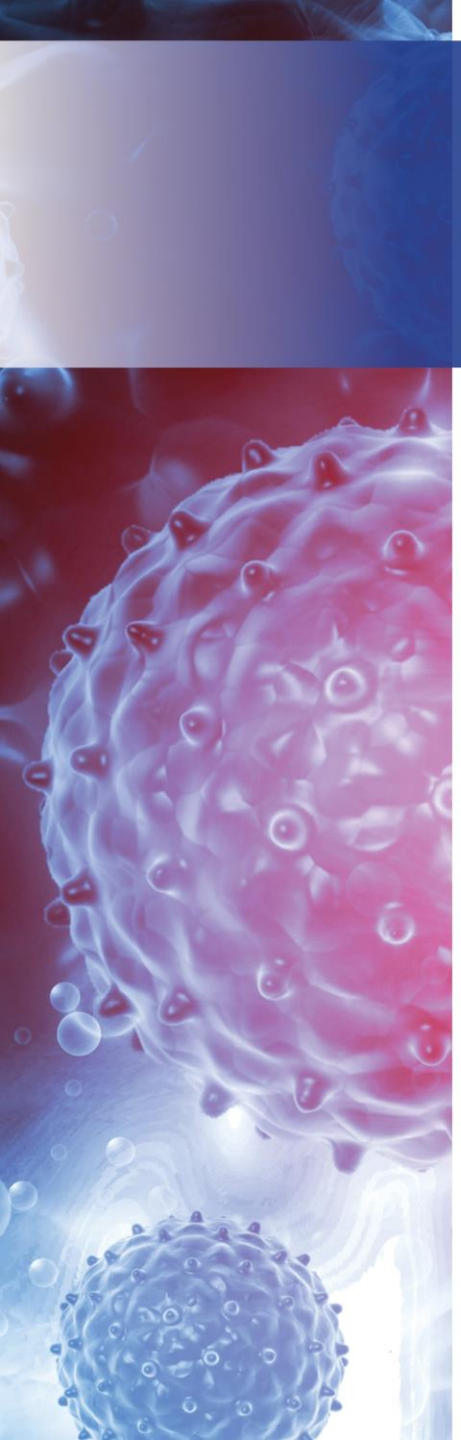
Improving Survivorship for Patients on Immune Checkpoint Inhibitors

Implications for Pharmacists



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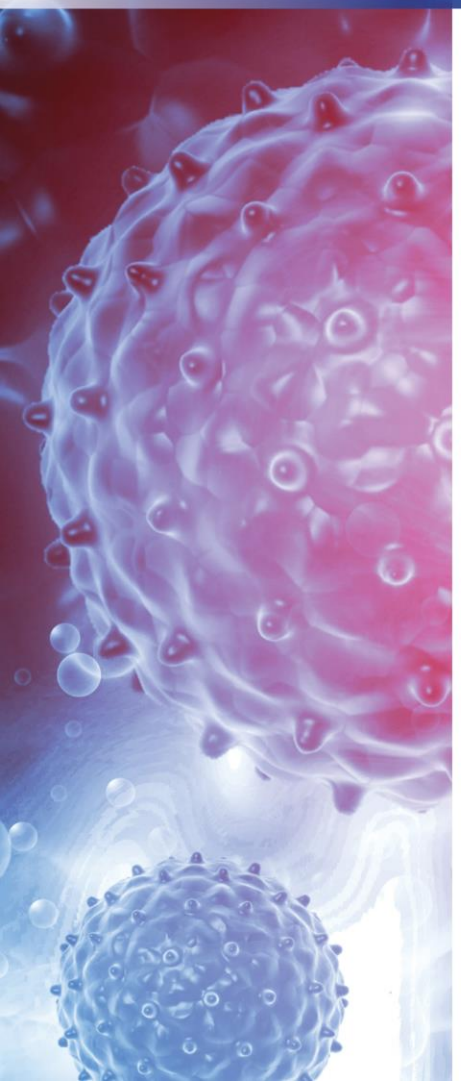
Disclosures



Dr. Adams has disclosed that he has no actual or potential conflict of interest in relation to this program.

The clinical reviewer, Megan May, PharmD, BCOP has no actual or potential conflicts of interest in relation to this program.

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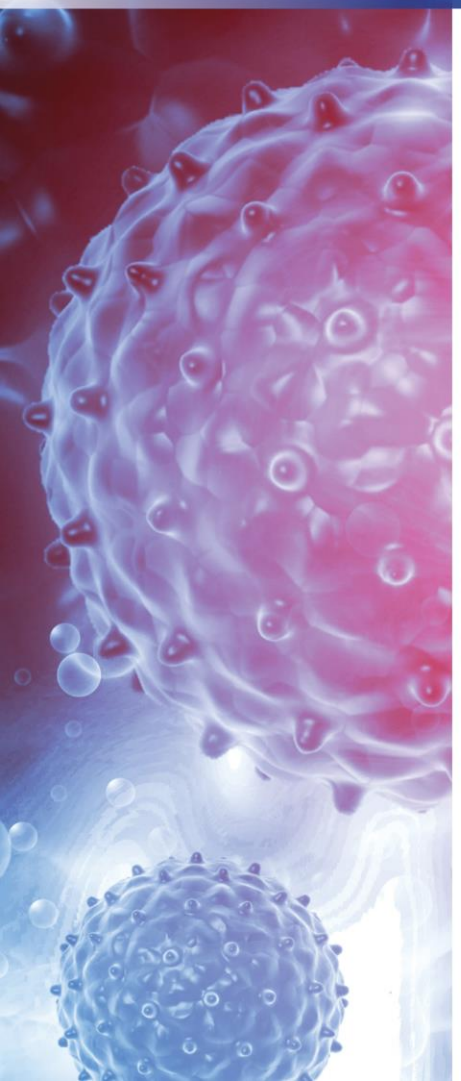

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UAN: 0430-0000-20-127-H01-P
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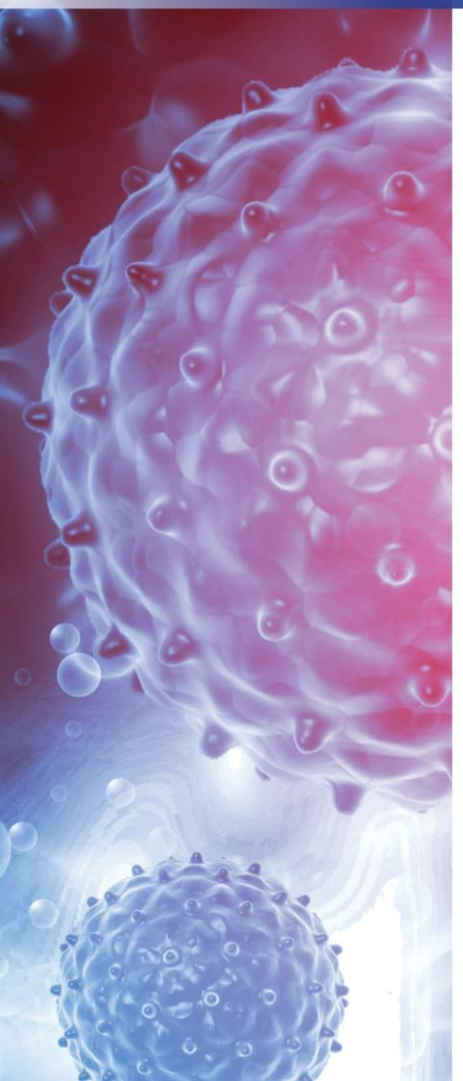
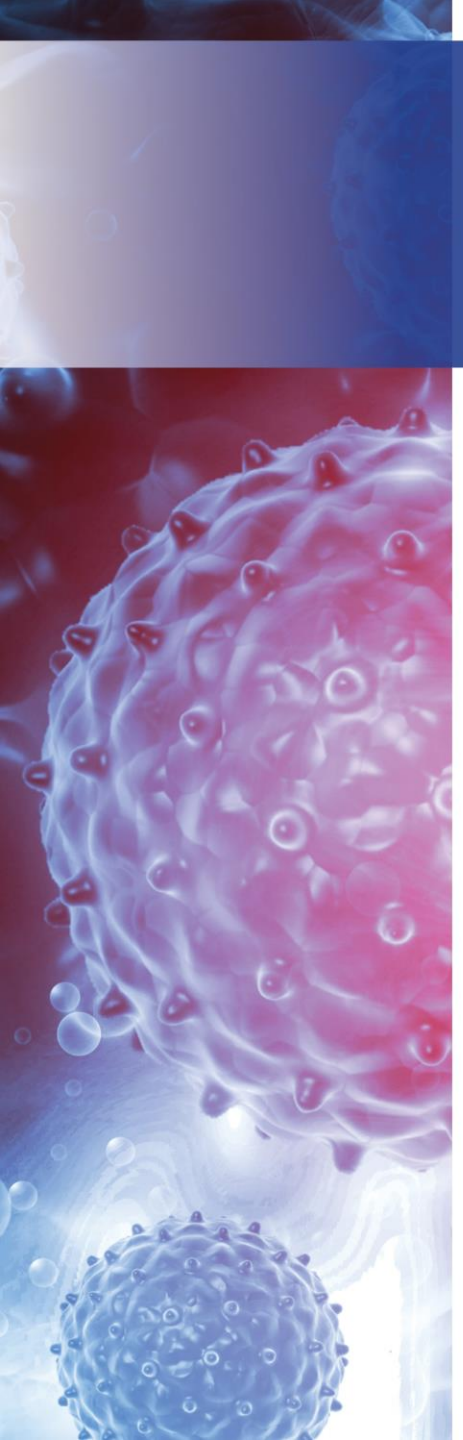
Type of Activity: Application

Learning Objectives

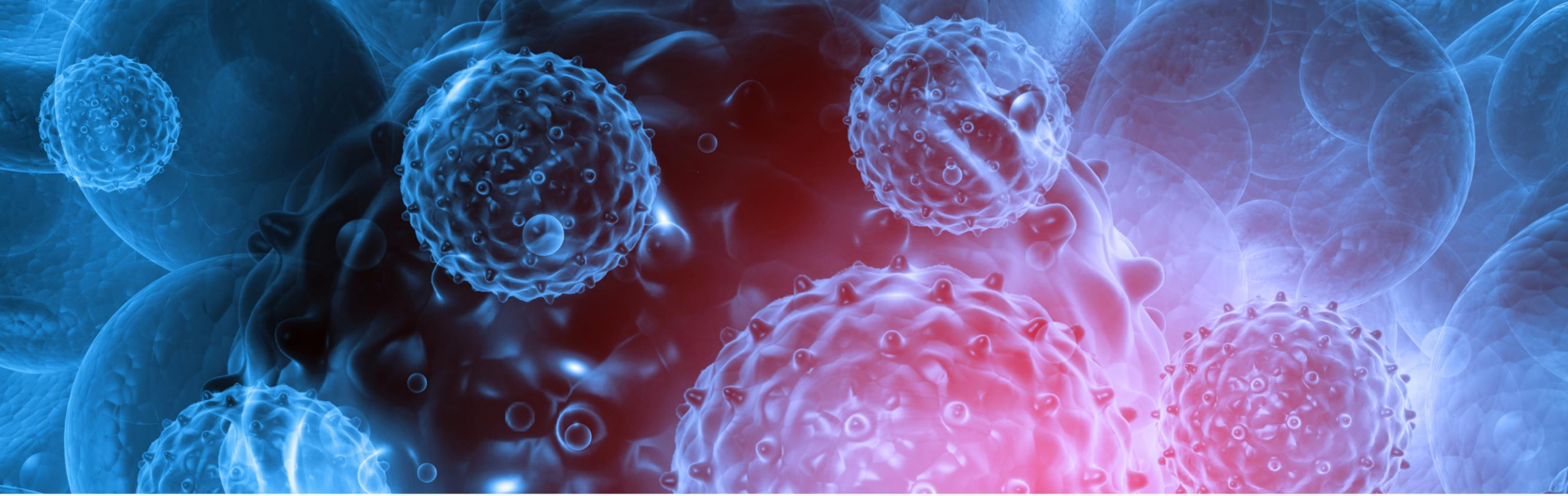


- **Assess** long-term and delayed adverse events and their unique management strategies associated with immune checkpoint inhibitors
- **Identify** issues with and formulate strategies to improve the quality of life for patients actively receiving or post treatment with immune checkpoint inhibitors
- **Recognize** the unique survivorship needs of cancer patients receiving immune checkpoint inhibitors

Optimize Benefit, Minimize Toxicity



- Selecting the best therapy can optimize benefit
- Minimizing toxicity
  - Monitor
    - Patient self-monitoring and query for signs and symptoms at every visit
    - Laboratory monitoring to define toxicity
  - Early diagnosis and intervention when toxicity is mild to moderate in severity
    - Less morbidity for patient
    - Longer therapy duration to optimize efficacy
- Knowing what to expect and communicating with patients and caregivers is essential



What are Immune Checkpoint Inhibitors (ICI)?

Drugs/Mechanism of Action

Checkpoint Inhibitors

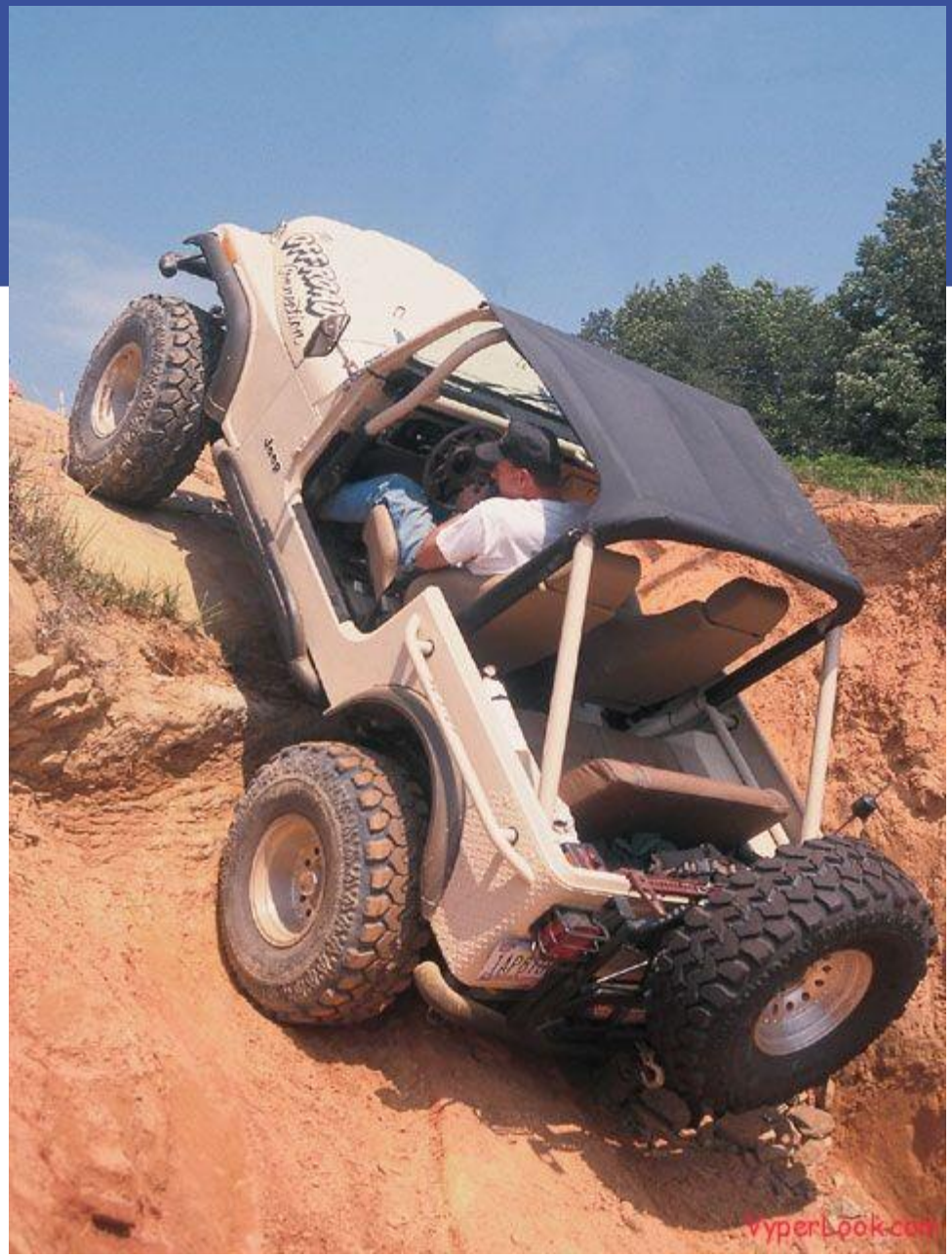
Drug	Indications (see prescribing information for details)
Atezolizumab (PD-L1i)	NSCLC, bladder CA, SCLC, breast CA (TNBC), HCC, melanoma
Avelumab (PD-L1i)	Merkel cell carcinoma, bladder CA, renal cell CA
Durvalumab (PD-L1i)	NSCLC, bladder CA, SCLC
Nivolumab (PD-1i)	Melanoma, NSCLC, SCLC, renal cell CA, Hodgkin lymphoma, head and neck CA, bladder CA, MSI-H/dMMR colorectal CA, hepatocellular CA, mesothelioma, esophageal CA
Pembrolizumab (PD-1i)	Melanoma, NSCLC, SCLC, Hodgkin lymphoma, head and neck CA, bladder CA, MSI-H/dMMR CA, gastric CA, NHL, esophageal CA, cervical CA, hepatocellular CA, Merkel cell carcinoma, renal cell CA, endometrial CA, TMB-H, cutaneous squamous cell carcinoma
Cemiplimab (PD-1i)	Cutaneous squamous cell carcinoma
Ipilimumab (CTLA-4i)	Melanoma, renal cell CA, MSI-H/dMMR colorectal CA, HCC, NSCLC, mesothelioma

Abbreviations: CA, cancer; CTLA-4i, cytotoxic T-lymphocyte-associated protein 4 inhibitor; dMMR, mismatch repair deficient; HCC, hepatocellular carcinoma; MSI-H, microsatellite instability-high; NHL, non-Hodgkin lymphoma; NSCLC, non-small cell lung cancer; PD-1i, programmed cell death protein 1 inhibitor; PD-L1i, programmed death-ligand 1 inhibitor; SCLC, small cell lung cancer; TMB-H, tumor mutation burden-high; TNBC, triple-negative breast cancer

Bavencio [prescribing information]; 2020.; Imflinzi [prescribing information]; 2020.; Keytruda [prescribing information]; 2020.; Libtayo [prescribing information]; 2020.; Opdivo [prescribing information]; 2020.; Tecentriq [prescribing information]; 2020.; Yervoy [prescribing information]; 2020.

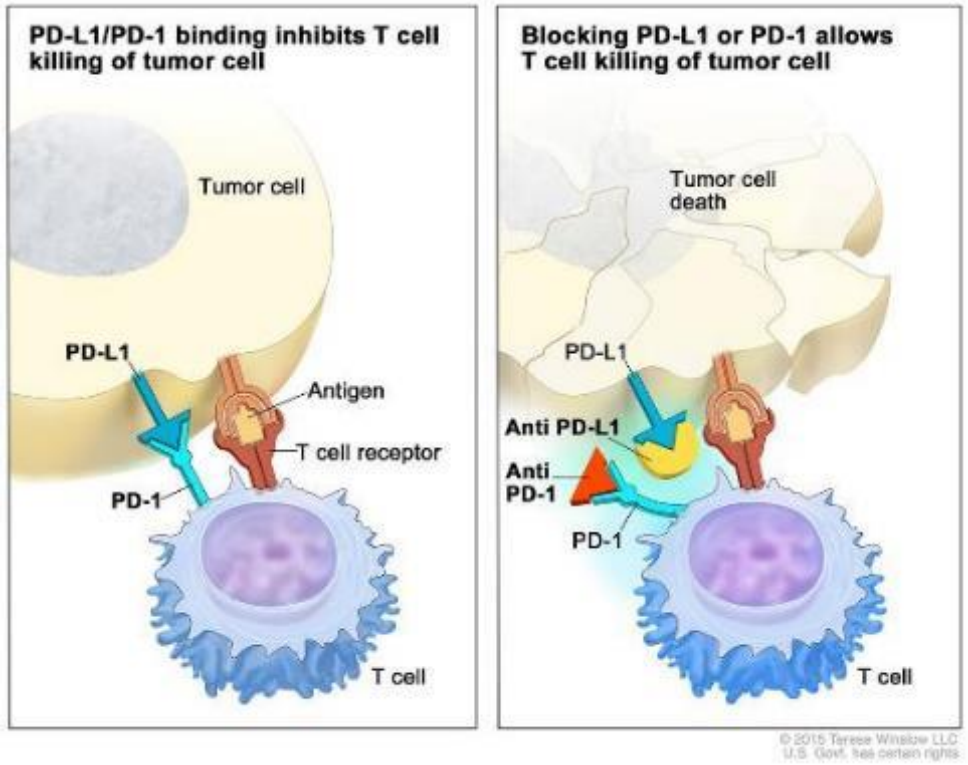
Getting Things Moving

Give it the gas or take off the brakes?



Approved Immune Checkpoint Inhibitors for NSCLC

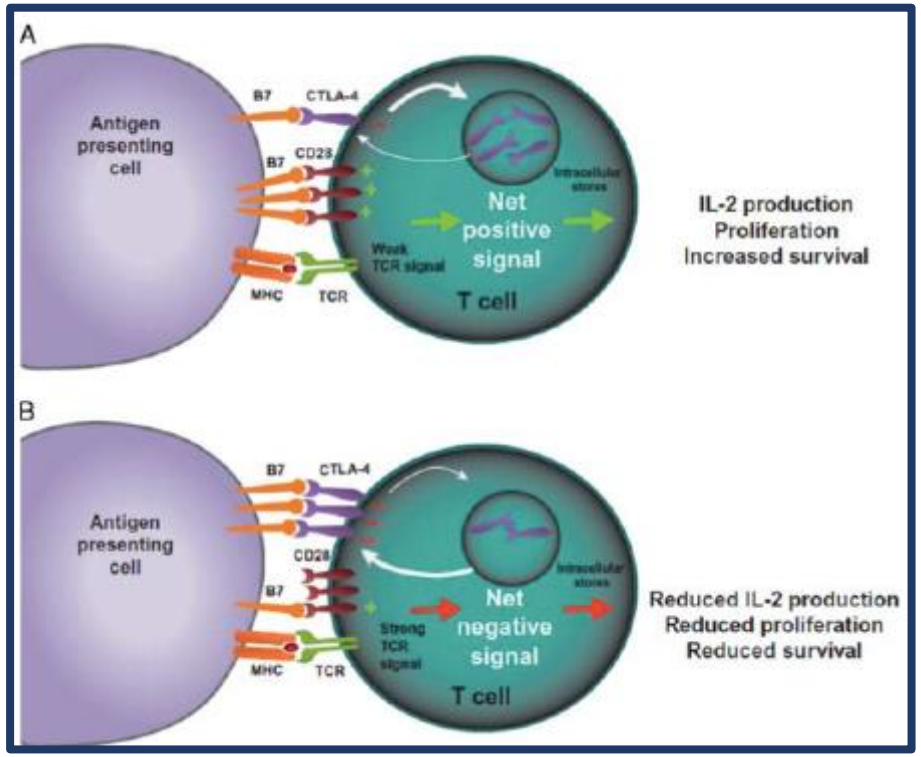
- **PD-1 blocking antibodies**
  - **Nivolumab**
  - **Pembrolizumab**
  - **Cemiplimab**
- **PD-L1 blocking antibodies**
  - **Atezolizumab**
  - **Avelumab**
  - **Durvalumab**



Abbreviations: NSCLC, non-small cell lung cancer; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1.
With permission from National Cancer Institute/Terese Winslow. https://www.cancer.gov/news-events/cancer-currents-blog/2015/pembrolizumab-nsclc.

CTLA-4 Pathway

- **CTLA-4 is expressed exclusively on T cells after activation**
- **CTLA-4 competes with costimulatory molecule CD28 to bind to B7**
- **This checkpoint occurs at an early stage of T- cell activation, when T cells are still within primary lymphoid tissue**
- **Ipilimumab is a CTLA-4 inhibitor**



Abbreviations: CTLA-4, cytotoxic T-lymphocyte associated antigen 4; IL, interleukin.
With permission from Buchbinder EI, Desai A. *Am J Clin Oncol.* 2016;39:98-106.

Pharmacokinetic Parameters

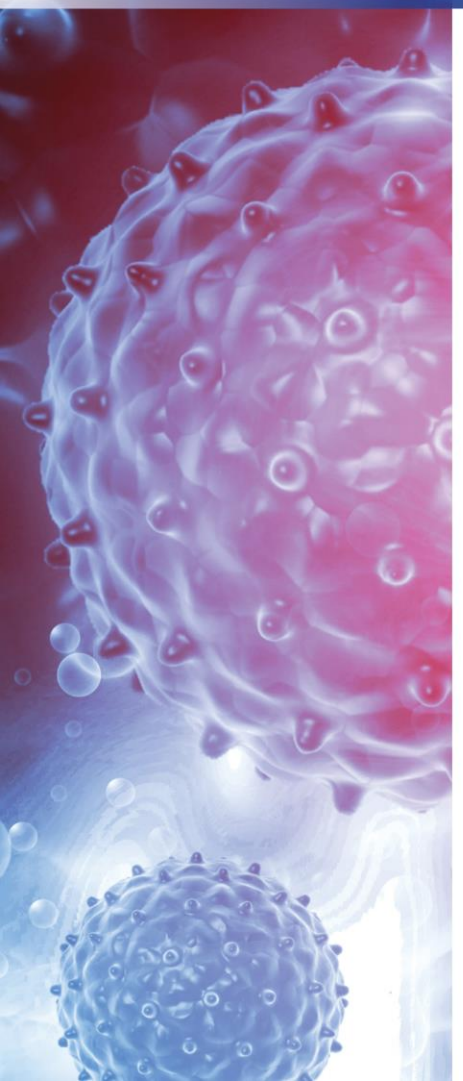
Agents Approved for NSCLC Treatment

	Binding	T ½	Vd	Clearance
Atezolizumab	PD-L1	27 days	6.9 L	↓ over time
Avelumab	PD-L1	6.1 days	4.7 L	↓ over time
Cemiplimab	PD1	19 days	5.2 L	↓ over time
Durvalumab	PD-L1	18 days	5.6 L	↓ over time
Ipilimumab	CTLA-4	15 days	7.2 L	
Nivolumab	PD1	25 days	6.8 L	↓ over time
Pembrolizumab	PD1	22 days	6 L	↓ over time

Abbreviations: CTLA-4, cytotoxic T-lymphocyte-associated protein 4; PD1, programmed cell death protein 1; PD-L1, programmed death ligand 1; T ½, half-life; Vd, volume of distribution

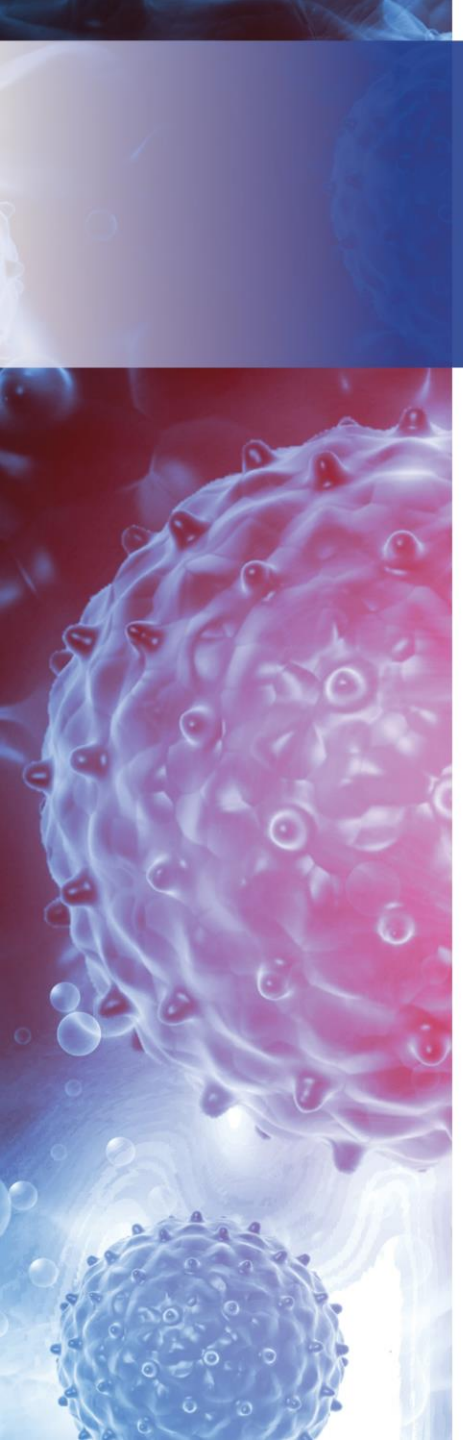
1. Pembrolizumab [package insert]. 2. Nivolumab [package insert]. 3. Durvalumab [package insert]. 4. Atezolizumab [package insert]. 5. Avelumab [package insert]. 6. Cemiplimab [package insert]. 7.Trinh, VA, Hagen, B. J Oncol Pharm Pract. 2013;19:195–201

Toxicity and Timing



- Comparison to cytotoxic therapy
- Monotherapy with immuno-oncology (IO) therapies
- Combination IO therapies
- In combination with cytotoxic therapy
- Compared to targeted therapies
- In combination with targeted therapies

ARS Question #1:



PJ is a 65 YOF with node positive, hormone receptor positive stage II breast cancer. The plan is to treat PJ with docetaxel and cyclophosphamide (TC).

What toxicity would you anticipate with this regimen?

- Neutropenia +/- infection
- Nausea and vomiting
- Alopecia
- All the above

Toxicity Reported from a Randomized Clinical Trial

Frequency of the Most Common Adverse Events (all grades)

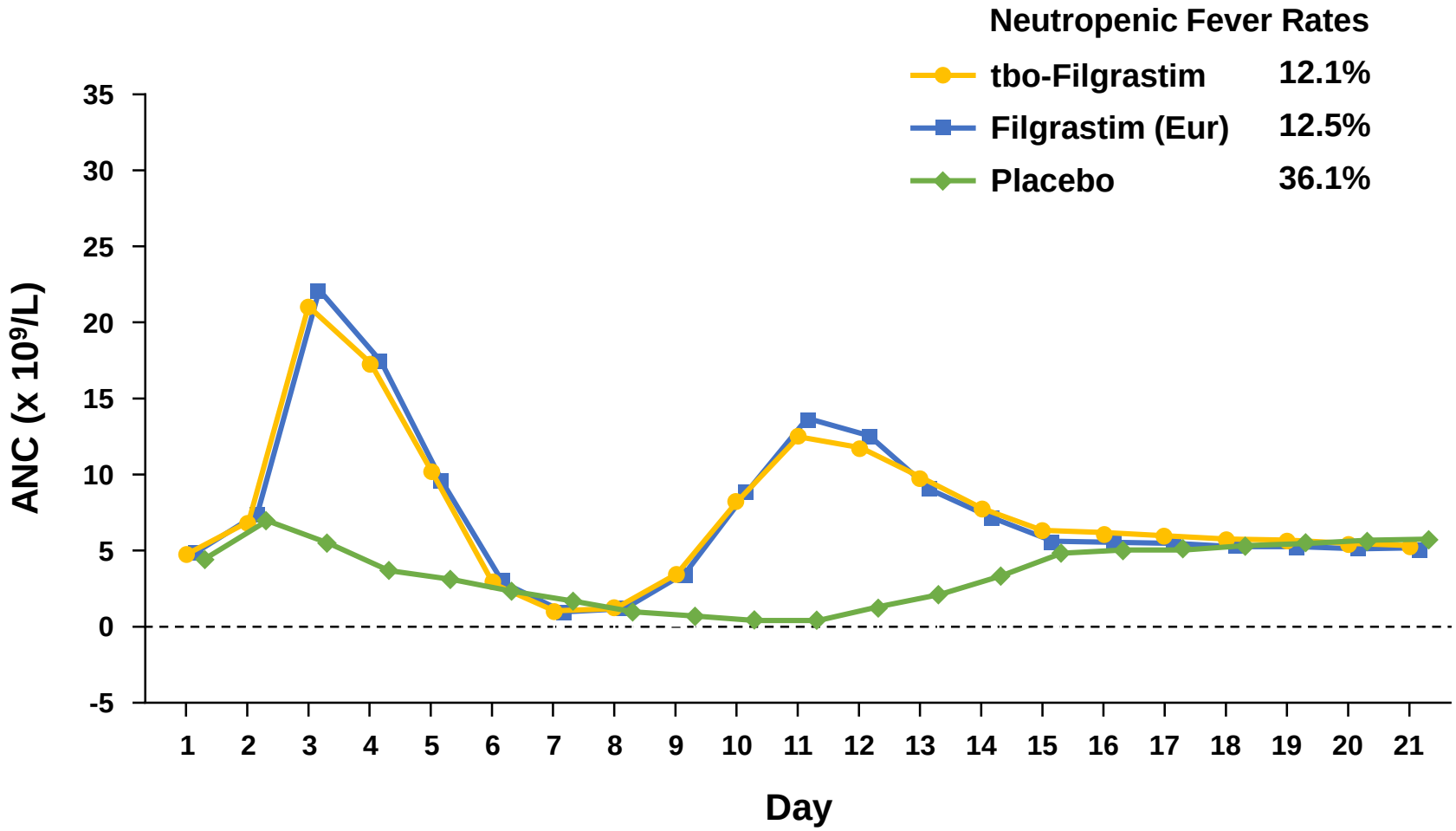
	TC Patients (n = 506)			
	Grade (%)			
Adverse Event*	1	2	3	4
Hematologic				
Anemia	3	2	< 1	< 1
Neutropenia	< 1	1	10	51
Thrombocytopenia	< 1	< 1	0	< 1
Nonhematologic				
Asthenia	43	32	3	< 1
Edema	27	7	< 1	0
Fever	14	5	3	2
Infection	8	4	7	< 1
Myalgia	22	10	1	< 1
Nausea	38	13	2	< 1
Phlebitis	8	3	< 1	0
Stomatitis	23	10	< 1	< 1
Vomiting	9	5	< 1	< 1

Neutropenia - 63%
Infection – 20%
Nausea – 54%

Alopecia not reported
76% from the PI

Jones, SE, et al. J Clin Oncol 24:5381-538
http://products.sanofi.us/taxotere/Taxotere.pdf

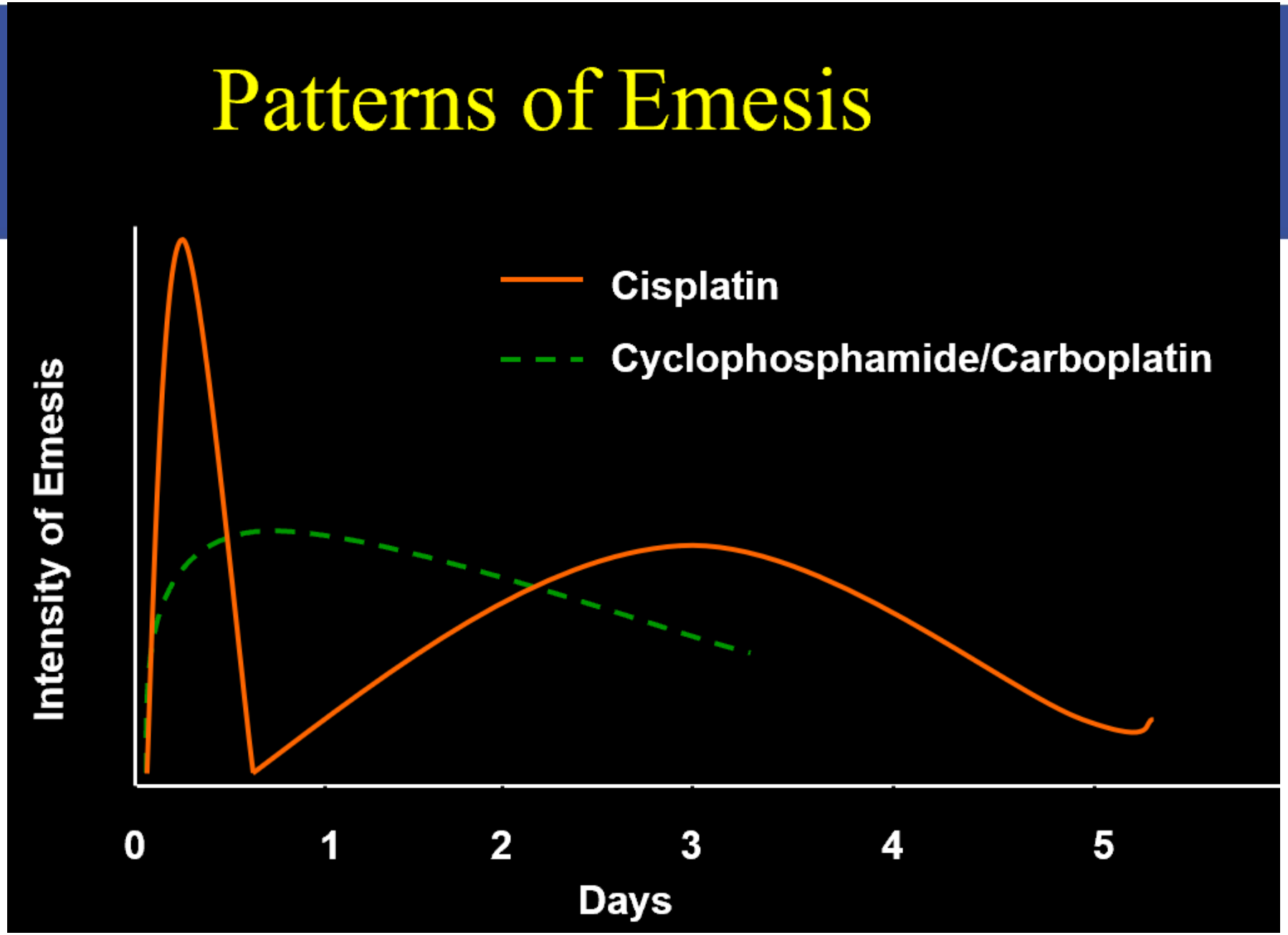
Timing of Neutropenia w/ and w/o G-CSF



Del Giglio A, et al. *BMC Cancer.* 2008;8:332.

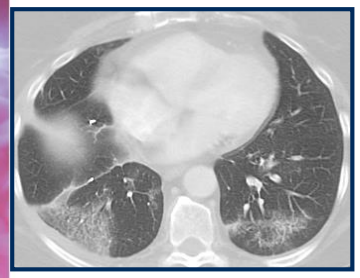
Abbreviation: G-CSF, granulocyte colony-stimulating factor

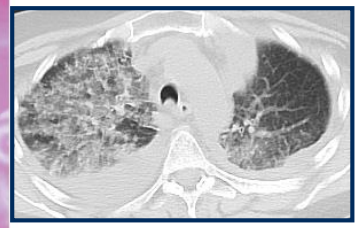
Patterns of Emesis

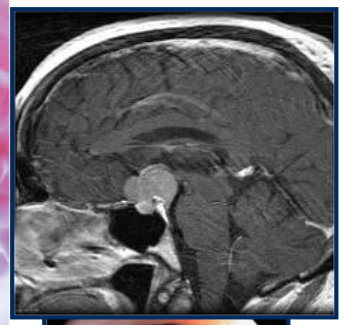


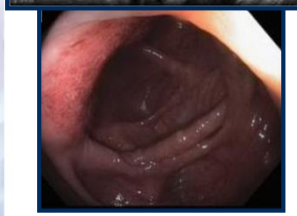
Martin M. *Oncology.* 1996;53(suppl 1):26-31.

Immune-Related Adverse Events by System









<u>Pulmonary</u>: Pneumonitis, interstitial lung disease

<u>Endocrine</u>: Thyroiditis, hypothyroidism, hyperthyroidism, hypophysitis, adrenal insufficiency

<u>Cardiac</u>: Pericarditis, myocarditis

<u>GI</u>: Enterocolitis, hepatitis, gastritis, pancreatitis

<u>Heme</u>: Red cell aplasia, aplastic anemia, autoimmune neutropenia

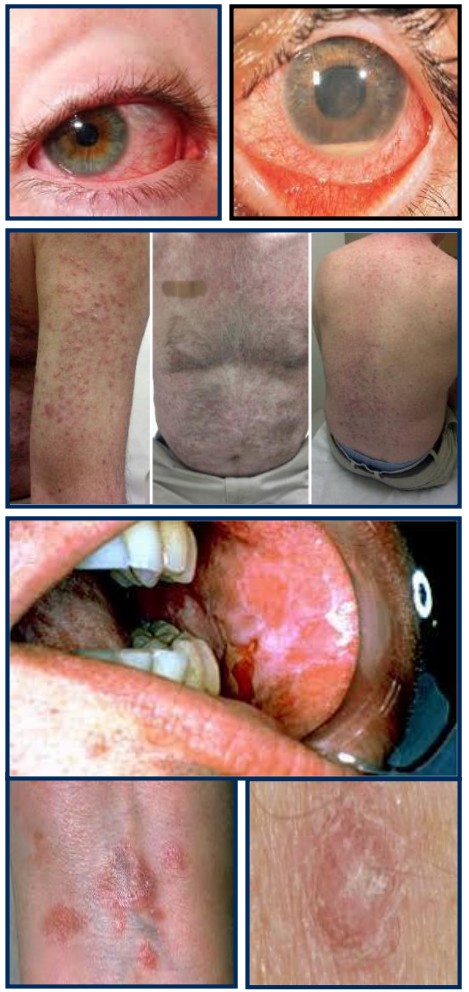
<u>Ocular</u>: Uveitis, conjunctivitis, scleritis, orbital inflammation

<u>Skin</u>: Vitiligo, psoriasis, lichenoid dermatitis

<u>Kidney</u>: Nephritis, renal tubular acidosis

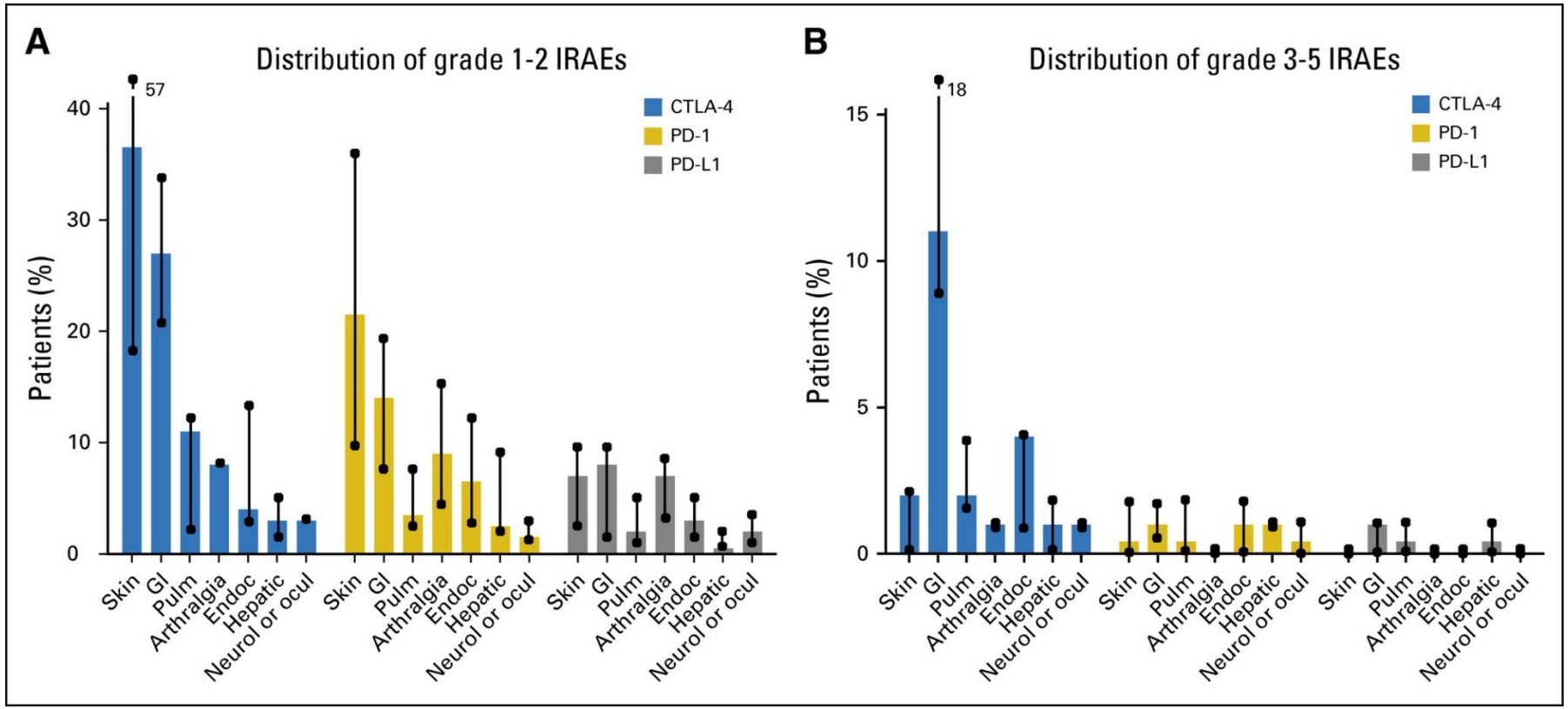
<u>Musculoskeletal</u>: Myositis, myalgias

<u>Neurologic</u>*:* Neuropathy, meningitis, Guillain-Barré syndrome, myasthenia gravis



Ramos-Casals, M., *et al. Nat Rev Dis Primers* 2020;6:38:1-21

Checkpoint Inhibitor Toxicity

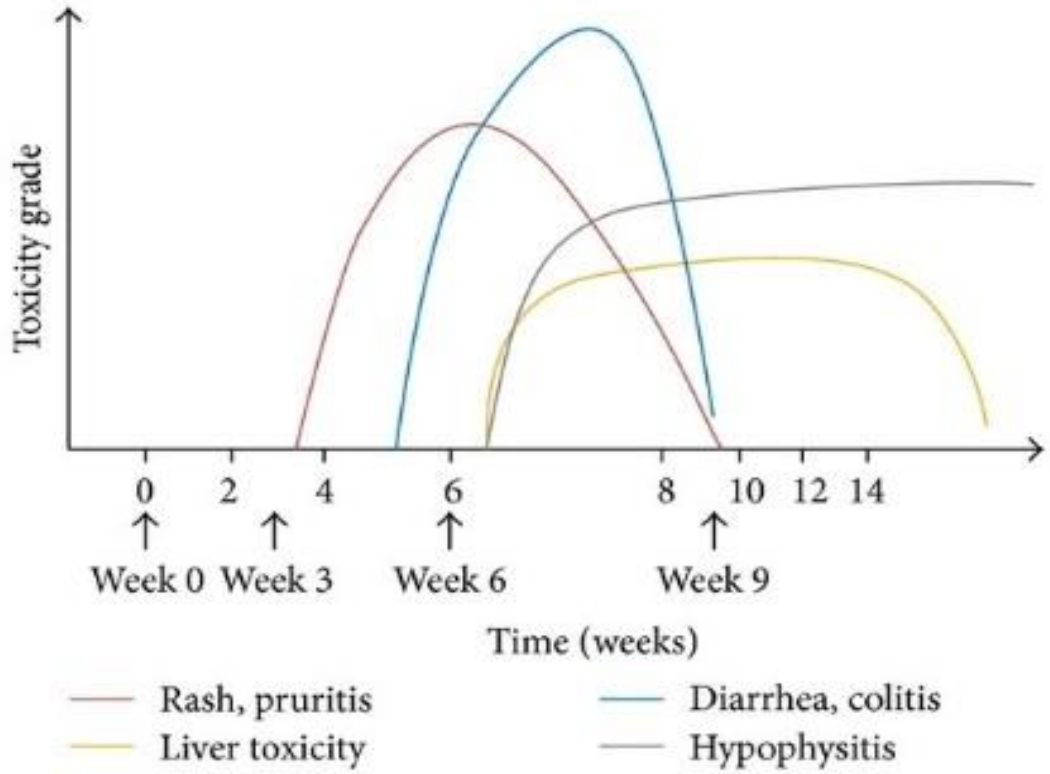


Distribution of (A) grade 1 to 2 and (B) grade 3 to 5 irAEs for all tumor types in the main clinical trials with anti–CTLA-4, anti-PD-1, or anti–PD-L1 antibodies as single therapies. The values quoted are the median (range) irAE rates for the set of clinical trials as a whole. Adapted from Michot JM, et al. *Eur J Can.* 2016;54:139-49.

Abbreviations: CTLA-4, cytotoxic T-lymphocyte-associated protein 4; Endoc, endocrinology; GI, gastrointestinal; irAE, immune-related adverse events; Neurol, neurology; Ocul, ocular; Pulm, pulmonary; PD1, programmed cell death protein 1; PD-L1, programmed death ligand 1

Pattern of Immune-Related Adverse Events

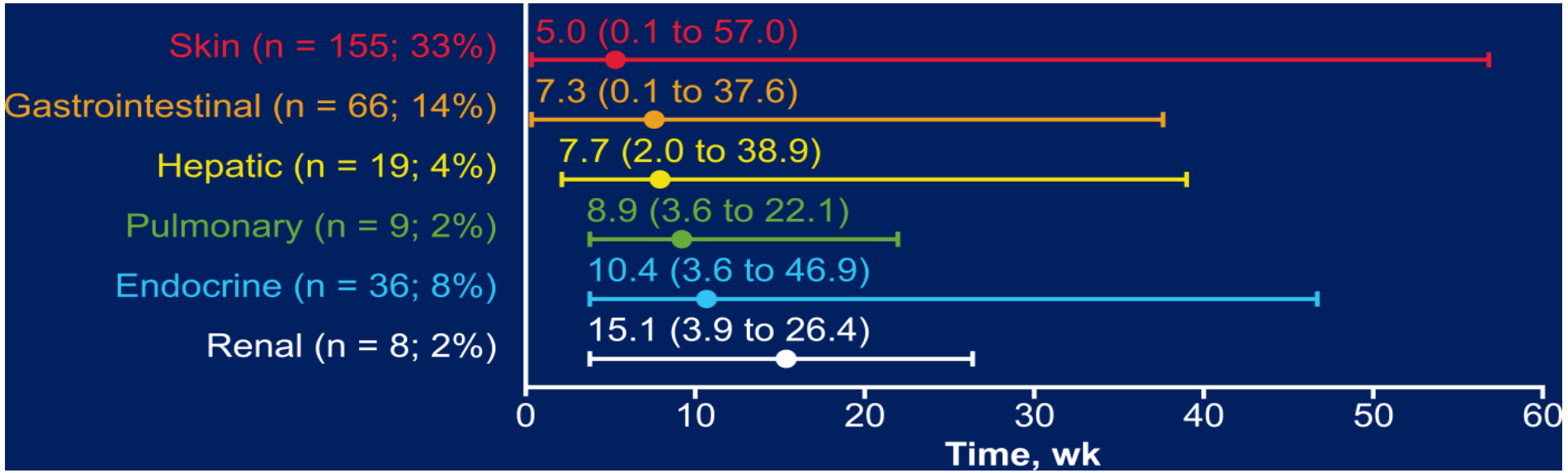
- Onset:
  - Average is 6–12 weeks after therapy initiation
    - Within days of the first dose
    - After several months of treatment
    - After discontinuation of therapy
- Severity: Asymptomatic to severe and life-threatening
- Increased in combination with other immunotherapy agents, chemotherapy, or radiation



Weber et al. *J Clin Oncol.* 2012;30:2691-2697. For educational purposes only.

Immunotherapy-Related AEs

Time to Onset of Select Treatment-Related AEs (any grade; *N* = 474)

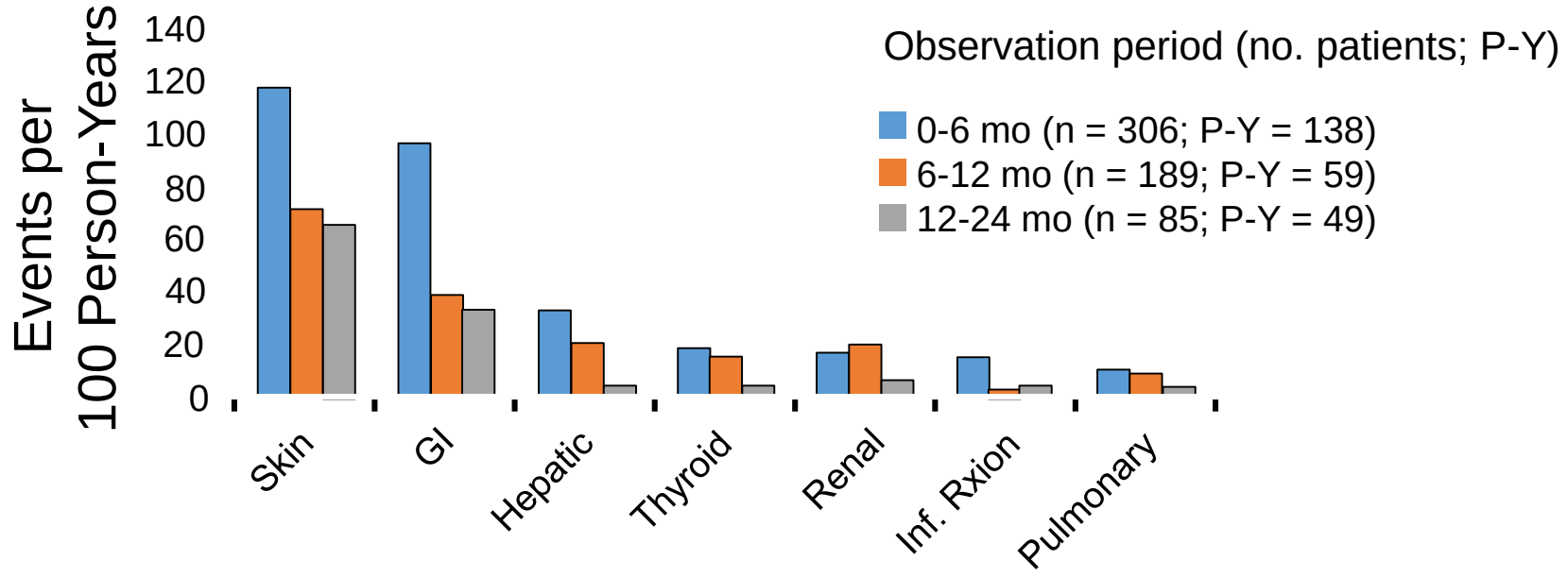


- Median time to onset for treatment-related select AEs ranged from 5 weeks for skin AEs to 15.1 weeks for renal AEs.
- Circles represent median; bars signify ranges.

AE = adverse event.

With direct permission from Dr Wolchok. Wolchok J, et al. *J Clin Oncol*. 2015;33:abstract LBA1.

Nivolumab Toxicity Over Time



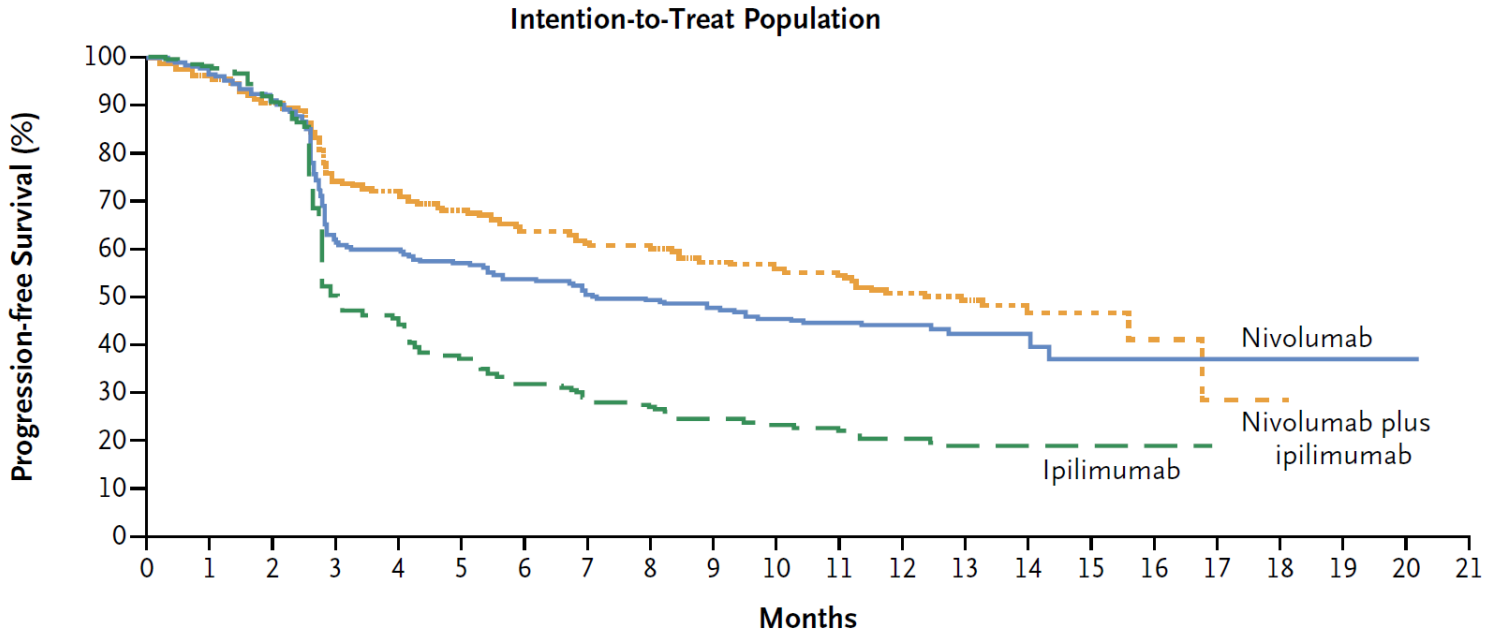
Overall 17% had Grade 3 to 4 toxicities

Abbreviations: Inf. Rxion, infusion reaction; P-Y, person-year

Topalian SL, et al. *J Clin Oncol.* 2014;32(1):1020-1030.

Melanoma: CTLA4 or PD1 or Both?

Antagonism 1 + 1 = 1 Additive 1 + 1 = 2 Synergy 1 + 1 = 3



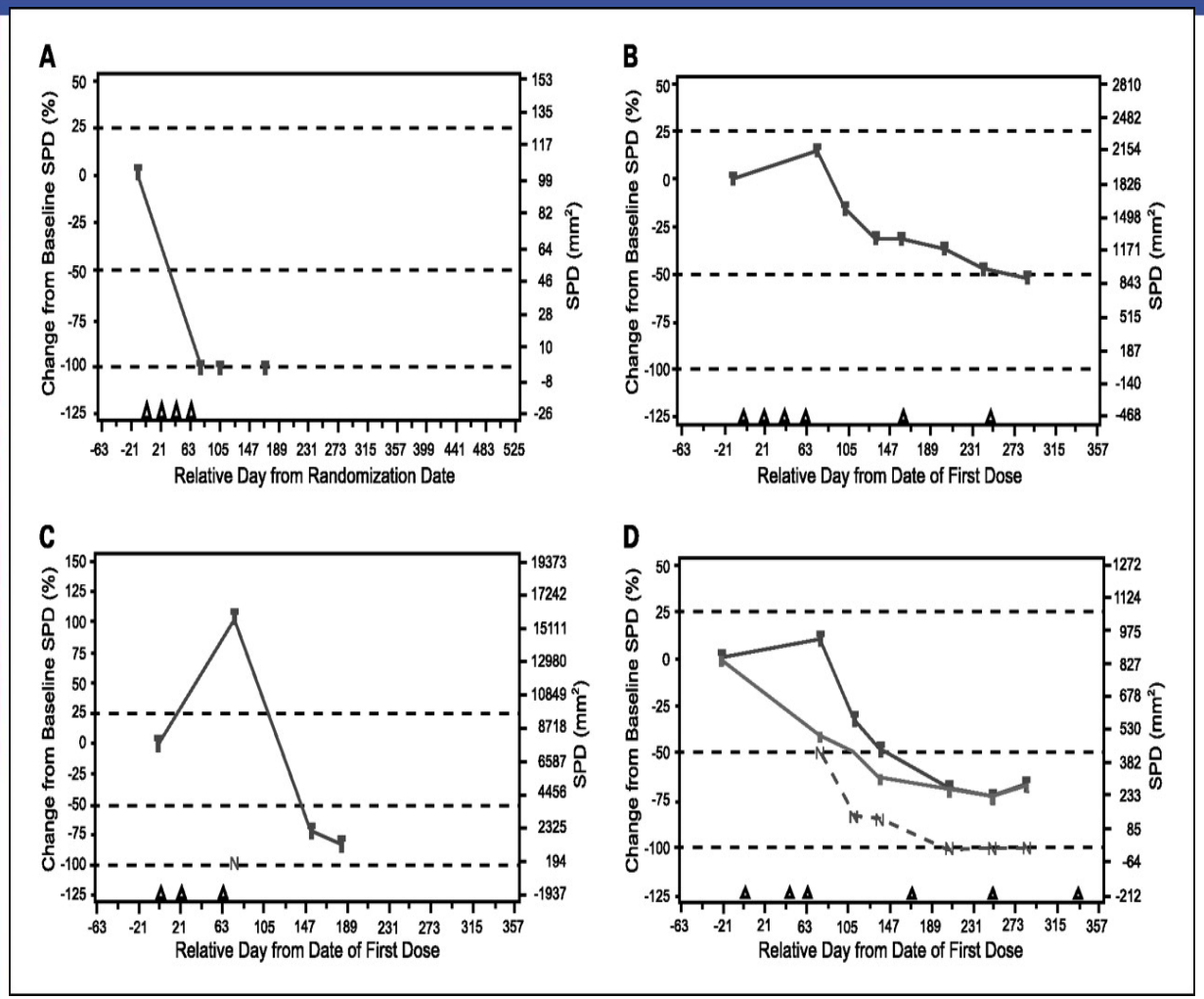
No. at Risk

Nivolumab	316	292	271	177	170	160	147	136	132	124	106	86	50	38	14	9	6	2	1	1	1	0
Nivolumab plus ipilimumab	314	293	275	219	208	191	173	164	163	151	137	116	65	54	18	11	7	2	1	0	0	0
Ipilimumab	315	285	265	137	118	95	77	68	63	54	47	42	24	17	7	4	3	0	0	0	0	0

Abbreviations: CTLA-4, cytotoxic T-lymphocyte-associated protein 4; PD1, programmed cell death protein 1

Larkin, J, et al. N Engl J Med 2015;373:23-34.

Side Bar: Ipilimumab Response Patterns in Advanced Melanoma



- Tumors can get larger before they respond to therapy
- Generally everyone is treated for 12 weeks

Abbreviation: SPD, sum of the product of perpendicular diameters

Wolchok et al. *Clin Cancer Res*. 2009;15:7412-7420.

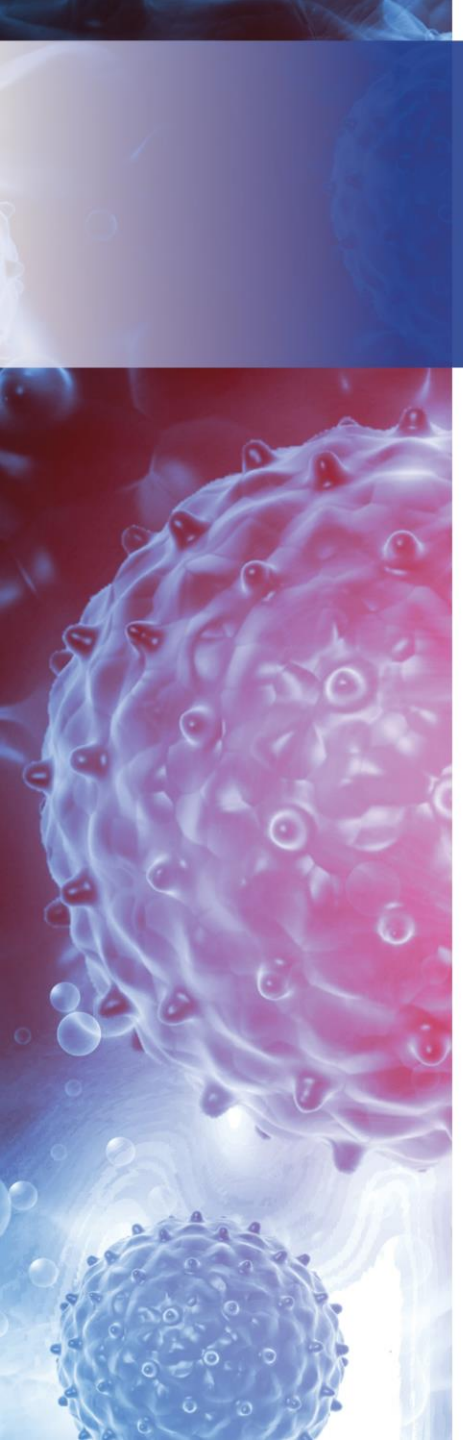
Immune Related Response Criteria (iRECIST)

Comparison of RECIST 1.1 and iRECIST

	RECIST 1.1	iRECIST
Definitions of measurable and non-measurable disease; numbers and site of target disease	Measurable lesions are ≥10 mm in diameter (≥15 mm for nodal lesions); maximum of five lesions (two per organ); all other disease is considered non-target (must be ≥10 mm in short axis for nodal disease)	No change from RECIST 1.1; however, new lesions are assessed as per RECIST 1.1 but are recorded separately on the case report form (but not included in the sum of lesions for target lesions identified at baseline)
Complete response, partial response, or stable disease	Cannot have met criteria for progression before complete response, partial response, or stable disease	Can have had iUPD (one or more instances), but not iCPD, before iCR, iPR, or iSD
Confirmation of complete response or partial response	Only required for non-randomised trials	As per RECIST 1.1
Confirmation of stable disease	Not required	As per RECIST 1.1
New lesions	Result in progression; recorded but not measured	Results in iUPD but iCPD is only assigned on the basis of this category if at next assessment additional new lesions appear or an increase in size of new lesions is seen (≥5 mm for sum of new lesion target or any increase in new lesion non-target); the appearance of new lesions when none have previously been recorded, can also confirm iCPD
Independent blinded review and central collection of scans	Recommended in some circumstances —eg, in some trials with progression-based endpoints planned for marketing approval	Collection of scans (but not independent review) recommended for all trials
Confirmation of progression	Not required (unless equivocal)	Required
Consideration of clinical status	Not included in assessment	Clinical stability is considered when deciding whether treatment is continued after iUPD

"i" indicates immune responses assigned using iRECIST. RECIST=Response Evaluation Criteria in Solid Tumours. iUPD=unconfirmed progression. iCPD=confirmed progression. iCR=complete response. iPR=partial response. iSD=stable disease.

Seymour L, et al. *Lancet Oncol.* 2017;18:e143-e152.



Back to the Toxicity Discussion

Comparison of Toxicity: Ipilimumab, Nivolumab, or Both

Event	Nivolumab (N=313)	Nivolumab plus Ipilimumab (N=313)	Ipilimumab (N=311)
	Grade 3 or 4	Grade 3 or 4	Grade 3 or 4
Any adverse event	136 (43.5)	215 (68.7)	173 (55.6)
Treatment-related adverse event†	51 (16.3)	172 (55.0)	85 (27.3)
Diarrhea	7 (2.2)	29 (9.3)	19 (6.1)
Rash	2 (0.6)	15 (4.8)	6 (1.9)
Nausea	0	7 (2.2)	2 (0.6)
Increase in alanine amino-transferase level	4 (1.3)	26 (8.3)	5 (1.6)
Vomiting	1 (0.3)	8 (2.6)	1 (0.3)
Colitis	2 (0.6)	24 (7.7)	27 (8.7)
Dyspnea	1 (0.3)	2 (0.6)	0
Treatment-related adverse event leading to discontinuation	16 (5.1)	92 (29.4)	41 (13.2)

Larkin, J, et al. N Engl J Med 2015;373:23-34.

Optimizing Dosing to Minimize Toxicity

- Melanoma regimen:
  - Ipilimumab 3 mg/kg IV q3week x 4
  - Nivolumab 1 mg/kg IV q3week x 4, then 3 mg/kg IV q2week
- NSCLC regimen:
  - Ipilimumab 1 mg/kg IV q6week
  - Nivolumab 360 mg IV q3week

Abbreviations: IV, intravenous; NSCLC, non-small cell lung cancer

Hellmann MD, et al. *N Engl J Med.* 2019; 381:2020-2031, Larkin J, et al. N Engl J Med 2015;373:23-34

Nivolumab ± Ipilimumab in NSCLC

Nivolumab plus Ipilimumab (N=576)

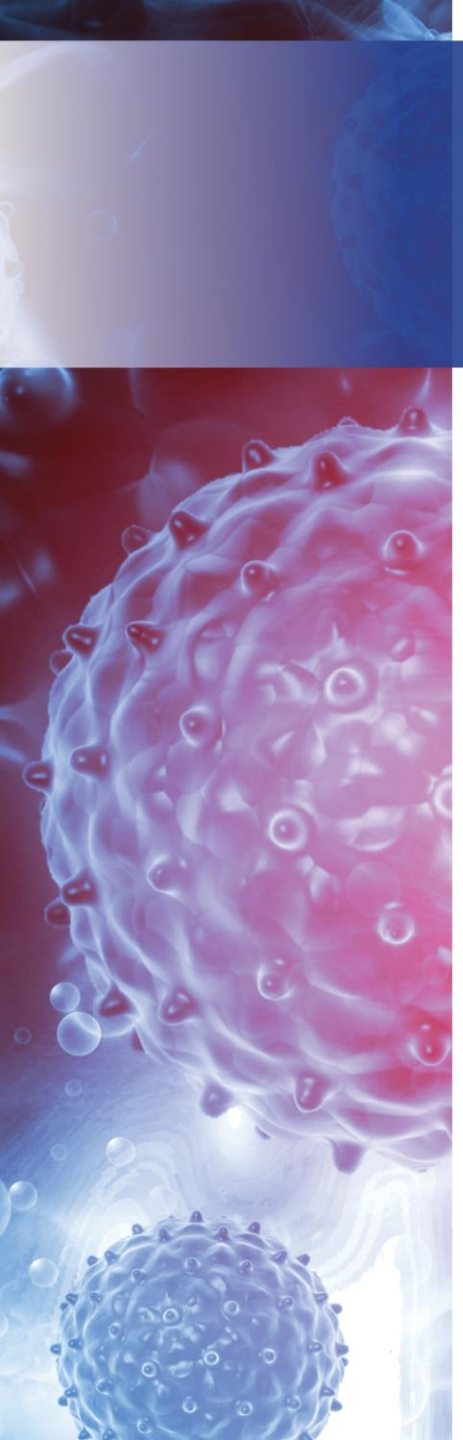
	Grade 3–4
Treatment-related adverse events leading to discontinuation	71 (12.3)

Treatment-Related Select AEs*	All Treated Patients			
	Nivolumab plus Ipilimumab† (N=576)		Nivolumab‡ (N=391)	
	Any Grade	Grade 3–4	Any Grade	Grade 3–4
	number of patients (percent)			
Skin	196 (34.0)	24 (4.2)	83 (21.2)	4 (1.0)
Endocrine	137 (23.8)	24 (4.2)	51 (13.0)	2 (0.5)
Gastrointestinal	105 (18.2)	14 (2.4)	50 (12.8)	4 (1.0)
Hepatic	91 (15.8)	47 (8.2)	42 (10.7)	15 (3.8)
Pulmonary	48 (8.3)	19 (3.3)	30 (7.7)	6 (1.5)
Renal	25 (4.3)	4 (0.7)	6 (1.5)	3 (0.8)
Hypersensitivity/Infusion reaction	23 (4.0)	0	17 (4.3)	2 (0.5)

Minimum follow-up was 28.3 months.

Appendix: Hellman, et al. N Engl J Med 2019;381:2020-31.

Comparison of IO vs Chemotherapy



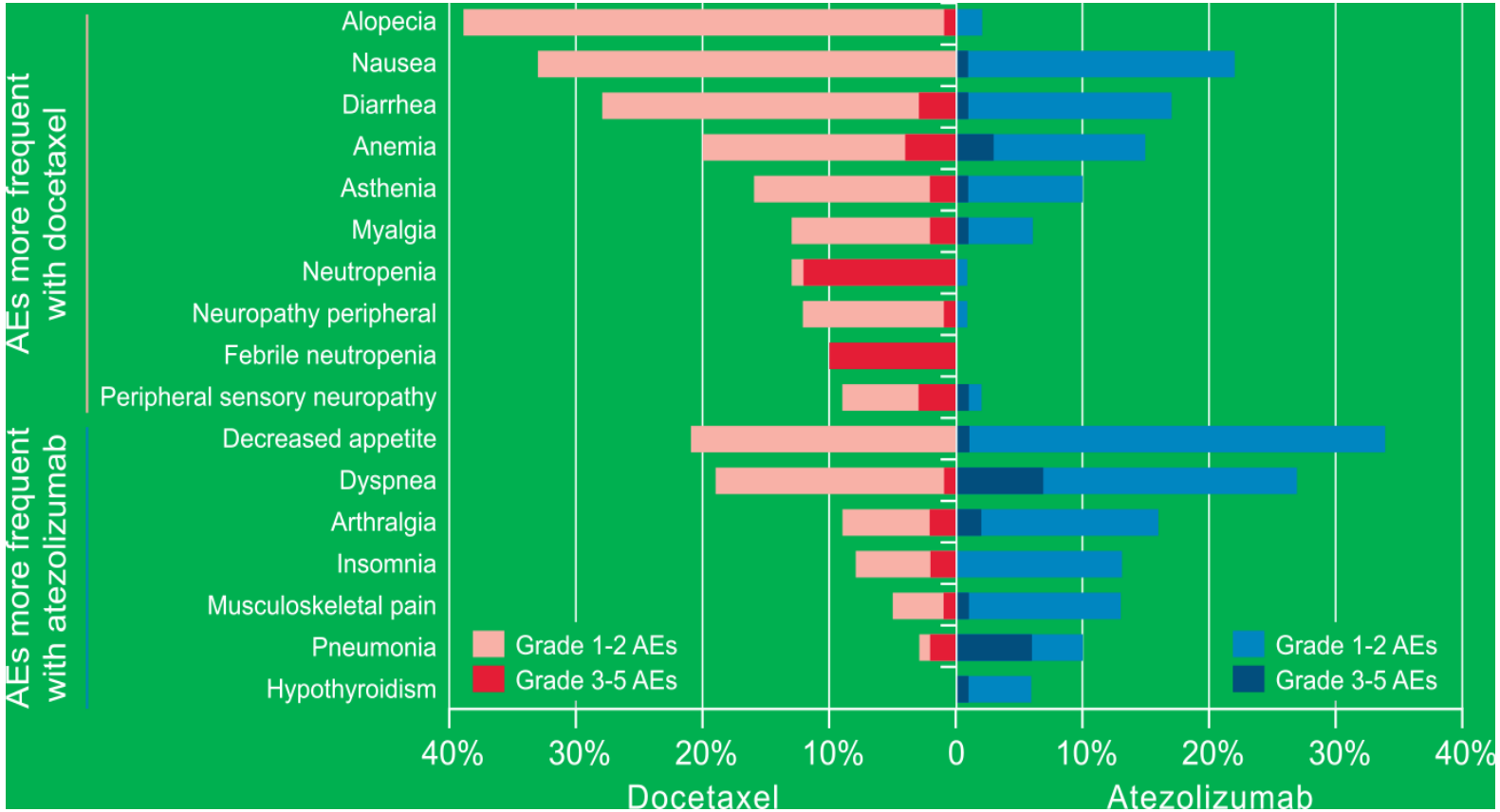
Monotherapy

- NSCLC – Docetaxel vs Atezolizumab

Combination ICI vs Chemotherapy

- NSCLC - Nivolumab + Ipilimumab vs Chemotherapy

POPLAR: All-Cause AEs (≥5% difference between arms)



- AE profiles consistent with previous studies
- For atezolizumab, other immune-mediated AEs (any grade) included:
  - AST increased (4%)
  - ALT increased (4%)
  - Pneumonitis (2%)
  - Colitis (1%)
  - Hepatitis (1%)

- **Dry skin, stomatitis, and nail disorder were additional AEs with ≥5% higher frequency with docetaxel.**
- **Safety population includes patients who received any amount of either study treatment.**
- **Data cut-off January 30, 2015**

ALT = alanine aminotransferase; AST = aspartate aminotransferase.

With direct permission from Dr Spira. Spira et al. *J Clin Oncol.* 2015;33:abstract 8010.

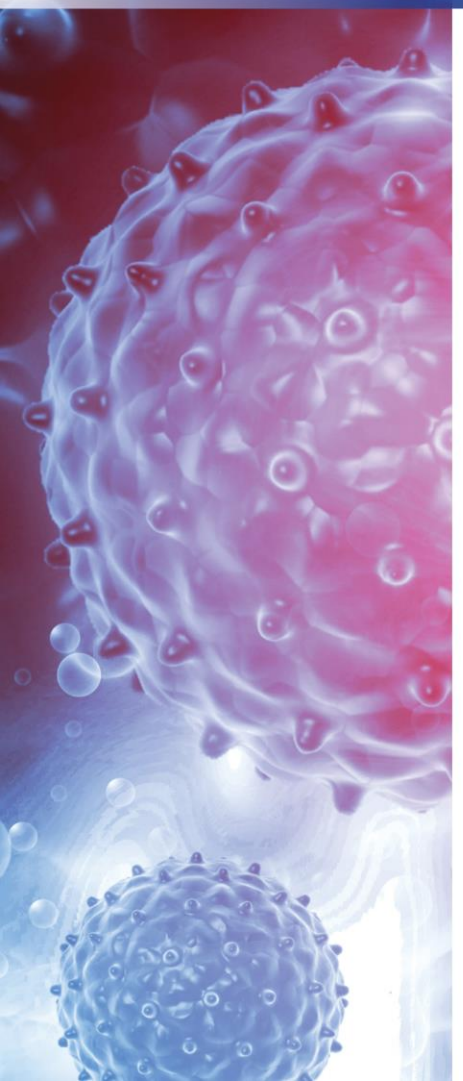
Nivolumab + Ipilimumab vs Chemo in NSCLC

Adverse Event	Nivolumab plus Ipilimumab (N=576)		Chemotherapy (N=570)	
	Any Grade	Grade 3–4	Any Grade	Grade 3–4
Treatment-related adverse events				
All events	442 (76.7)	189 (32.8)	467 (81.9)	205 (36.0)
Reported in ≥15% of patients				
Diarrhea	98 (17.0)	10 (1.7)	55 (9.6)	4 (0.7)
Rash	98 (17.0)	9 (1.6)	30 (5.3)	0
Fatigue	83 (14.4)	10 (1.7)	108 (18.9)	8 (1.4)
Decreased appetite	76 (13.2)	4 (0.7)	112 (19.6)	7 (1.2)
Nausea	57 (9.9)	3 (0.5)	206 (36.1)	12 (2.1)
Anemia	22 (3.8)	8 (1.4)	188 (33.0)	66 (11.6)
Neutropenia	1 (0.2)	0	98 (17.2)	54 (9.5)
Treatment-related serious adverse events	141 (24.5)	106 (18.4)	79 (13.9)	61 (10.7)
Treatment-related adverse events leading to discontinuation†	104 (18.1)	71 (12.3)	52 (9.1)	28 (4.9)

More common w/ IO

More common w/ Chemo

Comparison of IO vs Targeted Therapy



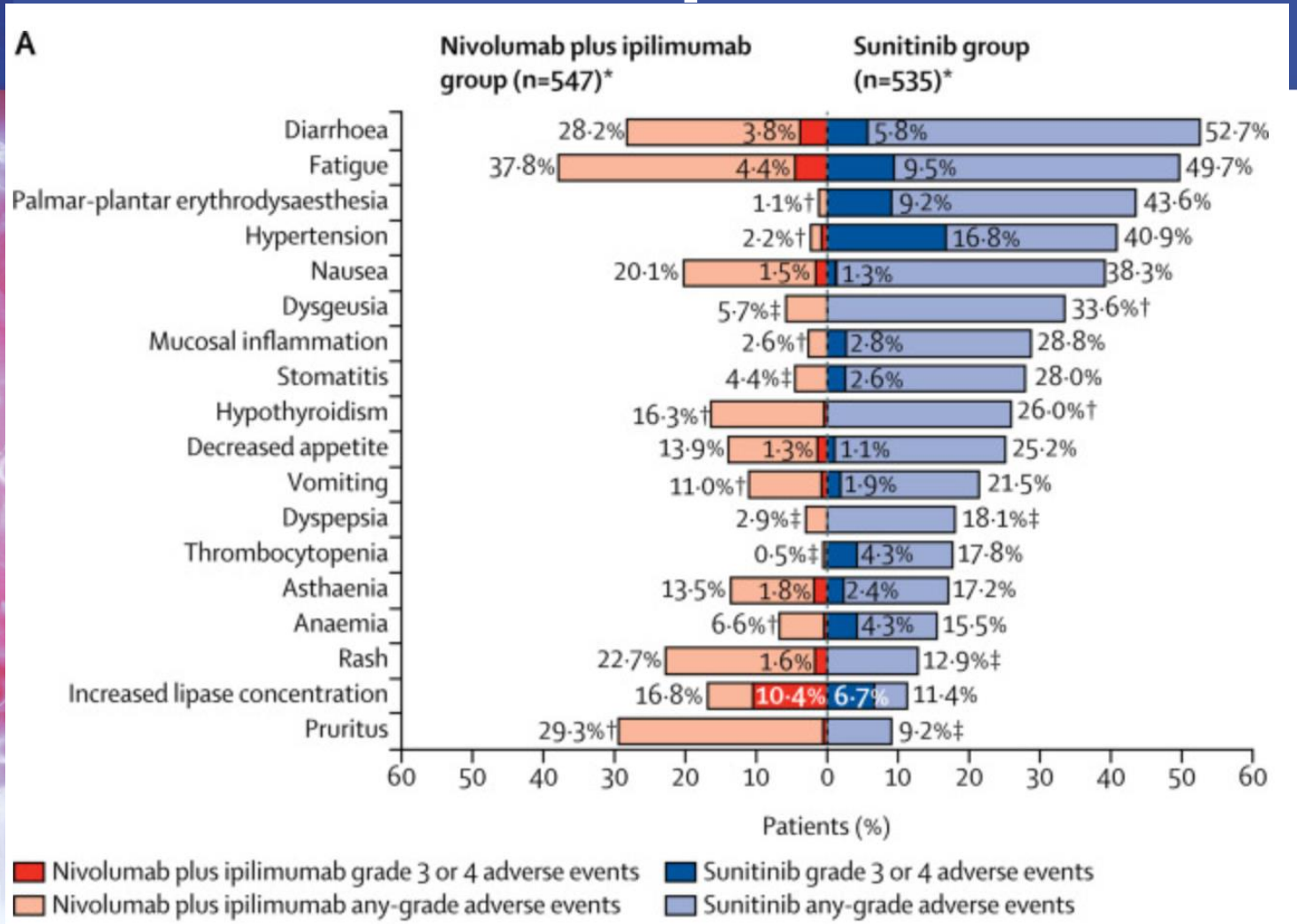
Combination IO vs TKI

- Renal Cell – Nivolumab + Ipilimumab vs Sunitinib

Combination IO and TKI

- Renal Cell – Avelumab + Axitinib vs Sunitinib

Nivolumab + Ipilimumab vs Sunitinib



Nivo/Ipi

Less toxic overall

Grade 3-4 Increase in Lipase

Higher w/ Nivo/Ipi

More effective – PFS and OS

Motzer, R.J, et al. Lancet Oncol, 2019;10:1370-85.

Abbreviations: Ipi, ipilimumab; Nivo, nivolumab; OS, overall survival; PFS, progression-free survival

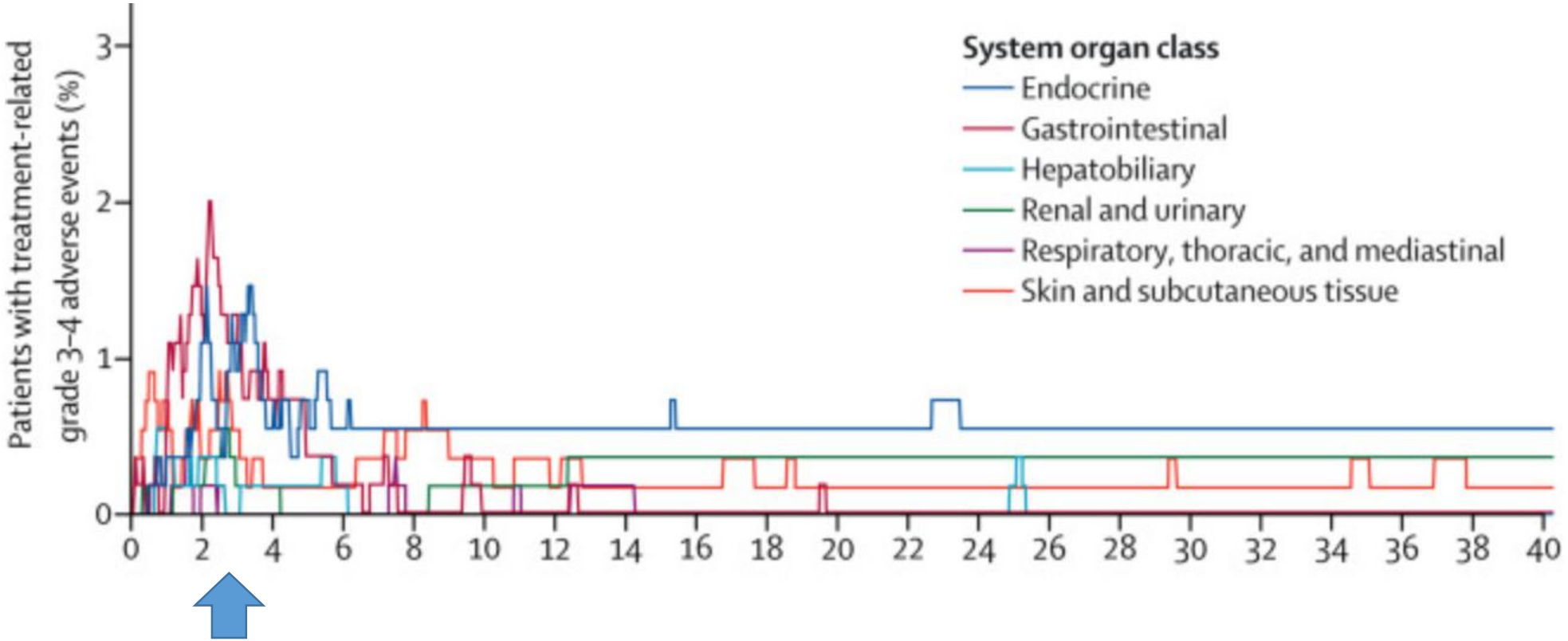
Avelumab + Axitinib vs Sunitinib

Grade 3/4 > 5%

Variable	Avelumab plus Axitinib (N=434)		Sunitinib (N=439)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
	number of patients (percent)			
Patients with any events	432 (99.5)	309 (71.2)	436 (99.3)	314 (71.5)
Diarrhea	270 (62.2)	29 (6.7)	209 (47.6)	12 (2.7)
Hypertension	215 (49.5)	111 (25.6)	158 (36.0)	75 (17.1)
Fatigue	180 (41.5)	15 (3.5)	176 (40.1)	16 (3.6)
Nausea	148 (34.1)	6 (1.4)	172 (39.2)	7 (1.6)
Palmar–plantar erythrodysesthesia syndrome	145 (33.4)	25 (5.8)	148 (33.7)	19 (4.3)
Dysphonia	133 (30.6)	2 (0.5)	14 (3.2)	0
Decreased appetite	114 (26.3)	9 (2.1)	126 (28.7)	4 (0.9)
Hypothyroidism	108 (24.9)	1 (0.2)	61 (13.9)	1 (0.2)
Stomatitis	102 (23.5)	8 (1.8)	103 (23.5)	4 (0.9)
Cough	100 (23.0)	1 (0.2)	83 (18.9)	0
Headache	89 (20.5)	1 (0.2)	71 (16.2)	1 (0.2)

Motzer, R.J. et al. N Engl J Med 2019; 380:1103-1115

Time to Toxicity: Nivo/Ipi vs Sunitinib

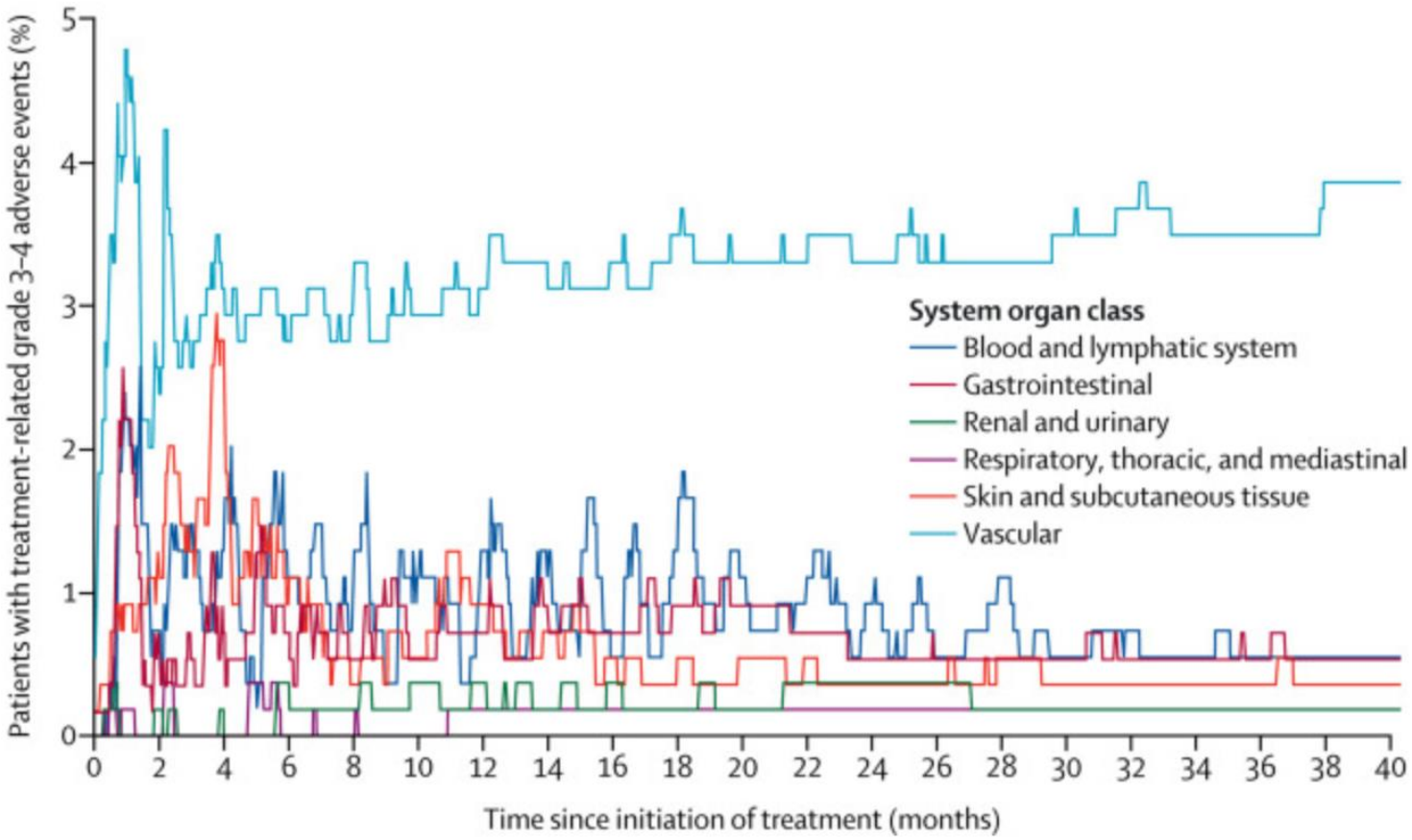


Most toxicity from Nivo/Ipi occurs around 6-7 weeks, but the range is very large

Motzer, R.J, et al. Lancet Oncol, 2019;10:1370-85

Abbreviations: Ipi, ipilimumab; Nivo, nivolumab

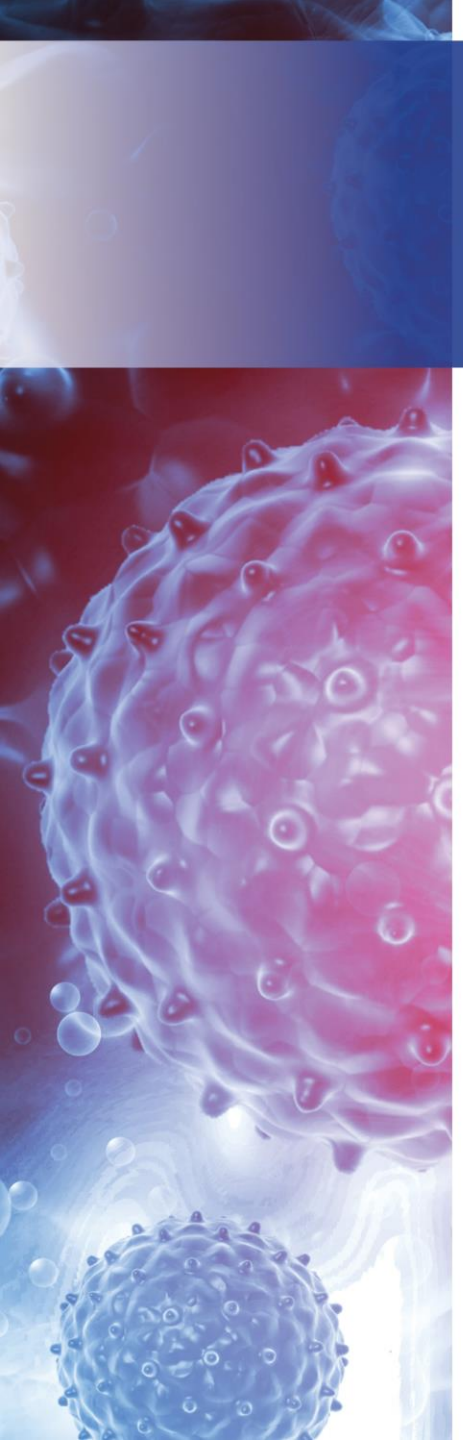
Time to Toxicity: Sunitinib



Most sunitinib toxicity occurs around 3-4 weeks, but the range is large

Motzer, R.J, et al. Lancet Oncol, 2019;10:1370-85

Toxicity and Timing Summary



- **IO Toxicity by class**
  - CTLA-4i + PD1i > CTLA-4i > PD1i ≥ PD-L1i
- **Between Class toxicity**
  - PD1i < Chemotherapy
  - Chemotherapy ≥ CTLA-4i + PD1i
  - Targeted therapy > CTLA-4i + PD1i
  - Targeted therapy + PD-L1 ≥ Targeted therapy

Time to toxicity is delayed with immunotherapy and can occur beyond a year of use and even after stopping treatment.

Abbreviations: CTLA-4i, cytotoxic T-lymphocyte-associated protein 4 inhibitor; PD1i, programmed cell death protein 1 inhibitor; PD-L1, programmed death-ligand 1; PD-L1i, programmed death-ligand 1 inhibitor

The Case of SJ

- SJ is a 61-year-old white female who presents with 5 loose stools yesterday and is being seen in clinic today – Normal is 1 stool every other day
- HPI: Began having pulmonary symptoms about 10 months ago. X-ray shows a lung mass; further workup demonstrates lesions in the liver and she is being treated with pembrolizumab monotherapy (cycle 4 administered 2 weeks ago)
- PMH: N/A
- FH/SH: Married with 2 sons, aged 28 and 34 years (none smoke)

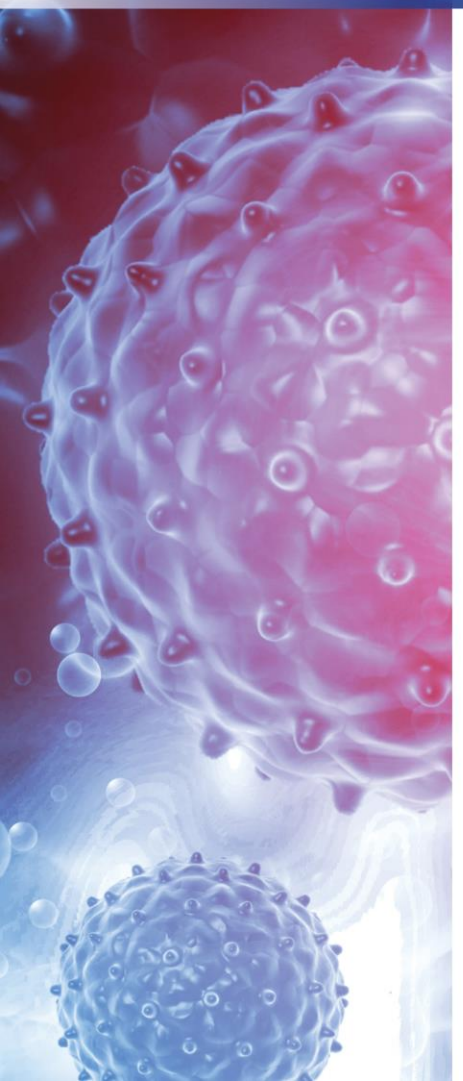
Abbreviations: FH, family history; HPI, history of present illness; N/A, not applicable; SH, social history

SJ — Background

- Drug history: NKDA
- PE: Findings consistent with lung cancer (lung findings), otherwise WNL (PS 0–1)
- Laboratory tests: Hepatic, renal, and chemistry levels WNL
- Radiology: Multiple lesions in the liver – stage IV (last scan showed PR based on RECIST)
- Pathology: Kras WT, EGFR WT, ALK WT, PD-L1 + (TPS 62%)

Abbreviations: ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; NKDA, no known drug abuse; PD-L1, programmed death ligand 1; PE, physical examination; PR, partial response; PS, performance status; RECIST, Response Evaluation Criteria in Solid Tumors; TPS, tissue polypeptide-specific antigen; WNL, within normal limits; WT, wild type

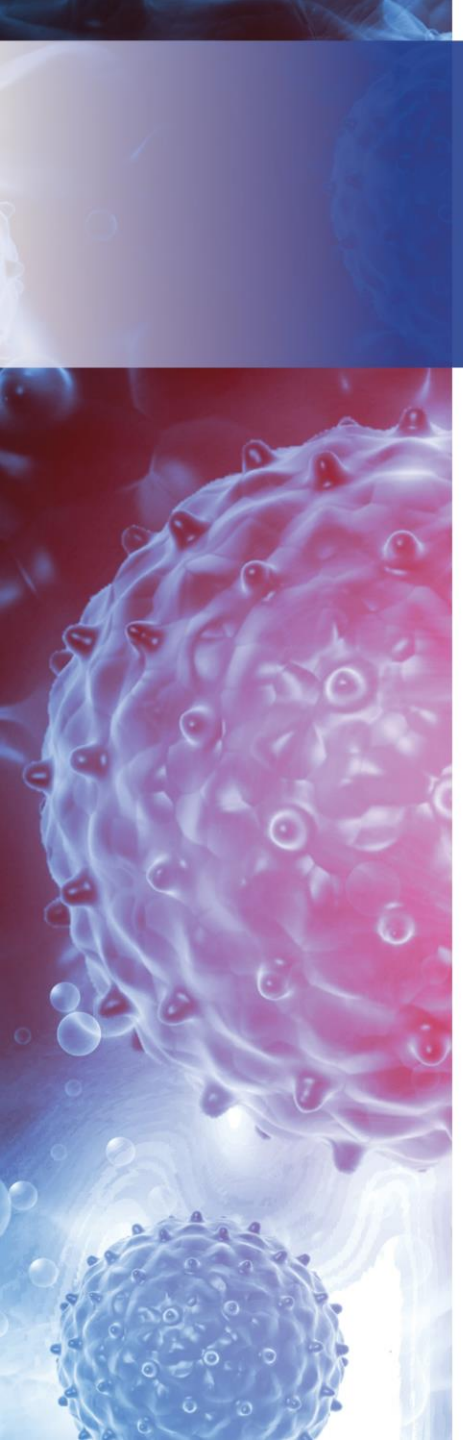
ARS Question #2:
SJ — Best Treatment



What is the best step to manage her diarrhea?

- Recommend hydration and loperamide
- Recommend hydration and infectious workup, including *Clostridium difficile* (common in this population)
- Begin low-dose prednisone (60 mg PO daily)
- Hospitalize patient and recommend infliximab

General Managements of Immune-Related Adverse Effects

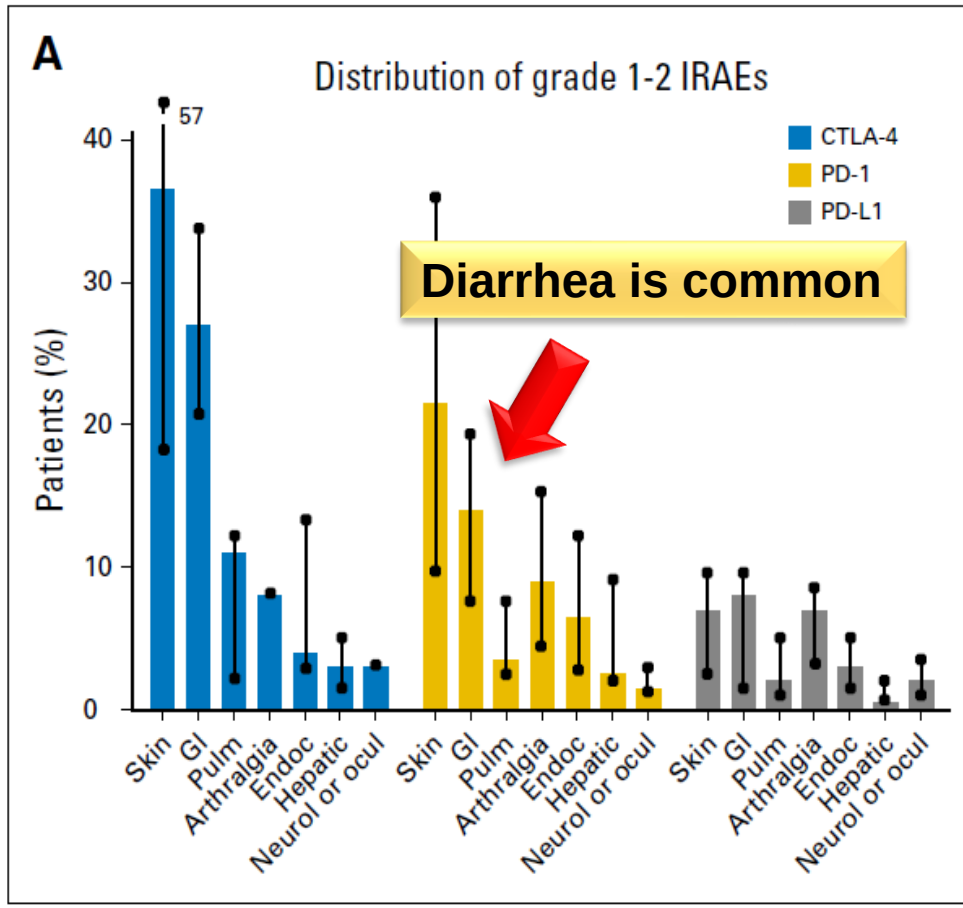


Several groups have made consensus recommendations for the management of immune-related adverse effects:

- American Society for Clinical Oncology (ASCO) in collaboration with the National Comprehensive Cancer Network (NCCN)[1]
- Society for Immunotherapy of Cancer (SITC)[2]
- European Society for Medical Oncology (ESMO)[3]

1. Brahmer JR, et al. *J Clin Oncol*. 2018;36:1714-1768. 2. Puzanov I, et al. *J Immunother Cancer*. 2017;5:95. 3. Haanen JBAG, et al. *Ann Oncol*. 2017;28(suppl 4): iv119-iv142.

SJ — Immune-Related Adverse Effects by Class



Grading (based on CTCAE for diarrhea, as most often used clinically)

All patients

G1: Increase of fewer than four stools per day over baseline; mild increase in ostomy output compared with baseline

G2: Increase of four to six stools per day over baseline; moderate increase in ostomy output compared with baseline

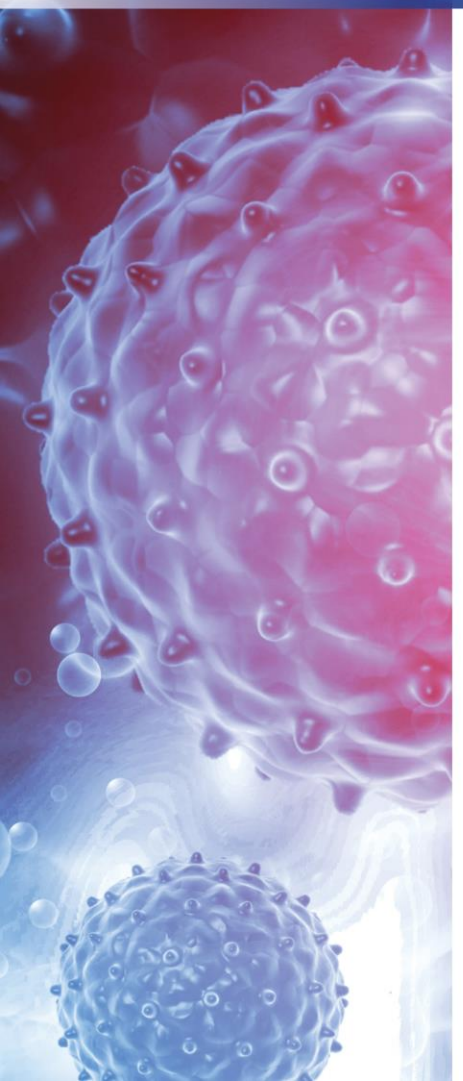
G3: Increase of seven or more stools per day over baseline, incontinence, hospitalization indicated, severe increase in ostomy output compared with baseline, limiting self-care ADL

G4: Life-threatening consequences; urgent intervention indicated

Abbreviations: ADL, activities of daily living; CTCAE, Common Terminology Criteria for Adverse Events; CTLA-4, cytotoxic T-lymphocyte associated antigen 4; GI, gastrointestinal; IRAE, immune-related adverse effect; Neurol, neurologic; Ocul, ocular; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1, Pulm, pulmonary.

Brahmer JR, et al. *J Clin Oncol.* 2018;11:132-137.

General Management



Grade 1	Grade 2	Grade 3	Grade 4
Continue ICPi Monitor for symptoms every 2-3 days	Suspend ICPi Consider restarting when grade 1 Corticosteroids may be started (Pred or MethylPred 0.5 mg/kg)	Suspend ICPi, Start high-dose corticosteroids (Pred or MethylPred 1-2 mg/kg; taper over 4-6 weeks) Additional immune suppression for refractory patients	Discontinue therapy Hospitalize Start high-dose corticosteroids (Pred or MethylPred 1-2 mg/kg; taper over 4-6 weeks) Additional immune suppression for refractory patients

See organ-specific recommendations

www.asco.org/supportive-care-guidelines. Accessed February 16, 2018.

ICPi, immune checkpoint inhibitor; MethylPred, methylprednisolone; Pred, prednisone.

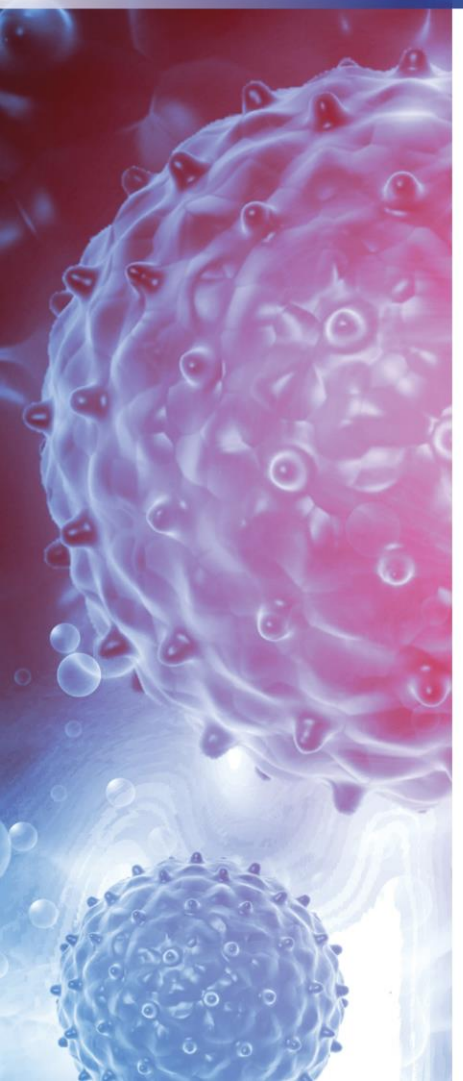
Diarrhea-Specific Management

- Should **hold ICPi temporarily** until patient's symptoms recover to G1; may restart PD-1/PD-L1 agents if patient can recover to G1 or less
- Concurrent immunosuppressant maintenance therapy (10 mg prednisone equivalent dose) may be offered only if clinically indicated in individual cases
- May also include supportive care with medications (e.g., Imodium) if infection has been ruled out
- Administer corticosteroids, unless diarrhea is transient, starting with initial dose of **1 mg/kg/day prednisone or equivalent**
- When symptoms improve to G1 or less, **taper corticosteroids over at least 4-6 weeks before…**
- **Resuming treatment**, although resuming treatment while on low-dose corticosteroid may also be an option after an evaluation of the risks and benefits

Abbreviations: G1, grade 1; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1

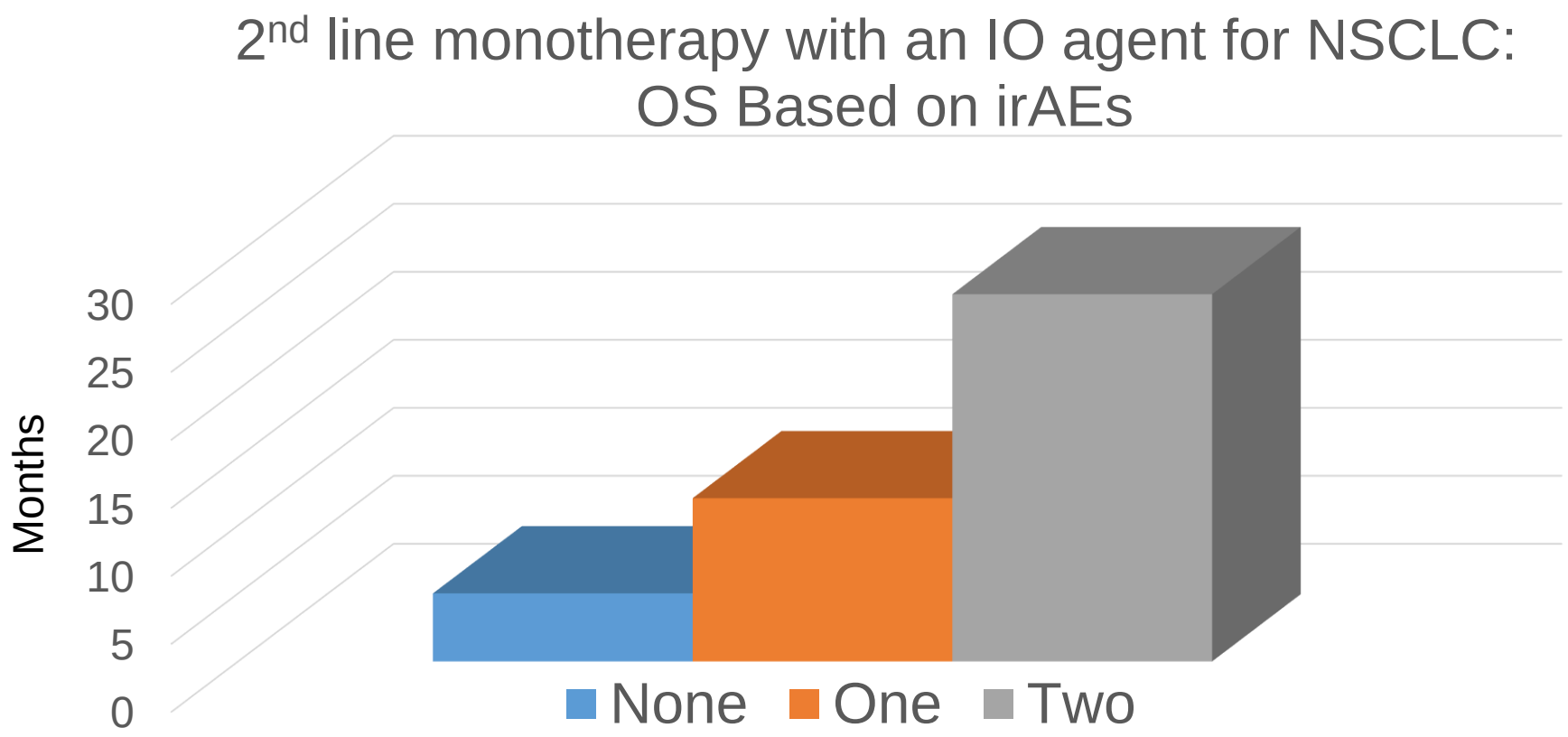
Brahmer JR, et al. *J Clin Oncol.* 2018;11:132-137

ARS Question #3: Restarting IO Therapy After Toxicity



- **Which of the following is true when it comes to restarting IO treatment after a G2 toxicity event?**
  - The same toxicity is likely to recur
  - It is not safe to restart treatment if it is truly an irAE
  - Most patients experience a worse prognosis with therapy delay due to toxicity
  - A temporary hold due to irAE and management may improve outcome

Retrospective Trial Evaluating Outcome After irAEs by Lung Cancer Patients

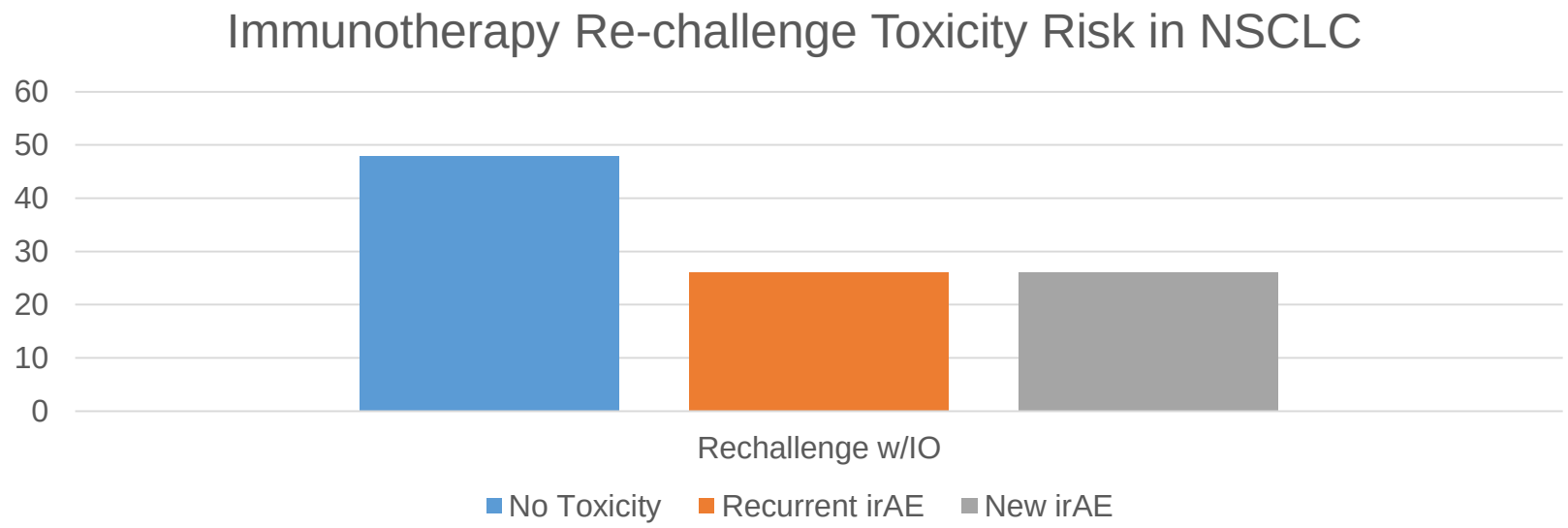


Abbreviation: OS, overall survival

Ricciuti, B. et al. J Cancer Res Clin Oncol 2019;145:479-85

irAE recurrence with rechallenge

- Recurrence in patients with lung cancer with just PD1/PD-L1 monotherapy shows more than half of patients will experience an irAE with re-challenge.



Abbreviations: irAE, immune-related adverse event; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1

Santini, FC., et al. Cancer Immunol Res 2018;6:1093–9

Key Elements of irAEs

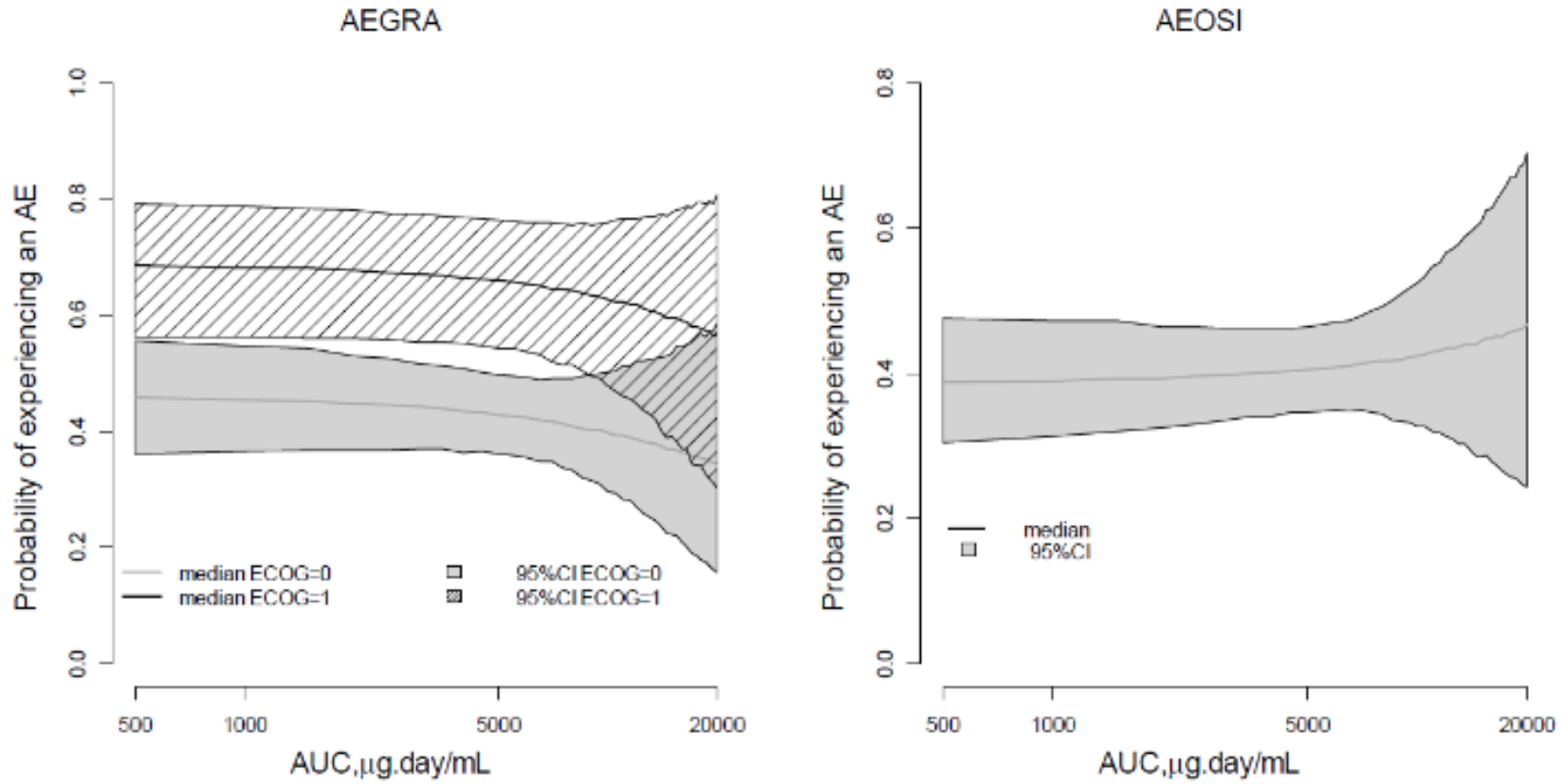
- Minimize toxicity progression risk with early intervention
- Intervention of Grade 2 or greater starts with steroids
- Early grade toxicity can be managed and treatment restarted
- irAEs seem to predict benefit from treatment

ARS Question #4:
SJ's diarrhea has resolved and she completed 4 weeks of a steroid taper…

- **The oncologist has elected to rechallenge SJ with IO therapy. Recall that she was receiving pembrolizumab 200 mg IV q3week for NSCLC. What recommendations would you recommend for SJ's next cycle?**
  - Pembrolizumab 100 mg IV q3week (50% reduction)
  - Pembrolizumab 150 mg IV q3week (25% reduction)
  - Pembrolizumab 400 mg IV q6week (extended interval)
  - Pembrolizumab 200 mg IV q3week (no change)

AUC Does Not Correlate with AE

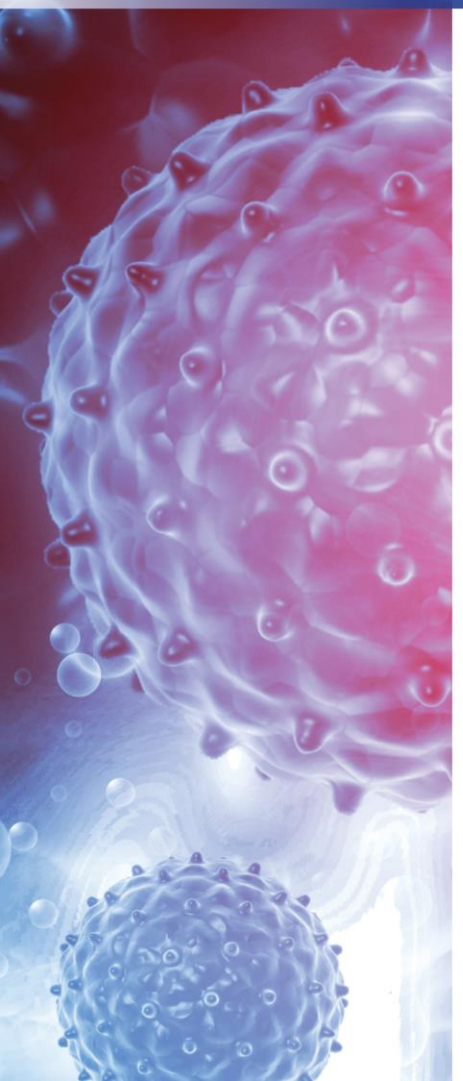
Figure 1: Simulated Probability of Experiencing an AE in Function of Exposure with the Associated 95% CIs



Source: exposure-response report of 03tlcn, Pages 51-52

Pembrolizumab FDA review. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/125514Orig1s000ClinPharmR.pdf

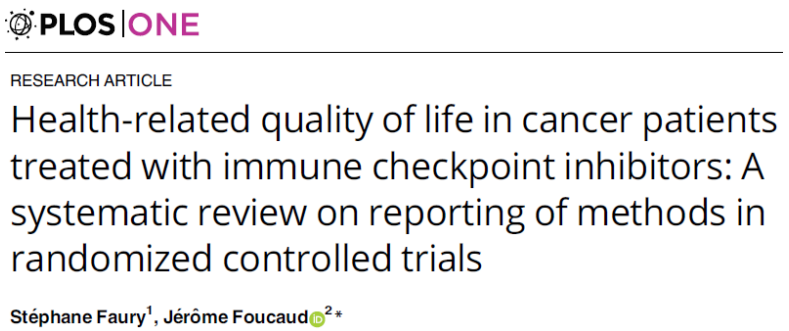
Restarting IO Therapy



- Unlike chemotherapy or targeted therapy, there is no exposure – toxicity relationship
- Consequently, no recommendation for dose reduction with re-initiation of treatment

Quality of Life with IO Treatment

- Evaluation built into many prospective randomized trials; however, it still has been deemed to have major flaws



PLOS ONE

RESEARCH ARTICLE

Health-related quality of life in cancer patients treated with immune checkpoint inhibitors: A systematic review on reporting of methods in randomized controlled trials

Stéphane Faury[1], Jérôme Foucaud[2]*

Of the 144 publications – they only identified 15 trials – they still felt the 15 had issues

"The results suggest that even though the overall reporting of HRQOL was deemed to be of good quality, the data available was marred by methodological aspects such as the lack of HRQOL research hypotheses and the lack of questionnaires validated for cancer patients treated with immunotherapy."

- Empirically, patients feel like IO therapy is much better tolerated than chemotherapy

Faury S, F. PLoS ONE 2020;15(1): e0227344.

Abbreviation: HRQOL, health-related quality of life

EORTC QLQ-C30

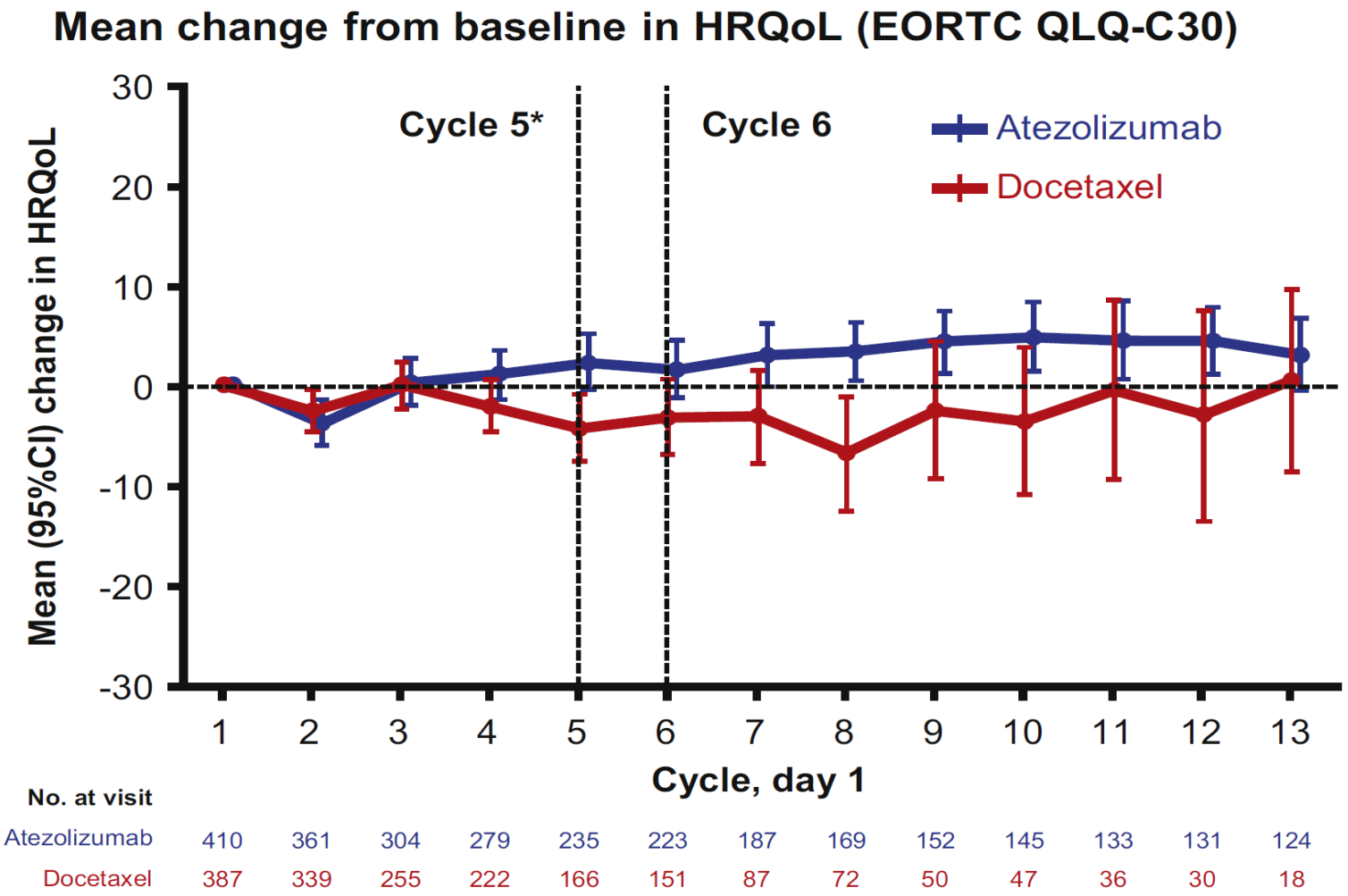
Table 1. Content of the nine QLQ-C30 dimension scales

QOL dimension	No. of questions	Literal interpretations of the lowest and highest scores: 'In the past week I was . . .'	
		Lowest possible = 0	**Highest possible = 100**
Global QOL	2	Overall physical condition and quality of life was very poor.	Overall physical condition and quality of life was excellent.
Physical Function	5	Was confined to bed, needed help dressing, washing and eating.	Was able to do strenuous physical activities.
Role Function	2	Was completely unable to work at a job or do household jobs.	Was not limited at all in doing either work or household jobs.
Emotional Function	4	Felt very tense, irritable and depressed and worried a lot.	Did not feel at all tense, irritable or depressed and did not worry at all.
Social Function	2	Physical condition and medical treatment interfered very much with family life and social activities.	Physical condition and medical treatment did not interfere at all with family life and social activities.
Cognitive Function	2	Had a lot of difficulty concentrating and remembering things.	Did not have any difficulty concentrating or remembering things.
Nausea and Vomiting	2	Did not feel at all nauseated and did not vomit.	Felt very nauseated and vomited a lot.
Pain	2	Did not have any pain, and pain did not interfere at all with daily activities.	Had a lot of pain, and it interfered very much with daily activities.
Fatigue	3	Did not feel at all weak or tired, and did not need to rest at all.	Felt very weak and tired, and needed to rest a lot.

- Comparisons are usually made from baseline, then over time
- Also between groups, larger differences are more impactful
- Variation of dimensions are usually interrelated

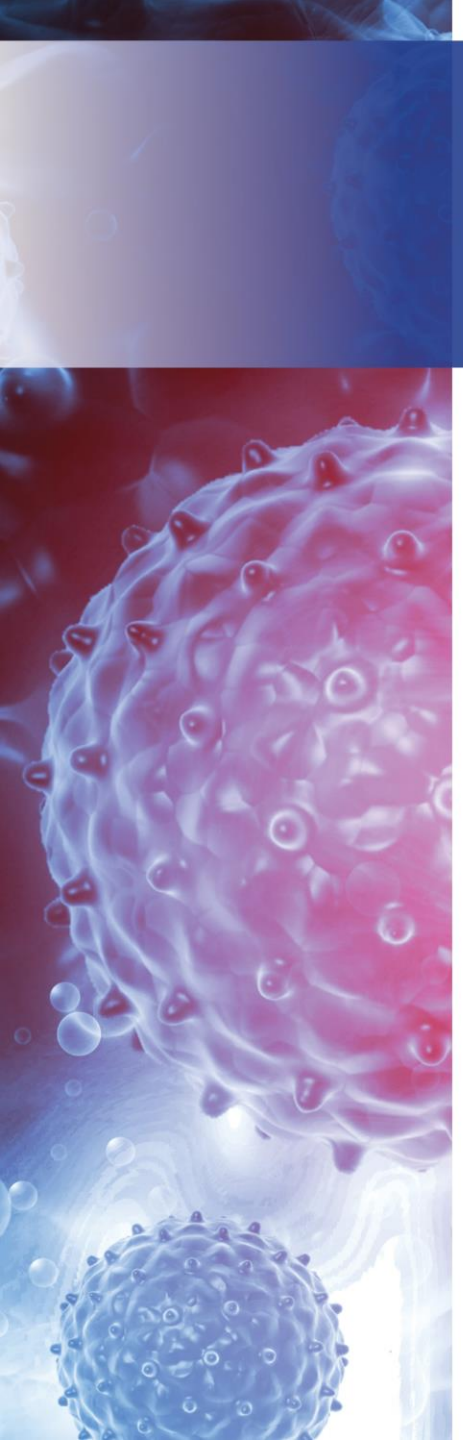
King, MT. Quality of Life Research 1996;5:555-567

Health Related Quality of Life: IO vs Chemotherapy



Clinical Lung Cancer, 2018;19: 441-9

Quality of Life: Clinical Pharmacist Focus



- Optimizing patient outcomes:
  - Minimize grade 3-5 toxicity
  - Minimize chronic grade 2 toxicity that leads to discontinuation (tolerance)
- Proper monitoring and communication with patients
- Rapid evaluation and early intervention for irAEs
- Fatigue continues to be an issue – empirically patients feel better on IO treatment

Chronic Toxicity

- Immune related damage to non-cancer tissue may be permanent
  - Pancreatic damage leading to type I diabetes
  - Joint and arthritic damage may not be reversible
  - Fibrotic changes to tissues (e.g., lung or kidney) are not always reversible
- Early intervention and stopping the damage is key to minimize the severity

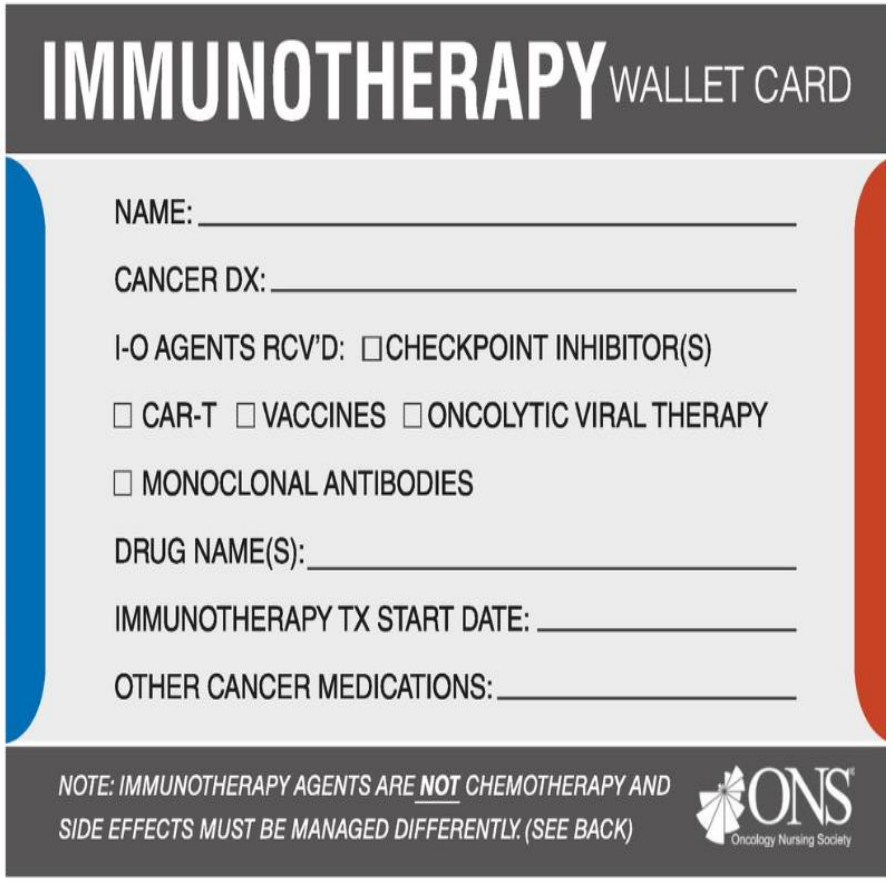
M. Michot et al. / Eur J Cancer 2016;54:139-48

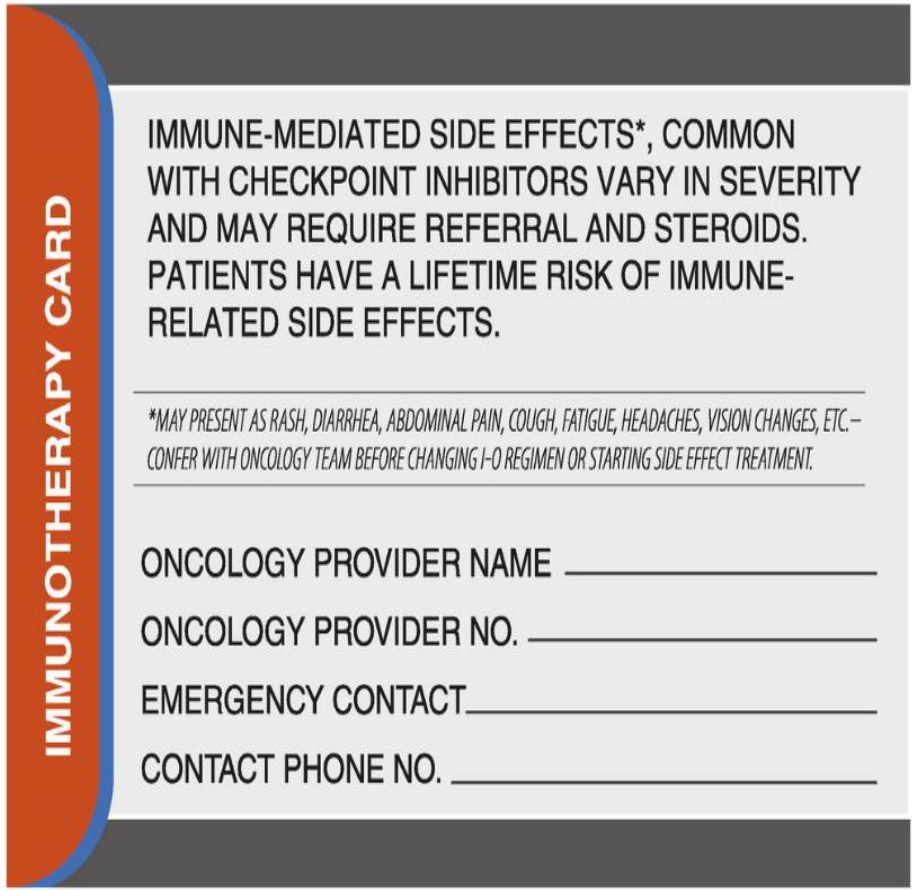
Patient and Family Education

- Time to response differs from standard therapy
  - Response in baseline lesions
  - Stable disease with slow tumor volume decline
  - Response following initial tumor volume increase or new lesion
  - Patients may develop signs of disease progression after treatment
    - Sudden and painful increase in tumor size, rash, low-grade fever, bone pain
    - Treatment can continue through this disease “pseudo-progression”
- Different AE profile than chemotherapy
- Early irAE recognition is essential
- Patients must notify their care provider if
  - symptoms develop
  - they are admitted to a local facility
- irAEs are related to immunotherapies’ mechanisms of action
- irAEs are treatable and responsive to steroids

Abbreviation: irAE = immune-related adverse event

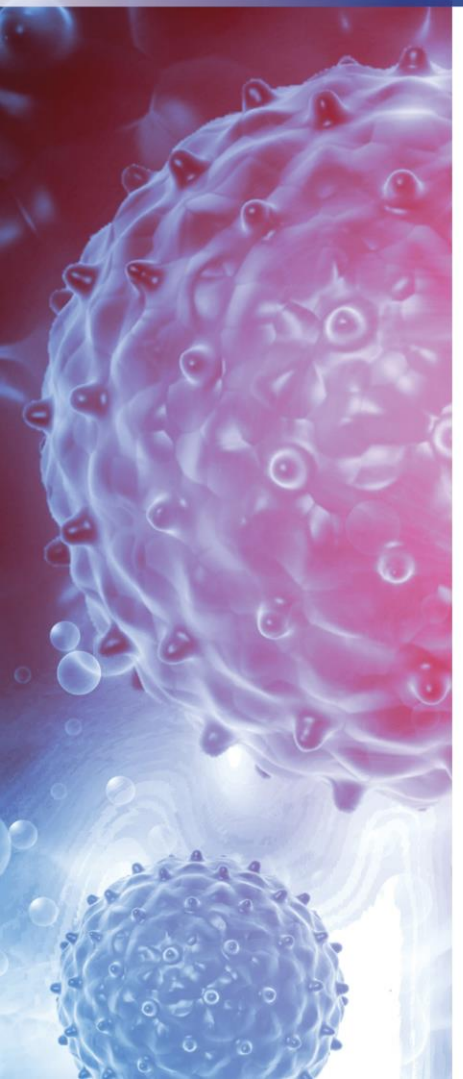
Communication Tool





www.asco.org/supportive-care-guidelines. Accessed 2/16/2018.

Importance of Navigation

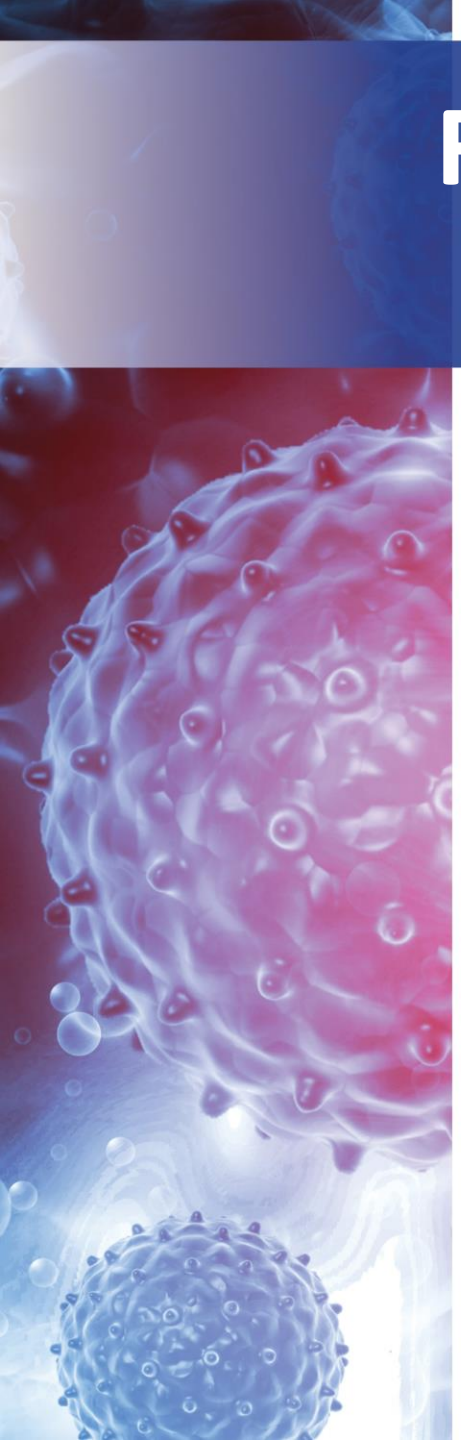


Given the cost implications, additional conversations are needed to determine best treatment decision (financial toxicity)

Cancer Center staff is instrumental in key conversations with patients and caregivers

Pharmacists act as an extension of the care team

Financial Toxicity



Financial concerns are often associated with oral therapies, given cost sharing

- Oral therapies covered by patient's pharmacy benefit as opposed to medical benefit
- 10%–20% co-pay vs fixed dollar amount

Immunotherapies can carry their own cost implications for patients

- Although drugs are administered on medical benefits, there are still concerns
- Cost of managing side effects, which can occur right away, 5 weeks after treatment, or even up to 15 weeks out

General Payer Oncology Management

What ARE and What WILL Payers Do to Manage Increasing Cost of Oncolytics

Mature Stage

1. Increase Utilization Management Efforts (reduce inappropriate utilization)
2. Reduce profit incentive (level playing field low/high cost drugs)
3. Incentivize patients to choose cost-effective options
4. Direct care to most cost-effective settings
5. Encourage appropriate end-of-life care
6. Change relationships with providers and manufacturers to align incentives – value-based care

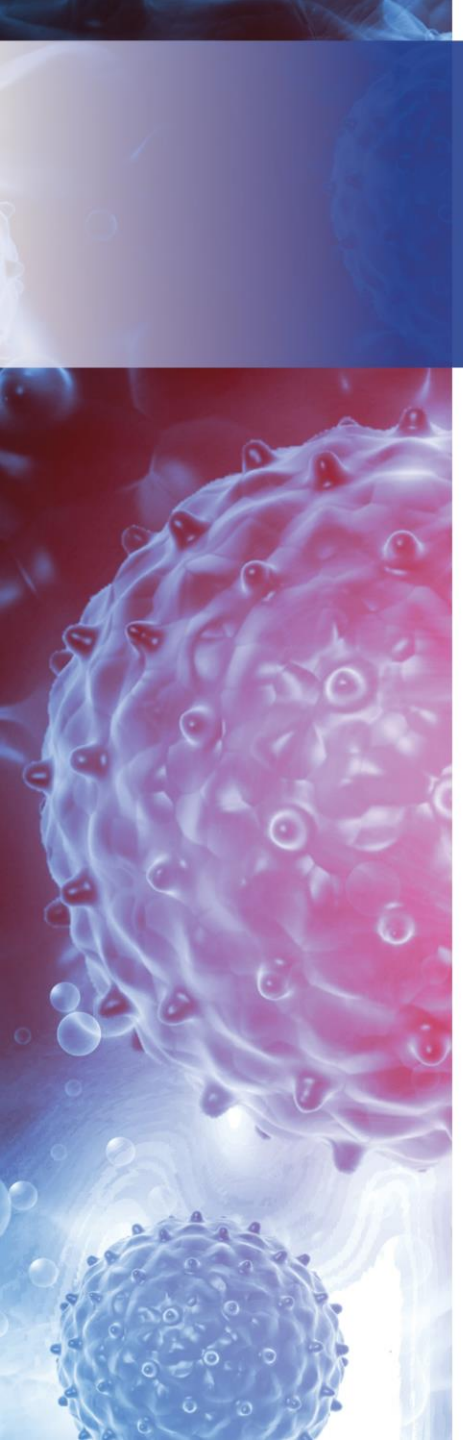
Early Stages

Financial Toxicity

- Survey of 105 patients receiving immunotherapy
- 48% were aware of financial difficulty
- 34% had pre-treatment finance discussion
- Difficulties:
  - 35% high medical co-pay
  - 33% decreased income
  - 21% high medication co-pay
- Addressing the difficulties:
  - 39% used personal finances
  - 28% trimmed private expenses
  - 24% got help from family and friends

Vorobiof, et al. Clin Oncol 38, 2020 (suppl 5; abstr 90)

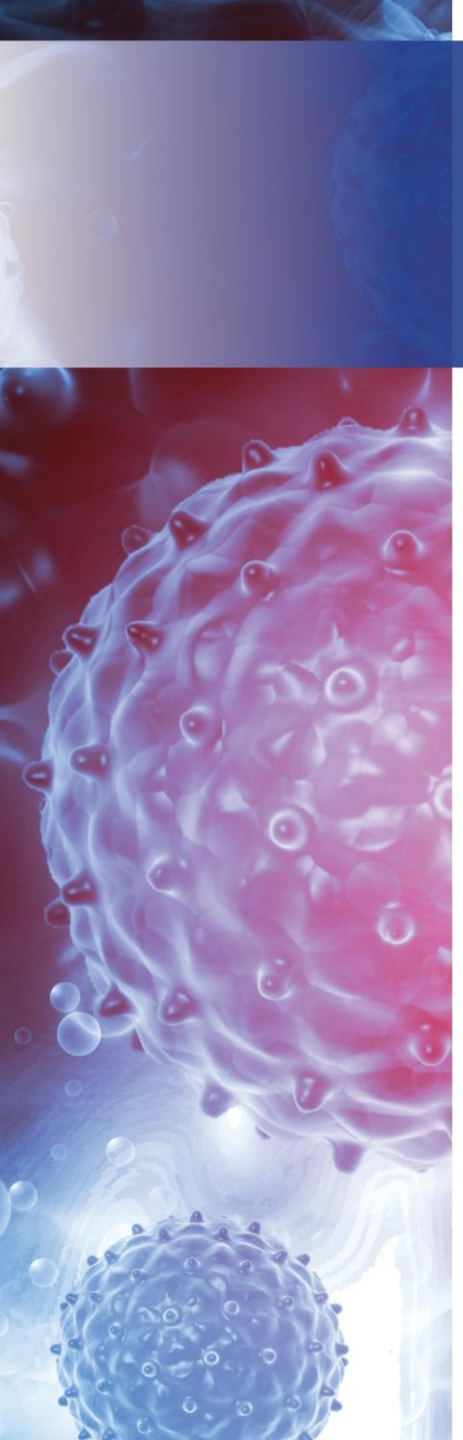
IO Toxicity Management Strategies and Care Coordination



- Educate patients who have received or are receiving immunotherapy who to call for toxicity issues
- Continuously educate providers, patients/caregivers, and non-clinical staff
- Triage patients based on symptoms
- Develop same-day care models (e.g., via “quick clinics” or a symptom management workspace)
- Establish standard-of-practice irAE management guidelines

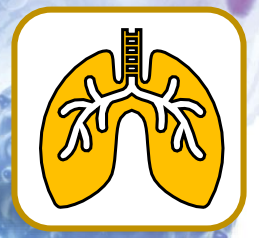
Source: Association of Community Cancer Center 2017-2018: IMMUNO-ONCOLOGY: Transforming the Delivery of Cancer Care in the Community

Real-World Communications Challenges



- Setting patient expectations can be more than challenging
- Genomics and impact on immunotherapy

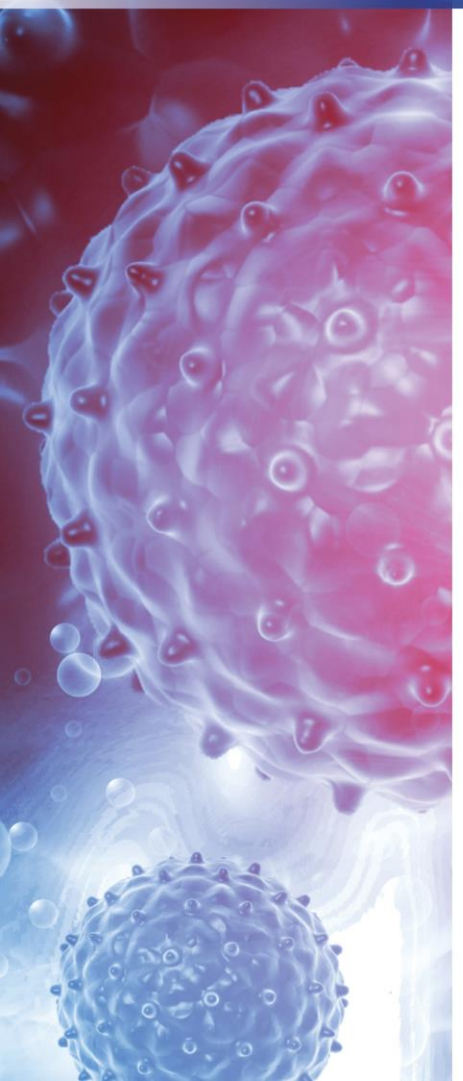
Patient PL



61 yo Asian female currently inpatient presented to ED yesterday with SOB (O2 sat=80%.)

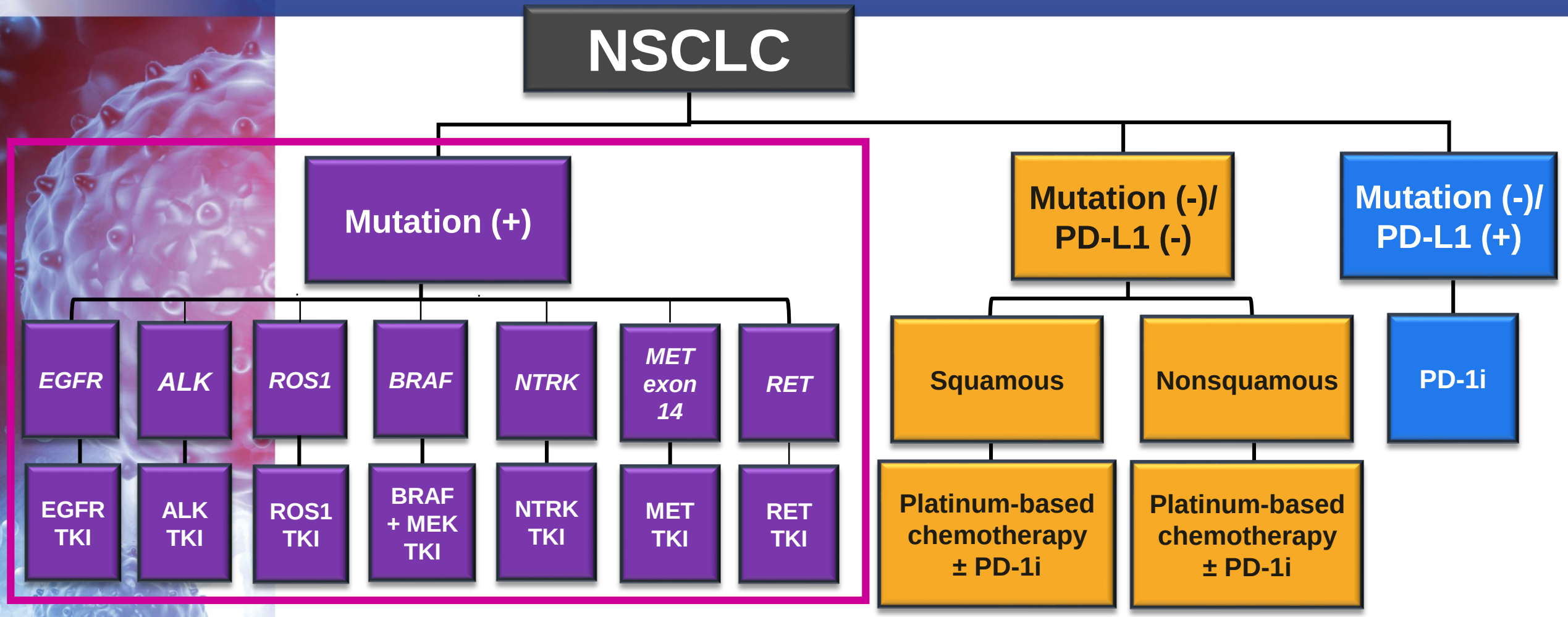
- No significant PMH (negative for asthma or other pulmonary disease)
- Does not smoke, and drinks wine occasionally
- NKDA; takes daily vitamin but no other drugs/supplements
- Hepatic, renal, and chemistry levels WNL
- Afebrile, neurologically intact
- Lung exam: decreased breath sounds on left low lobe
- Liver is not tender or painful, performance status
- X-ray and f/u CT scan: large central mass in the left lung main stem bronchi causing atelectasis
  - CT slices through the liver show multiple small lesions consistent with cancer
- Pathology reveals poorly differentiated carcinoma
  - More tissue needed to complete histology and genomics testing

ARS Question #5:
What treatment would you recommend?



- Alectinib
- Pembrolizumab
- Carboplatin – paclitaxel
- Osimertinib
- Carboplatin-pemetrexed - pembrolizumab
- Wait for more tumor testing results

Treating Advanced/Metastatic NSCLC

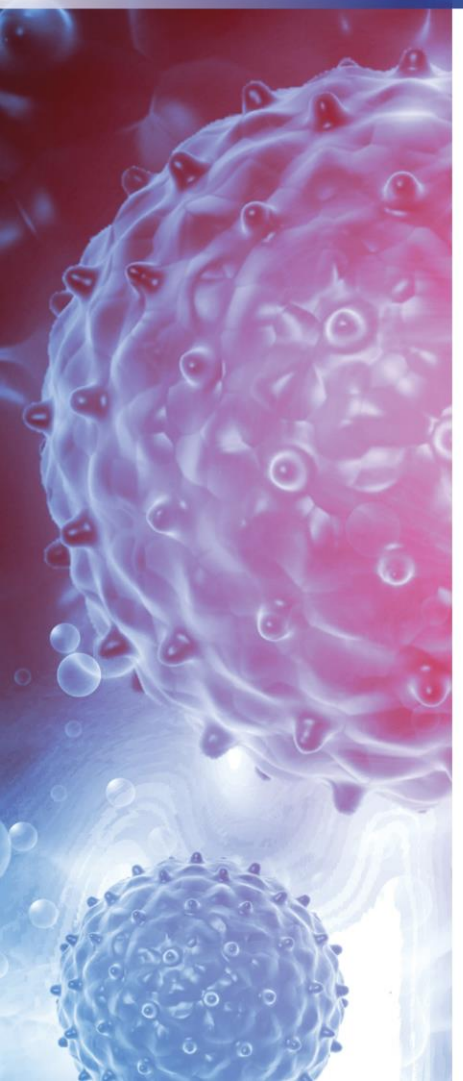


NCCN. NSCLC Guidelines. v8.2020.

Limitations

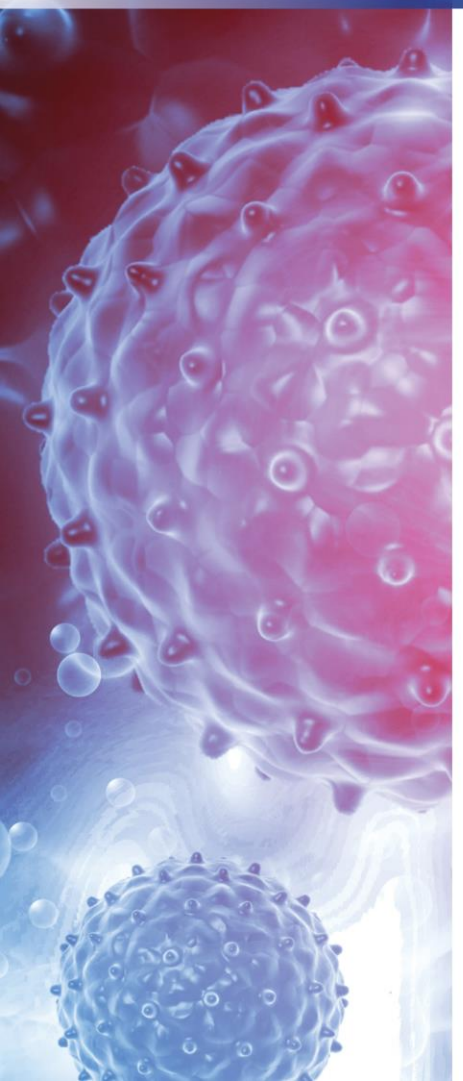
- Lack of efficacy
  - Targeted therapy in patients without a mutation
  - PD1 inhibitor in patients with low PD-L1 expression
  - Pemetrexed ineffective against squamous histology
- Safety concerns
  - Bevacizumab should not be used in patients with squamous histology
  - Early immunotherapy use appears to increase toxicity risk from targeted therapies

PL's Plan



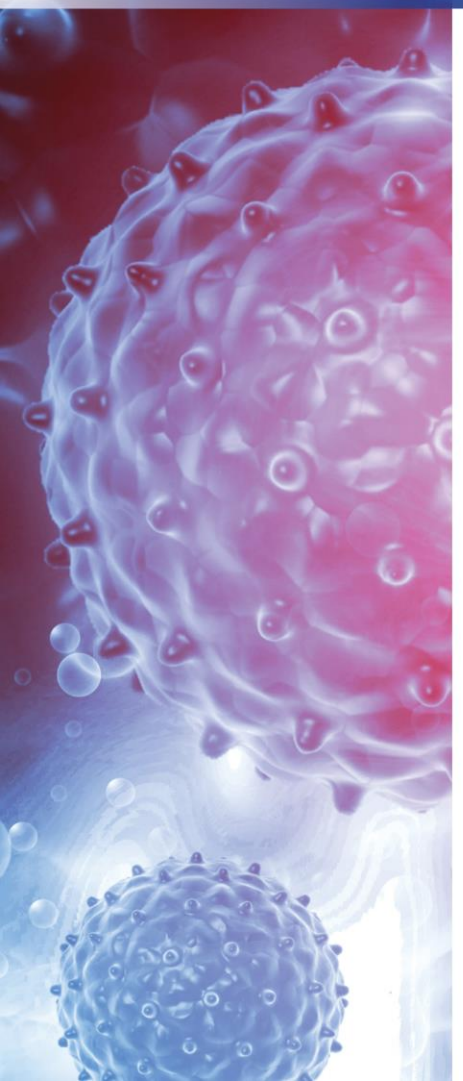
- PL is given carboplatin and paclitaxel inpatient
- Four days later her O2 sats on room air are 94%, and her symptoms improved
- She is discharged home and scheduled to come back to the infusion center for another treatment

Tissue is Required



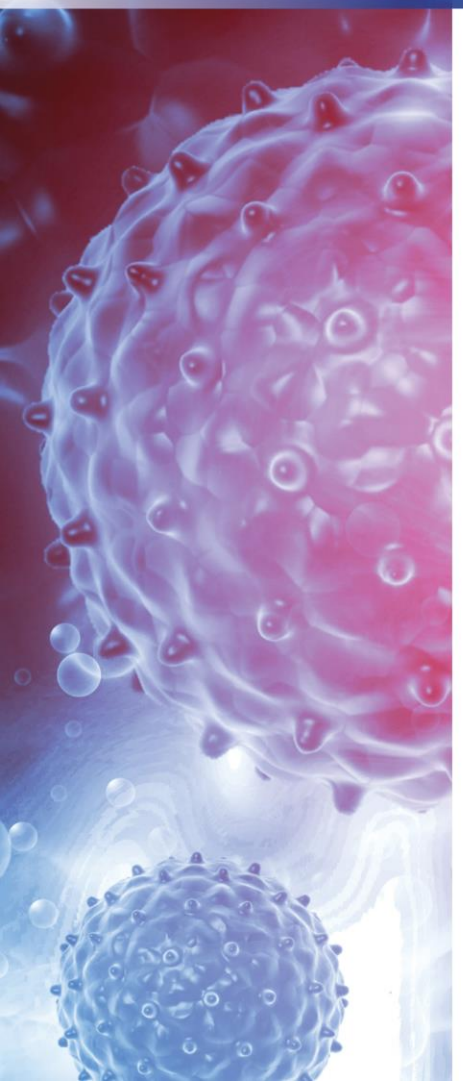
- H&E demonstrated the mass to be a poorly differentiated cancer (NSCLC)
- Pathology Subtyping:
  - IHC to assess TTF-1 + and P40/P63 - (adenocarcinoma), PD-L1 = 23% positive
  - NGS testing (pending)

ARS Question #6:
What treatment would you recommend?



- Carboplatin – paclitaxel (same treatment as C1)
- Alectinib
- Carboplatin - Pemetrexed
- Osimertinib
- Carboplatin - pemetrexed - pembrolizumab
- Postpone treatment - wait for test results

ARS Question #7: PL visit for Cycle 3

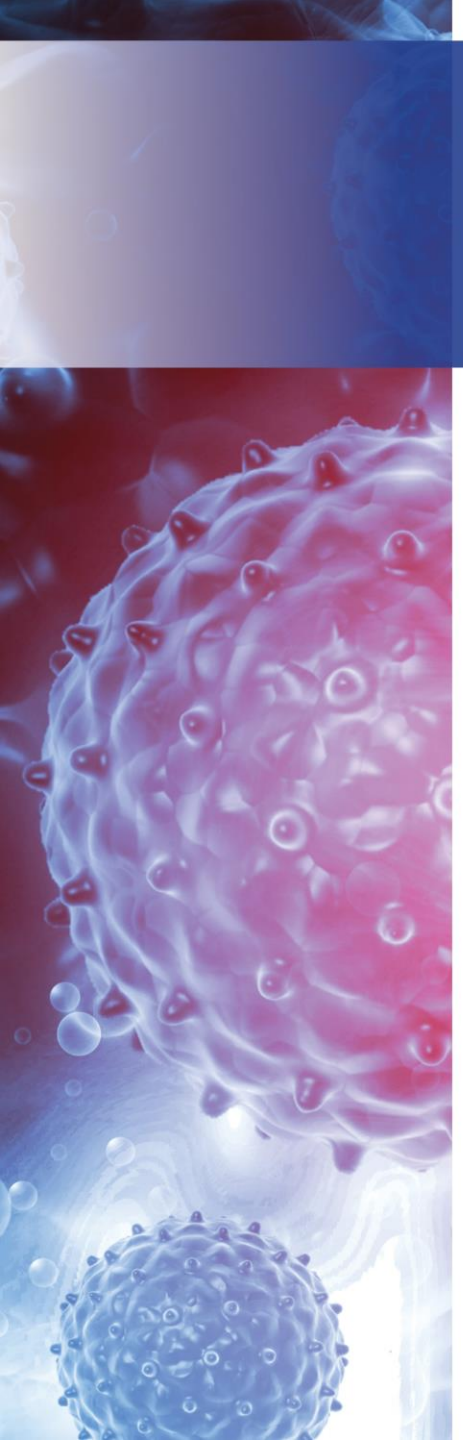


NGS report shows no targetable driver mutation. What is the best therapy for Cycle #3?

- Carboplatin – Paclitaxel
- Carboplatin – Pemetrexed
- Carboplatin – Pemetrexed – Pembrolizumab
- Carboplatin – Paclitaxel – Bevacizumab - Atezolizumab

Abbreviation: NGS, next generation sequencing

Building an Infrastructure



- ACCC (Association of Community Cancer Centers)
  - Educate patients & staff
  - Have dedicated people to answer and triage toxicity calls
  - Same-day clinics
- Requires resources to cover these functions (primary and back-up)
- Must be scaled for continuous monitoring, assessment, education, and barrier resolution
- Looks different than 4-6 cycles of chemotherapy or oral specialty drugs

Patient and Family Education

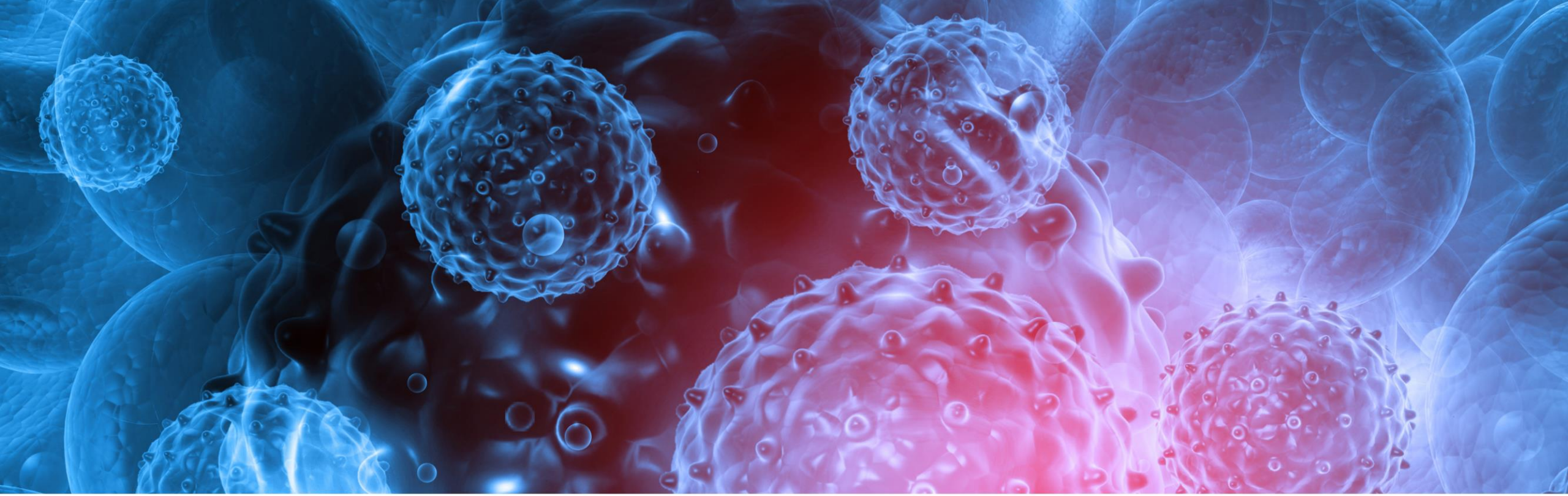
- ICI time to response differs from standard therapy
  - Response in baseline lesions
  - Stable disease with slow tumor volume decline
  - Response following initial tumor volume increase or new lesion
  - Patients may develop signs of disease progression after treatment
    - Sudden and painful increase in tumor size, rash, low-grade fever, bone pain
    - Treatment can continue through this disease “pseudo-progression”

Wood, LS, et al. **CJON** 2019; 23: 271-80

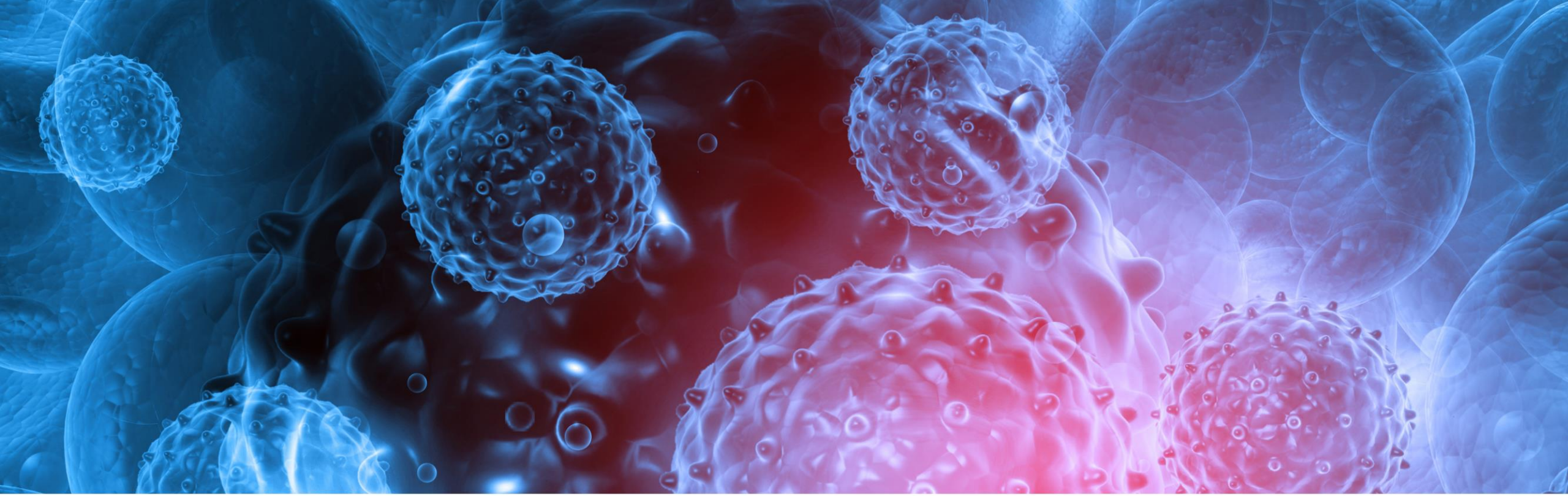
Patient and Family Education

- Different Adverse Event (AE) profile than chemotherapy
- Early irAE recognition is essential
- Patients must notify their care provider if
  - symptoms develop
  - they are admitted to a local facility
- irAEs are related to immunotherapies' mechanisms of action
- irAEs are treatable and responsive to steroids

Abbreviations: AE, adverse event; irAE, immune-related adverse event



Questions and Answers



Thank You!