Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Immunotherapy for the Treatment of Breast Cancer

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AAEM American Academy of Emergency Medicine — Champion of the Emergency Physician

ACCC Association of Community Cancer Centers

HOPA Hematology/Oncology Pharmacy Association

Society for Immunotherapy of Cancer

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Disclosures

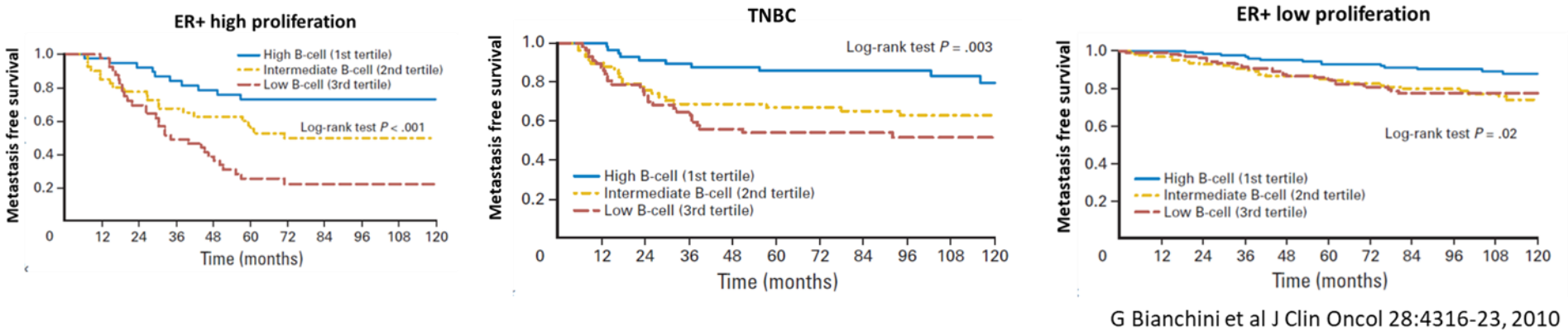
Consulting Fees:
Seattle Genetics, Pfizer, Astra Zeneca, Merck, Novartis, Bristol-Myers Squibb, Pfizer, Genentech, Eisai, Pieris, Immunomedics, Clovis, Syndax, H3Bio, Radius Health, and Daiichi, institutional research funding from Seattle Genetics, AstraZeneca, Merck, Pfizer and Bristol Myers Squibb.

Contracted Research:
Bristol Myers Squibb; Pfizer, Seattle Genetics, Merck, Astra Zeneca

I will be discussing non-FDA approved indications during my presentation.

Prognostic and chemotherapy response predictive role of immune infiltration in breast cancer

The pure prognostic function of a B-cell immune gene signature in breast cancer subtypes (no systemic adjuvant therapy)



G Bianchini et al J Clin Oncol 28:4316-23, 2010

Are the immune cells cause the good prognosis or this is a mere association?

The chemotherapy predictive function of TILs in breast cancer subtypes

Pathologic complete response (pCR) rates to neoadjuvant chemotherapy by baseline TIL count

	No Lymphocytes		Some Lymphocytes		Lymphocyte Predominant (>50%)		
Factor	No. of Tumors	pCR rate %	No. of Tumors	pCR rate %	lo. of Tumors	pCR rate %	χ^2 for trends)
GeparTrio							
All tumors	138	7.2	602	15.4	100	40.0	< .0005
TAC therapy	110	8.2	515	17.5	93	41.9	< .0005
TAC/NX therapy	28	3.6	87	3.4	7	14.3	.44
ER positive and/or PR positive	104	5.8	378	8.2	30	23.3	.018
ER negative/PR negative	22	18.2	137	32.1	60	51.7	.001
Grade 1/2	90	6.7	331	9.4	34	32.4	.001
Grade 3	31	6.5	192	24.0	55	41.8	< .0005
Lobular tumor	45	4.4	70	10.0	4	25	.14
Nonlobular tumor	93	8.6	528	15.7	94	40.4	< .0005
Age < 50 years	45	13.3	291	15.8	52	50.0	< .0005
Age ≥ 50 years	93	4.3	311	15.1	48	29.2	< .0005
HER-2 negative	88	8.0	300	14.0	54	48.1	< .0005
HER-2 positive	23	4.3	202	19.3	29	31.0	.016
Tumor size < 4 cm	61	8.2	241	14.9	41	46.3	< .0005
Tumor size ≥ 4 cm	77	6.5	352	15.6	55	34.5	< .0005

20% 74% 6%

10% 62% 28%

C Denkert et al. *J Clin Oncol* 28:105-13, 2010

1. High levels of immune infiltration in breast cancer are associated with (i) better prognosis regardless of therapy, and with (ii) higher chemotherapy sensitivity.

2. Due to the highly correlated presence of immune cells, and co-expression of a large number of immune-related genes, there are many different immune markers that show similar prognostic or predictive values.

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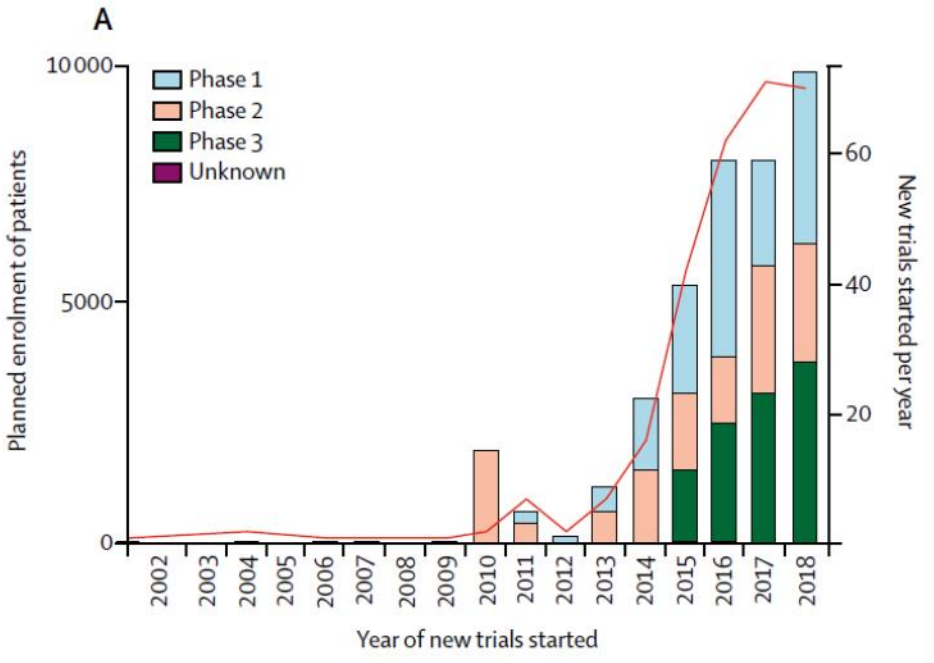
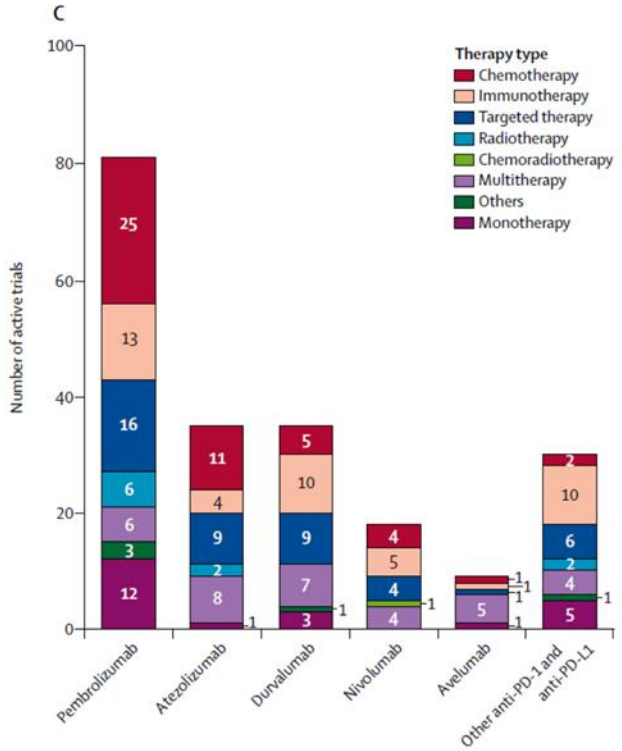
Immuno-oncology trial landscape of in breast cancer

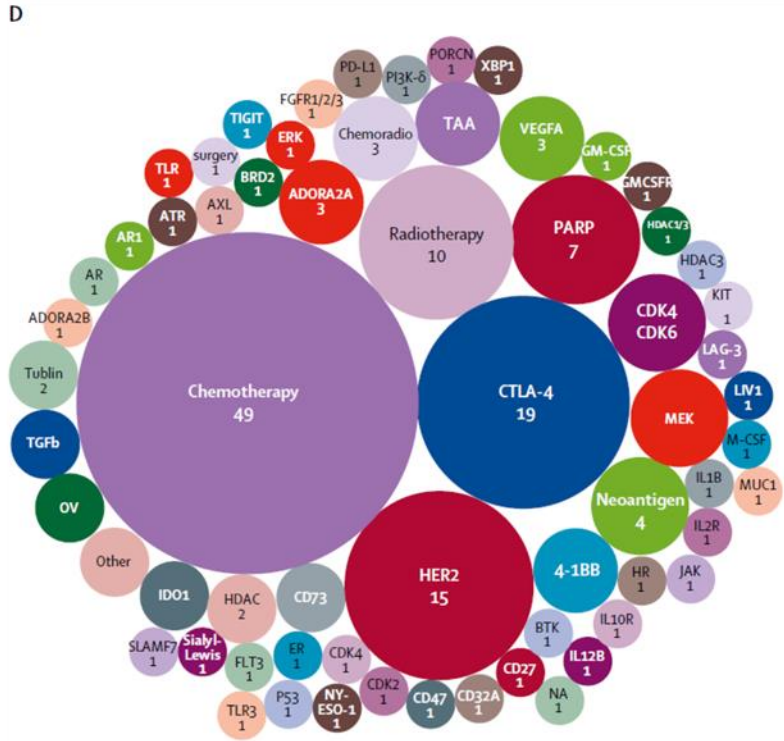
285 IO trials aiming to accrue 38,424 breast cancer patients



Breast cancer trials by type of immunotherapy agent



IO combination partners



We can only discuss a few seminal trials to illustrate major advances and highlight consistent emerging themes in these results.

F Esteva et al. *Lancet Oncol* 2019; 20: e175-86

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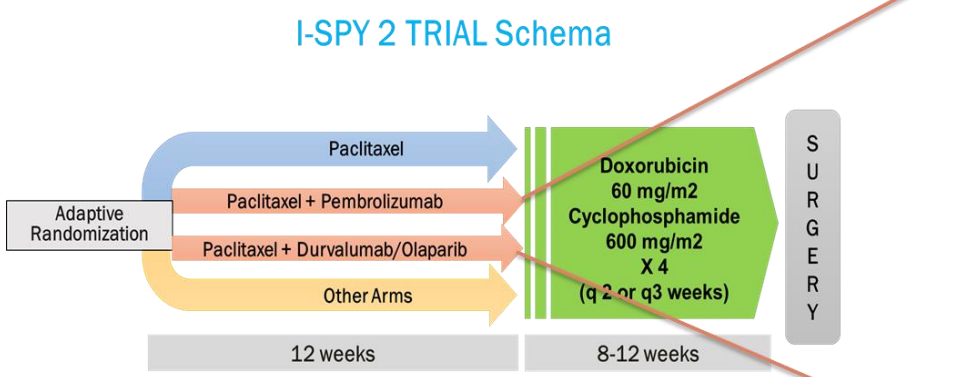
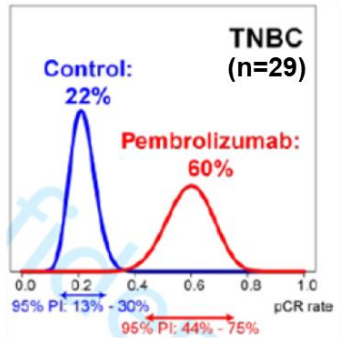
What have we learned from randomized neoadjuvant immune checkpoint inhibitor trials in early stage breast cancer (mostly TNBC)?

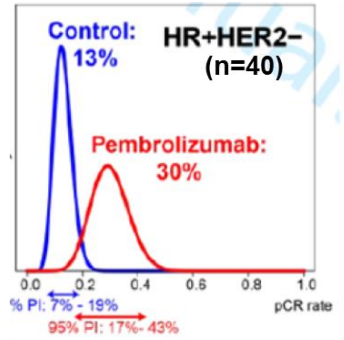
I-SPY2 (+)
KN-522 (+)
Impassion 031 (+)
GeparNuevo (n.s. trend)
NeoTrip-aPDL (-)

I-SPY2 Adoptively Randomized Phase II Neoadjuvant (preoperative) Trial:

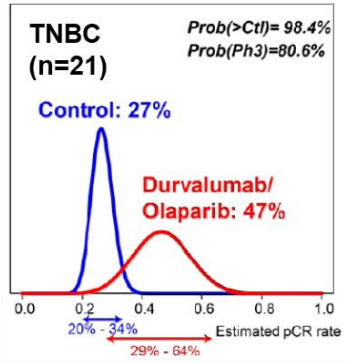
Pembrolizumab + paclitaxel and Durvalumab/olaparib + paclitaxel arms versus chemotherapy

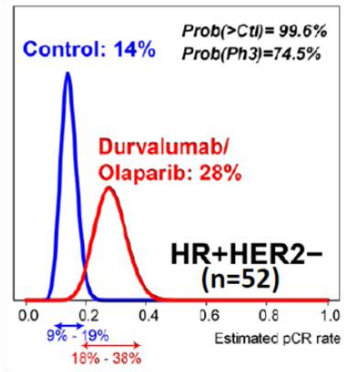






R Nanda et al. SABCS 2017 (JAMA 2020)





L Pusztai et al. AACR 2020

Adding pembro or durvalumab + oleparib to paclitaxel increased **pathologic complete eradication of the cancer** from the breast and lymph nodes **(pCR)** in TNBC and also high risk ER+ breast cancers.

Historically, patients with pCR had excellent long term survival!
(D. Yee et al. *JAMA Onc*. 6:1355-62, 2020)

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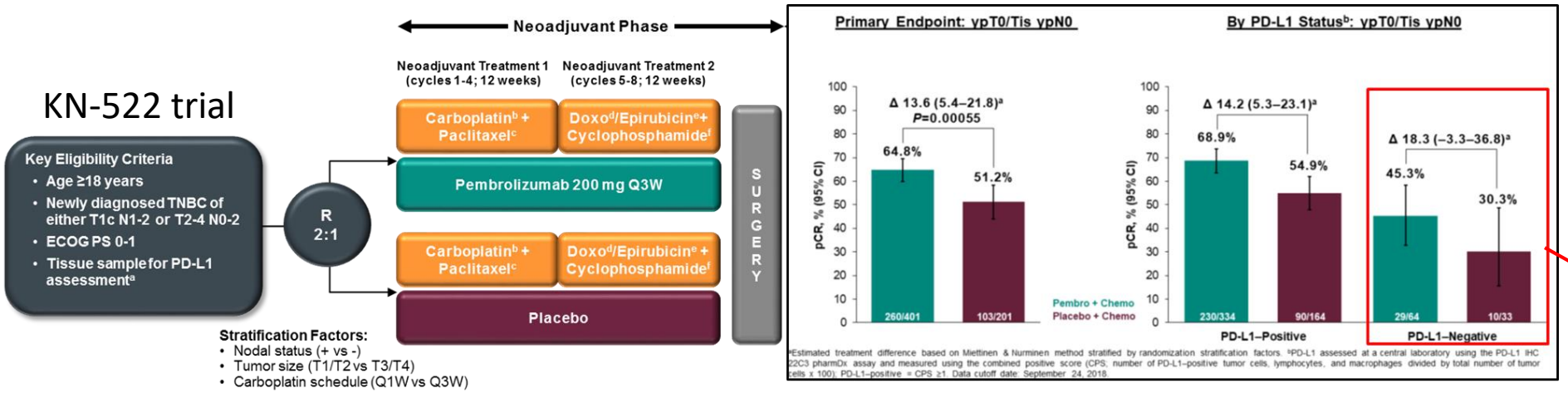
The **KN-522** (pembrolizumab) and **IMpassion-031** (atezolizumab) randomized trials confirmed that immune checkpoint inhibitors increase pathologic complete response (pCR) rates in early stage triple negative breast cancer (TNBC)

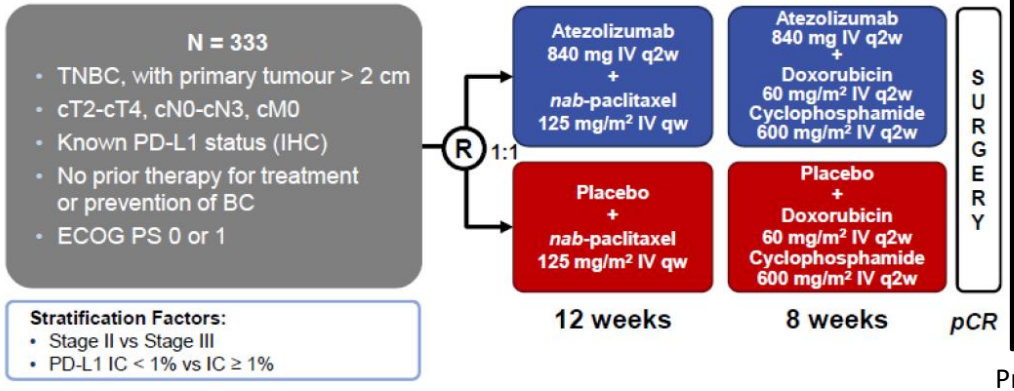
KN-522 trial

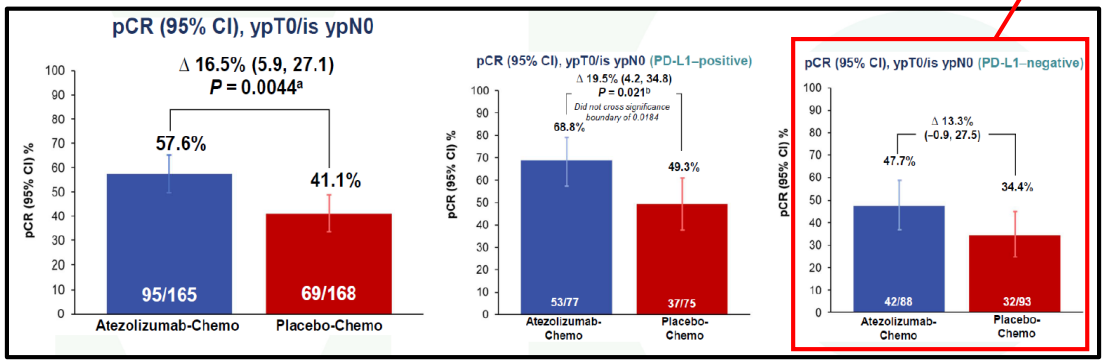


P. Schmid et al. *New Eng J Med*. 382:810-21, 2020

Benefit from IO therapy is seen in both PDL-1 positive and negative patients

Impassion-031 trial





Presented by N Harbeck at ESMO 2020 and published on-line *The Lancet*, September 20, 2020

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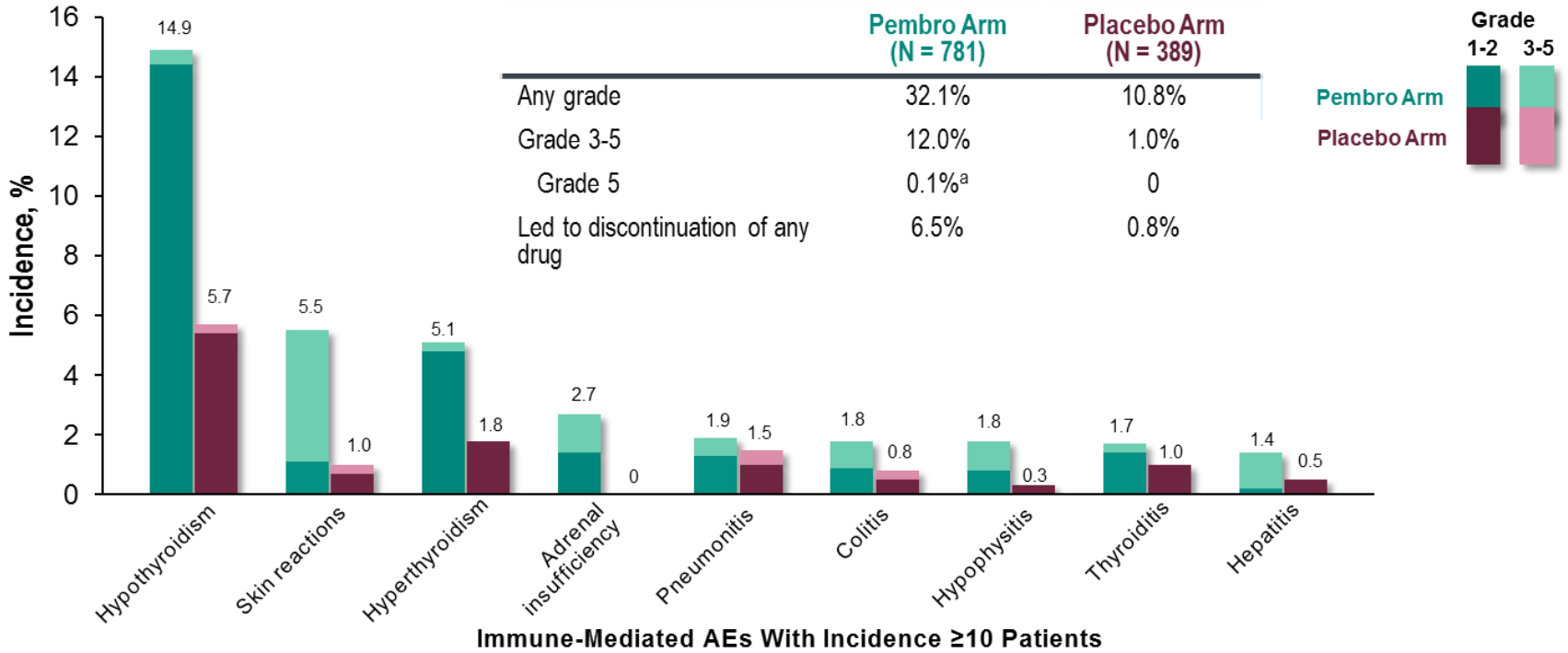
Immunotherapy related adverse events in KN522

Immune-Mediated AEs in Combined Phases



	Pembro Arm (N = 781)	Placebo Arm (N = 389)
Any grade	32.1%	10.8%
Grade 3-5	12.0%	1.0%
Grade 5	0.1%[a]	0
Led to discontinuation of any drug	6.5%	0.8%

Grade 1-2 3-5

Pembro Arm

Placebo Arm

[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.
IA2, second interim analysis. Data cutoff date: April 24, 2019.

P. Schmid et al. *New Eng J Med*. 382:810-21, 2020

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Summary of results in early stage TNBC

1. Four randomized trials demonstrated statistically significant increase in pCR rate with inclusion of a checkpoint inhibitor with chemotherapy.

2. One randomized Phase II trial, Geparnuevo (durvalumab) showed a 9% improvement in pCR that has not reached statistical significance.

3. One trial neoTRIP-aPDL1 (atezolizumab)demonstrated no improvement in pCR.

4. pCR rates are higher in PDL1+ cancers in both arm, PDL1 expression does not define the population that selectively benefits from IO therapy in the neoadjuvant setting

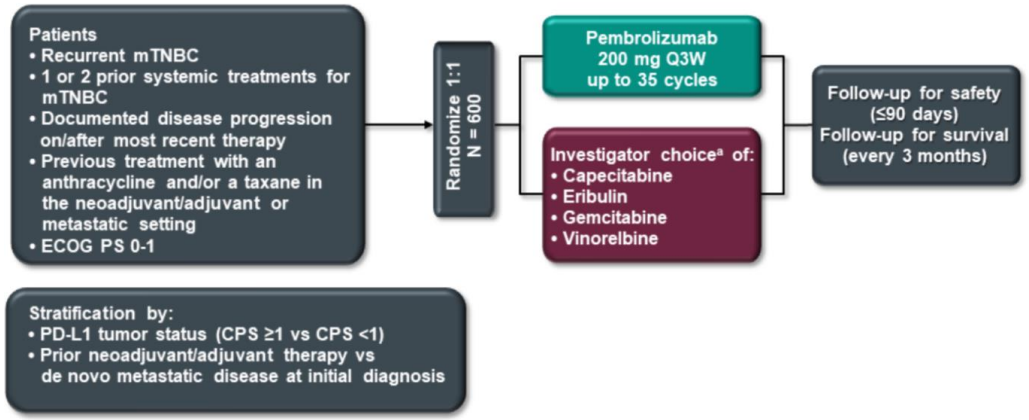
As of October 2020, there is no FDA approved IO agent as neoadjuvant therapy for breast cancer.

What have we learned from metastatic immune checkpoint inhibitor trials in TNBC ?

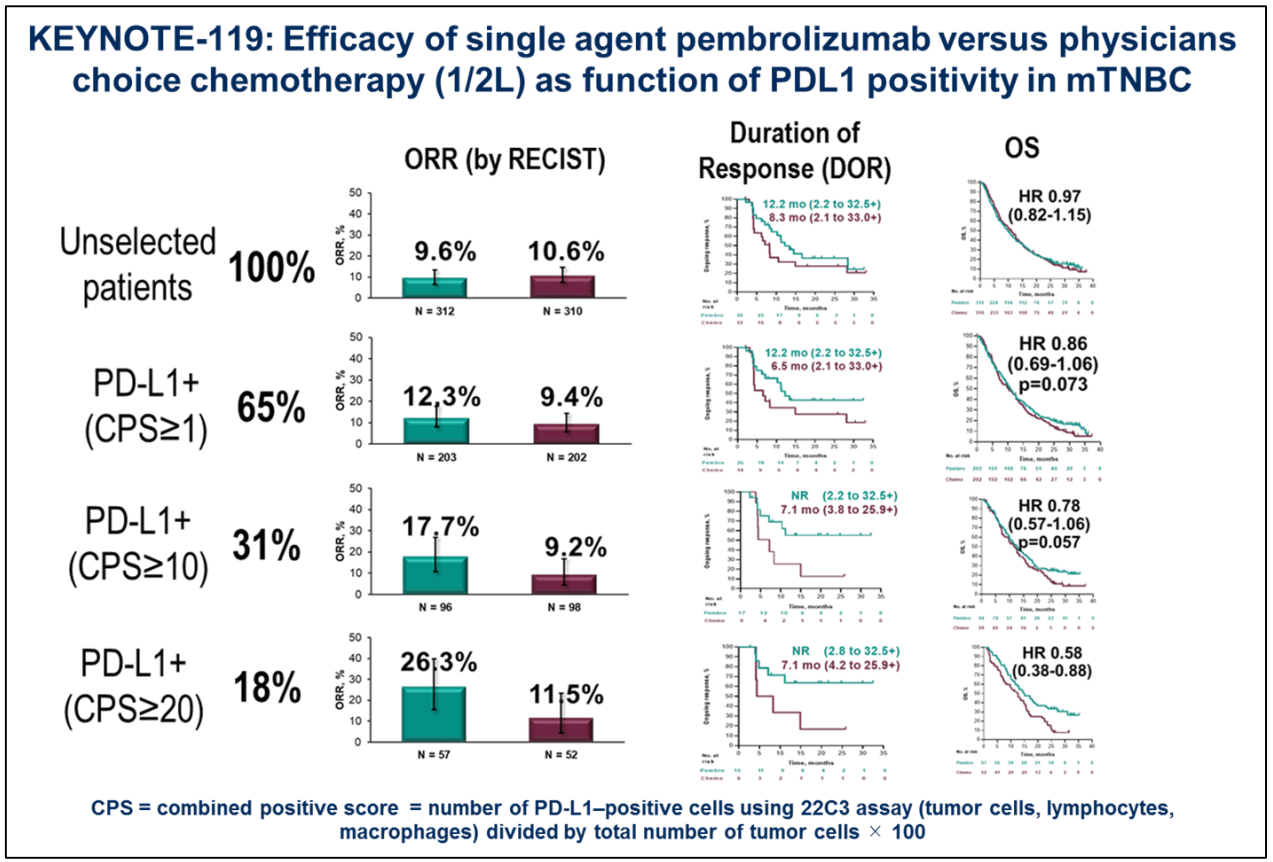
Keynote 119 (single agent pembrolizumab)
IMpassion 130 (atezolizumab + nab-paclitaxel)
Keynote 355 (pembrolizumab + paclitaxel/nab=paclitaxel, or gem/carbo)
Impassion 131 (atezolizumab + paclitaxel)

In metastatic TNBC, benefit from immune checkpoint therapy requires PDL-1 expression

KN-119 trial (N=622)



Presented by J Cortes at ESMO 2019



KN119 has not met its primary endpoints in the CPS >10 and CPS>1 populations but demonstrated increasing benefit from single agent pembrolizumab as 2st or 3nd line therapy for mTNBC as PD-L1 expression increased.

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Impassion-130: Phase III trial of Atezolizumab + nab-paclitaxel versus placebo + nab-paclitaxel as first line therapy for metastatic TNBC

Impassion-130 trial (N=622)

Key IMpassion130 eligibility criteria[a]:

- Metastatic or inoperable locally advanced TNBC
  - Histologically documented[b]
- No prior therapy for advanced TNBC
  - Prior chemo in the curative setting, including taxanes, allowed if TFI ≥ 12 mo
- ECOG PS 0-1

Stratification factors:

- Prior taxane use (yes vs no)
- Liver metastases (yes vs no)
- PD-L1 status on IC (positive [≥ 1%] vs negative [< 1%])[c]

R 1:1

Atezo + nab-P arm:
Atezolizumab 840 mg IV
- On days 1 and 15 of 28-day cycle

+ *nab*-paclitaxel 100 mg/m^2 IV
- On days 1, 8 and 15 of 28-day cycle

Plac + nab-P arm:
Placebo IV
- On days 1 and 15 of 28-day cycle

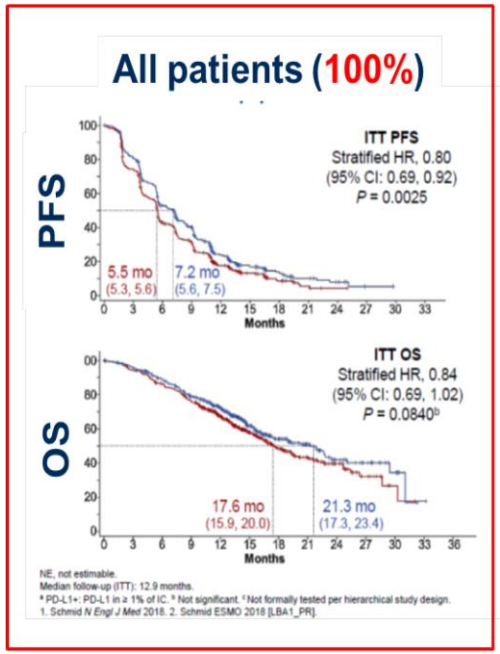
+ *nab*-paclitaxel 100 mg/m^2 IV
- On days 1, 8 and 15 of 28-day cycle

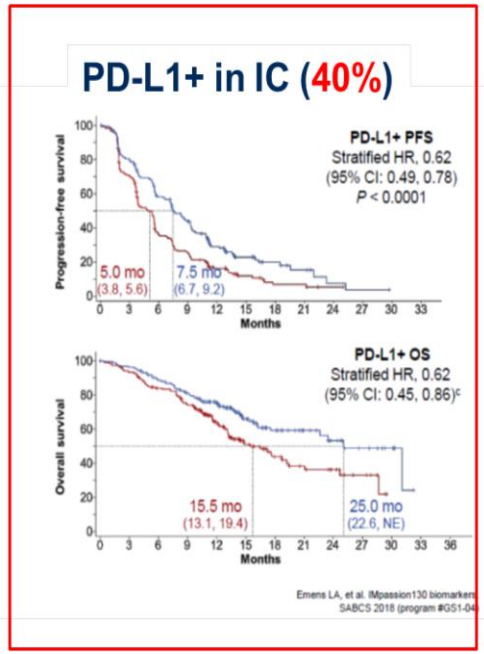
Double blind; no crossover permitted

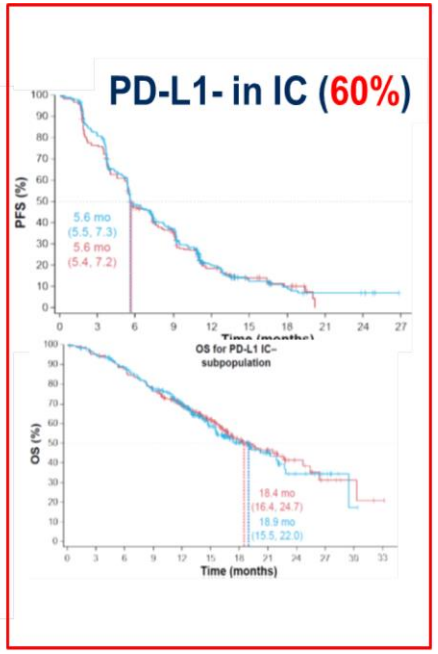
RECIST v1.1
PD or toxicity

- Co-primary endpoints were PFS and OS in the ITT and PD-L1+ populations[d]

Schmid P et al. *New Eng J Med* 379:2108-21, 2018







On March 8, 2019, the FDA approved atezolizumab in combination with nab-paclitaxel patients with unrespectable locally advanced or metastatic TNBC whose tumors express PD-L1 ≥ 1% by the VENTANA PD-L1 (SP142) Assay*.

*Expected benefit varies by type of PDL-1 IHC assay; not all assays identify the population that benefits from IO therapy equally accurately!
Rugo HS et al. *Ann Oncol*. 2019;30(suppl_5):v851-v934.

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The KN-355 trial of pembrolizumab + chemotherapy versus placebo + chemotherapy as first line therapy for metastatic TNBC showed very similar results to Impassion-130

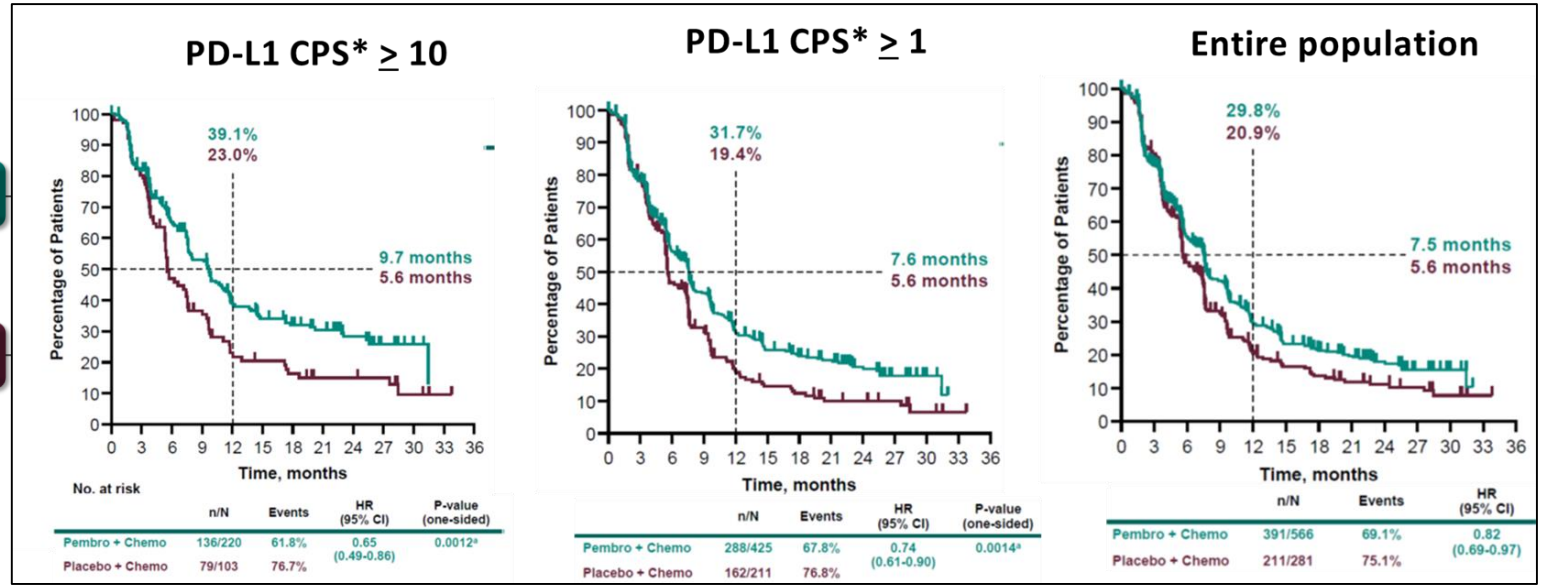
KN-355 trial (N=847)

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

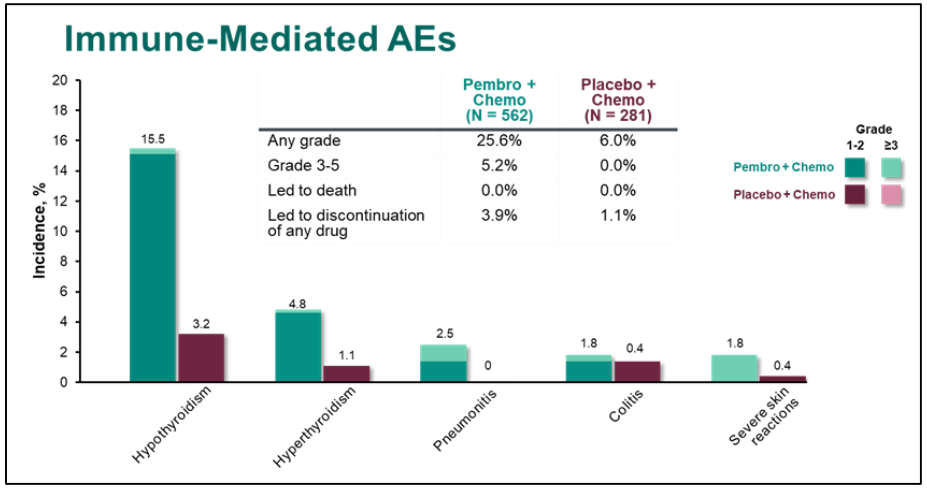
R 2:1

- Pembrolizumab[a] + Chemotherapy[b]
- Placebo[c] + Chemotherapy[b]

J. Cortes et al. *J Clin Oncol*. 2020;38(suppl 15; abstr 1000)



[a]Pembrolizumab 200 mg intravenous (IV) every 3 weeks (Q3W)
[b]Chemotherapy dosing regimens are as follows:
Nab-paclitaxel 100 mg/m² IV on days 1, 8, and 15 every 28 days
Paclitaxel 90 mg/m² IV on days 1, 8, and 15 every 28 days
Gemcitabine 1000 mg/m²/carboplatin AUC 2 on days 1 and 8 every 21 days



Pembrolizumab is not FDA approved for the treatment of metastatic TNBC as of October 2020

Impassion-131; a negative trial; Atezolizumab + paclitaxel versus placebo + paclitaxel as first line therapy for metastatic TNBC

IMpassion131 trial design (N=651)

Double-blind placebo-controlled randomised phase 3 trial

- Metastatic or unresectable locally advanced TNBC
- No prior chemotherapy or targeted therapy for advanced TNBC
- Previous eBC treatment completed ≥12 months before randomisation
- Taxane eligible
- Measurable disease
- ECOG PS 0/1

R 2:1

Atezolizumab 840 mg d1 & 15 + paclitaxel 90 mg/m² d1, 8 & 15

8–10 mg dexamethasone or equivalent for at least the first 2 infusions, cycles repeated q28d

Placebo d1 & 15 + paclitaxel 90 mg/m² d1, 8 & 15

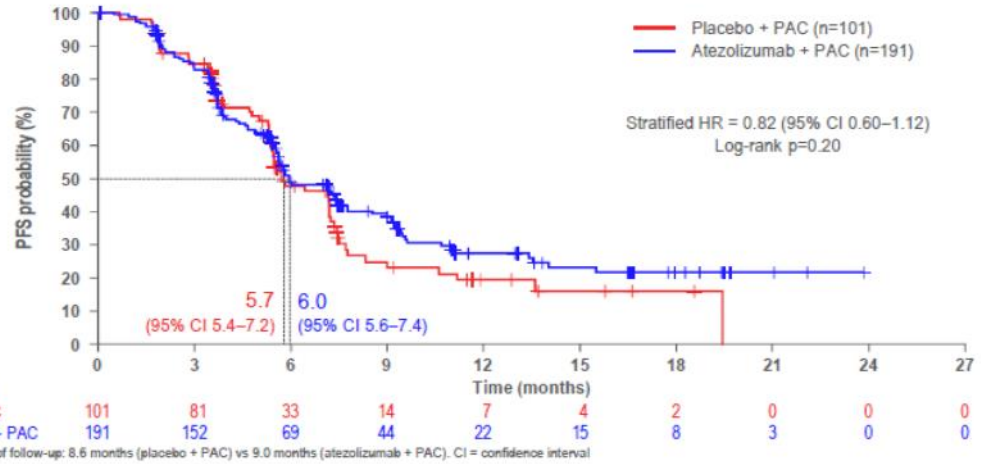
Primary endpoint: PFS (investigator assessed)
Secondary endpoints include:
- OS, ORR, PFS (IRC assessed)
- PROs
- Safety
- Translational research

Stratification:
- Prior taxane (yes vs no)
- Tumour PD-L1 status (IC <1% vs ≥1%)[a]
- Liver metastases (yes vs no)
- Geographical region (N America vs W Europe/Australia vs E Europe/Asia Pacific vs S America)

[a]PD-L1 IC: area of PD-L1-stained tumour-infiltrating ICs as a percentage of tumour area by VENTANA SP142 immunohistochemistry assay. eBC = early breast cancer; ECOG PS = Eastern Cooperative Oncology Group performance status; IC = immune cell; IRC = independent review committee; ORR = objective response rate; PRO = patient-reported outcome; q28d = every 28 days; R = randomisation

Primary analysis: PFS in the PD-L1+ population

Events in 61% of patients (data cut-off: 15 Nov 2019)



Median duration of follow-up: 8.6 months (placebo + PAC) vs 9.0 months (atezolizumab + PAC). CI = confidence interval

Presented by D Miles at ESMO 2020

Does the choice of chemotherapy drug, paclitaxel (require steroid premedication) versus nab-paclitaxel (no steroids), or differences in patient population, or "bad luck" (small sample size) account for the negative result?

1. KN-355 showed benefit with both paclitaxel or nab-paclitaxel.
2. In general IO agents show synergy with a broad range of chemo drugs in multiple disease types.
3. Pembrolizumab or durvalumab were synergistic with paclitaxel in 3 neoadjuvant trials that all used steroid premedication.

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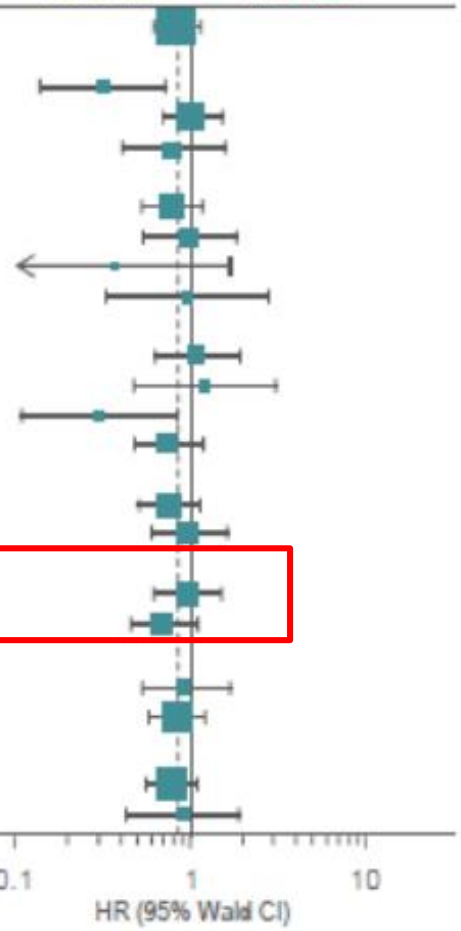
Impassion-131 efficacy within clinical patient subsets

Baseline risk factors	Total n	Placebo + PAC (n=101) n	Placebo + PAC (n=101) Median, months	Atezolizumab + PAC (n=191) n	Atezolizumab + PAC (n=191) Median, months	HR (95% Wald CI)
All patients	292	101	5.7	191	5.9	0.84 (0.62–1.14)
Age group						
18–40 years	38	16	3.4	22	5.5	0.32 (0.14–0.72)
41–64 years	182	62	6.4	120	5.6	1.03 (0.70–1.53)
≥65 years	72	23	7.7	49	9.4	0.80 (0.41–1.58)
Race						
White	170	59	5.7	111	5.9	0.79 (0.53–1.17)
Asian	87	30	7.2	57	7.3	1.00 (0.54–1.84)
Black/African American	12	4	3.6	8	7.1	0.38 (0.08–1.71)
Other	23	8	5.5	15	5.6	0.96 (0.33–2.78)
Geographical region						
Eastern Europe/Asia Pacific	109	35	7.2	74	7.3	1.10 (0.63–1.92)
North America	29	11	7.4	18	5.4	1.21 (0.48–3.06)
South America	25	10	3.6	15	4.9	0.31 (0.11–0.84)
Western Europe/Australia	129	45	5.7	84	5.9	0.76 (0.48–1.19)
ECOG PS						
0	177	59	7.1	118	7.2	0.76 (0.51–1.13)
1	115	42	5.5	73	5.6	0.99 (0.60–1.62)
Prior taxane therapy						
Yes	151	54	7.2	97	7.4	0.97 (0.62–1.50)
No	141	47	5.5	94	5.8	0.71 (0.46–1.10)
Presence of liver metastases						
Yes	61	24	5.3	37	3.9	0.94 (0.53–1.69)
No	231	77	7.2	154	7.4	0.84 (0.58–1.21)
Number of sites						
0–3	244	88	6.4	156	7.2	0.78 (0.56–1.10)
>3	48	13	5.4	35	5.2	0.90 (0.43–1.89)



Presented by D Miles at ESMO 2020

Additional rare biomarkers that can identify breast cancer patients who could benefit from immunotherapy

- Microsatellite instability (FDA approved indication)
- Hight Tumor Mutation Burden (FDA approved indication)

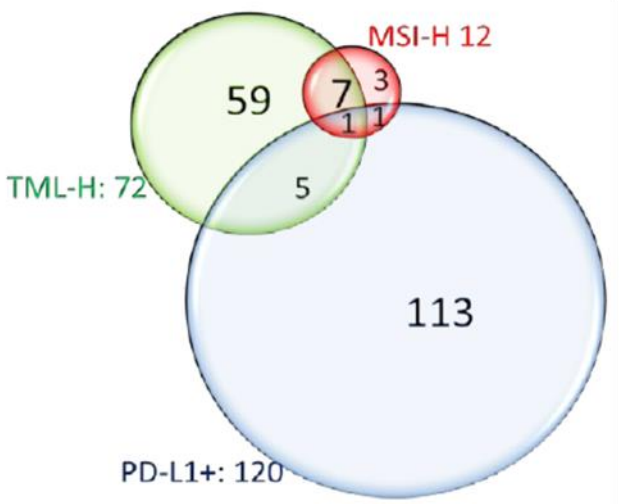
Microsatellite Unstable (MSI high by IHC) Cancers and Pembrolizumab Response

0.6% of breast cancers are MSI high (10% in endometrial, 5% in colorectal).

Response to Pembrolizuamb in MSI-high/MMR deficient (by IHC or PCR) cancers N=149

	N	Objective response rate n (%)	95% CI	DOR range (months)
CRC	90	32 (36%)	(26%, 46%)	(1.6+, 22.7+)
Non-CRC	59	27 (46%)	(33%, 59%)	(1.9+, 22.1+)
Endometrial cancer	14	5 (36%)	(13%, 65%)	(4.2+, 17.3+)
Biliary cancer	11	3 (27%)	(6%, 61%)	(11.6+, 19.6+)
Gastric or GE junction cancer	9	5 (56%)	(21%, 86%)	(5.8+, 22.1+)
Pancreatic cancer	6	5 (83%)	(36%, 100%)	(2.6+, 9.2+)
Small intestinal cancer	8	3 (38%)	(9%, 76%)	(1.9+, 9.1+)
Breast cancer	2	PR, PR		(7.6, 15.9)
Prostate cancer	2	PR, SD		9.8+
Bladder cancer	1	NE		
Esophageal cancer	1	PR		18.2+
Sarcoma	1	PD		
Thyroid cancer	1	NE		
Retroperitoneal adenocarcinoma	1	PR		7.5+
Small cell lung cancer	1	CR		8.9+
Renal cell cancer	1	PD		

Frequencies of MSI (by NGS), TMB (by NGS), and PD-L1+ (by IHC) status in the CARIS LIFE Science database of 1,952 metastatic breast cancers



E. Obeid et al. SABCS 2017. Abs. PD6-03

On May 23, 2017, the FDA approved pembrolizumab for patients with metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors, …..regardless of histology

Clinical Outcome in KEYNOTE-158 single agent pembrolizumab trials by Tumor Mutation Burden (TMB)

Table 59: Response by Tumor Type (TMB ≥10 mut/Mb)

	N	Objective Response Rate n (%)	95% CI	Duration of Response range (months)
Overall*	102	30 (29%)	(21%, 39%)	(2.2+, 34.8+)
Small cell lung cancer	34	10 (29%)	(15%, 47%)	(4.1, 32.5+)
Cervical cancer	16	5 (31%)	(11%, 59%)	(3.7+, 34.8+)
Endometrial cancer	15	7 (47%)	(21%, 73%)	(8.4+, 33.9+)
Anal cancer	14	1 (7%)	(0.2%, 34%)	18.8+
Vulvar cancer	12	2 (17%)	(2%, 48%)	(8.8, 11.0)
Neuroendocrine cancer	5	2 (40%)	(5%, 85%)	(2.2+, 32.6+)
Salivary cancer	3	PR, SD, PD		31.3+
Thyroid cancer	2	CR, CR		(8.2, 33.2+)
Mesothelioma cancer	1	PD		

A. Marabelle, et al. Annals Onc, 30:v477-v478, 2019
FDA label: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125514s066lbl.pdf

On June 17, 2020, the FDA approved pembrolizumab as a monotherapy for the treatment unresectable or metastatic solid tumors with High-TMB by the Foundation One CDx test, that have progressed following prior treatment and who have no satisfactory alternative treatment options,….histology agnostic indication……

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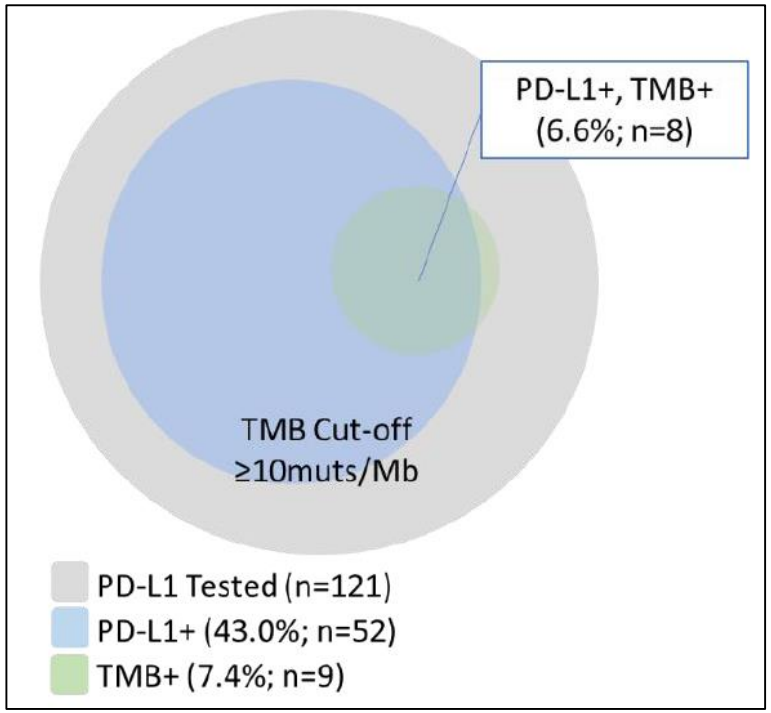
Single agent pembrolizumab in the TMB-high (≥10 mut/MB by F1CDx) metastatic breast cancer in the TAPUR trial

ASCO TAPUR metastatic breast cancer (N=28)

Muts/Mb, median (range)	13 (9, 37)
DC rate, % (OR or SD16+) (90% CI)	37% (24%, 46%)
OR rate, % (CR or PR) (95% CI)	21% (8%, 41%)
Median PFS, wks (95% CI)	10.6 (7.7, 21.1)
Median OS, wks (95% CI)	31.6 (11.9, inf)
Drug-related AEs, grades 3-4 (% of pts)	7%
Drug-related SAEs, grades 3-4 (% of pts)	4%
Median age, yrs (range)	63 (36, 78)
ECOG Performance Status, %	
0	36%
1	64%
Prior systemic regimens, %	
2	7%
≥3	93%

A.S. Alva et al. J Clin Oncol, 37 (no. 15_suppl): 1014-1014

PDL-1 IHC expression and TMB (≥10 mut / MB) in the Foundation Medicine database



R.S.P. Huang et al. The Oncologist, published on-line Sept 1, 2020

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Conclusions

- Immune checkpoint inhibitors added to standard of care neoadjuvant chemotherapy increase pathologic complete response in TNBC, and in some ER+ cancers (less data).
  - In the neoadjuvant setting, PDL-1 expression is not required for benefit from these drugs.
  - Currently, there is no immune checkpoint inhibitor approved for neoadjuvant use in breast cancer by the US FDA.

- In metastatic TNBC, PDL1 IHC positivity is required for benefit from pembrolizumab (KN119, KN355), atezolizumab (Impassion-130) and durvalumab (Safir02).
  - Atezolizumab plus nab-paclitaxel is approved by the FDA as first line therapy for PD-L1 positive metastatic TNBC based on the Impassion 130 trial results.
  - KN355 trial demonstrated similar results as Impassion 130 but pembrolizumab is not (yet) approved for PDL1+ metastatic TNBC

- Pembrolizumab is approved as single agent therapy for cancers regardless of histologic status with high tumor mutation burden or microsatellite instability.