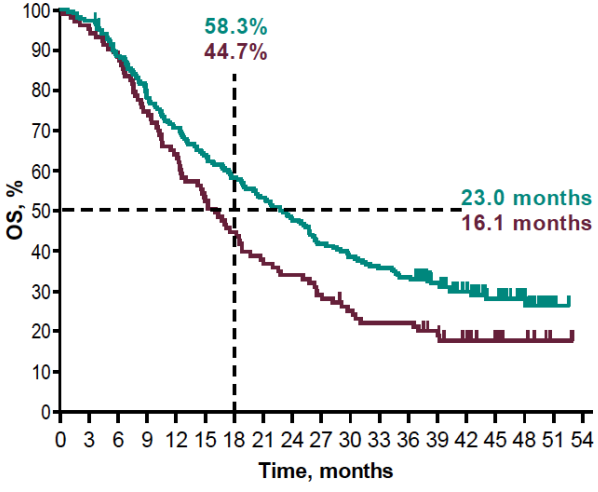
[a]Prespecified *P* value boundary of 0.00411 met.
Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. Data cutoff December 11, 2019.

Cortes J et al, Lancet 2020

Overall Survival at Final Analysis

PD-L1 CPS ≥10

	n/N	Events	HR (95% CI)	*P*-value (one-sided)
Pembro + Chemo	155/220	70.5%	0.73 (0.55-0.95)	0.0093[a]
Placebo + Chemo	84/103	81.6%		

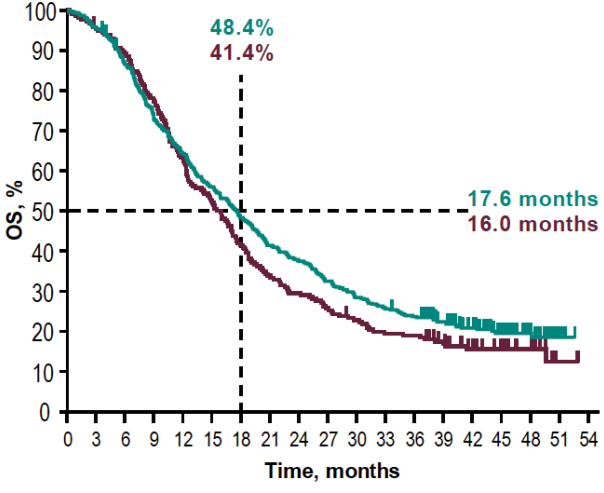


No. at risk

220	214	193	171	154	139	127	116	105	91	84	78	73	59	43	31	17	2	0
103	98	91	77	66	55	46	39	35	30	25	22	22	17	12	8	6	2	0

PD-L1 CPS ≥1

	n/N	Events	HR (95% CI)	*P*-value (one-sided)
Pembro + Chemo	336/425	79.1%	0.86 (0.72-1.04)	0.0563[b]
Placebo + Chemo	177/211	83.9%		

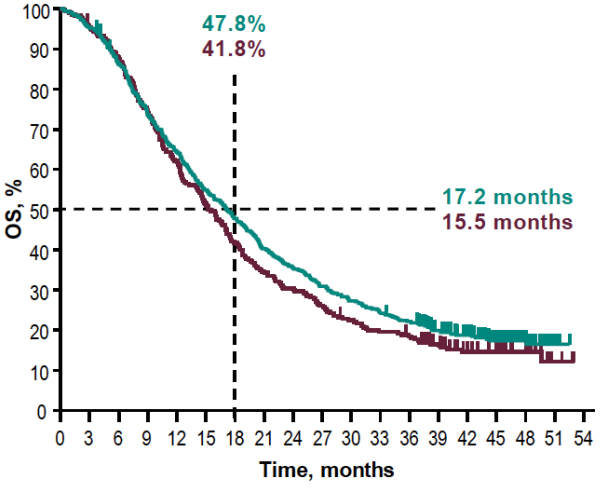


No. at risk

425	406	365	308	271	236	204	175	159	137	120	108	99	80	60	38	21	3	0
211	200	187	163	133	110	87	71	62	54	47	40	39	30	21	15	10	2	0

ITT

	n/N	Events	HR (95% CI)
Pembro + Chemo	460/566	81.3%	0.89 (0.76-1.05)[c]
Placebo + Chemo	238/281	84.7%	

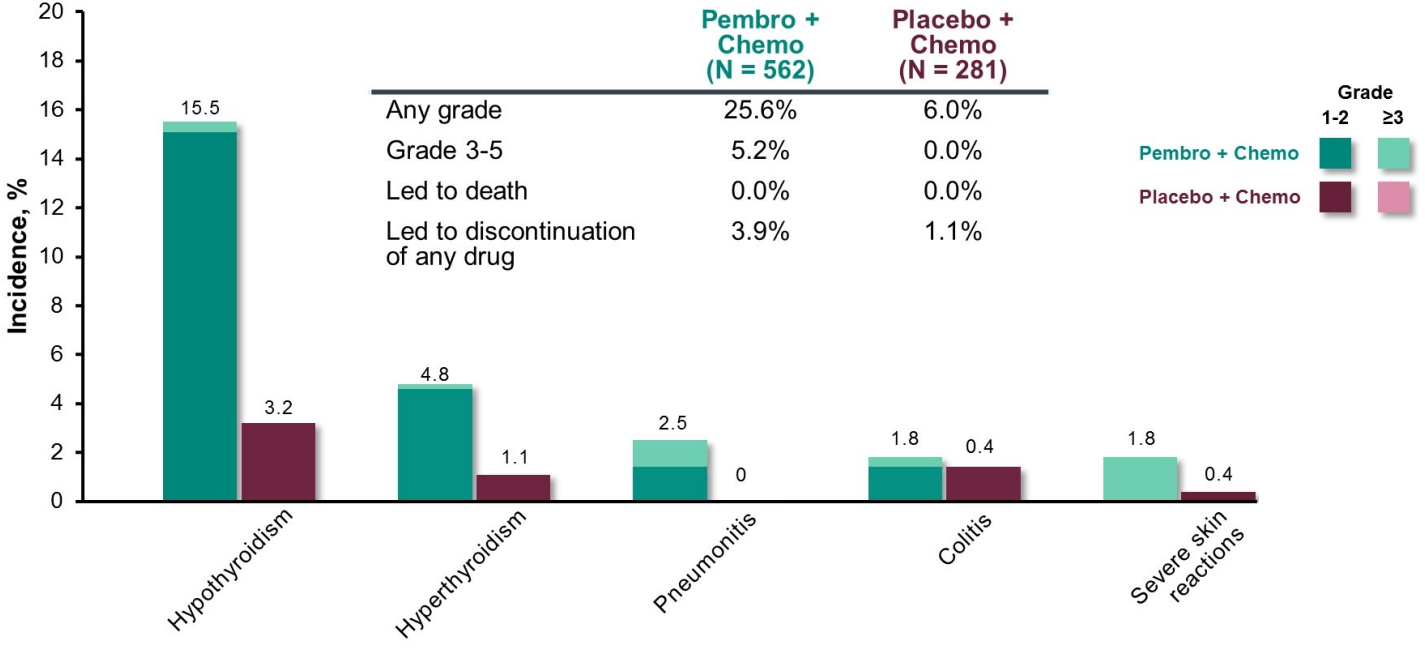


No. at risk

566	539	486	415	363	309	269	226	200	174	153	137	124	94	69	42	22	4	0
281	267	246	209	174	144	117	97	85	73	62	54	50	38	25	18	12	3	0

[a]Prespecified *P*-value boundary of 0.0113 met. [b]Prespecified *P*-value boundary of 0.0172 not met. [c]Statistical significance not tested due to the prespecified hierarchical testing strategy. Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. Data cutoff: June 15, 2021.

Immune-Mediated AEs



	Pembro + Chemo (N = 562)	Placebo + Chemo (N = 281)
Any grade	25.6%	6.0%
Grade 3-5	5.2%	0.0%
Led to death	0.0%	0.0%
Led to discontinuation of any drug	3.9%	1.1%

Immune-Mediated AEs with Incidence ≥10 Patients in Either Treatment Group[a]

[a]Based on a list of terms prespecified by the sponsor and included regardless of attribution to study treatment or immune relatedness by the investigator; related terms included.
Data cutoff date: December 11, 2019.

Cortes J et al, Lancet 2020

FDA grants accelerated approval to pembrolizumab for locally recurrent unresectable or metastatic triple negative breast cancer

Drug Approvals and Databases

Resources for Information | Approved Drugs

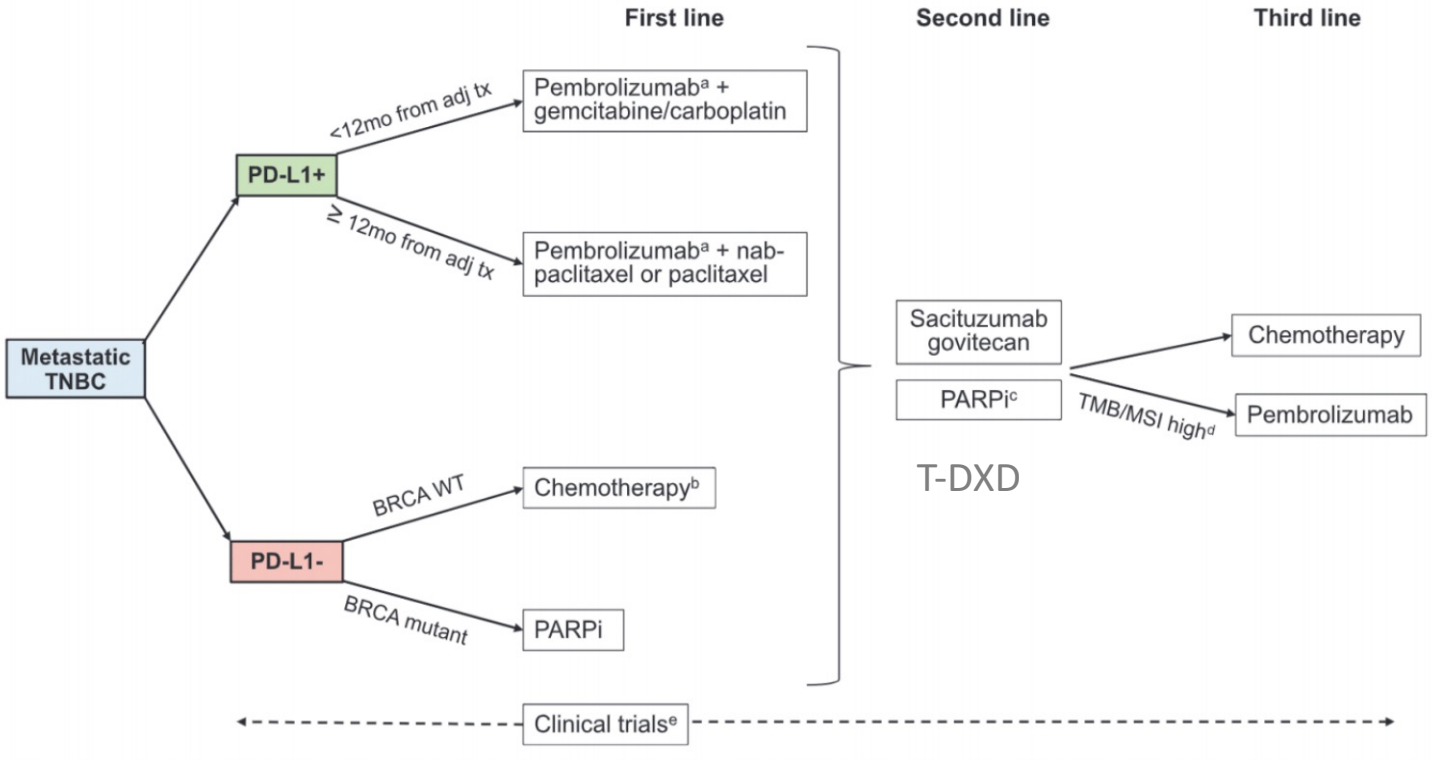
On November 13, 2020, the Food and Drug Administration granted accelerated approval to pembrolizumab in combination with chemotherapy for the treatment of patients with locally recurrent unresectable or metastatic triple-negative breast cancer (TNBC) whose tumors express PD-L1 (CPS ≥10) as determined by an FDA approved test.

FDA also approved the PD-L1 IHC 22C3 pharmDx as a companion diagnostic for selecting patients with TNBC for pembrolizumab.

Content current as of:
11/13/2020

Regulated Product(s)
Drugs
Prescription Drugs

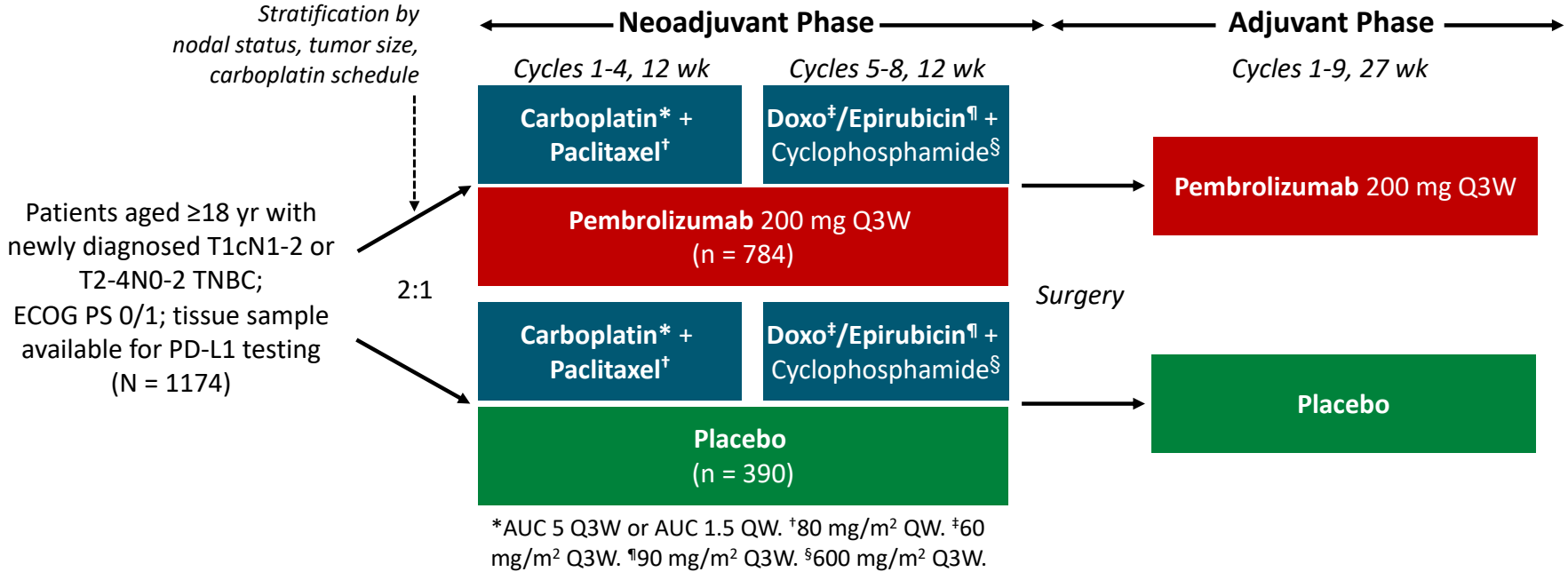
How to integrate?



L. A. Huppert, O. Gumusay, H. S. Rugo
Therapeutic Advances in Medical Oncology(2022)

EARLY STAGE DISEASE

KEYNOTE-522: Study Design

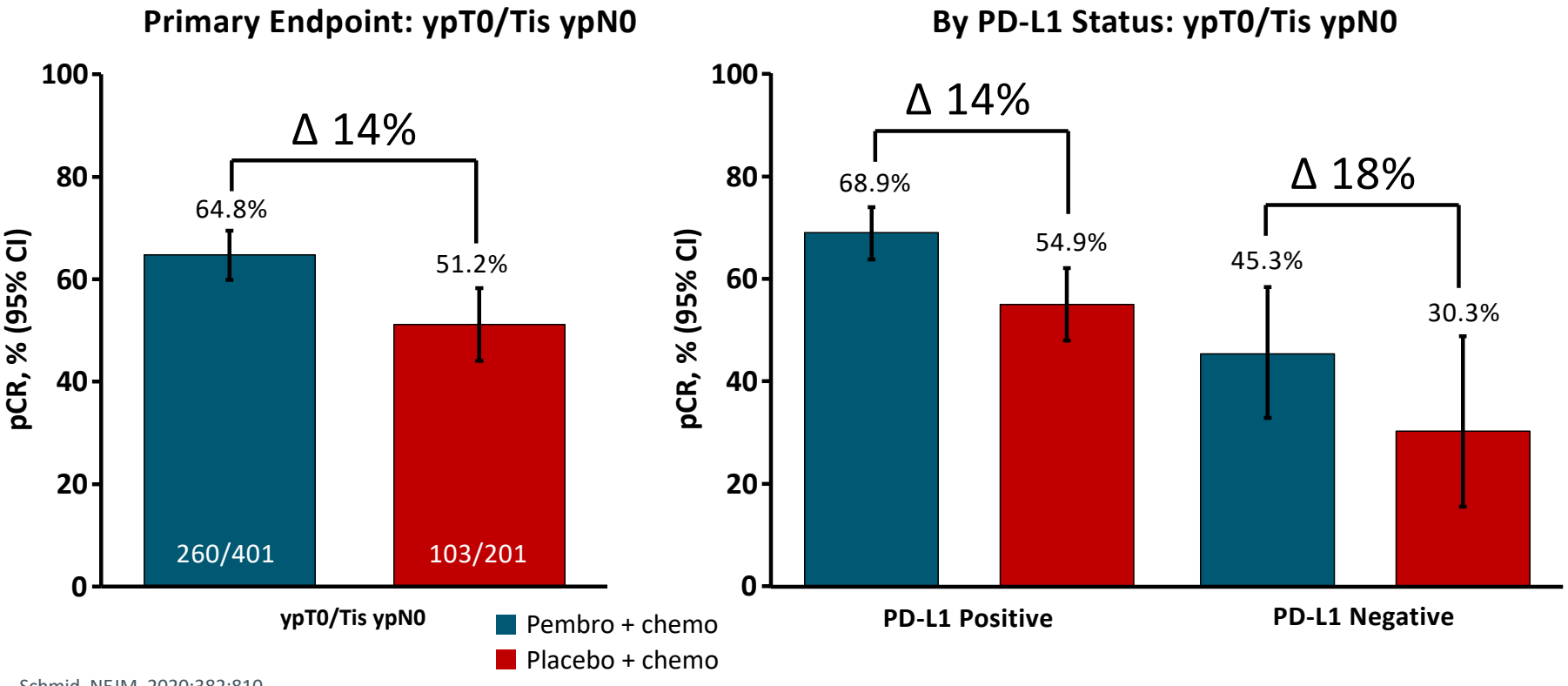


- **Primary endpoints:** pCR (ypT0/Tis ypN0) by local review, EFS by local review

- Secondary endpoints: pCR (ypT0 ypN0 and ypT0/Tis), OS, EFS, AE
- Exploratory endpoints: RCB, pCR by subgroups, EFS by pCR

Schmid. NEJM. 2020;382:810.

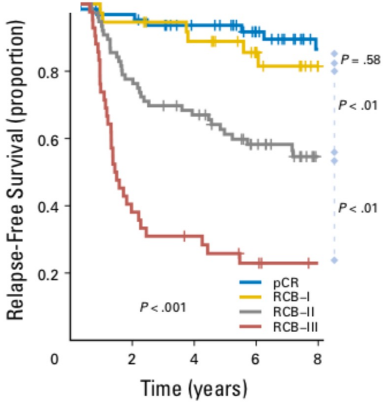
KEYNOTE-522: pCR at IA1



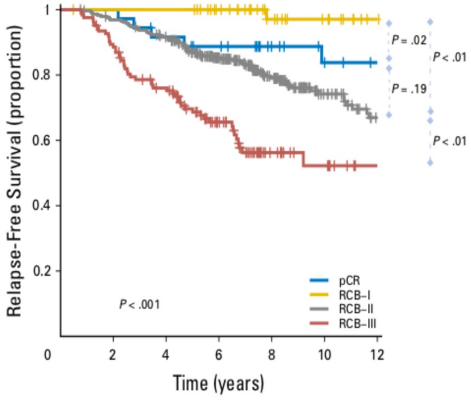
Schmid. NEJM. 2020;382:810.

RFS and RBC according to tumor subtype

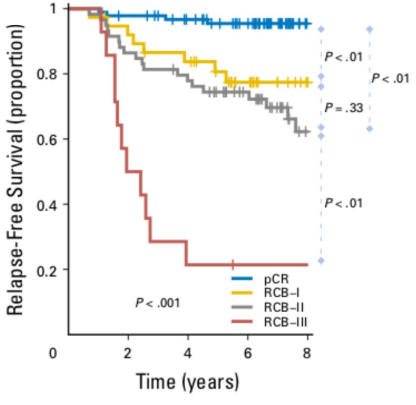
TNBC



HR+ and HER2-



All HER2+



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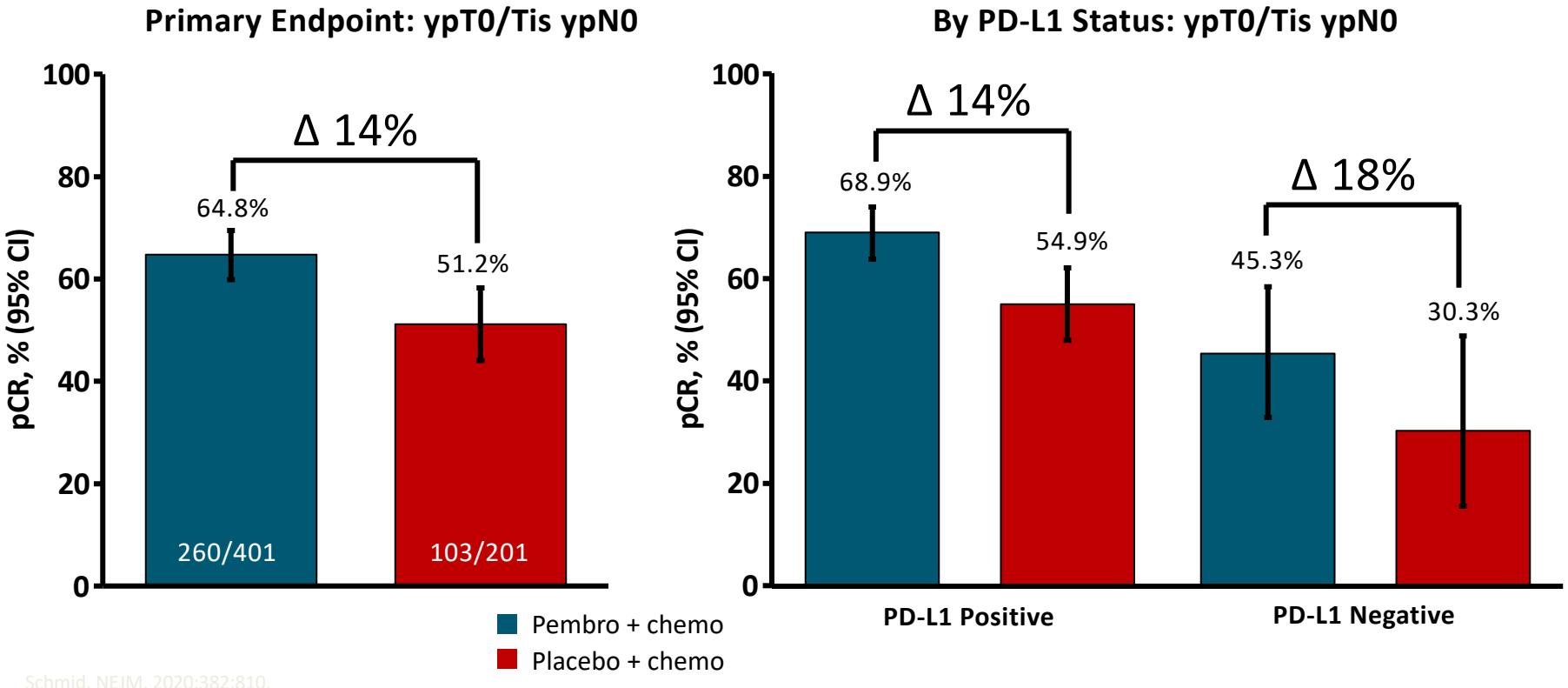
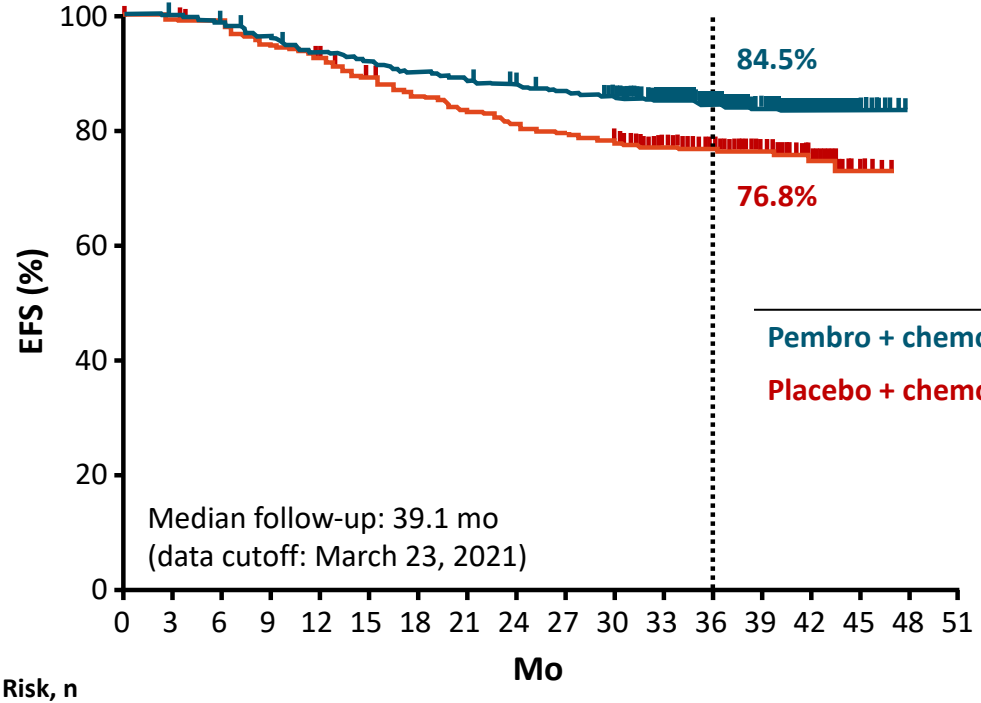
Symmans et al, JCO 2017

KEYNOTE-522: pCR at IA1



Schmid. NEJM. 2020;382:810.

KEYNOTE-522: EFS at IA4



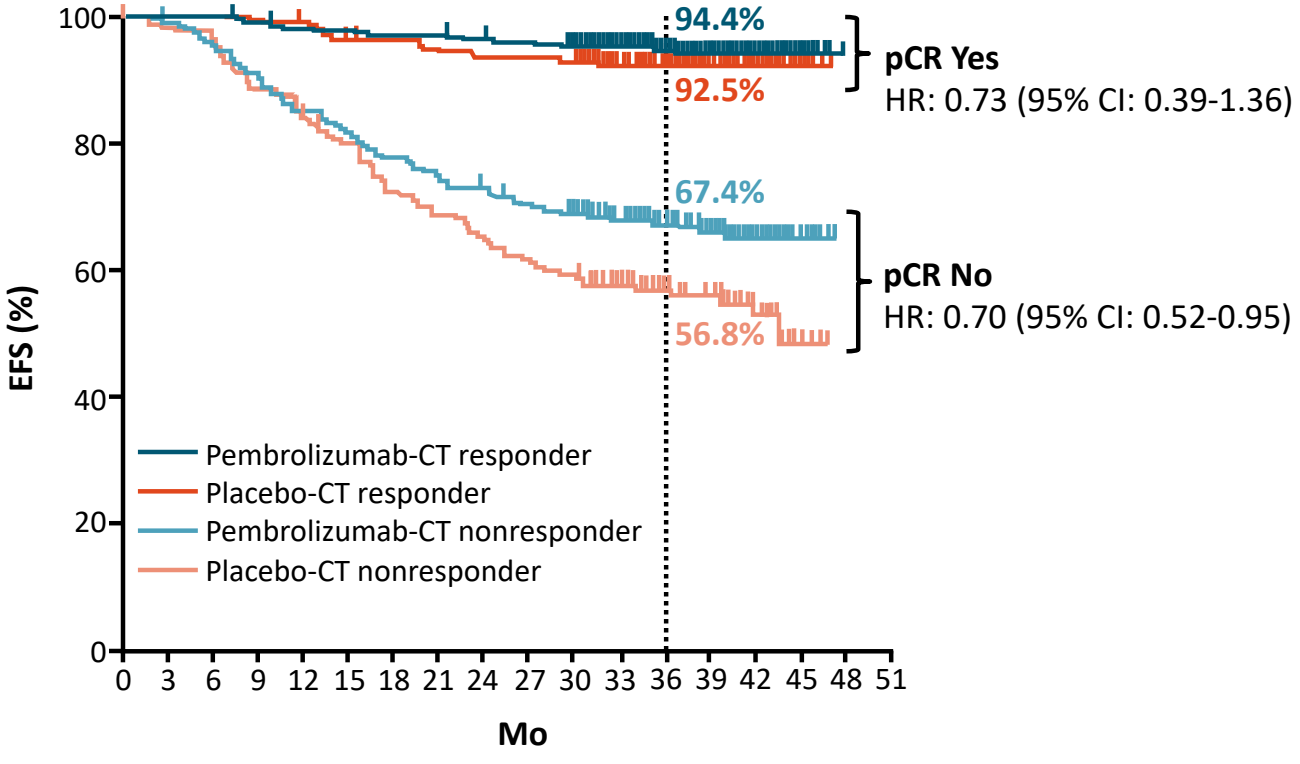
	Events, %	HR (95% CI)
Pembro + chemo	15.7	0.63 (0.48-0.82; *P* <.001*)
Placebo + chemo	23.8	

*Crossed prespecified boundary of *P* = .01034.

Patients at Risk, n																		
Pembro + chemo	784	781	769	751	728	718	702	692	681	671	652	551	433	303	165	28	0	0
Placebo + chemo	390	386	382	368	358	342	328	319	310	304	297	250	195	140	83	17	0	0

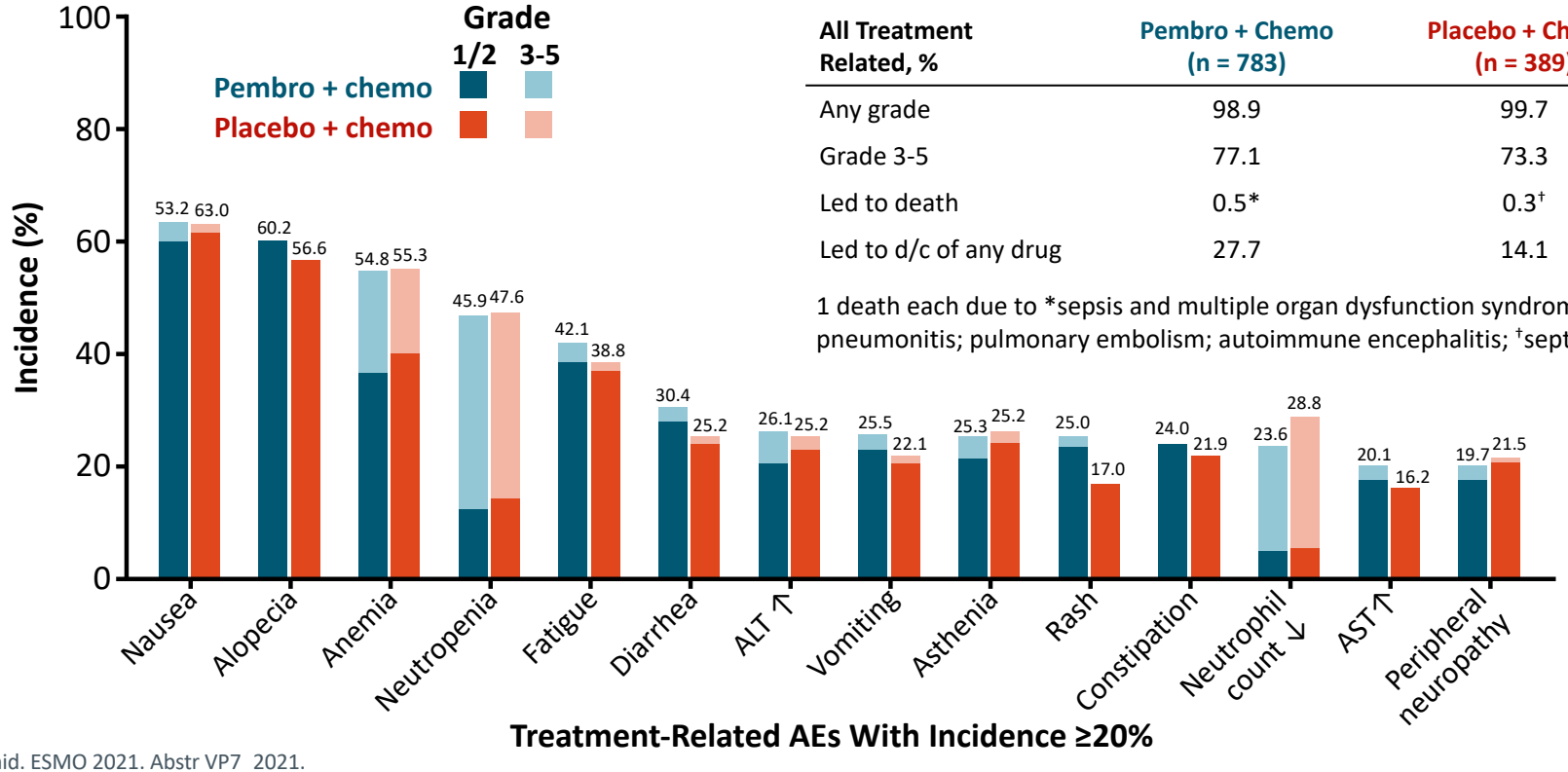
Schmid. NEJM. 2022;386:556.

KEYNOTE-522: EFS by pCR



Schmid. NEJM. 2022;386:556.

KEYNOTE-522: Treatment-Related Adverse Events

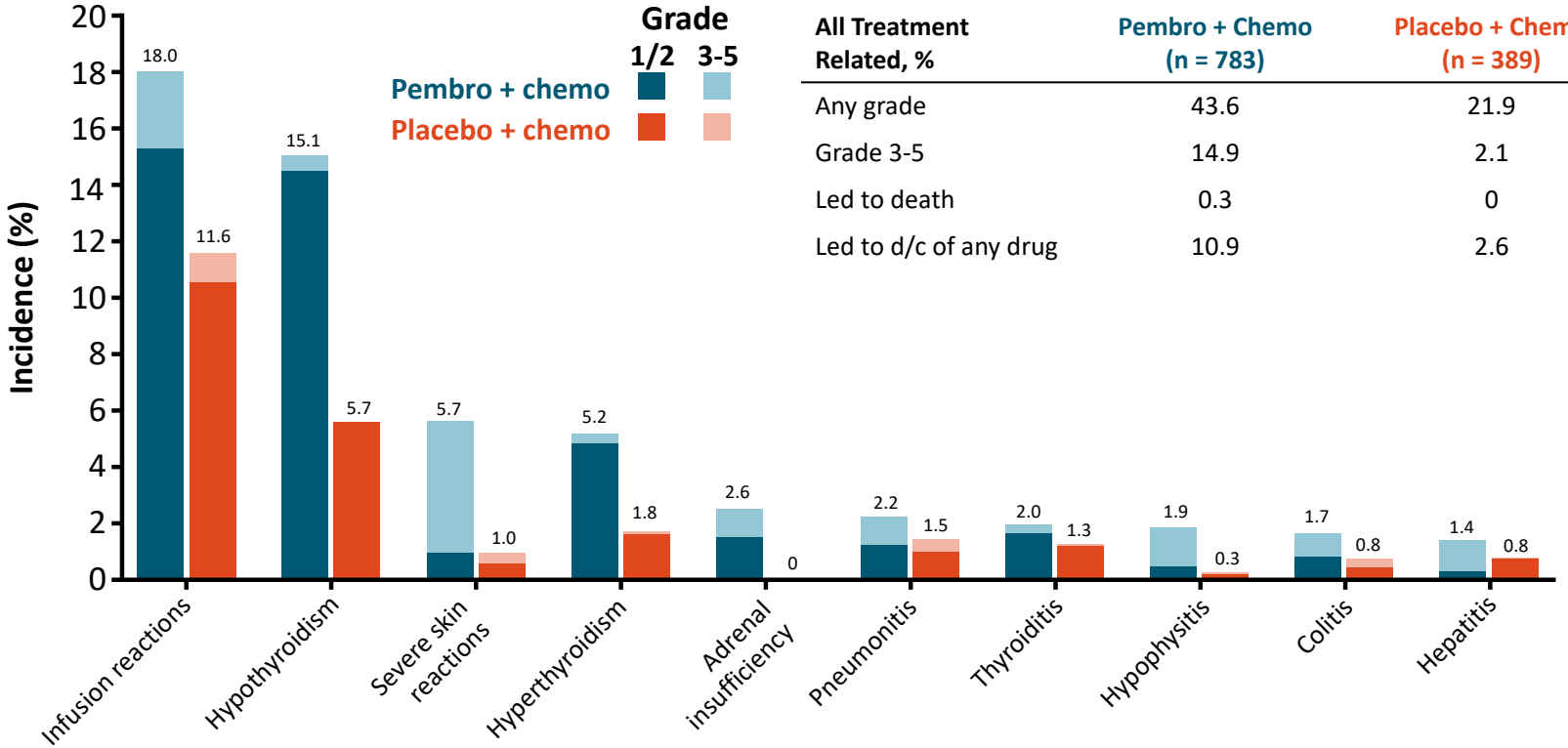


All Treatment Related, %	Pembro + Chemo (n = 783)	Placebo + Chemo (n = 389)
Any grade	98.9	99.7
Grade 3-5	77.1	73.3
Led to death	0.5*	0.3†
Led to d/c of any drug	27.7	14.1

1 death each due to *sepsis and multiple organ dysfunction syndrome; pneumonitis; pulmonary embolism; autoimmune encephalitis; †septic shock.

Schmid. ESMO 2021. Abstr VP7_2021.

KEYNOTE-522: Immune-Related Adverse Events

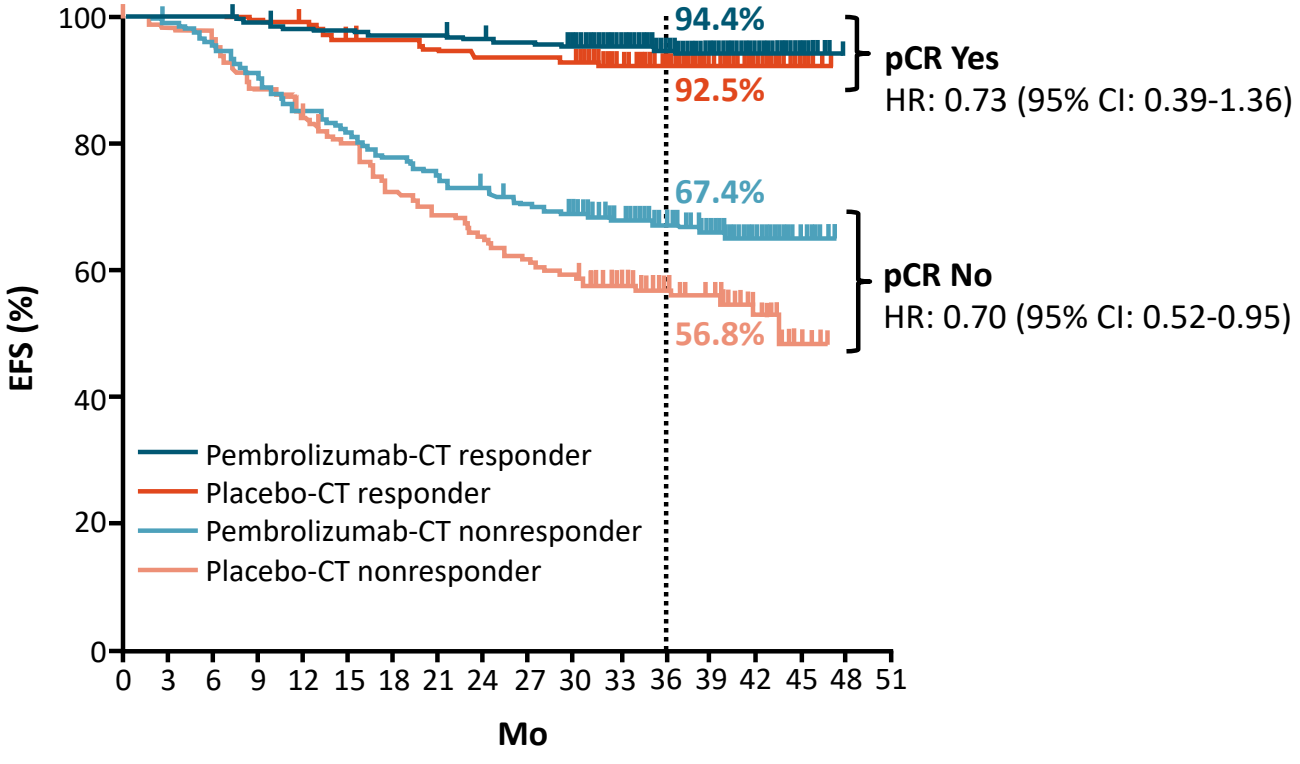


All Treatment Related, %	Pembro + Chemo (n = 783)	Placebo + Chemo (n = 389)
Any grade	43.6	21.9
Grade 3-5	14.9	2.1
Led to death	0.3	0
Led to d/c of any drug	10.9	2.6

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

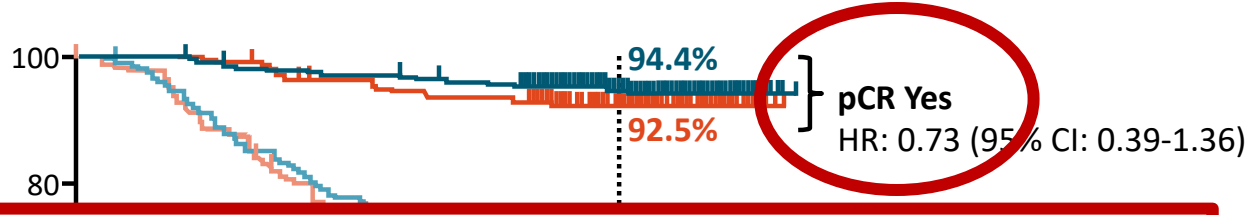
Schmid. ESMO 2021. Abstr VP7_2021.

KEYNOTE-522: EFS by pCR



Schmid. NEJM. 2022;386:556.

KEYNOTE-522: EFS by pCR



Forgo adjuvant pembro?

Briefer neoadjuvant IO exposure?

Neoadjuvant chemo alone?

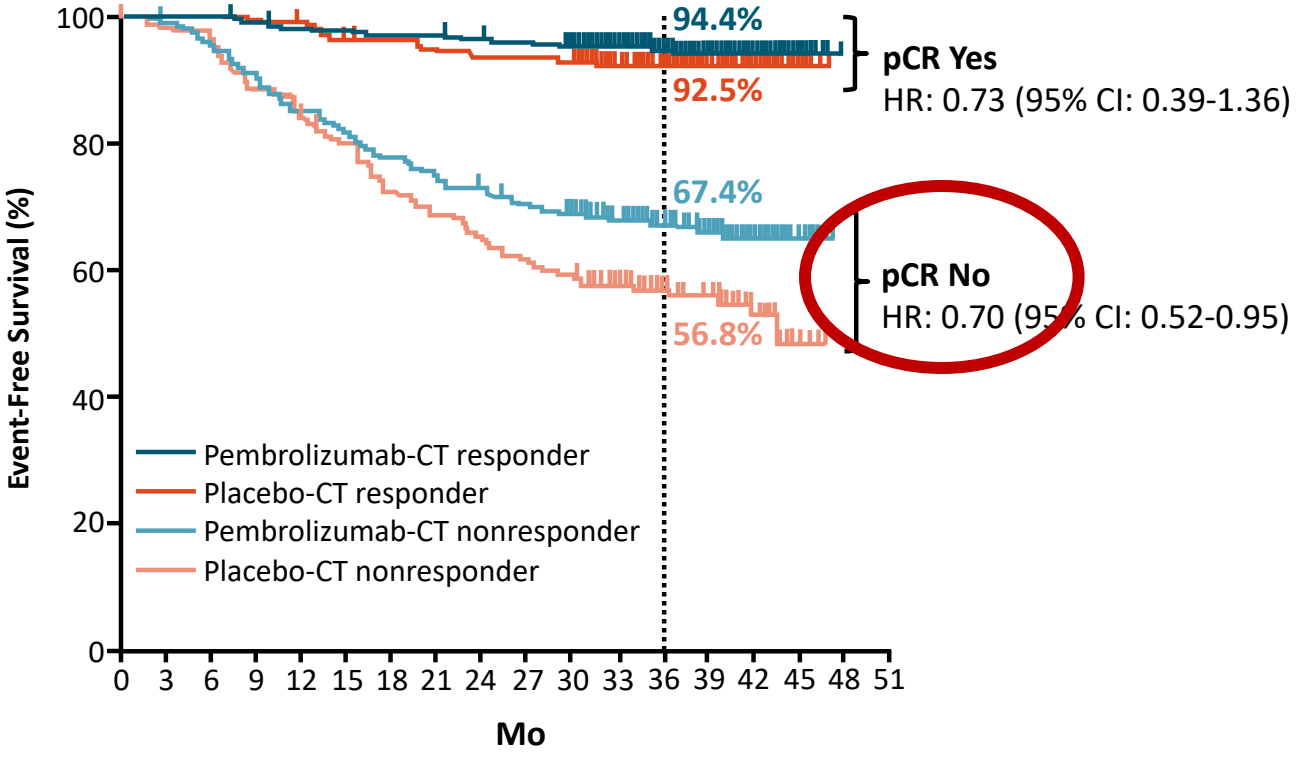
Chemo optimization?

Biologic combinations?

Need for upfront pCR predictors!

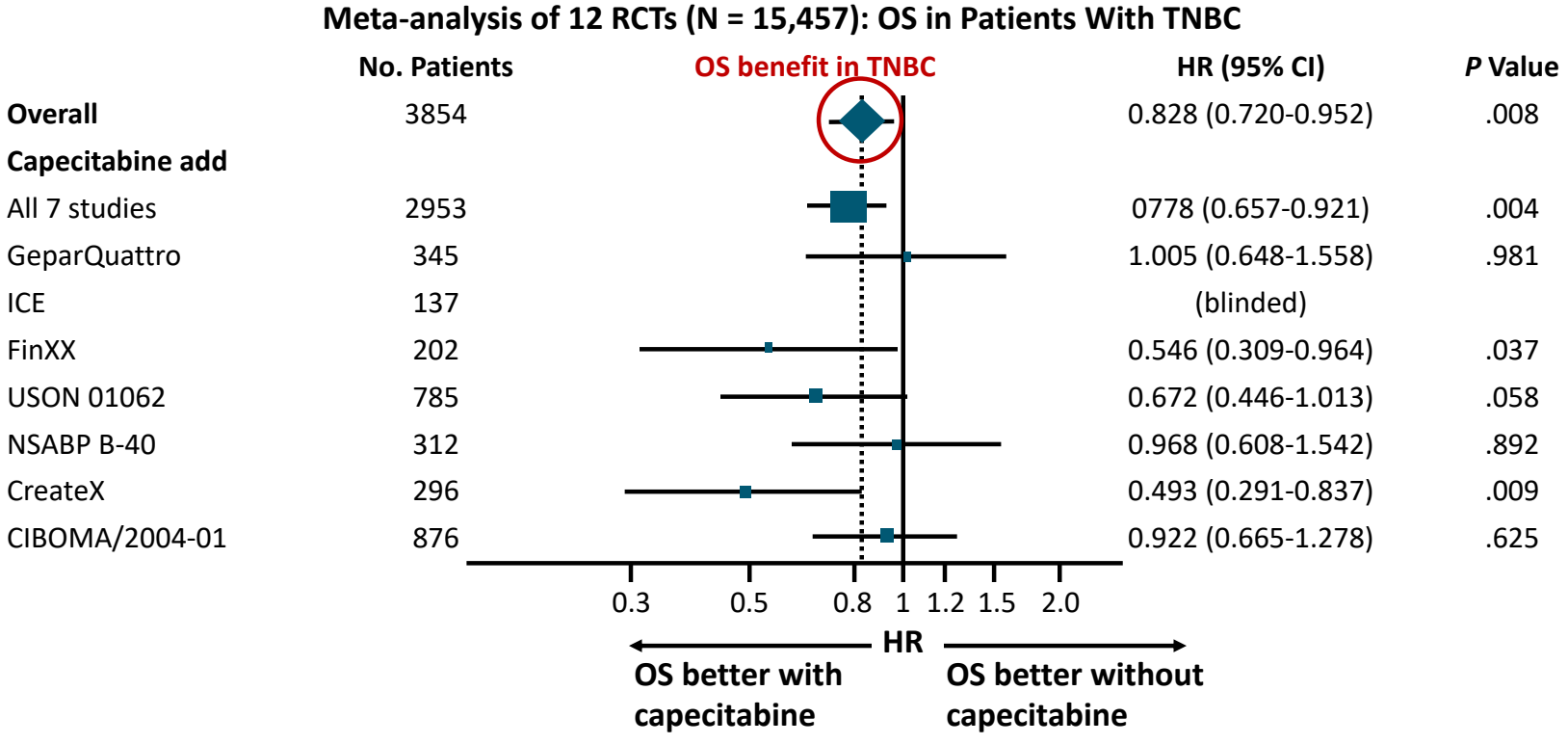
Schmid. NEJM. 2022;386:556.

KEYNOTE-522: EFS by pCR



Schmid. NEJM. 2022;386:556.

How Do We Reconcile With SOC Capecitabine?

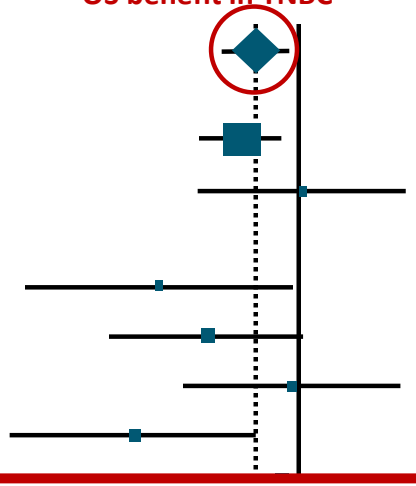


van Mackelenbergh. SABCS 2019. Abstr GS1-07.

How Do We Reconcile With SOC Capecitabine?

Meta-analysis of 12 RCTs (N = 15,457): OS in Patients With TNBC

	No. Patients	OS benefit in TNBC	HR (95% CI)	*P* Value
Overall	3854		0.828 (0.720-0.952)	.008
Capecitabine add				
All 7 studies	2953		0778 (0.657-0.921)	.004
GeparQuattro	345		1.005 (0.648-1.558)	.981
ICE	137		(blinded)	
FinXX	202		0.546 (0.309-0.964)	.037
USON 01062	785		0.672 (0.446-1.013)	.058
NSABP B-40	312		0.968 (0.608-1.542)	.892
CreateX	296		0.493 (0.291-0.837)	.009
CIBC				

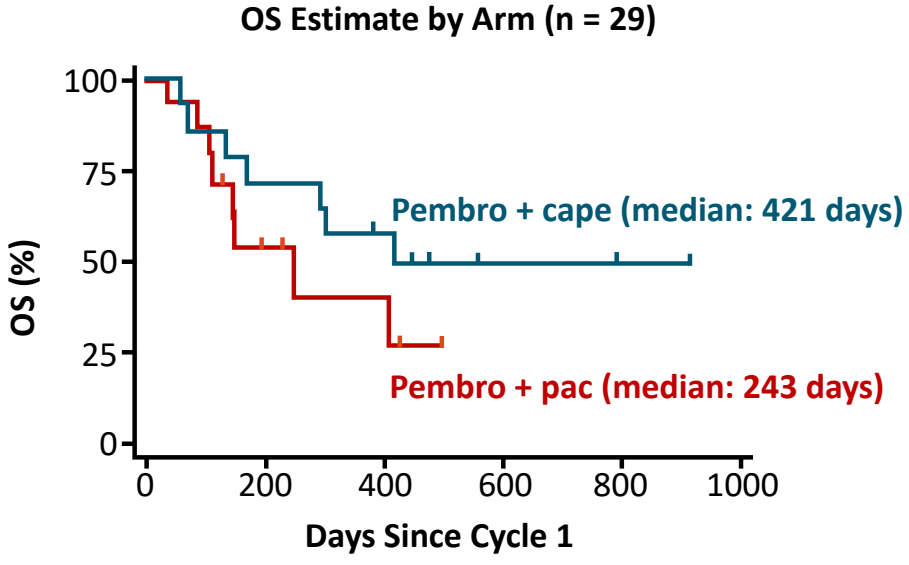


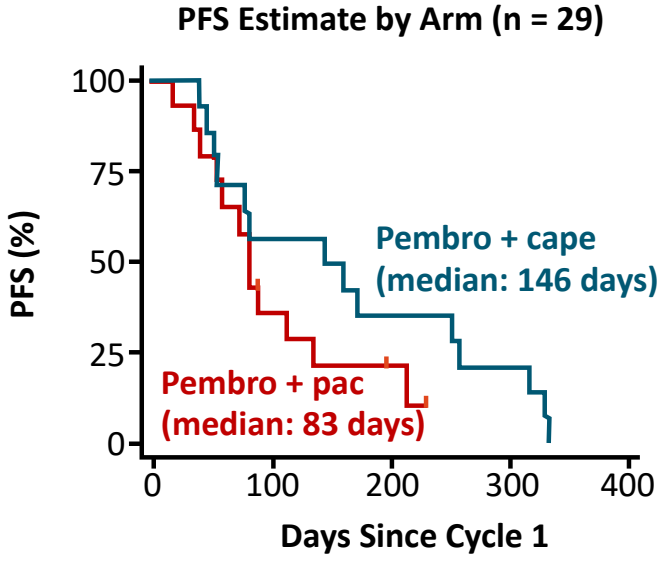
Adjuvant capecitabine not permitted on KEYNOTE-522
Concurrent with IO?

capecitabine **capecitabine**

van Mackelenbergh. SABCS 2019. Abstr GS1-07.

First-line/Second-line Pembrolizumab With Paclitaxel or Capecitabine in mTNBC





Wk 12 ORR: 43% with pembro + cape
Coadministration was safe
Coadministration of adjuvant pembro/cape may be reasonable in
selected high-risk patients with residual TNBC after NAC

Page. ASCO 2019. Abstr 1015.

How to integrate?

- Neadjuvant therapy
  - Node Negative: AC-taxol
  - Node Positive: KN-522
  - Limited PS: Evaluate carbo
- Adjuvant therapy
  - PCR: Observation vs pembro if KN-522
  - no PCR:
    - Capecitabine
    - Pembro
    - Capecitabine + Pembro?
    - BRCA+
      - Olaparib
      - Olaparib + Pembro?

What to Give in the Adjuvant Setting Now for High-Risk Early Breast Cancer?

In my opinion only, because we do not have all the data needed:

- **HR+ g*BRCA*wt**
  - Tamoxifen or AI ± ovarian suppression and **abemaciclib**
- **HR+ g*BRCA*m**
  - Tamoxifen or AI ± ovarian suppression and **olaparib**

  Consider starting ET + abemaciclib after olaparib completed?

- **TNBCg *BRCA*wt**
  - Capecitabine
    - **Continue the adjuvant immunotherapy**
- **TNBC g*BRCA*m**
  - **Olaparib** ± continued immunotherapy
- Waiting on SWOG 1418 to give more information on the benefit of adjuvant immunotherapy

Take home messages

- Early resistance, early recurrence and death
- New therapies are improving outcomes, but better therapies are needed
- Immunotherapy is now part of the treatment of patients with TNBC
- Take advantage of heterogeneity/Biomarkers
- Early-stage patients:Majority need to be treated with NST
  - Target those with residual disease
  - De-escalation

Gracias