Society for Immunotherapy of Cancer

Cancer Immunotherapy GUIDELINES

Immunotherapy for the Treatment of Breast Cancer Guideline Overview

October 29, 2021

1 – 2 p.m. ET

Jointly provided by Postgraduate Institute for Medicine and the Society for Immunotherapy of Cancer.

This webinar was funded solely by SITC.

Webinar faculty

Rita Nanda, MD – *University of Chicago*

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David B. Page, MD – *Earle A. Chiles Research Institute*

Learning objectives

- Select appropriate diagnostics and biomarker testing tailored to the clinical setting for a patient being considered for immunotherapy based on the expert panel recommendations in the SITC Clinical Practice Guideline (CPG)
- Implement immunotherapy treatments effectively and appropriately for breast cancer according to the recommendations in the CPG
- Appraise patterns of response to immunotherapy in order to appropriately monitor and manage patients during treatment

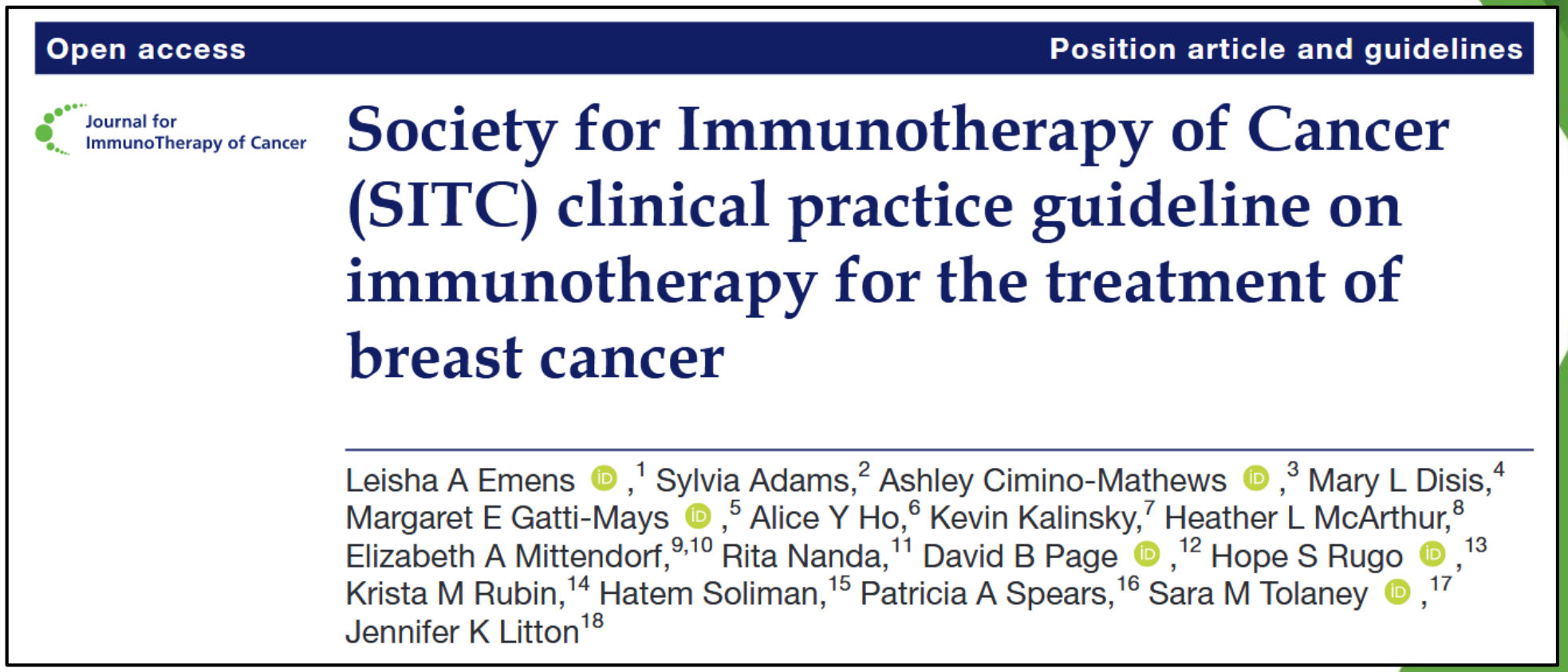
Webinar outline

- Introduction to the Guideline
- Biomarkers for immunotherapy in breast cancer
- Early-stage TNBC
- Advanced/metastatic TNBC
- Response evaluation with immunotherapy
- Immunotherapy toxicities

Development of the Guideline

- Developed according to the Institute of Medicine's Standards for Developing Trustworthy Clinical Practice Guidelines
- Panel consisted of 17 experts in the field
- Recommendations are based upon published literature evidence, or clinical evidence where appropriate
- Consensus was defined at 75% approval among voting members

Development of the Guideline



Open access Position article and guidelines

Journal for ImmunoTherapy of Cancer

Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immunotherapy for the treatment of breast cancer

Leisha A Emens ,[1] Sylvia Adams,[2] Ashley Cimino-Mathews ,[3] Mary L Disis,[4] Margaret E Gatti-Mays ,[5] Alice Y Ho,[6] Kevin Kalinsky,[7] Heather L McArthur,[8] Elizabeth A Mittendorf,[9,10] Rita Nanda,[11] David B Page ,[12] Hope S Rugo ,[13] Krista M Rubin,[14] Hatem Soliman,[15] Patricia A Spears,[16] Sara M Tolaney ,[17] Jennifer K Litton[18]

General guidance for patients receiving immunotherapy

- For patients receiving immunotherapy, **education** should be provided, including the differences between chemotherapy and immunotherapy.
- Patients and providers should be educated about **potential irAEs**, including expected timing of symptom onset and management of toxicities with immunotherapies, rationale for holding doses as opposed to dose reductions, and detailed parameters for when to contact their care team.
- Education should include the importance of early recognition and management of irAEs, emphasizing that some of the more common toxicities have **vague symptoms** and therefore any change from baseline should be reported.
- **Clinical trial** enrollment should be considered if available.

Emens, J Immunother Cancer 2021

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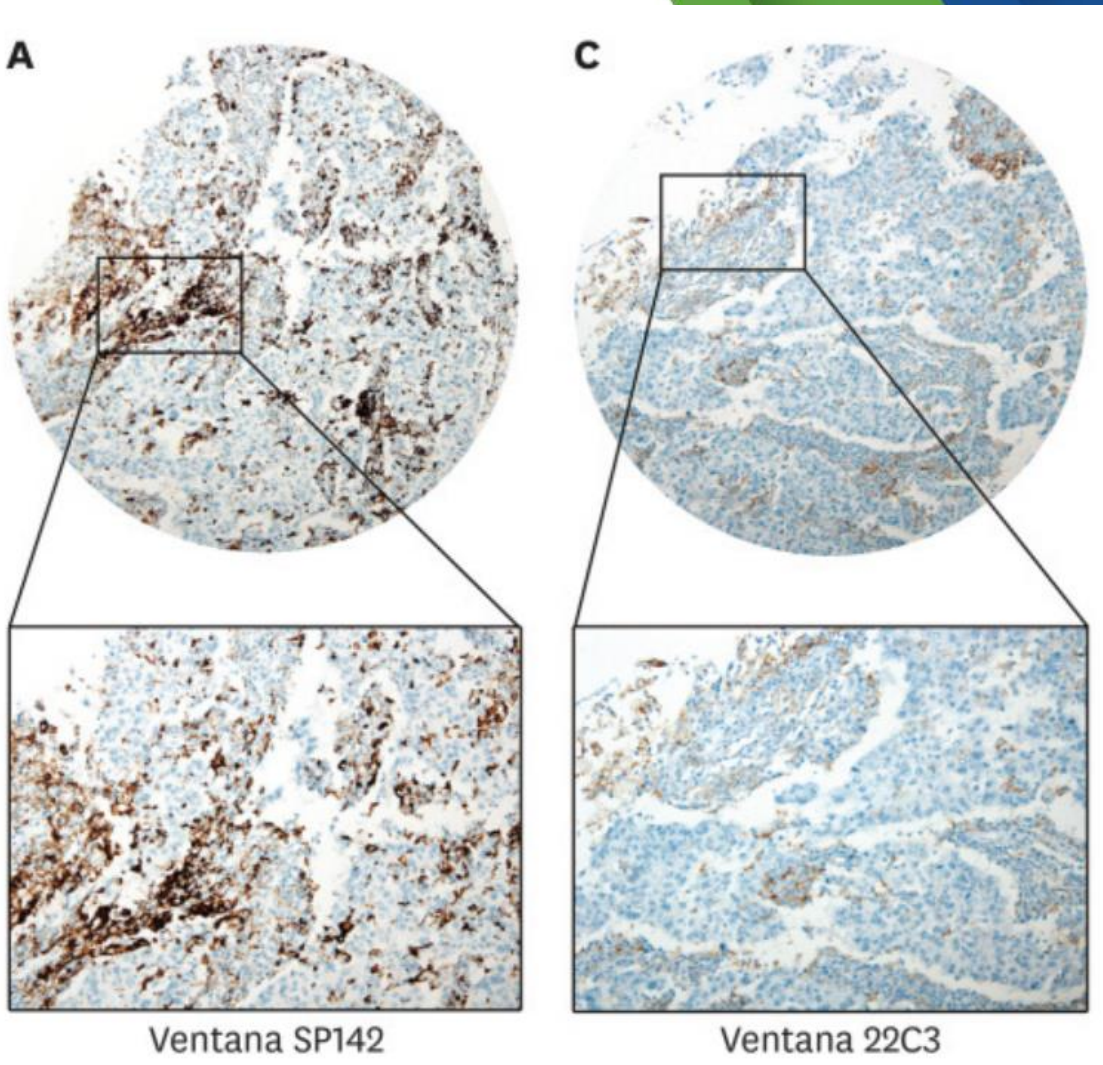
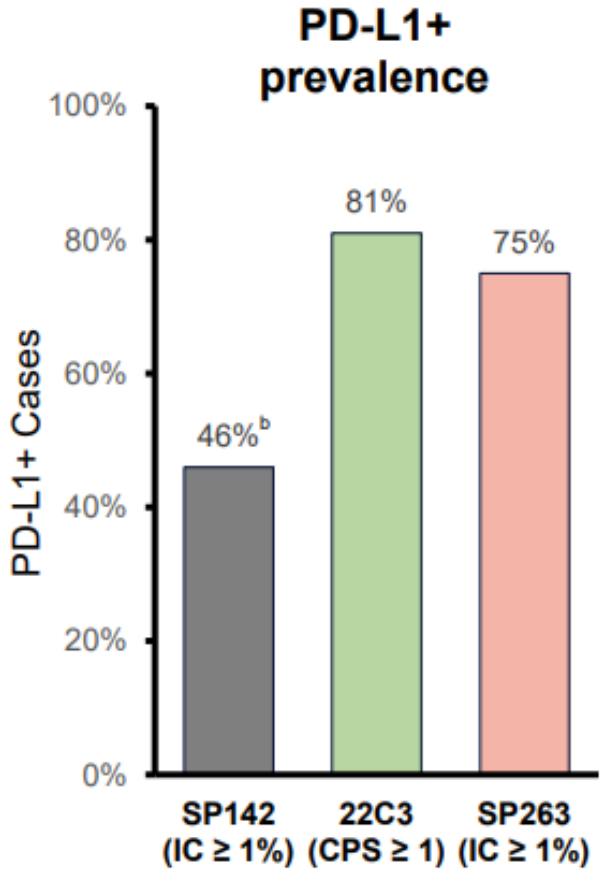
PD-L1 assays in TNBC

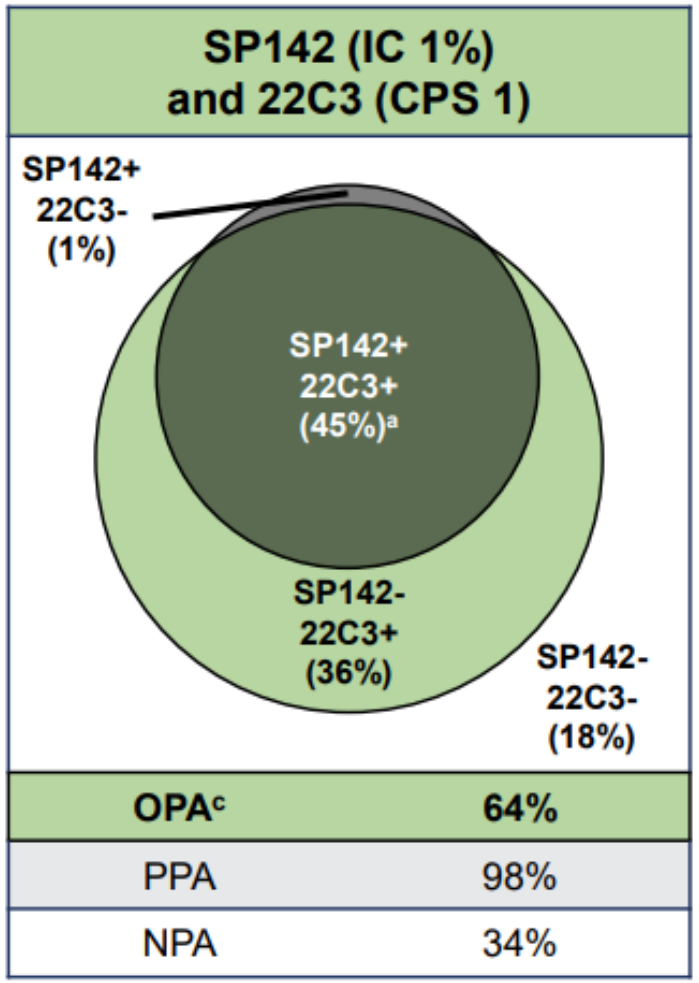
- **SP142**: IC ≥ 1%, companion diagnostic for atezolizumab
- **22C3**: CPS ≥ 10, companion diagnostic for pembrolizumab



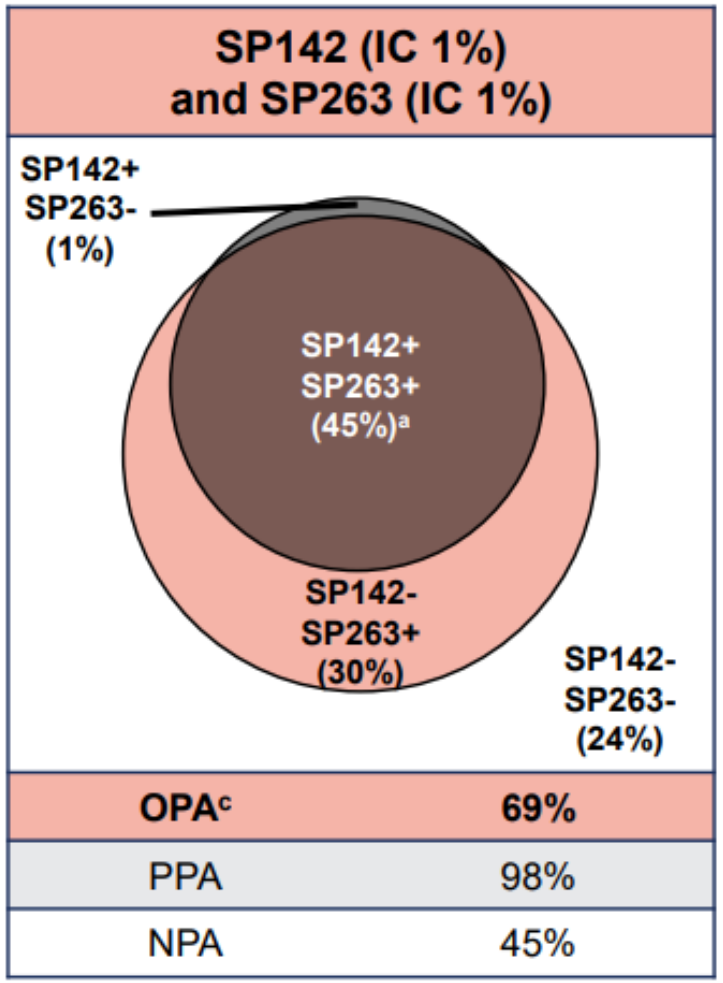
Lee, J Breast Cancer 2020

PD-L1 IHC assays: prevalence and analytical concordance





OPA[c]	64%
PPA	98%
NPA	34%



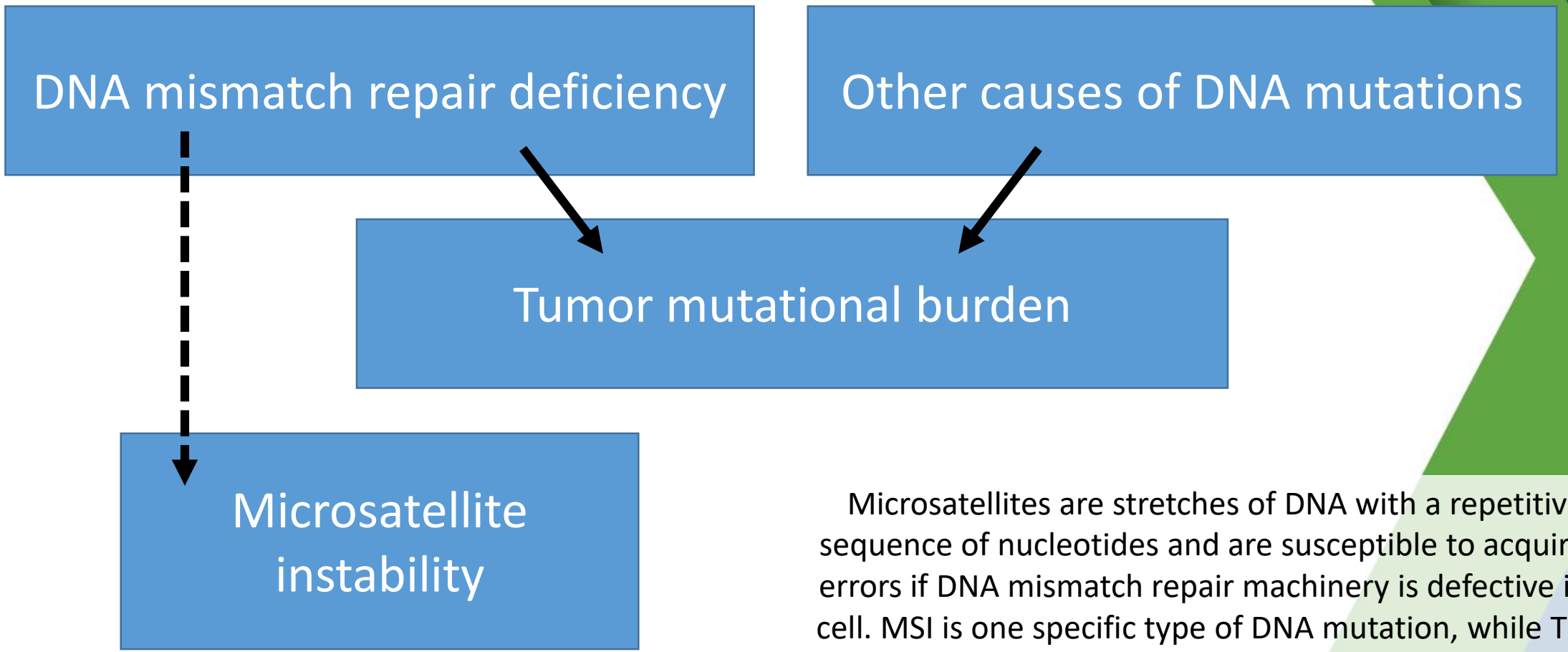
OPA[c]	69%
PPA	98%
NPA	45%

NPA, negative percentage agreement; OPA, overall percentage agreement; PPA, positive percentage agreement.
[a] > 97% of SP142+ samples included in 22C3+ or SP263+ samples. [b] Compared with 41% in ITT (Schmid, *New Engl J Med* 2018).
[c] ≥ 90% OPA, PPA ***and*** NPA required for analytical concordance.

Rugo et al. Abstract 6571
IMpassion130 PD-L1 IHC
https://bit.ly/30OmOqz

Rugo, ESMO 2019

MSI, dMMR and TMB



Microsatellites are stretches of DNA with a repetitive sequence of nucleotides and are susceptible to acquiring errors if DNA mismatch repair machinery is defective in a cell. MSI is one specific type of DNA mutation, while TMB measures all types of DNA mutations.

Panel recommendations for biomarkers in breast cancer

- All patients with advanced TNBC should have tumor tissue tested for PD-L1, TMB and MSI by FDA-approved tests.
- All patients who are candidates for immunotherapy should have tumor tissue tested for PD-L1 at least once, irrespective of prior therapies.
- PD-L1 testing is not recommended for patients with early-stage breast cancer at this time.
- When considering metastatic sites to test for PD-L1, it is preferable to prioritize extrahepatic sites or the primary tumor, if available.
- Biomarker assessment, including repeat receptor profiles, PD-L1 and NGS should be considered at first relapse.

Emens, J Immunother Cancer 2021

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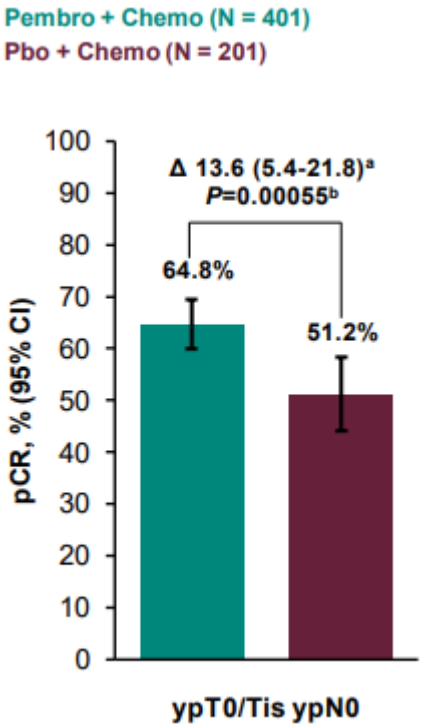
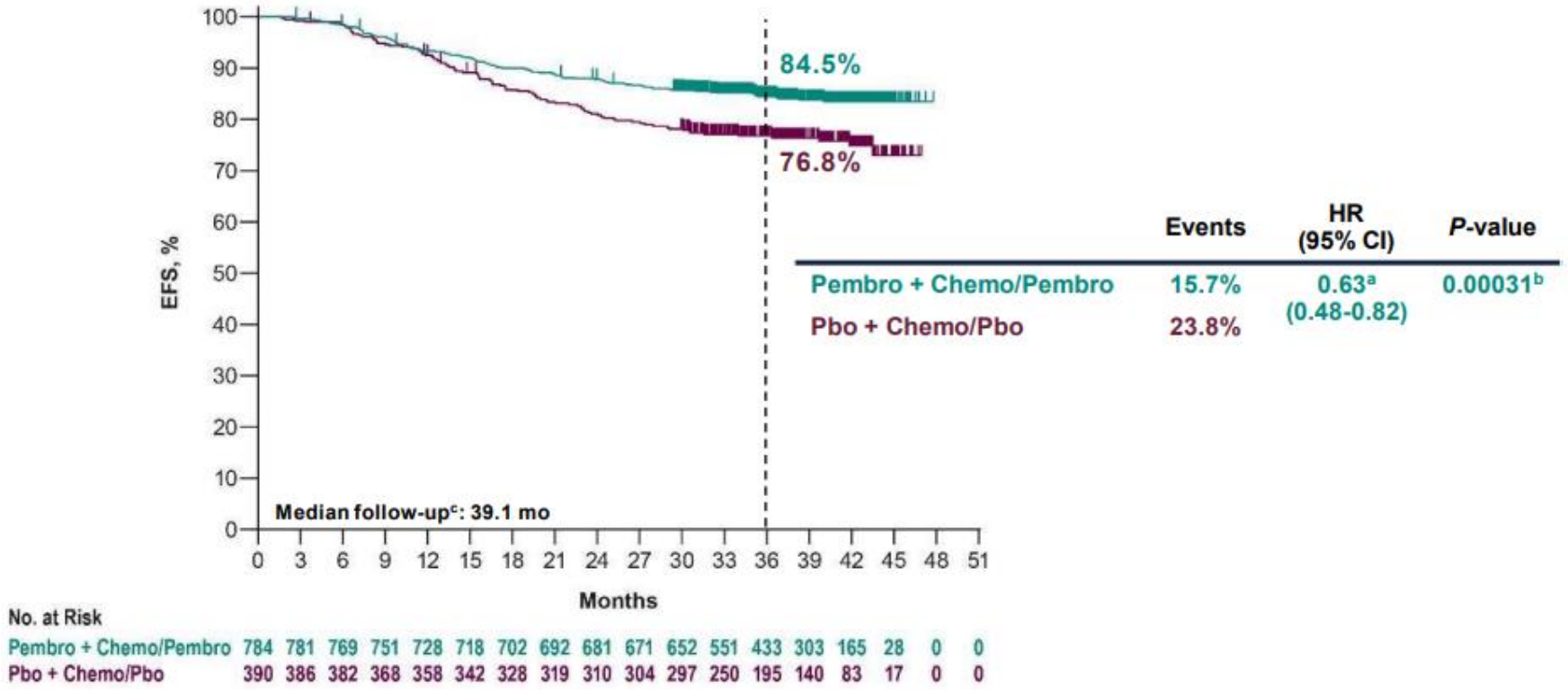
FDA-approved immunotherapy for early-stage TNBC

Regimen	Approved	Indication	Dose
Pembrolizumab + chemotherapy (neoadjuvant) & Pembrolizumab monotherapy (adjuvant)	2021	High-risk, early-stage TNBC	Pembrolizumab 200 mg Q3W or 400 mg Q6W **Neoadjuvant**: pembrolizumab + chemotherapy for 24 weeks **Adjuvant**: pembrolizumab for 27 weeks

Clinical trials in early-stage TNBC: KEYNOTE-522





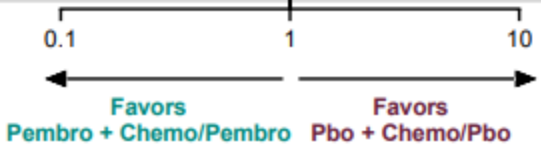
	Events	HR (95% CI)	*P*-value
Pembro + Chemo/Pembro	15.7%	0.63[a] (0.48-0.82)	0.00031[b]
Pbo + Chemo/Pbo	23.8%		

Schmid, ESMO Virtual Plenary 2021

Clinical trials in early-stage TNBC: KEYNOTE-522

EFS in Patient Subgroups

Subgroup	No. Events/No. Patients (%) Pembro + Chemo/Pembro	Pbo + Chemo/Pbo	Hazard Ratio (95% CI)
Overall	123/784 (15.7)	93/390 (23.8)	0.63 (0.48 to 0.82)
Nodal status			
Positive	80/408 (19.6)	57/196 (29.1)	0.65 (0.46 to 0.91)
Negative	43/376 (11.4)	36/194 (18.6)	0.58 (0.37 to 0.91)
Tumor size			
T1/T2	64/581 (11.0)	59/290 (20.3)	0.51 (0.36 to 0.73)
T3/T4	59/203 (29.1)	34/100 (34.0)	0.84 (0.55 to 1.28)
Carboplatin schedule			
Every 3 weeks	50/334 (15.0)	37/167 (22.2)	0.65 (0.42 to 0.99)
Weekly	71/444 (16.0)	56/220 (25.5)	0.60 (0.42 to 0.86)
PD-L1 status			
Positive	98/656 (14.9)	68/317 (21.5)	0.67 (0.49 to 0.92)
Negative	25/128 (19.5)	25/69 (36.2)	0.48 (0.28 to 0.85)
Age category			
<65 years	103/700 (14.7)	79/342 (23.1)	0.61 (0.45 to 0.82)
≥65 years	20/84 (23.8)	14/48 (29.2)	0.79 (0.40 to 1.56)
ECOG PS			
0	101/678 (14.9)	80/341 (23.5)	0.60 (0.45 to 0.80)
1	22/106 (20.8)	13/49 (26.5)	0.81 (0.41 to 1.62)



Schmid, ESMO Virtual Plenary 2021

Toxicity considerations in early-stage TNBC

- Risk tolerance may be different in early-stage disease than for late-stage
- Potential for long-term adverse events must be considered

Table 3. Adverse Events during the Neoadjuvant Phase at the Second Interim Analysis.*

Event	Pembrolizumab–Chemotherapy (N=781)		Placebo–Chemotherapy (N=389)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)			
Any adverse event	777 (99.5)	633 (81.0)	389 (100.0)	295 (75.8)
Treatment-related adverse event†	773 (99.0)	600 (76.8)	388 (99.7)	281 (72.2)
Nausea	490 (62.7)	26 (3.3)	246 (63.2)	5 (1.3)
Alopecia	471 (60.3)	14 (1.8)	220 (56.6)	8 (2.1)
Anemia	430 (55.1)	142 (18.2)	215 (55.3)	58 (14.9)
Neutropenia	365 (46.7)	270 (34.6)	183 (47.0)	129 (33.2)
Fatigue	321 (41.1)	27 (3.5)	147 (37.8)	6 (1.5)
Diarrhea	230 (29.4)	17 (2.2)	92 (23.7)	5 (1.3)
Elevated alanine aminotransferase level	199 (25.5)	41 (5.2)	96 (24.7)	9 (2.3)
Vomiting	199 (25.5)	18 (2.3)	85 (21.9)	6 (1.5)
Asthenia	191 (24.5)	25 (3.2)	99 (25.4)	9 (2.3)
Constipation	185 (23.7)	0	82 (21.1)	0
Decreased neutrophil count	185 (23.7)	146 (18.7)	112 (28.8)	90 (23.1)
Rash	170 (21.8)	7 (0.9)	59 (15.2)	1 (0.3)
Peripheral neuropathy	154 (19.7)	15 (1.9)	82 (21.1)	4 (1.0)
Adverse event of interest‡	304 (38.9)	101 (12.9)	71 (18.3)	7 (1.8)
Infusion reaction	132 (16.9)	20 (2.6)	43 (11.1)	4 (1.0)
Hypothyroidism	107 (13.7)	3 (0.4)	13 (3.3)	0
Hyperthyroidism	36 (4.6)	2 (0.3)	4 (1.0)	0
Severe skin reaction	34 (4.4)	30 (3.8)	4 (1.0)	1 (0.3)
Adrenal insufficiency	18 (2.3)	10 (1.3)	0	0

* Listed are all adverse events that occurred during the trial period or within 30 days after the trial period (within 90 days for serious events). The events are listed in descending order of frequency in the pembrolizumab–chemotherapy group. The as-treated population included all the patients who had undergone randomization and received at least one trial treatment. The severity of adverse events was graded according to the Common Terminology Criteria for Adverse Events, version 4.0, of the National Cancer Institute.

† Treatment-related adverse events were events that were attributed to a trial treatment by the investigators. Treatment-related adverse events that occurred in at least 20% of the patients or those that were considered by the investigators to be medically relevant are reported. Patients may have had more than one event.

‡ Adverse events of interest were determined according to a list of terms specified by the sponsor, regardless of attribution to any trial treatment by the investigators. Adverse events of interest that occurred in at least 15 patients are reported.

Schmid, N Engl J Med 2020

Panel recommendations for early-stage TNBC

- For patients with stage II and III TNBC, improved pCR rates with either neoadjuvant pembrolizumab or atezolizumab have been observed, regardless of PD-L1 status.
- Immunotherapy regimens for stage II or III TNBC should at least include an anthracycline and a taxane with or without carboplatin.
- For patients with high-risk early-stage TNBC, pembrolizumab + chemotherapy as neoadjuvant treatment and then continued as a single agent as adjuvant treatment after surgery is a standard of care based on KEYNOTE-522.

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- Introduction to the Guideline
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FDA-approved immunotherapies for advanced TNBC

Regimen	Approved	Indication	Dose
Pembrolizumab + chemotherapy	2020	Locally recurrent/metastatic TNBC with PD-L1 CPS ≥ 10	200 mg Q3W or 400 mg Q6W
Pembrolizumab	2017/2020	MSI-H/dMMR or TMB-high solid tumors with progression on prior treatment	200 mg Q3W or 400 mg Q6W

Formerly approved regimen	Approved/ Withdrawn	Indication	Dose
Atezolizumab + nab-paclitaxel or paclitaxel protein-bound	2019	Advanced/metastatic TNBC with PD-L1 ≥1% immune cells	840 mg atezolizumab Q2W + 100 mg/m^2 nab-paclitaxel on days 1, 8, 15

Clinical trials in metastatic TNBC

Trial	Treatment arm(s)	Patient selection criteria	n	ORR	Median PFS (months)	Median OS (months)
IMpassion130	Atezolizumab + nab-paclitaxel	Metastatic TNBC without prior therapy	451	ITT: 56.0% PD-L1+: 58.9%	ITT: 7.2 PD-L1+: 7.5	ITT: 21.3 PD-L1+: 25.0
	Placebo + nab-paclitaxel		451	ITT: 45.9% PD-L1+: 42.6%	ITT: 5.5 PD-L1+: 5.0	ITT: 17.6 PD-L1+: 15.5
IMpassion131	Atezolizumab + paclitaxel	Metastatic TNBC without prior therapy	431	ITT: 54% PD-L1+: 63%	ITT: 5.7 PD-L1+: 6.0	ITT: 19.2 PD-L1+: 22.1
	Placebo + paclitaxel		220	ITT: 47% PD-L1+: 55%	ITT: 5.6 PD-L1+: 5.7	ITT: 22.8 PD-L1+: 28.3
KEYNOTE-086	Pembrolizumab	A: Metastatic TNBC at 2nd line or greater	170	5.3% CR: 1.2%	2.0	9.0
		B: PD-L1+ metastatic TNBC without prior therapy	84	21.4% CR: 4.7%	2.1	18.0
KEYNOTE-119	Pembrolizumab	Metastatic TNBC with 1-2 prior therapies	312	ITT: 9.6% CPS >10: 18%	ITT: 2.1 CPS>10: 2.1	ITT: 9.9 CPS>10: 12.7
	Single-agent chemotherapy		310	ITT: 10.6% CPS >10: 9%	ITT: 3.3 CPS>10: 3.4	ITT: 10.8 CPS>10: 11.6
KEYNOTE-355	Pembrolizumab + chemotherapy*	Locally recurrent inoperable or metastatic TNBC without prior therapy	566	ITT: 40.8 CPS >10: 52.7	ITT: 7.5 CPS >10: 9.7	ITT: 17.2 CPS >10: 23.0
	Placebo + chemotherapy		281	ITT: 37.0 CPS >10: 40.8	ITT: 5.6 CPS >10: 5.6	ITT: 15.5 CPS >10: 16.1

**FDA-approved*

Schmid, N Engl J Med 2020; Adams, Ann Oncol 2019; Cortes, Lancet 2020; Miles, Ann Oncol 2021; Winer, Lancet Oncol 2021; Rugo, ESMO 2021

Clinical trials in HR+ or HER2+ breast cancer

Trial	Treatment arm(s)	Patient selection criteria	n	ORR	Median PFS (months)	Median OS (months)
KEYNOTE-028	Pembrolizumab	ER+/HER2-, PD-L1+ breast cancer	25	12.0% CR: 0%	1.8	8.6
KEYNOTE-014/PANACEA	Pembrolizumab + trastuzumab	HER2+ breast cancer with progression on trastuzumab	58	PD-L1+: 15% CR: 4% PD-L1-: 0%		
KATE2	Atezolizumab + trastuzumab emtansine	HER2+ advanced breast cancer with previous trastuzumab and a taxane	133	ITT: 45% PD-L1+: 54%	ITT: 8.2 PD-L1+: 8.5	ITT 1-year: 89.1% PD-L1+: 94.3%
	Trastuzumab emtansine		69	ITT: 43% PD-L1+: 33%	ITT: 6.8 PD-L1+: 4.1	ITT 1-year: 89.0% PD-L1+: 87.9%

Rugo, Clin Cancer Res 2018; Loi, Lancet Oncol 2019; Emens Lancet Oncol 2020

Panel recommendations for advanced TNBC

- For patients with locally advanced/metastatic TNBC, pembrolizumab should only be added to chemotherapy if tumors express PD-L1 with CPS ≥ 10 by the 22C3 assay.
- *For patients with locally advanced/metastatic TNBC, atezolizumab should only be added to nab-paclitaxel if tumor-infiltrating immune cells expressing PD-L1 occupy ≥1% of the tumor area by SP142 assay.*
- *Nab-paclitaxel is the only chemotherapy backbone that should be used with atezolizumab for advanced/metastatic TNBC.*
- *Patients deriving clinical benefit from atezolizumab-based treatment in the absence of clinically significant toxicity or disease progression should continue on atezolizumab plus nab-paclitaxel rather than change therapy.*

Emens, J Immunother Cancer 2021

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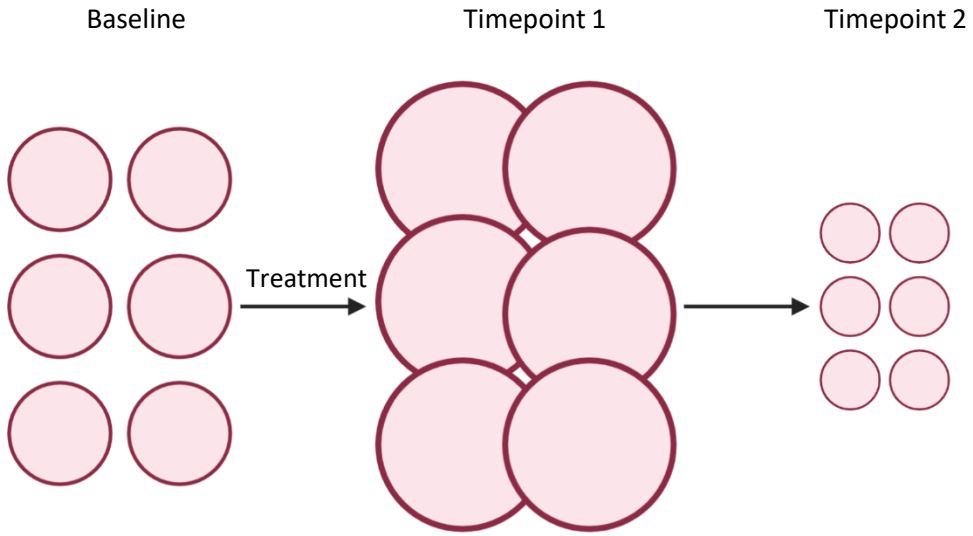
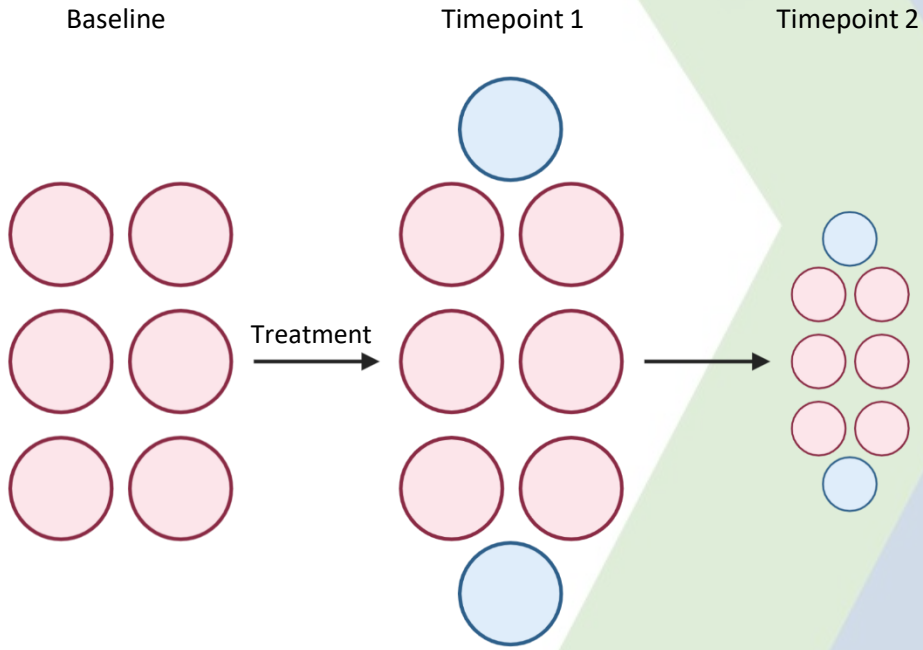
Pseudoprogression

Pseudoprogression: Growth of pre-existing lesions

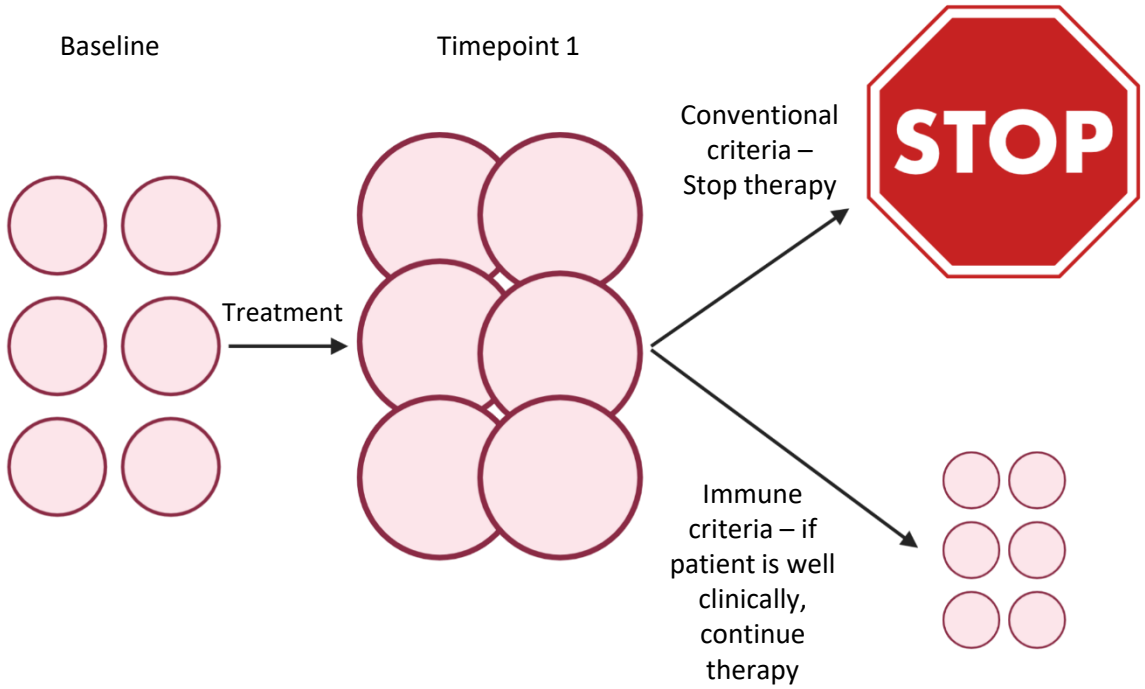


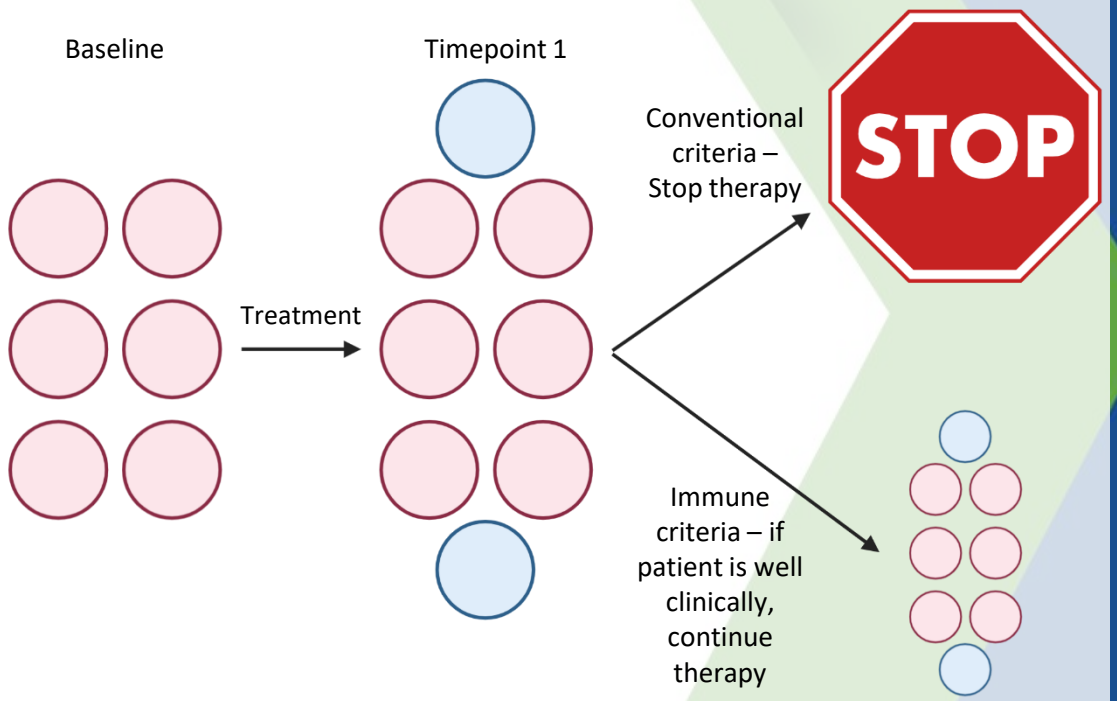
Pseudoprogression: Appearance of new lesions



Wang, RadioGraphics 2017.

Pseudoprogression





Wang, RadioGraphics 2017.

Distinguishing pseudoprogression from true progression

Characteristic	Pseudoprogression	True progression
Clinical symptoms	Should not deteriorate	May deteriorate
Imaging findings	Initial increase that is not confirmed on follow-up scan	Confirmed on two sequential scans
Biopsy	High immune infiltrate present in tumor	No immune infiltrate increase; primarily cancer cells
Time to progression	Varies	Varies

Lauber, Am Soc Clin Oncol Ed Book 2019.

Panel recommendations for response evaluation

- When **pseudoprogression** is suspected and treatment beyond progression is being considered, the patient should have stable or improved clinical condition, no severe laboratory abnormalities and be tolerating the treatment well with limited/mild side effects.
- For management of **isolated site(s) of progression** for a patient receiving immunotherapy, it is reasonable to consider local therapy for the isolated site(s) of progression as long as the patient has good performance status and it otherwise responding to the current treatment. However, there is no data that local treatment will improve clinical outcomes.

Emens, J Immunother Cancer 2021

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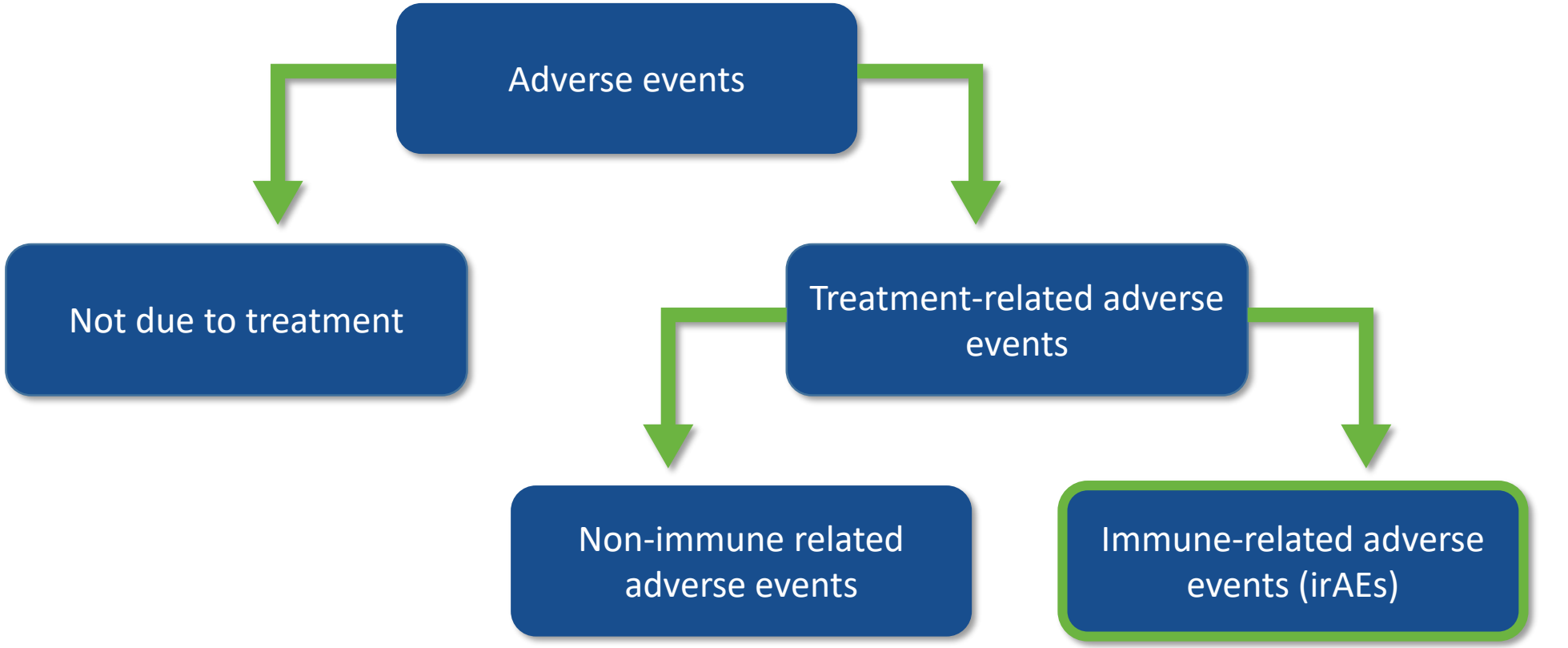
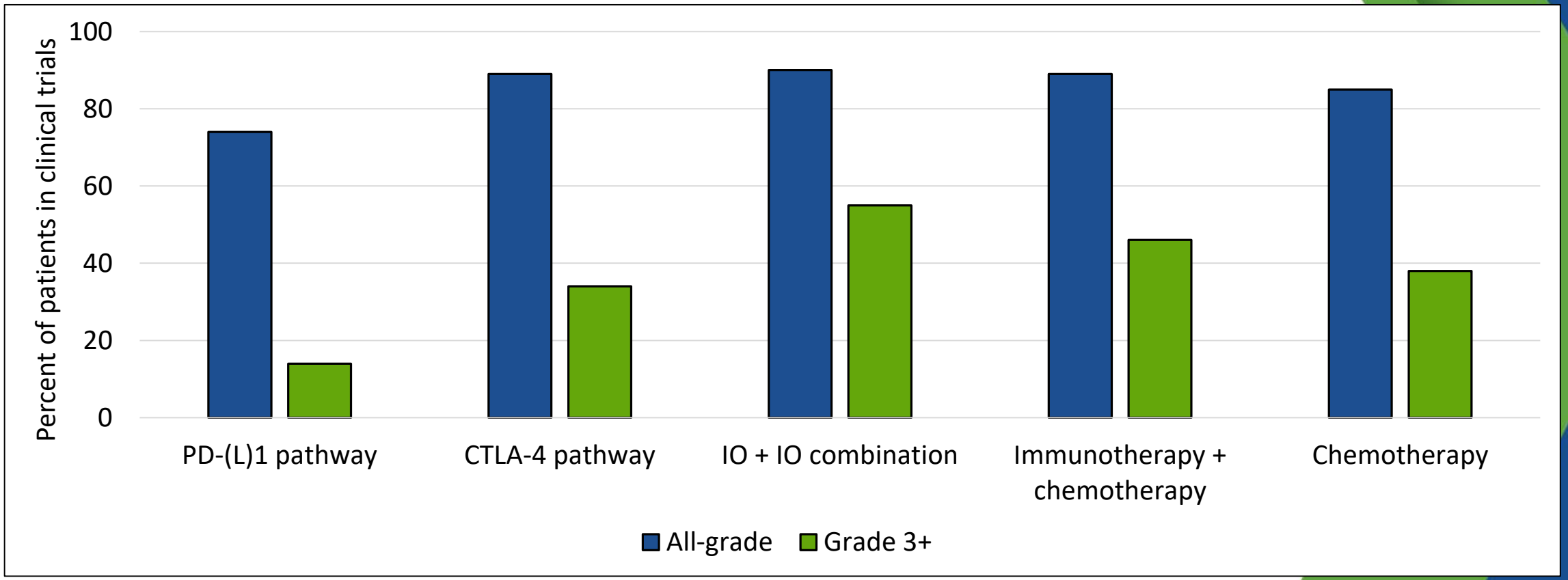
Types of adverse events



- Can result from all ICIs
- Can impact any organ system

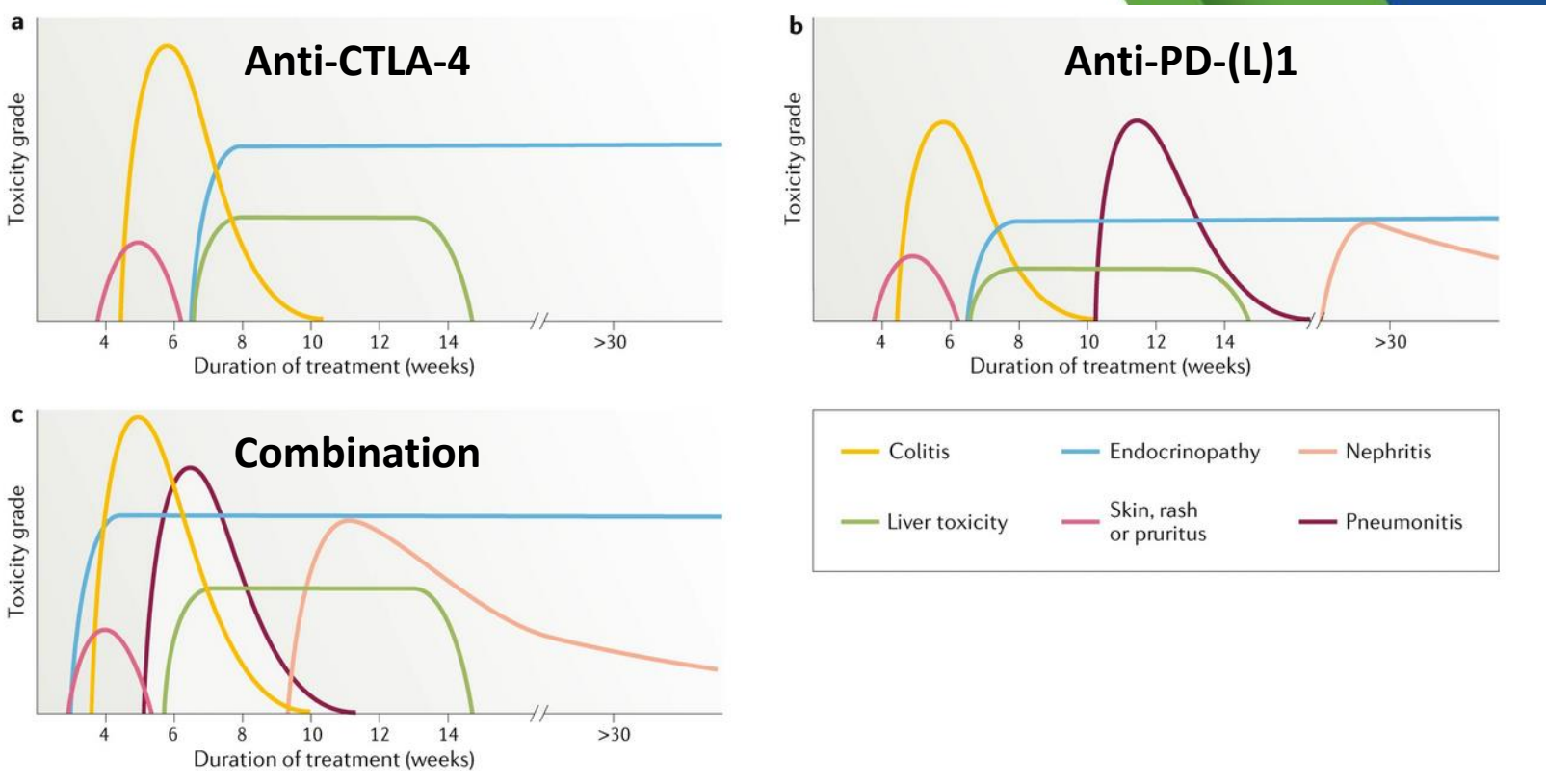
Toxicity with immune checkpoint inhibitors



Wang, Front Pharmacol 2017.
Kelly, Cancer 2018.
Bertrand, BMC Med 2015.

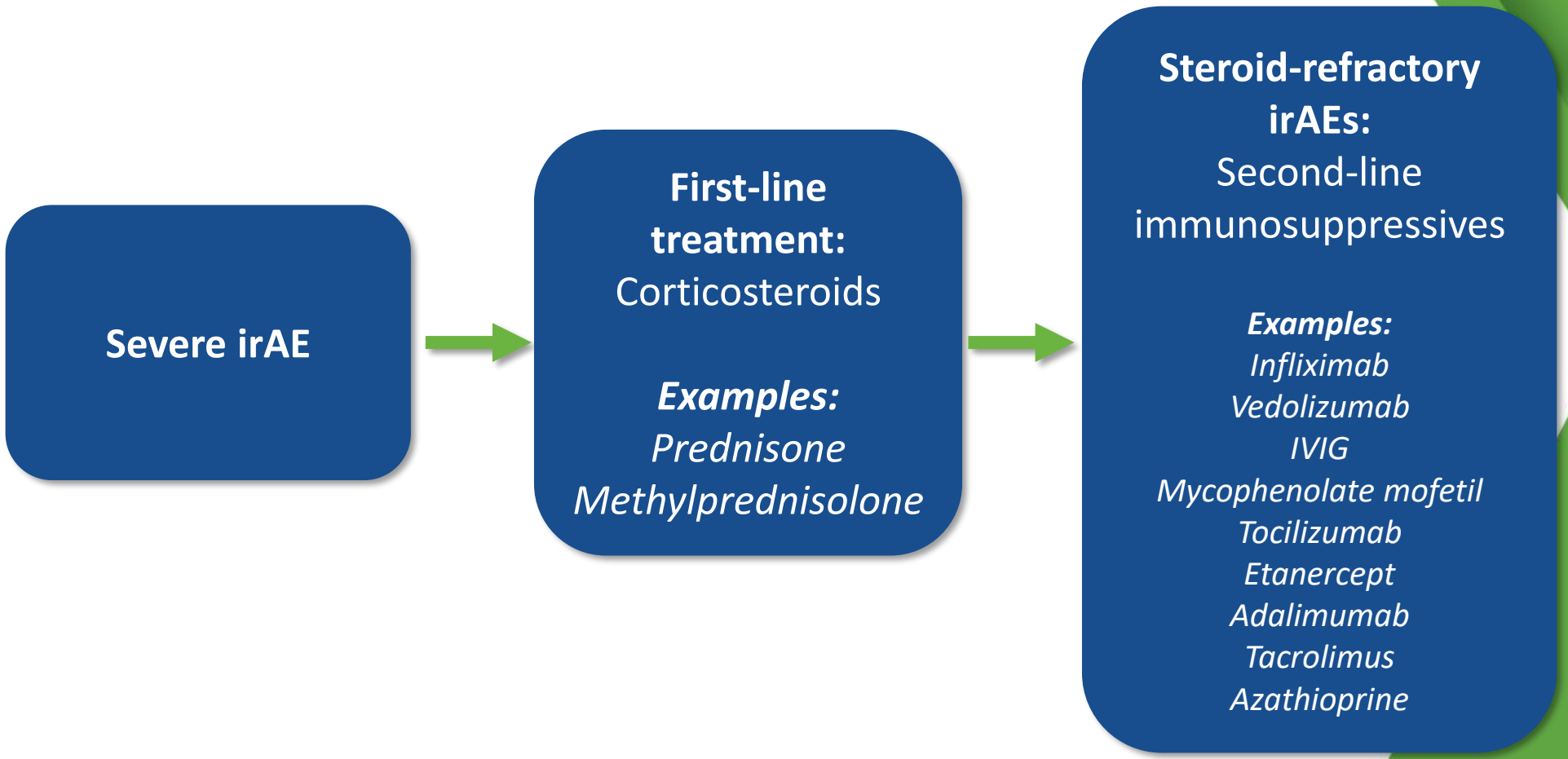
Kinetics of immune-related adverse events

- Can be days to months after therapy initiation
- Very early or very late AEs may warrant special concern
- May occur even after treatment is discontinued
- Important to identify patients who are currently **OR** previously on ICI treatment



Martins, Nat Rev Clin Oncol 2019

General irAE management



Brahmer, J Immunother Cancer 2021

Endocrinopathies

- Many have non-specific and/or overlapping cancer-related symptoms (fatigue, headache, malaise)
- Usually late-onset
- Assumed to be long-lasting or chronic
- Include:
  - Primary or secondary **thyroid dysfunction**
  - **Hypophysitis**
  - **Secondary adrenal insufficiency** (primary AI is exceedingly rare)
  - **Type 1 diabetes mellitus** (rare but life threatening)

Brahmer, J Immunother Cancer 2021

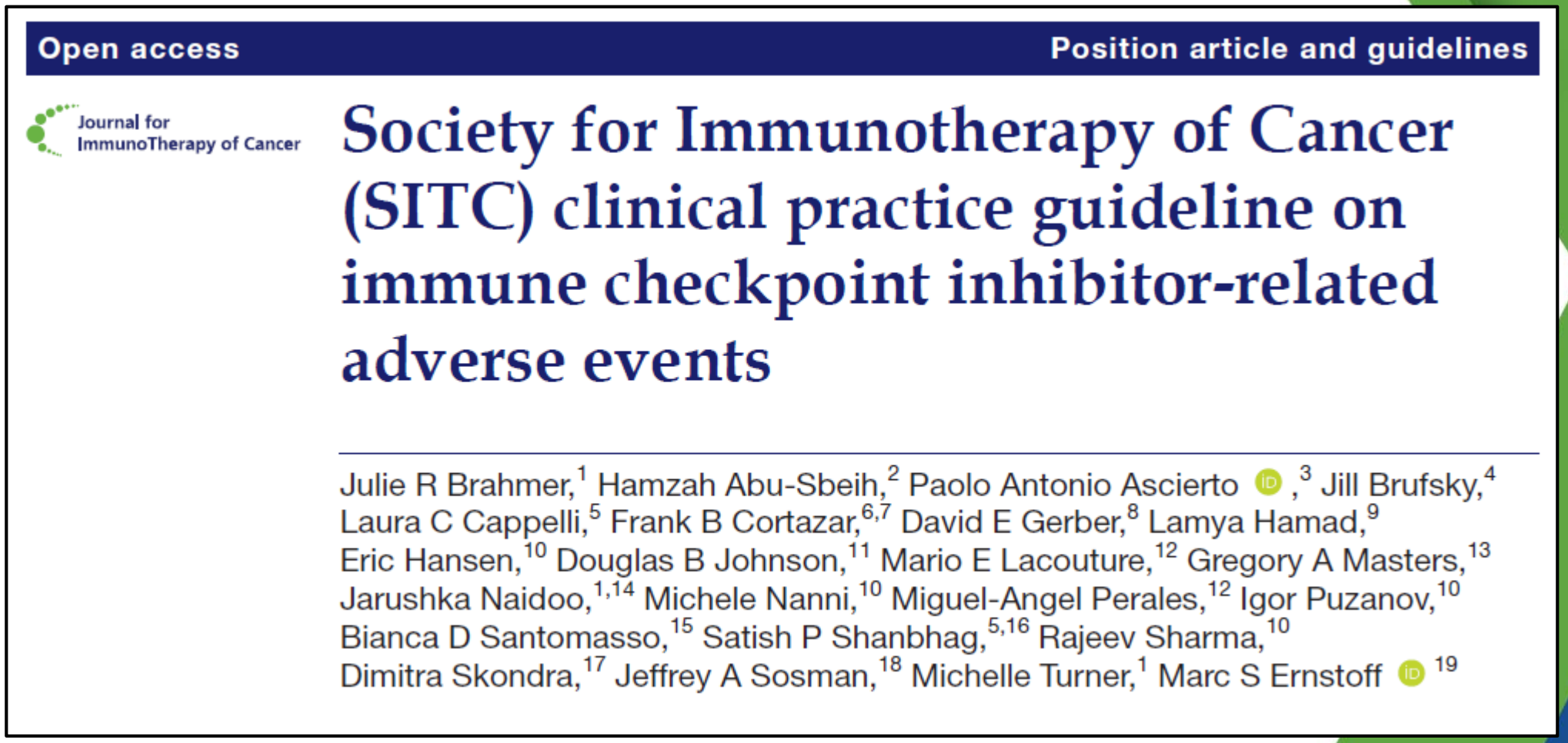
Distinguishing immunotherapy and chemotherapy toxicities

Example: Elevation in LFTs – taxane versus immune mediated?

Useful strategies:

- More frequent blood monitoring
- Dose hold and re-challenge

SITC's Guidelines on irAEs



Open access Position article and guidelines

Journal for ImmunoTherapy of Cancer

Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immune checkpoint inhibitor-related adverse events

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sitc Society for Immunotherapy of Cancer

Cancer Immunotherapy GUIDELINES

Practical Management Pearls for Immunotherapy for the Treatment of Breast Cancer

November 17, 2021, 11:30 a.m. – 12:30 p.m. ET

Case Studies in Immunotherapy for the Treatment of Urothelial Cancer

November 5, 2021, 5:30 – 6:30 p.m. ET

Learn more and register at:
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