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HARNESSING THE FULL POTENTIAL OF FRONTLINE IMMUNOTHERAPY IN ADVANCED NSCLC

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This activity is supported by an independent medical education grant from Regeneron Pharmaceuticals, Inc and Sanofi.

AGENDA

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Event 1

USE OF BIOMARKER TESTING IN ADVANCED NSCLC

Prof. MUDr. Aleš Ryška

Event 2

SELECTING FRONTLINE IMMUNOTHERAPY IN ADVANCED NSCLC

Dr. Jared Weiss

Event 3

MANAGING IMMUNOTHERAPY-RELATED ADVERSE EVENTS IN NSCLC

Dr. Mihaela Aldea

NSCLC, non-small cell lung cancer

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Use of Biomarker Testing in Advanced NSCLC

Prof. MUDr. Aleš Ryška, MD, PhD
Charles University
Hradec Králové University Hospital
Prague, Czech Republic

NSCLC Management Has Become Complex

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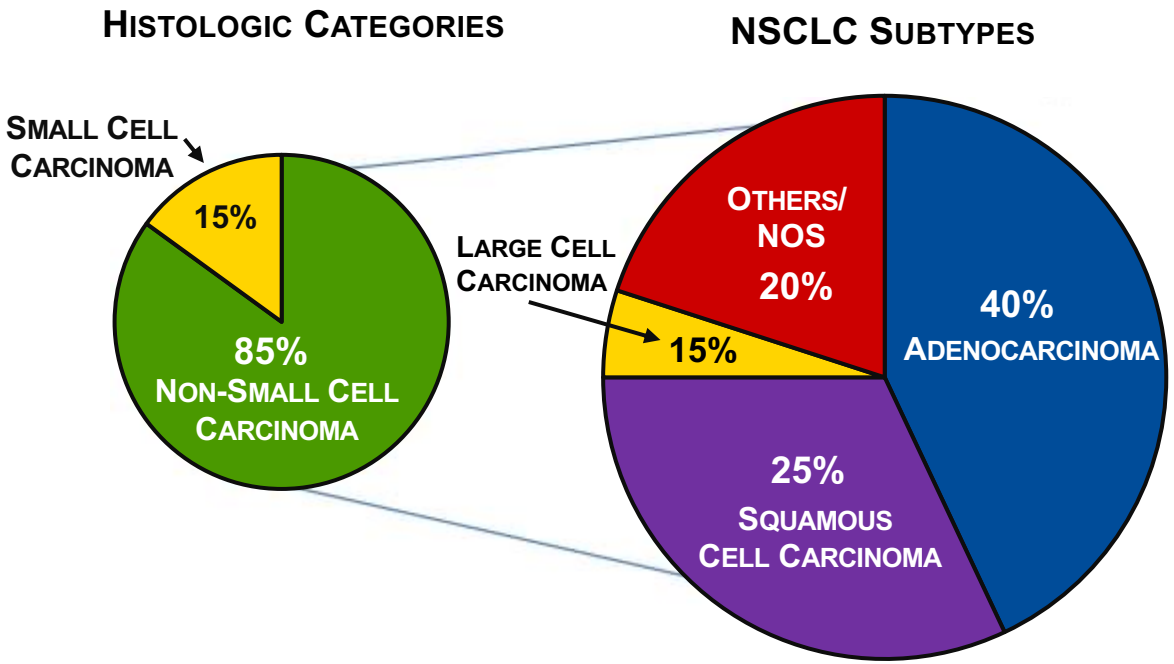
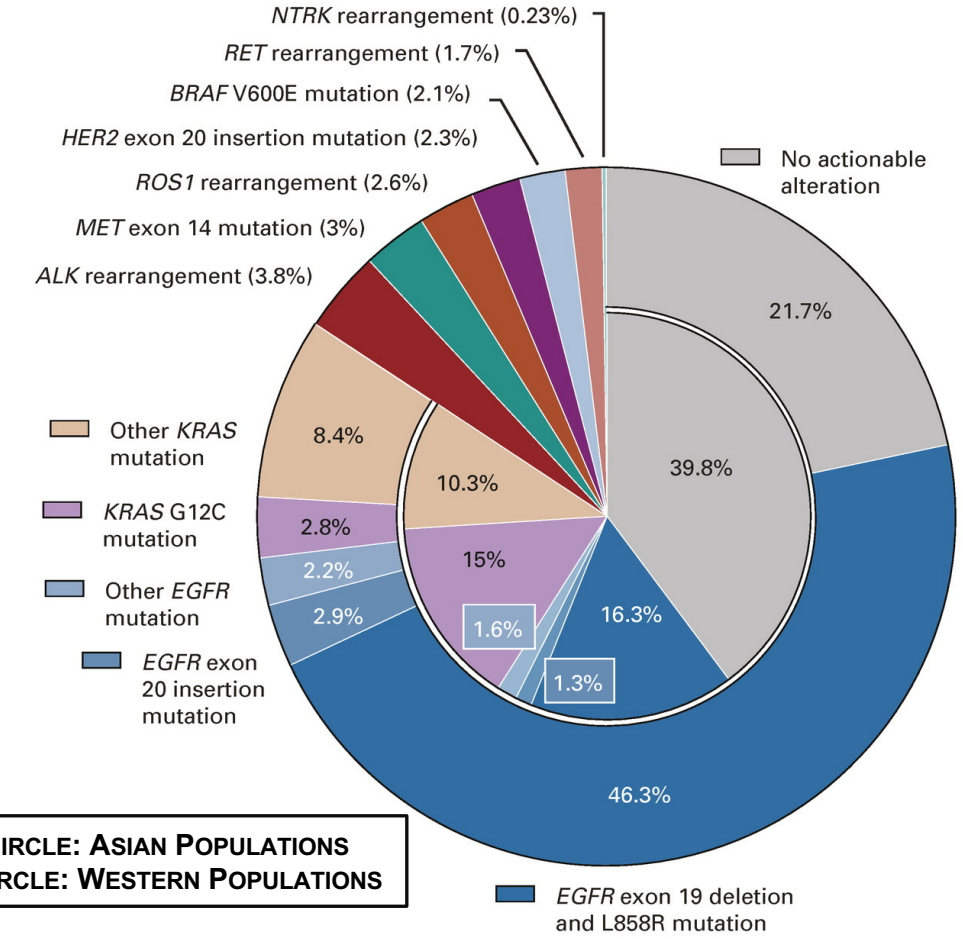
Classification of Lung Cancer



Molecular Alterations in Adenocarcinoma



Schabath MB, Cote ML. *Cancer Epidemiol Biomarkers Prev*. 2019;28(10):1563-1579.
Tan AC, Tan DSW. *J Clin Oncol*. 2022;40(6):611-625

Driver Mutations with Approved Agent or Accessible Via Clinical Trial

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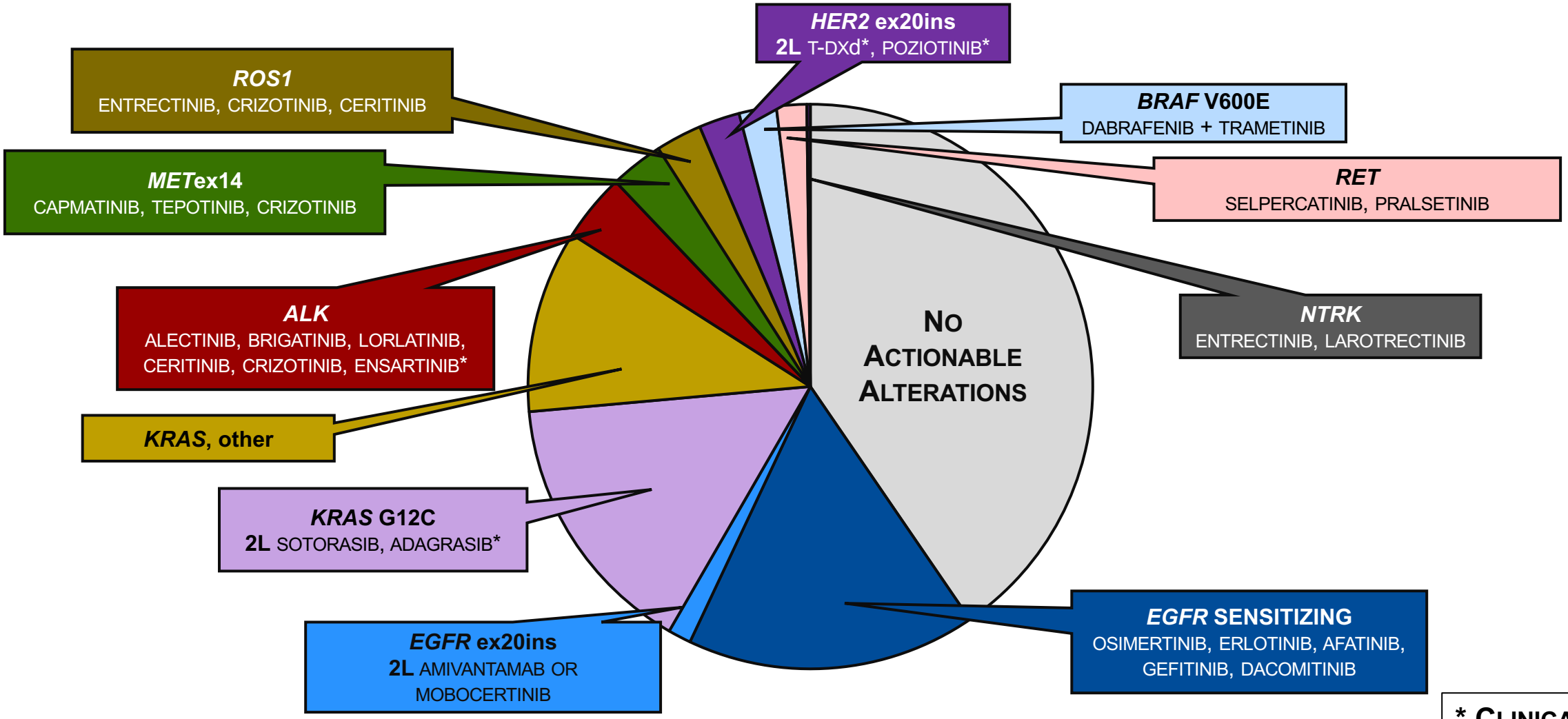

* Clinical Trial

NCCN Guidelines. NSCLC. Version 3.2022. Updated 3/16/2022. Tan AC, Tan DSW. *J Clin Oncol*. 2022;40(6):611-625

PD-L1 is Expressed in 60% of NSCLC

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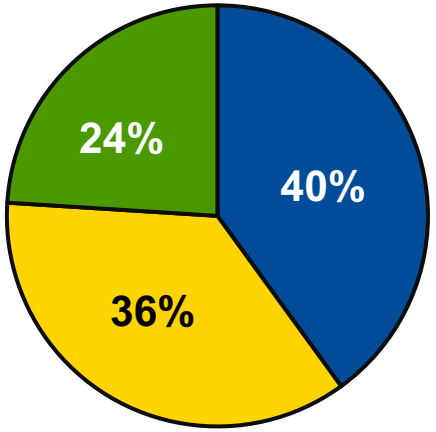
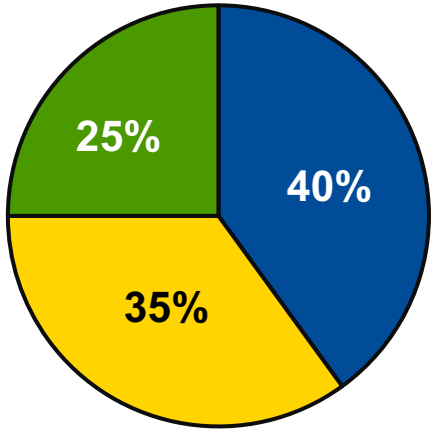
Total PD-L1 Positivity (N=703)



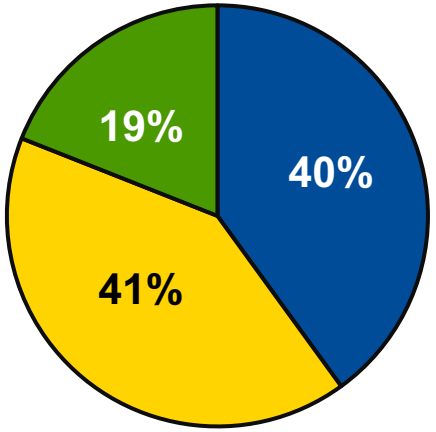
■ <1% ■ 1-49% ■ >50%

Adenocarcinomas



■ <1% ■ 1-49% ■ >50%

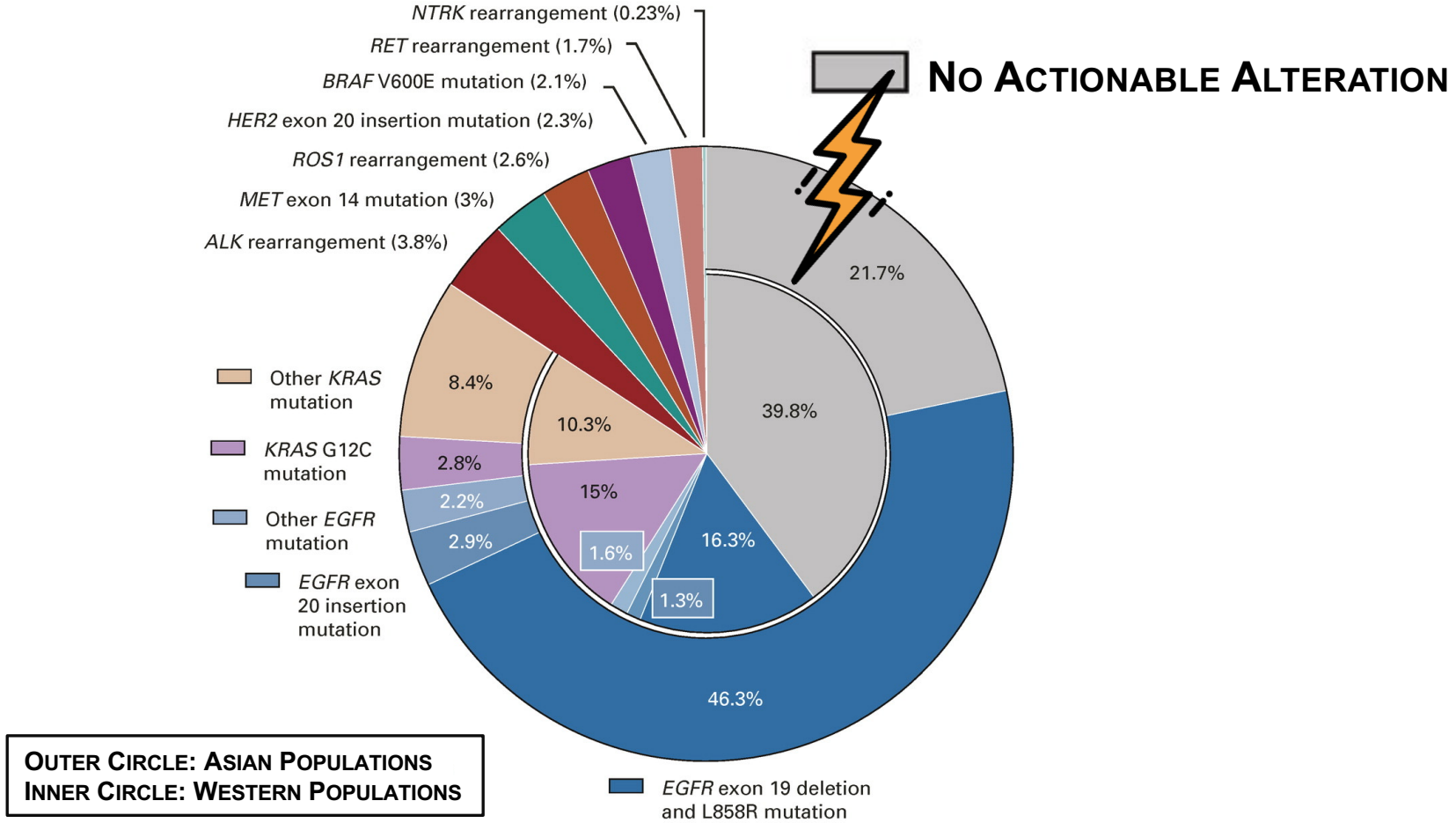
Squamous Cell Carcinomas



■ <1% ■ 1-49% ■ >50%

Humphries MP et al. *Cancers (Basel)*. 2020;12(5):1114.

Role and Place of Immune Checkpoint Inhibitors (ICI)

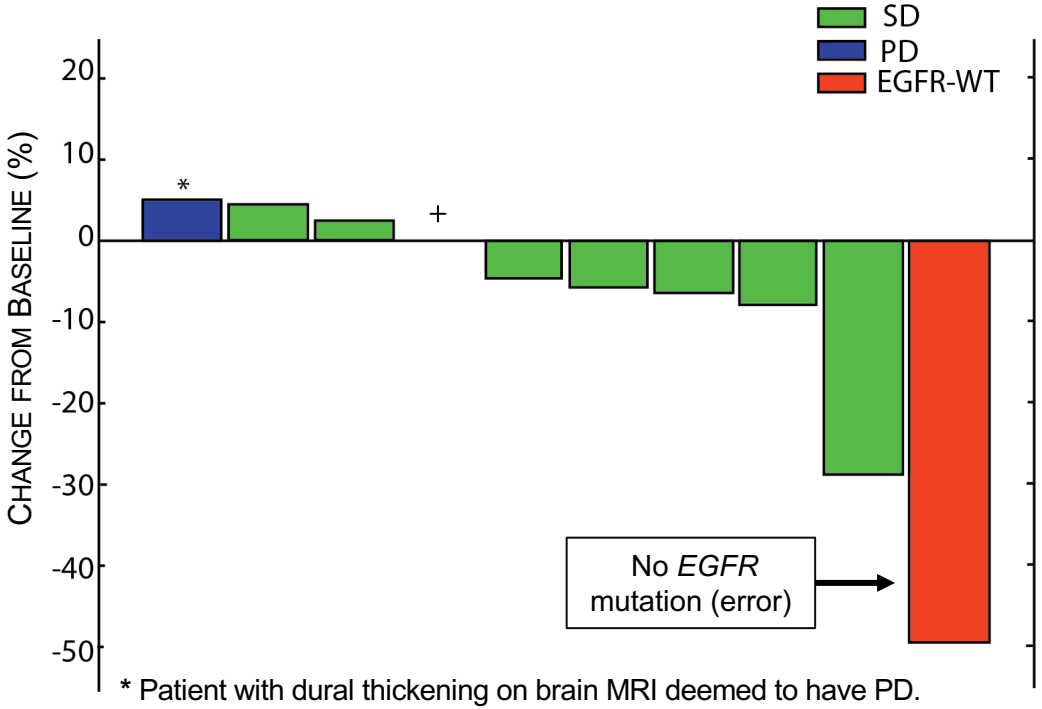


NCCN Guidelines. NSCLC. Version 3.2022. Updated 3/16/2022. Tan AC, Tan DSW. *J Clin Oncol*. 2022;40(6):611-625

Poor Efficacy in *EGFR*+ NSCLC

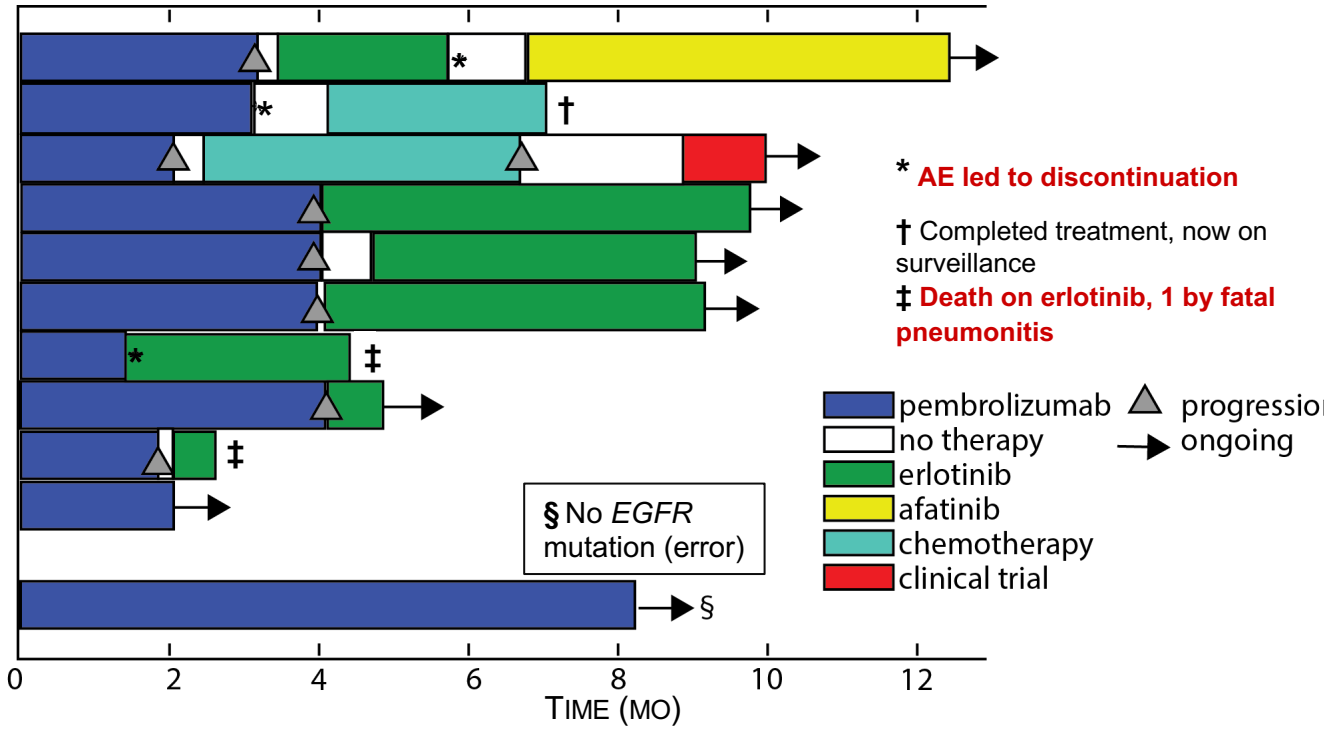
- Phase 2 study of pembrolizumab in patients with PD-L1+, *EGFR*-mutated advanced NSCLC
- Planned to enroll 25 patients; stopped for futility at 11 patients

Best Response for Target Lesions



* Patient with dural thickening on brain MRI deemed to have PD.
† Patient had CR of target lesion but nontarget progression on first scan.

Time on Trial and Subsequent Therapies



Lisberg A et al. *J Thorac Oncol*. 2018;13(8):1138-1145.

Role of Driver Mutations — Not Black & White!

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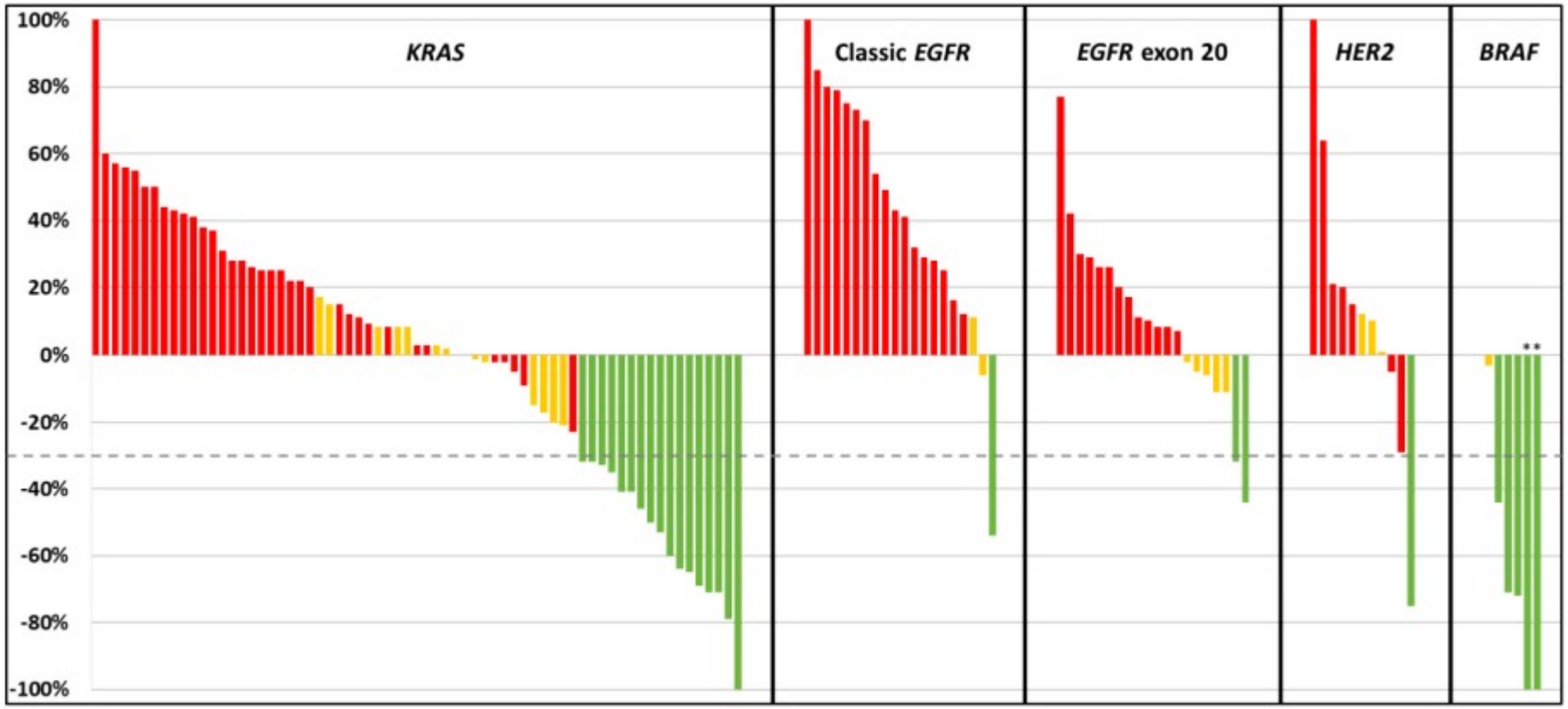
Overall Response Rate with Frontline Mono-ICI



Negrao MV et al. *J Immunother Cancer*. 2021 Aug;9(8):e002891.

ICI, Immune Checkpoint Inhibitor.

IMMUNOTHERAPY → TKI: A PATH TO TOXICITY

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REFERENCE	PHASE	ONCOGENIC DRIVER	N	ARMS/TREATMENT	SAFETY
Lin et al.	RETROSPECTIVE	**ALK (3), ROS1 (3), MET (5)**	11	PEMBRO →CRIZOTINIB NIVO → CRIZOTINIB ATEZO → CRIZOTINIB IPI/NIVO → CRIZOTINIB	**GRADE 3/4 ↑ ALT (45.5%, 5/11)** **GRADE 3/4 ↑ AST (36.4%, 4/11)**
Shoenfeld et al.	RETROSPECTIVE	**EGFR**	41	NIVO → OSIMERTINIB PEMBRO → OSIMERTINIB ATEZO → OSIMERTINIB	**SEVERE IRAE (15%, 6/41)** • **GRADE 3 PNEUMONITIS (4)** • **GRADE 3 COLITIS (1)** • **GRADE 4 HEPATITIS (1)**
Oshima et al.	RETROSPECTIVE	**EGFR**	70	NIVO → TKI	**ILD (25.7%, 18/70)**
Garassino et al.	PHASE 2	EGFR	111	TKIs → DURVALUMAB	GRADE 3/4 AE (5%, 6/111) • GRADE 3 PNEUMONITIS (1)

Adderly H et al. *Cancer Immunol Immunother*. 2021; 70(3): 589–595.

Immunotherapy → Osimertinib: Toxicity

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Retrospective review of patient records to identify severe toxicity with ICIs and EGFR TKIs, regardless of sequence, in patients with *EGFR*+ NSCLC (N=126)

- Osimertinib within 3 months after ICI → **24% severe irAE rate**
- Osimertinib before ICI → **0% severe irAE rate**

Patient No.	IO Regimen	Time on IO	Time From IO to Osimertinib	Time to Toxicity Onset After 1st Osimertinib Dose	Toxicity	Toxicity Grade	Need for Hospitalization?	Response to Steroids?
1	Nivolumab	14 days	29 days	24 days	Pneumonitis	3	Yes	Yes
2	Carboplatin, pemetrexed, pembrolizumab	21 days	23 days	15 days	Pneumonitis	3	No	Yes
3	Ipilimumab, nivolumab	392 days	22 days	167 days	Pneumonitis	3	Yes	Yes
4	Pembrolizumab	126 days	28 days	14 days	Colitis	3	Yes	No
5	Pembrolizumab	126 days	314 days	15 days	Pneumonitis	3	Yes	Yes
6	Nivolumab	68 days	39 days	39 days	Hepatitis	4	Yes	No

ICI, Immune Checkpoint Inhibitor. irAE, Immune-related adverse event

Schoenfeld AJ et al. *Ann Oncol*. 2019;30(5):839-844.

Ruling Out Targetable Molecular Alterations in Advanced NSCLC

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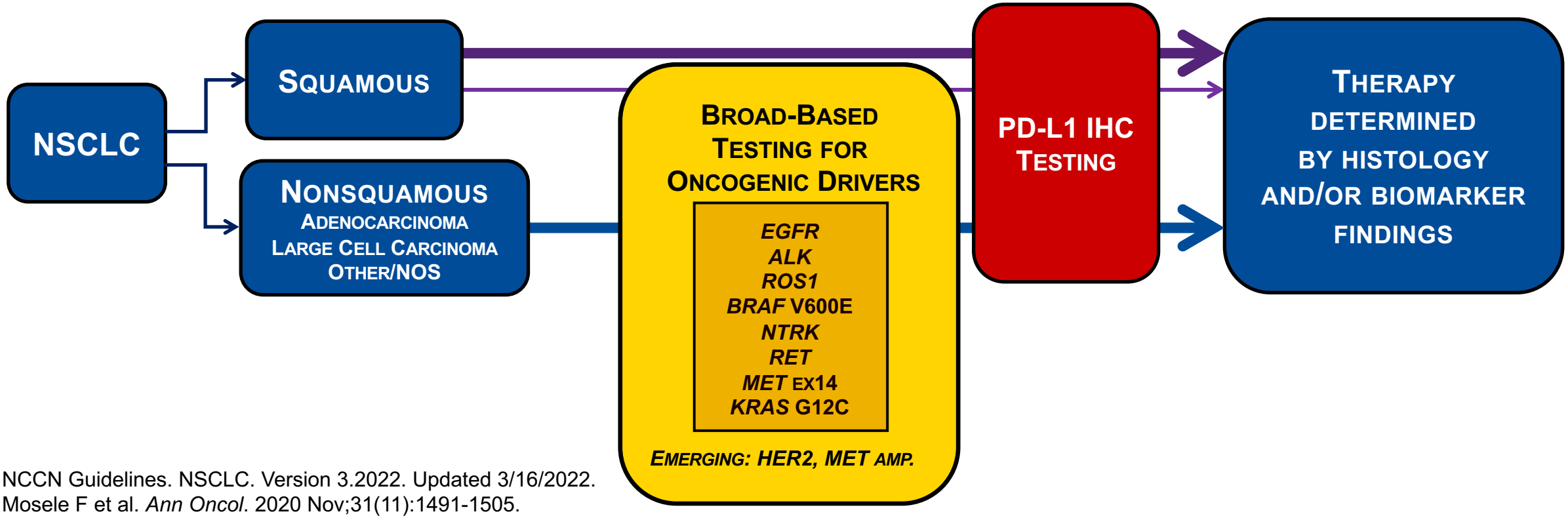
Biomarker testing at diagnosis is essential to guide frontline treatment decisions.



NCCN Guidelines. NSCLC. Version 3.2022. Updated 3/16/2022.
Mosele F et al. *Ann Oncol*. 2020 Nov;31(11):1491-1505.

Testing Guidelines Vary Internationally…

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Predictive Biomarkers	ESMO Guidelines	NCCN Guidelines	CAP/IASLC/ AMP Guidelines	ASCO Guidelines	Pan-Asian Guidelines
EGFR	🟢	🟢	🟢	🟢	🟢
ALK	🟢	🟢	🟢	🟢	🟢
ROS1	🟢	🟢	🟢	🟢	🟢
BRAF	🟢	🟢	🔵	🟢	🟢
PD-L1	🟢	🟢	🔴	🔴	🟢
NTRK	🟢	🔵	🔴	🔴	🔴

Emerging Biomarkers	ESMO Guidelines	NCCN Guidelines	CAP/IASLC/ AMP Guidelines	ASCO Guidelines	Pan-Asian Guidelines
KRAS	🔴	🔵	🟡	🔵	🔴
MET	🔴	🔵	🔵	🔵	🔴
RET	🔴	🔵	🔵	🔵	🔴
ERBB2/ HER2	🔴	🔵	🔵	🔵	🔴
TMB	🔴	🔴	🔴	🔴	🔴

🟢 **Testing Recommended**

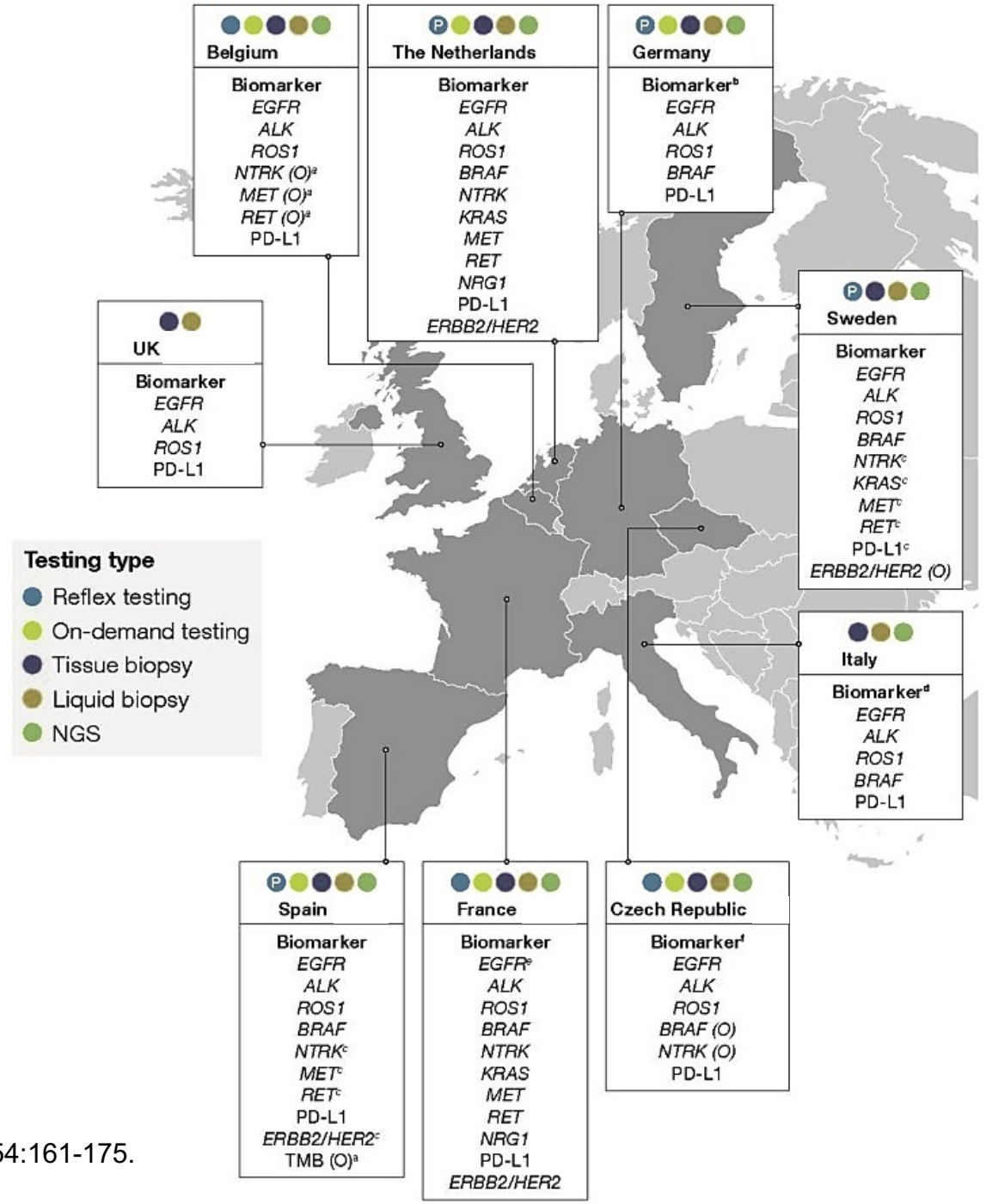
🔵 **Expanded panel testing recommended**

🟡 **Single gene or expanded panel testing recommended**

🔴 **No guideline recommendations to date**

Kerr KM et al. *Lung Cancer*. 2021 Apr;154:161-175.

…AND BY COUNTRY



Kerr KM et al. *Lung Cancer*. 2021 Apr;154:161-175.

When to Order an NGS Test in NSCLC

- NGS is indicated in advanced NSCLC:
  - To detect **ANY AND ALL** targetable molecular alterations
  - To rule out actionable targets prior to initiation of immunotherapy
  - To prevent tissue exhaustion prior to completion of the required profiling
  - For cost containment
  - To detect emerging biomarkers that may denote clinical trial eligibility
- RNA-based sequencing tests may be more sensitive to detect gene fusions and *MET* exon-14 alterations than DNA-based methods.
- Consider rapid assays in addition to NGS for assessment of common markers to improve turnaround time.

Relative Sensitivity of Molecular Diagnostic Techniques in NSCLC

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	Tissue PCR Sequencing	Tissue allele specific PCR sequencing	Tissue FISH	Tissue IHC	Tissue NGS	ctDNA PCR	ctDNA NGS	Tissue RNA
EGFR (sensitizing and T790M)	+	++	0	0	++	+	+	+
ERBB2/HER2 Mutation	+	++	0	0	++	+	+	+
*MET*ex14 mutation	0	++	0	0	++	+	+	++
BRAF mutation	+	++	0	0	++	+	+	+
KRAS mutation	+	++	0	0	++	+	+	+
ALK rearrangement	0	0	++	++	+	+	+	++
ROS1 rearrangement	0	0	++	0	+	0	+	++
MET amplification	0	0	++	0	+	0	+	+
RET rearrangement	0	0	++	0	+	+	+	++
PD-L1 protein expression	0	0	0	++	0	0	0	0
NTRK fusion	0	0	++	+	+	0	+	++
NRG1 fusion	0	0	++	+	+	0	+	++

++ Highest Sensitivity + Lower Sensitivity 0: Not Useful

Sequist LV, Neal JW. In: UpToDate, Lilenbaum RC (Ed), UpToDate, Waltham, MA. https://bit.ly/3ml2k5l

TISSUE, PLASMA, OR BOTH?

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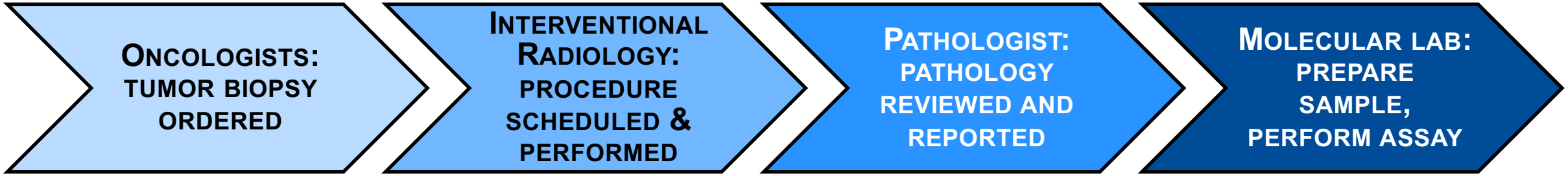
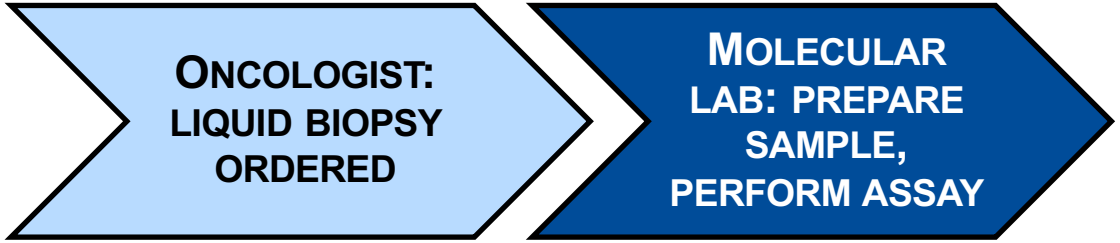
- Tumor biopsies involve multiple steps:



- Liquid biopsies (plasma genotyping) involve fewer steps:



Current Recommendations for ctDNA Analysis

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	IASLC	ASCO/CAP	ESMO NSCLC	NCCN NSCLC
Plasma over serum	✓	✓		
Prioritise histologic diagnosis	✓	✓		✓
If tissue insufficient, medically unfit, or expected delay, consider plasma testing	✓			✓
Plasma genotyping at progression to detect targetable alteration	✓	✓	✓	✓
If plasma negative, tissue biopsy recommended	✓	✓	✓	✓
A positive, actionable ctDNA-detected alteration is sufficient to initiate treatment	✓	✓	✓	✓
NGS is preferred for detecting fusions	✓			
Reports to include platform used and molecular findings	✓	✓		
Establish analytical validity of each assay	✓	✓		✓
Account for CHIP-related alterations	✓	✓		✓

Garcia-Pardo M et al. *Br J Cancer*. 2022 Mar 26. Online ahead of print.

cfDNA-NGS vs Tissue Molecular Tests

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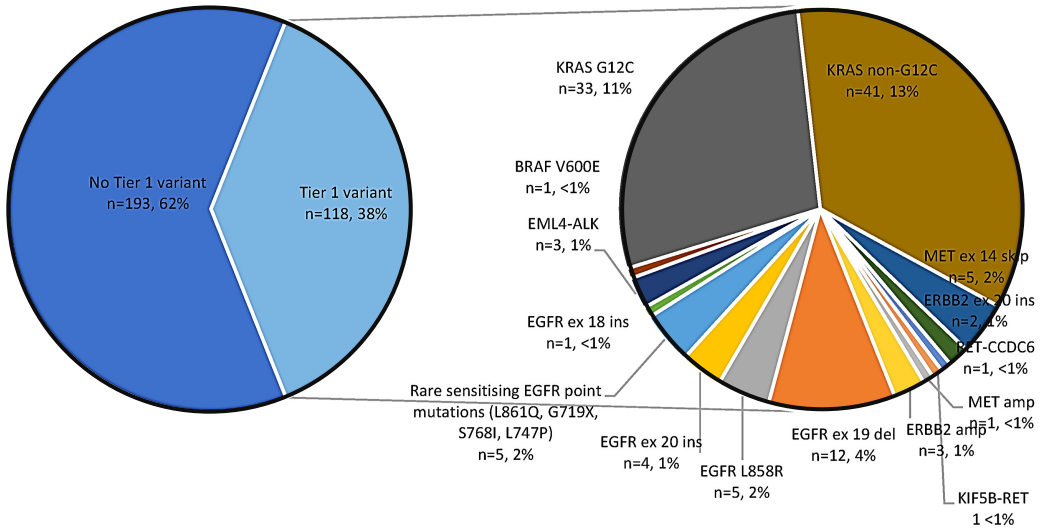
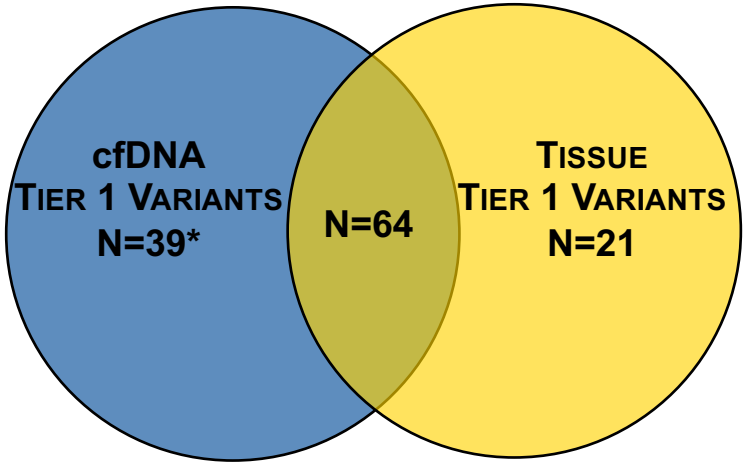
Tier-1 variants detected on cfDNA-NGS (*N* = 311)

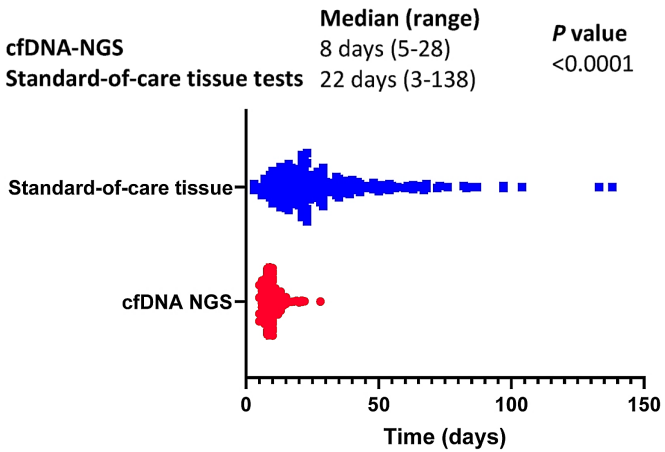


Concordance: 243 Paired Tests



*** 17 of 39 (44%) additional variants detected by cfDNA-NGS alone were actionable**

Turn-Around Times



Cui W et al. *Eur J Cancer*. 2022;171:44-54.

PD-L1 IHC Assays for Frontline Mono-ICI

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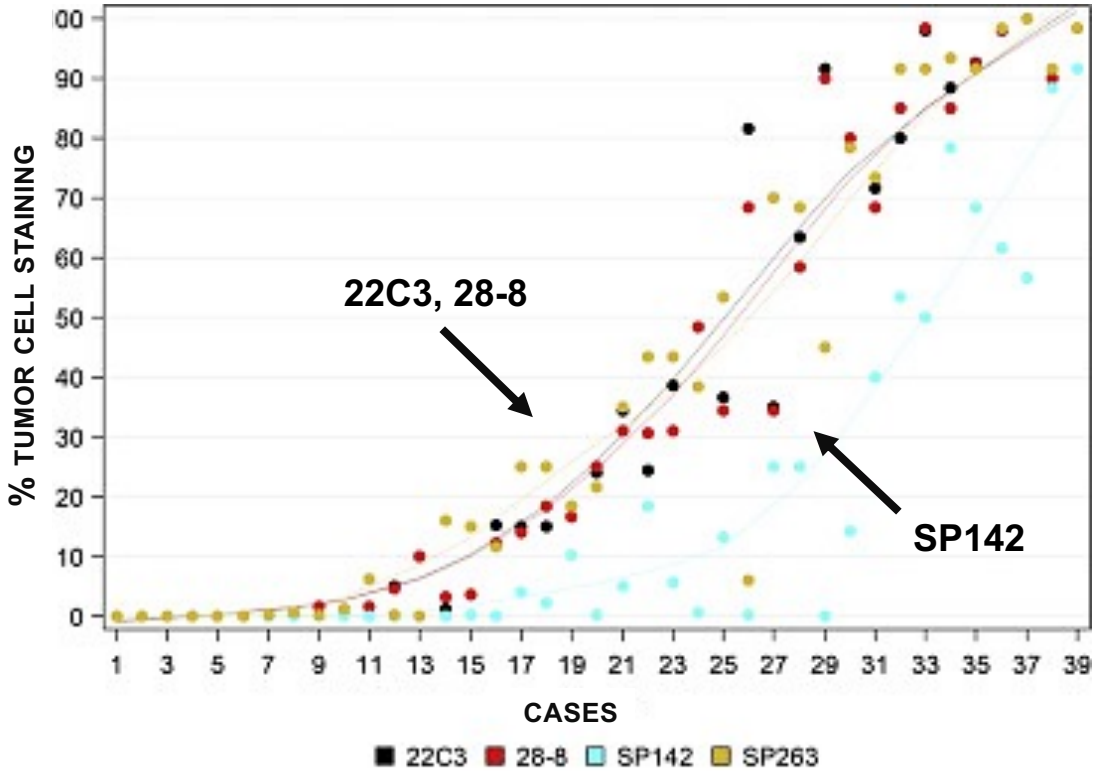
PD-L1 IHC Assays for ICI Alone

Immunotherapy	Clone	Frontline Indication
PEMBROLIZUMAB	22C3	US: TPS ≥1% EU: TPS ≥50%
CEMIPLIMAB	22C3	TPS ≥50%
ATEZOLIZUMAB	SP142	TC ≥50% or IC ≥10%
IPILIMUMAB + NIVOLUMAB	28-8	US: TPS ≥1% EU: NOT APPROVED ALONE

ICI, Immune Checkpoint Inhibitor.

Blueprint PD-L1 IHC Assay Comparison Project



FDA. List of Cleared or Approved Companion Diagnostic Devices. Updated 6/14/22. https://bit.ly/34w6P7i. Pembrolizumab. FDA prescribing information. Updated 5/20/22; Pembrolizumab. EMA EPAR. Updated 5/23/22. Atezolizumab. FDA prescribing information. Updated 1/21/22. Atezolizumab, EMA EPAR, product information. Updated 5/11/22. Cemiplimab. FDA prescribing information. Updated 2/22/2021; Cemiplimab, EMA EPAR. Updated 2/4/2022; Nivolumab, FDA prescribing information. Updated 5/27/22. Nivolumab, EMA EPAR. Updated 5/10/22. Hirsch FR et al. *J Thorac Oncol*. 2017;12:208-222.

Immunotherapy Extends Survival in Advanced Nondriver NSCLC

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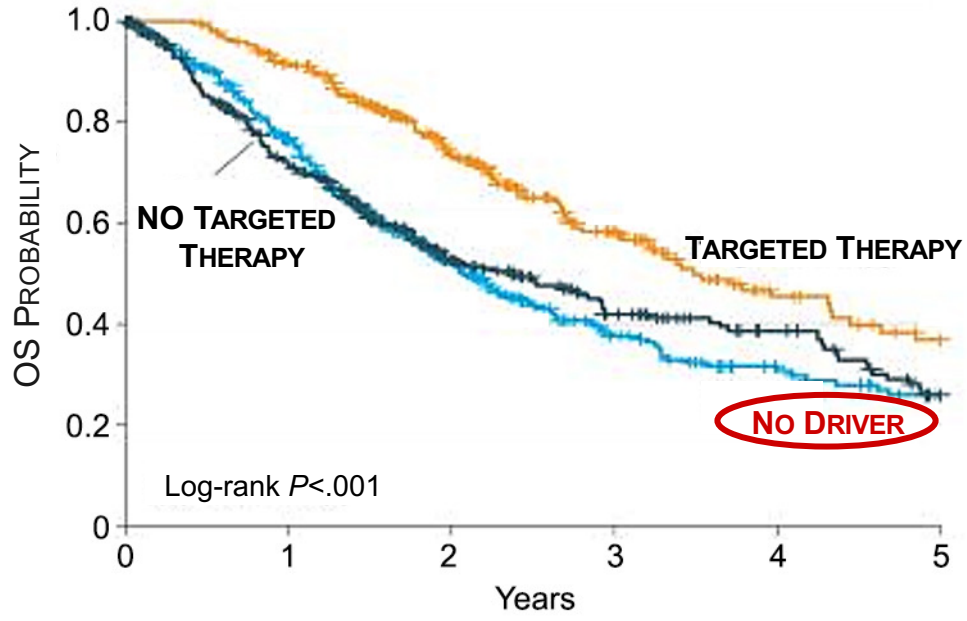
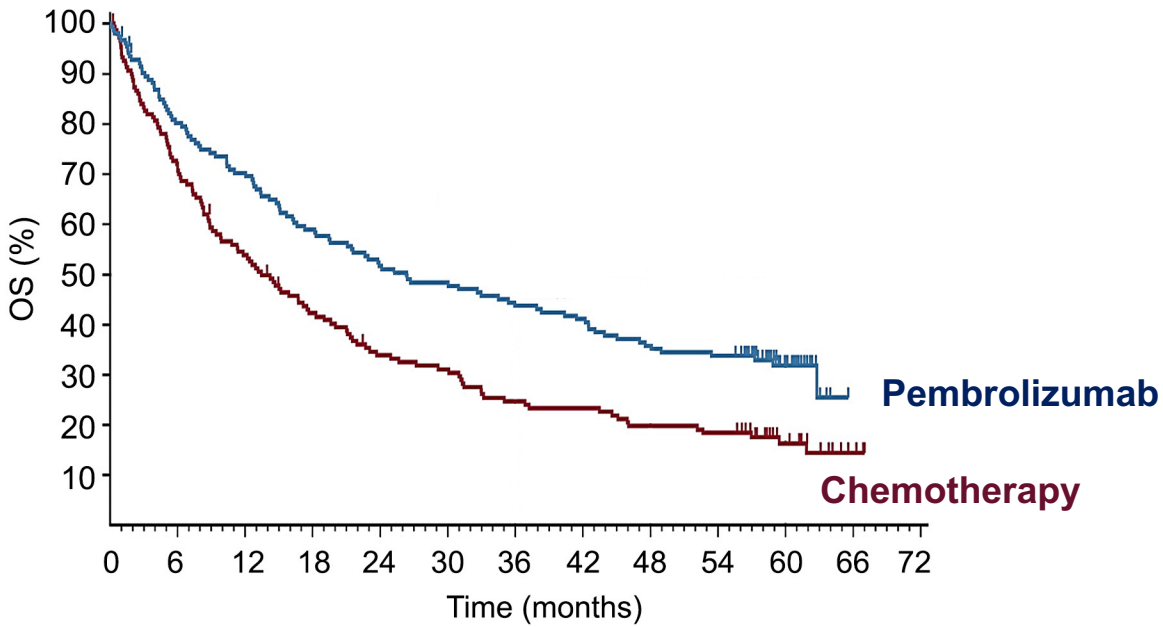
Oncogenic Driver Targets

Patients with a driver mutation who did and did not receive targeted therapy, and patients without a driver mutation



Pembrolizumab

PD-L1 ≥50%, EGFR, ALK *WT*
(KEYNOTE-024)



Kris MG et al. *JAMA*. 2014;311(19):1998-2006; Reck M et al. *J Clin Oncol*. 2021;39(21):2339-2349.

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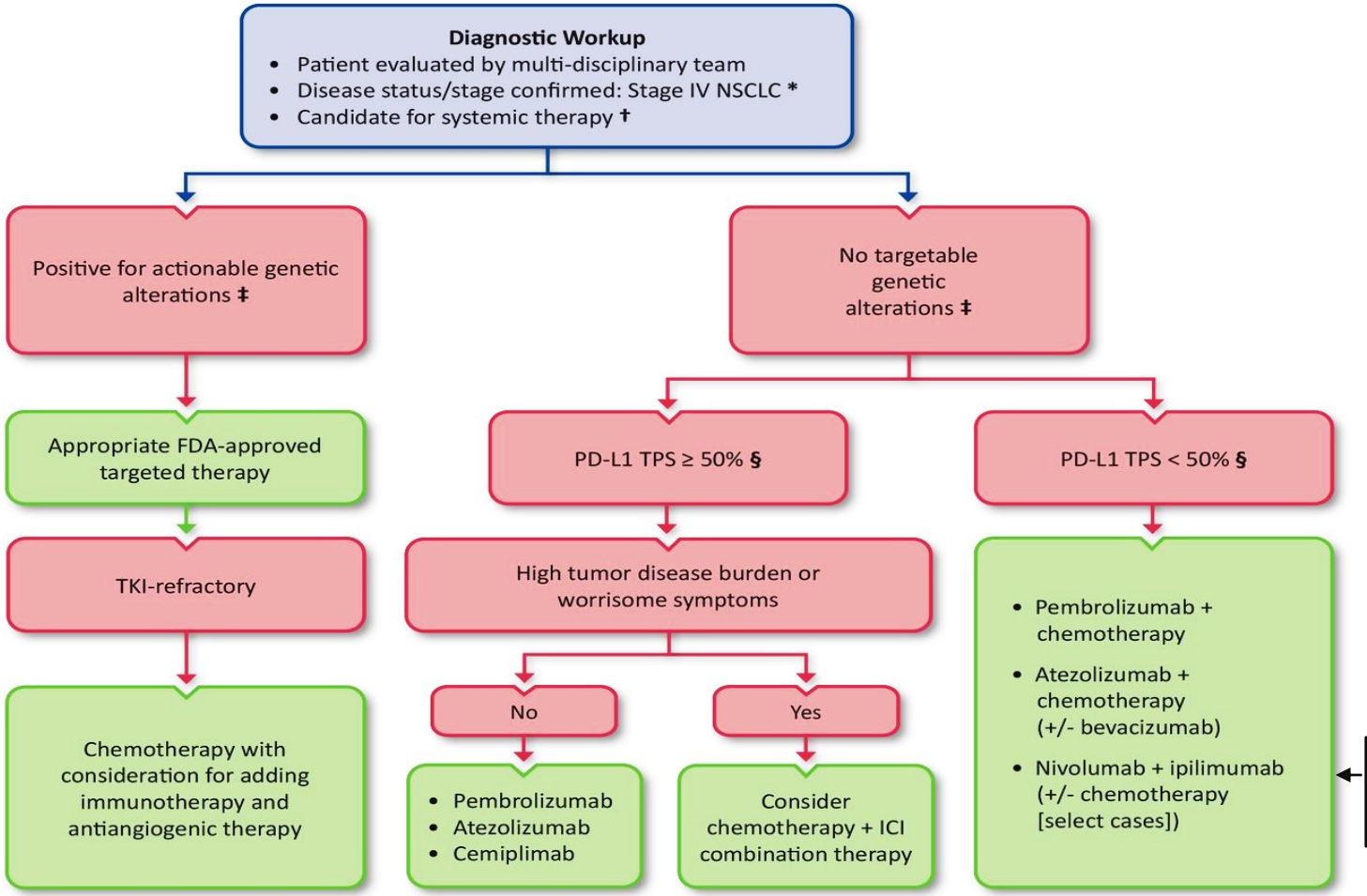
Selecting Frontline Immunotherapy in Advanced NSCLC

Jared M. Weiss, MD
Professor, Medicine
Lineberger Comprehensive Cancer Center
The University of North Carolina at Chapel Hill
Chapel Hill, United States

SITC: Advanced NSCLC Treatment Algorithm



*PD-L1 testing may be considered in select patients with stage III NSCLC to determine eligibility for adjuvant ICIs or predict clinical benefit in the unresectable setting. **†A multidisciplinary approach is recommended for patients with comorbid active autoimmune conditions, solid organ transplant, baseline ILD, or high pneumonitis risk**. ‡Comprehensive next-generation sequencing (NGS) is recommended for molecular testing. If NGS is not available, tumor tissue should be tested for molecular driver genetic alterations.§ The 22C3, 28–8, and SP263 assays are interchangeable; the SP142 assay is not.

Govindan R et al. *J Immunother Cancer*. 2022 May;10(5):e003956. Nivolumab, EMA EPAR. Updated 5/10/22.

Frontline Immunotherapy: Data at a Glance

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TRIAL	COMPARISON	SELECTION	ORR, %	PFS HR	OS HR
KEYNOTE-024	**PEMBRO** VS. PLAT-DOUBLET CHEMO	PD-L1 ≥50%	46.1 vs 31.1	0.50	0.62
IMPOWER110	**ATEZO** VS. PLAT-DOUBLET CHEMO	PD-L1 ≥50% (TC) OR 10% (IC)	40.2 vs 28.6	0.59	0.69
EMPOWER-LUNG 1	**CEMIPLIMAB** VS. PLAT-DOUBLET CHEMO	PD-L1 ≥50%	39.2 vs 20.4	0.54	0.57
KEYNOTE-042	**PEMBRO** VS. PLAT-DOUBLET CHEMO	PD-L1 ≥1%	27.3 vs 26.7	1.03	0.79
KEYNOTE-189	CARBO/PEM **± PEMBRO**	PD-L1 UNSELECTED, **NON-SQ**	48.3 vs 19.9	0.49	0.56
IMPOWER130	CARBO/NAB-PAC **± ATEZO**	PD-L1 UNSELECTED, **NON-SQ**	49.2 vs 31.9	0.64	0.79
IMPOWER150	CARBO/PAC + BEV **± ATEZO**	PD-L1 UNSELECTED, **NON-SQ**	63.5 vs 48.0	0.57	0.80
KEYNOTE-407	CARBO/PAC OR NAB-PAC **± PEMBRO**	PD-L1 UNSELECTED, **SQ**	62.6 vs 38.8	0.59	0.71
EMPOWER-LUNG 3	PLAT-DOUBLET CHEMO **± CEMIPLIMAB**	PD-L1 UNSELECTED **SQ/NON-SQ**	43.3 vs 22.7	0.56	0.71
CHECKMATE 227	**IPI/NIVO** VS. PLAT-DOUBLET CHEMO	PD-L1 ≥1%	36.4 vs 30.0	0.79	0.77
		PD-L1 **<1%**	27.3 vs 23.1	0.75	0.65
CHECKMATE 9LA	PLAT-DOUBLET CHEMO **± IPI/NIVO**	PD-L1 ≥1%	42.2 vs 27.5	0.71	0.74
		PD-L1 **<1%**	31.9 vs 20.2	0.69	0.67

Reck M, et al. *J Clin Oncol*. 2021;39(21):2339-2349. Jassem J, et al. *J Thorac Oncol*. 2021;16(11):1872-1882. Sezer A, et al. *Lancet*. 2021;397(10274):592-604. Rodriguez-Abreu D, et al. *Ann Oncol*. 2021;32(7):881-895. West H, et al. *Lancet Oncol*. 2019;20(7):924-937. Socinski M, et al. *J Thorac Oncol*. 2021;16(11):1909-1924. Robinson AG, et al. ELCC 2021. Abstract 970. Gogishvili M, et al. ESMO 2021. Abstract LBA51. Paz-Ares LG, et al. *J Thorac Oncol*. 2022;17(2):289-308. Hellmann MD et al. *NEJM*. 2019;381:2020. Brahmer JR et al. ASCO 2022. Poster LBA9025. Paz-Arez LG et al. ASCO 2022. Poster LBA9026.

CONSIDERING PD-L1 EXPRESSION LEVELS

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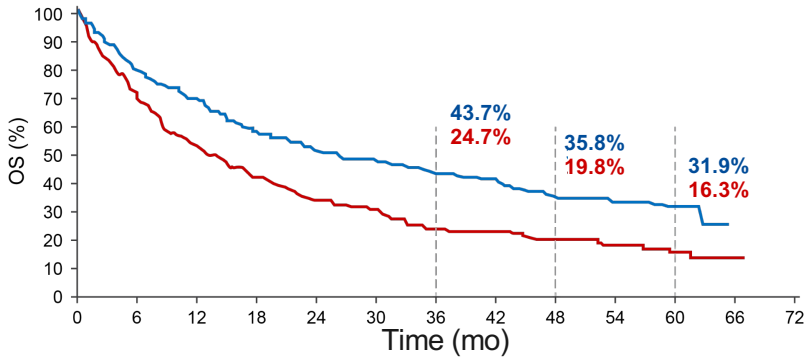
KEYNOTE-024, 5Y DATA

TPS ≥50%

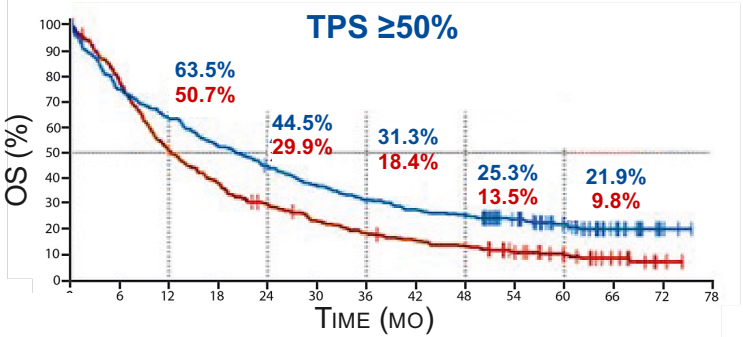


Median OS (95% CI): **26.3** vs **13.4** mo
HR (95% CI): **0.62** (0.48, 0.81)

PEMBROLIZUMAB
CHEMOTHERAPY

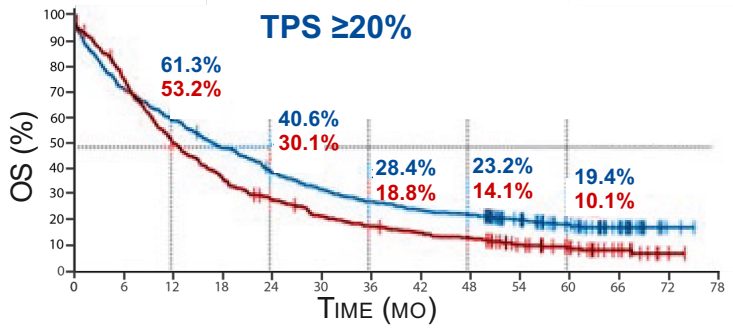
KEYNOTE-042, 5Y DATA

TPS ≥50%



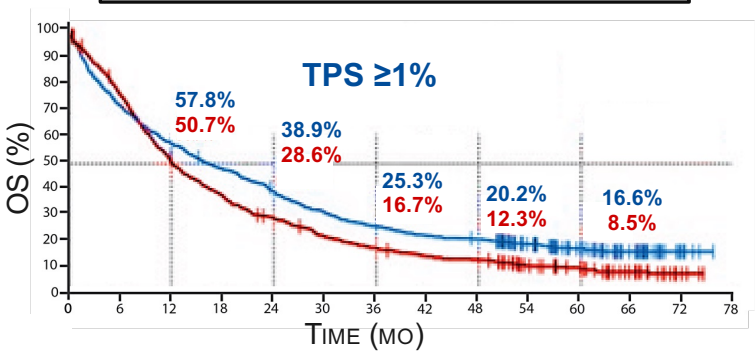
Median OS (95% CI): **20.2** vs **12.2** mo
HR (95% CI): **0.68** (0.57, 0.81)

TPS ≥20%



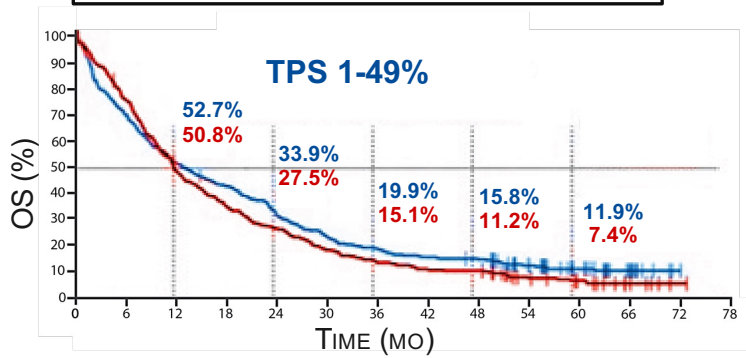
Median OS (95% CI): **18.0** vs **13.0** mo
HR (95% CI): **0.75** (0.64, 0.87)

TPS ≥1%



Median OS (95% CI): **16.4** vs **12.1** mo
HR (95% CI): **0.79** (0.70, 0.89)

TPS 1-49%



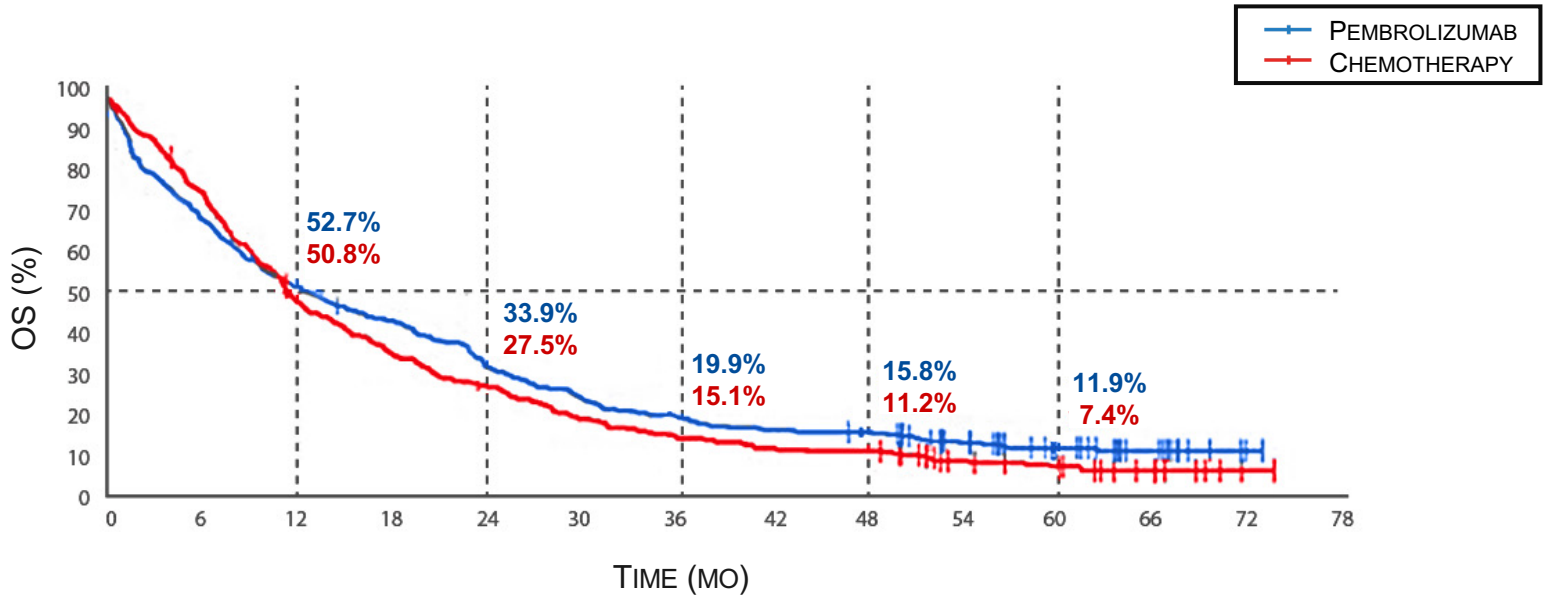
Median OS (95% CI): **13.4** vs **12.1** mo
HR (95% CI): **0.88** (0.75, 1.04)

Reck M et al. *J Clin Oncol*. 2021;39(21):2339-2349. De Castro G et al. *J Immunother Cancer*. SITC 2021.

PD-L1 Levels of 1-49%

Clinical OLYMPICS℠

KEYNOTE-042, 5Y Data



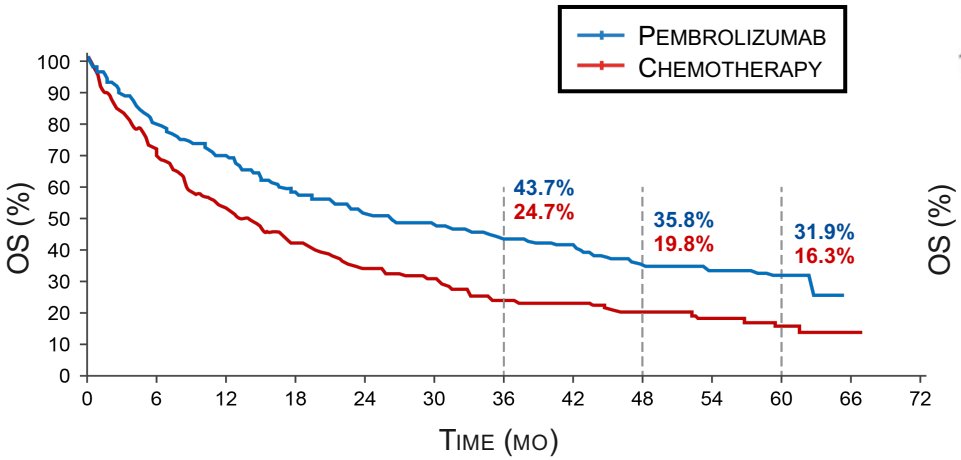
Median OS (95% CI): **13.4** vs **12.1** mo
HR (95% CI): **0.88** (0.75, **1.04**)

De Castro G et al. *J Immunother Cancer*. SITC 2021.

Survival Benefit: Frontline IO-Mono in NSCLC with High PD-L1 Expression

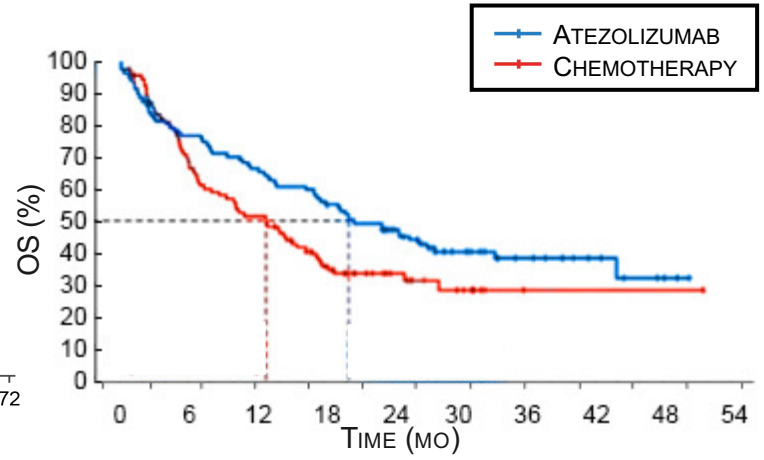
Clinical OLYMPICS℠

KEYNOTE-024
TPS ≥50%



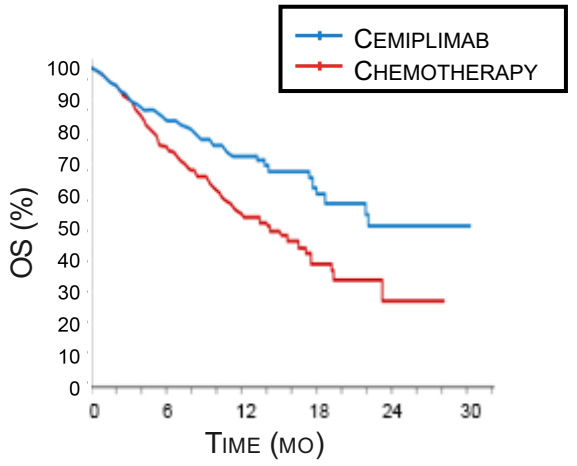
Median OS (95% CI): **26.3** vs **13.4** mo
HR (95% CI): **0.62** (0.48, 0.81)

IMpower 110*
TC ≥50% OR IC ≥10%



Median OS (95% CI), **20.2** vs **13.0** mo
HR (95% CI): **0.69** (0.48, 0.99)

EMPOWER-Lung 1
TPS ≥50%

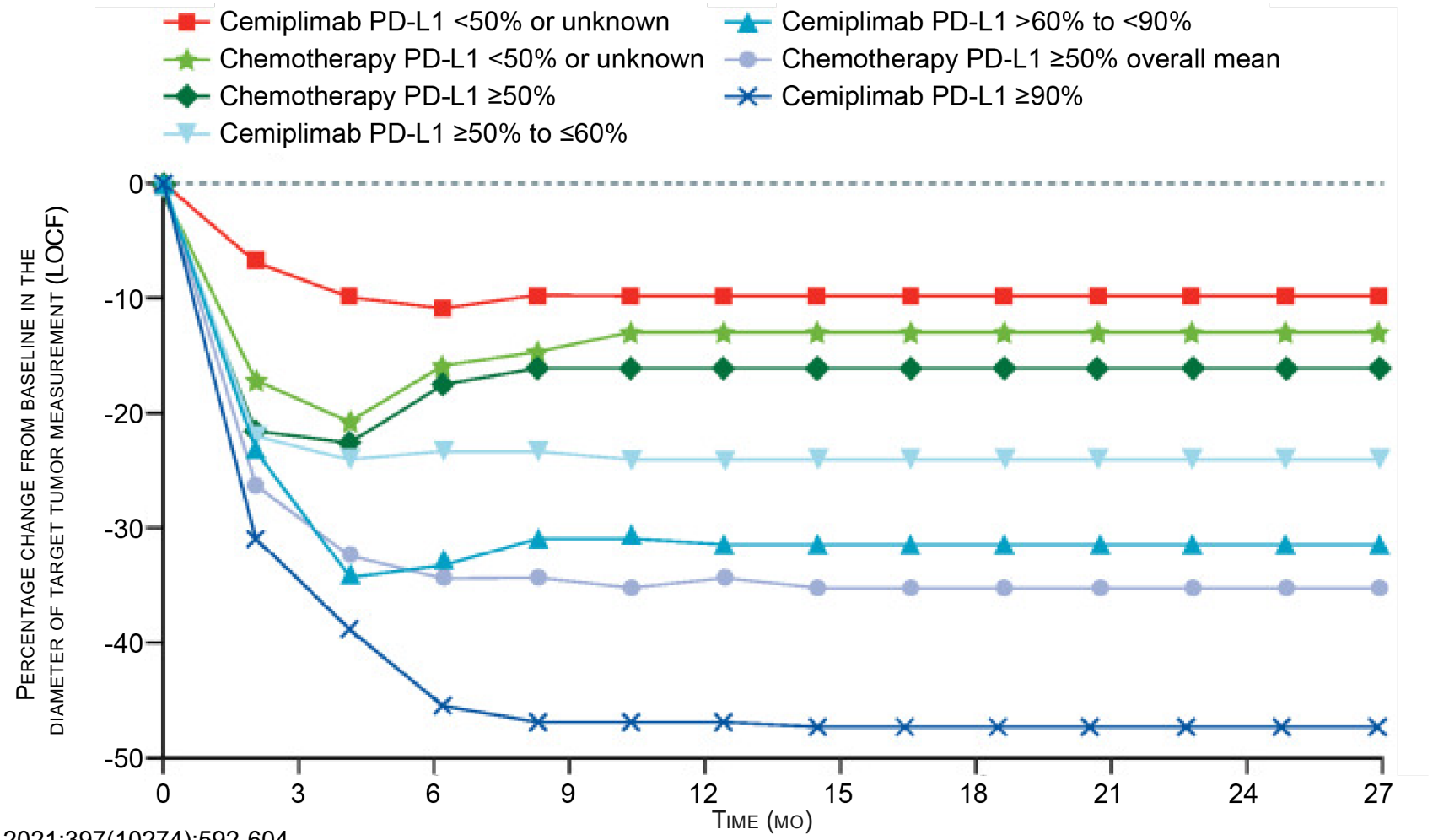


Median OS (95% CI), **NR** (17.9, NE) vs **14.2** mo
HR (95% CI): **0.57** (0.42, 0.77); *P*=.0002

* Adjusted for NPT, Non-Protocol Therapy

Reck M et al. *J Clin Oncol*. 2021;39(21):2339-2349. Jassem J et al. *J Thorac Oncol*. 2021;16(11):1872-1882. Sezer A et al. *Lancet*. 2021;397(10274):592-604.

Change in Tumor Size by PD-L1 Level

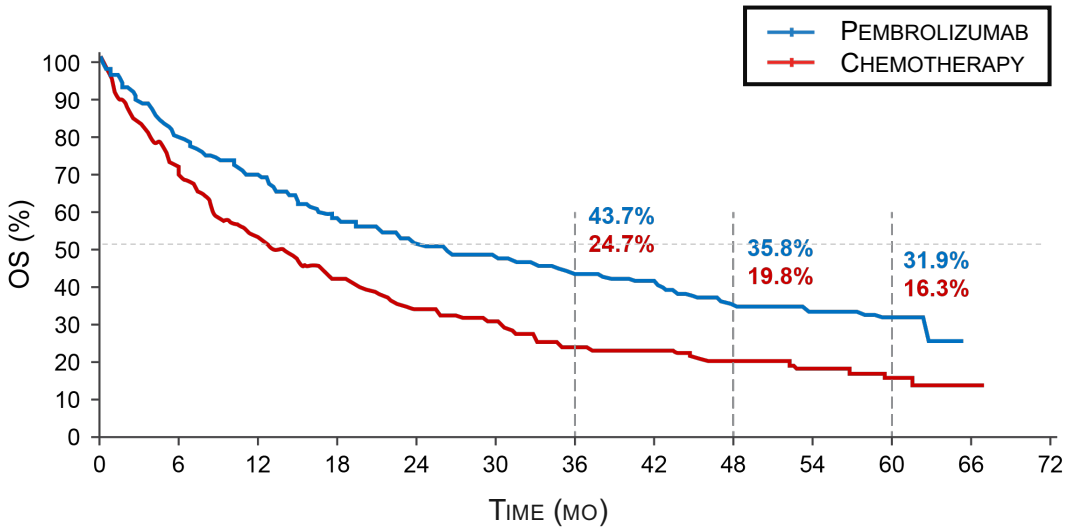


Sezer A et al. *Lancet*. 2021;397(10274):592-604.

Does Chemo Add Benefit with PD-L1 ≥50%?

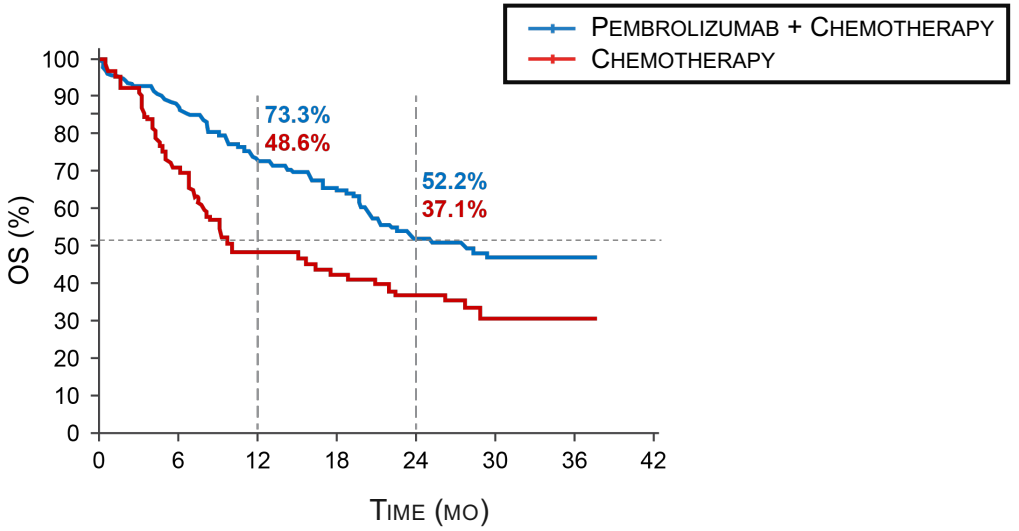
Clinical OLYMPICS℠

KEYNOTE-024 (81-82% non-SQ)
PD-L1 ≥50%



Median OS (95% CI), **26.3** (18.3, 40.4) vs **13.4** (9.4, 18.3) mo
HR (95% CI): **0.62** (0.48, 0.81)

KEYNOTE-189 (non-SQ)
PD-L1 ≥50% Subgroup



Median OS (95% CI), **27.7** (20.4, NR) vs **10.1** (7.5, 22.0) mo
HR (95% CI): **0.59** (0.40, 0.86)

Reck M et al. *J Clin Oncol*. 2021;39(21):2339-2349. Rodriguez-Abreu D et al. *Ann Oncol*. 2021;32(7):881-895.

FDA Pooled Analysis: 1L Chemo-IO vs. IO in NSCLC with PD-L1 ≥50% (N=3,189)

Clinical OLYMPICS℠

Chemo-IO Trials		IO-only Trials	
Trial	Investigational Regimen	Trial	Investigational Regimen
KEYNOTE-021*	Pembrolizumab + Chemo**	CheckMate 026	Nivolumab**
KEYNOTE-189	Pembrolizumab + Chemo**	KEYNOTE-024	Pembrolizumab**
KEYNOTE-407	Pembrolizumab + Chemo**	KEYNOTE-042	Pembrolizumab**
IMpower150	Atezolizumab + Bevacizumab + Chemo***	IMpower110	Atezolizumab**
IMpower130	Atezolizumab + Chemo**	CheckMate 227	Nivolumab + Ipilimumab**
CheckMate-9LA	Nivolumab + Ipilimumab + Chemo**	EMPOWER-Lung 1	Cemiplimab**

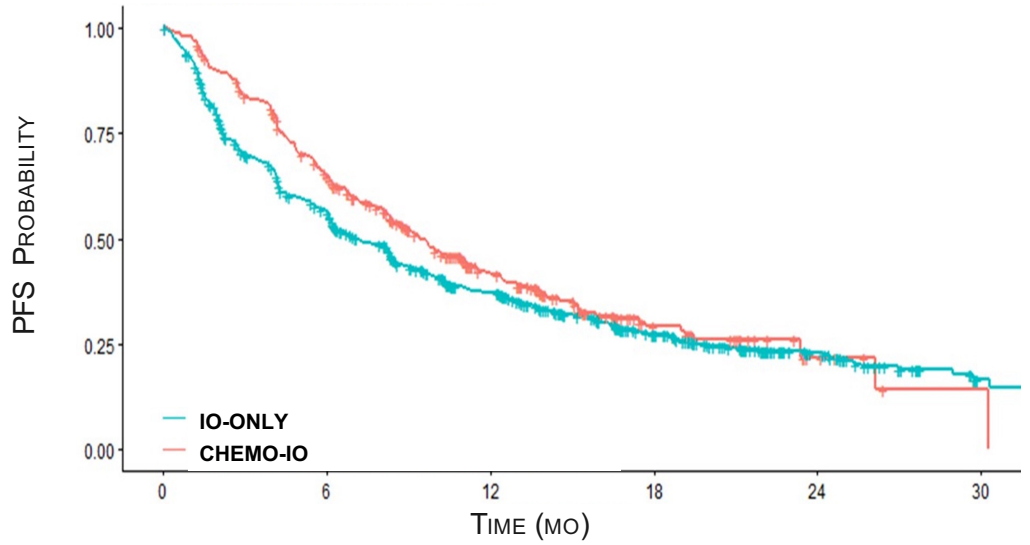
* Cohort G
** Control arms: Platinum-based doublet chemotherapy
*** Control arm in IMpower150: Bevacizumab + platinum-based doublet chemotherapy

Akinboro O et al. ASCO 2022. Abstract 9000.

FDA Pooled Analysis: Exploratory Survival Endpoints

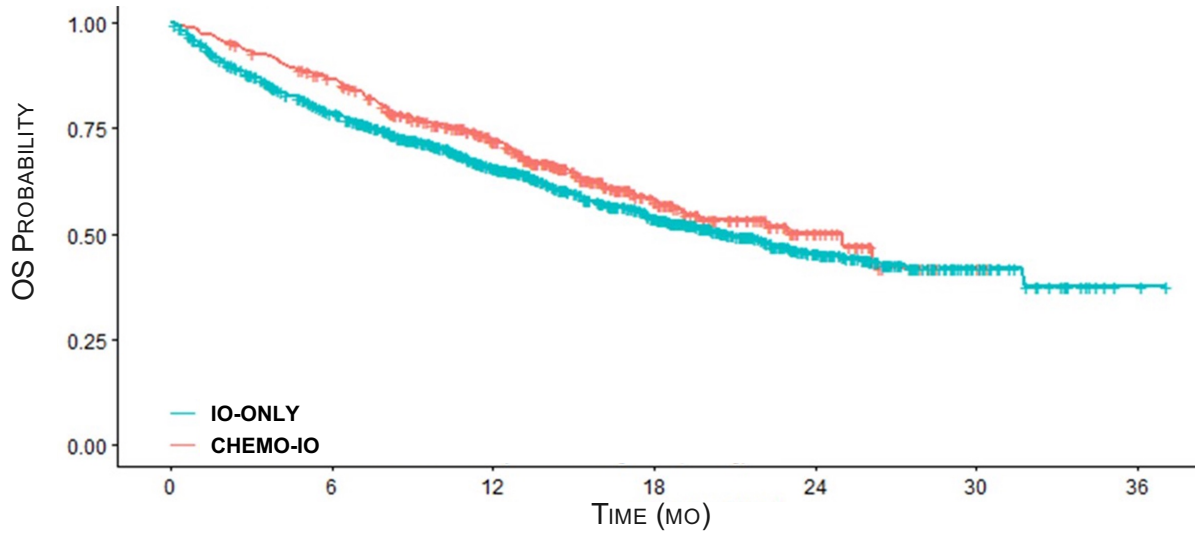
Clinical OLYMPICS℠

PFS in Chemo-IO vs. IO-only Arms of Randomized Trials Supporting Approval in 1L NSCLC, PD-L1 ≥50%



Median PFS (95% CI), **9.6** (8.4,11.1) vs **7.1** (6.3, 8.3) mo
HR (95% CI): 0.69 (0.55, 0.87)

OS in Chemo-IO vs. IO-only Arms of Randomized Trials Supporting Approval in 1L NSCLC, PD-L1 ≥50%



Median OS (95% CI), **25.0** (19.0, NE) vs **20.9** (18.5, 23.1) mo
HR (95% CI): 0.82 (0.62, **1.08**)

ORR: 61% vs 43%
OR (95% CI): 1.2 (1.1, 1.3)

Akinboro O et al. ASCO 2022. Abstract 9000.

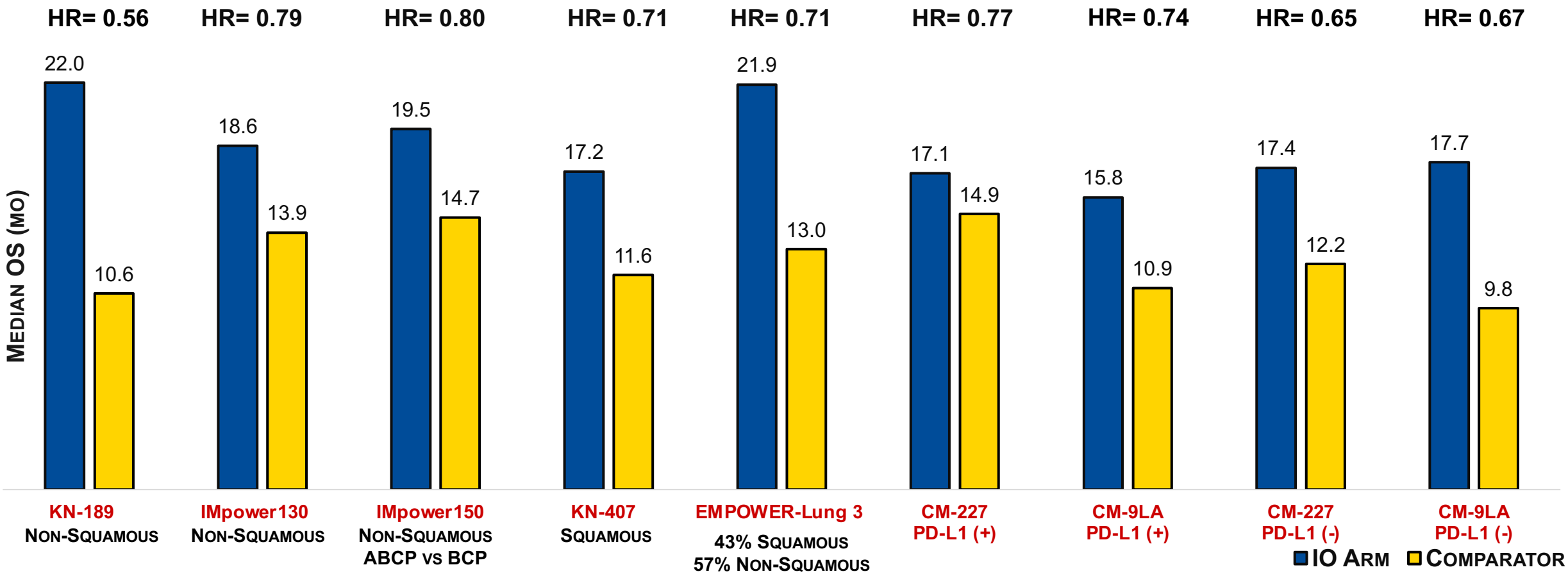
Demographic & Baseline Characteristics

Clinical OLYMPICS℠

		Chemo-IO (*N*=455)	IO alone (*N*=1,298)	Chemo (*N*=1,436)	Overall (*N*=3,189)
Age	Median	65	64	64	64
	<65 years, %	49	53	50	51
	65-75 years, %	41	36	39	38
	≥75 years, %	10	11	11	11
Sex	Female	37	29	31	31
Race	White, %	91	77	80	80
	Black, %	1	1	2	1
	Asian, %	8	20	16	16
Smoking History	Ever Smoked, %	87	89	88	89
ECOG PS	≥1, %	59	68	67	66
Histology	Non-Squamous, %	78	69	68	70

Akinboro O et al. ASCO 2022. Abstract 9000.

COMBINATION THERAPIES: MEDIAN OS

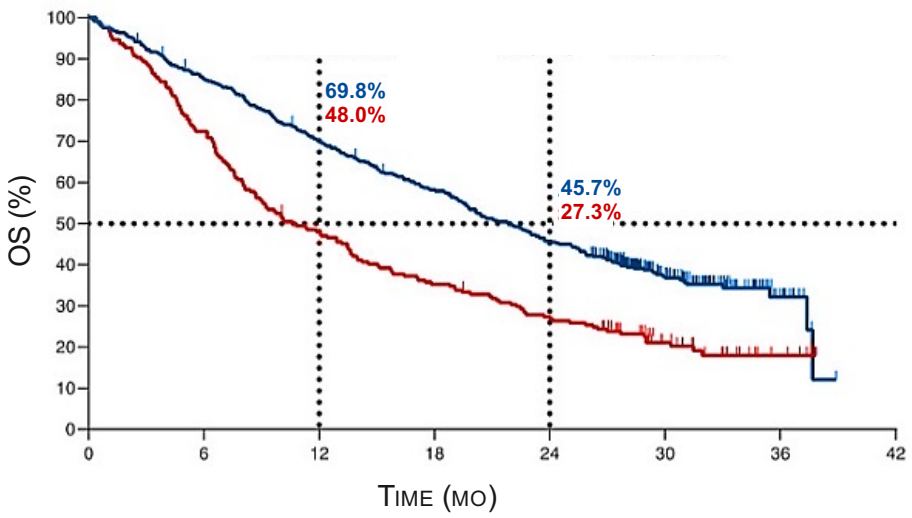


Rodriguez-Abreu D et al. *Ann Oncol*. 2021;32(7):881-895. West H et al. *Lancet Oncol*. 2019;20(7):924-937. Socinski M et al. *J Thorac Oncol.* 2021;16(11):1909-1924. Robinson AG et al. ELCC 2021. Abstract 970. Brahmer JR et al. ASCO 2022. Abstract LBA9025. Paz-Ares LG et al. ASCO 2022. Abstract LBA9026.

IMPACT OF PD-L1 IN CHEMO-IO: KN-189

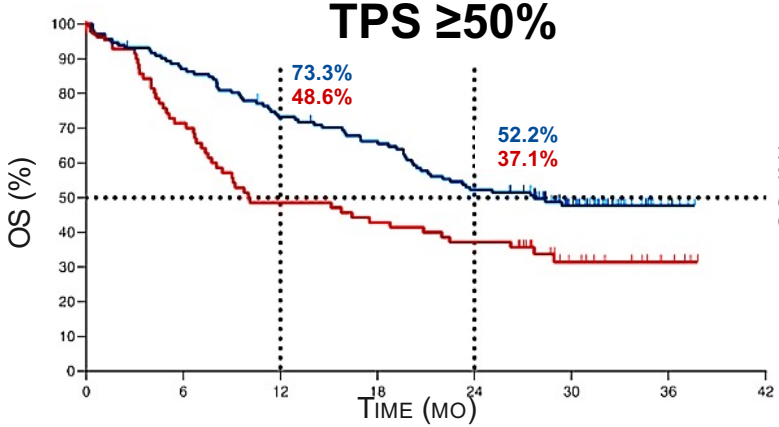
Clinical OLYMPICS℠

ITT POPULATION



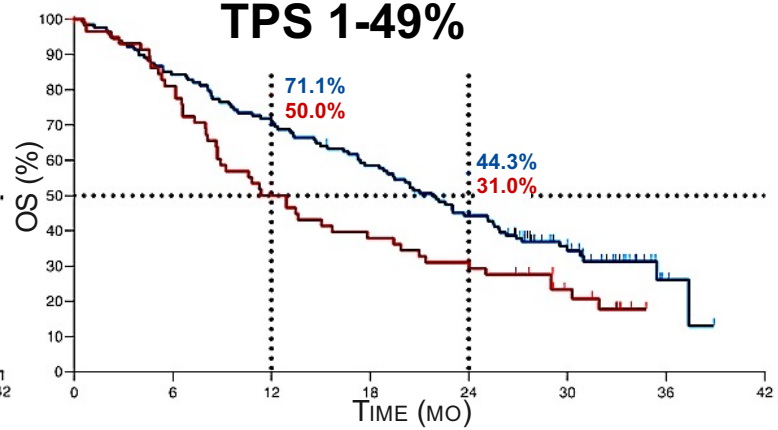
Median OS(95% CI): **22.0** vs **10.6** mo
HR (95% CI): **0.56** (0.46, 0.69)

TPS ≥50%



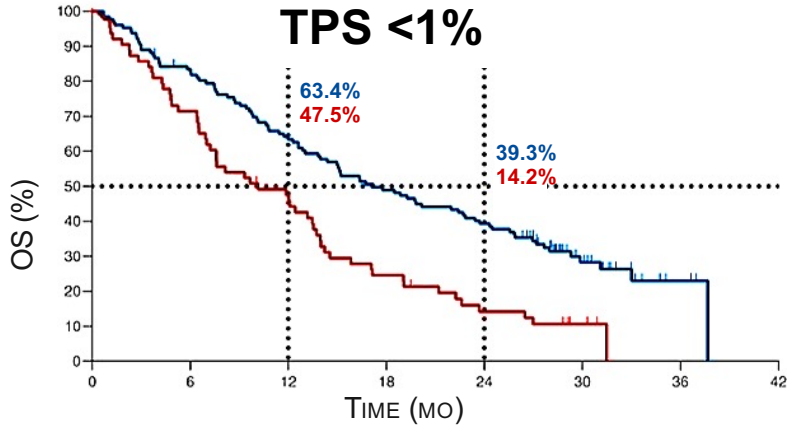
Median OS (95% CI): **27.1** vs **10.01** mo
HR (95% CI): **0.59** (0.40, 0.86)

TPS 1-49%



Median OS (95% CI): **21.8** vs **12.1** mo
HR (95% CI): **0.66** (0.46, 0.96)

TPS <1%



Median OS (95% CI): **17.2** vs **10.2** mo
HR (95% CI): **0.51** (0.36, 0.71)

PEMBROLIZUMAB + CHEMOTHERAPY
CHEMOTHERAPY

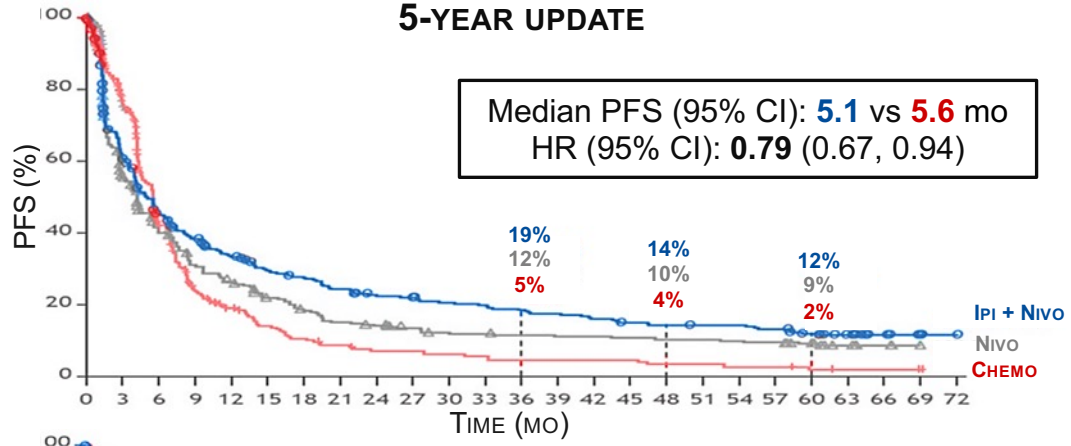
Reck M et al. *J Clin Oncol*. 2021;39(21):2339-2349.
De Castro G et al. *J Immunother Cancer*. SITC 2021.

CheckMate 227 vs CheckMate 9LA: Progression-Free Survival

Clinical OLYMPICS℠

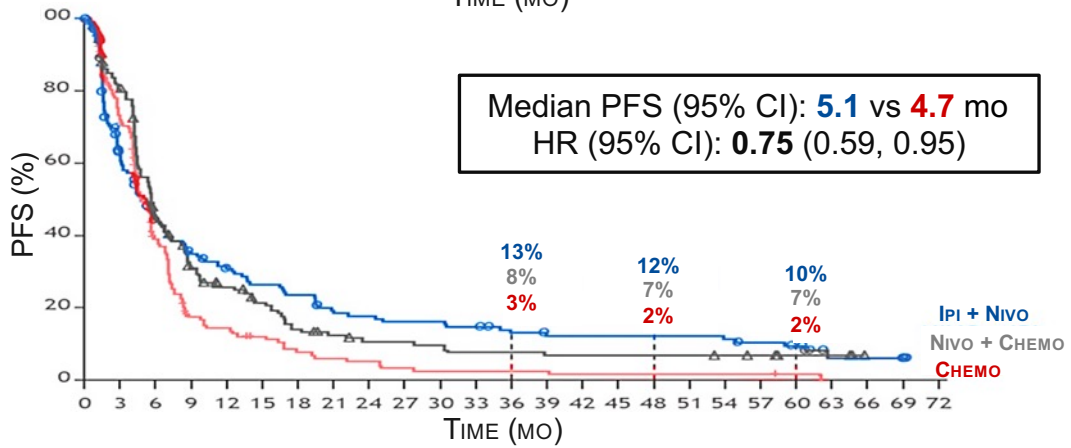
CheckMate 227
5-year update

PD-L1 ≥1%



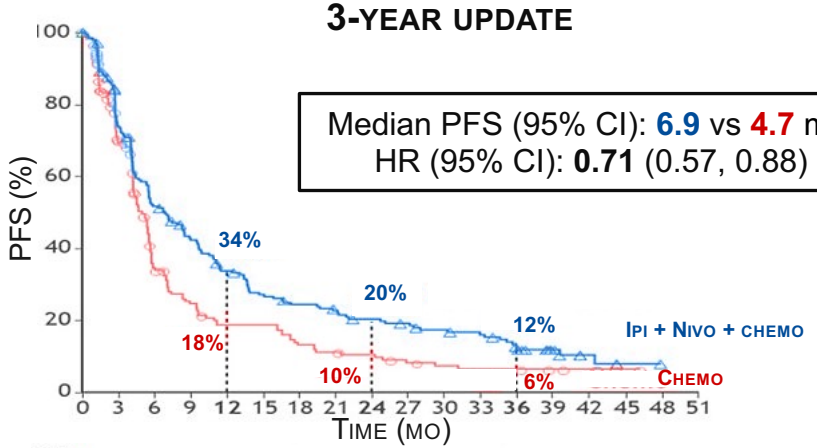
Median PFS (95% CI): **5.1** vs **5.6** mo
HR (95% CI): **0.79** (0.67, 0.94)

PD-L1 <1%

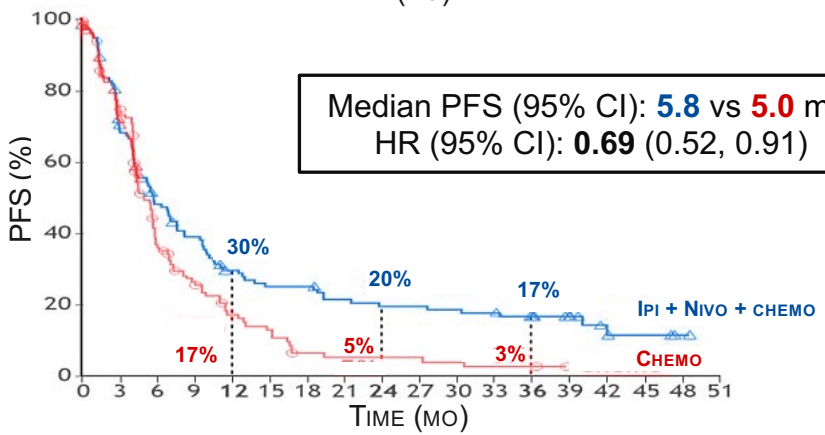


Median PFS (95% CI): **5.1** vs **4.7** mo
HR (95% CI): **0.75** (0.59, 0.95)

CheckMate 9LA
3-year update



Median PFS (95% CI): **6.9** vs **4.7** mo
HR (95% CI): **0.71** (0.57, 0.88)



Median PFS (95% CI): **5.8** vs **5.0** mo
HR (95% CI): **0.69** (0.52, 0.91)

Ipilimumab + Nivolumab (Not Approved in EU, Limited to PD-L1+ in US)
Chemotherapy

Ipilimumab + Nivolumab + 2 Cycles Chemotherapy
Chemotherapy

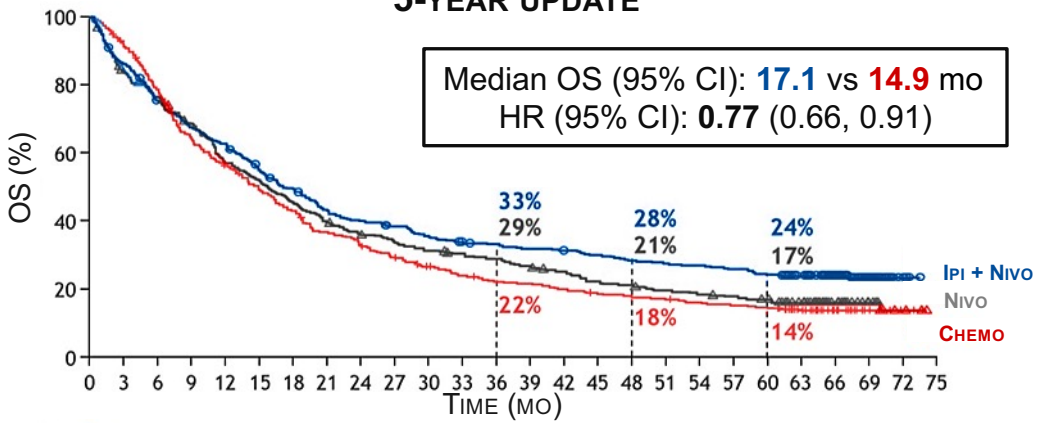
Brahmer JR et al. ASCO 2022. Abstract LBA9025. Paz-Ares LG et al. ASCO 2022. Abstract LBA9026.

CheckMate 227 vs CheckMate 9LA: Overall Survival

Clinical OLYMPICS℠

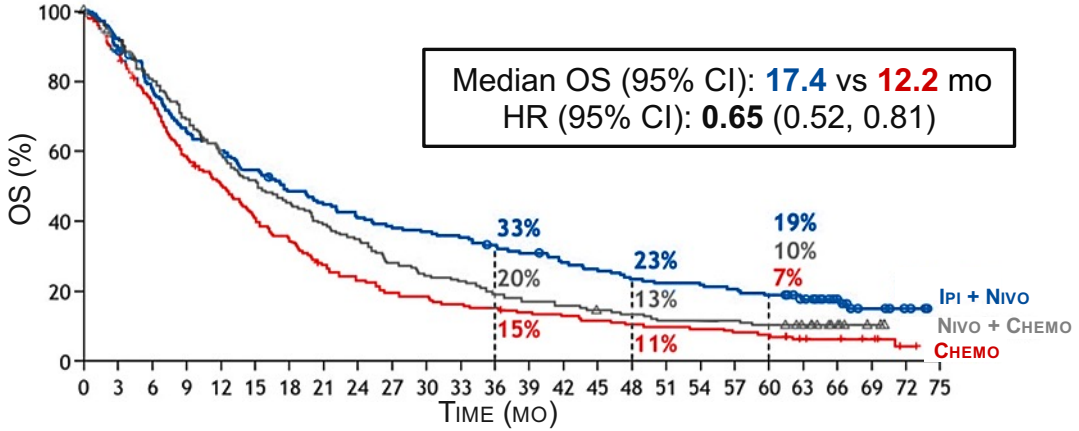
CheckMate 227
5-year update

PD-L1 ≥1%



Median OS (95% CI): **17.1** vs **14.9** mo
HR (95% CI): **0.77** (0.66, 0.91)

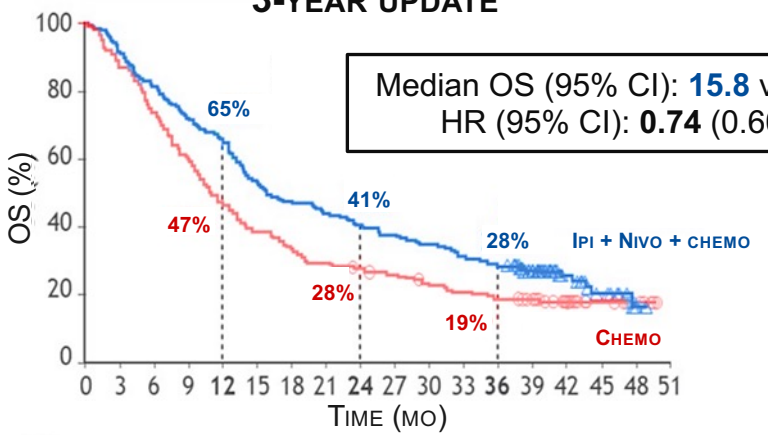
PD-L1 <1%



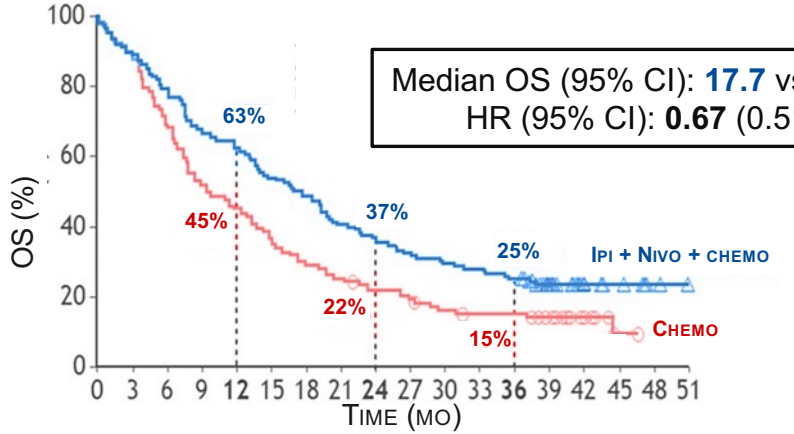
Median OS (95% CI): **17.4** vs **12.2** mo
HR (95% CI): **0.65** (0.52, 0.81)

Ipilimumab + Nivolumab (Not Approved in EU, Limited to PD-L1+ in US)
Chemotherapy

CheckMate 9LA
3-year update



Median OS (95% CI): **15.8** vs **10.9** mo
HR (95% CI): **0.74** (0.60, 0.93)



Median OS (95% CI): **17.7** vs **9.8** mo
HR (95% CI): **0.67** (0.51, 0.88)

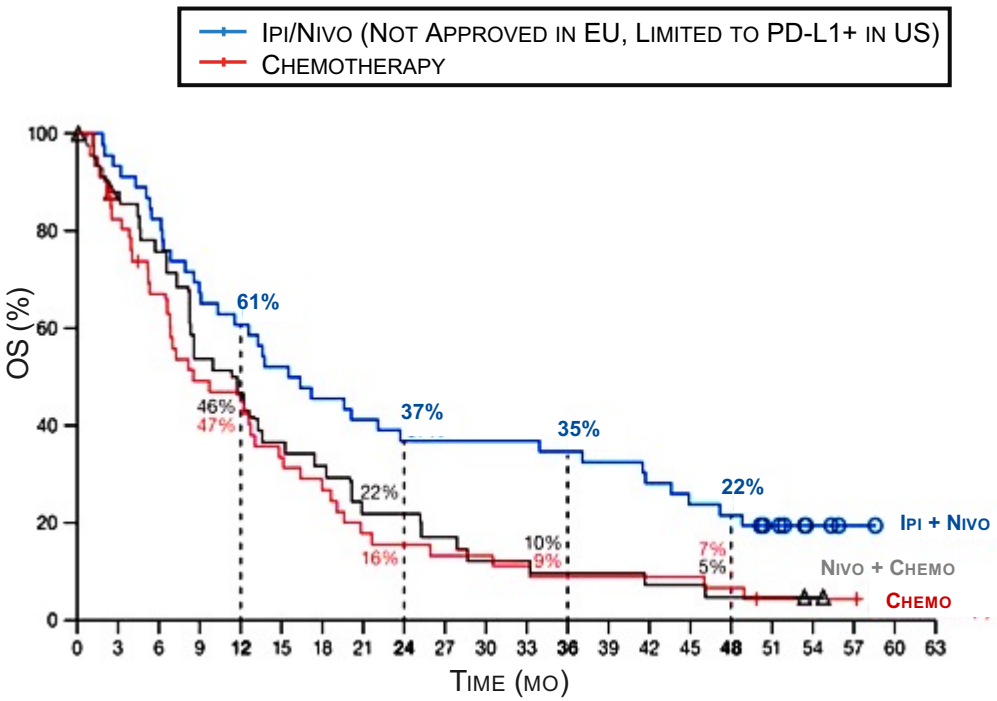
Ipilimumab + Nivolumab + 2 Cycles Chemotherapy
Chemotherapy

Brahmer JR et al. ASCO 2022. Abstract LBA9025. Paz-Ares LG et al. ASCO 2022. Abstract LBA9026.

Squamous Histology and PD-L1 <1%

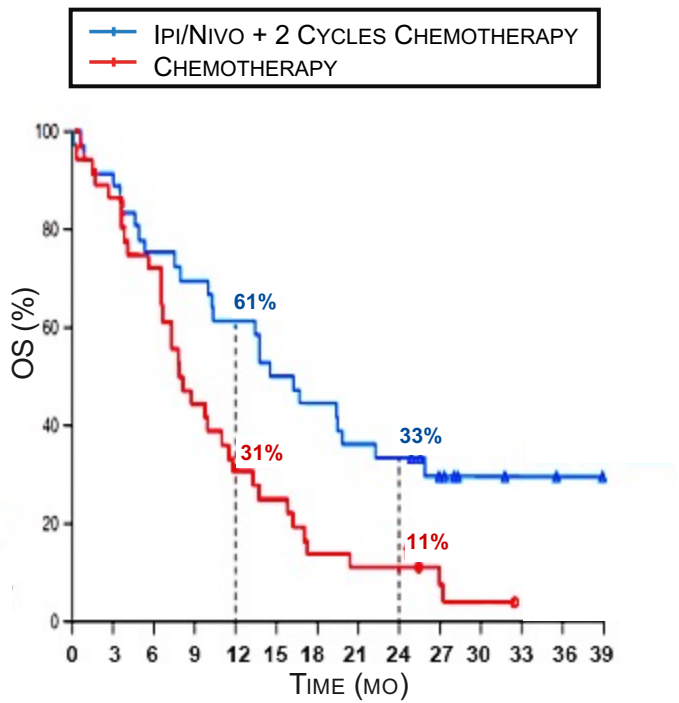
Clinical OLYMPICS℠

CheckMate 227



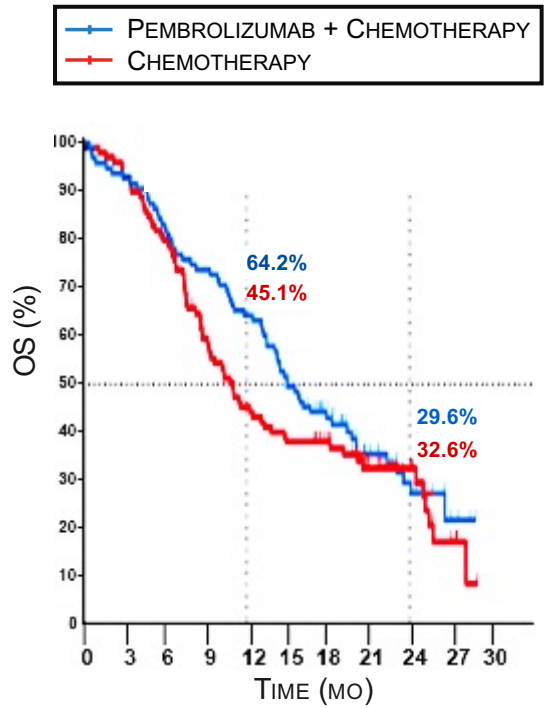
Median OS (95% CI), **15.9** **vs** **8.5** mo
HR (95% CI): **0.53** (0.34, 0.84)

CheckMate 9LA



Median OS (95% CI), **15.3** vs **8.0** mo
HR (95% CI): **0.48** (0.28, 0.81)

KEYNOTE-407

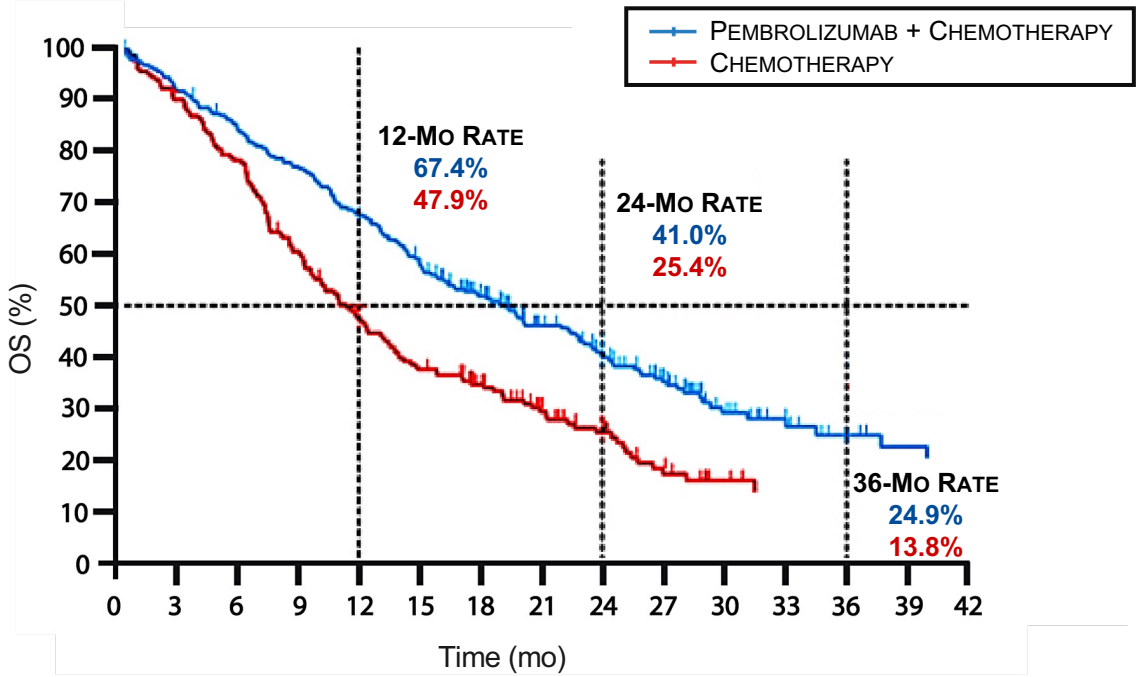


Median OS (95% CI), **15.0** **vs** **11.0** mo
HR (95% CI): **0.79** (0.56, 1.11)

Paz-Ares LG et al. *J Thorac Oncol*. 2022 Feb;17(2):289-308. Reck M et al. *ESMO Open*. 2021;6(5):100273, supplementary data.
Paz-Ares LG et al. *J Thorac Oncol*. 2020;15(10):1657-1669.

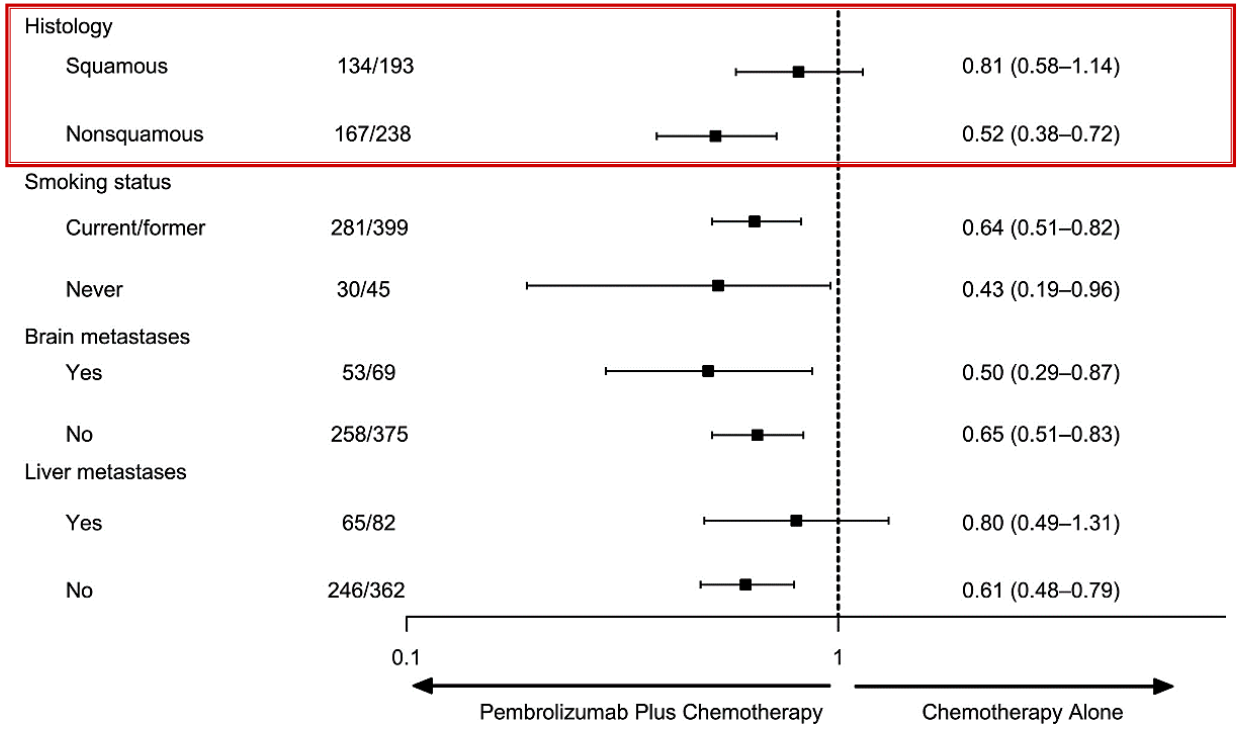
POOLED ANALYSIS: KN-021, -189, -407

OS, PD-L1 (TPS) <1%



Median OS (95% CI), **19.0** vs **11.4** mo
HR (95% CI): **0.63** (0.50, 0.79)

SUBGROUP ANALYSIS

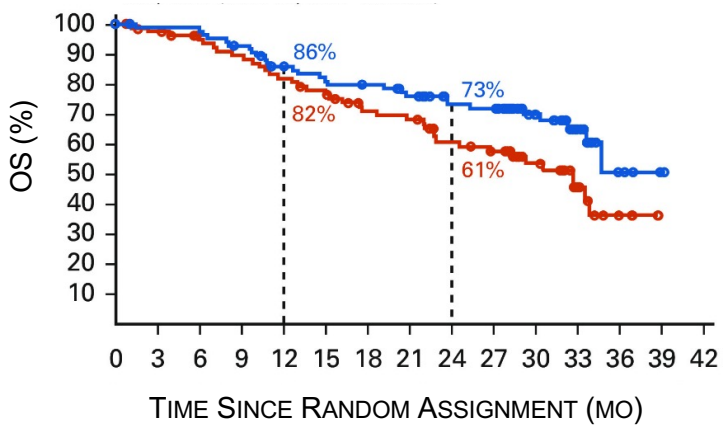


Borghaei H et al. *Cancer*. 2020;126(22):4867-4877.

Optimal Duration of Therapy
Insights from CheckMate 153 (2L Nivolumab)

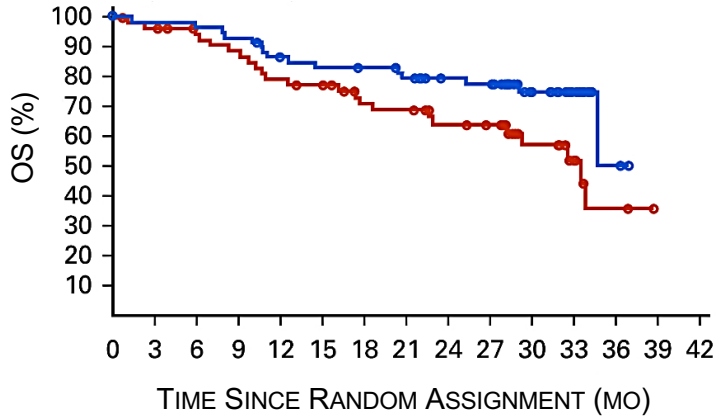
Clinical OLYMPICS℠

OS in the PFS Population



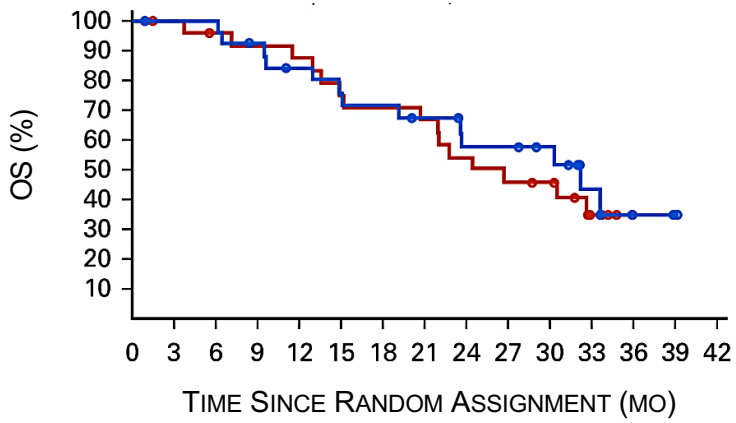
mOS (95% CI), **NR** (33.6, NR) vs **32.5** (22.9, NR) mo
HR (95% CI): **0.61** (0.37, 0.99)

OS in the CR/PR Population



mOS (95% CI), **NR** (34.7, NR) vs **33.5** (22.9, NR) mo
HR (95% CI): **0.50** (0.26, 0.97)

OS in the SD Population



mOS (95% CI), **32.2** (15.1, NR) vs **26.6** (15.2, NR) mo
HR (95% CI): **0.88** (0.42, 1.84)

Continuous
1 Y Fixed Duration*

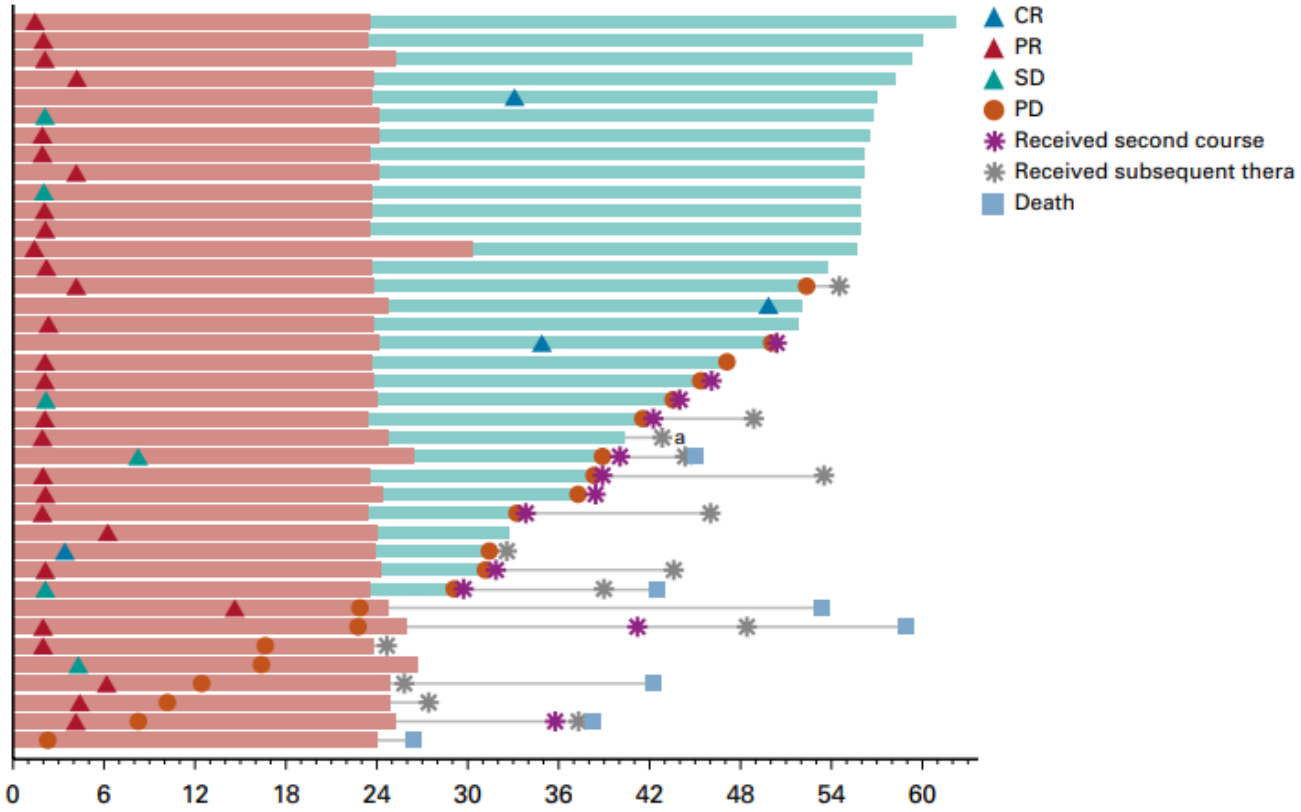
**Optional retreatment allowed at PD*

Waterhouse DM et al. *J Clin Oncol*. 2020;38(33):3863-3873.

KEYNOTE-024: 2 Years of Pembrolizumab. What Happens Next?

Clinical OLYMPICS℠

Treatment Duration and Time to Response in Patients Completing 35 Cycles



Outcome	n=39
3-year OS rate from 2y pembrolizumab	81%
Objective Response	82.1%
Best Objective Response	
Complete Response (CR)	10.3%
Partial Response (PR)	71.8%
Stable Disease (SD)	15.4%
Progressive Disease (PD)	2.6%

At cut-off, 46.2% of patients were alive without PD or subsequent therapy

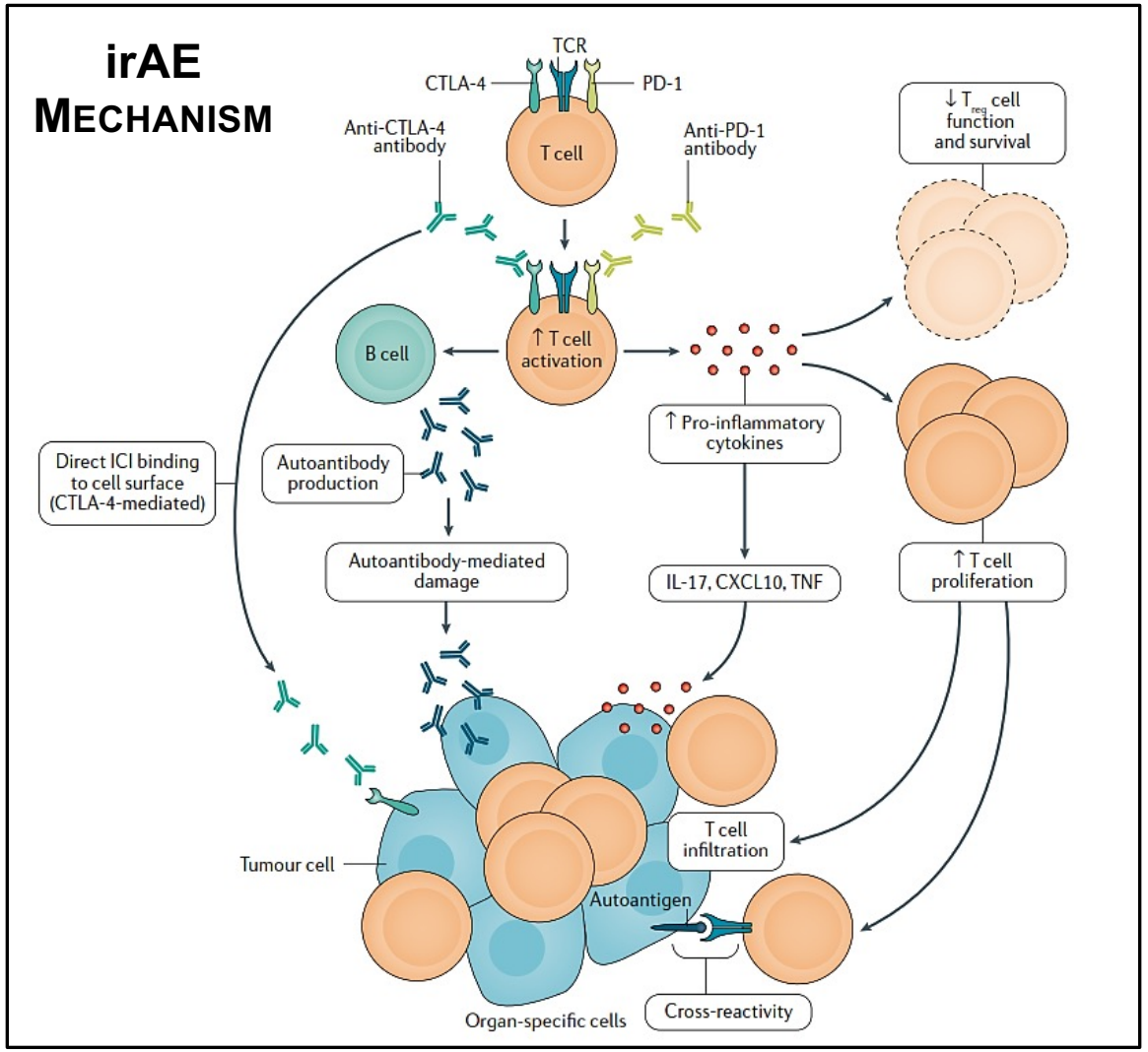
Reck M et al. *J Clin Oncol*. 2021 Jul 20;39(21):2339-2349.

Managing Immunotherapy-Related Adverse Events in NSCLC

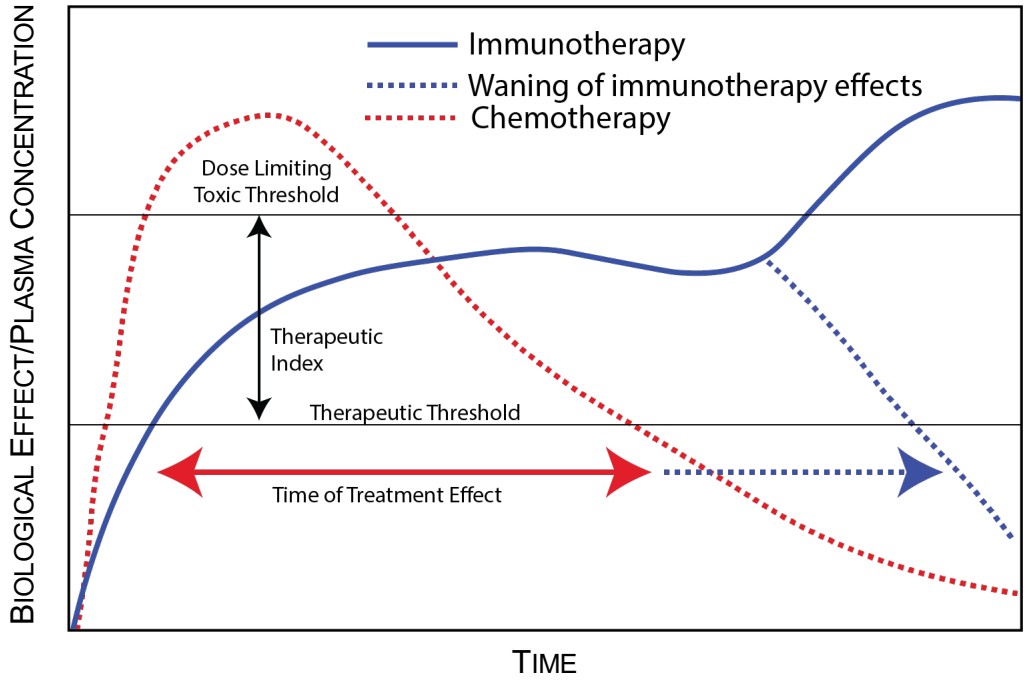
Mihaela Aldea, MD, PhD

Associate Professor, Medical Oncology
Paris-Saclay University
Gustave Roussy
Villejuif, France

Checkpoint Inhibitors: Using the Immune System to Target Cancer Cells



Pharmacokinetic/dynamic Differences: Immunotherapy vs Chemotherapy

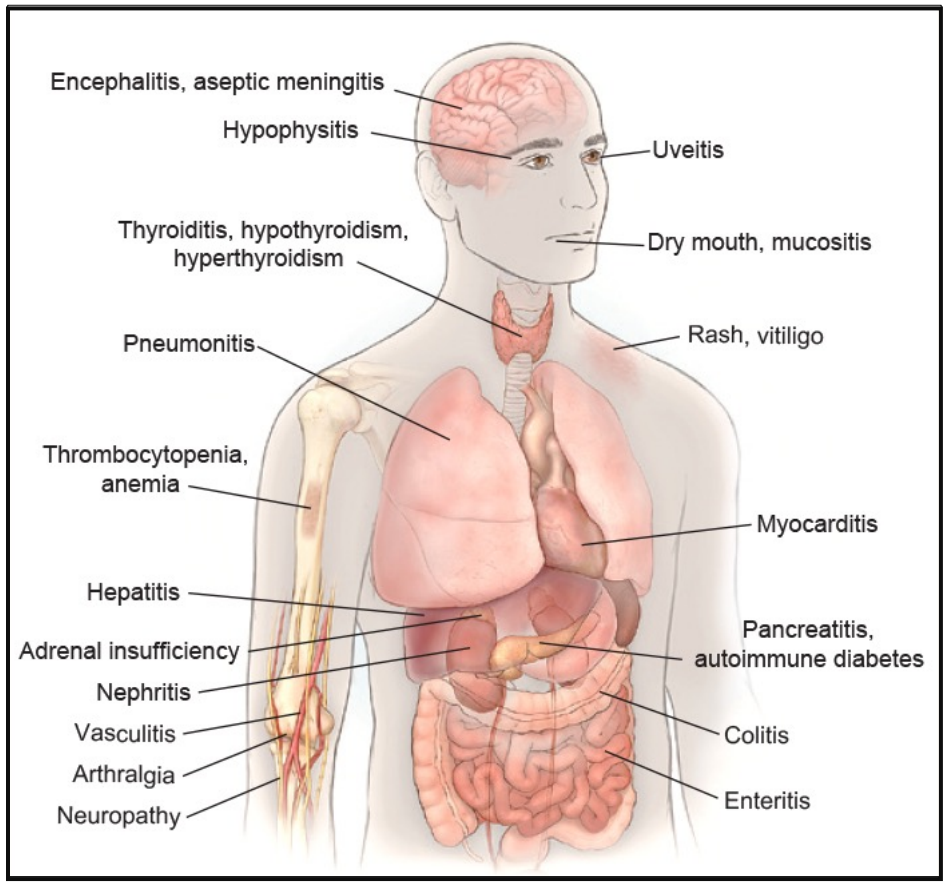


Ramos-Casals M et al. *Nat Rev Dis Primers*. 2020 May 7;6(1):38. Puzanov I et al. *J Immunother Cancer*. 2017 Nov 21;5(1):95.

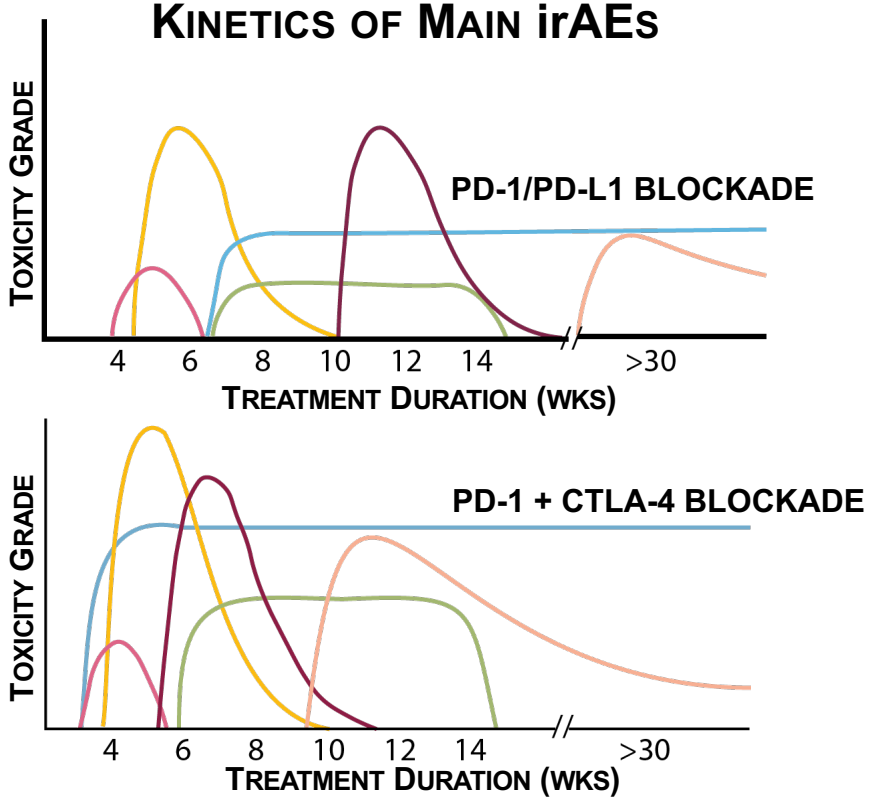
Toxicity: Any Time, Any Organ

Clinical OLYMPICS℠

Immune-Related Adverse Events (irAEs) Can Affect Any Organ(s)



Kinetics of Main irAEs

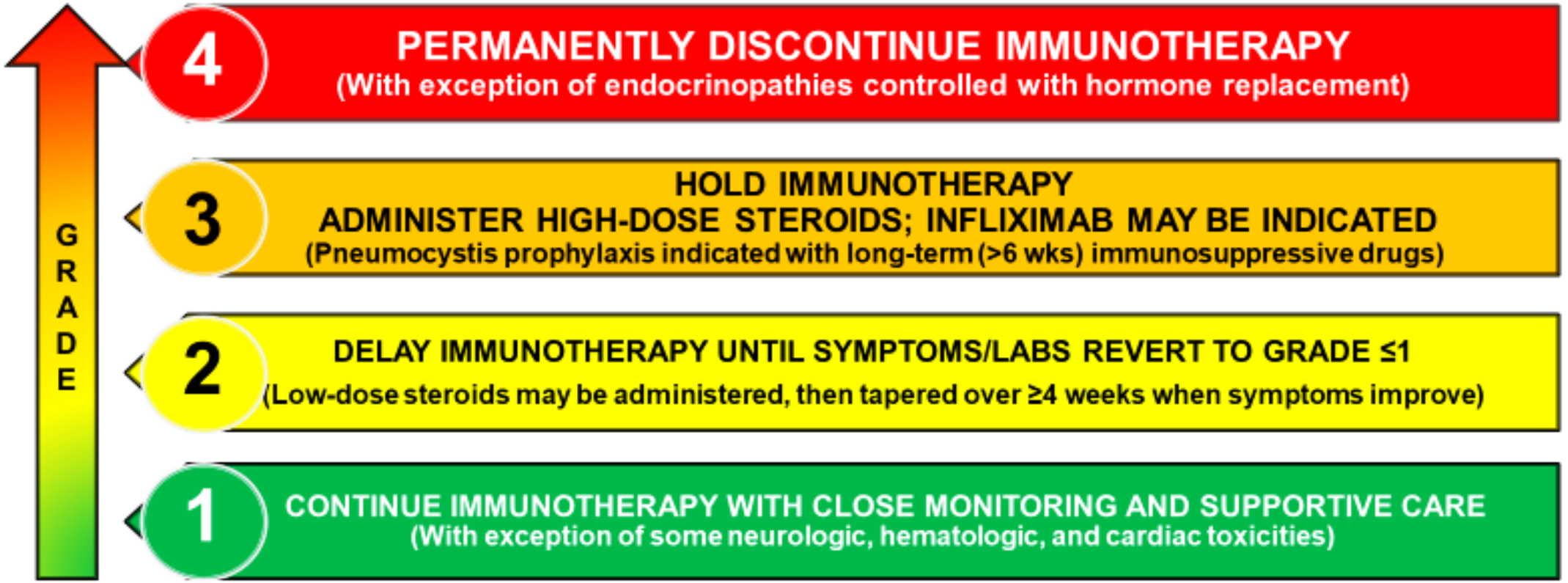


Postow MA et al. *N Engl J Med*. 2018;378(2):158-68. Martins F et al. *Nat Rev Clin Oncol.* 2019;16(9):563-580.

Immune-Related Toxicity: General Management Principles

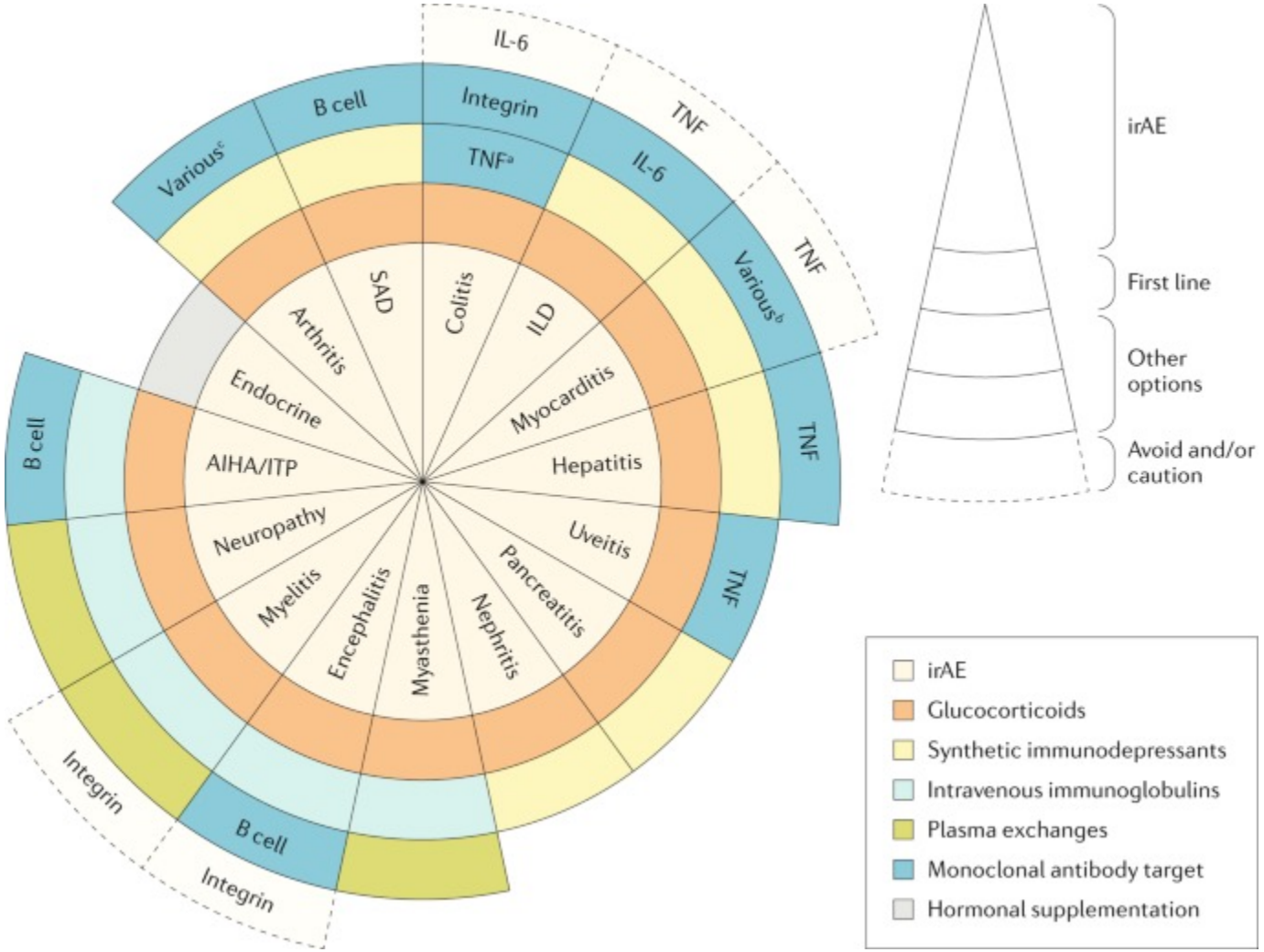
Clinical OLYMPICS℠

- ✓ Always suspect an irAE
- ✓ Rule out competing diagnoses (infection, progression)
- ✓ Treat early to avoid complications
- ✓ Identify the toxicity (eg, diarrhea vs. colitis)
- ✓ Grade the toxicity via CTCAE
- ✓ Consult a specialist



Brahmer JR et al. *J Immunother Cancer.* 2021; 9(6): e002435; Haanen JBAG et al. *Ann Oncol*. 2017;28(suppl_4):iv119-iv142: Slide Set

Therapeutic Algorithm for Organ-Specific irAE Management

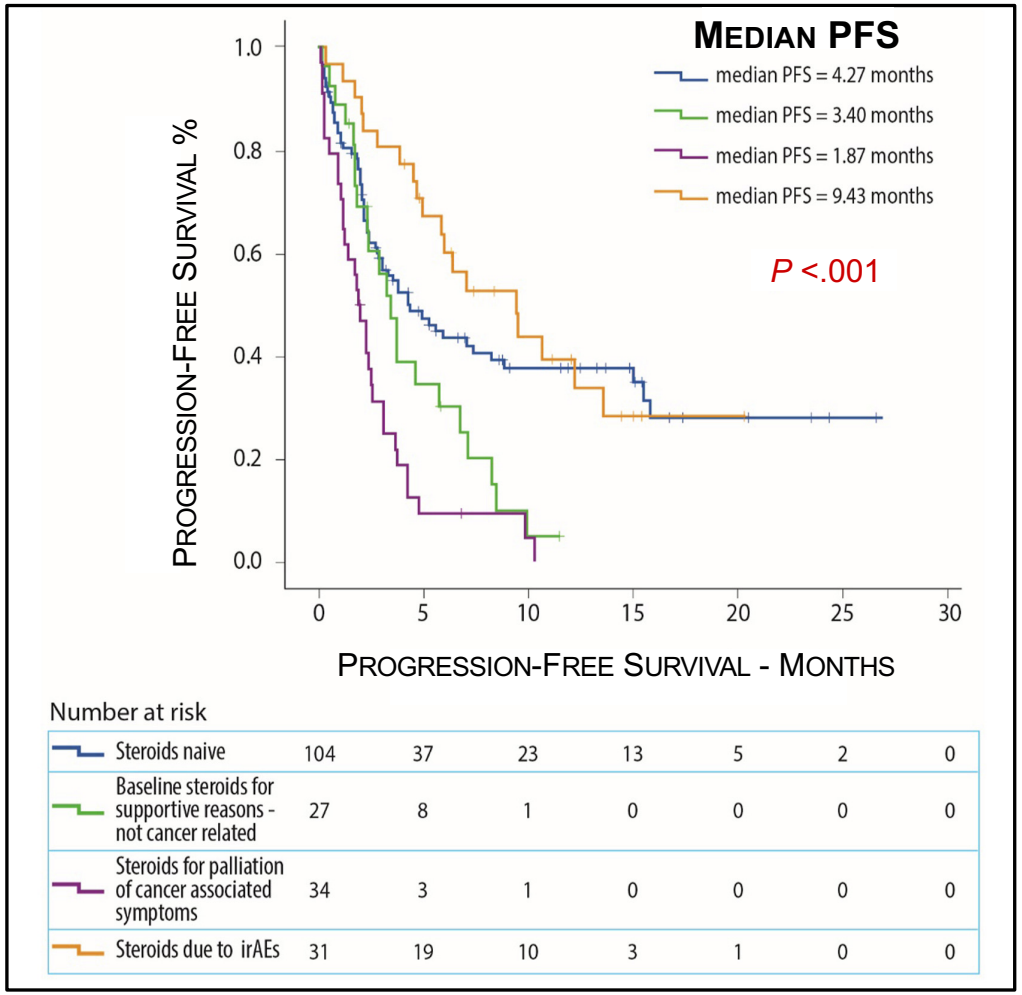


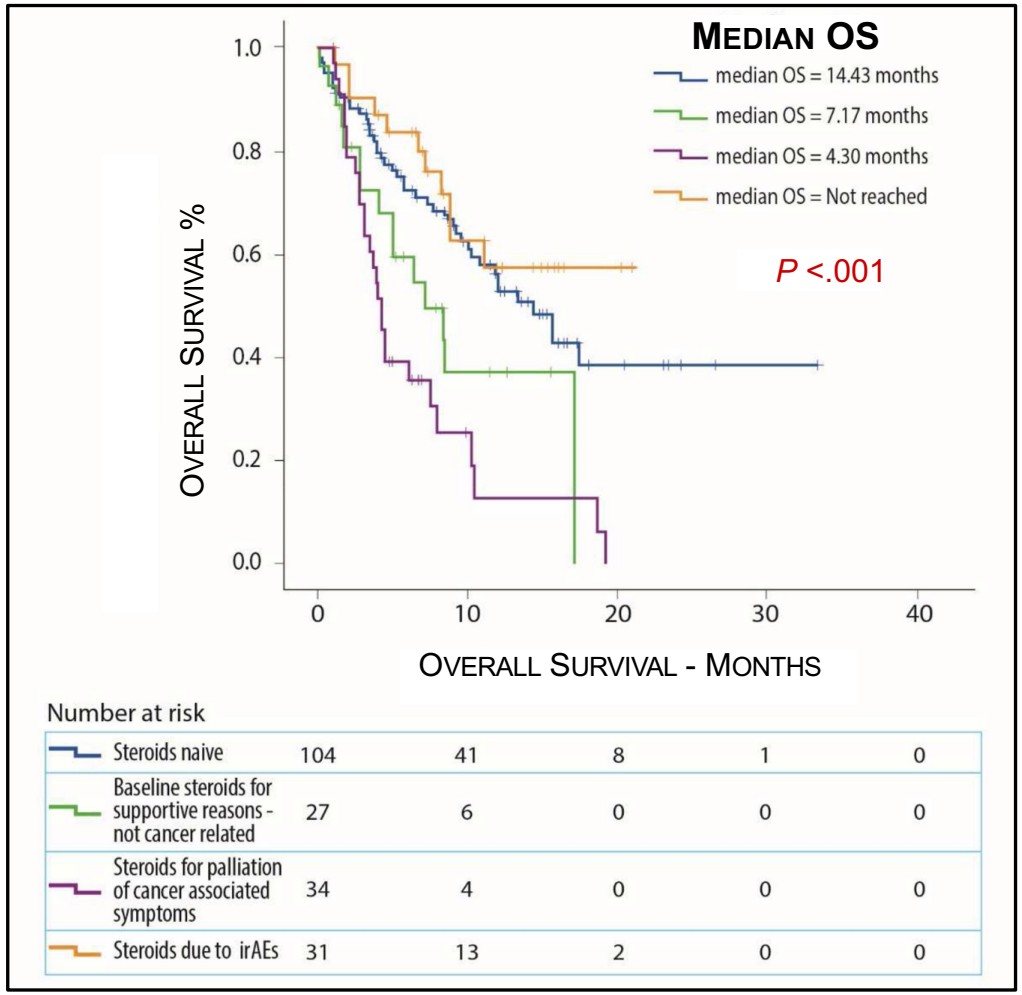
[a] Avoid etanercept owing to the risk of autoimmune inflammatory colitis.
[b] Consider abatacept or alemtuzumab.
[c] Consider infliximab or tocilizumab.

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

Corticosteroids: No Negative Impact When Used for irAEs

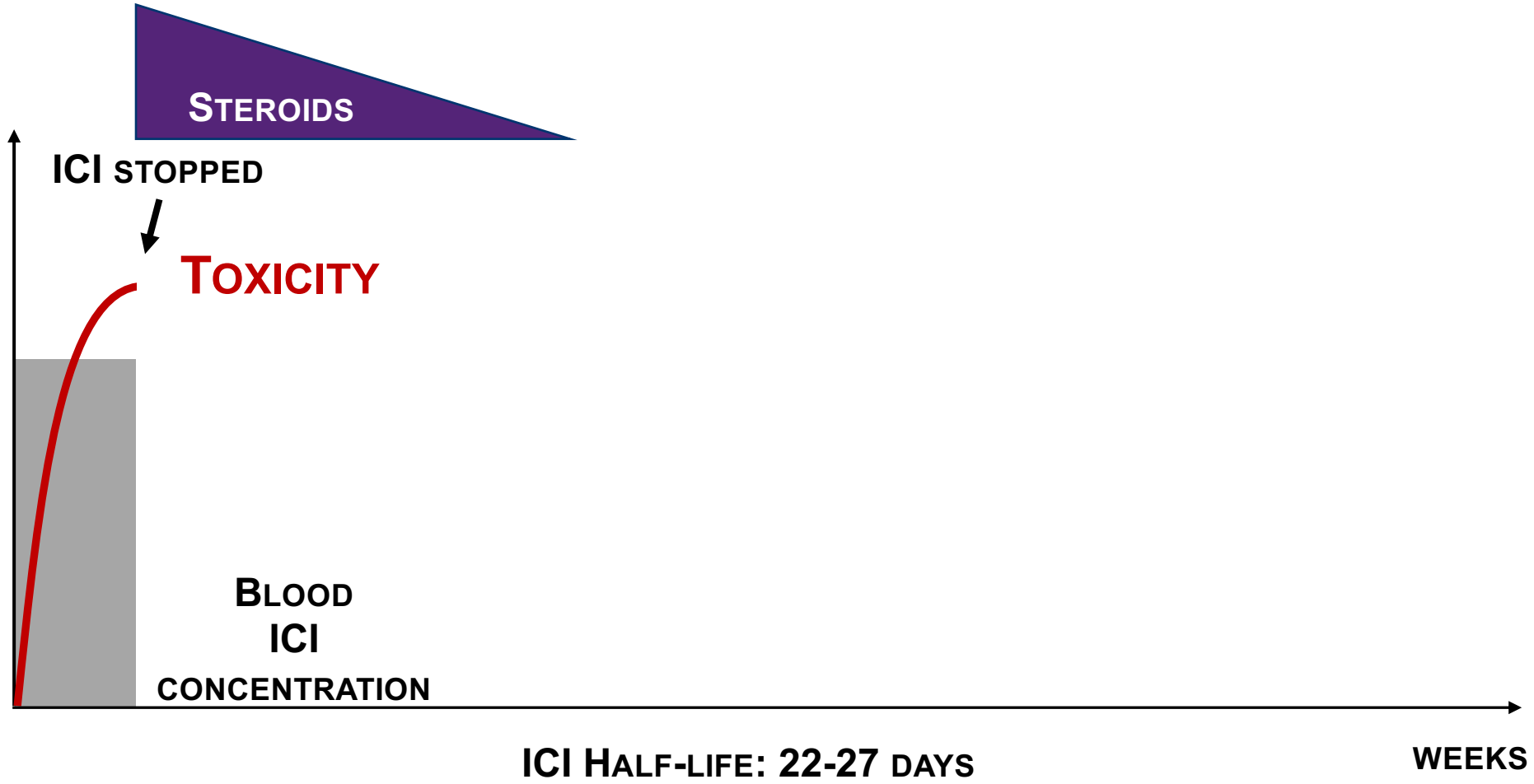
Clinical OLYMPICS℠





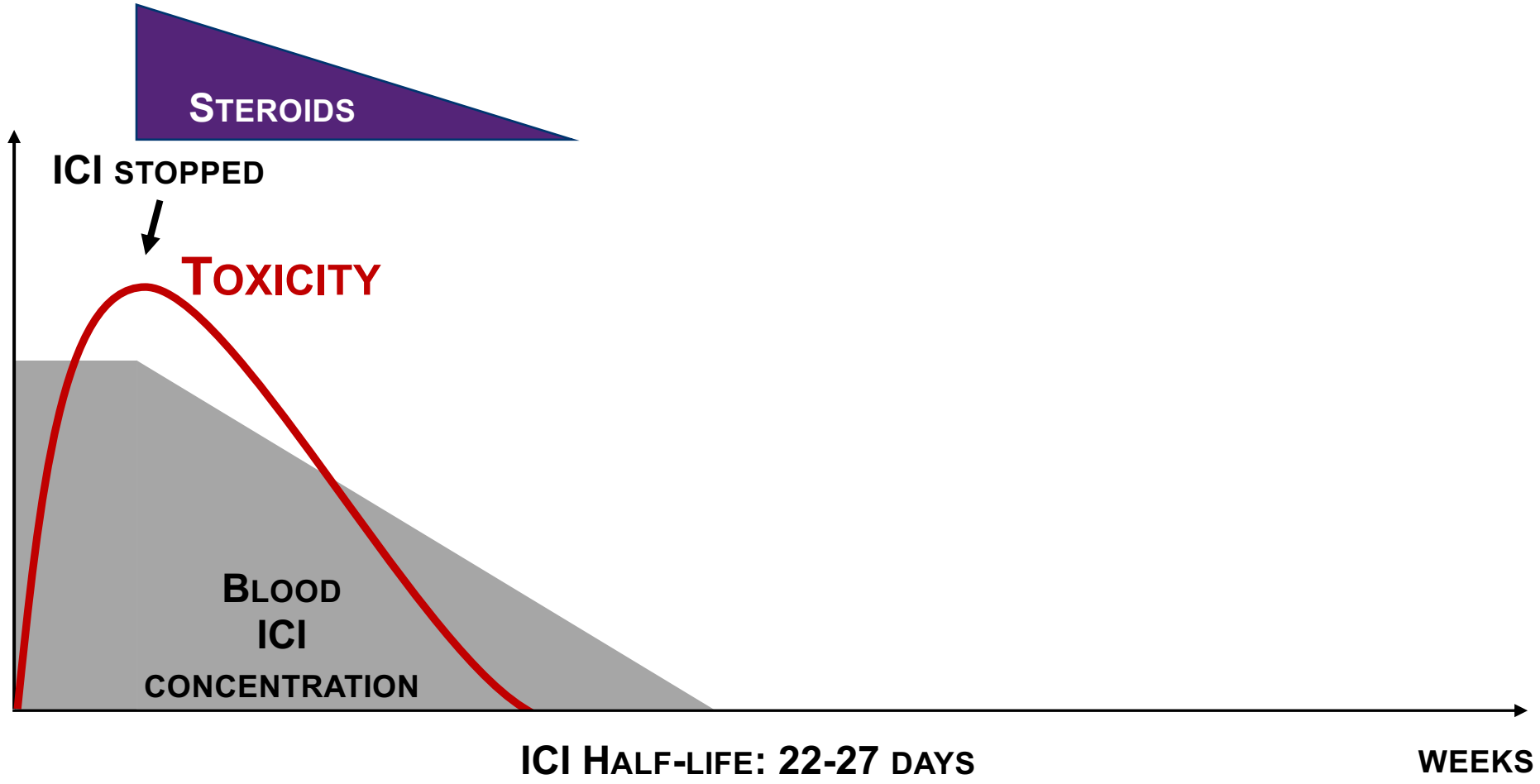
Skribek M et al. *Eur J Cancer*. 2021 Mar;145:245-254.

TOXICITIES AND ICI HALF-LIFE



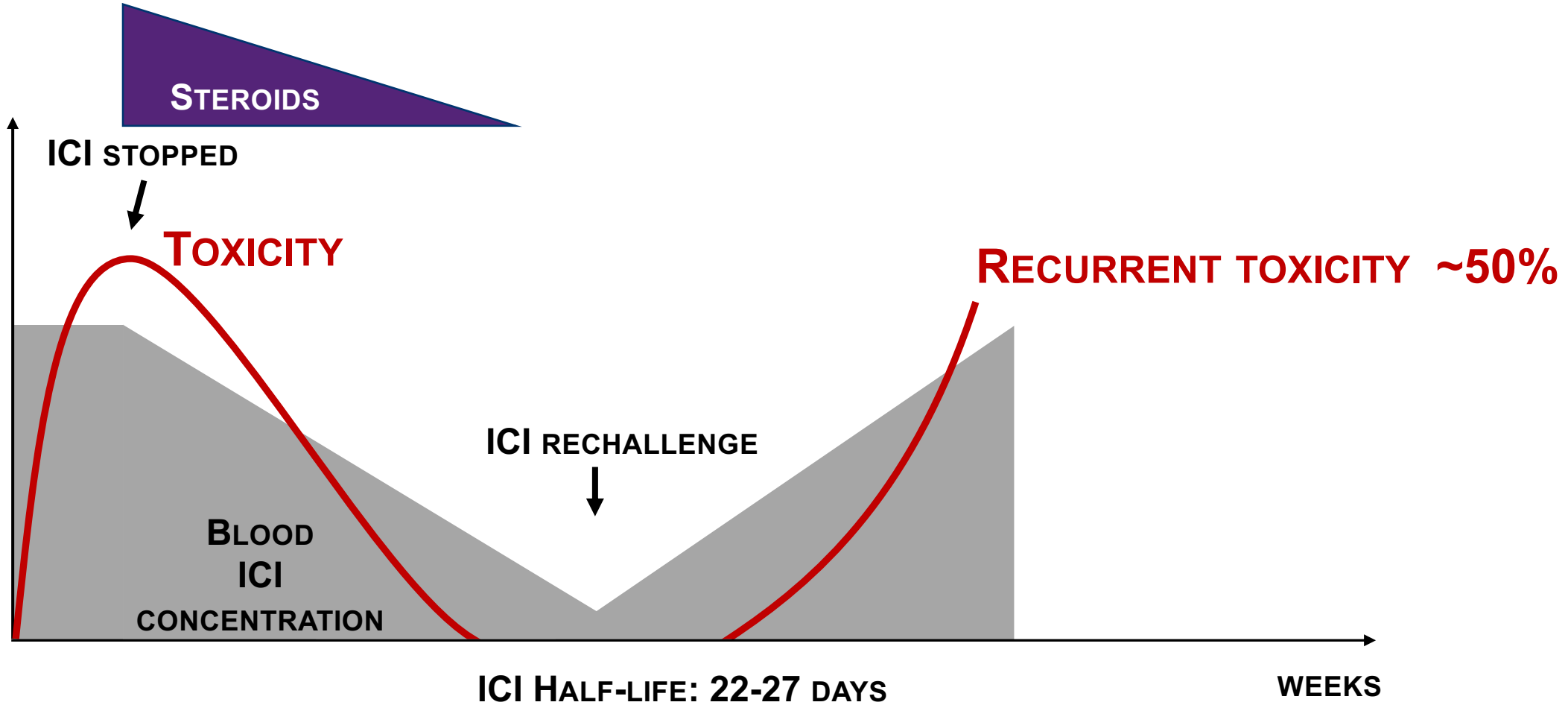
Simonaggio A et al. *JAMA Oncol*. 2019 Sep 1;5(9):1310-1317. Santini FC et al. *Cancer Immunol Res*. 2018 Sep;6(9):1093-1099.

TOXICITIES AND ICI HALF-LIFE



Simonaggio A et al. *JAMA Oncol*. 2019 Sep 1;5(9):1310-1317. Santini FC et al. *Cancer Immunol Res*. 2018 Sep;6(9):1093-1099.

TOXICITIES AND ICI HALF-LIFE



Simonaggio A et al. *JAMA Oncol*. 2019 Sep 1;5(9):1310-1317. Santini FC et al. *Cancer Immunol Res*. 2018 Sep;6(9):1093-1099.

Immune-Related Dermatologic irAEs

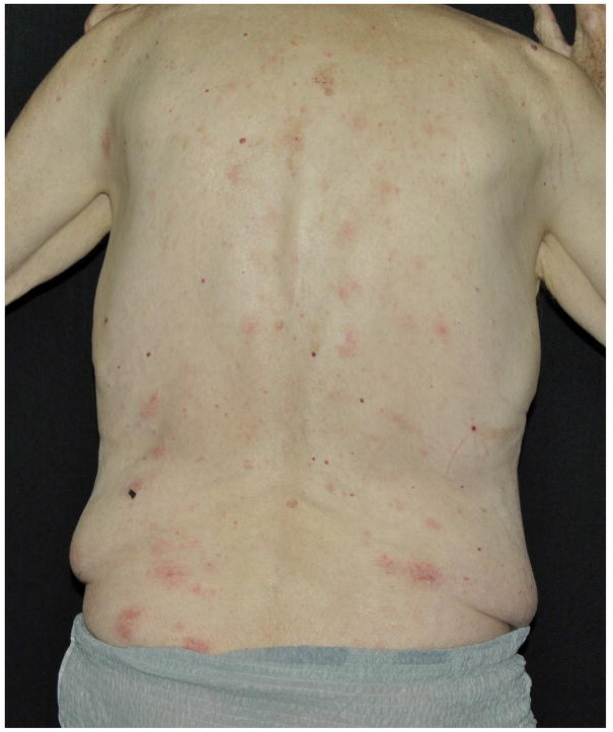
Clinical OLYMPICS℠

Grading and treatment:

- Grade 1: <10% BSA; Grade 2: 10-30% BSA
  - Grade 1-2: Topical corticosteroid cream ± oral or topical antihistamines for itch; continue immunotherapy
- Grade 3: >30% BSA or Grade 2 with substantial symptoms; Grade 4: Skin sloughing >30% BSA with associated symptoms
  - Grade 3-4: High-dose corticosteroids + topical interventions; hold/discontinue ICI. Workup should include dermatology referral and biopsy.
- Grade ≥2 events may recur after steroid taper. A dermatologic consultation or use of steroid-sparing agent is recommended.
  - Urticaria/pruritis: omalizumab
  - Eczema: dupilumab
  - Pemphigus, bullous pemphigoid: rituximab
  - Lichenoid rash: infliximab

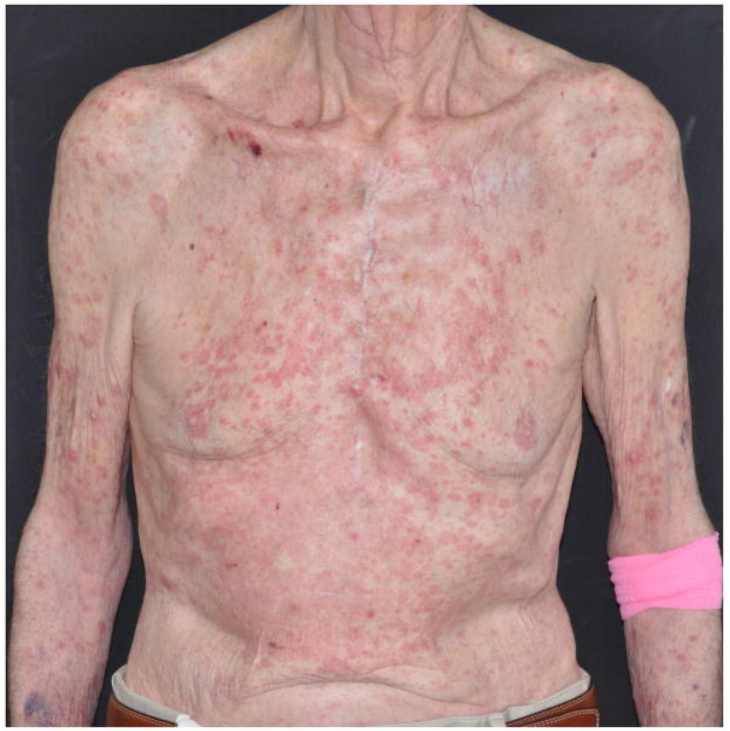
Grade 2 Rash

After 6 weeks of pembrolizumab



Grade 3 Rash

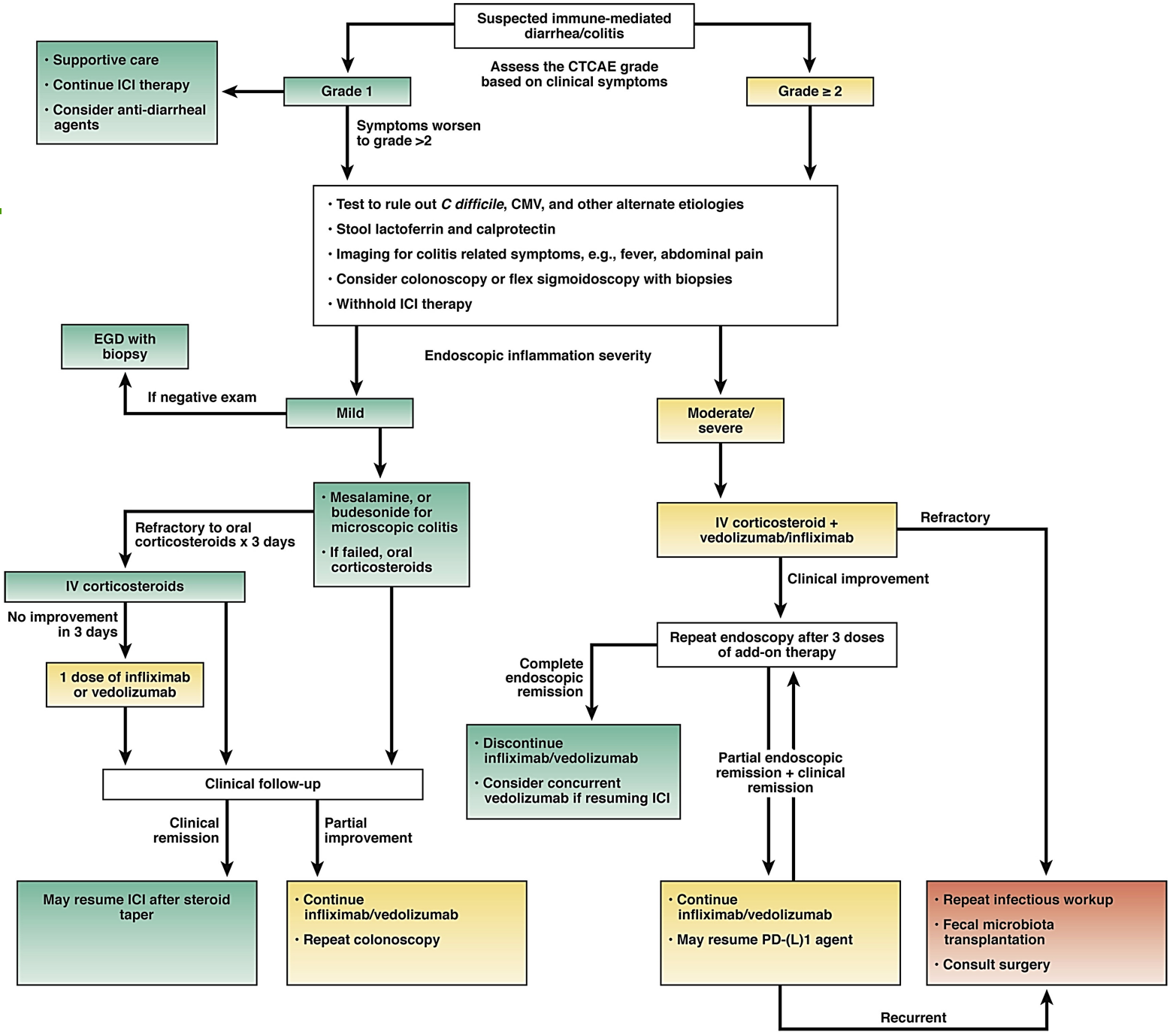
After 2 months of pembrolizumab



Brahmer JR et al. *J Immunother Cancer*. 2021 Jun;9(6):e002435. Haanen JBAG et al. *Ann Oncol*. 2017 Jul 1;28(suppl_4):iv119-iv142.
Belum VR et al. *Eur J Cancer*. 2016 Jun;60:12-25.

COLITIS

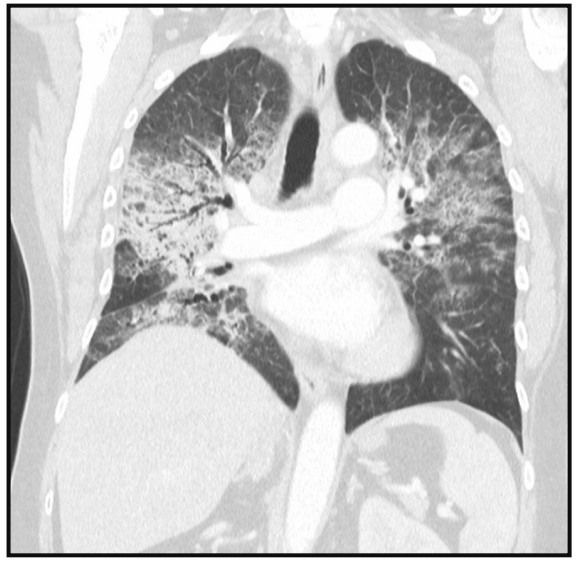
- Common complication with CTLA-4 blockade; less common but similar severity with PD-1 blockade
- Early diagnosis and treatment are key to successful management
- High-dose corticosteroids are the mainstay of treatment
- Grade 1: CBC, CMP, fecal lactoferrin
- Grade ≥2: add tests for fecal calprotectin and stool infectious analysis (stool ova/parasites, *C. difficile* and CMV testing via PCR or among other studies that may include COVID-19).
  - Imaging may be indicated for suspected complications (eg, perforation, toxic megacolon).
  - ICI can be temporarily withheld and rechallenge is possible if symptoms are stable (Grade ≤3 or baseline) with <10 mg/day prednisone or equivalent



Brahmer JR et al. *J Immunother Cancer*. 2021 Jun;9(6):e002435.
Dougan M et al. *Gastroenterology*. 2021 Mar;160(4):1384-1393

PNEUMONITIS

- Fairly uncommon, potentially serious
- More common with dual-ICI therapy
- Signs and symptoms:
  - Shortness of breath
  - Dry cough
  - ↓ O2 saturation on room air
  - New/increasing oxygen requirements
  - May be detected just on imaging



SIGNS OF PNEUMONITIS ON CHEST CT

CLINICAL MANAGEMENT OF PNEUMONITIS

MILD (GRADE 1)	MODERATE (GRADE 2)	SEVERE (GRADE 3-4)
• Consider holding immunotherapy • Reassess in 1 to 2 weeks • Pulse oximetry (resting and with ambulation) • Consider CT chest ± contrast • Repeat CT in 4 weeks or as clinically indicated for worsening symptoms	• Hold immunotherapy • Consult pulmonary specialist • Rule out infection (nasal swab, sputum, blood culture, urine culture) • Bronchoscopy • Chest CT • Empiric antibiotics if infection not resolved • Prednisone/methylprednisolone 1 to 2 mg/kg/day – monitor every 3 to 7 days	• Permanently discontinue immunotherapy • Inpatient care • Infectious workup • Bronchoscopy • Methylprednisolone 1 to 2 mg/kg/day – assess response within 48 hours and plan to taper over 6 weeks • If not improved after 48 hours, **THEN**

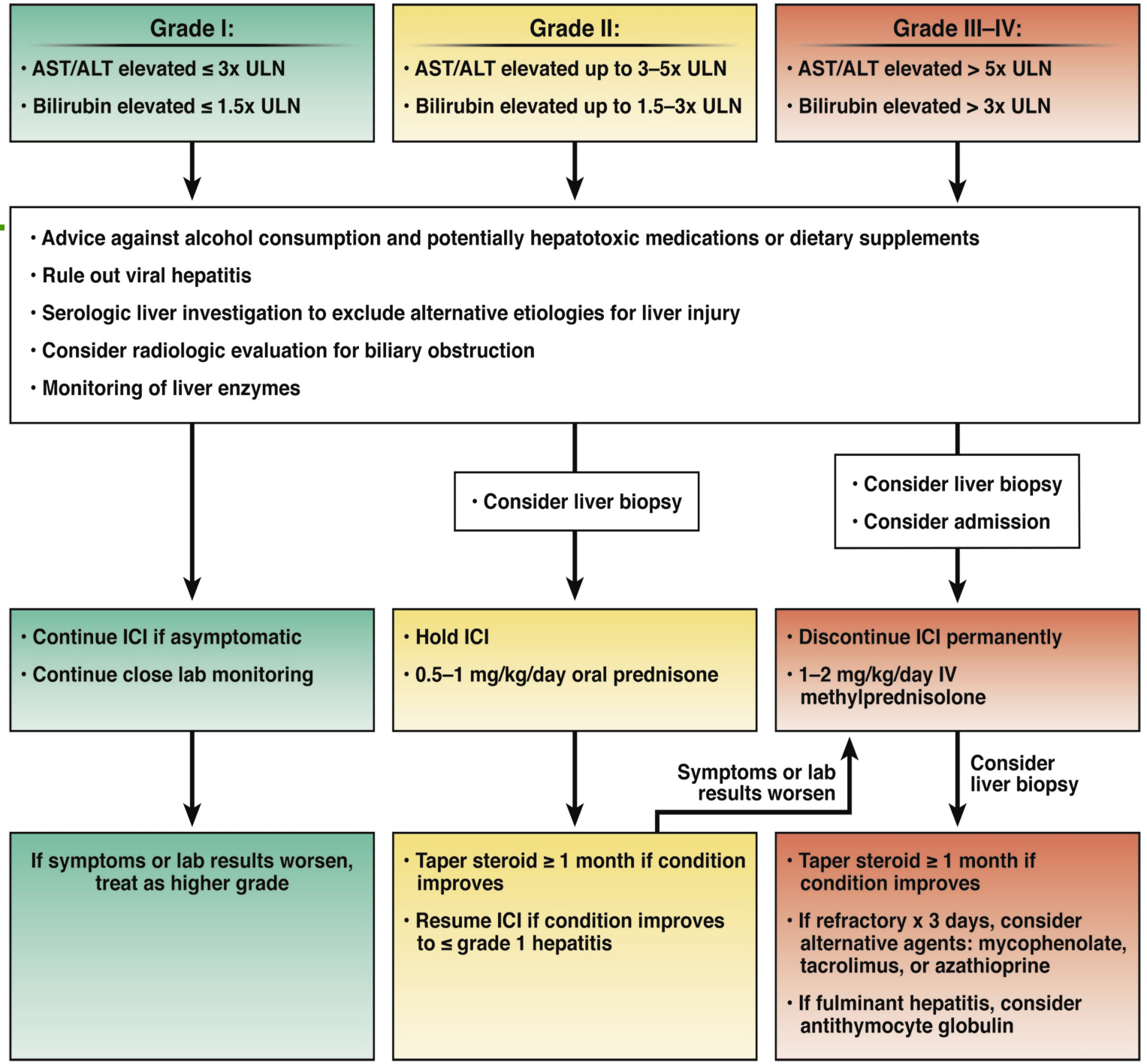
CONSIDER ADDING:

- Infliximab 5 mg/kg IV, 2nd dose may be repeated after 14 days at discretion of provider
- IVIG
- Mycophenolate mofetil 1 to 1.5 g BID then taper in consultation with pulmonary service

NCCN. Management of Immunotherapy-Related Toxicities. Version 1.2022. Issued 2/28/22. Picard S et al. *J Med Case Rep*. 2021 Jul 3;15(1):332.

HEPATITIS

- Often asymptomatic
- Evaluate ALT, AST, and other liver enzymes at baseline and periodically during treatment
- Liver function tests (LFTs):
  - Prior to each infusion
  - Weekly for Grade 1-2 liver toxicities
  - Every 1-2 days for Grade ≥3 liver toxicity
- Abdominal imaging if:
  - Grade ≥3 liver toxicity in patients with preexisting disease
  - Concern for progression/metastasis
- Mycophenolate mofetil if:
  - ALT/AST do not improve to Grade ≤1 after 10-14 days of steroids
  - Liver toxicity recurs after steroid tapering
- Liver biopsy if:
  - ALT/AST do not improve to Grade ≤1 after 10-14 days of mycophenolate mofetil

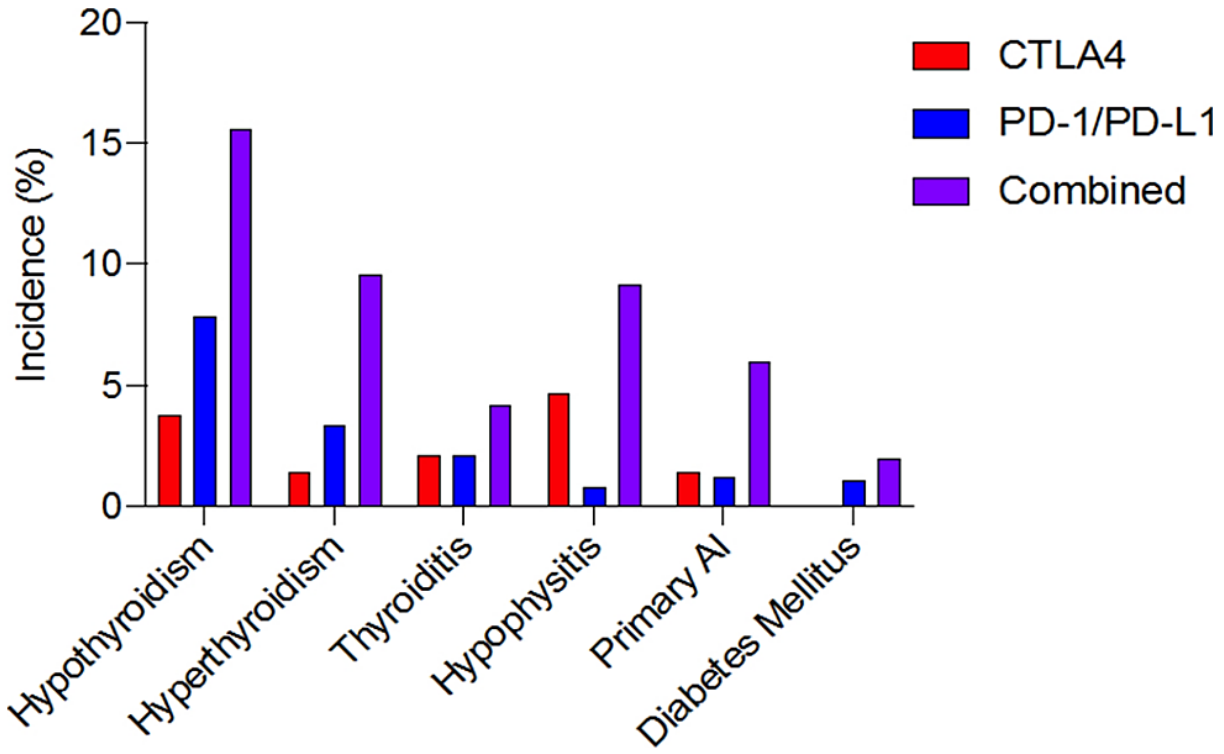


Brahmer JR et al. *J Immunother Cancer*. 2021 Jun;9(6):e002435.
Dougan M et al. *Gastroenterology*. 2021 Mar;160(4):1384-1393.

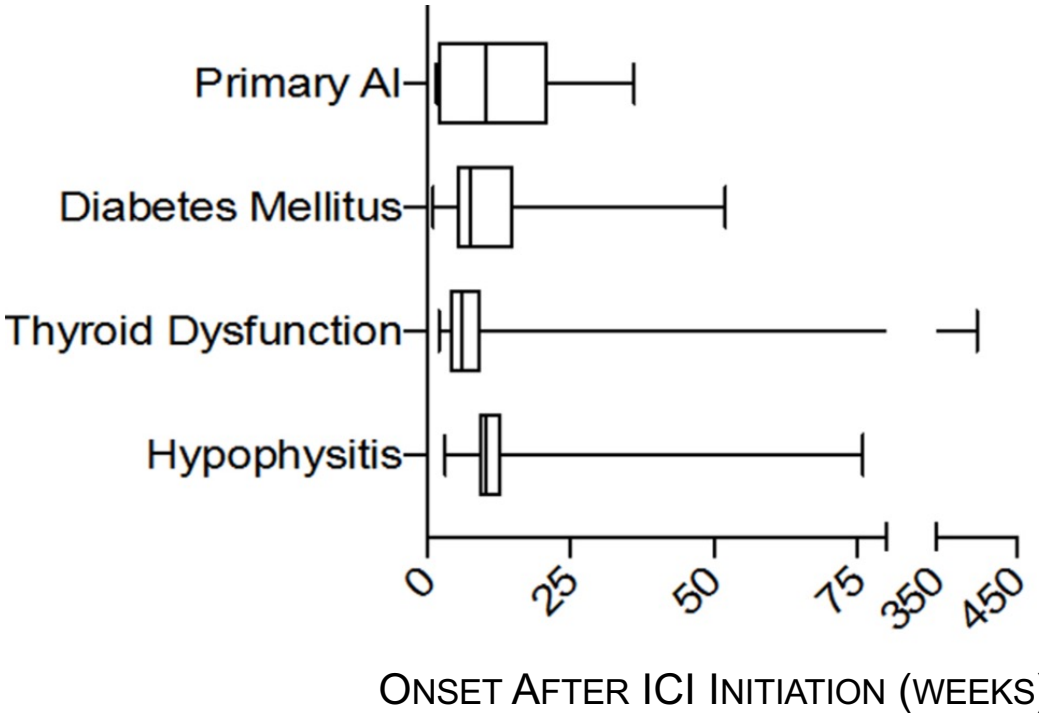
Endocrine Toxicity

Clinical OLYMPICS℠

Incidence by Organ and ICI Type



Median Time to Onset of Endocrinopathy

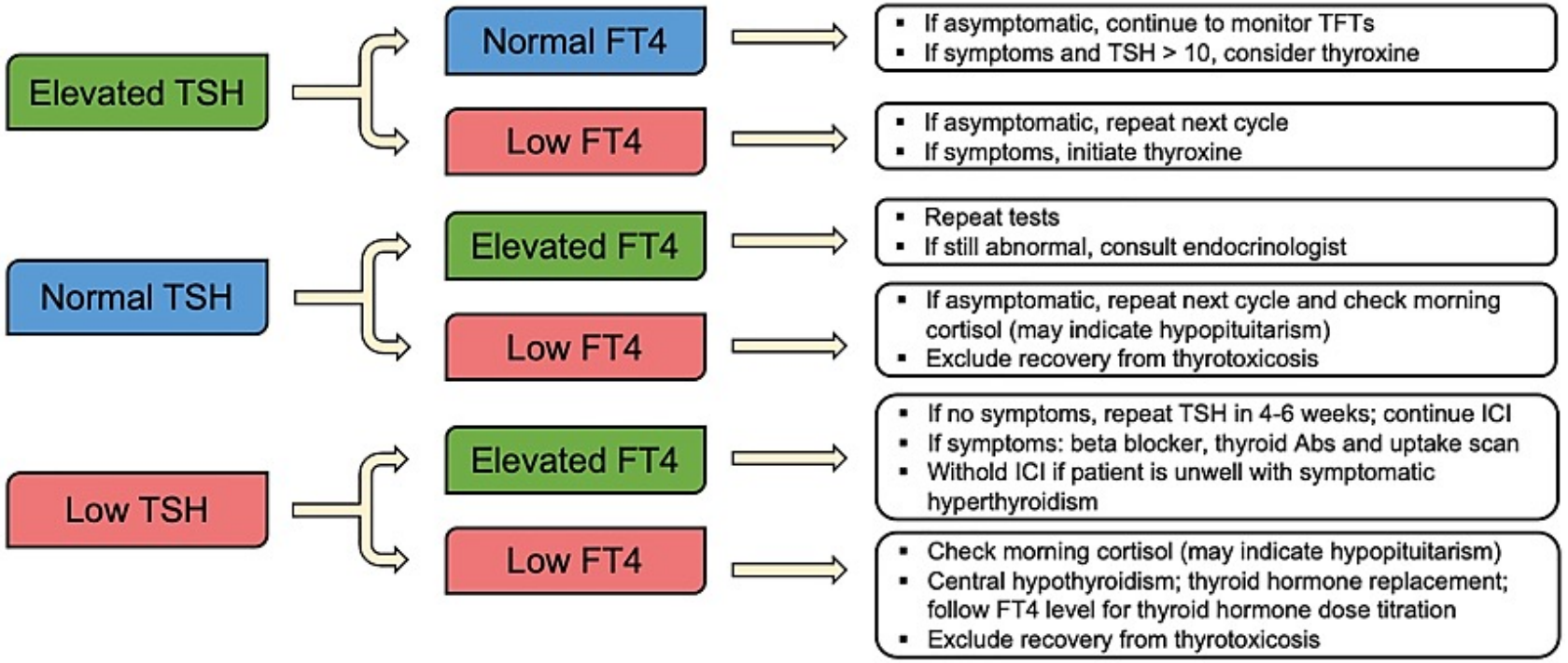


Wright JJ et al. *Nat Rev Endocrinol*. 2021 Jul;17(7):389-399.

SPOTLIGHT ON HYPO/HYPERTHYROIDISM

- One of the most common ICI-related endocrinopathies
- May be permanent
- More common with PD-1 vs CTLA-4 inhibitors, and with combination ICI
- Often mild (CTCAE Grades 1-2)
- Mainly consists of hypothyroidism:
  - Fatigue
  - Sensitivity to cold
  - Constipation
  - Weight gain
- Test thyroid function every 4-6 weeks during treatment and every 6-12 months after end of therapy
- Treat with hormone replacement, and continue ICI as soon as patients are stable (often without interruption)
- Does not generally require corticosteroids

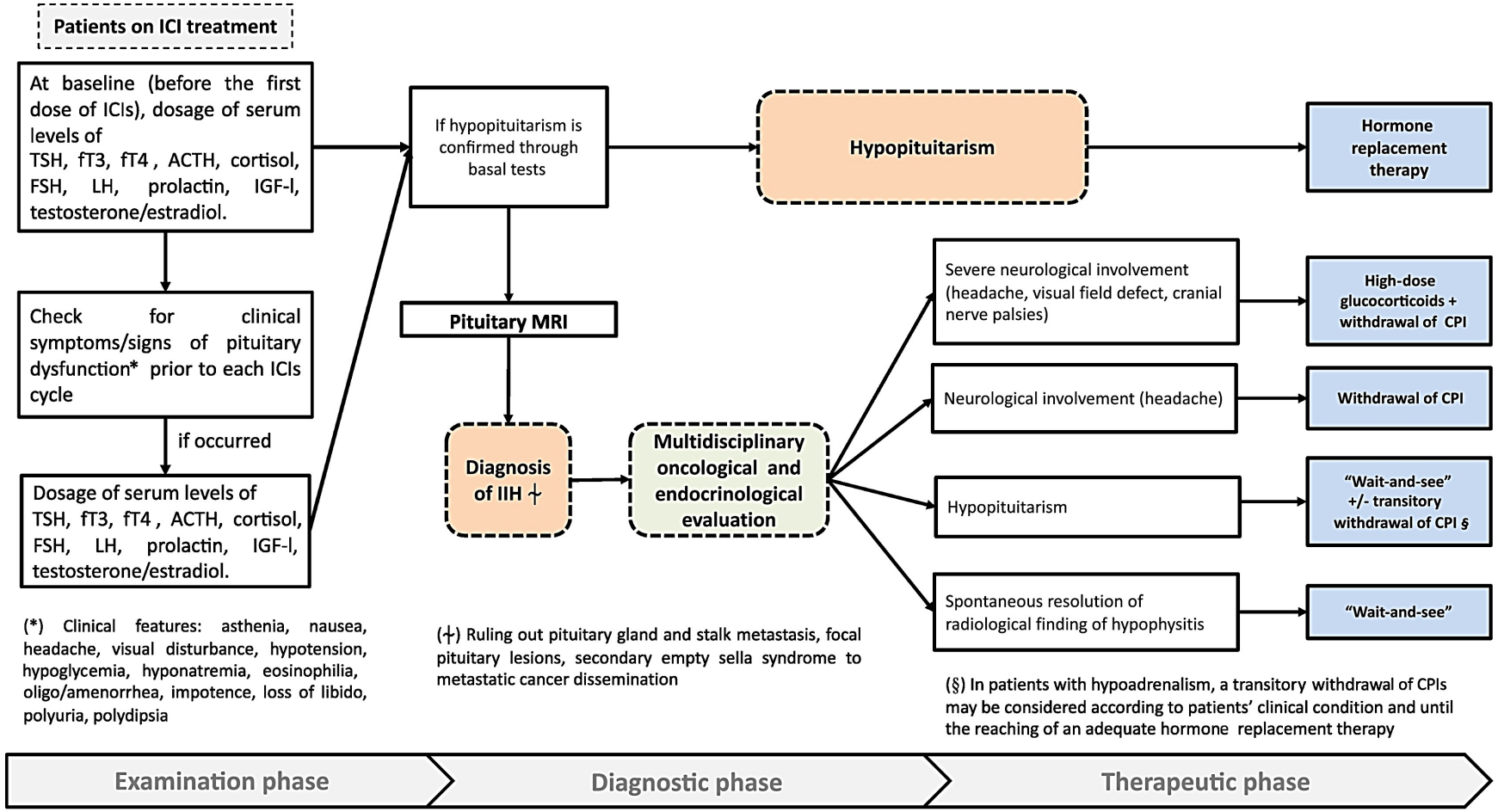
CLINICAL MANAGEMENT OF THYROID TOXICITIES



Ramos-Casals M et al. *Nat Rev Dis Primers*. 2020 May 7;6(1):38. Gumusay O et al. *Breast Cancer Res Treat*. 2022 Feb;192(1):1-17.

SPOTLIGHT ON HYPOPHYSITIS

- Headache, asthenia are the most common onset symptoms
- Secondary adrenal insufficiency is reported in 30-73% of cases
- Test ACTH levels and morning cortisol if TSH is low and fT4 is normal/low
- Low ACTH, low morning cortisol → test for FSH, TSH, fT4, and sex hormones
- Interrupt ICI and administer corticosteroids for acute hypophysitis
- Patients with hypophysitis should receive replacement hydrocortisone 10-12 mg/m^2/day

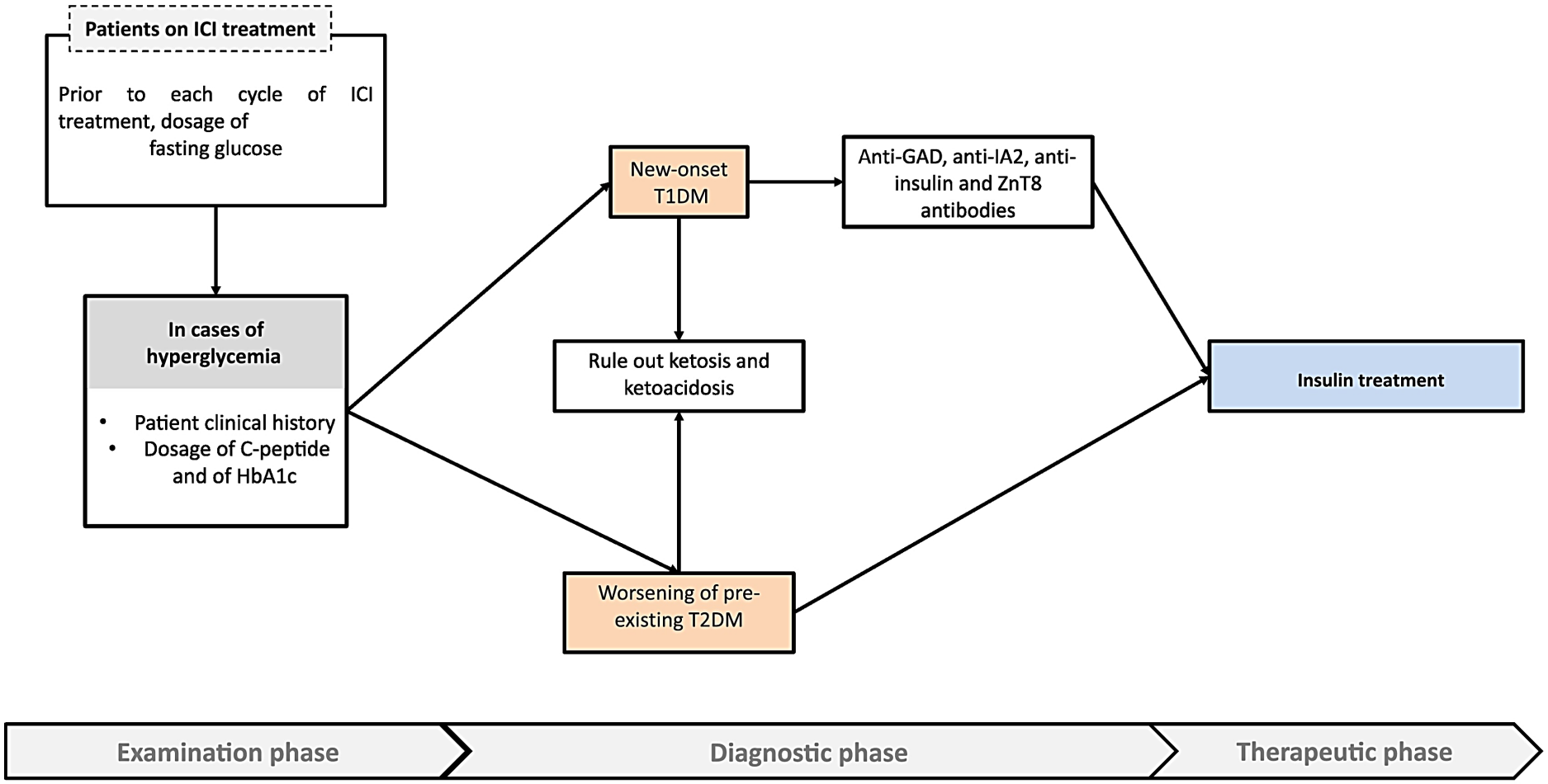


Chiloiro S et al. *Trends Endocrinol Metab*. 2022 Feb;33(2):87-104.

CPI, CHECKPOINT INHIBITION

SPOTLIGHT ON DIABETES

- Relatively rare
- Typically occurs after a median of 4 doses but can be delayed >1 year
- Typically occurs as rapid-onset hyperglycemia with a high risk for progressing to diabetic ketoacidosis (DKA) without prompt treatment
- Evaluate patients with hyperglycemia for DKA, hold ICI until DKA is resolved



Chiloiro S et al. *Trends Endocrinol Metab*. 2022 Feb;33(2):87-104.