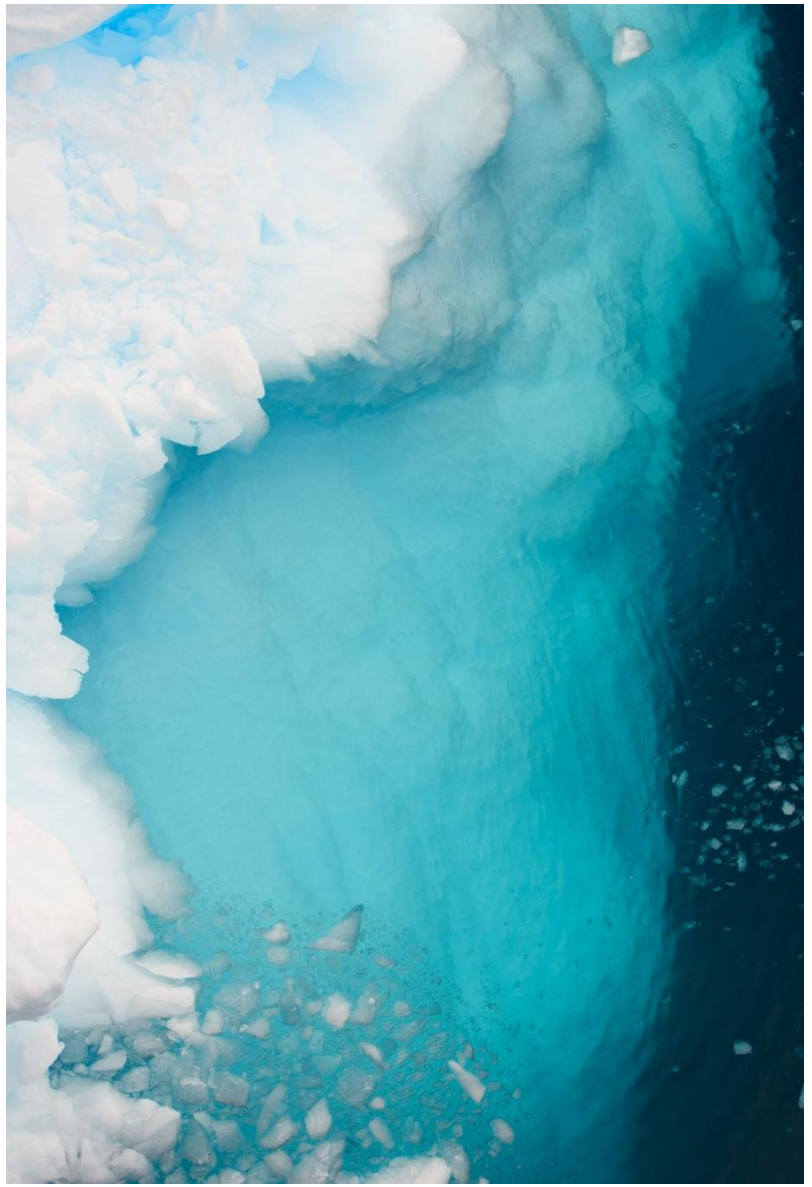
CURRENT MEDICAL ONCOLOGY

Opportunities and challenges



Learning Objectives

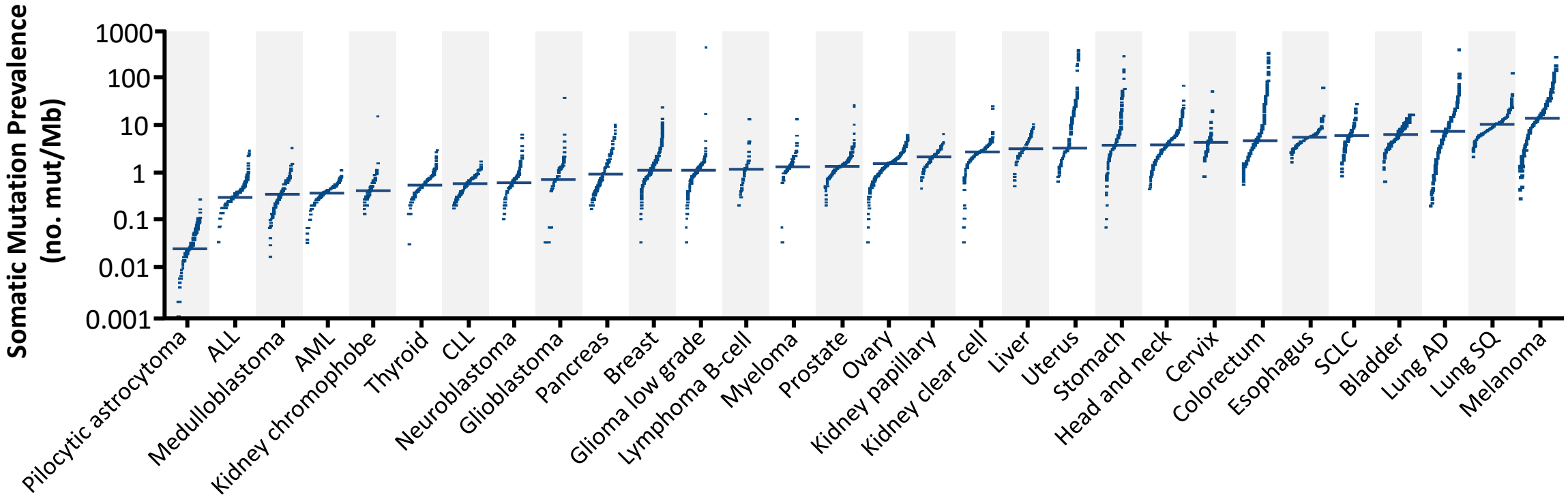
Common and rare side effects of immunotherapy.

New targeted treatment for lung cancer ,breast cancer and prostate cancer .

Role of ADC in different solid tumor.

ADC related toxicity

Prevalence of Somatic Mutations Across Tumor Types



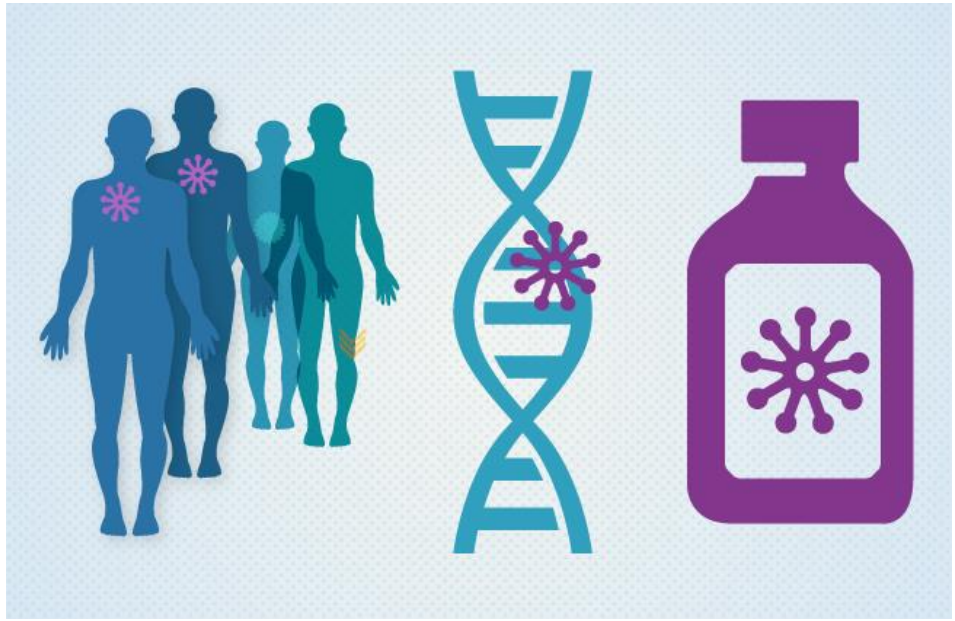
Alexandrov. Nature. 2013;500:415.

Slide credit: clinicaloptions.com

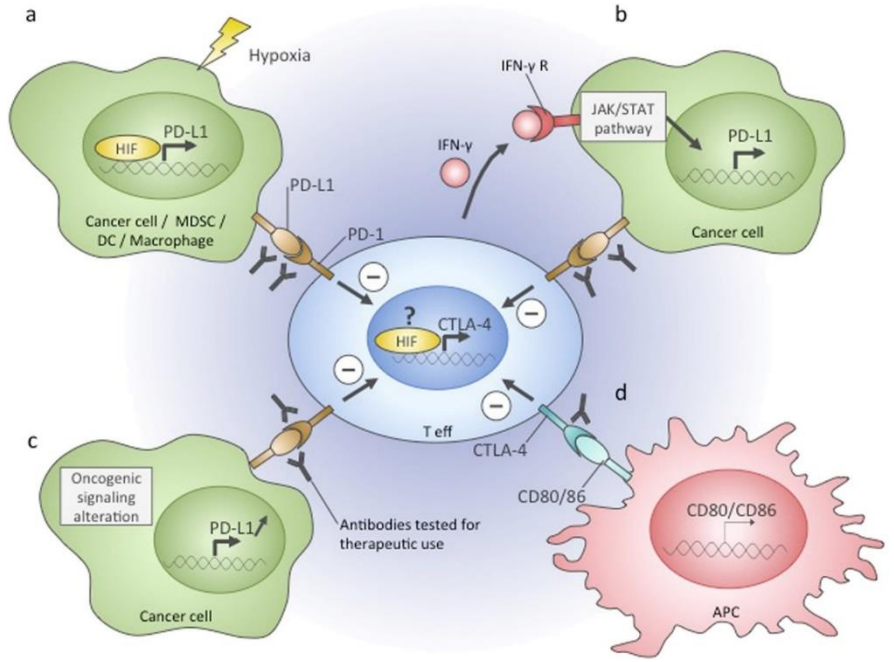
Lung Cancer

Emergence of 2 Major Paradigms in the Treatment of Advanced NSCLC

Targeted Therapy

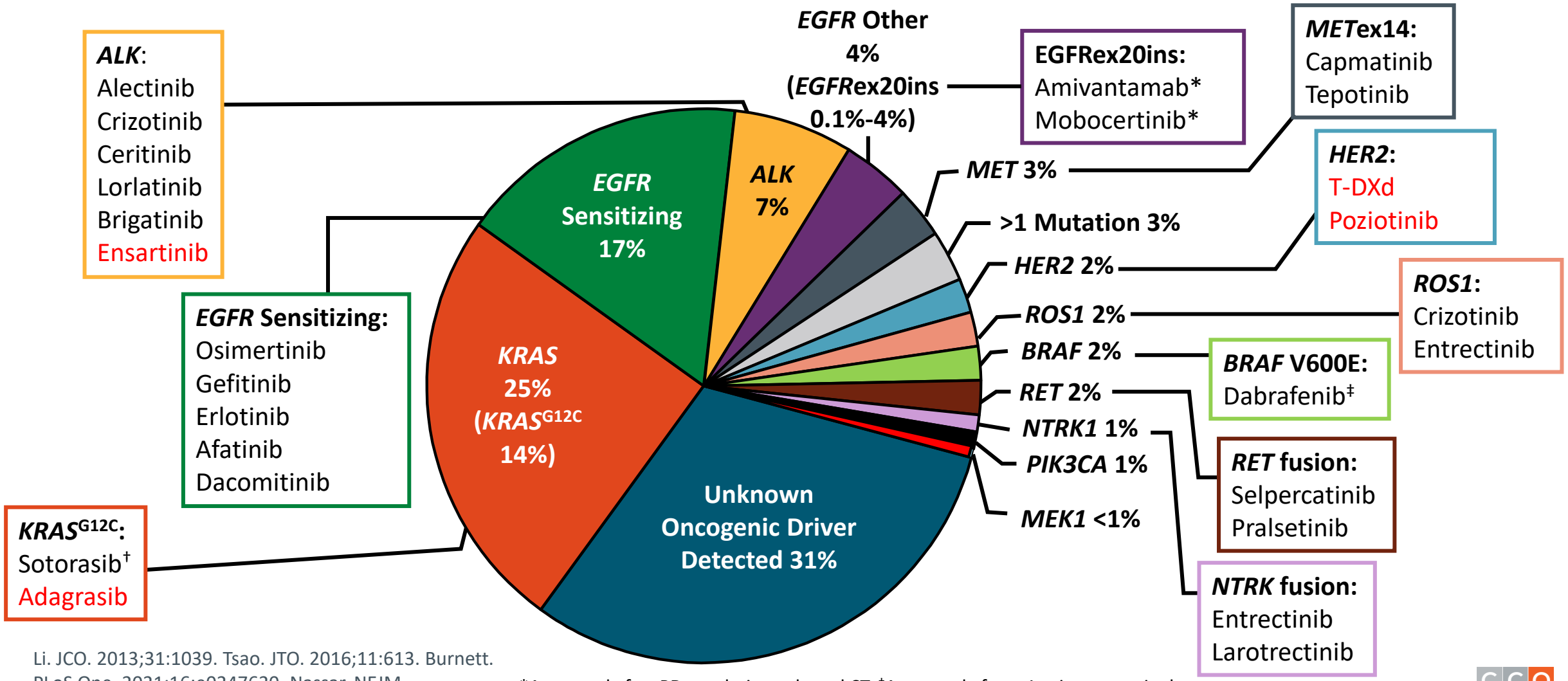


Immunotherapy



Slide credit: clinicaloptions.com

Targetable Driver Mutations in Advanced Nonsquamous NSCLC

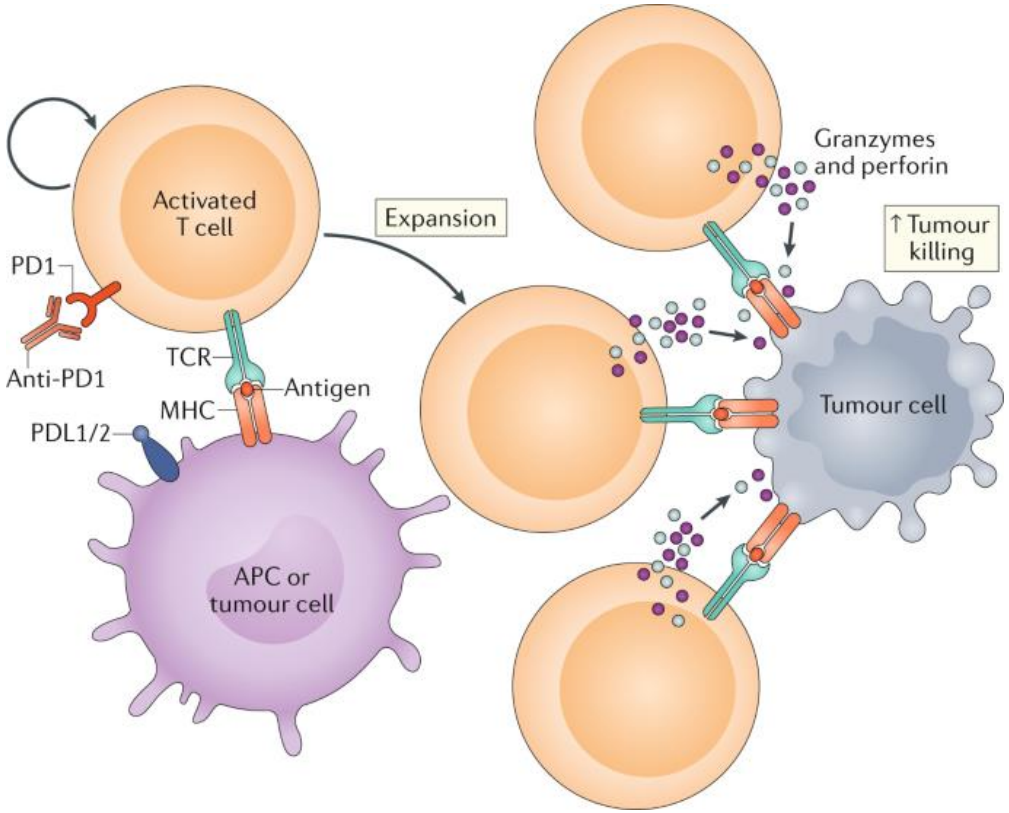


Li. JCO. 2013;31:1039. Tsao. JTO. 2016;11:613. Burnett. PLoS One. 2021;16:e0247620. Nassar. NEJM. 2021;384:185.

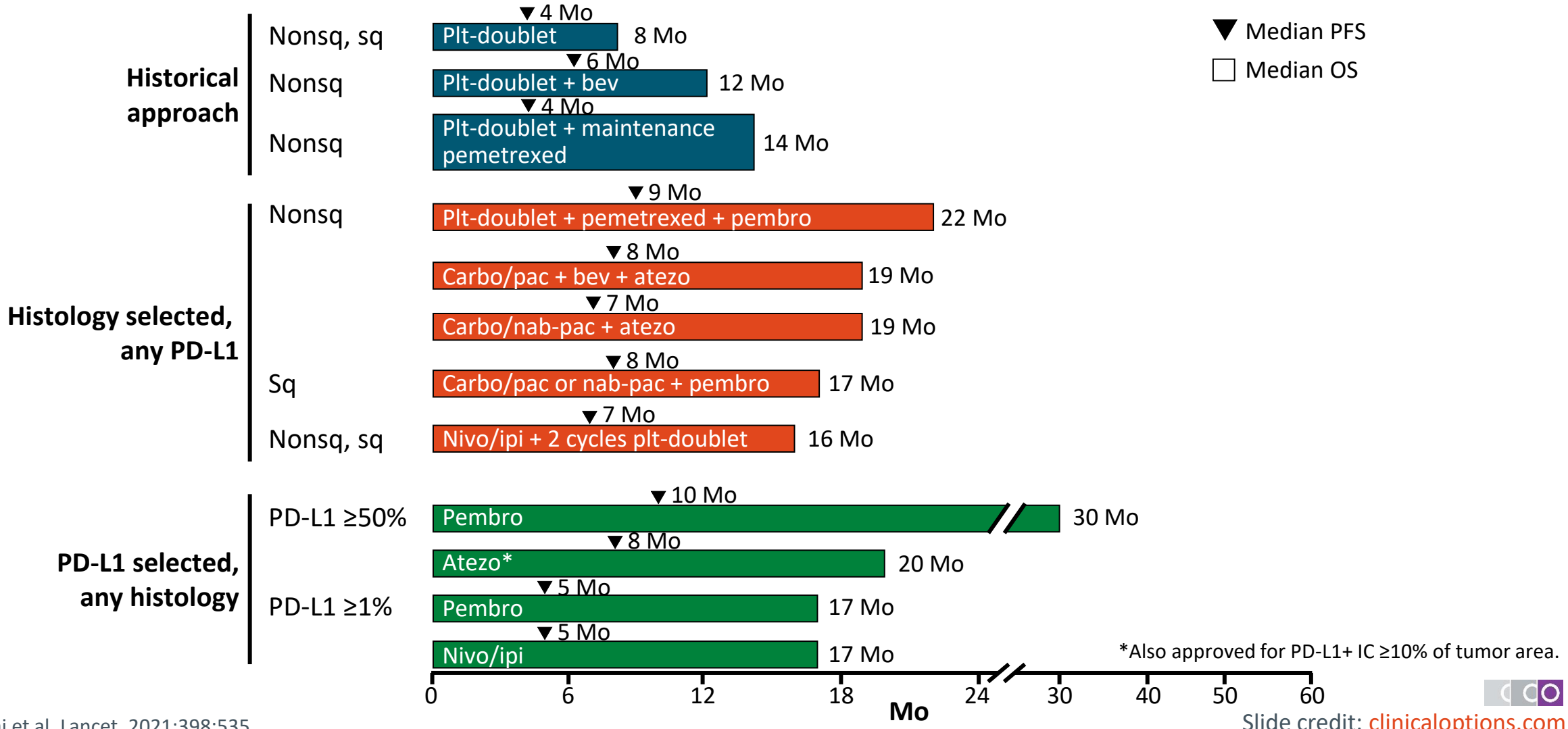
*Approved after PD on platinum-based CT. †Approved after ≥1 prior systemic therapy.
‡Approved in combination with trametinib (MEK inhibitor) for *BRAF* V600E mutation.

Slide credit: clinicaloptions.com

IMMUNOTHERAPY



PD-(L)1 Inhibitors in Stage IV NSCLC



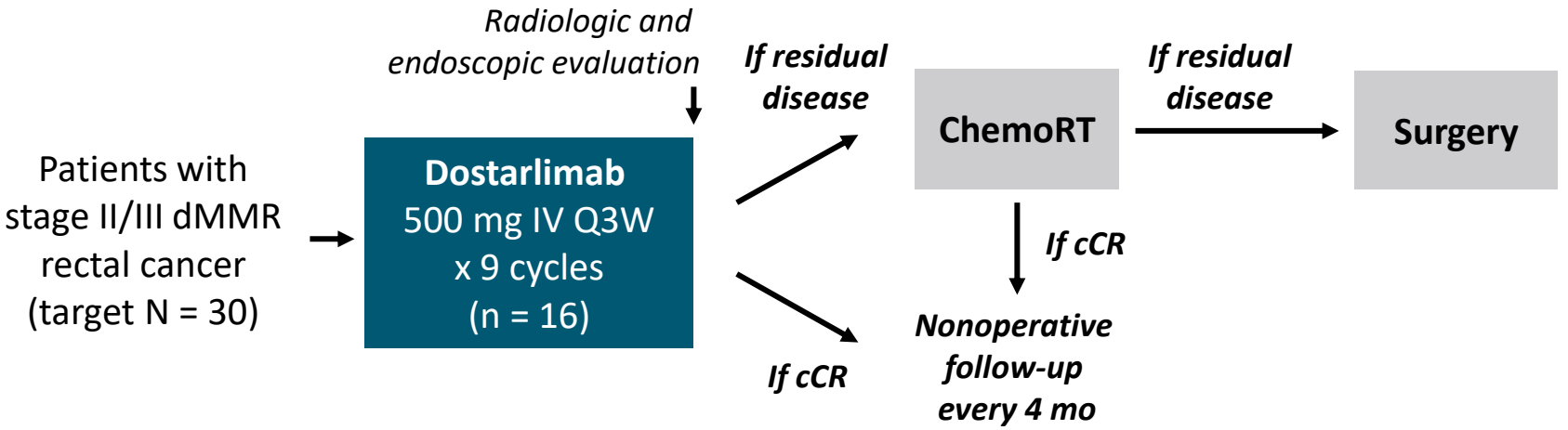
Thai et al. Lancet. 2021;398:535.

Slide credit: clinicaloptions.com

Cure without surgery

Dostarlimab for Locally Advanced dMMR Rectal Cancer: Study Design

- Single-arm phase II study

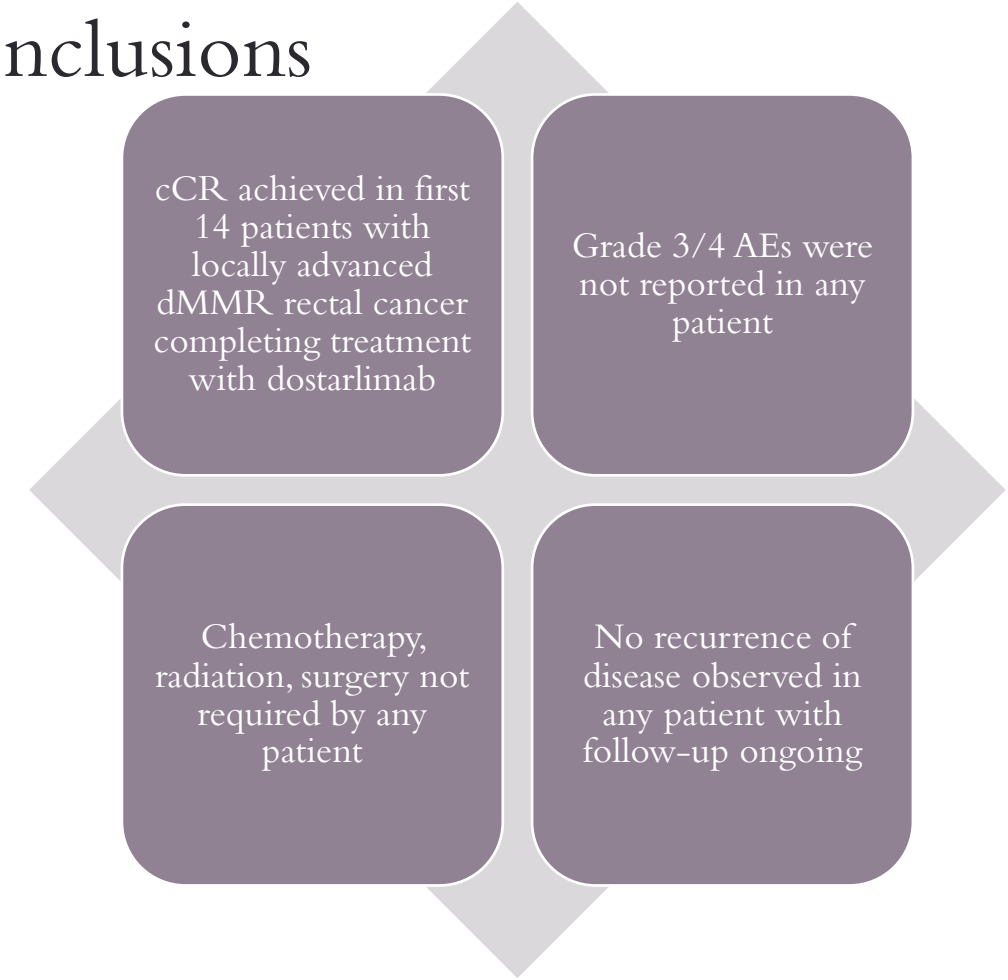


- Primary objectives:
  - **Overall response to dostarlimab ± chemoRT (reported in this analysis)**
  - Sustained cCR 12 mo after completion of dostarlimab (if no surgery) *or* pCR (if surgery) after completion of dostarlimab ± chemoRT
- Secondary objectives: safety, tolerability

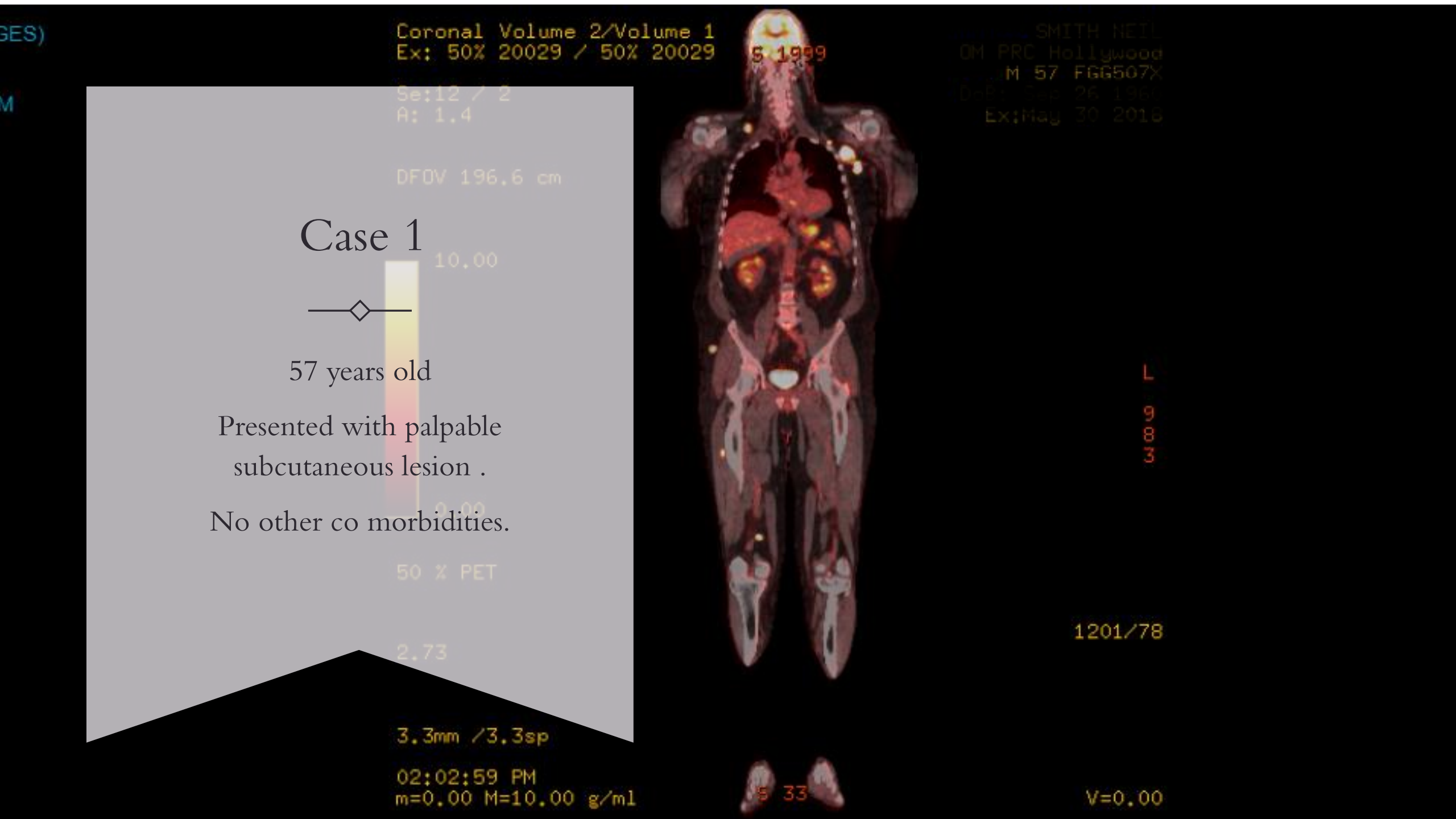
Cercek. NEJM. 2022;[Epub]. Cercek. ASCO 2022. Abstr LBA5.

Slide credit: clinicaloptions.com

Dostarlimab for Locally Advanced dMMR Rectal Cancer: Investigator Conclusions



Cercek. NEJM. 2022;[Epub]. Cercek. ASCO 2022. Abstr LBA5.

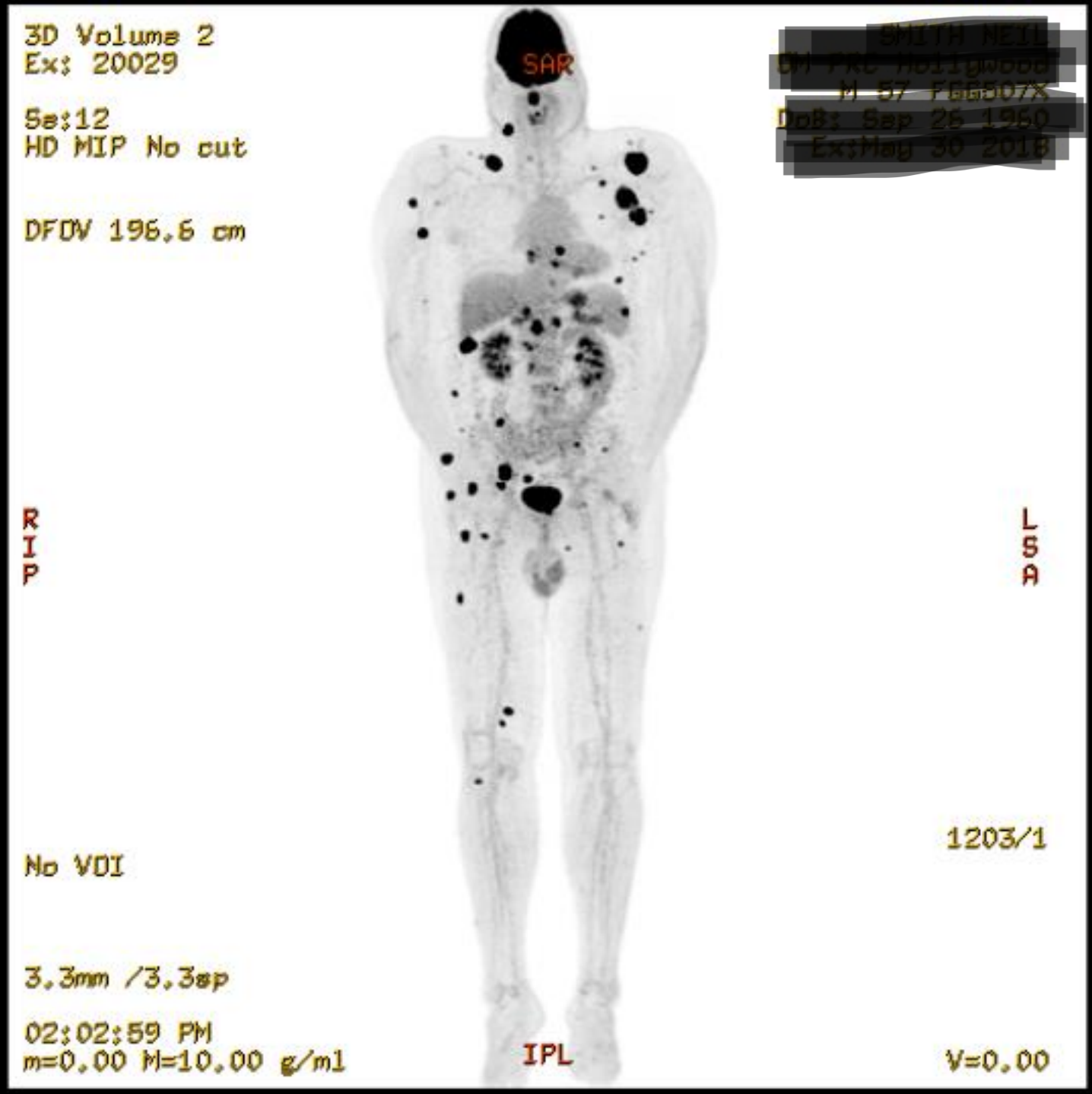


Case 1

57 years old

Presented with palpable subcutaneous lesion .

No other co morbidities.


3D Volume 2
Ex: 20029
Se:12
HD MIP No cut
DFOV 196.6 cm
SAR
[redacted]
R
I
P
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A
No VOI
1203/1
3.3mm /3.3sp
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m=0.00 M=10.00 g/ml
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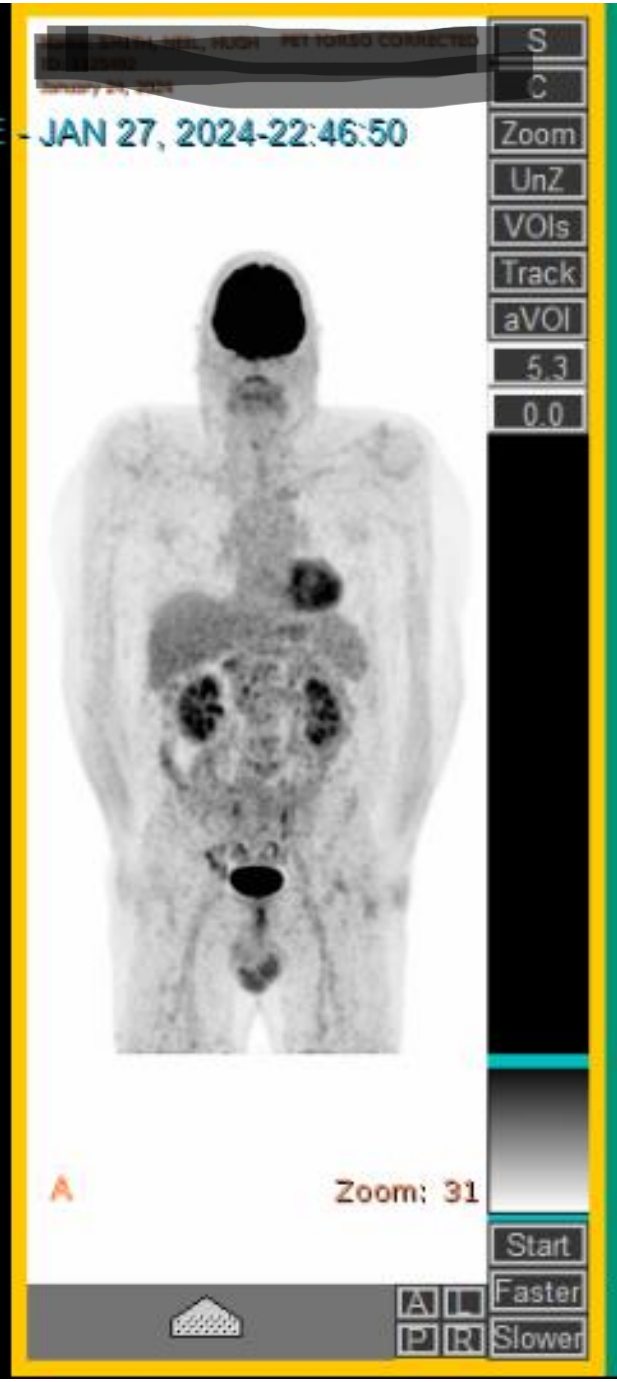
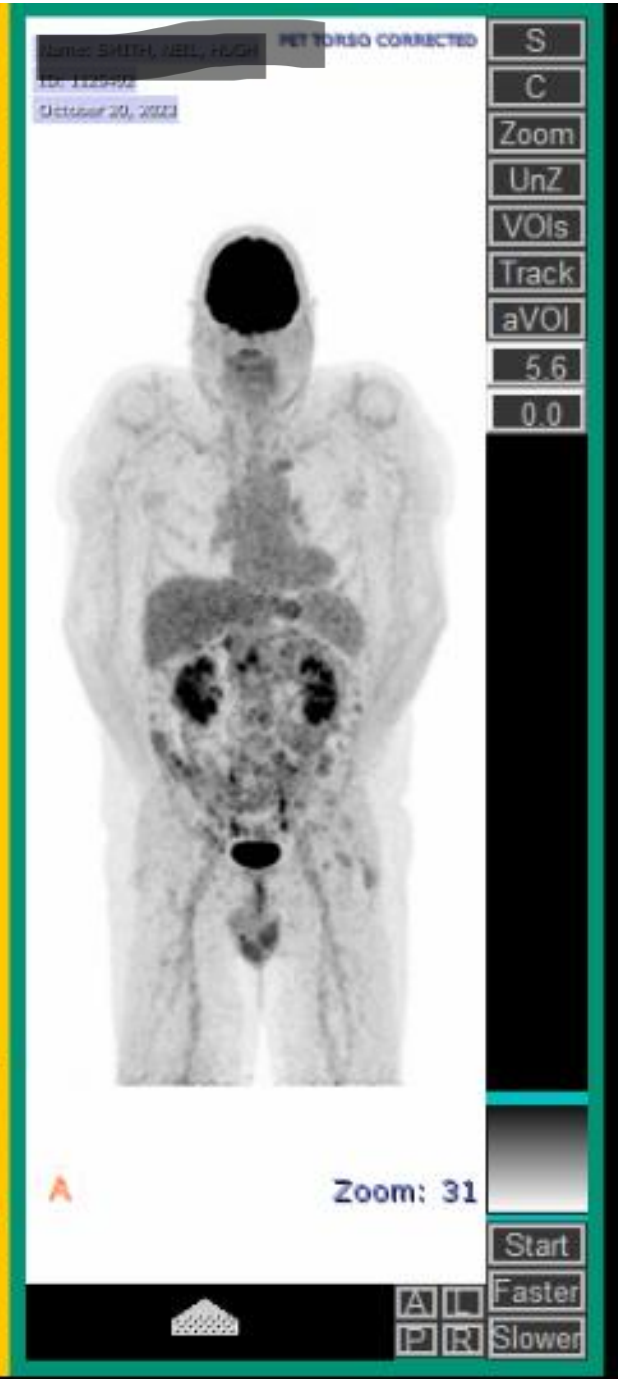
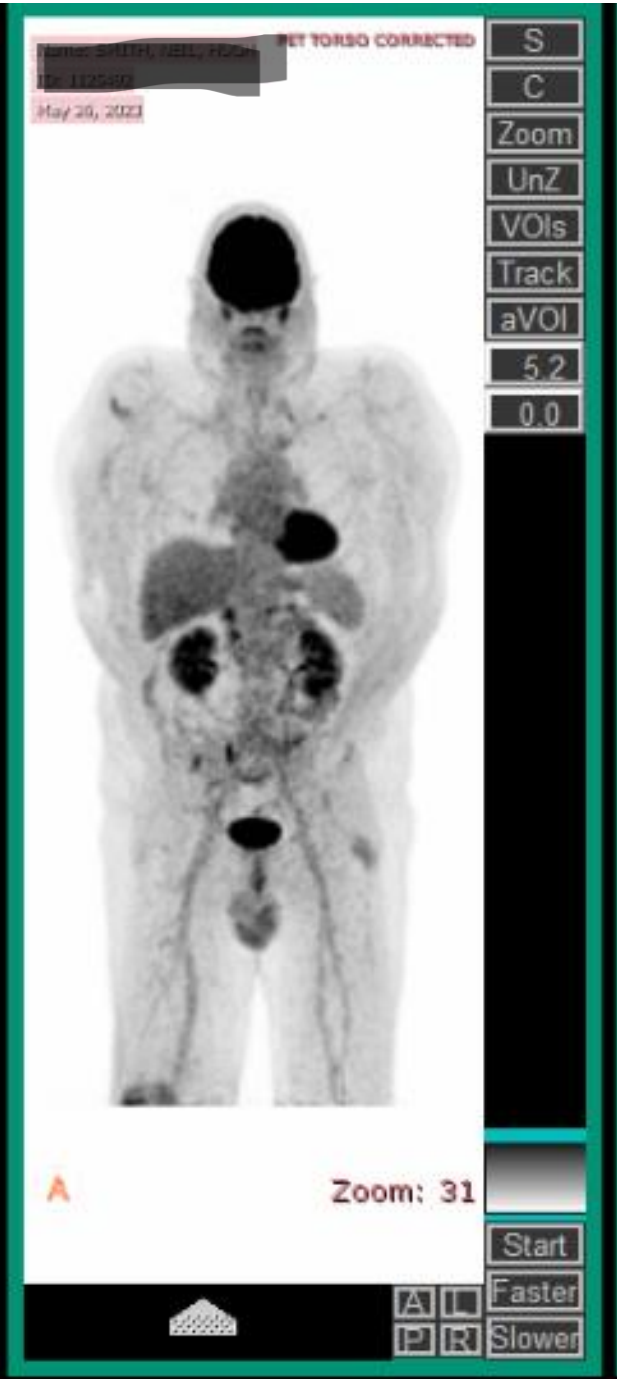
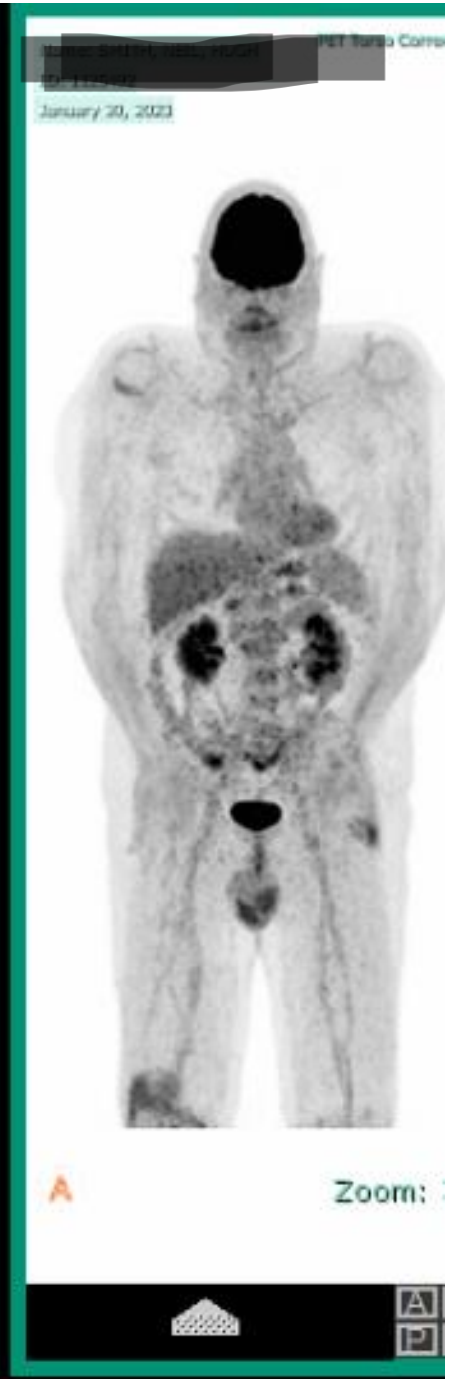








Progress

Had combined immunotherapy for 4 cycles.

Currently on maintenance immunotherapy .

Working full time.

No AE from immunotherapy.

Case 2

88 years old

ECOG 0

Not on any medication

Newly diagnosed sarcomatoid mesothelioma .

Symptomatic with recurrent pleural effusion and chest wall pain.

Started on combined immunotherapy with Nivolumab and Ipilimumab late August .

Presented with ptosis of both eyelids in 3 weeks post cycle one.

Progress

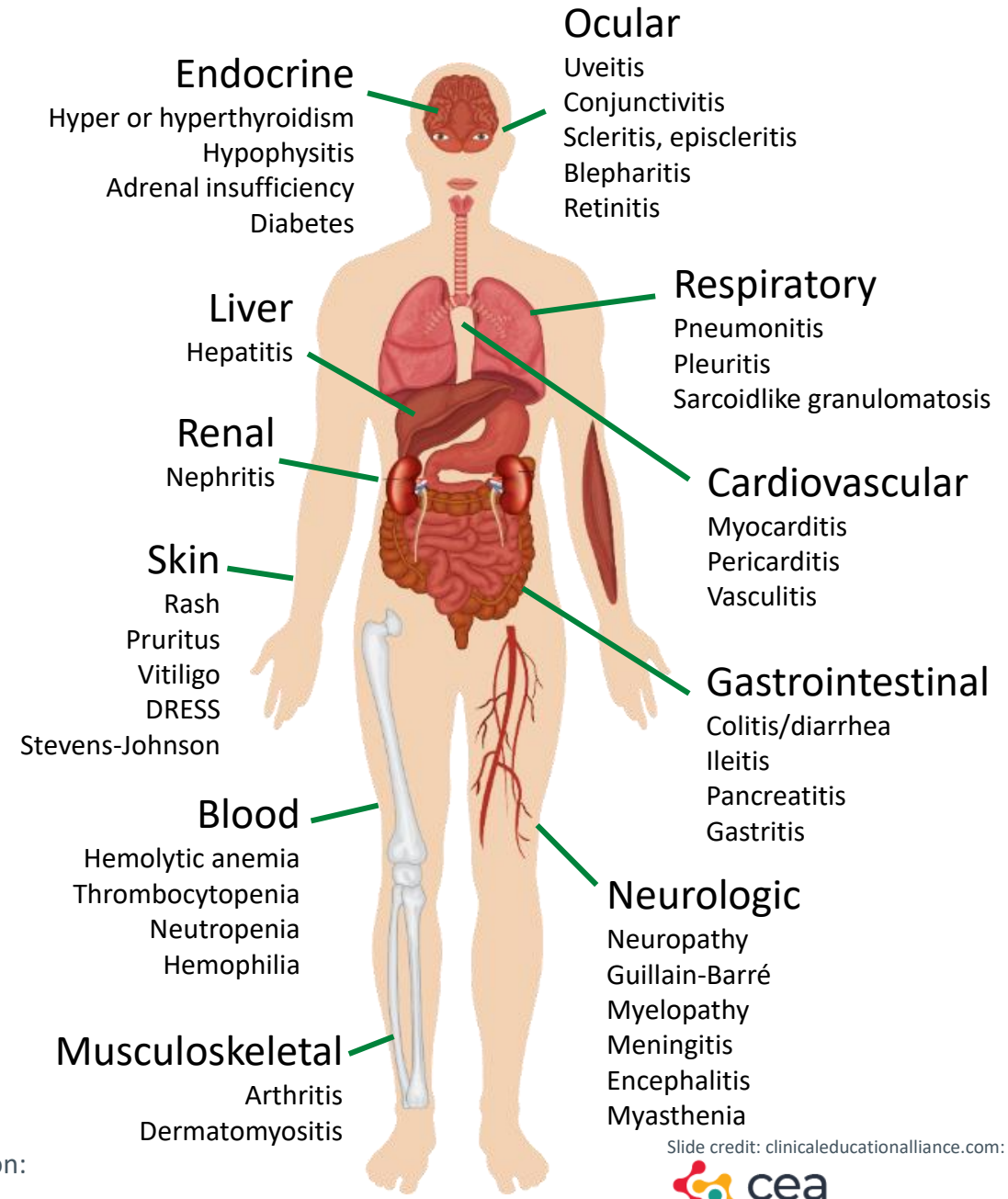
?Immunotherapy associated myasthenia Gravis

- CT brain no acute intracranial pathology
- CK 3000 on admission
- Had 2mg/kg IV methylprednisolone for 4 days and trial of pyridostigmine at 60mg TDS
- Pyridostigmine ceased as felt there was no benefit
- Ach Rec negative, anti Musk ab negative
- Methylpred was increased to 1000mg after discussion with neurology team .
- Received 4 days of 1000mg then decreased to 2mg/kg IV methylprednisolone for 4 days then 100mg prednisolone
- Received 5 days of IVIG (finished on 13/10)
- Ptosis and dysphagia improving
- Peak flow normal throughout

-Mobilising with walker

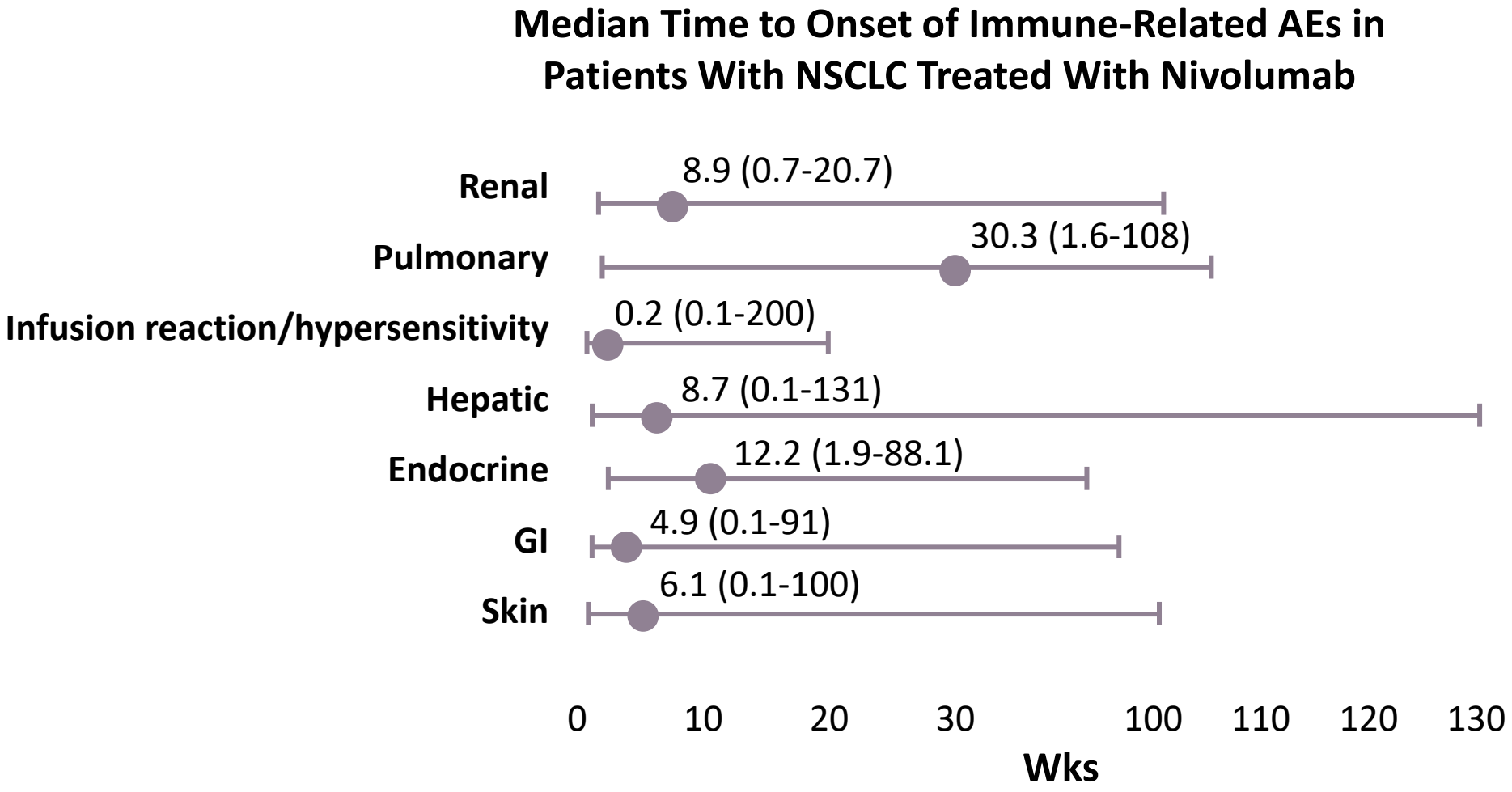
Spectrum of Immune-Related AEs

- irAEs can affect **any** organ of the body
- Onset varies
  - Usually 2-3 mo after starting tx
  - Up to 2 yr after tx completion
- Maintain high level of suspicion for irAEs when new symptoms develop
- If irAEs are suspected, conduct a complete workup, including lab tests, to rule out other causes



Schneider. JCO. 2021;39:4073. Zimmerman. Am Soc Clin Oncol Educ Book. 2018;38:682. Champiat. Ann Oncol. 2016;27:559. Michot. Eur J Cancer. 2016;54:139. Steven. Rheumatology (Oxford). 2019;58:vii29. Winer. J Thorac Dis. 2018;10:S480. Robert. ASCO 2017. Education session: checkpoint inhibitor immunotherapy.

Time to Onset of Immune-Related AEs With Immune Checkpoint Inhibition



Remon. J Thorac Dis. 2018;10(suppl 13):S1516.

Slide credit: clinicaloptions.com

Dermatitis

Signs and symptoms: •rash •skin blisters •pruritus •**new or worsening skin lesions** •**hand-foot syndrome** •**loss of skin pigmentation**	**Grade 1:** Rash covering <10% BSA, which may or may not be associated with symptoms of pruritus or tenderness; symptoms do not affect instrumental ADL or controlled with topical regimen **Grade 2:** Rash covering 10% to 30% BSA with or without symptoms (e.g. pruritus, burning and tightness); limiting instrumental ADL; rash covering >30% BSA with or without mild symptoms	Rash covering >30% of BSA with moderate or severe symptoms; limiting self-care ADL	Rash – Severe consequences requiring hospitalisation or urgent intervention indicated or life threatening Stevens-Johnson syndrome, toxic epidermal necrolysis; or rash complicated by full thickness dermal ulceration, or necrotic, bullous, haemorrhagic manifestations

Slide credit: clinicaleducationalliance.com:

cea clinical education alliance

Case

70 years old ,male

- Stage IV lung adenocarcinoma Histology confirmed adenocarcinoma PD-L1 70%, 1.2
- Had first line immunotherapy with pembrolizumab. Partial response.
- Treatment complicated by immune induced hepatitis and nephritis responded with steroid.

- Creatinine – 127
- AST -189
- ALT 108
- ALP -280
- GGT 846

Progression

- Had prolong tapering dose of prednisolone
- Hepatitis responded with steroid
- With in 6 months had disease progression
- Had rechallenge with immunotherapy
- Developed severe hepatitis
- Did not respond to steroid.
- Started on Mycophenolate.

Typical and Select Rare Presentations of Common irAEs

Common irAEs	Typical Presentation
Dermatologic[1,2]	Maculopapular rash with or without pruritus, predominantly on trunk and to lesser extent the upper limbs, spreading to extremities; eczematous, lichenoid, psoriasiform manifestations; blistering skin reactions; sicca syndrome[4,5]
Diarrhea/colitis[2]	Diarrhea, abdominal pain, hematochezia, weight loss, fever, vomiting
Hepatic[2]	Often asymptomatic and diagnosed via routine blood tests
Pancreatic[2]	Asymptomatic elevation in amylase/lipase; clinical findings of pancreatitis; severe abdominal pain, vomiting, and hemodynamically unstable
Endocrine[2,3]	Headaches, visual disturbances, fatigue, altered consciousness, deranged electrolytes (particularly hyponatremia), mood changes

1. Sibaud. Am J Clin Dermatol. 2018;19:345. 2. Pickwell-Smith. Br J Hosp Med (Lond). 2018;79:372.
3. Sznol. Cancer Treat Rev. 2017;58:70. 4. Segawa. IJU Case Rep. 2023;6:147. 5. Warner. Oncologist. 2019:24:1259.

Less Common irAEs: Presenting Signs and Symptoms

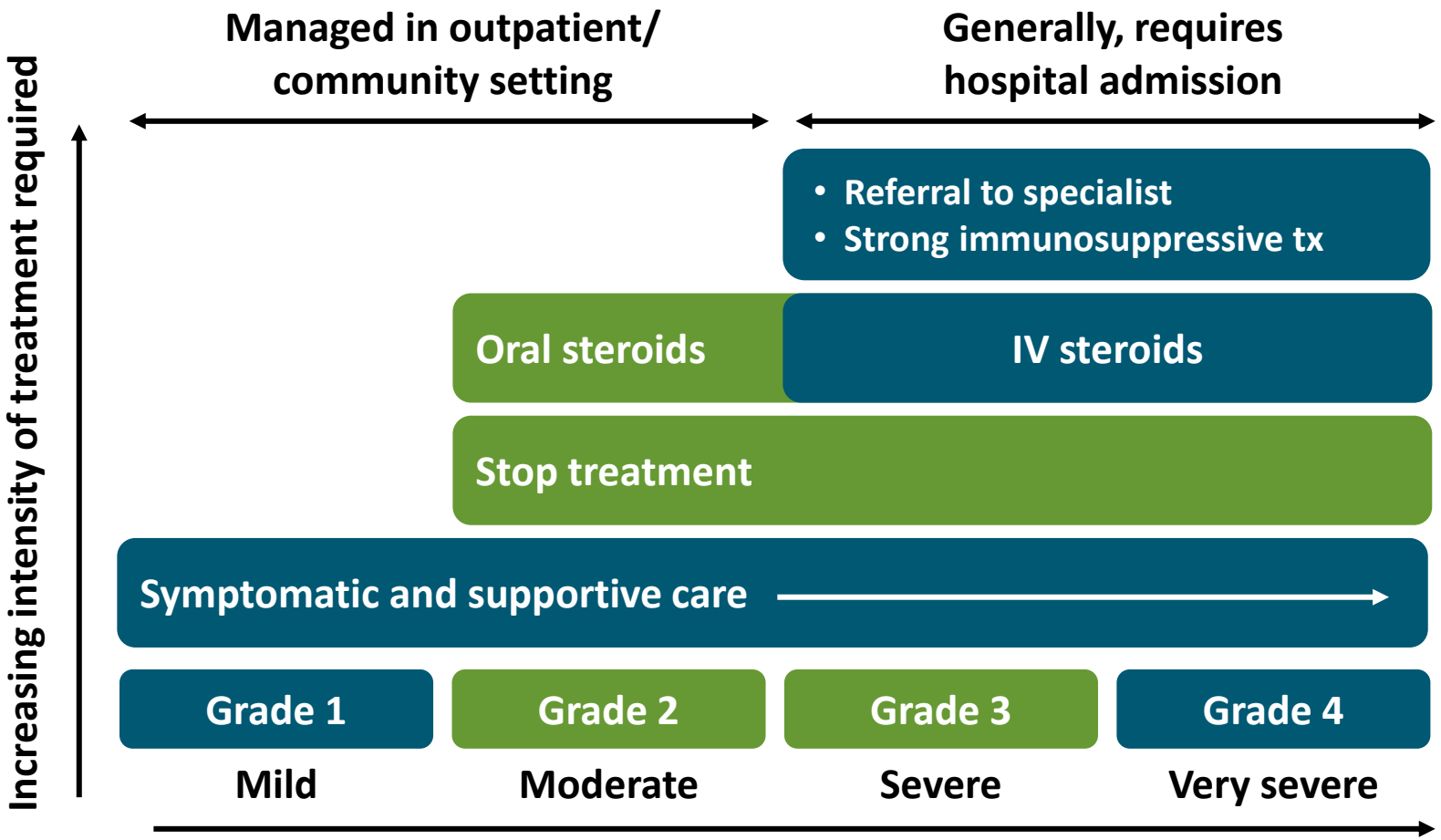
Less Common irAEs	Typical Presentation
Pneumonitis[1]	Dyspnea, cough, fever, chest pain
Renal[2]	Elevated serum creatinine, azotemia, inability to maintain acid–base or electrolyte balance, urine output change, edema
Ocular[2]	Vision changes, photophobia, tenderness/pain, eyelid swelling, proptosis, red/purple discoloration, eye redness
Neurologic[2]	Progressive or fluctuating muscle weakness, usually proximal to distal; absent/reduced deep tendon reflexes; sensory–motor deficit; headache, photophobia, neck stiffness with nausea/vomiting; confusion, altered behavior, seizures, short-term memory loss, depressed level of consciousness, focal weakness, speech abnormality
Cardiovascular[3]	Generalized malaise and fatigue, dyspnea, edema, decreased ejection fraction on ECHO
Musculoskeletal[4]	Joint pain, swelling; inflammatory symptoms; stiffness after inactivity; improvement with heat; myalgias; myositis

1. Pickwell-Smith. Br J Hosp Med (Lond). 2018;79:372. 2. Spiers. Rheumatology (Oxford). 2019;58:vii7.
3. Brumbaugh. Cardiol Rev. 2019;27:97. 4. Steven. Rheumatology (Oxford). 2019;58:vii29.

GI toxicity

	Grade 1	Grade 2	Grade 3 to 4
Signs and symptoms: •watery diarrhoea or more bowel movements than usual •**nocturnal bowel movements** •blood or mucous in stools •dark, tarry, sticky stools •abdominal pain, cramping, tenderness or urgency •systemic symptoms eg **fever, hypotension,** nausea and vomiting	**Diarrhoea:** <4 stools per day over baseline **Colitis:** asymptomatic	**Diarrhoea:** 4-6 stools per day over baseline; not interfering with ADL **Colitis:** abdominal pain; mucous or blood in stool	**Grade 3 diarrhoea**: ≥7 stools per day over baseline; interfering with ADL **Grade 3 colitis**: severe abdominal pain; peritoneal signs **Grade 4**: life threatening diarrhoea or colitis or perforation
Treatment with anti-PD-1 or anti-PD-L1			

General Recommendations for Treatment of irAEs



- Pneumonitis/ILD can occur with immunotherapy
  - Closely monitor patients for signs of infection
  - Have low threshold for corticosteroids use for grade ≥2 pneumonitis
  - Consider bronchoscopy to rule-out infection if suspect ILD or pneumonitis
- Steroids (PO/IV): 0.5-2 mg/kg/day prednisone or equivalent; slow taper over 4-6 wk
- For some irAEs, ICI can be restarted after resolution (eg, rash)
- Endocrinopathies: ICI can generally be continued with management

Haanen. Ann Oncol. 2022;33:1217. NCCN. Clinical practice guidelines in oncology: management of immunotherapy-related toxicities. v.1.2024.

Understanding Antibody–Drug Conjugates: Key Structural Elements and Target Antigens

Target

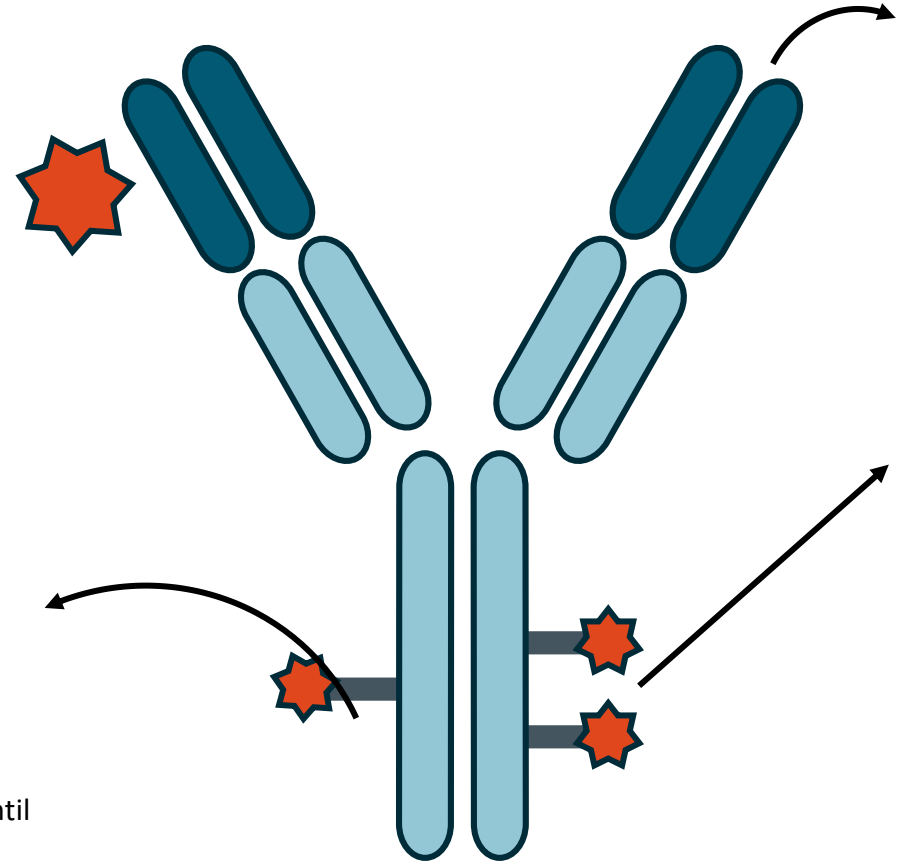
- Tumor specific with homogeneous expression
- High levels of expression
- No to minimal expression on normal tissue
- Internalized on ADC binding

Linker

Stability
- Must be stable in plasma to prevent premature release of the payload

Cleavable linker
- Releases payload within the target cell under specific conditions, ie, acidic environment or presence of specific enzymes
- Enhanced killing through bystander effect

Noncleavable linker
- Remains intact and do not release the payload until entire ADC is degraded inside the tumor cell
- Limits diffusion to nearby cells and bystander effect



Antibody

Target choice
- Expression of target on normal tissue or low specificity can lead to off-target toxicity
- Homogenous expression on tumor cells may enhance treatment response
- IgG1 is the most used mAb
  - IgG1 is effective in activating immune responses such as ADCC and CDCC

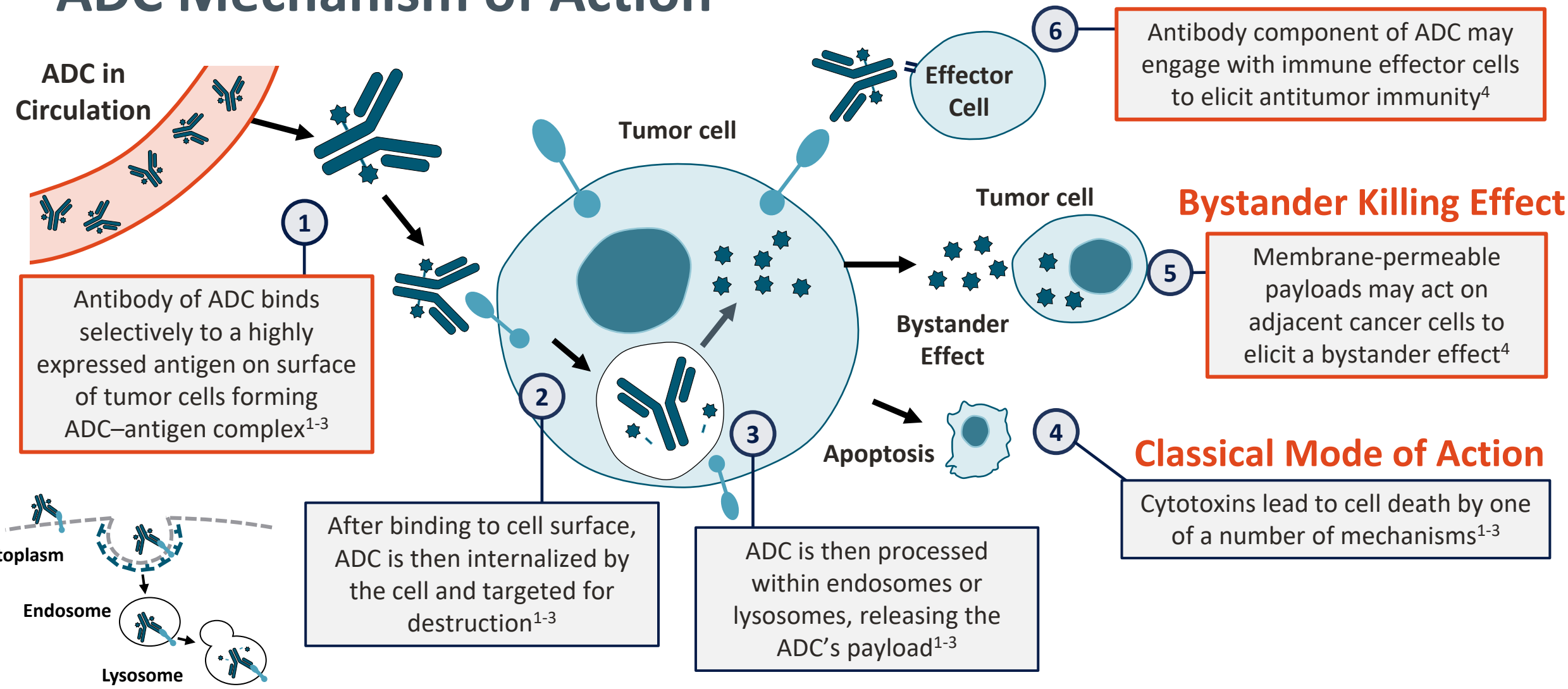
Payload

Cytotoxic mechanism
- Topoisomerase-I inhibitor
- Microtubule inhibitors
- DNA disruptor
- Immune stimulant

Potency
- ADC payloads (subnanomolar IC50) are ~100-1000x more potent than small-molecule chemotherapeutic payloads

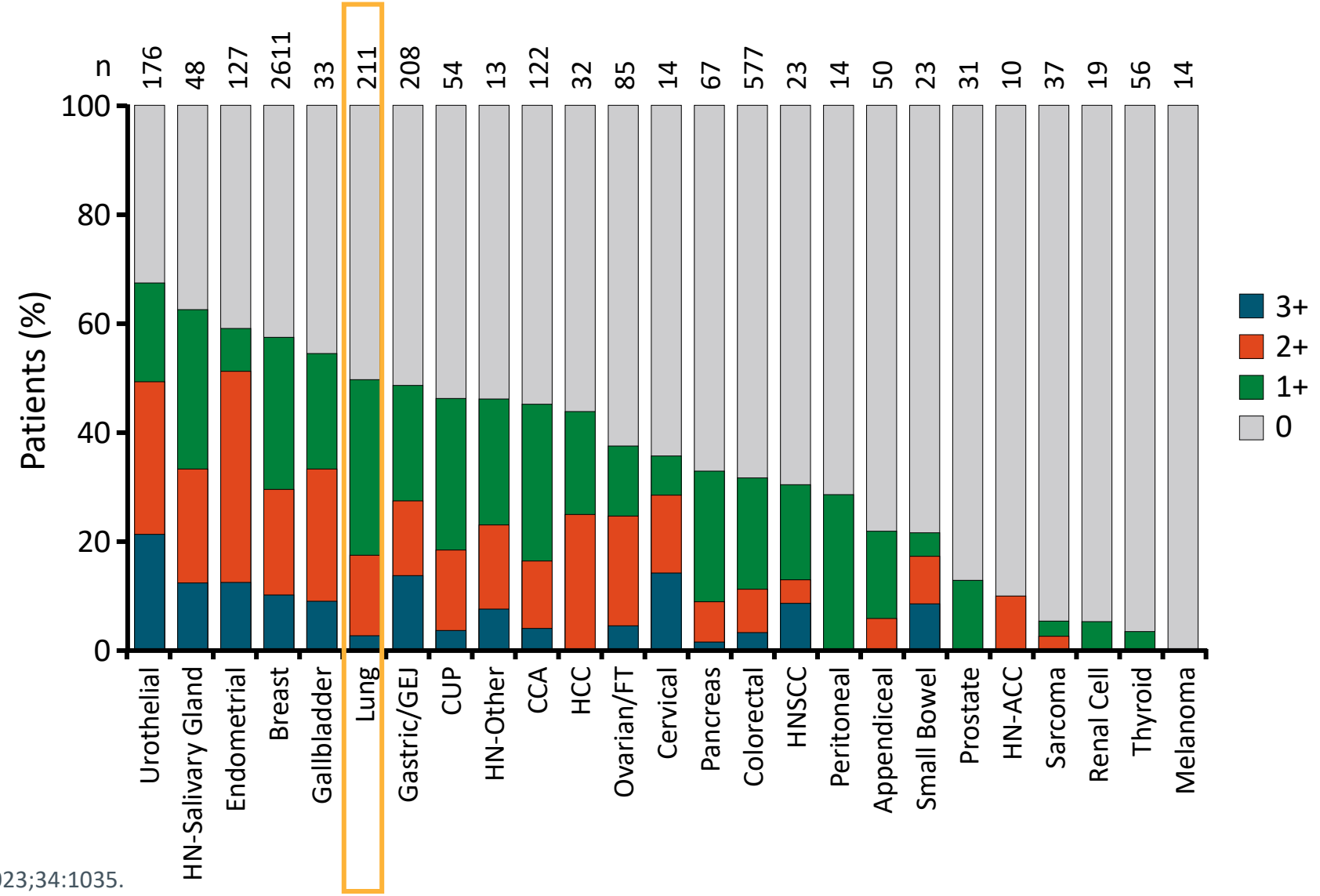
Theocharopoulos.. Vaccines (Basel). 2021;9:1111.

ADC Mechanism of Action



1. Bouchard. Bioorg Med Chem Lett. 2014;24:5357. 2. Peters. Biosci Rep. 2015;35:e00225.
3. Diamantis. Br J Cancer. 2016;114:362. 4. Fu. Signal Transduct Target Ther. 2022;7:93.

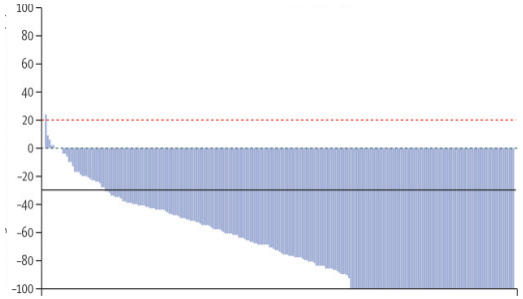
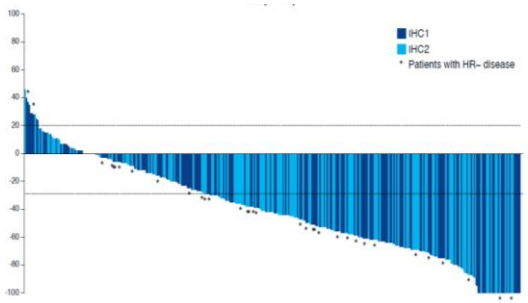
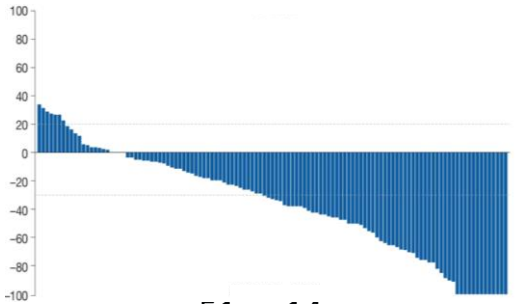
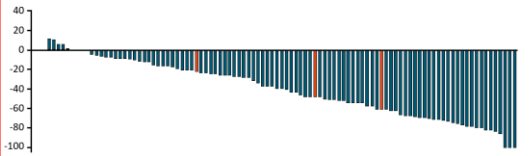
HER2 Expression Across Solid Tumor Types



Uzunparmak. Ann Oncol. 2023;34:1035.

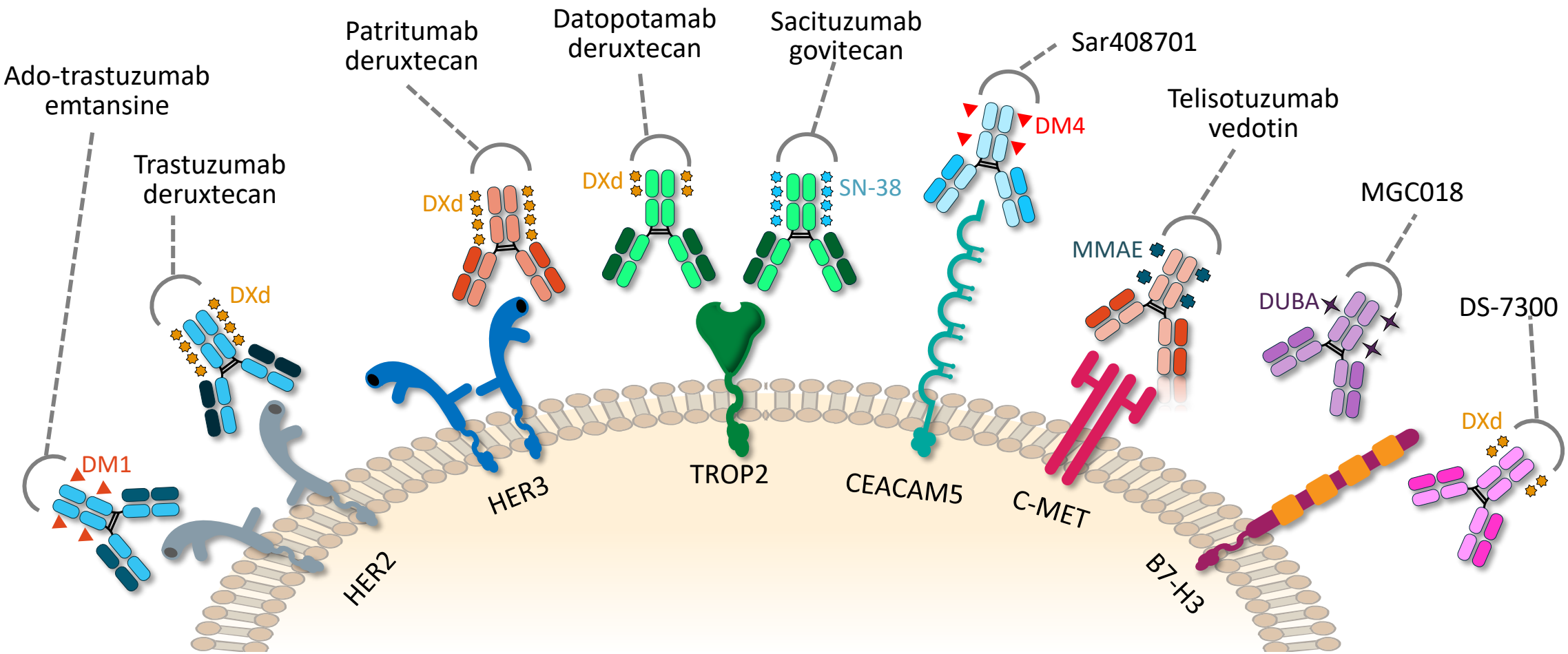
T-DXd: FDA-Approved Indications for Specific Tumor Types

Now FDA approved for advanced HER2+ NSCLC

	2L+ HER2-Positive mBC	3L+ HER2-Low mBC	3L+ HER2-Positive Gastric/ GEJ Adenocarcinoma	2L+ *HER2*-Mutated NSCLC
Trial	DESTINY-Breast03: T-DXd vs T-DM1	DESTINY-Breast04: T-DXd vs Physician's Choice	DESTINY-Gastric01: T-DXd vs Physician's Choice	DESTINY-Lung02: T-DXd
Best response				
ORR, %	79 vs 35	52.3 vs 16.3	51 vs 14	55
mPFS, mo	28.8 vs 6.8	10.1 vs 5.4	5.6 vs 3.5	8.2
HR	0.33; *P* <.0001	0.51; *P* <.001	0.47	
FDA approval	December 2019 (accelerated) May 2022 (full)	August 2022 (full)	January 2021 (full)	August 2022 (accelerated)
Indication	Unresectable or metastatic HER2-positive BC after HER2-based regimen	Unresectable or metastatic HER2-low BC after prior chemotherapy	LA or metastatic HER2-positive gastric/GEJ adenocarcinoma after trastuzumab-based regimen	2L+ *HER2*-mutated NSCLC

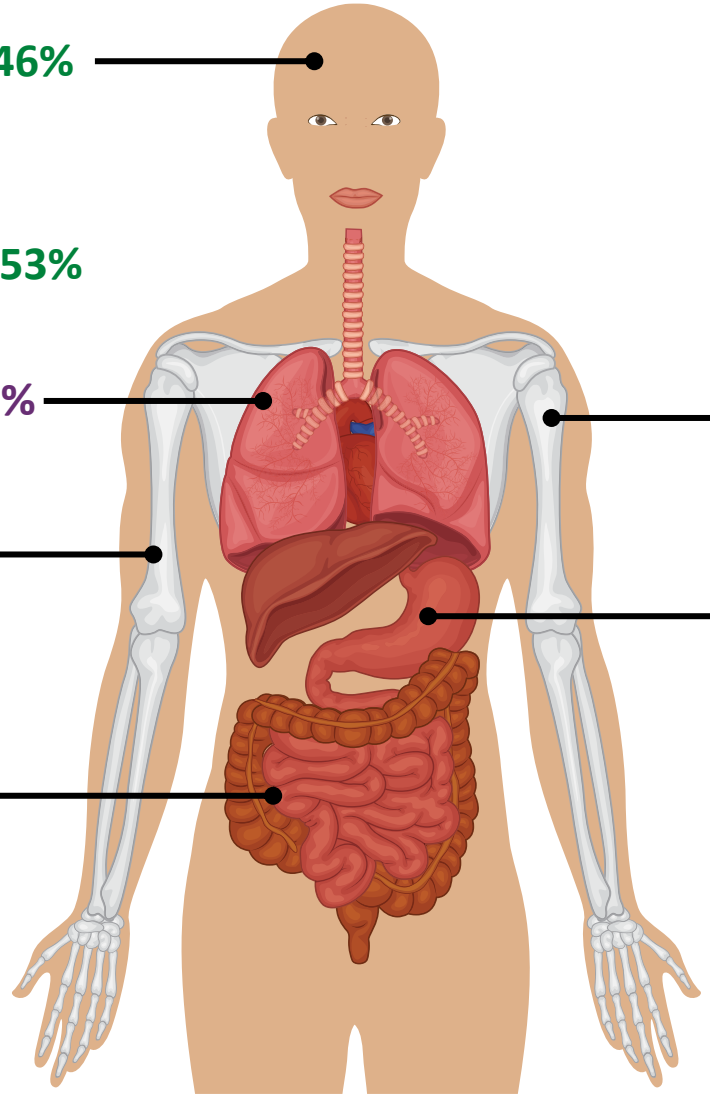
Hurvitz. Lancet. 2023;401:105. Modi. N Engl J Med. 2022;387:9. Yamaguchi. ASCO GI 2022. Abstr 242. Goto. J Clin Oncol. 2023;41:4852.

Select ADC Targets Under Investigation



Passaro. J Clin Oncol. 2023;41:3747.

T-DXd: Common and Notable AEs in NSCLC (Any Grade)



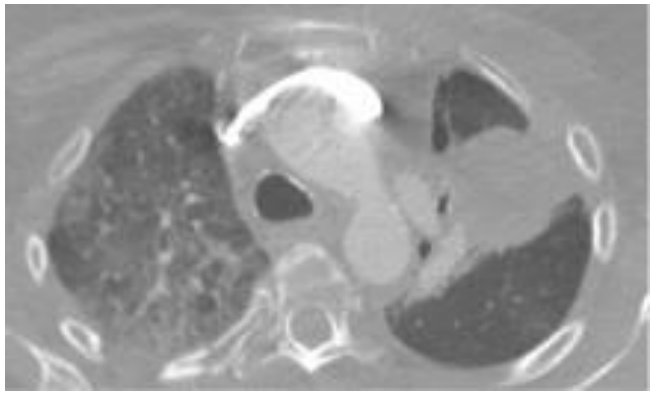
Li. ESMO 2021. Abstr LBA45. Goto. J Clin Oncol. 2023;41:4852. Jänne. WCLC 2023. Abstr MA13.10.

Assessment of ILD Associated With T-DXd

Signs and Symptoms to Look for:

- Shortness of breath, particularly on exertion
- Dry cough
- Chest discomfort
- Fatigue
- Decrease in oxygen saturation, worse on exertion

Radiographic Findings:



- **Ground-glass opacities (GGOs):** Mild, hazy areas on imaging that indicate partial filling of air spaces or interstitial thickening
- **Reticular patterns:** Subtle linear opacities may be present, reflecting slight fibrosis or interstitial involvement

Promptly investigate any evidence of suspected ILD/pneumonitis with high-resolution CT, pulmonologist consult, and infectious work-up

Trastuzumab deruxtecan PI. NIH Common Terminology Criteria for Adverse Events v5.0.
Swain. Cancer Treat Rev. 2022;106:102378. Image courtesy of Rebecca Heist, MD, MPH.

CLINICAL CARE OPTIONS®
ONCOLOGY

Breast Cancer

Targeted Rx

Clinical Significance of CDK4/6i in HR+/HER2- MBC

- Historically HR+ HER2- MBC had a median PFS of 9-12 mo on 1L endocrine therapy or single-agent chemotherapy
- In 2015 PALOMA-1 of palbociclib + letrozole vs letrozole alone showed doubling of median PFS with acceptable toxicity profile
- In 2017, findings reinforced in PALOMA-2 and replicated with abemaciclib (MONARCH 3) and ribociclib (MONALEESA-2)
- Now median PFS 2-3 yr in front-line HR+ HER2- MBC setting with CDK4/6i + ET
- CDK4/6i + ET is now SOC 1L treatment in the metastatic setting per NCCN/ASCO guidelines

Finn. Lancet Oncol. 2015;16:25. Finn. NEJM. 2016;375:1925. Jhaveri. Cancer Treat Rev. 2023;123:102670. Goetz. J Clin Oncol. 2017;35:3638. Hortobagyi. NEJM. 2022;386:942. NCCN. Clinical practice guidelines in oncology: breast cancer. v4.2024. nccn.org. society.asco.org/practice-patients/guidelines/breast-cancer#/9676. onclive.com/view/factors-in-selecting-1l-therapy-for-patients-with-hr-positive-metastatic-breast-cancer.

Summary Data for First-line Combinations of CDK4/6 Inhibitors and ET in HR+/HER2-Breast Cancer: PFS and OS

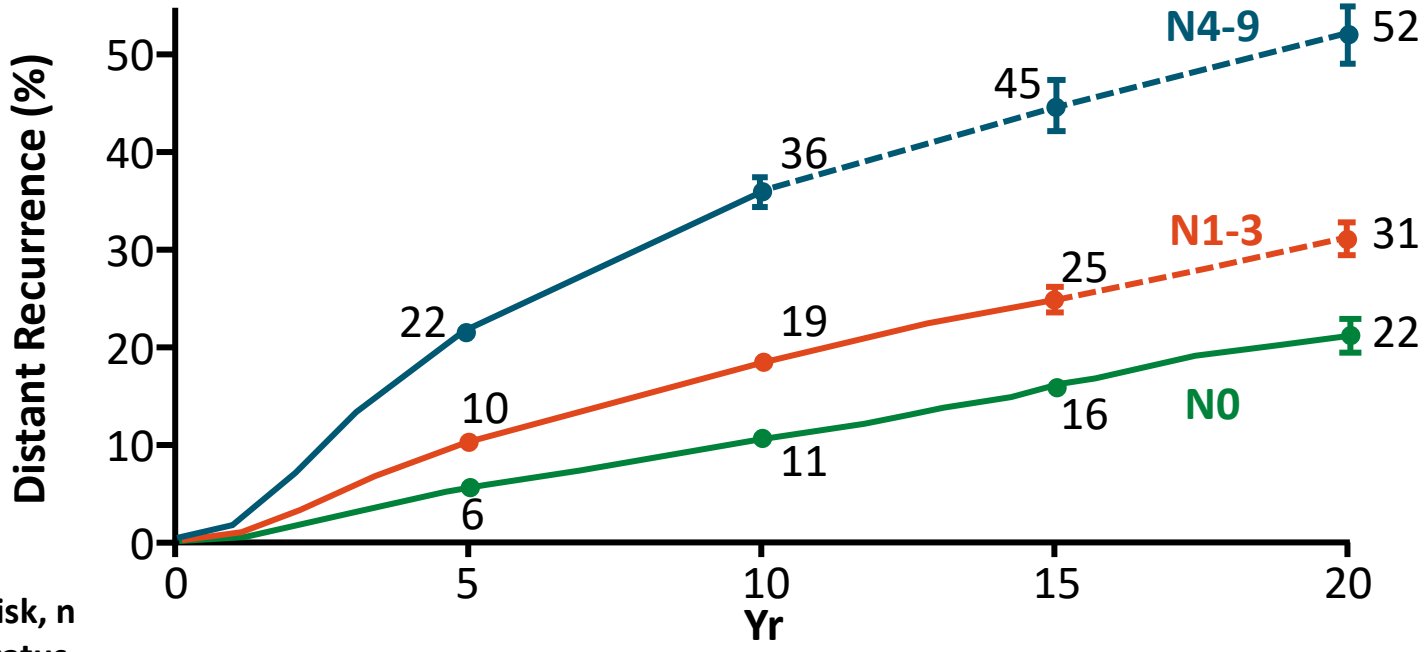
	PALOMA-2[1-3] (N = 666)	PALOMA-3[4,5] (N = 521)	MONALEESA-2[6-8] (N = 668)	MONALEESA-3[9,10] (N = 726)	MONALEESA-7[11-13] (N = 672)	MONARCH-2[14,15] (N = 669)	MONARCH-3[16,17] (N = 493)
Treatment arms	Letrozole ± **palbociclib**	Fulvestrant ± **palbociclib**	Letrozole ± **ribociclib**	Fulvestrant ± **ribociclib**	Tamoxifen, anastrozole, or letrozole ± **ribociclib**	Fulvestrant ± **abemaciclib**	Anastrozole or letrozole ± **abemaciclib**
Patient population	Postmenopausal adv BC; no previous systemic tx	Any menopausal status; prior ET; MBC	Postmenopausal adv BC with recurrent or MBC; no previous systemic tx	Postmenopausal adv BC; ≤1 prior ET for adv BC; no previous systemic tx	Premenopausal/ perimenopausal adv BC; no previous ET for adv BC	Any menopausal status; prior ET; advanced or MBC	Locally advanced or MBC; postmenopausal; no previous systemic tx
Median PFS, CDK4/6i + ET vs ET, mo	27.6 vs 14.5 (HR: 0.56)[2]	9.5 vs 4.6 (HR: 0.46)[4]	25.3 vs 16.0 (HR: 0.57)[7]	20.5 vs 12.8 (HR: 0.59)[9]	23.8 vs 13.0 (HR: 0.55)[11]	16.4 vs 9.3 (HR: 0.55)[14]	29.0 vs 14.8 (HR: 0.54)[16]
Median OS, CDK4/6i + ET vs ET, mo	53.8 vs 49.8 (HR: 0.92)[3]	34.8 vs 28.0 (HR: 0.81)[5]	63.9 vs 51.4 (HR: 0.76)[8]*	67.6 vs 51.8 (HR: 0.67)[10]*	58.7 vs 48.0 (HR: 0.76)[13]*	46.7 vs 37.3 (HR: 0.757)[15]	66.8 vs 53.7 (HR: 0.80)[16]

*Statistically significant.

1. Finn. NEJM. 2016;375:1925. 2. Rugo. Breast Cancer Res Treat. 2019;174:719. 3. Slamon. JCO. 2024;42:994. 4. Cristofanilli. Lancet Oncol. 2016;17:425. 5. Cristofanilli. Clin Cancer Res. 2022;28:3433. 6. Hortobagyi. NEJM. 2016;375:1738. 7. Hortobagyi. Ann Oncol. 2018;29:1541. 8. Hortobagyi. NEJM. 2022;386:942. 9. Slamon. JCO.2018;36:2465. 8. Neven. Breast Can Res. 2023;25:103. 10. Tripathy. Lancet Oncol. 2018;19:904. 11. Im. NEJM. 2019;381:307. 12. Lu. Clin Cancer Res. 2022;28:851. 13. Goetz. JCO. 2017;35:3638. 14. Sledge Jr. J Clin Oncol. 2017;35:2875-2884. 15. Neven. Breast Cancer Res. 2021;23:87. 16. Johnston. NPJ Breast Cancer. 2019;5:5. 17. Goetz. Ann Oncol. 2024;[Epub].

Risk of Distant Recurrence After 5 Yr of Endocrine Therapy

- Meta-analysis of patients with ER+ BC diagnosed in 1976-2011 who received 5 yr of ET and were disease free at 5 yr (N = 71,194)[1]



Patients at Risk, n Nodal Status					
N4-9	12,333	8116	2165	259	52
N1-3	31,936	23,576	7250	949	183
N0	29,925	24,081	8571	1982	414

Dashed line indicates event rate for 5-yr period, not individual yr.

- In updated analysis, 20-yr risk of DR was one third lower for **N0 ER+ EBC** diagnosed after vs before 2000[2]

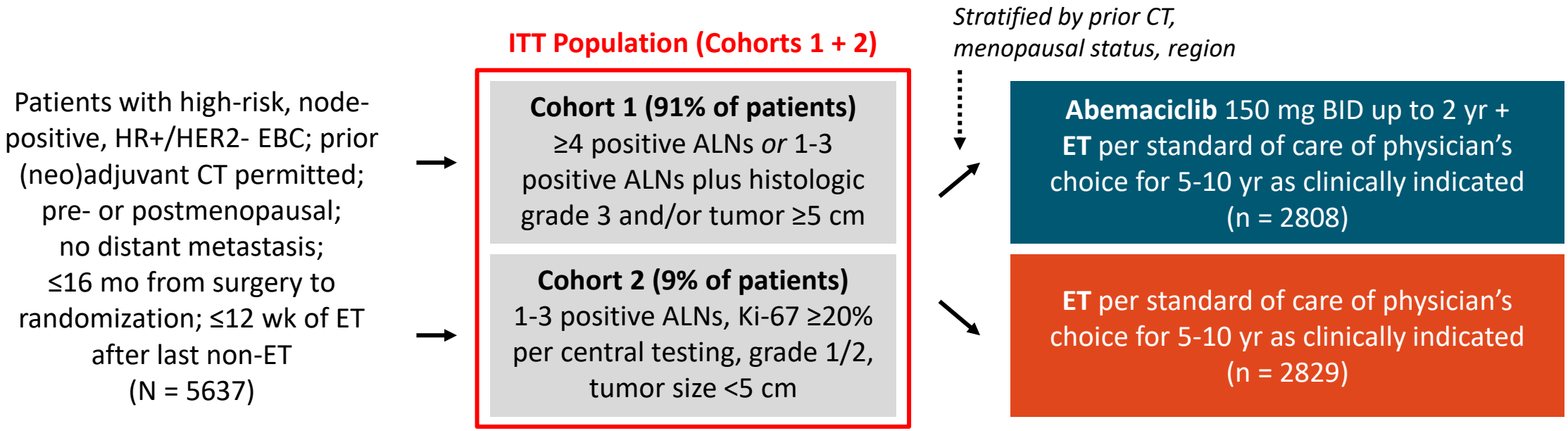
20-Yr Risk of DR, %	N0 ER+ EBC	
	T1N0	T2N0
Diagnosed before 2000	13	19
Diagnosed after 2000*	8	14

*Projected.

1. Pan. NEJM. 2017;377:1836. 2. Pan. SABCS 2019. Abstr GS2-04.

monarchE: Adjuvant Abemaciclib + ET in High-Risk, Node-Positive HR+/HER2- EBC

- International, randomized, open-label phase III trial

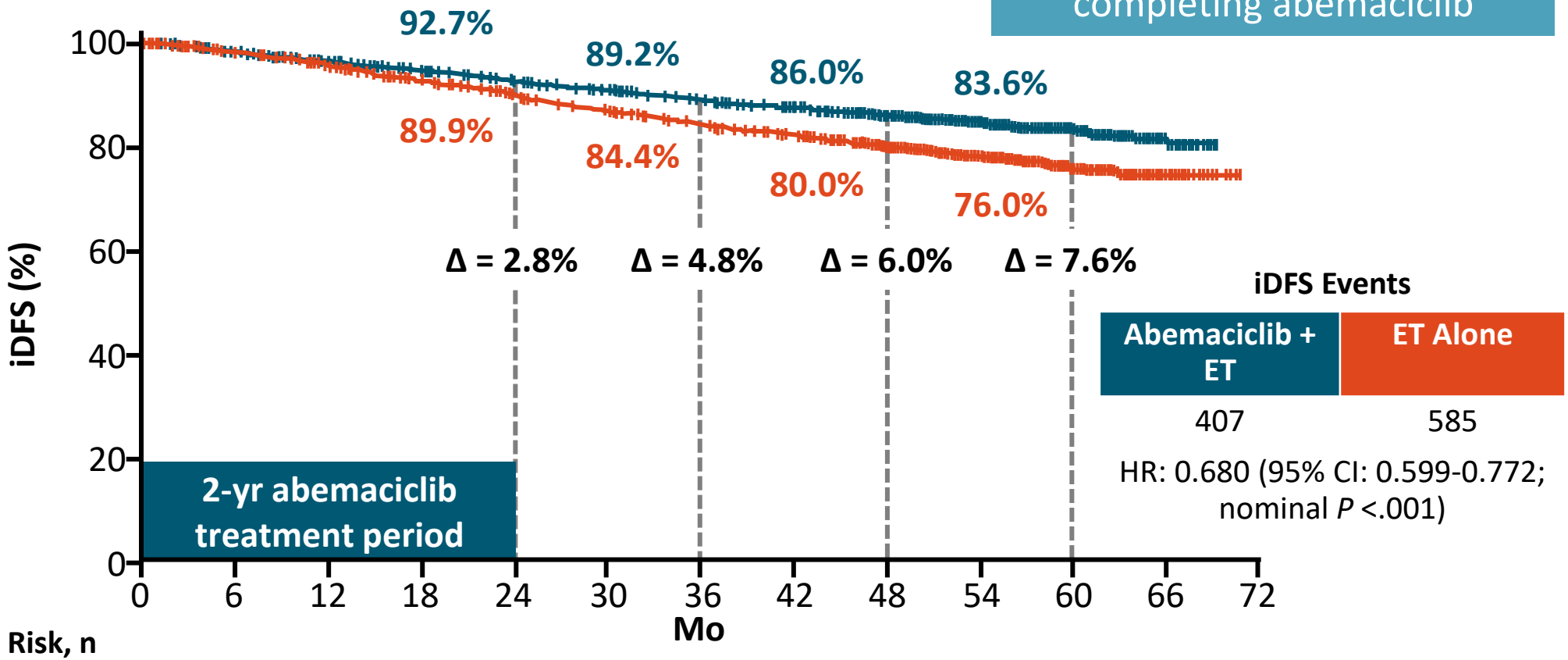


- **Primary endpoint:** iDFS
- **Key secondary endpoints:** iDFS in Ki-67 high (≥20%) population, DRFS, OS, safety, PROs

Rastogi. J Clin Oncol. 2024;42:987. Johnston. JCO. 2020;38:3987.

monarchE: iDFS in ITT Population at Median Follow-up of 4.5 Yr (OS IA3)

At OS IA3:
All patients off abemaciclib; >80% followed for ≥2 yr since completing abemaciclib



iDFS Events

Abemaciclib + ET	ET Alone
407	585

HR: 0.680 (95% CI: 0.599-0.772; nominal *P* <.001)

Patients at Risk, n

Abemaciclib + ET	2808	2621	2549	2479	2408	2347	2284	2220	2095	1175	490	74	0
ET alone	2829	2653	2573	2474	2374	2281	2195	2125	1974	1124	473	67	0

Consistent benefit across all patient and disease subgroups, independent of Ki-67 index

Rastogi. J Clin Oncol. 2024;42:987.

monarchE: Safety With Adjuvant Abemaciclib + ET

- Aromatase inhibitor preferred vs tamoxifen due to VTE risk[1]
- 2/15 deaths in abemaciclib arm related to abemaciclib (1 each diarrhea, pneumonitis)[1,2]
- n = 10 deaths in ET alone arm[1]
- AE rates comparable between patients aged <65 vs ≥65 yr[3]
  - Patients aged ≥75 yr experienced more AEs and had more discontinuations due to AEs

Common TEAEs,* %[2]	Abema + ET (n = 2791)		ET Alone (n = 2800)	
	Any	Gr ≥3	Any	Gr ≥3
Diarrhea	83.5	7.8	8.7	0.2
Neutropenia	45.9	19.7	5.6	0.9
Fatigue	40.9	2.9	18.0	0.1
Leukopenia	37.7	11.4	6.7	0.4
Abdominal pain	35.7	1.4	9.9	0.3
Nausea	29.6	0.5	9.1	0.1
Arthralgia	26.5	0.3	37.8	1.0
Anemia	24.4	2.0	3.8	0.4

Any-Grade AEs of Interest, %[1]	Abema + ET (n = 2791)	ET Alone (n = 2800)
VTE	2.5	0.7
▪ PE	1.0	0.1
VTE by first ET		
▪ Tamoxifen	4.3	0.7
▪ AI	1.8	0.6
ILD	3.3	1.3

*Grade 1/2 events in ≥10% or grade ≥3 in ≥1%.

1. Rugo. Ann Oncol. 2022;33:616. 2. Johnston. Lancet Oncol. 2023;24:77.
3. Hamilton. ASCO 2023. Abstr 501.

Key Adverse Events With CDK4/6 Inhibitors: Monitoring and Prevention

Diarrhea	Hepatobiliary Toxicity	Neutropenia	VTE	ILD/ Pneumonitis
Abemaciclib Ribociclib Palbociclib	Abemaciclib Ribociclib	Abemaciclib Ribociclib Palbociclib	Abemaciclib	Abemaciclib Ribociclib Palbociclib
Antidiarrheal therapy Increase oral hydration Notify healthcare professional Dietary modification	LFTs before starting treatment, Q2W x 2 mo, then: ▪ *Abemaciclib,* QM x 2 mo, then as indicated ▪ *Ribociclib,* at start of cycle x 4 cycles	CBC before starting treatment, then: ▪ *Abemaciclib,* Q2W x 2 mo, QM x 2 mo, then as indicated ▪ *Ribociclib and Palbociclib,* Q2W x 2 cycles, start of next 4 cycles, then as indicated	Monitor for signs and symptoms of thrombosis or pulmonary embolism	Monitor for pulmonary symptoms indicative of ILD or pneumonitis (eg, hypoxia, cough, dyspnea)

Abemaciclib PI. Palbociclib PI. Ribociclib PI.

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DESTINY-Breast06: Trastuzumab Deruxtecan vs CT in Previously Treated HR+/HER2-Low or HER2-Ultralow MBC

- Multicenter, open-label, randomized phase III trial

Stratified by: prior CDK4/6 inhibitor use (yes vs no); HER2 IHC 1+ vs 2+/ISH- vs 0; prior taxane in nonmetastatic setting (yes vs no)

Patients with HR+ metastatic breast cancer with PD on ≥2 previous ET ± targeted therapy (no prior CT) for MBC*; HER2 low (IHC 1+, or 2+/ISH-) or HER2 ultralow (IHC† >0 <1+) based on central IHC assessment using most recent evaluable IHC sample (N = 866)

1:1

T-DXd
5.4 mg/kg Q3W
(n = 436)

Physician's choice of CT
(capecitabine, paclitaxel, or *nab*-paclitaxel)
(n = 430)

Until PD or toxicity

*Also allowed: 1 prior line for MBC and PD ≤6 mo of starting 1L ET + CDK4/6 inhibitor or 1 prior line for MBC and recurrence ≤24 mo of starting adjuvant ET.
†HER2 IHC >0 defined by any IHC staining up to 10% of tumor cells.

- **Primary endpoint:** PFS (per BICR) in HER2-low population
- **Key secondary endpoint:** OS in HER2-low population, PFS (per BICR) and OS in ITT
- **Other secondary endpoints:** PFS (per INV) in HER2-low population, ORR and DoR (per BICR/INV) in HER2-low population and ITT, safety and tolerability, PROs

Curigliano. ASCO 2024. Abstr LBA1000. NCT04494425.

DESTINY-Breast06: Efficacy

HER2-Low Population	T-DXd (n = 359)	CT (n = 354)	HR (95% CI)	*P* Value
Median PFS by BICR, mo *Primary endpoint*	13.2	8.1	0.62 (0.51-0.74)	<.0001
12-mo OS rate,* %	87.6	81.7	0.83 (0.66-1.05)	.1181
HER2-ITT Population	**T-DXd (n = 436)**	**CT (n = 430)**	**HR (95% CI)**	***P* Value**
Median PFS by BICR, mo	13.2	8.1	0.63 (0.53-0.75)	<.0001
12-mo OS rate,† %	87.0	81.1	0.81 (0.65-1.00)	NR
HER2-Ultralow Population	**T-DXd (n = 76)**	**CT (n = 76)**	**HR (95% CI)**	***P* Value**
Median PFS by BICR, mo	13.2	8.3	0.78 (0.50-1.21)	NR
12-mo OS rate, %	84.0	78.7	0.75 (0.43-1.29)	NR

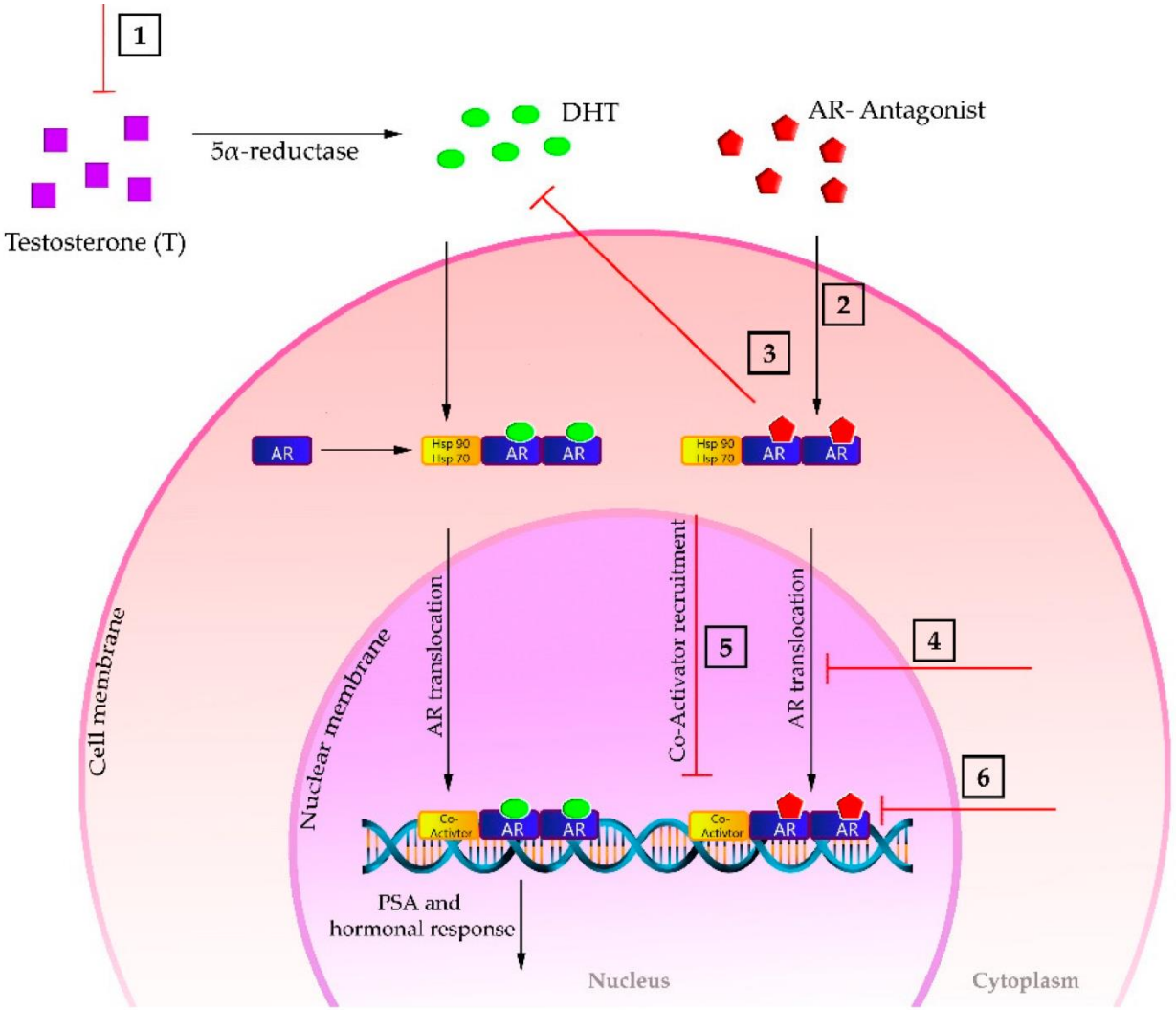
- T-DXd showed consistent PFS benefit across prespecified patient subgroups, regardless of age, HER2-low status, prior exposure to CDK4/6i or taxane, number of prior ET lines, endocrine resistance, or liver metastases

*20.1% of patients in the CT arm received T-DXd after CT discontinuation. †17.9% of patients in the CT arm received T-DXd after CT discontinuation.

Curigliano. ASCO 2024. Abstr LBA1000.

Prostate Cancer

Second-Generation AR Pathway Inhibitors in mHSPC



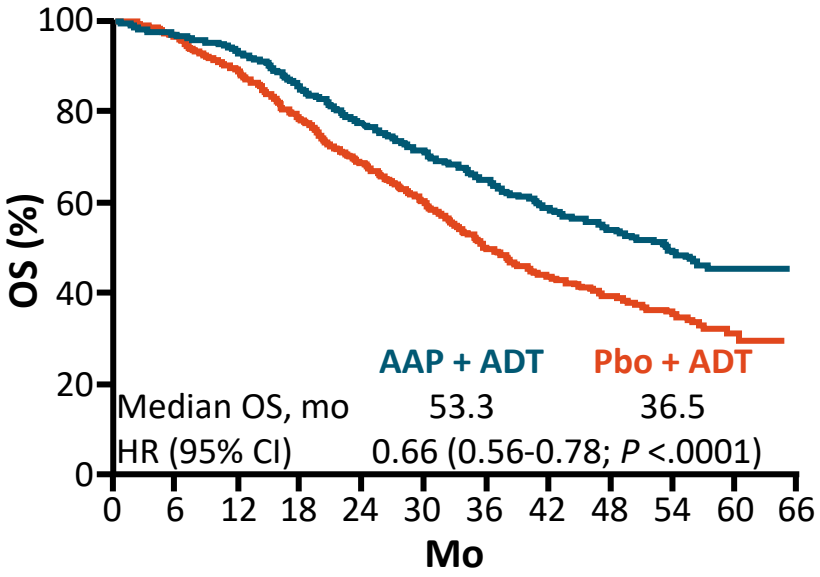
1. Suppresses androgen biosynthesis via CYP17
2. Binds competitively to AR
3. Prevents DHT-AR binding
4. Blocks AR translocation to nucleus
5. Impairs coactivator recruitment
6. Inhibits AR-DNA binding

Abiraterone acetate

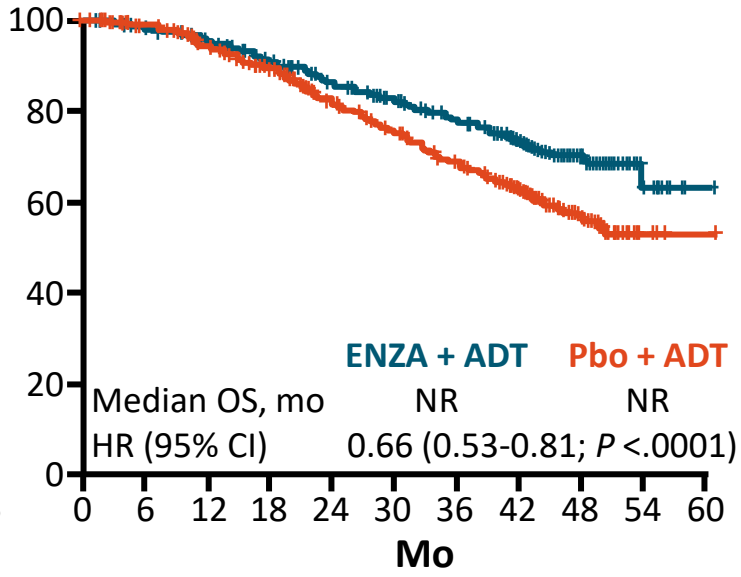
Apalutamide
Enzalutamide
Darolutamide

Final OS Results for Phase III Trials of ARPI + ADT in Patients With mHSPC

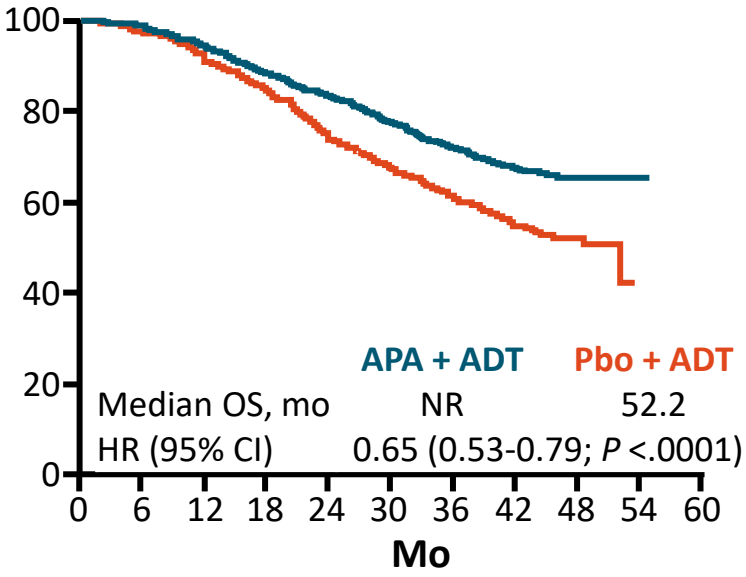
LATITUDE: ADT + Abiraterone vs ADT (N = 1199)[1]
Median f/u: 51.8 mo



ARCHES: ADT + Enzalutamide vs ADT (N = 1150)[2]
Median f/u: 44.6 mo



TITAN: ADT + Apalutamide vs ADT (N = 1052)[3]
Median f/u: 44.0 mo



Cross-trial comparisons have significant limitations. This information is presented to generate discussion, not to make direct comparisons among study results.

Slide credit: clinicaleducationalliance.com:
cea clinical education alliance

1. Fizazi. Lancet. 2019;20:686. 2. Armstrong. JCO. 2022;40:1616. 3. Chi. JCO. 2021;39:2294.

Safety Profiles of Second-Generation AR Inhibitors

AESI (~Gr 3/4 Rate)	Abiraterone/Prednisone	Enzalutamide	Apalutamide	Darolutamide
Cardiovascular (<4%)	Hypertension* (20%) Sudden cardiac failure/death	Hypertension Ischemic heart disease	Hypertension Cerebrovascular and ischemic events	Hypertension Ischemic heart disease
Endocrine (<1%)	Adrenocortical insufficiency		Hypothyroidism	
Musculoskeletal (1%)		Fractures	Fractures	
Neurologic (<1%)		Falls Seizures Dizziness Headaches	Falls Seizures Cognitive/memory impairment	Seizures
Skin (<1%)		Rash	Rash (6.3%) SCARs	Rash
Other	Fatigue Hepatotoxicity (6%) Fluid retention* (1%) Hypokalemia* (10%)	Fatigue Hypersensitivity (<1%)	Fatigue	Fatigue

*Due to mineralocorticoid excess.

Abiraterone PI. Apalutamide PI. Enzalutamide PI. Darolutamide PI.
Armstrong. JCO. 2022;40:1616. Chi. NEJM. 2019;381:13. Smith. NEJM. 2022;386:1132.

Skin Cancer

Original Article

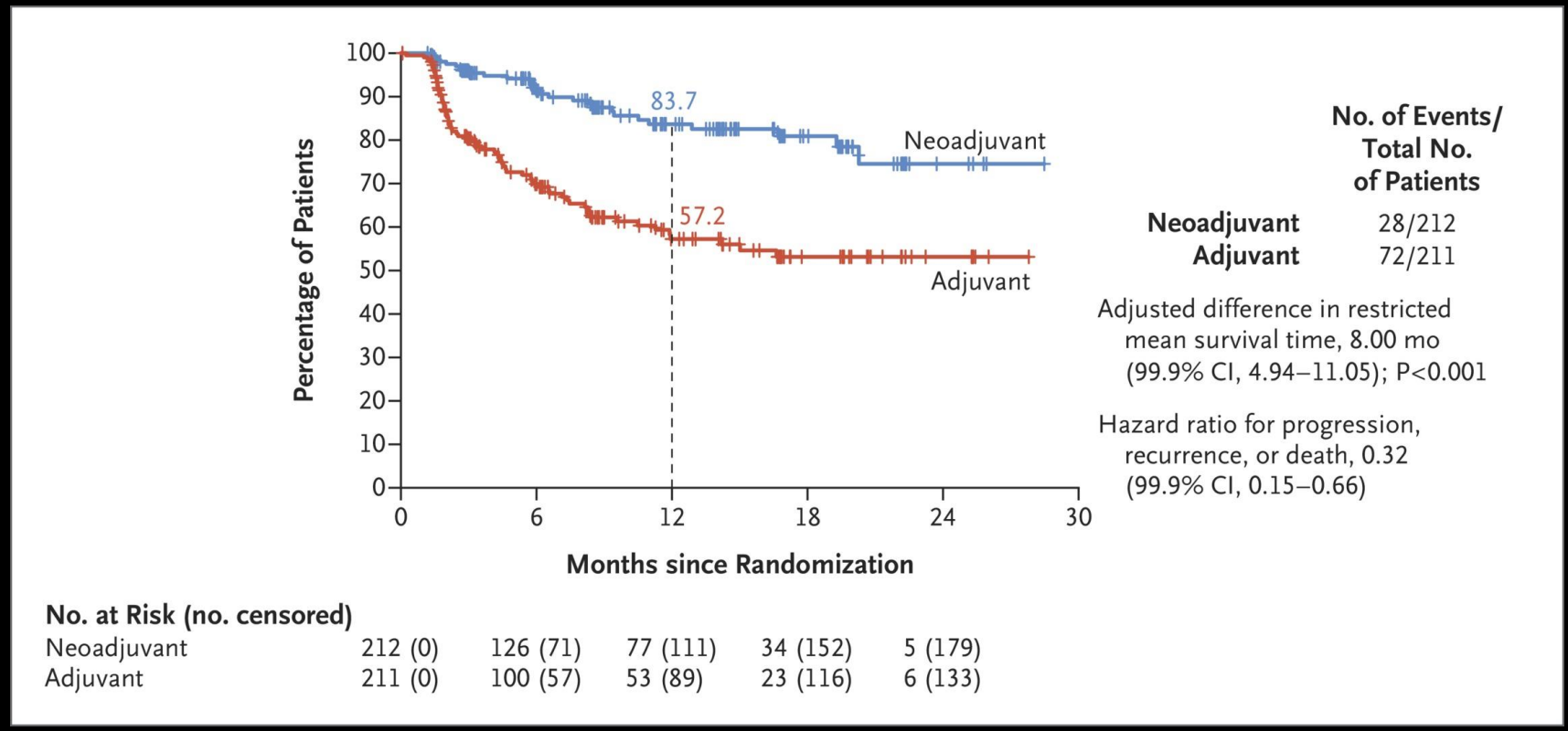
Neoadjuvant Nivolumab and Ipilimumab in Resectable Stage III Melanoma

Christian U. Blank, M.D., Ph.D., Minke W. Lucas, M.D., Richard A. Scolyer, M.D., Bart A. van de Wiel, M.D., Ph.D., Alexander M. Menzies, M.D., Ph.D., Marta Lopez-Yurda, Ph.D., Lotte L. Hoeijmakers, M.D., Robyn P.M. Saw, M.D., Judith M. Lijnsvelt, M.Sc., Nigel G. Maher, M.D., Saskia M. Pulleman, M.Sc., Maria Gonzalez, M.Sc., Alejandro Torres Acosta, M.Sc., Winan J. van Houdt, M.D., Ph.D., Serigne N. Lo, Ph.D., Anke M.J. Kuijpers, M.D., Ph.D., Andrew Spillane, M.D., W. Martin C. Klop, M.D., Ph.D., Thomas E. Pennington, M.D., Charlotte L. Zuur, M.D., Ph.D., Kerwin F. Shannon, M.D., Beatrijs A. Seinstra, M.D., Robert V. Rawson, M.D., John B.A.G. Haanen, M.D., Ph.D., Sydney Ch'ng, M.D., Ph.D., Kishan A.T. Naipal, M.D., Ph.D., Jonathan Stretch, M.D., Ph.D., Johannes V. van Thienen, M.D., Ph.D., Michael A. Rtshiladze, M.D., Sofie Wilgenhof, M.D., Ph.D., Rony Kapoor, M.D., Aafke Meerveld-Eggink, M.D., Ph.D., Lindsay G. Grijpink-Ongering, B.Sc., Alexander C.J. van Akkooi, M.D., Ph.D., Irene L.M. Reijers, M.D., David E. Gyorki, M.D., Dirk J. Grünhagen, M.D., Ph.D., Frank M. Speetjens, M.D., Ph.D., Sonja B. Vliek, M.D., Joanna Placzke, M.D., Lavinia Spain, M.D., Robert C. Stassen, M.D., Mona Amini-Adle, M.D., Céleste Lebbé, M.D., Ph.D., Mark B. Faries, M.D., Caroline Robert, M.D., Ph.D., Paolo A. Ascierto, M.D., Rozemarijn van Rijn, M.D., Ph.D., Franchette W.P.J. van den Berkmortel, M.D., Ph.D., Djura Piersma, M.D., Ph.D., Andre van der Westhuizen, M.D., Ger[illegible] Ph.D., Maureen J.B. Aarts, M.D., Ph.D., Marion A.M. Stevense-den Boer, M.D.,

N Engl J Med
Volume 391(18):1696-1708.
November 7, 2024

The NEW ENGLAND JOURNAL of MEDICINE

Event-free Survival in the Intention-to-Treat Population.



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Pathological Responses in the Neoadjuvant Group.

Table 2. Pathological Responses in the Neoadjuvant Group.*

Type of Response	Local Assessment (N=212)	Central Review (N=212)
	number (percent)	
Major pathological response	120 (56.6)	125 (59.0)
Pathological complete response†	97 (45.8)	100 (47.2)
Pathological near-complete response	23 (10.8)	25 (11.8)
Pathological partial response	20 (9.4)	17 (8.0)
Pathological nonresponse	53 (25.0)	56 (26.4)
Progression before surgery	5 (2.4)	5 (2.4)
Not reported	5 (2.4)	0
Not available‡	9 (4.2)	9 (4.2)

* Patients in the neoadjuvant group who received at least one dose of neoadjuvant treatment were assessed for pathological response. The pathological response was determined according to the International Neoadjuvant Melanoma Consortium criteria. A pathological complete response was defined as 0% residual viable tumor in the surgical resection specimen, pathological near-complete response as 0 to 10% residual viable tumor, pathological partial response as 11 to 50% residual viable tumor, and pathological nonresponse as more than 50% residual viable tumor. Major pathological response included pathological complete response and pathological near-complete response.

† As confirmed by central review, the material from surgical resection in 9 of 100 patients who had a complete pathological response did not show any signs of viable or regressed tumor, nor were there clinical indications that the tumor was still in situ.

‡ At the time of the data cutoff, no material from surgical resection was available for 9 patients (5 patients underwent surgery after the data-cutoff date, 3 patients had not undergone surgery because of toxic effects, and 1 patient had not undergone surgery for an unknown reason).

Blank CU et al. N Engl J Med2024;391:1696-1708

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