sitc 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

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Disclosures

- Participated in Pfizer Advisory Board in 2019
- My spouse participated as a speaker for Novartis in 2019
- I will be discussing non-FDA approved indications during my presentation.

Immunotherapy in breast cancer

- Standard-of-care treatment usually involves surgery, chemotherapy, radiation
- Application of immunotherapy is still in early stages

Current approvals

Drug	Approved	Indication	Dose
Pembrolizumab	2017	MSI-H/dMMR **advanced cancer** with progression on previous treatment	200 mg Q3W
Atezolizumab + nab-paclitaxel	2019	Advanced/Metastatic **TNBC** with PD-L1 ≥1%	840 mg atezo + 100 mg/m^2 paclitaxel

Est new cases

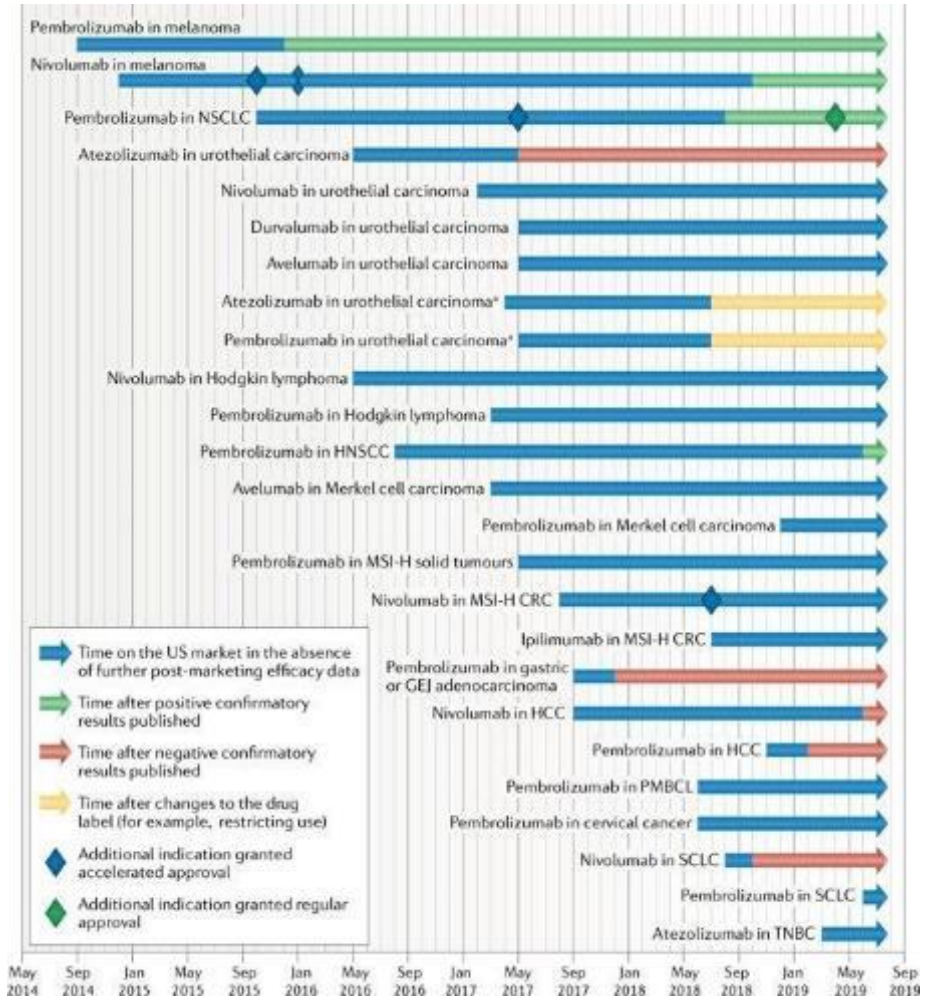
Female		
Breast	268,600	30%
Lung & bronchus	111,710	13%
Colon & rectum	67,100	7%
Uterine corpus	61,880	7%
Melanoma of the skin	39,260	5%
Thyroid	37,810	4%
Non-Hodgkin lymphoma	33,110	4%
Kidney & renal pelvis	29,700	3%
Pancreas	26,830	3%
Leukemia	25,860	3%
All sites	**891,480**	

Est deaths

Female		
Lung & bronchus	66,020	23%
Breast	41,760	15%
Colon & rectum	23,380	8%
Pancreas	21,950	8%
Ovary	13,980	5%
Uterine corpus	12,160	4%
Liver & intrahepatic bile duct	10,180	4%
Leukemia	9,690	3%
Non-Hodgkin lymphoma	8,460	3%
Brain & other nervous system	7,850	3%
All sites	**285,210**	

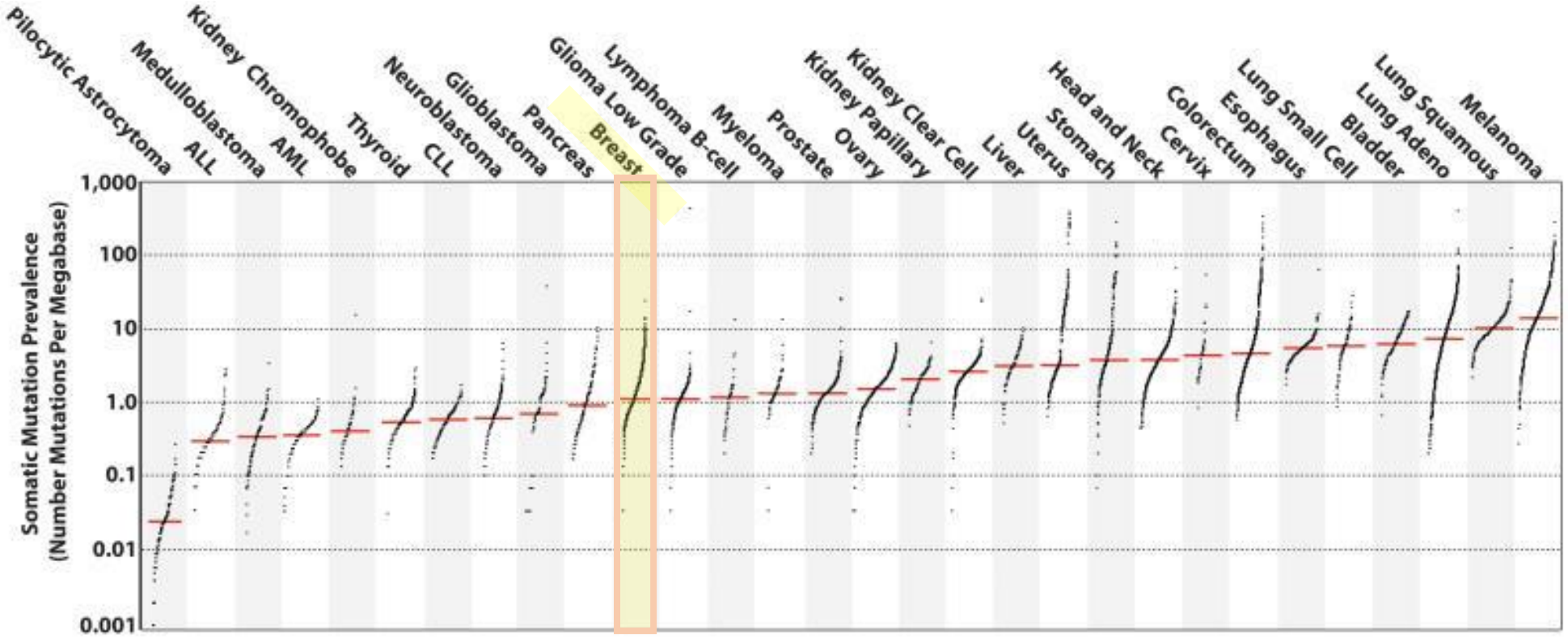
American Cancer Society

After # 24 accelerated approvals, we made it!



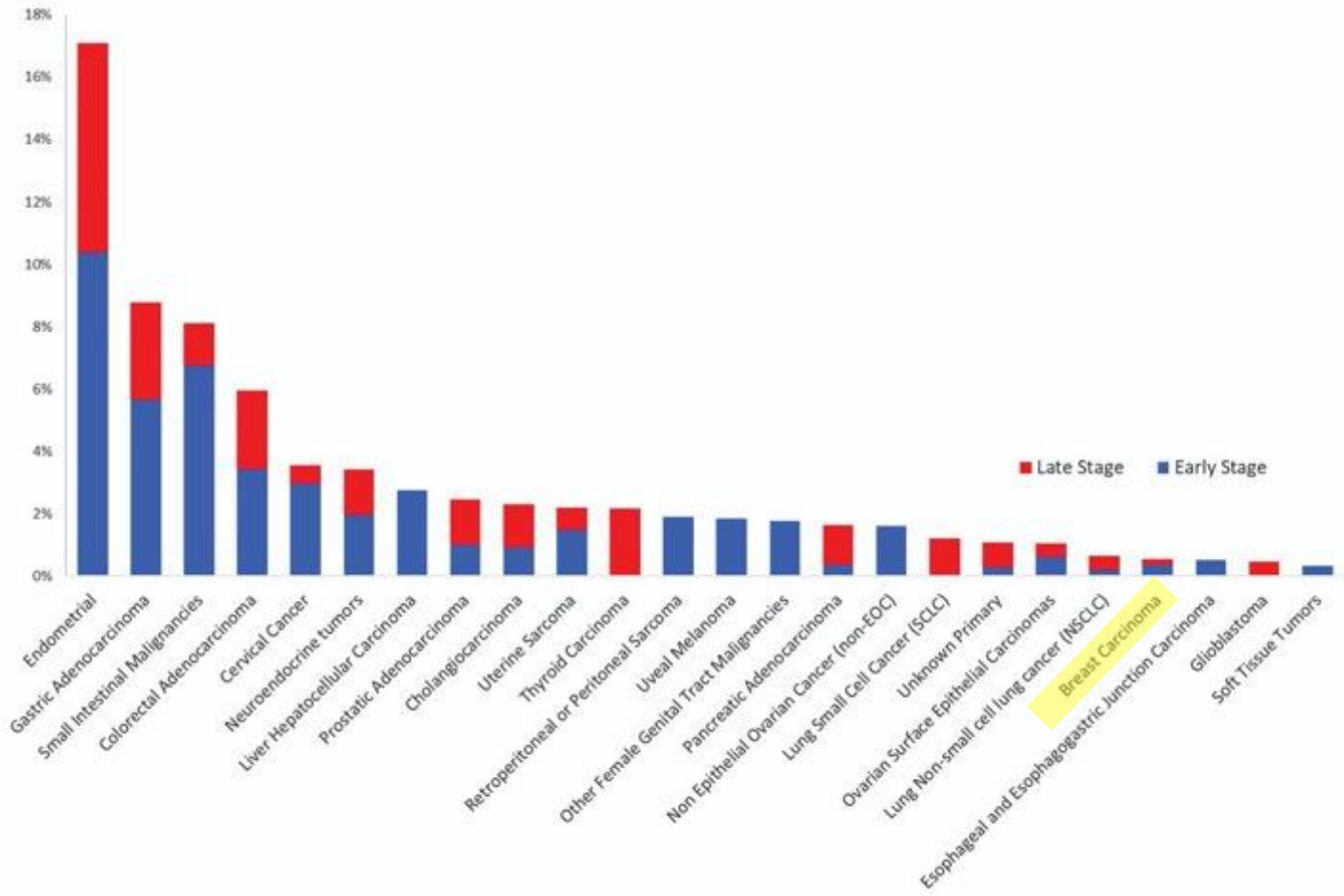
J Gill & V Prasad, Nature Review 2019

Immunotherapy in breast cancers



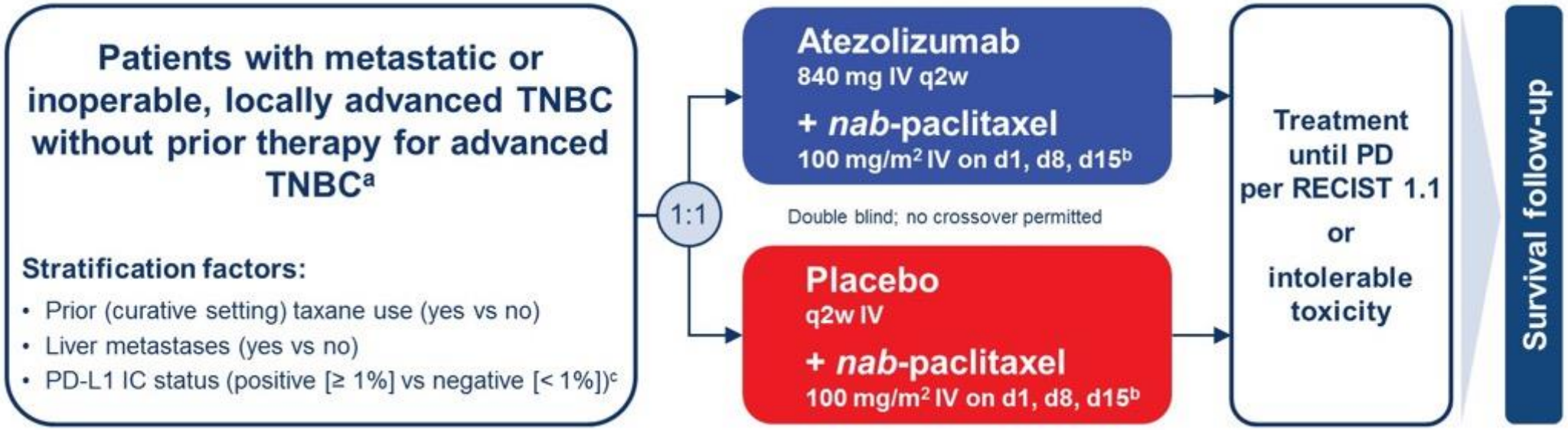
Alexandrov, Nature 2013.

Clinical Data – Pembrolizumab in MSI-high breast cancer



Le, Science 2017.

Clinical Data – IMpassion130 PD-L1+ TNBC

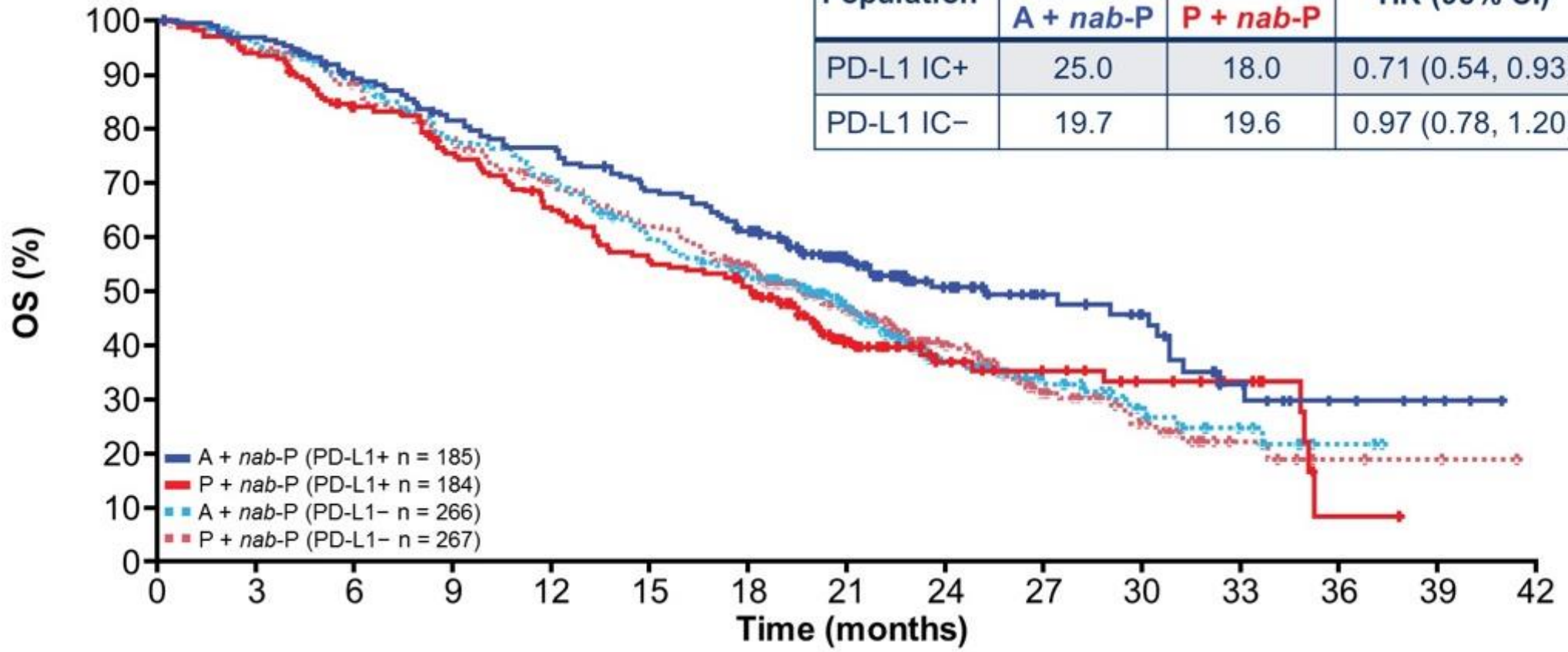


- Co-primary endpoints in ITT and PD-L1 IC+: PFS and OS[d]
- Pre-specified hierarchical testing of OS in ITT and, if significant, in PD-L1 IC+ patients
- In both treatment arms, 41% of patients were PD-L1 IC+

Schmid, ASCO 2019.

Clinical Data – IMpassion130
PD-L1+ TNBC

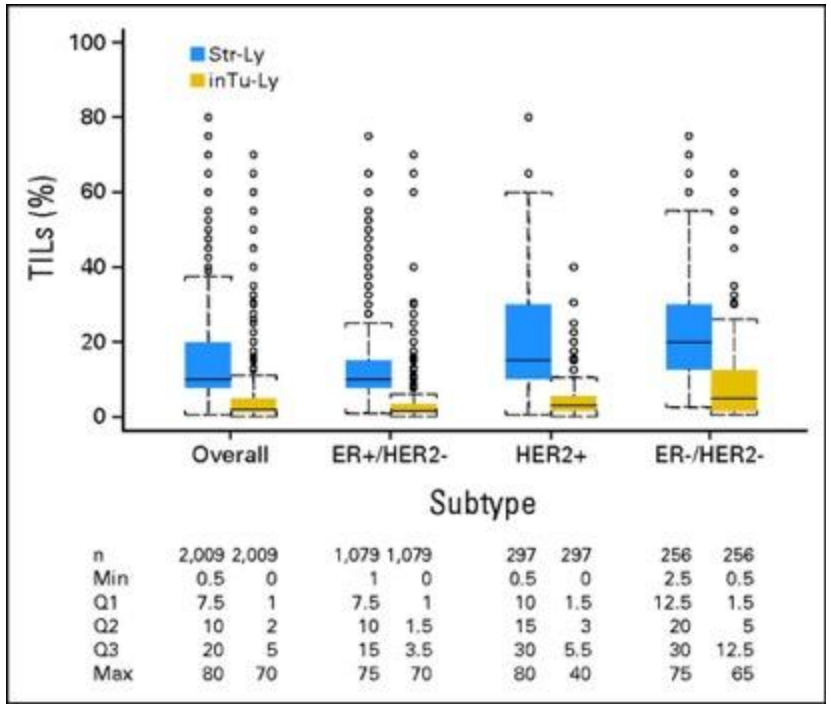
Population	Median OS, mo		HR (95% CI)
	A + *nab*-P	P + *nab*-P	
PD-L1 IC+	25.0	18.0	0.71 (0.54, 0.93)
PD-L1 IC−	19.7	19.6	0.97 (0.78, 1.20)



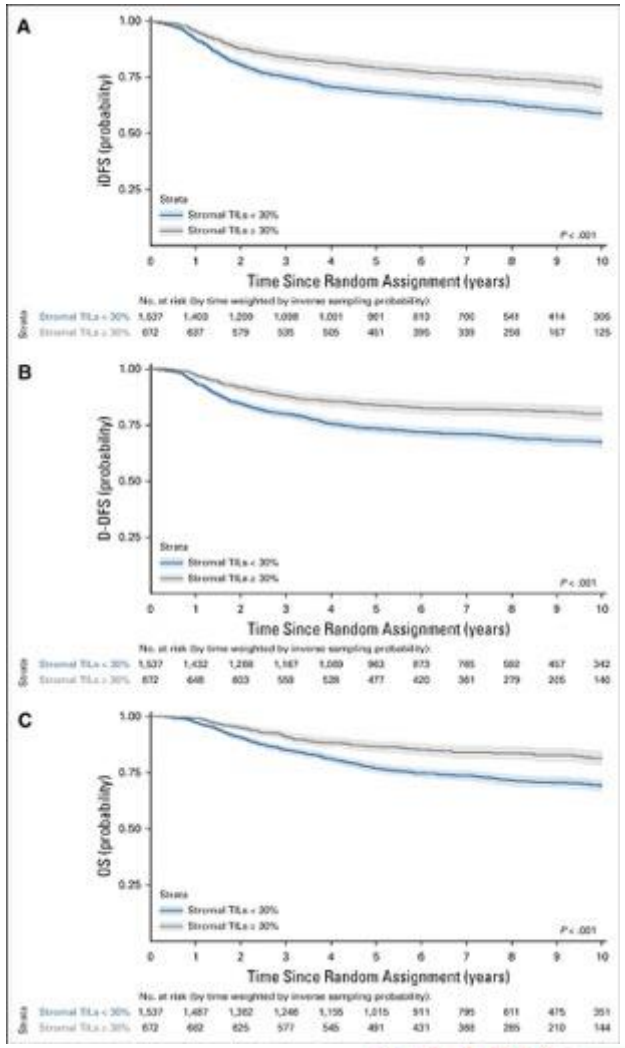
Schmid, ASCO 2019.

The Importance of Tumor Infiltrating Lymphocytes

Tumor-infiltrating lymphocytes (TILs) are associated with hormone receptor negativity



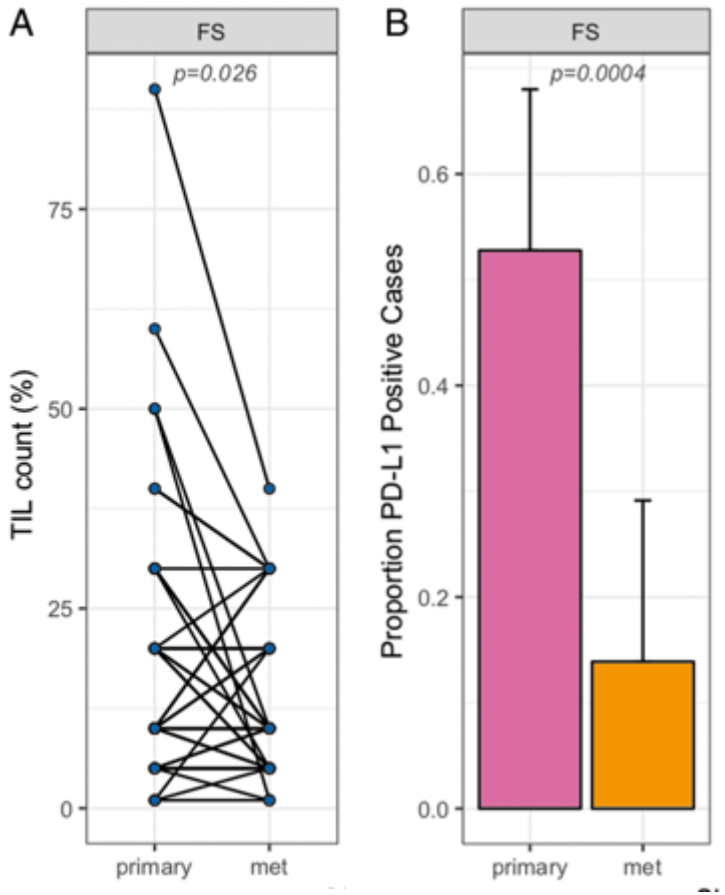
n	2,009	2,009	1,079	1,079	297	297	256	256
Min	0.5	0	1	0	0.5	0	2.5	0.5
Q1	7.5	1	7.5	1	10	1.5	12.5	1.5
Q2	10	2	10	1.5	15	3	20	5
Q3	20	5	15	3.5	30	5.5	30	12.5
Max	80	70	75	70	80	40	75	65



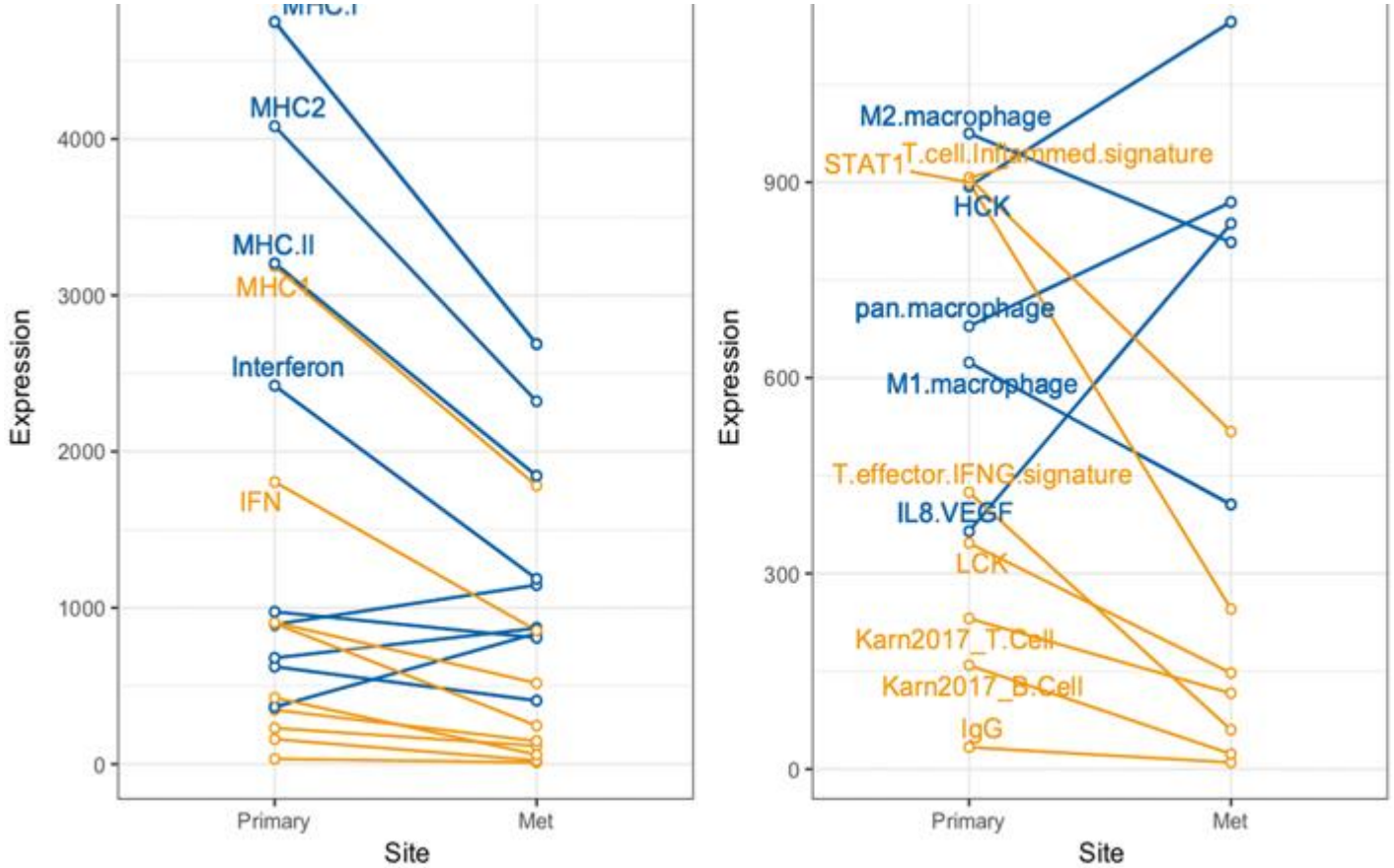
In TNBC, (A) invasive disease-free survival (iDFS), (B) distant disease-free survival (D-DFS), and (C) overall survival (OS) improve with stromal TILs > 30%

Most immune cell types and immune functions are depleted in metastases

TIL counts and PD-L1 expression were substantially lower in metastases compared with primary tumors

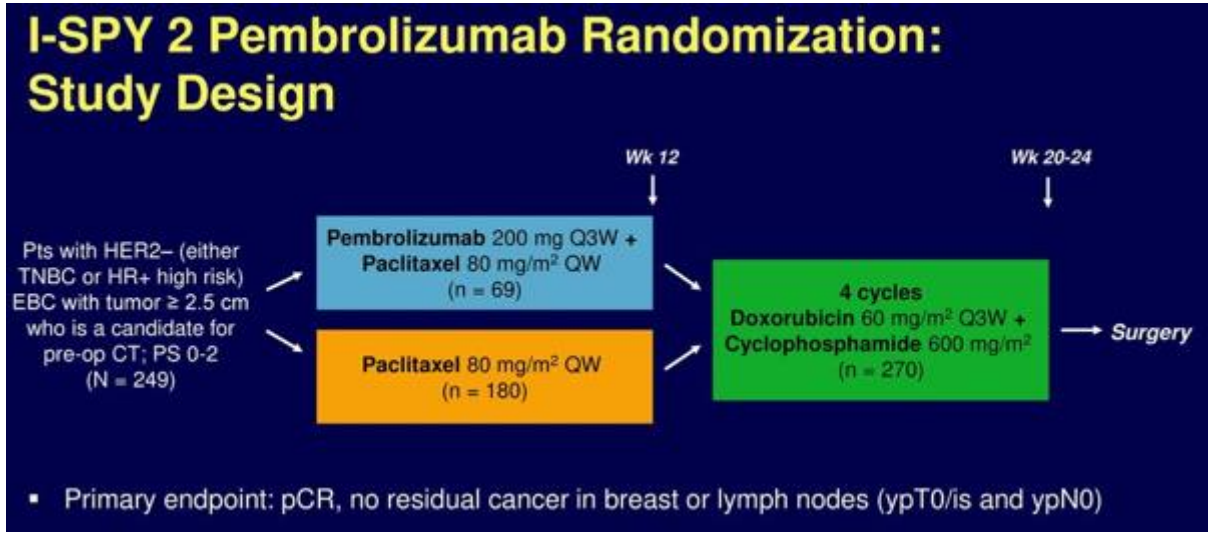


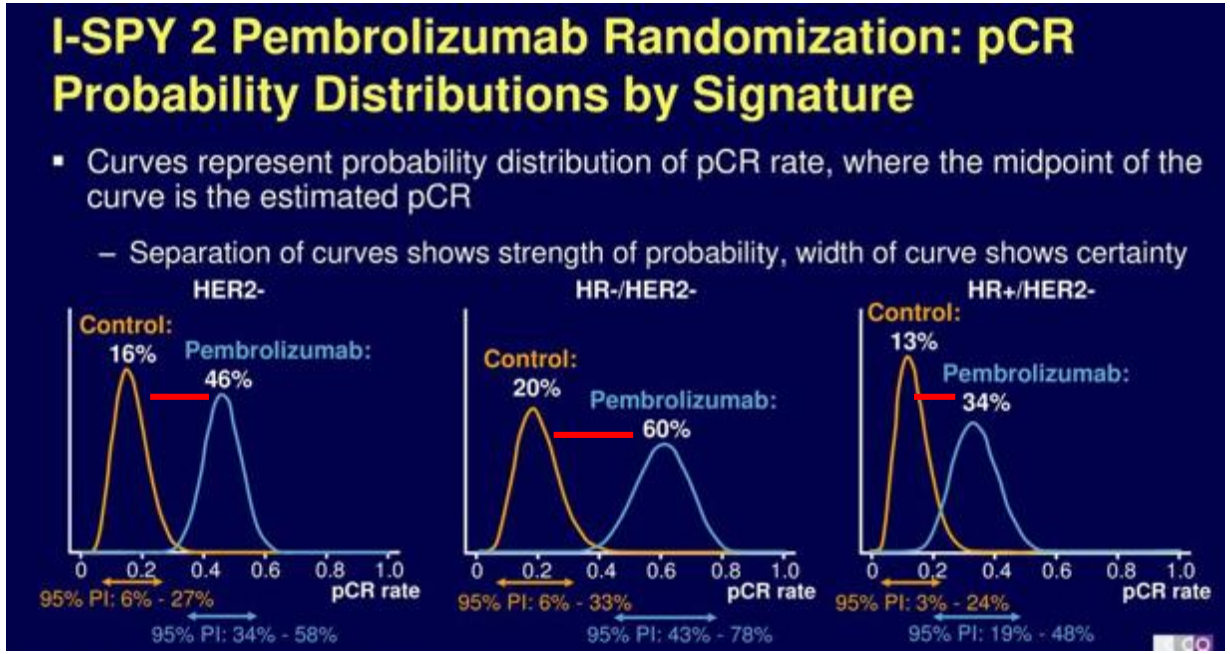
Expression of prognostic and immune checkpoint therapy response predictive signatures in paired primary and metastatic breast cancers



Szekely, Annals of Oncology 2019

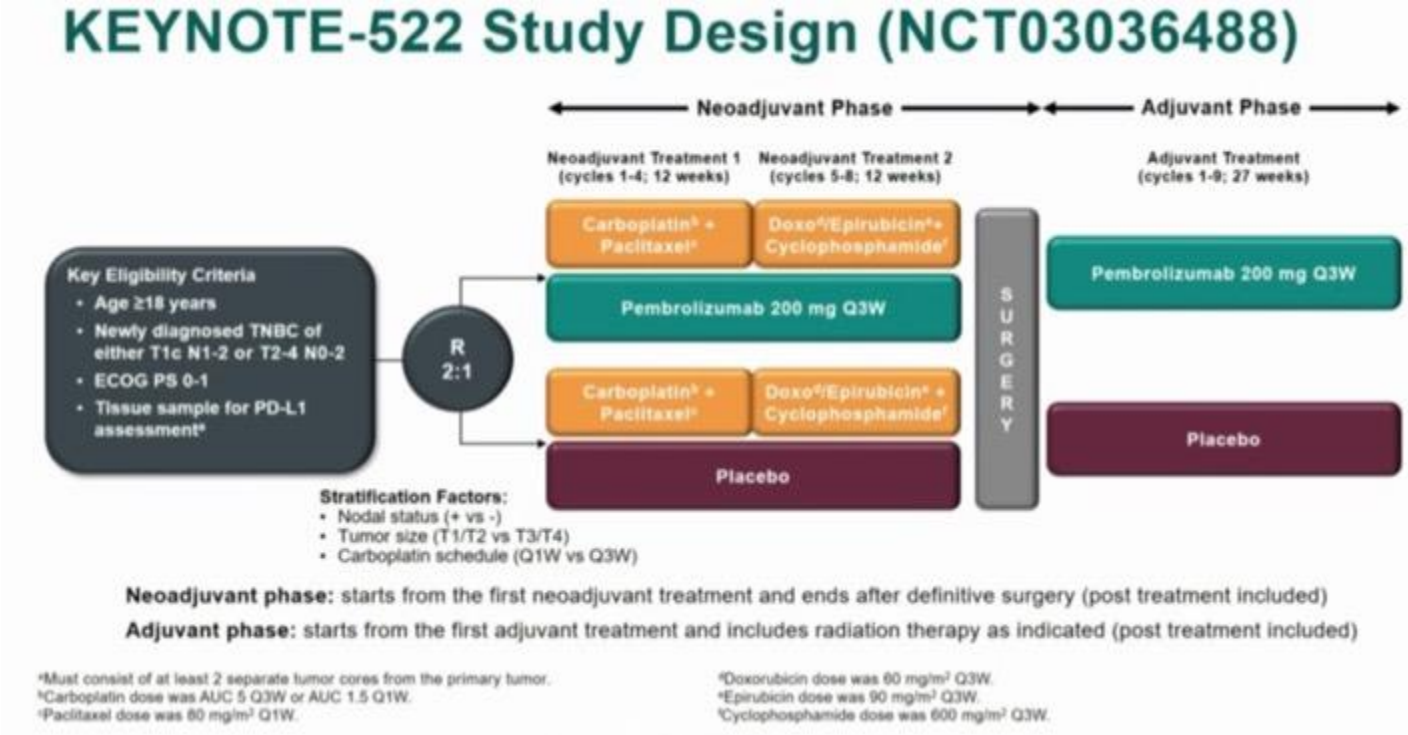
Taking Immunotherapy in early breast cancer – Graduation!





Nanda, ASCO 2017

Neoadjuvant Immunotherapy Plus Chemotherapy for Early Triple-Negative Breast Cancer



Primary Endpoints:

- pCR (ypT0/Tis ypN0)
- Event-free Survival (EFS)

Secondary Endpoints:

- OS
- pCR/EFS/OS in PD-L1+
- Safety

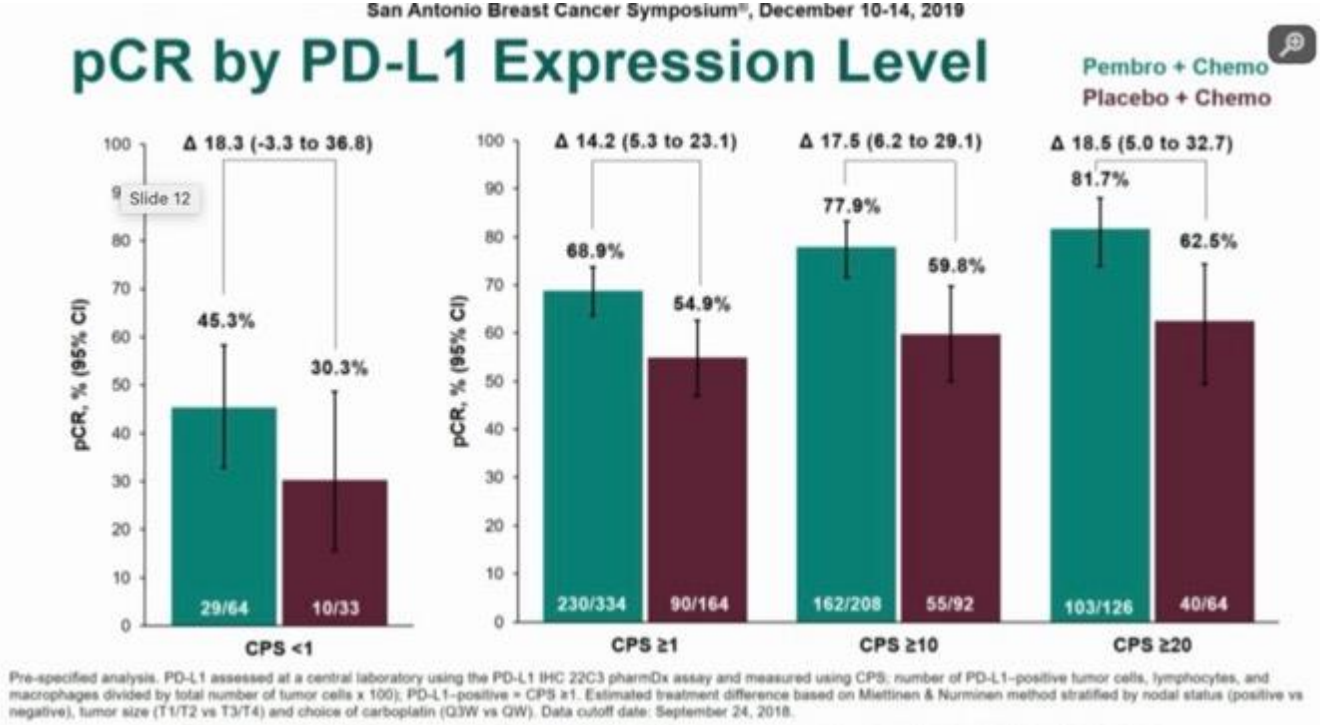
Exploratory Endpoints:

- Residual Tumor Burden
- pCR by patient subgroups
- EFS by pCR
- pCR and EFS by TILs

Schmid, ESMO and SABCS 2019

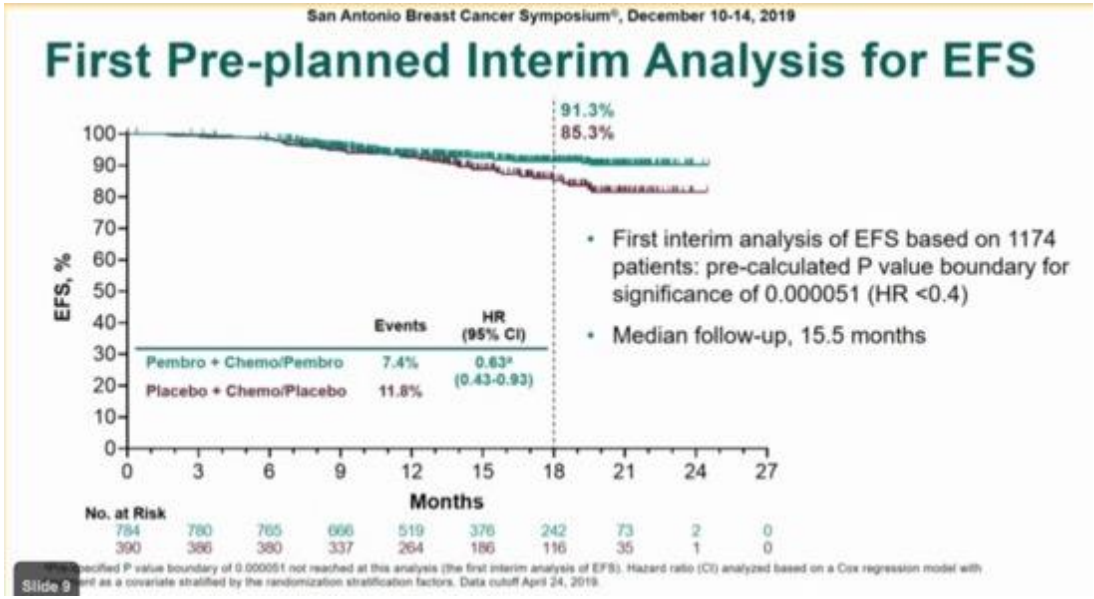
pCR Δ is equal or grater for PD-L1 negative breast tumors

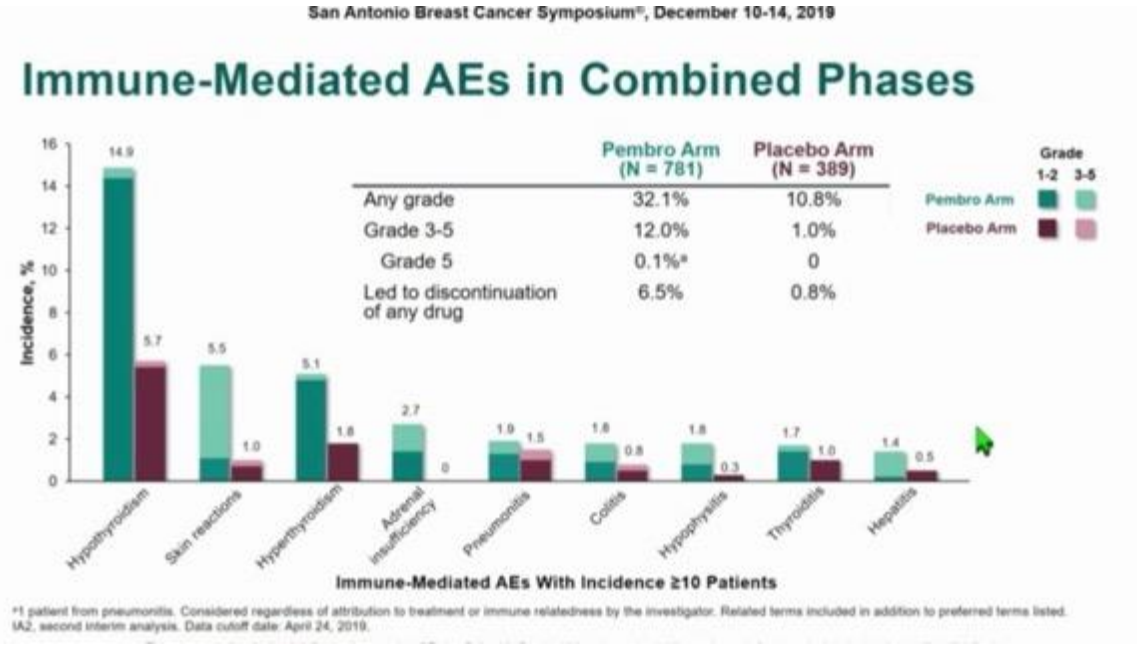
- KEYNOTE-522 is the first phase III trial to demonstrate that anti–PD-1 therapy significantly improves pCR rates, regardless of programmed cell death ligand 1 (PD-L1) status, when combined with chemotherapy as neoadjuvant therapy for TNBC.



Schmid, SABCS 2019

- Promising EFS preliminary data
- Concerning tolerability signal in curable disease

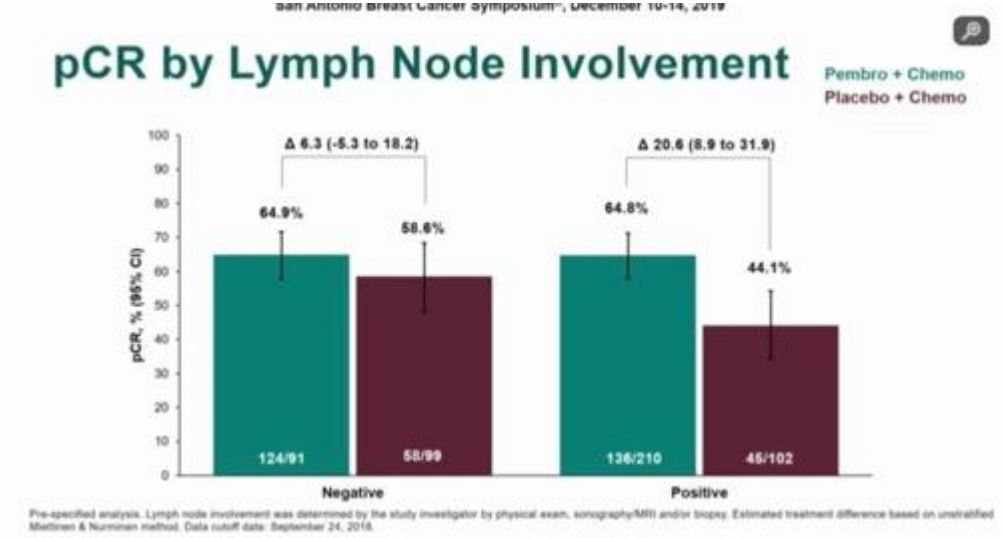




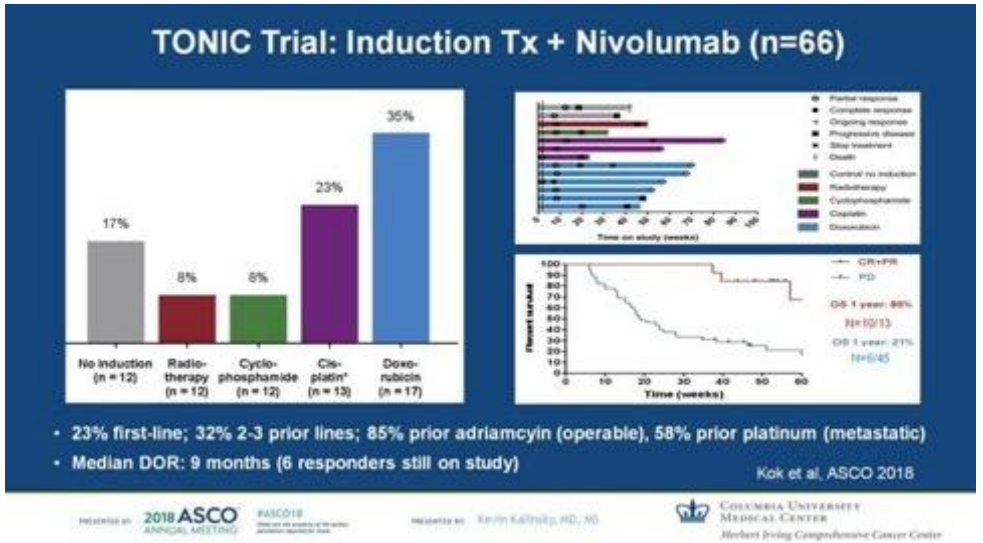
Schmid, SABCS 2019

Interesting points of discussion

Node positive disease has higher pCR Δ



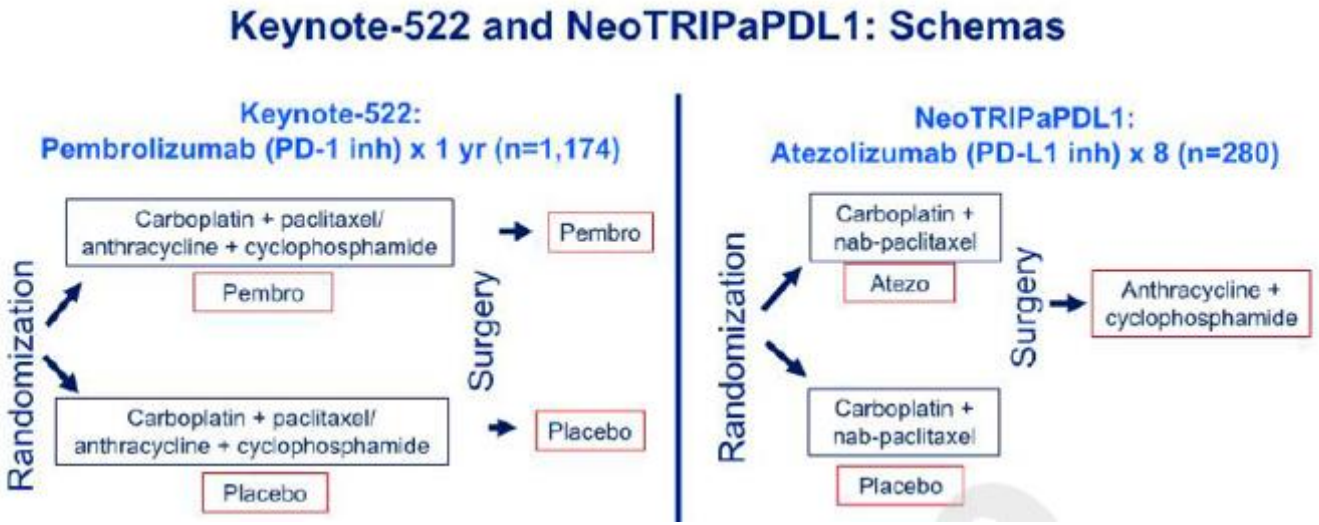
Anthracycline seems the best partner of checkpoint inhibitor

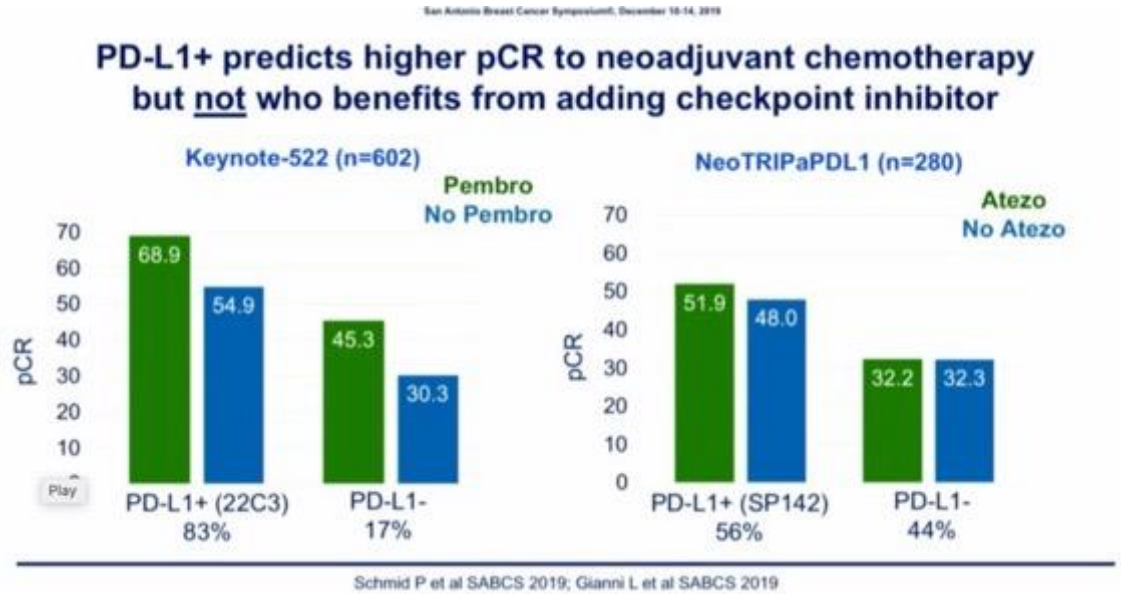


Kalynski, SABCS 2019

PD-L1 expression as predictive biomarker

PDL-1 positivity is Predicting higher rate of pCR of neoadjuvant chemotherapy but not identify who is specifically benefiting from adding checkpoint inhibitors





Kalinsky SABCS 2019

Multiomics Prediction of Response Rates to Therapies to Inhibit Programmed Cell Death 1 and Programmed Cell Death 1 Ligand 1

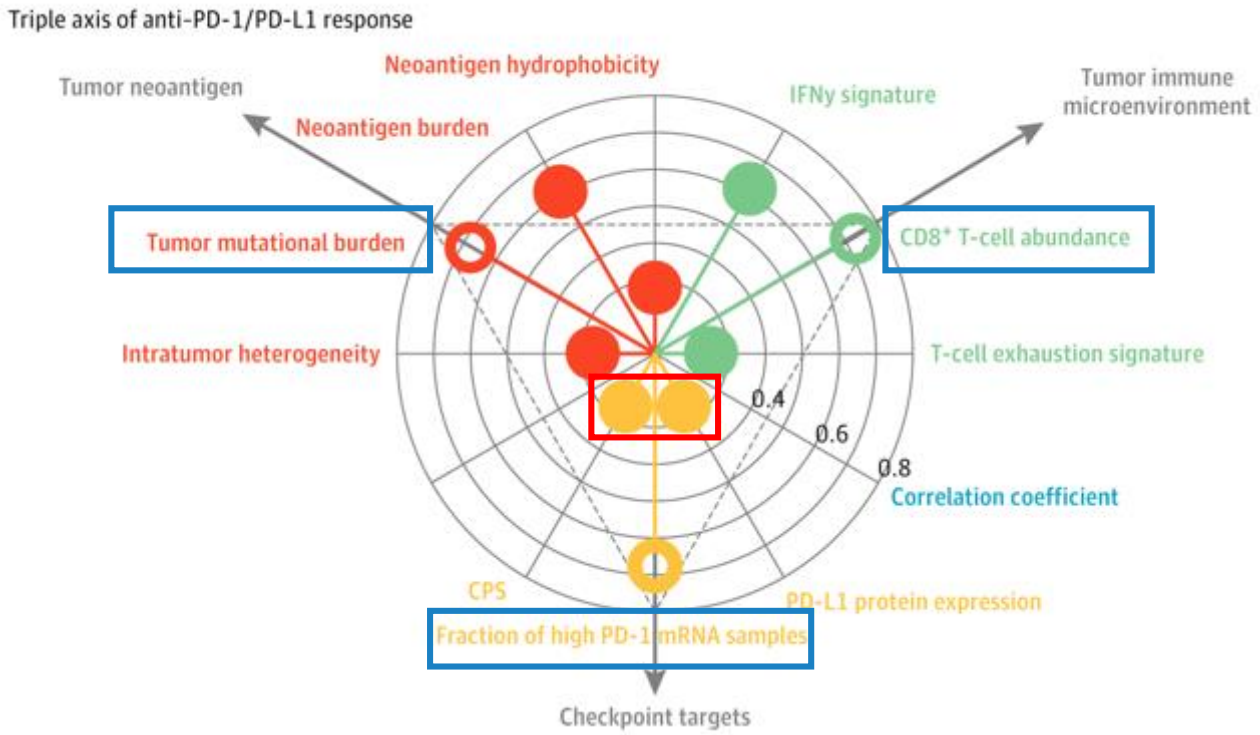
- Is PD-L1 status the best predictor of checkpoint inhibitor response?

TCGA data from 21 different tumors, n=7187

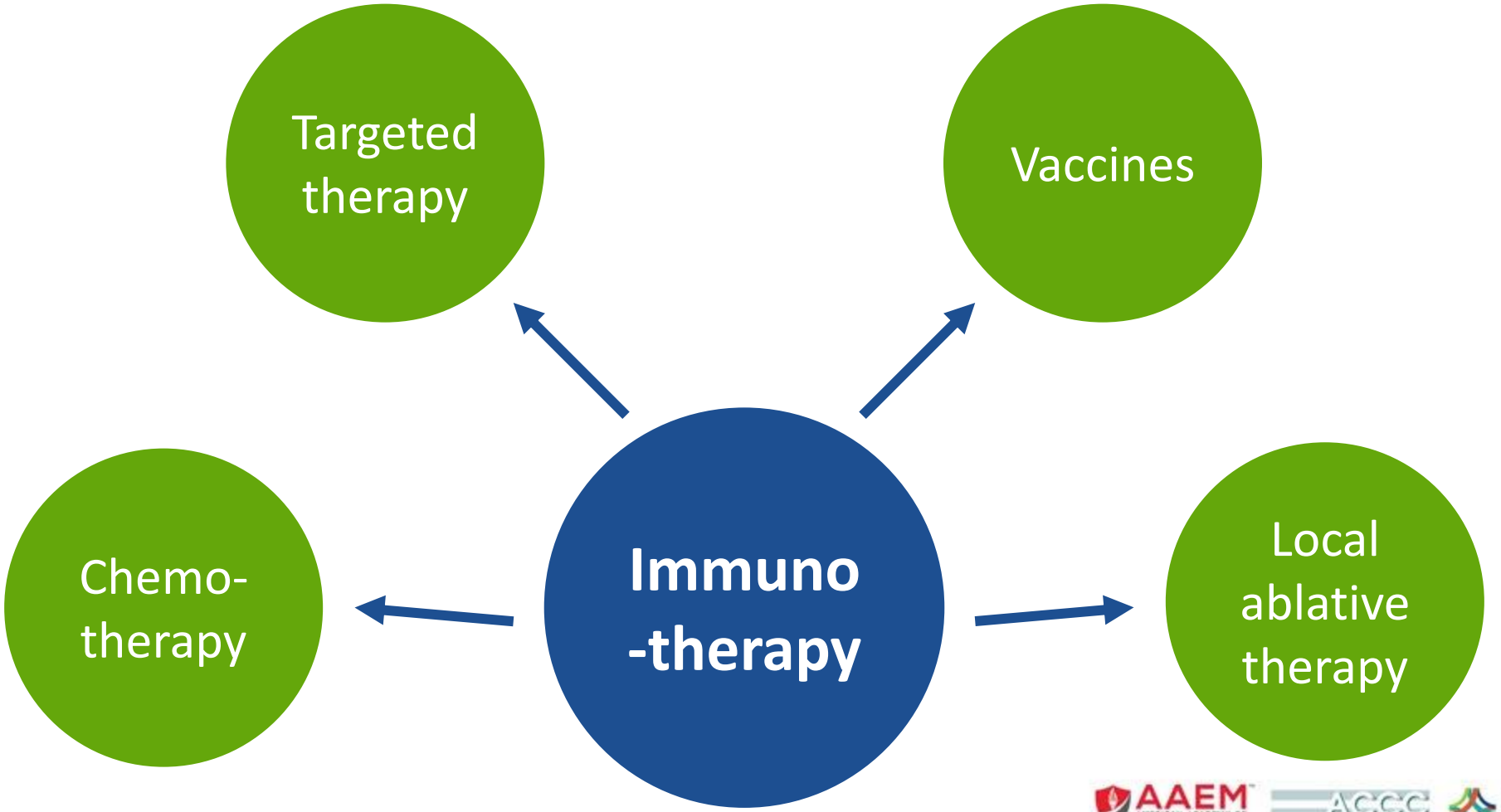
PD-L1 protein expression and CPS weakly correlate with predicted response

3 variables that highly correlate:

- **CD8+ T cell abundance**
- **Tumor mutational burden**
- **Fraction of high PD-1 mRNA samples**



In development: Breast cancer immunotherapy



Adams, JAMA Oncol 2019.

In development: Breast cancer immunotherapy

Trial	Population	Arms	Status
NCT03199885	1st line HER2+ metastatic breast cancer	• Pertuzumab + trastuzumab + paclitaxel + atezolizumab • Pertuzumab + trastuzumab + paclitaxel + placebo	Recruiting at MUSC
KEYNOTE-756	Neoadjuvant ER+/HER2- breast cancer	• Pembrolizumab + chemo → pembrolizumab + endocrine therapy • Placebo + chemo → placebo + endocrine therapy	Recruiting at MUSC
S1418/BR006	Adjuvant TNBC with residual disease after neoad ctx	• Pembrolizumab 1 year • Observation	Recruiting at MUSC
S1919 RUSTIC Trial	2nd line HER2- metastatic breast cancer	• Durvalumab + Capecitabine • Durvalumab + AZD4635 ($A_{2A}R$) • Durvalumab + SNDX-6352 (CSF-1R) • Durvalumab + Capivasertib (AKT)	Planned
And many more			

Conclusions

- Immunotherapy in breast cancer shows promise in certain subtypes (TNBC)
- Immune checkpoint inhibitors plus chemotherapy show promising results in neoadjuvant treatment of early stage breast cancer (high pCR rate, watch out toxicity)
- Ongoing research to identify the right patients, agents and timing of delivering immunotherapy

Case Studies

Case Study 1

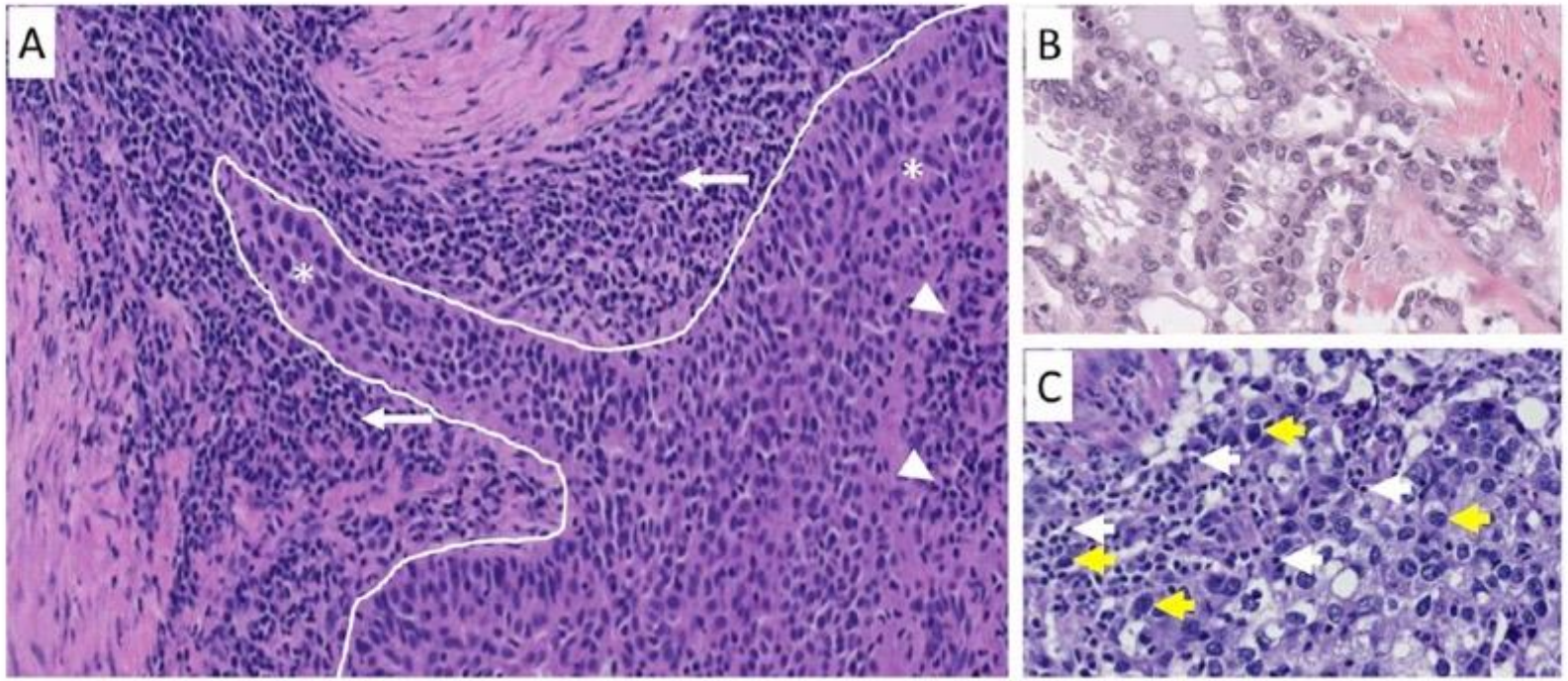
Ms. Serena is a 57 yo female who presents with right breast cancer and *de novo* metastatic disease to the liver. She undergoes liver MRI that shows two liver lesions of 3 and 2 cm, in the II and VIII segments. One of the liver lesion is biopsied and pathology shows adenocarcinoma with primary origin breast, ER-negative, PR-negative, HER2 1+. Additional tissue is sent for PD-L1 staining.

1. What staining will determine patient to be eligible for 1st line treatment with Atezolizumab and Nab-Paclitaxel?

    A. Combined Positive Score (CPS) ≥ 50%
    B. Combined Positive Score (CPS) ≥ 10%
    C. Combined Positive Score (CPS) ≥ 1%
    D. Ventana SP142 on Immune Cells ≥ 1%
    E. Ventana SP142 on Tumor Cells ≥ 1%

Photomicrograph showing the geographic assessment of lymphocyte infiltrates in the tumor microenvironment

- Text



Instructions - Case Study 2

1. PD-L1 by SP142 came back 5%. Patient was started on atezolizumab and nab-paclitaxel. After 3 cycles, she experiences fatigue and drowsiness. She gained 12 lbs. Lab work before cycle 4 shows a TSH = 14 and low FT4. What is the next step managing patient clinical course and treatment?

    A. Hold treatment with atezolizumab, continue nab-paclitaxel, and re-check TFTs before next cycle
    B. Permanently discontinue treatment with atezolizumab and nab-paclitaxel, treat with Thyroxine 0.5-1.5 µg/Kg
    C. Continue treatment with atezolizumab and nab-paclitaxel, treat with Thyroxine 0.5-1.5 µg/Kg
    D. Temporarily hold treatment with atezolizumab and nab-paclitaxel, treat with Thyroxine 0.5-1.5 µg/Kg, resume cancer treatment when TSH is < 10.

ICPi monitoring and management

- Thyroid Function

Baseline Endocrine Panel:
TSH, FT4, T3* TFTs

Baseline abnormal values do not preclude treatment; discuss with endocrinologist if uncertain
*when indicated

Monitoring during treatment:
Anti-CTLA-4 (including combination with anti-PD-1)
· TFTs every cycle
· TFTs 4-6 weeks after cycle 4 (i.e. with restaging CT)
Late endocrine dysfunction can occur

Anti-PD-1/Anti-PD-L1
· TFTs every cycle for first 3 months, every second cycle thereafter (in case of 2-weekly schedule)
· Cortisol as indicated by symptoms/falling TSH

A falling TSH across two measurements with normal or lowered T4 may also suggest pituitary dysfunction and weekly cortisol measurements should be performed

If TSH is abnormal, refer to algorithm below. Iodine from CT scans may impact TFTs

Hypothyroidism: Low FT4 with elevated TSH or TSH > 10 with normal FT4

Treatment: Thyroxine 0.5–1.5 µg/kg (start low in elderly, if cardiac history)

Continue ICPi

Thyrotoxicosis (DDx thyroiditis, Grave's disease):

Investigations: Anti-TSH receptor Ab, anti-TPO Ab, nuclear medicine thyroid uptake scan

Treatment: Propranolol or atenonol for symptoms; consider carbimazole if anti-TSH receptor Ab-positive

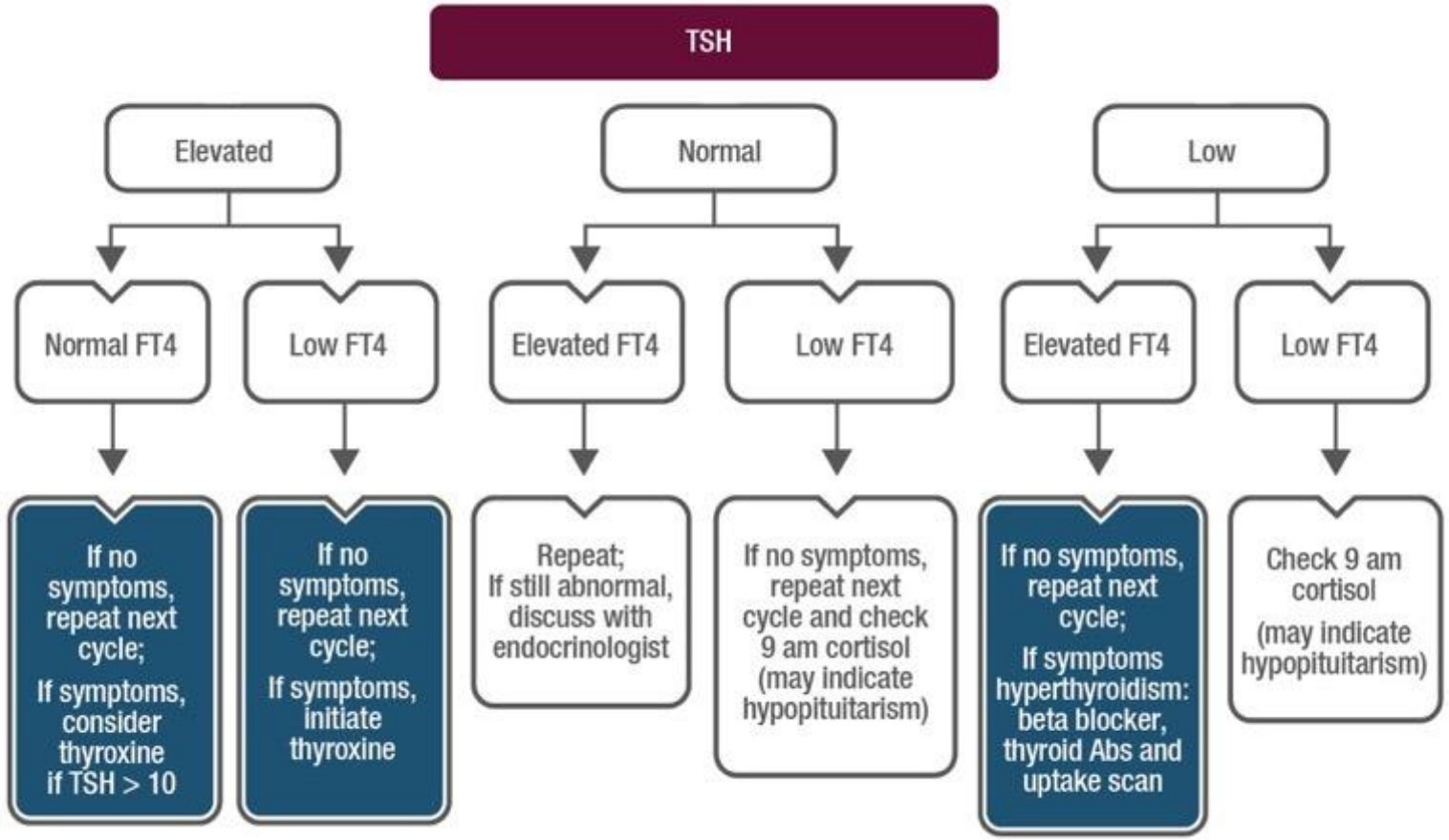
Painful thyroiditis – consider prednisolone 0.5 mg/kg and taper

If unwell, withhold ICPi and consider restarting when symptoms controlled

ESMO Guidelines 2018

Immune Related Toxicity: Thyroid Function

- Withhold ICPi if patient is unwell with symptomatic hyperthyroidism
- Subclinical hyperthyroidism often precedes overt hypothyroidism



ESMO Guidelines 2018