ICI USE IN BREAST CANCER - KEY TAKEAWAYS

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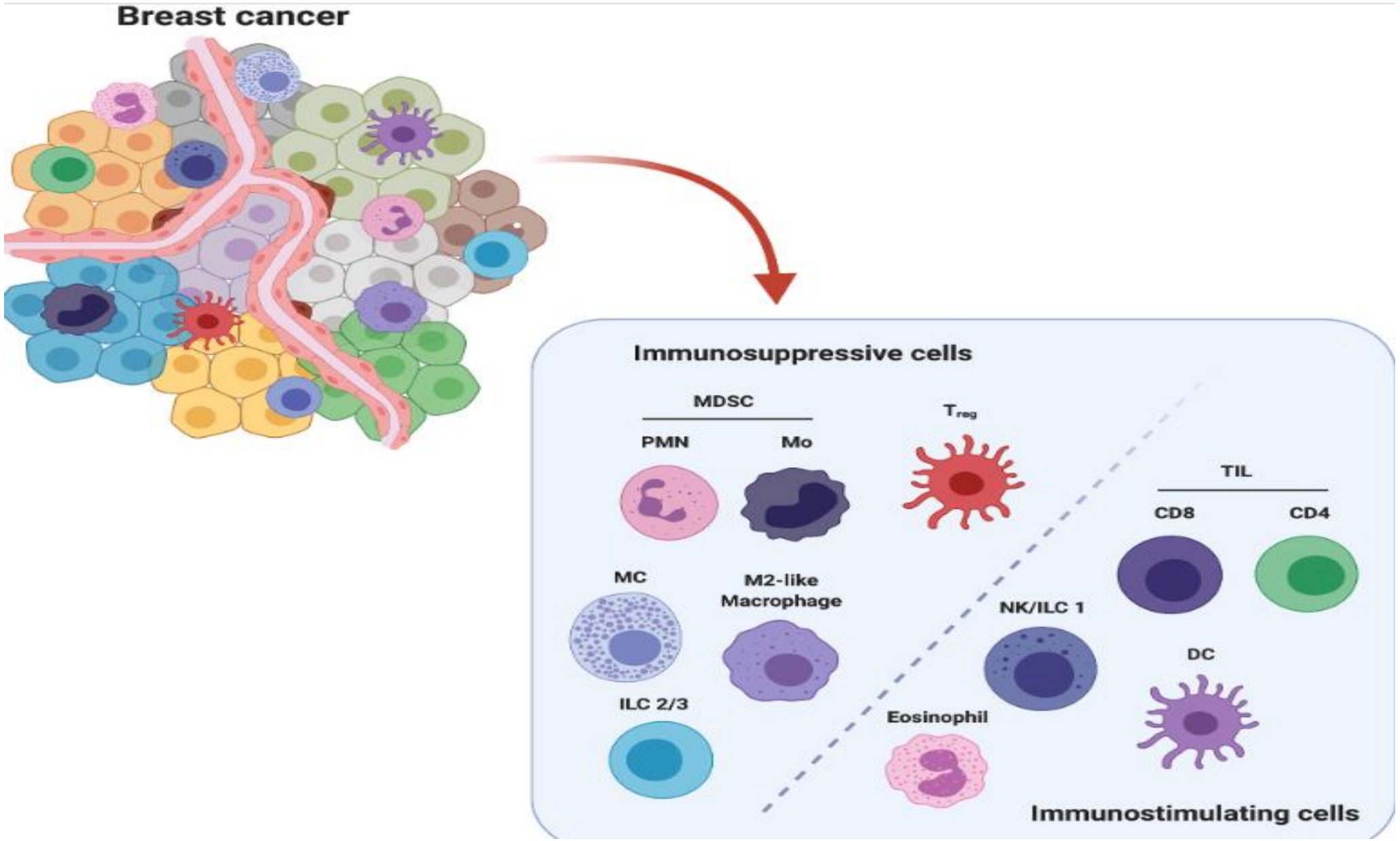
Is Breast Cancer Immunologically “COLD”?



INTRODUCTION

- Biology of aggressive breast cancer subtypes (TNBC and Her2 positive) may be deeply affected by immune couterpart of tumor microenvironment
- TNBC- high genomic instability and mutational load--> generation of neo antigens-->tumor immunogenecity
- Her 2 positive disease- High proliferation activity and over expression of Her 2----> Antibody dependent cell mediated cytotoxicity (ADCC) by anti Her 2 monoclonal antibodies --> increased immunogenecity

When to initiate ICI in the course of the disease?

- The tumor/immune co-evolution leads metastatic breast cancer to be commonly not inflamed. While the disease advances, less immune cells are observed in the tumor microenvironment and less immunogenic antigens are expressed by tumor cells; hence the immune escape progressively augments

- Hence, it would be reasonable to anticipate immunotherapy as earlier as possible in the course of the disease, thus moving it to the early stage

- Possibly, the different efficacy of immunotherapy in the neoadjuvant setting is at least partially attributable to the use of anthracyclines, which are known to induce immunogenic cell death, thus enhancing the tumor priming phase

Immunotherapy in Breast Cancer: Early-Stage vs Metastatic Breast Cancer

Chemotherapy is a rational partner for immunotherapy

- Disrupts tumor architecture
- Results in antigen shedding
- Induces rapid disease control

Parameter	EBC	MBC
Antigen presentation	↑	↓
Tumor clonality	↓	↑
Intratumor heterogeneity	↓	↑
TILs, CD8+ T-cells, DCs	↑	↓
PD-L1 positivity	↑	↓
Chemoattractants	↑	↓
Interferon signaling	↑	↓

Bianchini. Nat Rev Clin Oncol. 2022;19:91.

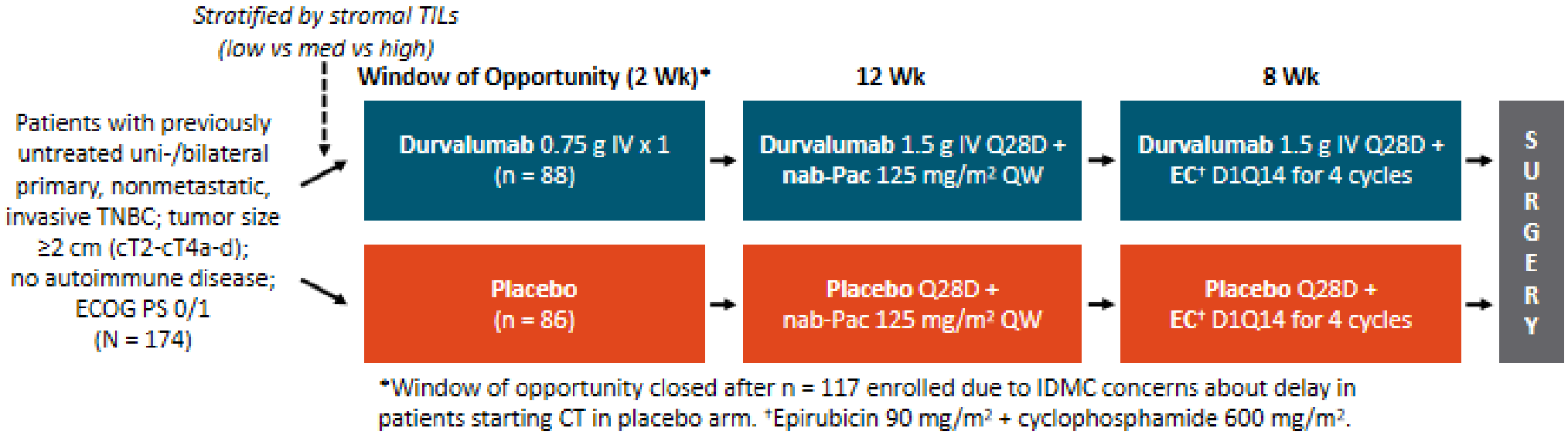
Slide credit: clinicaloptions.com

Completed Phase II/III Neoadjuvant Immunotherapy trials in EBC

Trial	Subtype	Control and immunotherapy arms	pCR rate (95%CI) investigational vs control
I- SPY 2 (phase II)	HER2-	Control (n=201): paclitaxel × 4 → doxorubicin+cyclophosphamide × 4 → surgery Investigational (n=69): paclitaxel+pembrolizumab × 4 → doxorubicin plus cyclophosphamide × 4 → surgery	HR+/HER2– 30% (17% to 43%) vs 13% (7% to 19%) TNBC 60% (44% to 75%) vs 22% (13% to 30%)
	HER2-	Control (n=295): paclitaxel × 4 → doxorubicin+cyclophosphamide × 4 → surgery Investigational (n=73): paclitaxel+pembrolizumab × 4 → pembrolizumab × 4 → surgery	HR+/HER2– 15% (1% to 29%) vs 15% (9% to 20%) TNBC 27% (9% to 45%) vs 27% (19% to 35%)
	HER2-	Control (n=299): paclitaxel × 4 → doxorubicin+cyclophosphamide × 4 → surgery Investigational (n=74): olaparib+durvalumab+paclitaxel × 4 → doxorubicin+cyclophosphamide × 4 → surgery	HR+/HER2– 28% (18% to 38%) vs 14% (9% to 19%) TNBC: 47% (29% to 64%) vs 27% (20% to 34%)

GeparNuevo: Neoadjuvant Durvalumab in TNBC

- Randomized, double-blind phase II trial



*Window of opportunity closed after n = 117 enrolled due to IDMC concerns about delay in patients starting CT in placebo arm. †Epirubicin 90 mg/m² + cyclophosphamide 600 mg/m².

- pCR rates: window cohort (61.0% vs 41.4%); stage ≥IIA (55.8% vs 38.6%)

Loibl. ASCO 2021. Abstr 506. Loibl. Ann Oncol. 2019;30:1279. Loibl. ASCO 2018. Abstr 104. NCT02685059.

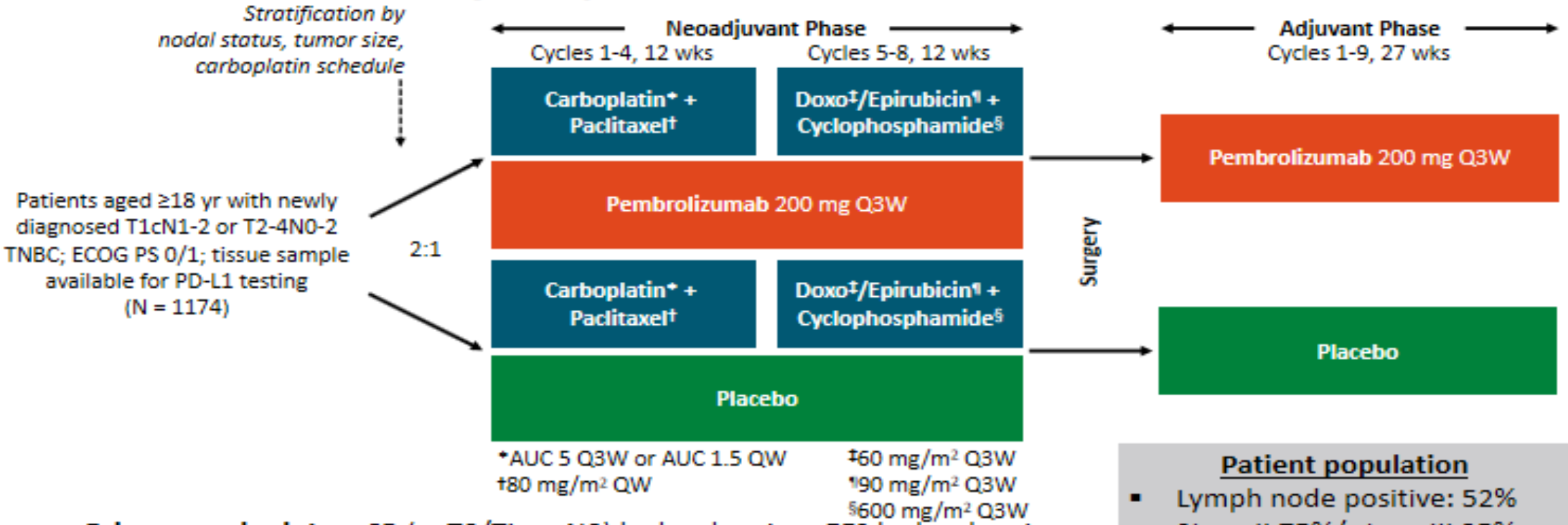
Slide credit: clinicaloptions.com

GeparNuevo: Efficacy

Rate, %[1]	Durvalumab	Placebo
pCR	53.4	44.2
	OR: 1.45 (95% CI: 0.797-2.63; *P* = .224)	
pCR (window cohort)[2]	61.0	41.4
	OR: 2.22 (95% CI: 1.06-4.64; *P* = .035)	
3-yr iDFS	85.6	77.2
	HR: 0.48 (95% CI: 0.24-0.97; *P* = .0356)	
3-yr dDFS	91.7	78.4
	HR: 0.31 (95% CI: 0.13-0.74; *P* = .0078)	
3-yr OS	95.2	83.5
	HR: 0.24 (95% CI: 0.08-0.72; *P* = .0108)	

1. Loibl. ASCO 2021. Abstr 506. 2. Loibl. Ann Oncol. 2019;30:1279.

KEYNOTE-522: Neoadjuvant Pembrolizumab or Placebo + CT Followed by Adjuvant Pembrolizumab or Placebo



Patient population

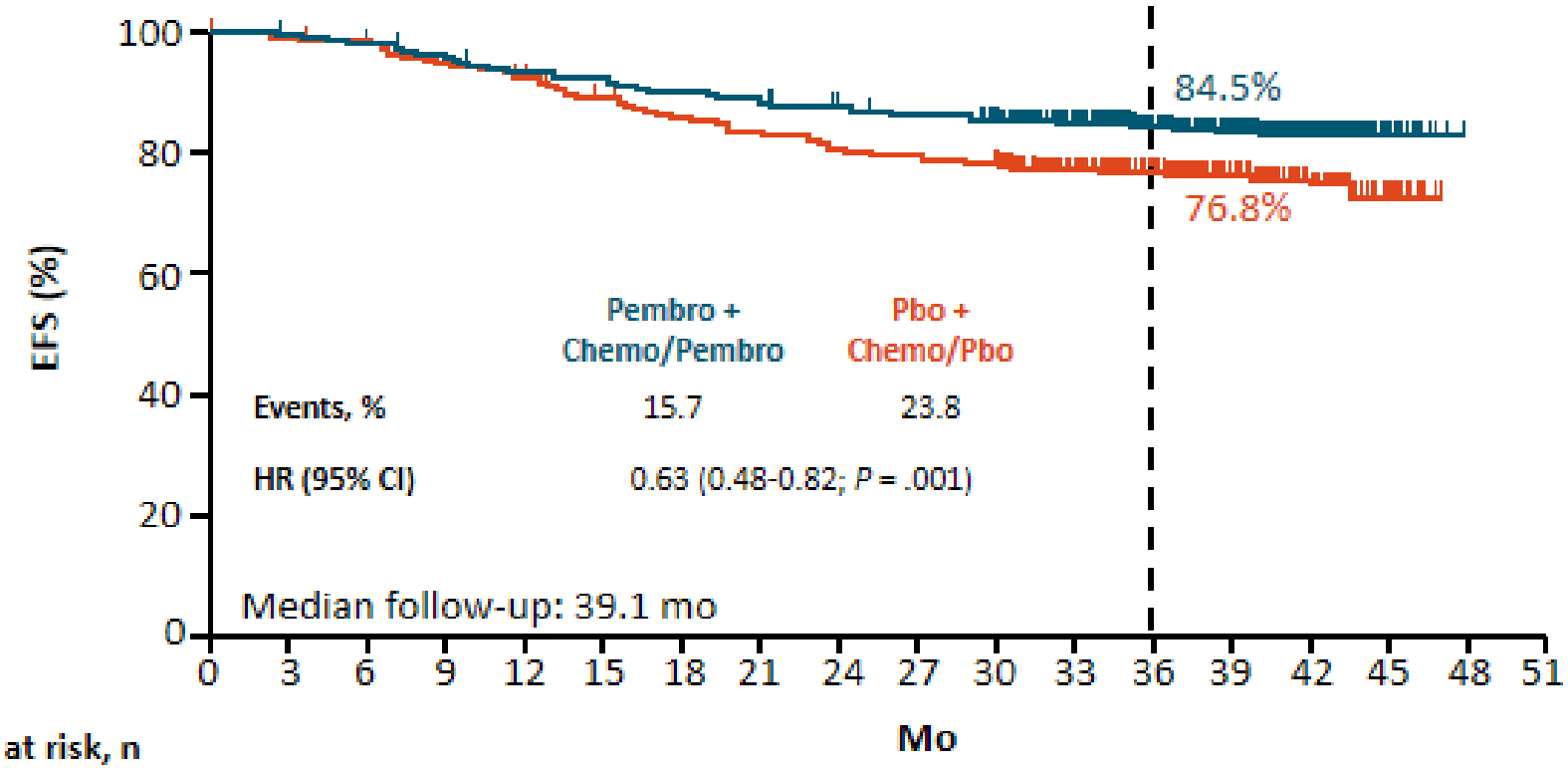
- Lymph node positive: 52%
- Stage II 75%/ stage III 25%
- Premenopausal: 56%

- **Primary endpoints:** pCR (ypT0/Tis ypN0) by local review, EFS by local review
- **Secondary endpoints:** pCR (ypT0 ypN0 and ypT0/Tis), OS, safety
- **Exploratory endpoints:** EFS by subgroups, EFS by pCR, DPFS, DRFS

Schmid. N Engl J Med. 2020;382.810. Schmid. N Engl J Med. 2022;386:556.

Slide credit: clinicaloptions.com

KEYNOTE-522: EFS at Interim Analysis 4



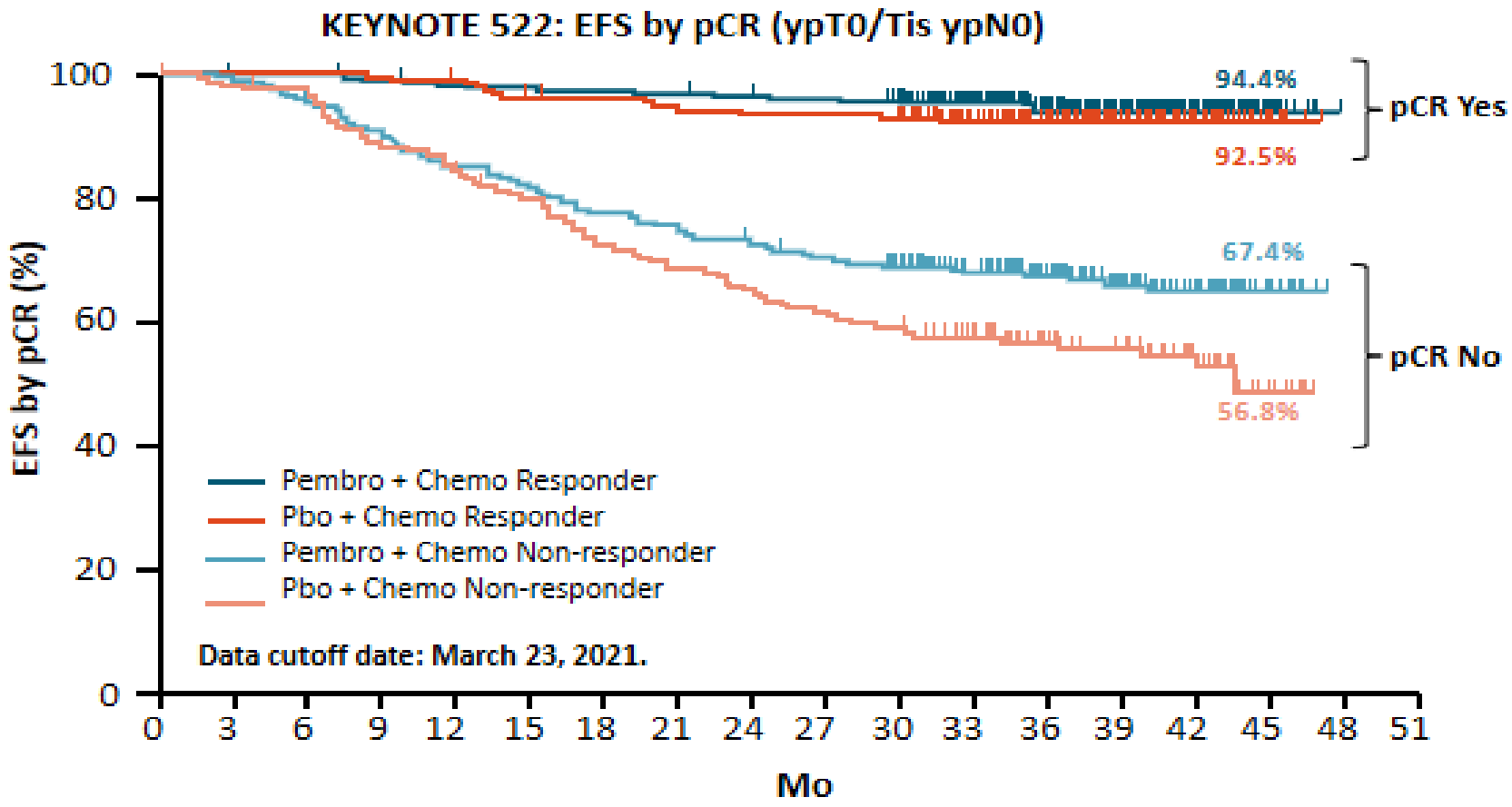
Patients at risk, n																		
Pembro + chemo	784	781	769	751	728	718	702	692	681	671	652	551	433	303	165	28	0	0
Pbo + chemo	390	386	382	368	358	342	328	319	310	304	297	250	195	140	83	17	0	0

- 6.3% increase in DRFS: 87% to 80.7%; HR: 0.61; 95% CI: 0.46-0.82.

Schmid. ESMO 2021. Abstr VP7-2021. Schmid. N Engl J Med. 2022;386:556.

Slide credit: clinicaloptions.com

KEYNOTE-522: EFS by pCR



pCR rates:

ITT
63%
vs 55.6%
PD-L1-positive
68.9% vs
54.9%
PD-L1-negative
45.3% vs
30.3%
LN-negative
64.9% (NR) vs
58.6%
(NR)
LN-positive
64.8% (NR) vs
44.1 (NR)

Schmid. ESMO 2021. Abstr VP7-2021. Schmid. N Engl J Med. 2022;386:556.

Slide credit: clinicaloptions.com

Completed Phase II/III Neoadjuvant Immunotherapy trials in EBC

Trial	Subtype	Control and immunotherapy arms	pCR rate (95%CI) investigational vs control
IMpassion031 (phaseIII)	TNBC	Control (n=165): placebo × 6+nab-paclitaxel × 12 →placebo+doxorubicin+cyclophosphamide × 4 → surgery ---> monitoring Investigational (n=168): atezolizumab × 6+nab-paclitaxel × 12----->atezolizumab+doxorubicin+cyclophosphamide × 4 --->surgery →atezolizumab	ITT 58% (50% to 65%) vs 41% (34% to 49%) PD-L1-positive 69% (57% to 79%) vs 49% (38% to 61%)
NeoTRIPaPDL1 (phase III)	TNBC	Control (n=142): nab-paclitaxel+carboplatin × 8 → surgery → doxorubicin+cyclophosphamide/ epirubicin+cyclophosphamide/5 FU+epirubicin+cyclophosphamide × 4 Investigational (n=138): nab-paclitaxel+carboplatin+atezolizumab × 8 → surgery → doxorubicin+cyclophosphamide/ epirubicin+cyclophosphamide/5 FU+epirubicin+cyclophosphamide × 4	ITT 43.5% (35.1% to 52.2%) vs 40.8% (32.7% to 49.4%) PD-L1-negative 32.2% (NR) vs 32.3% (NR) PD-L1-positive 51.9% (NR) vs 48% (NR)

Learning points

- Magnitude of pCR benefit with ICI was larger in lymph node positive breast cancer (6%-9% in node negative vs 20%-26% in node positive disease)- KEYNOTE-522 and IM PASSION 031 trials

- pCR benefit was regardless of PDL1 status

- Anthracyclines modify the TME, turning “cold” in to “hot” tumors and priming cancer cells for ICI response (low pCR rates in NeoTRIPa PDL1 study and highest response rate with doxorubicin in TONIC trial)

Questions to be addressed

- The ideal composition of chemotherapy backbone is not yet known:
- Data from the NeoTRIP trial suggest that anthracyclines are an important part of the backbone, but we do not yet know if this translates into an OS benefit
- As per KEY NOTE 522, patients received adjuvant pembrolizumab regardless of pathologic response. Future studies will address whether this is necessary in patients who achieve pCR
- SWOG S1418 is a randomized phase III trial evaluating pembrolizumab in the adjuvant setting for patients with residual TNBC measuring at least 1 cm in the breast and/ or lymph node involvement after neoadjuvant chemotherapy and definitive surgery

Questions to be addressed

- Adjuvant capeciatbine can be considered for patients without PCR. There is evidence on safety of combination of capecitabine plus pembro in metastatic setting. Although no data is available in adjuvant setting, combination is a reasonable consideration

- Patients who achieve a pCR with immunotherapy may not need a full year of therapy to benefit, whereas those who have residual disease following neoadjuvant chemotherapy may not always benefit from immunotherapy. The use of biomarkers may allow us to identify patients who will not benefit and spare them from the risk of toxicity

FDA approved Indications

- Only in TNBC
- **Early stage , High risk setting**
- Pembrolizumab (KEYNOTE 522)
- **Metastatic setting:**
- Pembrolizumab (KEYNOTE 355)
- Atezolizumab was voluntarily withdrawn (IM PASSION 130)

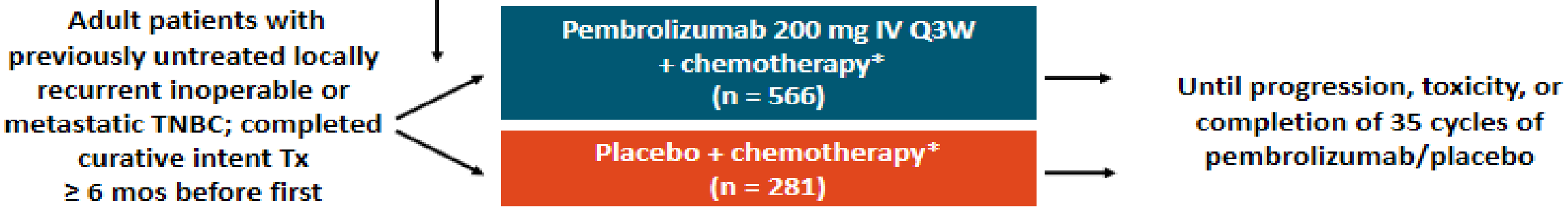
Why Atezolizumab was voluntarily withdrawn?

- Complexities in statistical design of IM PASSION 130 trial
- Negative result of IM PASSION -131 trial --?? due to pacliaxel
- Quick Changes in treatment landscape - KEYNOTE 355 trial

KEYNOTE-355: Study Design

- Randomized, double-blind, multicenter phase III trial

Stratified by chemotherapy (taxane vs gem/carbo); PD-L1 tumor expression (CPS > 1 vs < 1); previous Tx with same class of chemotherapy for EBC (Y vs N)



*Investigator's choice of chemotherapy was permitted:

- Nab-paclitaxel 100 mg/m^2 IV on Days 1, 8, 15 of 28-day cycle
- Paclitaxel 90 mg/m^2 IV on Days 1, 8, 15 of 28-day cycle
- Gem 1000 mg/m^2 + carbo AUC 2 on Days 1, 8 of 21-day cycle

- Primary endpoints: PFS and OS (PD-L1 CPS ≥ 10, PD-L1 CPS ≥ 1, and ITT)
- Secondary endpoints: ORR, DoR, DCR, safety

Cortes. ASCO 2020. Abstr 1000.

Slide credit: clinicaloptions.com

KEY NOTE 355 Trial- KEY POINTS

- Statistically significant 27% reduced risk of death with pembrolizumab plus chemotherapy vs chemotherapy alone in patients with metastatic TNBC who had PDL1 CPS of atleast 10 (38%)
- Median OS benefit (23 months vs 16.1 months) and median PFS benefit (9.7 months vs 5.6 months)
- Median duration of response in CPS >10 was 12.8 months (vs 7.3 months)
- Grade 3 to 5 immune related toxicities were observed in 5.3% (pembrolizumab) vs 0% (control arm). IRAE led to discontinuation of therapy in 2.8% vs 0%
- Most common IRAE- thyroid related (19%) followed by pneumonitis (2.5%)

KEYNOTE-355 Final Analysis: OS in PD-L1 CPS Subgroups

Median OS, mo	n	Pembrolizumab + CT	Placebo + CT	HR for Death (95% CI)
Overall	847	17.2	15.5	0.89 (0.76-1.05)
PD-L1 CPS cutoff of 1				
▪ CPS ≥1	636	17.6	16.0	0.86 (0.72-1.04)
▪ CPS <1	211	16.2	14.7	0.97 (0.72-1.32)
PD-L1 CPS cutoff of 10				
▪ CPS ≥10	323	23.0	16.1	0.71 (0.54-0.93)
▪ CPS <10	524	14.7	15.2	1.04 (0.85-1.26)
PD-L1 CPS cutoff of 20				
▪ CPS ≥20	204	24.0	15.6	0.72 (0.51-1.01)
▪ CPS <20	643	15.9	15.5	0.96 (0.80-1.14)

- OS outcomes were generally consistent across demographic and disease subgroups within CPS ≥10 and CPS ≥1 patient populations

Rugo. ESMO 2021. Abstr LBA16.

Tissue Agnostic FDA approvals

- One common driver for a highly mutagenic tumor phenotype is a deficiency in one or more components of the mismatch repair (MMR) machinery

- Full FDA approval of pembrolizumab for the treatment of MSI-H or dMMR tumors that have progressed on prior therapy regardless of tissue of origin, was first issued in May 2017

- This approval was based on durable responses among 149 patients with 15 different tumor types in five single-arm multicohort multicenter trials: KEYNOTE-016, KEYNOTE-164,KEYNOTE-012, KEYNOTE-028, and KEYNOTE-158 (which included five patients with histologically/cytologically confirmed MSI-H/dMMR advanced breast cancer)

Tissue agnostic FDA approvals

- TMB is generally considered a surrogate for neoantigen load and a predictive biomarker for T cell reactivity
- Pembrolizumab was also approved for non-MSI-H/dMMR tumors with high mutation burden (TMB-H) based on KEYNOTE-158 in June 2020 -TMB-H was defined in this study as ≥10 mutations per megabase (mut/Mb)
- It is important to note that breast cancers are rarely MSI-H. Current data suggest that roughly 1% of TNBC and fewer than 2% of breast cancers overall are MSI-H
- Roughly 5% TMB-H tumors, with slightly higher incidence in metastatic sites compared with the primary lesions

Phase II/III Immunotherapy trials in MBC

Trial	Setting	Arms	Outcome
IM PASSION 132 (Phase III)	Locally advanced/metastatic TNBC recurring less than 12 months after standard Neo adjuvant/ adjuvant therapy	Atezolizumab(vs Placebo) with capecitabine or gemcitabine/carboplatin	Evaluating Primary endpoint - OS
KEY NOTE 119 (Phase III)	MetastaticTNBC who had received one to two prior systemic therapies	Pembrolizumab vs physicians choice of chemotherapy (capecitabine, eribulin, gemcitabine, vinorelbine)	Single-agent pembrolizumab did not significantly improve OS compared with single agent chemotherapy in the ITT population nor the pre specified subgroups
KATE -2 (Phase II)	HER2-positive advanced breast cancer previously treated with trastuzumab and a taxane.	Trastuzumab emtansine (3·6 mg/kg of bodyweight) plus atezolizumab (1200 mg) or trastuzumab emtansine plus placebo	no statistically significant difference in overall PFS was observed between the two arms.
PANACEA (Phase IB/II)	HER2+, trastuzumab-resistant metastatic breast cancer.	Pembrolizumab in combination with trastuzumab	Combination was active and safe with ORR of 15%

Preferred PDL1 assay

- PD-L1 status was determined by the PD-L1 IHC 22C3 pharmDx assay, which assesses expression on both tumor cells (TCs) and ICs, resulting in a combined positive score (CPS), which is the number of PD-L1 staining cells (TCs, lymphocytes, macrophages) divided by the total number of viable TCs, multiplied by 100

- PD-L1 positivity is high in early stage lesions relative to metastatic sites

- The degree of immune infiltration and PD-L1 labeling varies between metastatic sites, with certain metastatic niches, such as lung, displaying greater IC and PD-L1 positivity than other immunologically colder niches, such as liver.

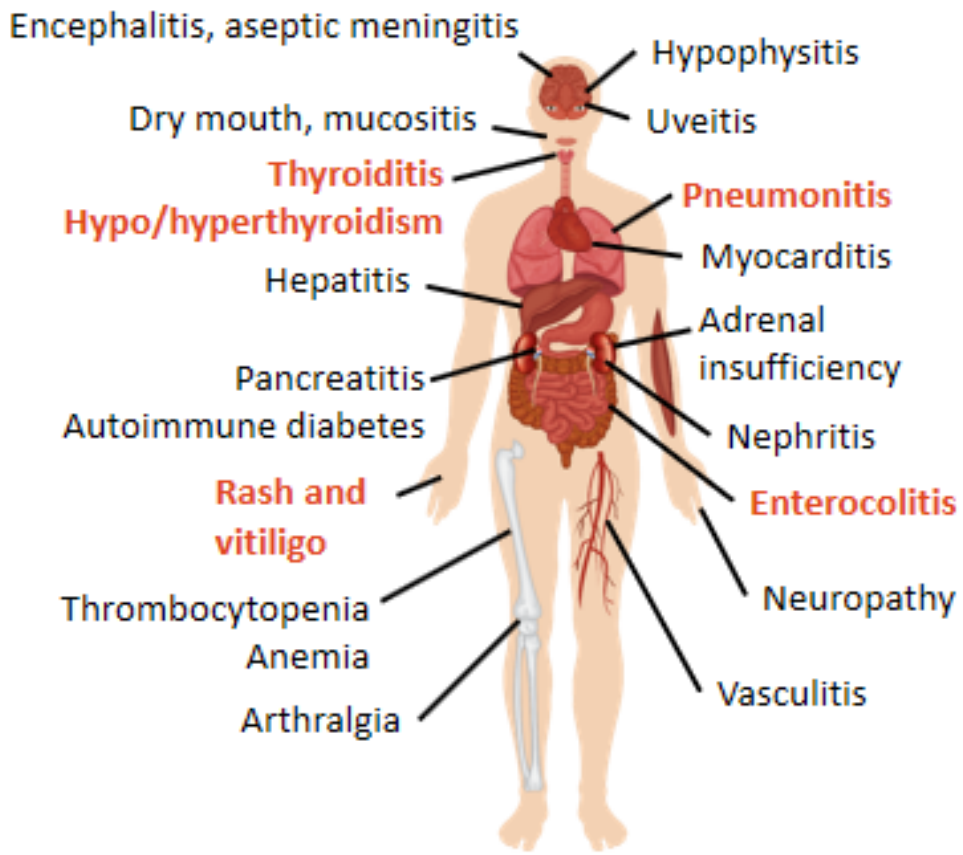
- Assays to measure PD-L1 should not be interchangeable

Choice of specimen for PD-L1 testing

- If possible, a non-lymph node tumor section is preferable for PD-L1 assessment.
- Neither the SP142 assay nor the 22C3 assay is validated for use in decalcified specimens or fine needle aspirated tissue smears or cell blocks, and these specimens should not be used for PD-L1 testing in this setting
- If multiple biopsy sites are available, testing for PD-L1 in liver samples should be avoided
- PD-L1 testing is not recommended for patients with early-stage breast cancer

Immune checkpoint inhibitor toxicities

Toxicities Associated With Immune Checkpoint Inhibitors



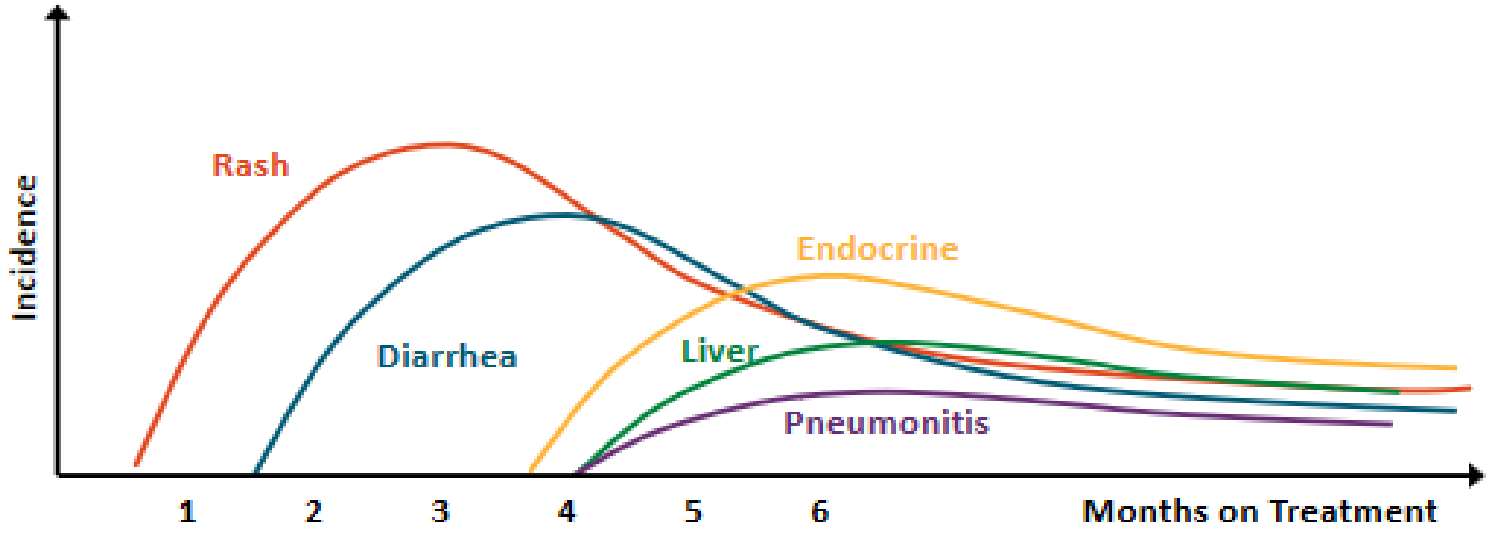
- Majority of irAEs are mild to moderate
- Severity can be asymptomatic to life-threatening; prompt recognition is crucial
- Onset is variable; can occur after cessation of therapy
- Most reversible with steroids; some require discontinuation of therapy
- Important to educate care team, patient, and caregivers on signs and symptoms of irAEs

Brahmer. 2018;36:1714. Postow. NEJM. 2018;378:158. Puzanov. JIC. 2017;5:95. Michot. EJC. 2016;54:139.

Slide credit: clinicaloptions.com

Toxicities Associated With Immune Checkpoint Inhibitors

- Timing can be highly variable
- irAE can occur months and even a year after the end of treatment
- Time course might be even more variable with novel combinations



Martins. Nat Rev Clin Oncol. 2019;16:563.

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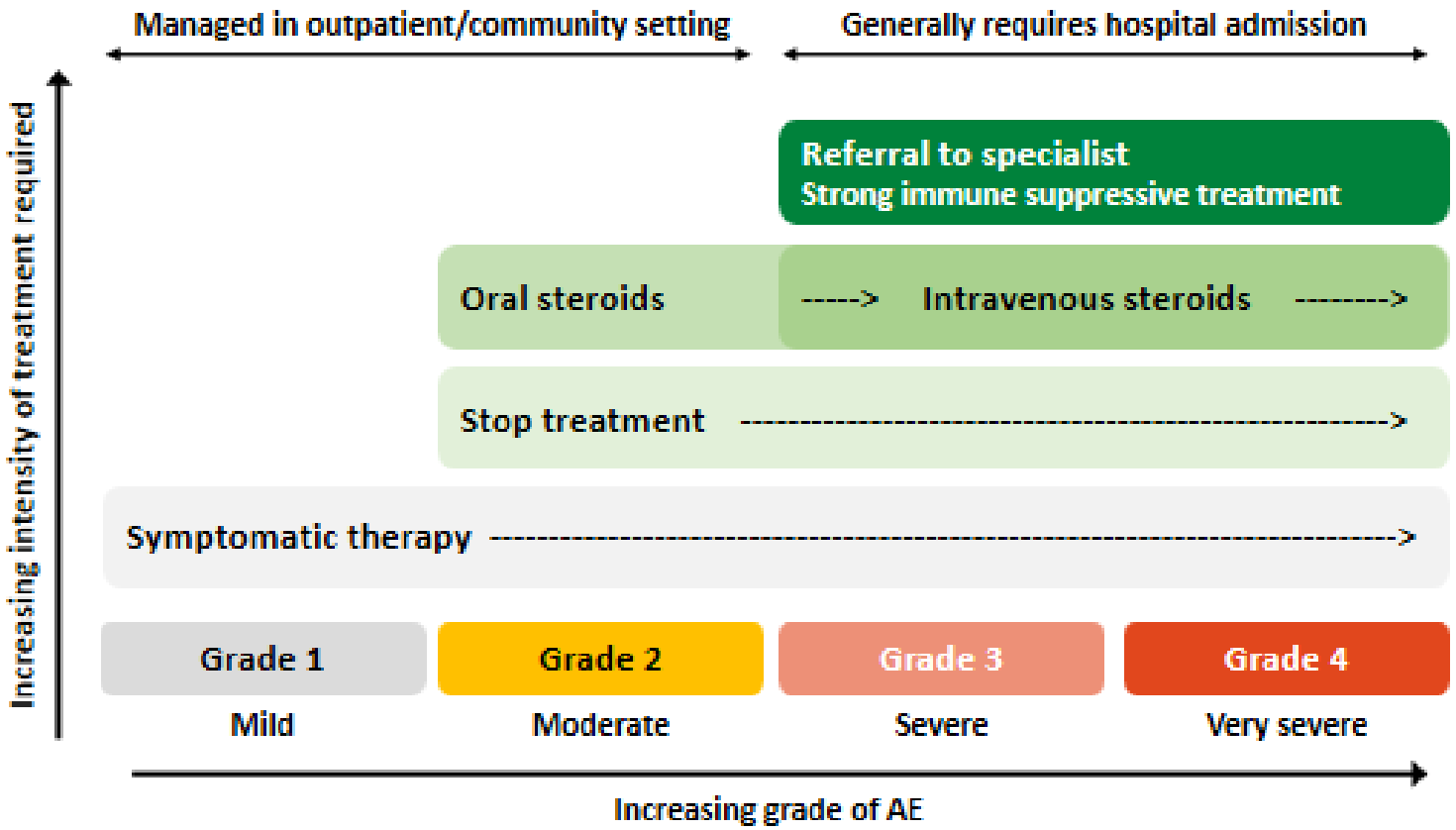
Management of ICI toxicities

Managing AEs From Immune Checkpoint Inhibitors



- Steroids (PO/IV): 1-2 mg/kg/day prednisone or equivalent, slow taper over 4-6 wk/52 days
- For some AEs, treatment can be restarted after resolution (eg, rash)
- For endocrinopathies:
  - ICI usually continued
  - Generally managed with hormone replacement, no steroids

Adapted from Champiat. ESMO Patient Guide Series. 2017.

Slide credit: clinicaloptions.com

Monitoring of IRAE

- Routine monitoring of patients is generally more frequent during the initial 4 cycles of treatment, with clinical assessments and laboratory testing complete blood count (CBC), comprehensive metabolic panel (CMP), hemoglobin A1c (HgbA1c), thyroid stimulating hormone (TSH), free T4 (FT4), and morning serum cortisol recommended at baseline and every 4 weeks.

- After the first four cycles then testing intervals can be increased to every 6–12 weeks, or as indicated.

- It is important to emphasize that immune effects can occur within a week to more than 1 year after initiation of therapy (including after cessation of therapy, and even after exposure to a single dose), so monitoring over a period of 12–24 months for symptoms of immune toxicities following therapy initiation is recommended.

Treatment beyond progression

- Clinical assessment and patient functional status are important when determining if a patient should continue on a given immunotherapy in the setting of progressive disease.

- Both ASCO and SITC guidelines specify that for patients to receive treatment beyond progression, the patient should have stable or improved clinical condition, have no severe laboratory abnormalities, and be tolerating the treatment well with limited/mild side effects. Most importantly, there should be no clinical progression and no additional progression noted on subsequent confirmation imaging scans.

- Isolated sites of progression -- local therapy + continuing immune checkpoint inhibitor

ICI usage in special population

Special Population	ICI usage
Pregnancy	limited safety data, discouraged
Vaccines	inactivated vaccines are safe, data lacking for live attenuated vaccines
HIV population	Prospective trials showed safety and efficacy
Auto immune disease	Decision on case basis
Breast cancer with prior organ transplant	Significant risk of graft rejection

Summary

- Triple negative breast cancer is the only subset where Immune checkpoint inhibitor is approved in early(T1c N1-N2 , T2-4 N0-2) and advanced stage
- Pembrolizumab is the only ICI currently approved in breast cancer
- PD-L1 testing is not required for early TNBC
- For patients with high-risk early-stage TNBC, pembrolizumab in combination with chemotherapy as neoadjuvant treatment and then continued as a single agent as adjuvant treatment after surgery is a standard of care
- Based on accumulated data to date, immunotherapy regimens for stage II and III TNBC should at least include an anthracycline and a taxane with or without carboplatin

Summary

- All patients with unresectable locally advanced or metastatic TNBC should have tumor tissue tested for PD-L1 (by 22c3 assay), TMB, MSI
- When considering metastatic sites to test for PD-L1, it is preferable to prioritize extrahepatic sites
- PD-L1 testing should not be performed on fine needle aspirated / cell-block specimens or decalcified bone
- For patients with locally advanced/metastatic TNBC and PD-L1+ tumors by CPS score ≥10 using the 22C3 assay, pembrolizumab plus nab-paclitaxel, paclitaxel, or carboplatin and gemcitabine is recommended as immunotherapy option for first-line treatment

Summary

- Development of Ideal biomarker that reliably predicts clinical response to pembrolizumab is the need of the hour
- Steroids are highly effective therapy in managing immune mediated AE and don’t affect efficacy of ICI
- Patients should be monitored for symptoms of immune toxicities during immunotherapy and for at least 12 months after discontinuation of treatment

THANK YOU