UCLA Jonsson Comprehensive Cancer Center

New developments in SCLC

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PRIMO
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Overview

Small cell lung cancer (SCLC)/high-grade neuroendocrine cancer continues to have a **poor prognosis** – median overall survival for limited stage is <2y; extensive stage ~1y

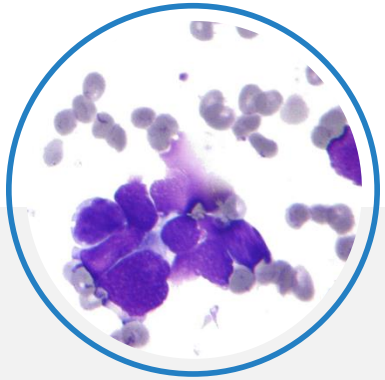
Molecular subtyping has suggested **treatment opportunities**, although this testing is not provided as standard of care

Advances in targeting the immune system include the **addition of anti-PDL1** first-line and **CD3-DLL3** bispecific T-cell engagers upon PD

Ongoing drug development in SCLC is **crucial to ongoing progress** in cancer-related mortality

Background

High-grade neuroendocrine carcinoma of the lung (small cell/oat cell carcinoma)



Diagnosis:
Pathology eval w/ IHC (**synaptophysin/CD56**); represents 15% of all lung cancers

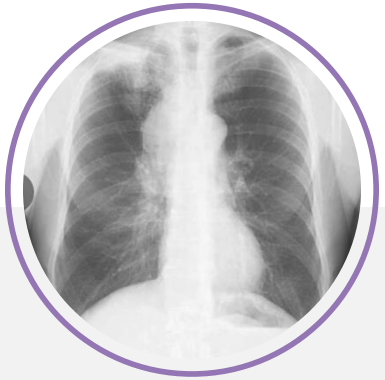
Dx

Risk factors:
smoking, chest radiation, occupational exposure (asbestos, arsenic chromium, beryllium)

Risk

Classic symptoms:
cough, chest pain, **hoarseness**, malaise, anorexia, weight loss, hemoptysis

Sx



Associated syndromes:
SIADH, SVC, Cushing's, paraneoplastic cerebellar degeneration, **Lambert-Eaton myasthenia**

Rare

Median survival:
W/o treatment: 2-4m,
Limited: 16-24m,
Extensive: 6-12m,
5-year survival: 5-10%

OS

Brief History

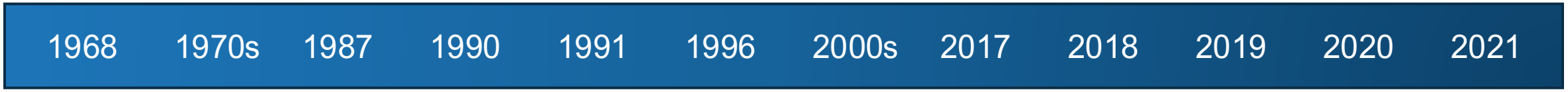
PFS <2m
OS <6m

SCLC is a neuro-endocrine tumor

RB1/TP53

Multimodality therapy ⟶ ***+ ICB***

SLFN11/DLL3



Anti-PD1s lose FDA approval based on KN-604/CM-032+ OS

Gadzar, Bunn, Minna Nat Rev Can 2017 PMID 29077690

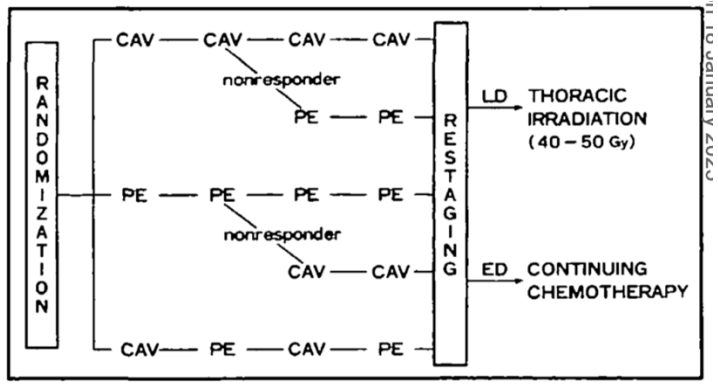
Brief History

PFS <2m
OS <6m

SCLC
is a neuro-endocrine tumor

RB1/TP53

Concurrent chemoXRT for LS
(with VMC-VAC)
CR 33%, ORR 73%, OS 14.3m
Kies JCO 1987



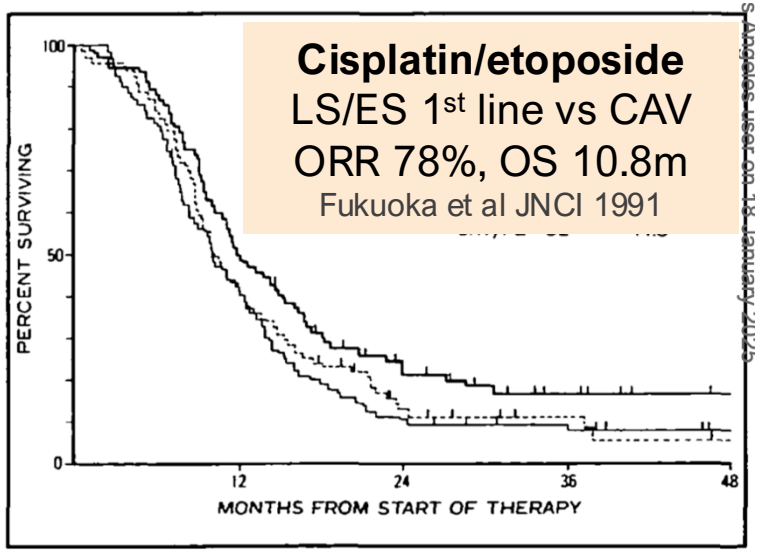
Multimodality therapy ⟶ + ICB

4-6 cycles PE
ORR 61%,OS 9.8m
Spiro BJC 1989

Carboplatin/etoposide 4C
non-inf if re-tx, OS 10.1m
Sunstrom JCO 1991

SLFN11/DLL3

1968 | 1970s | 1987 | 1990 | 1991 | 1996 | 2000s | 2017 | 2018 | 2019 | 2020 | 2021



Cisplatin/etoposide
LS/ES 1st line vs CAV
ORR 78%, OS 10.8m
Fukuoka et al JNCI 1991

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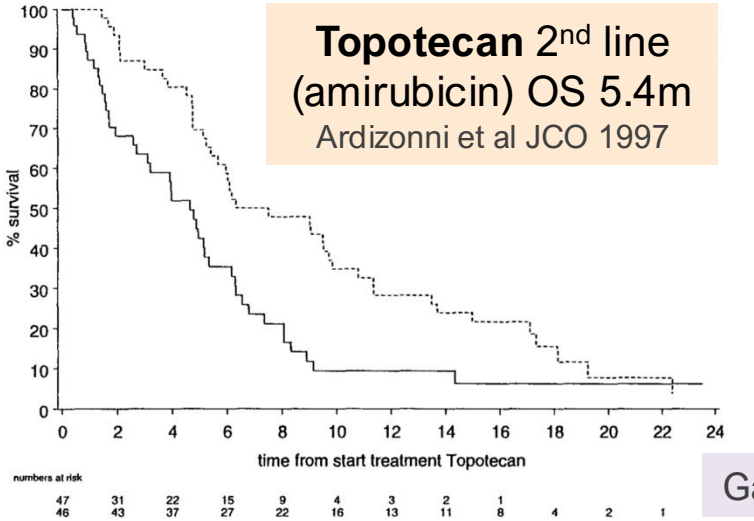

Topotecan 2nd line (amirubicin) OS 5.4m
Ardizonni et al JCO 1997

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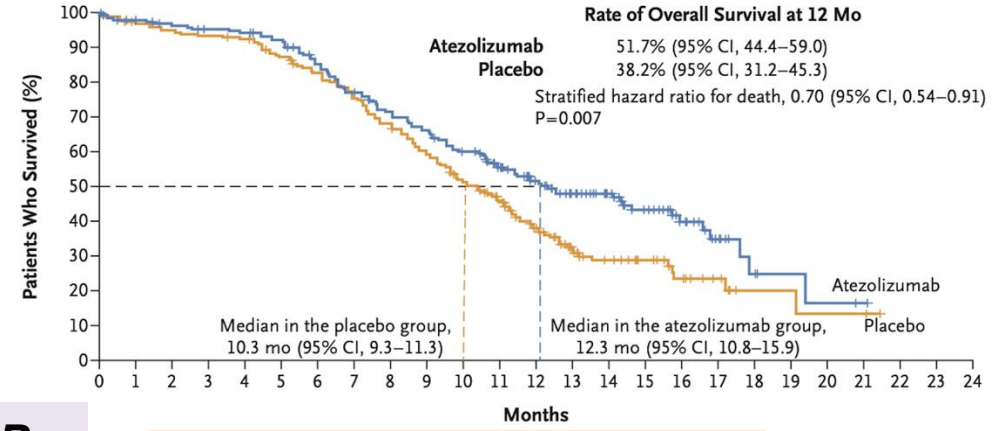

Impower 133
atezolizumab maintenance
(vs placebo) OS 12.3 vs 10.3m
Horn et al NEJM 2018

SLFN11/DLL3

1968	1970s	1987	1990	1991	1996	2000s	2017	2018	2019	2020	2021

Lurbinectidin 2nd line
PFS 3.5m, OS 9.3m
Trigo Lancet Oncol 2020

Anti-PD1s lose FDA approval based on KN-604/CM-032+ OS

CASPIAN
durvalumab maintenance
(vs placebo) OS 13.0 vs 10.3m
Paz Ares et al Lancet 2019

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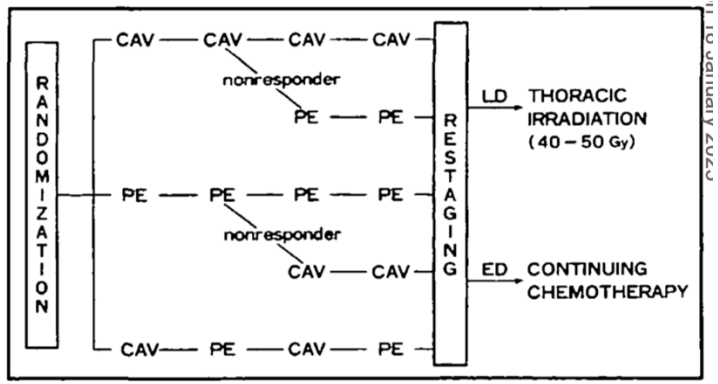

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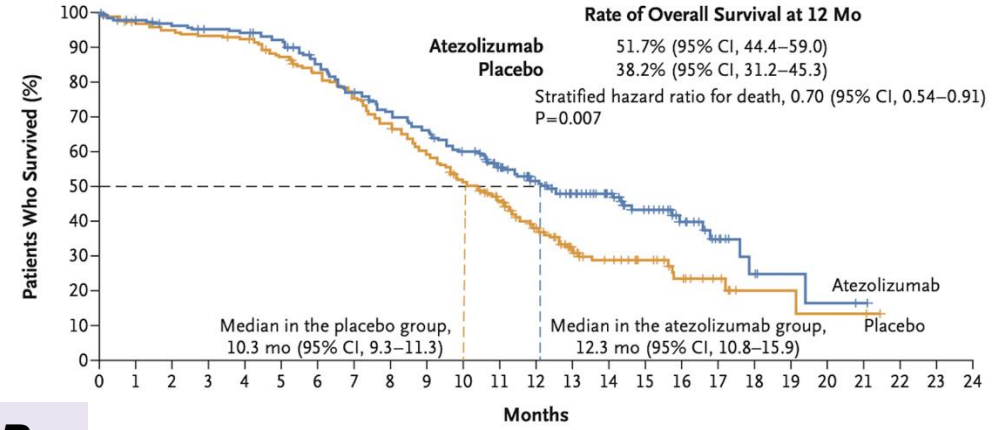
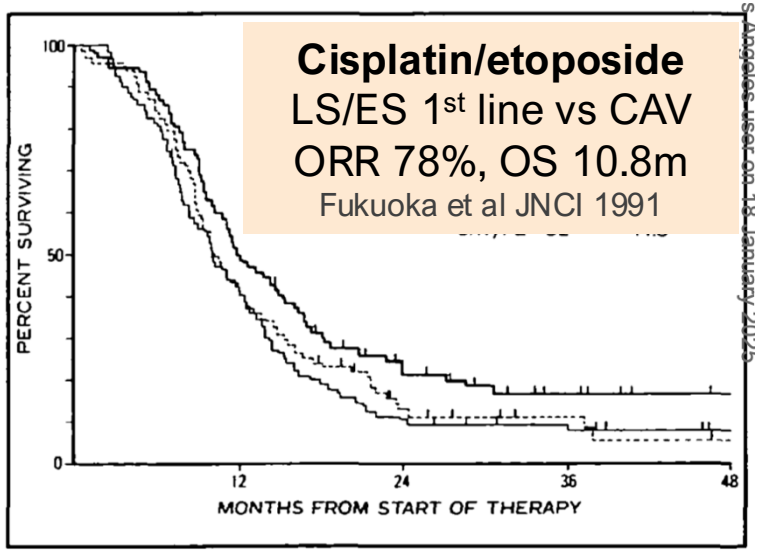


Impower 133
atezolizumab maintenance
(vs placebo) OS 12.3 vs 10.3m
Horn et al NEJM 2018

PFS 5m
OS 12m

1968 1970s 1987 1990 1991 1996 2000s 2017 2018 2019 2020 2021



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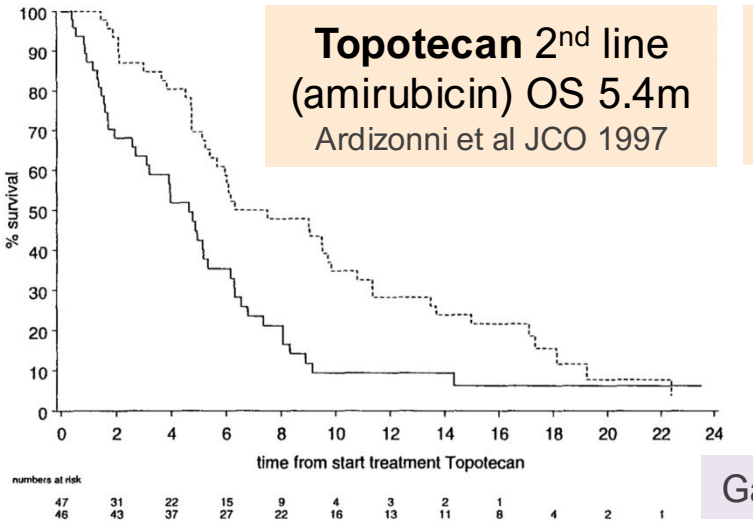

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ADRIATIC

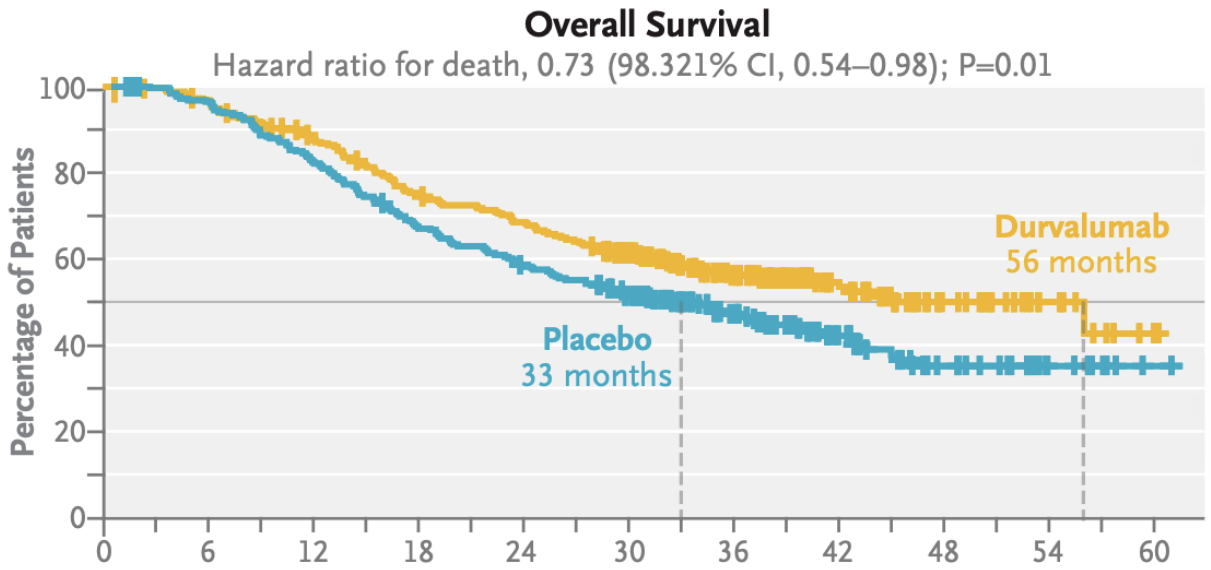
Co-primary endpoints, OS/PFS

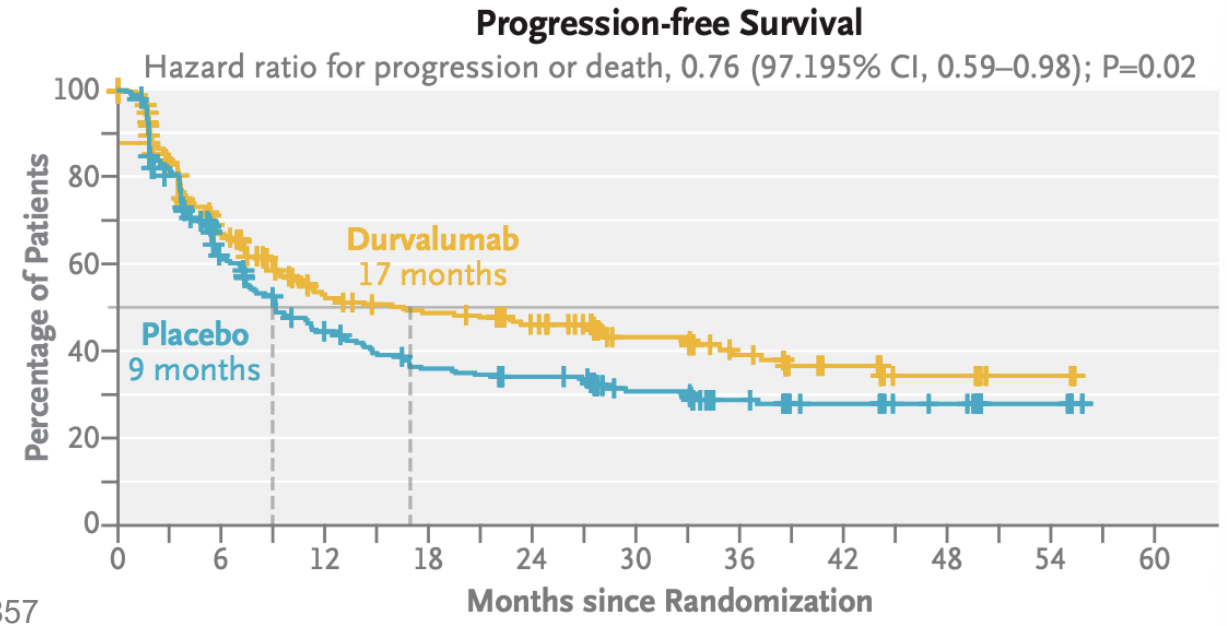
Durvalumab (± tremelimumab)

vs placebo **after chemoXRT**

LS-SCLC w/o PD (not platinum refractory)

every 4 weeks up to 24 months





Cheng et al NEJM 2024 PMID 39268857

Global, phase 3, double-blind, placebo-controlled randomized 1:1

730 enrolled
250 Asia, 75 US
D 264, D+T 266

OS

HR 0.73
55.9 vs 33.4m
p=0.01
(D+T still blinded)

PFS

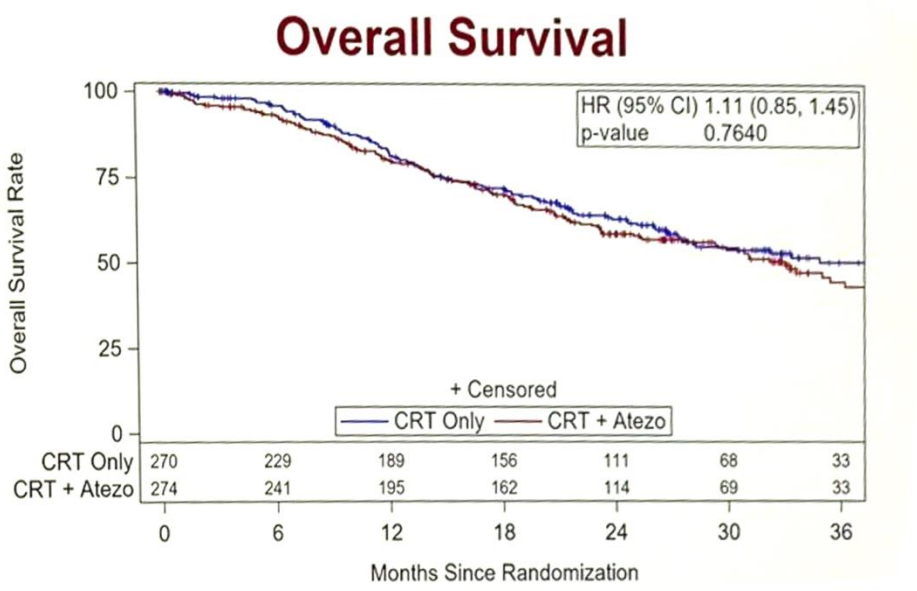
HR 0.76
16.6 vs 9.2m
p=0.02
(D+T still blinded)

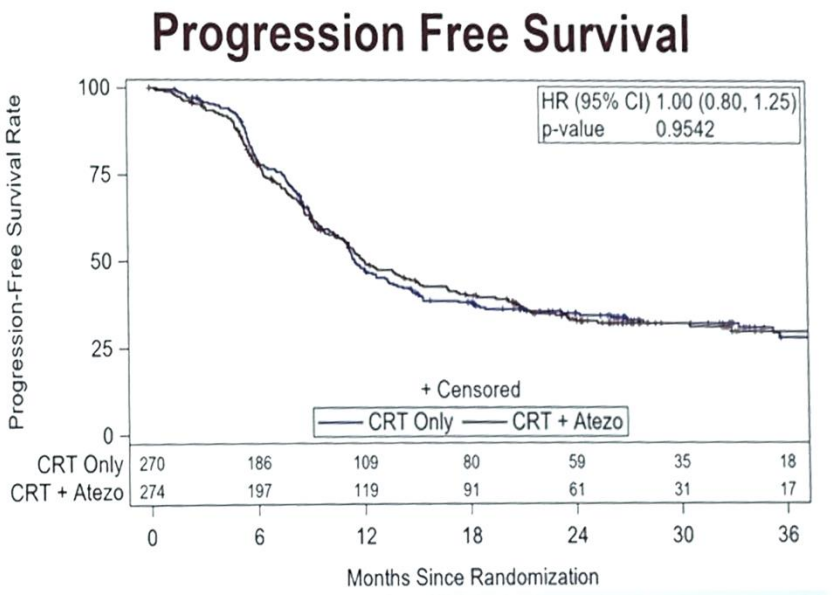
16.4% vs 10.9% discontinue rate, G3+ pneumonitis 1-2% both arms

NRG Oncology/Alliance LU005 (atezolizumab)

Co-primary endpoints PFS/OS

Standard **platinum doublet and <u>concurrent</u> TRT and atezolizumab vs placebo** every 3 weeks up to 12m (received 1 cycle chemo then randomized)





US & Japan, randomized 1:1

544 enrolled, 274 atezo

OS

HR 1.11
33.1 vs 39.5m

PFS

HR 1.00
11.5 vs 16.8m

G3+ pneumonitis
5.6% vs 3.1%
G5: 4 events

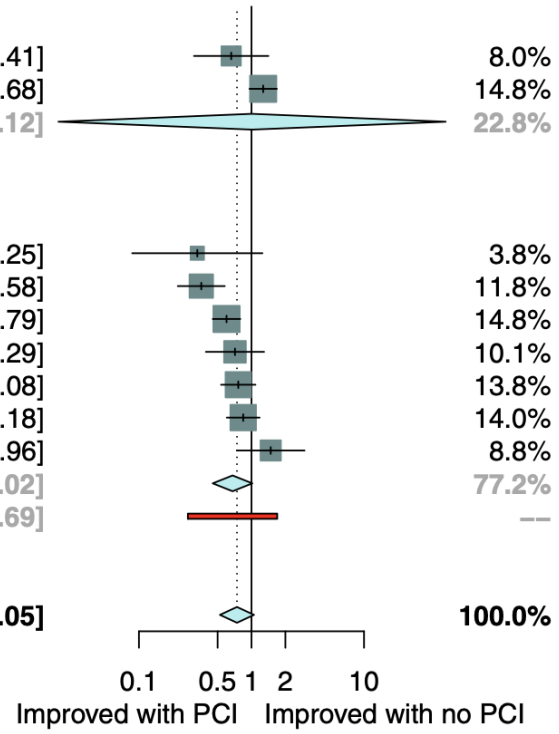
Higgins et al ASTRO 2024

IMPACT | **Checkpoint inhibition concurrent with radiation leads to inferior outcomes with working hypothesis that radiation suppresses lymphocytic anti-tumor response**

Prophylactic CNS irradiation (PCI)

Pivotal studies (Auperin NEJM 1999, Slotman NEJM 2007) suggested benefit, but others argued not reflective of clinical practice (no routine MRI), and harm not trivial (progressive cognitive/functional decline nearly universal long-term)

Author	Study design	No. patients (PCI)	No. patients (no PCI)	AHRQ/RoB	HR	95% CI
Disease stage = ED						
Yao et al., 2023	RCS	17	49	Good	0.66	[0.31; 1.41]
Takahashi et al., 2017	RCT	113	111	Low	1.27	[0.96; 1.68]
Random effects model					1.01	[0.02; 53.12]
Heterogeneity: I^2 = 60%, τ = 0.359, χ^2_1 = 2.5 (p = 0.114)						
Disease stage = LD						
Park et al., 2022	PCS	22	21	Good	0.33	[0.09; 1.25]
J Li et al., 2021	RCS	77	113	Good	0.36	[0.22; 0.58]
Qiu et al. , 2016	RCS	185	214	Poor	0.60	[0.45; 0.79]
Inoue et al. , 2021	RCS	32	32	Good	0.71	[0.39; 1.29]
Qi et al., 2022	RCS	75	75	Good	0.76	[0.54; 1.08]
Pezzi et al., 2020	RCS	84	84	Good	0.84	[0.60; 1.18]
Mamesaya et al., 2018	RCS	60	20	Good	1.48	[0.74; 2.96]
Random effects model					0.68	[0.45; 1.02]
Prediction interval						[0.27; 1.69]
Heterogeneity: I^2 = 62%, τ = 0.315, χ^2_6 = 15.65 (p = 0.016)						
Random effects model					**0.74**	**[0.52; 1.05]**
Heterogeneity: I^2 = 74%, τ = 0.363, χ^2_8 = 30.50 (p < 0.001)						



Toronto, Canada

223 studies including 56K pts (½ LS ½ ES)

PCI HR 0.59
p<0.001
+MRI HR 0.74
p=0.08

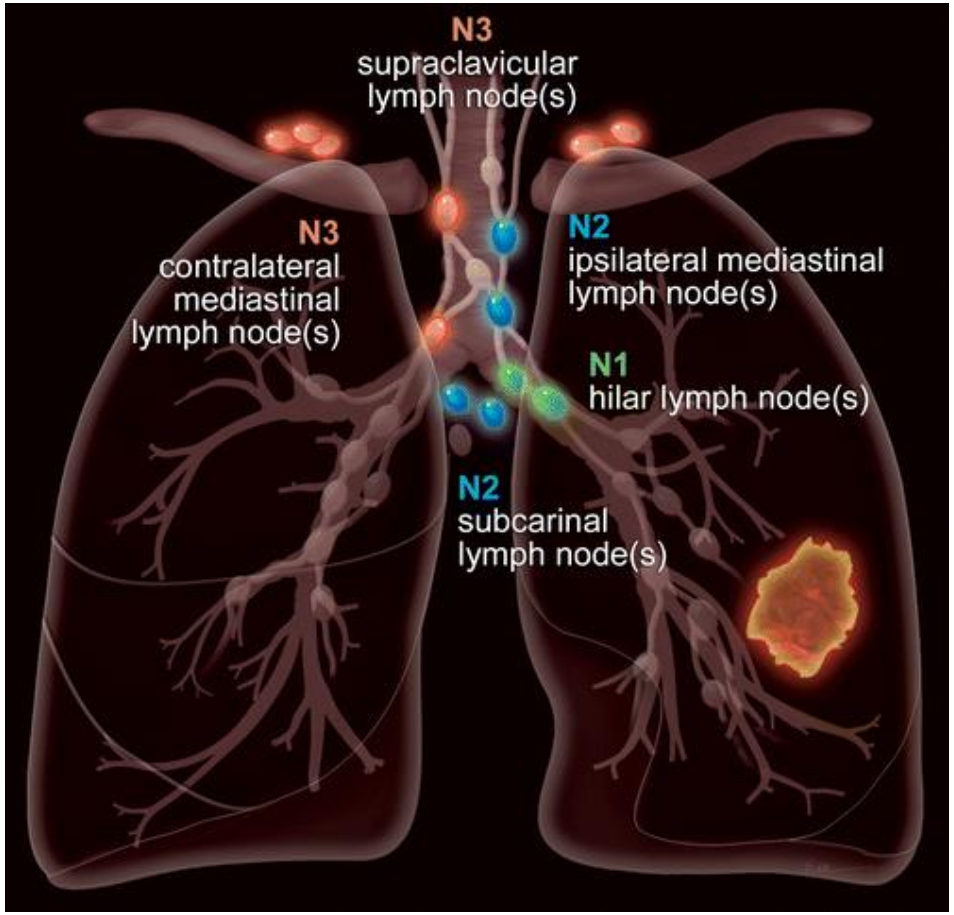
G3+ AE not evaluated

Gaebe et al Lancet 2023
PMID 38261885

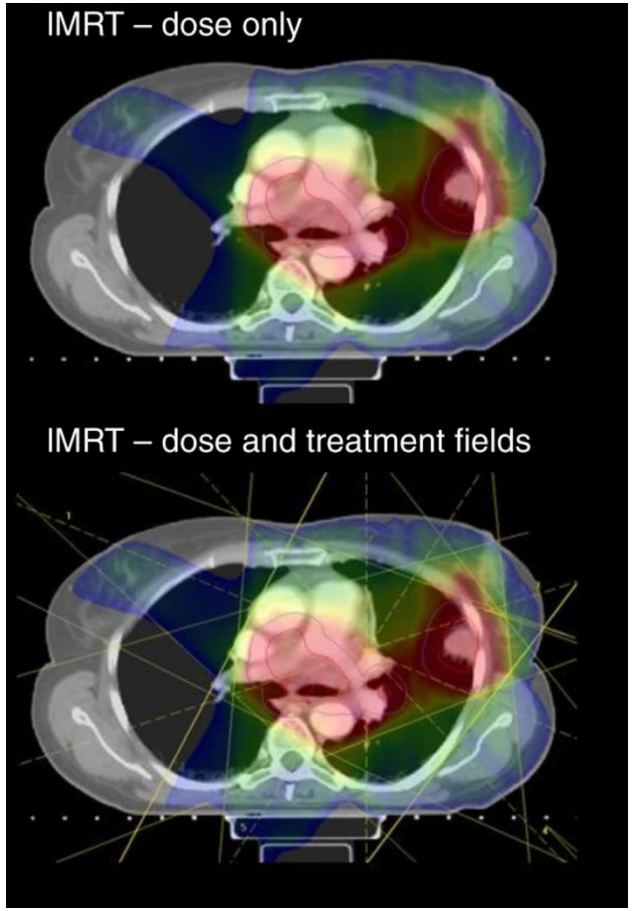
IMPACT | **Administration of PCI is associated with survival benefit, but not when lack of CNS disease is confirmed by imaging prior – prophylactic PCI should be reconsidered as SOC**

Standard-of-care: limited stage

Concurrent chemotherapy/radiation followed by 2 years anti-PDL1



Kandathil et al Radiographics 2018 PMID 30422775

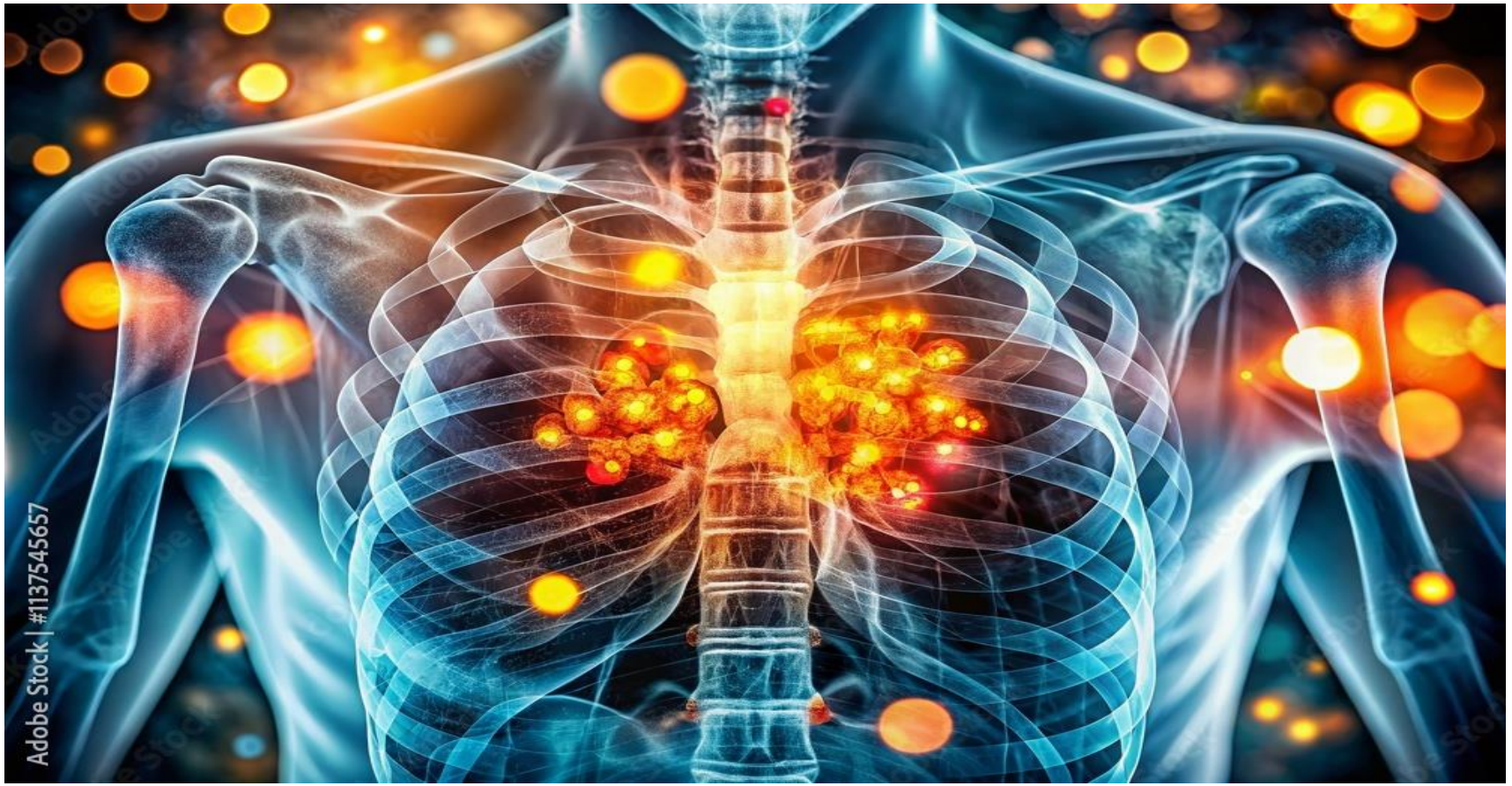


Storey et al BJC 2020 PMID 33293673

- Surgery: rarely
- Radiation: concurrent
- Chemotherapy: platinum+etoposide
- Immunotherapy: durvalumab
- CNS prophylaxis: debated

Standard-of-care: extensive stage (first-line)

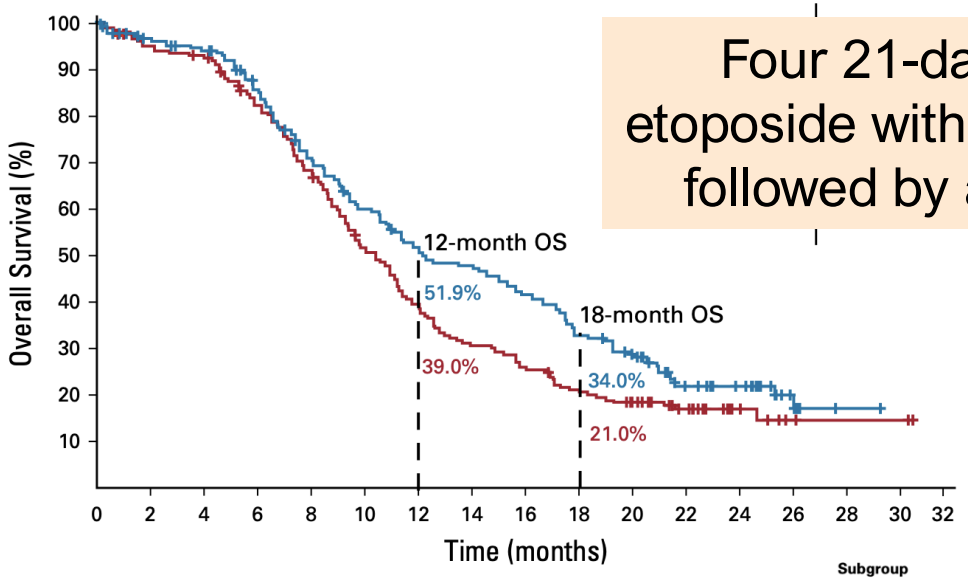
Chemoimmunotherapy with consideration of consolidation



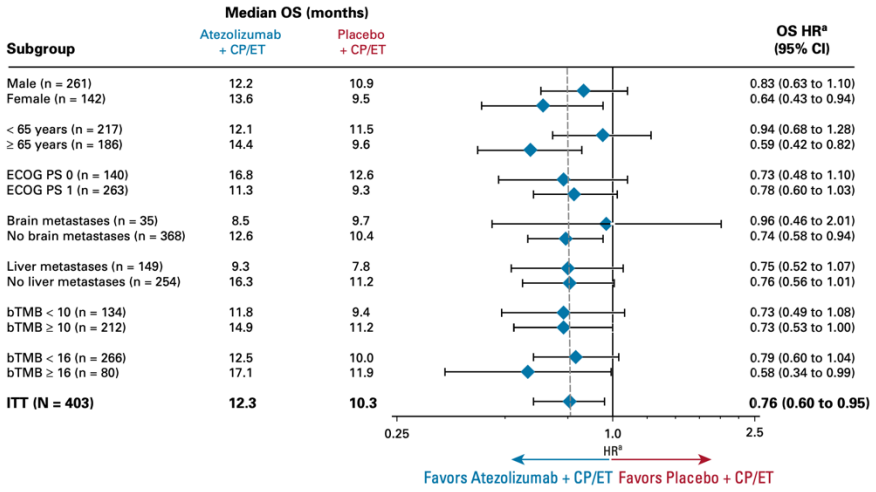
- Surgery: no
- Radiation: sx, consolidation
- Chemotherapy: carboplatin + etoposide
- Immunotherapy: atezolizumab, durvalumab
- CNS prophylaxis: debated

Three-year updated analysis of IMpower 133

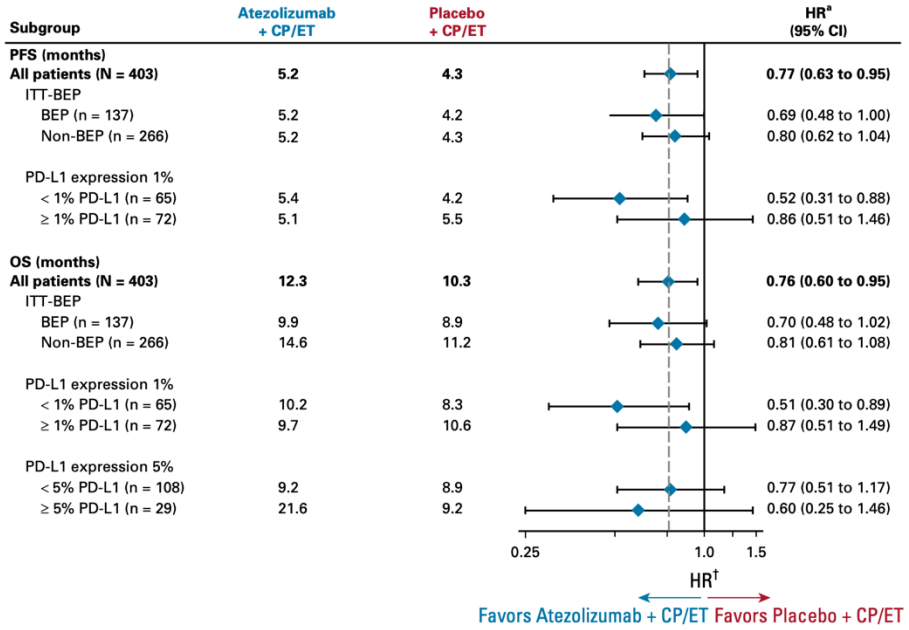
Primary overall survival



Four 21-day cycles of carboplatin etoposide with **atezolizumab vs placebo** followed by atezolizumab vs placebo



Subgroup	Median OS (months) Atezolizumab + CP/ET	Placebo + CP/ET	OS HR[a] (95% CI)
Male (n = 261)	12.2	10.9	0.83 (0.63 to 1.10)
Female (n = 142)	13.6	9.5	0.64 (0.43 to 0.94)
< 65 years (n = 217)	12.1	11.5	0.94 (0.68 to 1.28)
≥ 65 years (n = 186)	14.4	9.6	0.59 (0.42 to 0.82)
ECOG PS 0 (n = 140)	16.8	12.6	0.73 (0.48 to 1.10)
ECOG PS 1 (n = 263)	11.3	9.3	0.78 (0.60 to 1.03)
Brain metastases (n = 35)	8.5	9.7	0.96 (0.46 to 2.01)
No brain metastases (n = 368)	12.6	10.4	0.74 (0.58 to 0.94)
Liver metastases (n = 149)	9.3	7.8	0.75 (0.52 to 1.07)
No liver metastases (n = 254)	16.3	11.2	0.76 (0.56 to 1.01)
bTMB < 10 (n = 134)	11.8	9.4	0.73 (0.49 to 1.08)
bTMB ≥ 10 (n = 212)	14.9	11.2	0.73 (0.53 to 1.00)
bTMB < 16 (n = 266)	12.5	10.0	0.79 (0.60 to 1.04)
bTMB ≥ 16 (n = 80)	17.1	11.9	0.58 (0.34 to 0.99)
ITT (N = 403)	**12.3**	**10.3**	**0.76 (0.60 to 0.95)**



Subgroup	Atezolizumab + CP/ET	Placebo + CP/ET	HR[a] (95% CI)
PFS (months)			
All patients (N = 403)	**5.2**	**4.3**	**0.77 (0.63 to 0.95)**
ITT-BEP			
BEP (n = 137)	5.2	4.2	0.69 (0.48 to 1.00)
Non-BEP (n = 266)	5.2	4.3	0.80 (0.62 to 1.04)
PD-L1 expression 1%			
< 1% PD-L1 (n = 65)	5.4	4.2	0.52 (0.31 to 0.88)
≥ 1% PD-L1 (n = 72)	5.1	5.5	0.86 (0.51 to 1.46)
OS (months)			
All patients (N = 403)	**12.3**	**10.3**	**0.76 (0.60 to 0.95)**
ITT-BEP			
BEP (n = 137)	9.9	8.9	0.70 (0.48 to 1.02)
Non-BEP (n = 266)	14.6	11.2	0.81 (0.61 to 1.08)
PD-L1 expression 1%			
< 1% PD-L1 (n = 65)	10.2	8.3	0.51 (0.30 to 0.89)
≥ 1% PD-L1 (n = 72)	9.7	10.6	0.87 (0.51 to 1.49)
PD-L1 expression 5%			
< 5% PD-L1 (n = 108)	9.2	8.9	0.77 (0.51 to 1.17)
≥ 5% PD-L1 (n = 29)	21.6	9.2	0.60 (0.25 to 1.46)

Liu et al JCO 2021 PMID 33439693

Global, phase I/III double-blind, placebo-controlled randomized 1:1

Enrolled 403
201 atezolizumab

OS

HR 0.76
12.3 vs 10.3m
p=0.015

PFS

HR 0.77
5.2 vs 4.3m
p=0.02

PD-L1/TMB analyses unrevealing

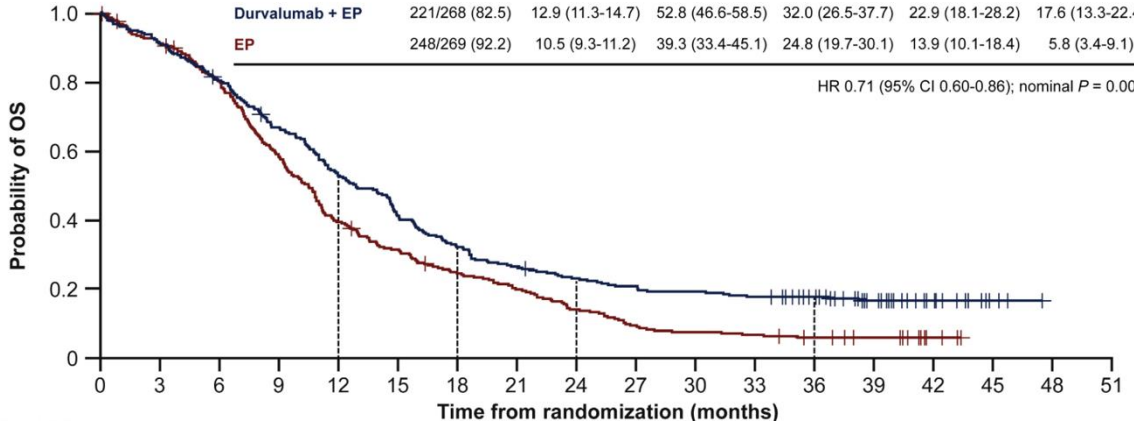
No new safety signals

Three-year updated analysis of CASPIAN

Primary overall survival durvalumab vs EP, durvalumab+tremelimumab vs EP

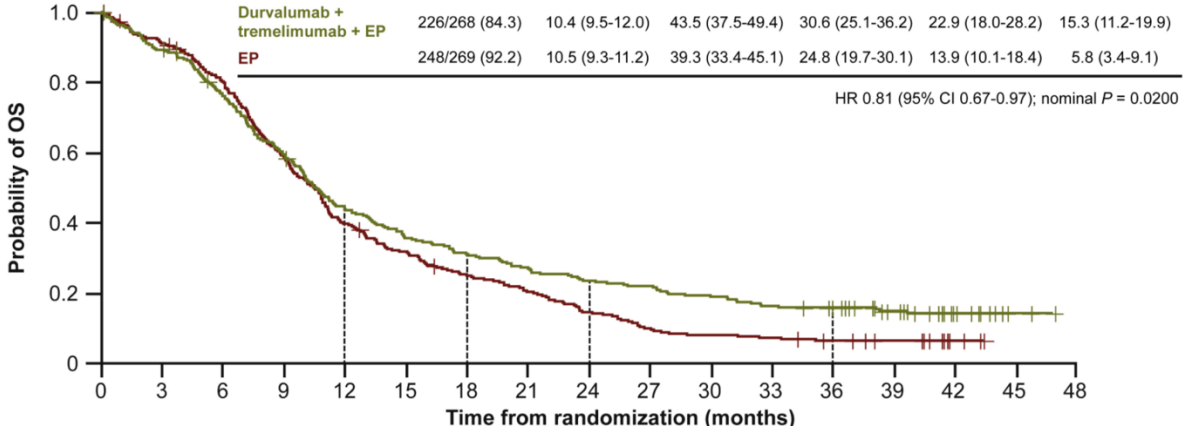
	Events/ patients, *n* (%)	Median OS (95% CI), months	12-month OS rate (95% CI), %	18-month OS rate (95% CI), %	24-month OS rate (95% CI), %	36-month OS rate (95% CI), %
Durvalumab + EP	221/268 (82.5)	12.9 (11.3-14.7)	52.8 (46.6-58.5)	32.0 (26.5-37.7)	22.9 (18.1-28.2)	17.6 (13.3-22.4)
EP	248/269 (92.2)	10.5 (9.3-11.2)	39.3 (33.4-45.1)	24.8 (19.7-30.1)	13.9 (10.1-18.4)	5.8 (3.4-9.1)

HR 0.71 (95% CI 0.60-0.86); nominal *P* = 0.0003



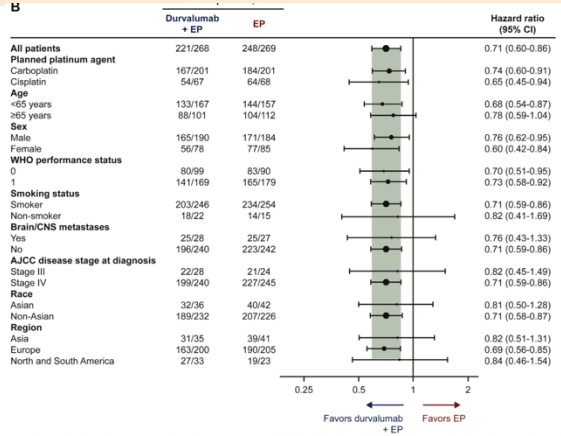
	Events/ patients, *n* (%)	Median OS (95% CI), months	12-month OS rate (95% CI), %	18-month OS rate (95% CI), %	24-month OS rate (95% CI), %	36-month OS rate (95% CI), %
Durvalumab + tremelimumab + EP	226/268 (84.3)	10.4 (9.5-12.0)	43.5 (37.5-49.4)	30.6 (25.1-36.2)	22.9 (18.0-28.2)	15.3 (11.2-19.9)
EP	248/269 (92.2)	10.5 (9.3-11.2)	39.3 (33.4-45.1)	24.8 (19.7-30.1)	13.9 (10.1-18.4)	5.8 (3.4-9.1)

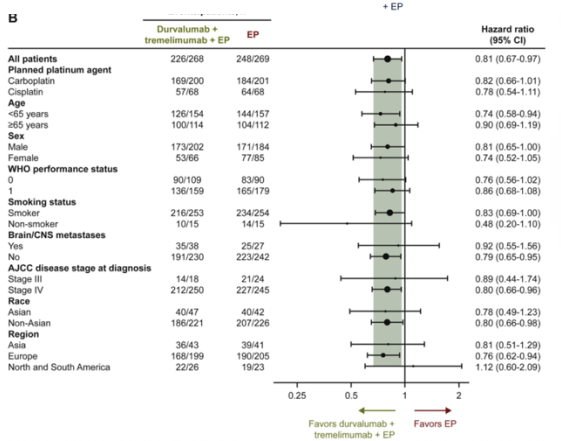
HR 0.81 (95% CI 0.67-0.97); nominal *P* = 0.0200



Paz-Ares et al ESMO 2022 PMID 35279527

Four 21-day cycles of carboplatin etoposide with **durvalumab or durvalumab + trelimumumab vs placebo** followed by durvalumab or durvalumab + trelimumumab





Global, phase 3, double-blind, placebo-controlled, randomized 1:1:1

805 enrolled
D: 268
D+T: 268

OS1

D: HR 0.71
3y: 17.6% vs 5.8%
12.9 vs 10.5m

OS2

D+T: HR 0.81
3y: 15.3% vs 5.8%
10.4 vs 10.5m

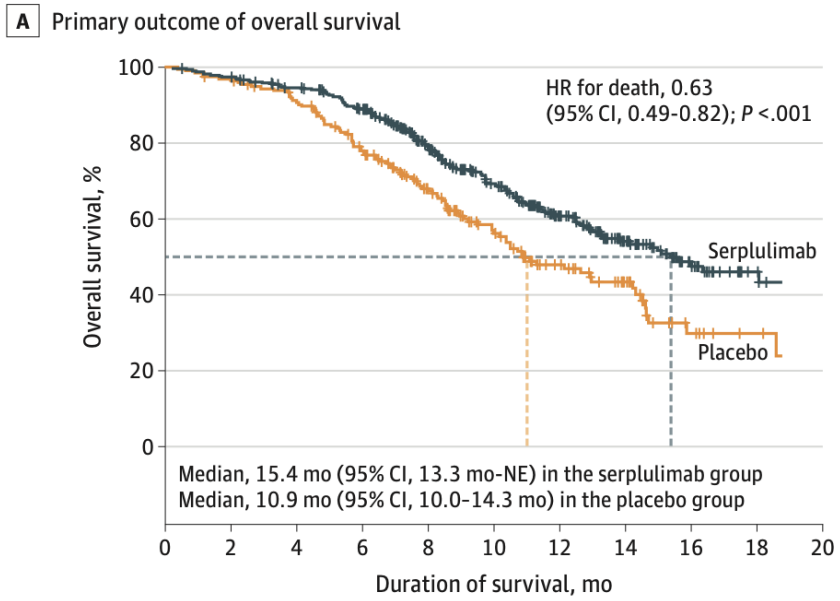
G3+ AE (any)
D 32.5 % D+T 47.4% (control 36.5%)
Pneumonitis
1.1%, 1.9%, 1.1%

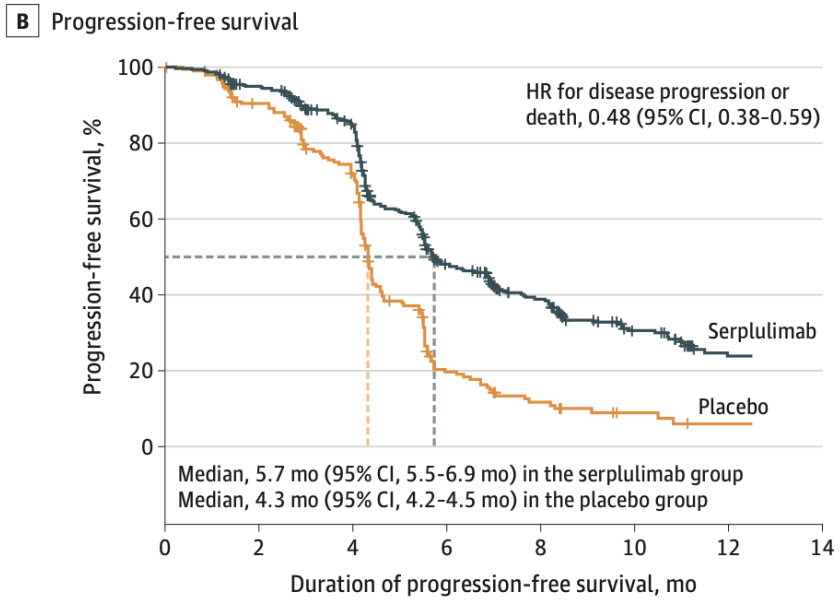
ASTRUM-005 (serplulimab)

Primary overall survival

Four 21-day cycles of carboplatin etoposide with **4.5 mg/kg serplulimab (PD-1 Ig G4) vs placebo** ongoing

PD-1 IgG4 thought to bind more avidly to PD-L1 and lead to weaker CD28 cis





Global, phase 3 double-blind placebo-controlled randomized 2:1

Enrolled 585
389 serliplulimab

OS

HR 0.63
P<0.001
15.4 vs 10.9m

PFS

HR 0.48
p<0.001
5.7 vs 4.3m

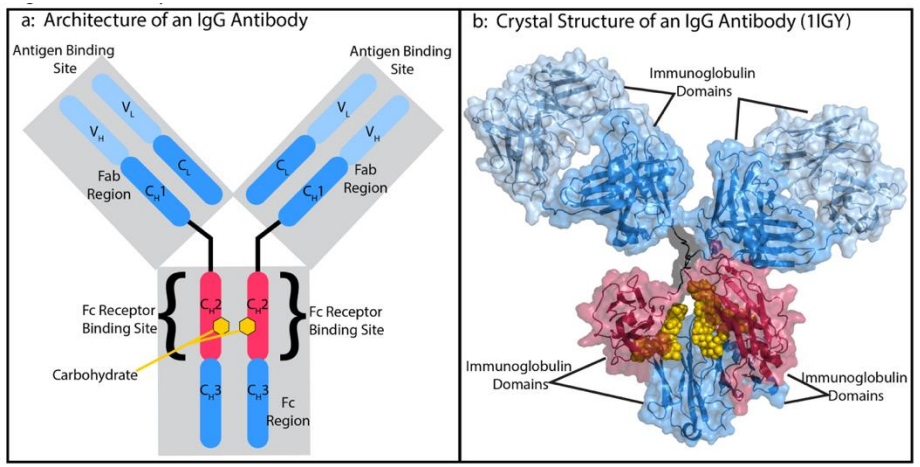
G3+ AE
33.2 vs 27.6%

Cheng et al JAMA 2022 PMID 36166026

Socazolimab

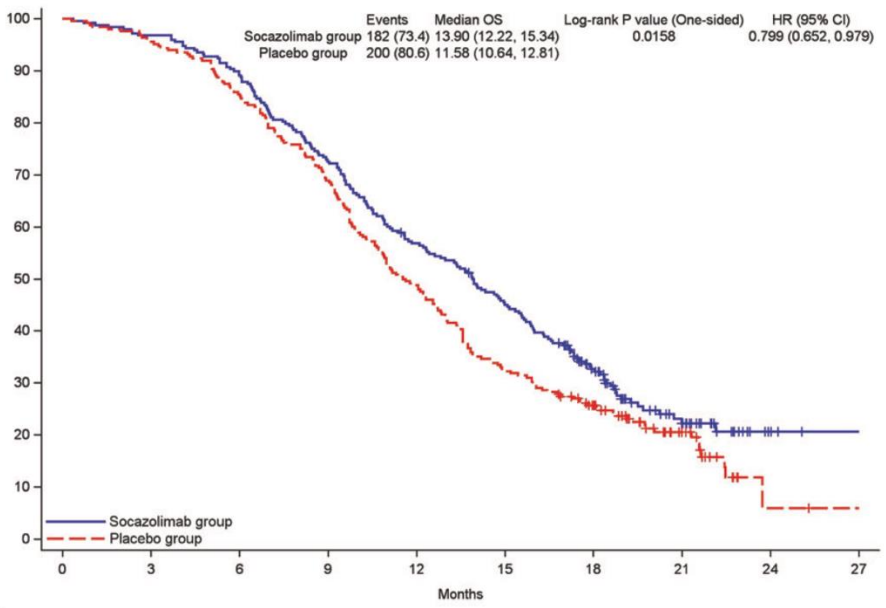
Primary overall survival

Four 21-day cycles of carboplatin etoposide with **socazolimab vs placebo** followed by socazolimab vs placebo

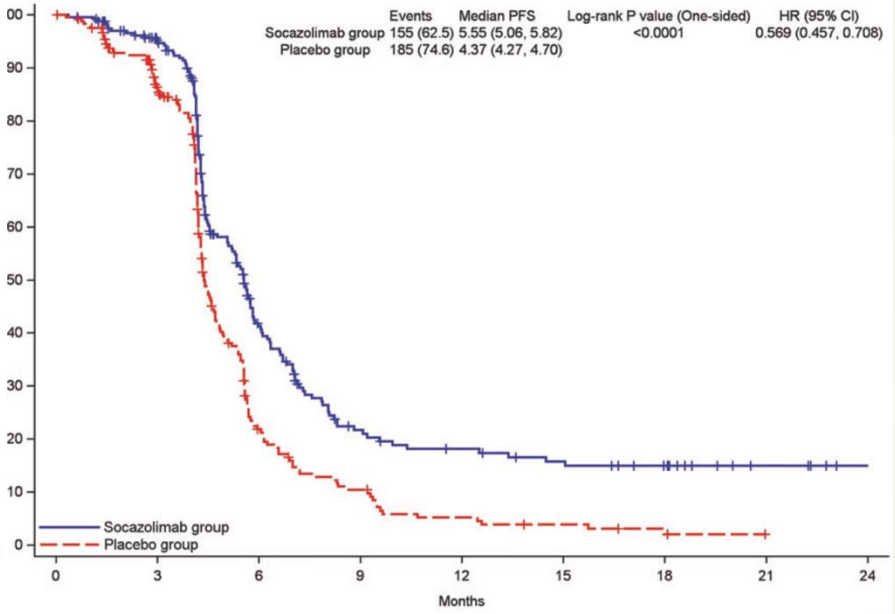


PD-L1 + Ig G1 Fc segment recognized by NK cells

Overall survival



Progression-free survival



Chen et al Sig Transduct Target Ther 2025 PMID 39800716

54 hospitals in China; phase 3 double-blind placebo-controlled randomized 1:1

Enrolled 498
250 socazolimab

OS

HR 0.799
p=0.0158
13.9 vs 11.6m

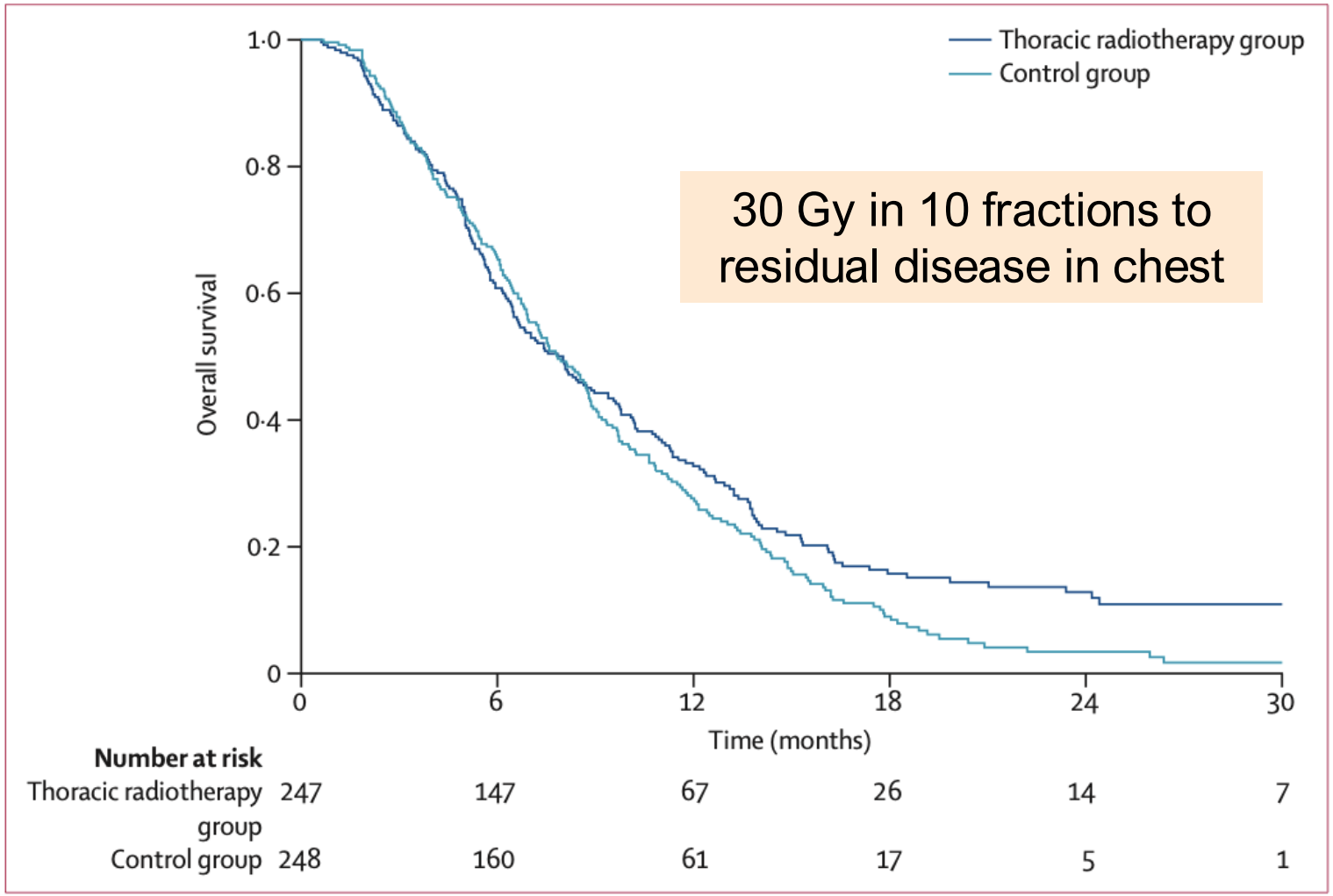
PFS

HR 0.569
p<0.001
5.6 vs 4.4m

G3+ AE
irAE 19.3 vs 9.7%
PNA 4.4 vs 2.4%

Thoracic radiotherapy consolidation

Primary 1-year overall survival in intention-to-treat; secondary PFS



UK, Netherlands, Belgium

498 ES-SCLC
247 XRT

OS

1y: 33% vs 28%
p=0.06
2y: 13% vs 3%
p=0.004

PFS

HR 0.73 p=0.001
@6m 24% vs 7%

Dysphagia 1.6%
No G4-5

Slotman et al Lancet 2015 PMID 25230595

Amifampridine for LEMS

Double-blinded, placebo-controlled withdrawal trial

K+ blocker that increases release of acetylcholine

Rare but underdiagnosed cause of weakness/fatigue

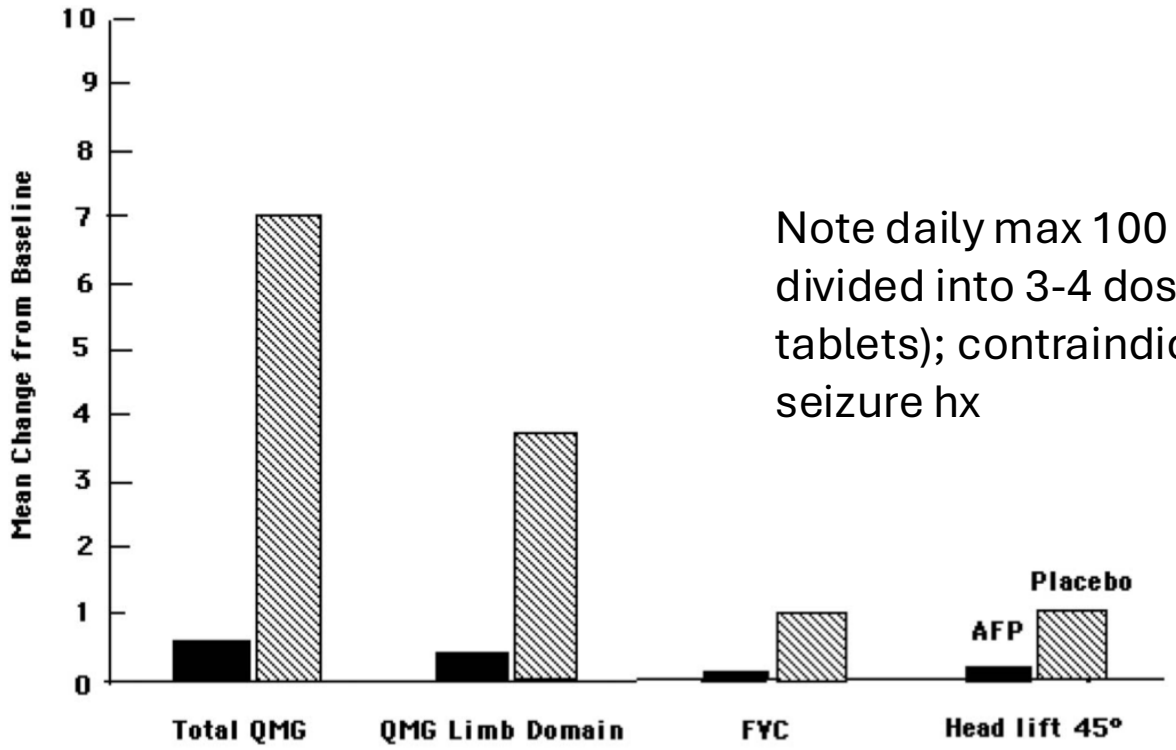


FIGURE 2. Mean CFB after 4 days of amifampridine (AFP; black column) or placebo (hatched column) in total QMG score, QMG-LD score, FVC, and head lift to 45 degrees (head lift 45 degrees).

Note daily max 100 mg divided into 3-4 doses (10 mg tablets); contraindicated for seizure hx

United States

26 enrolled, 1:1

Primary endpoint
QMG score

Exploratory
3TUG

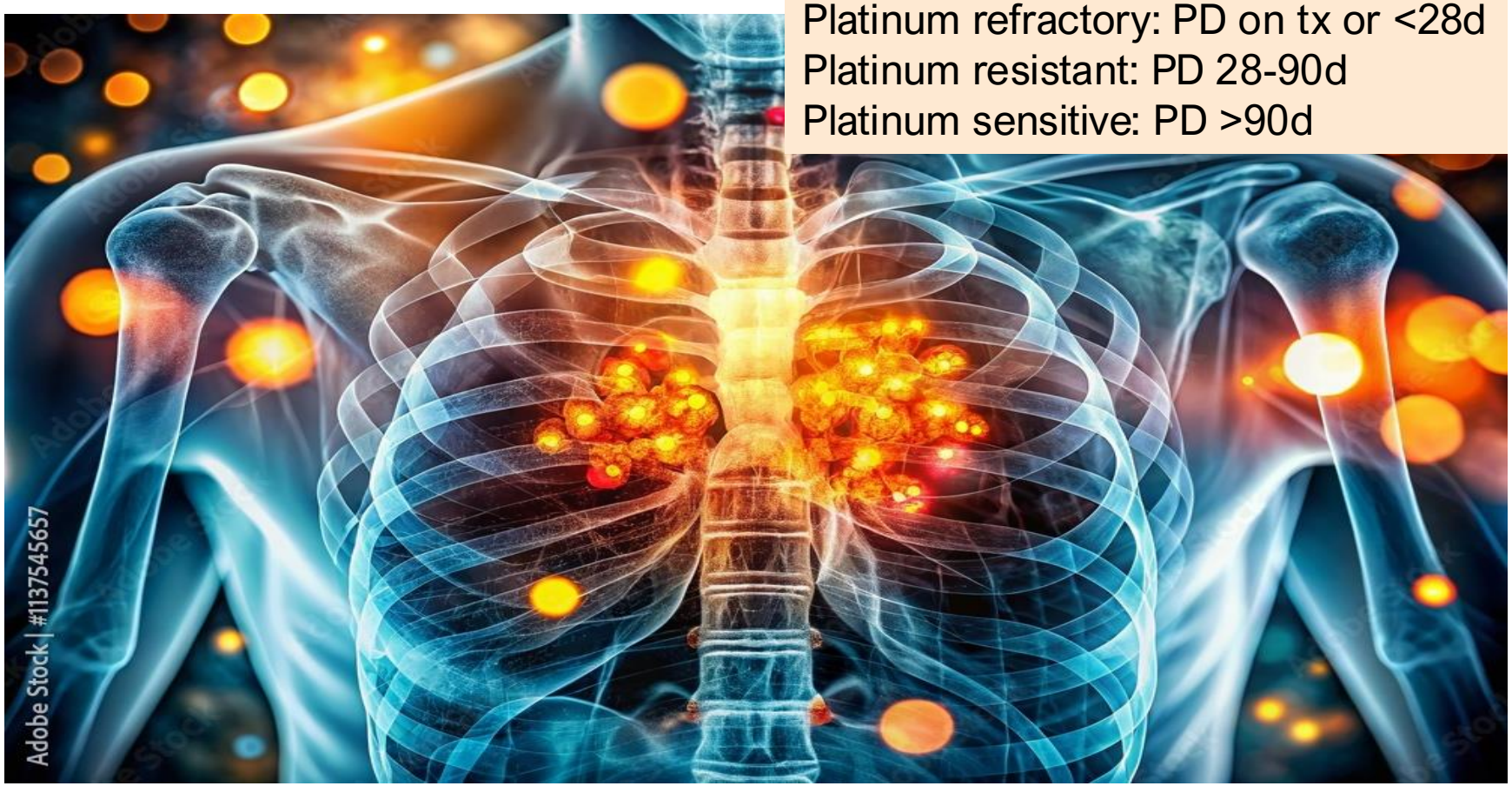
No G3+

Shieh et al J Clin Neuromuscul Dis 2019 PMID 30801481

Standard-of-care: extensive stage (second-line+)

Topotecan hasn't been beaten officially, although tarlatamab appears promising

Platinum refractory: PD on tx or <28d
Platinum resistant: PD 28-90d
Platinum sensitive: PD >90d



Surgery: no

Radiation: only for sx

Chemotherapy: lurbinectdin, topotecan

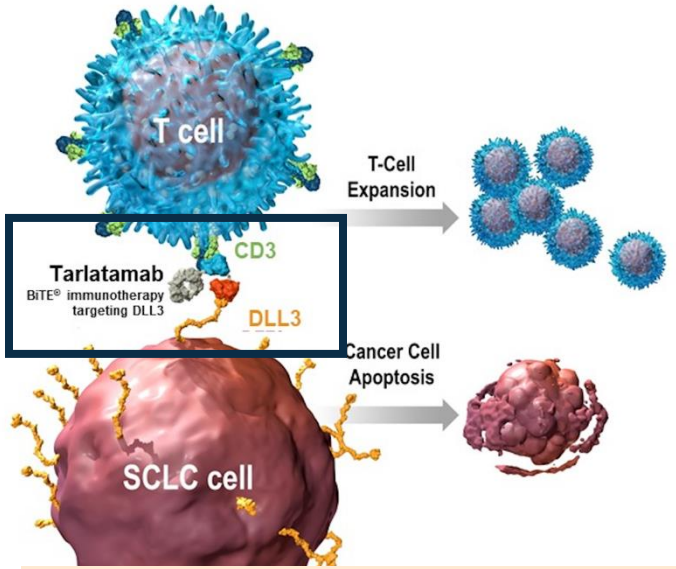
Immunotherapy: tarlatamab

CNS prophylaxis: no

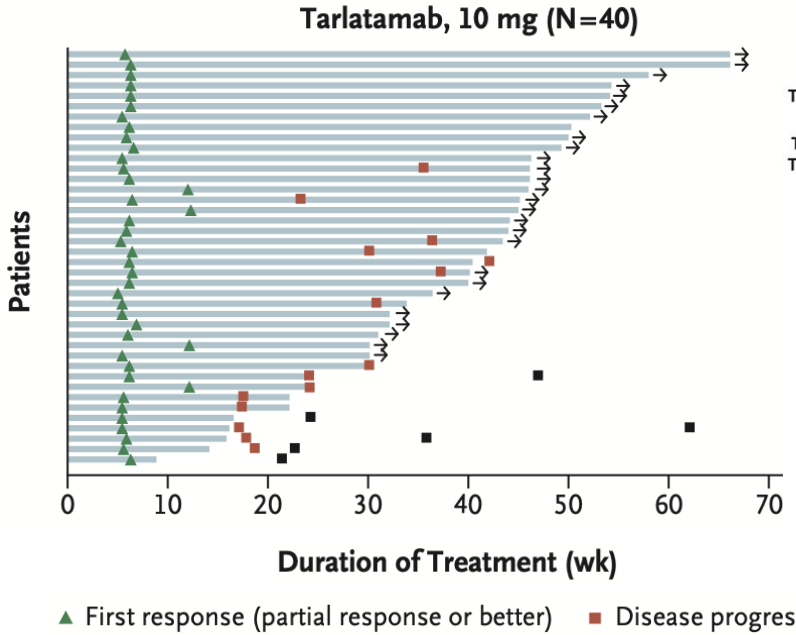
DeLLphi-301

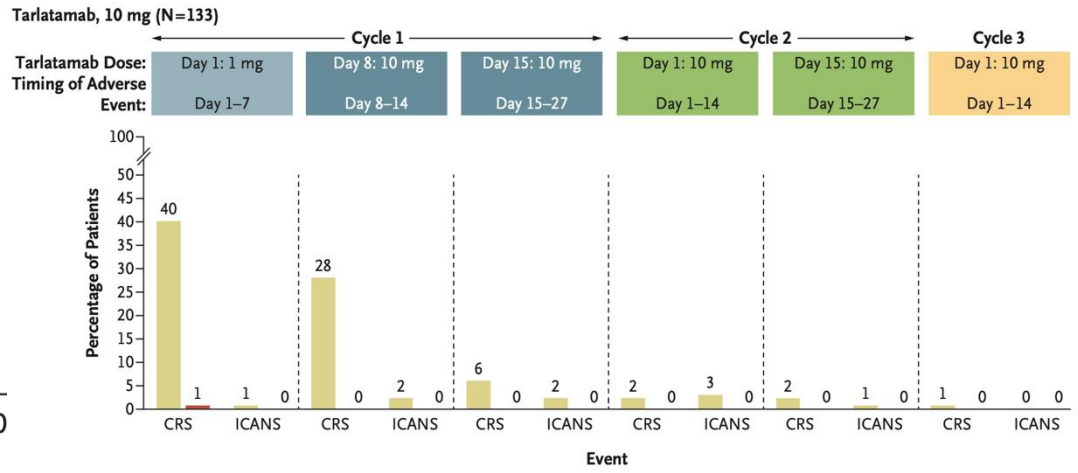
Primary objective response

Tarlatamab-dlle administered by IV every 2 weeks* at 10 or 100 mg in patients with previously treated SCLC



CD3 (T cells)-DLL3 (tumor)





Global phase 2

220 enrolled

ORR

40% in 10 mg
32% in 100 mg
mDOR 9.6m

OS

@9m
68% in 10 mg
update: 14.3m

PFS

4.9m in 10 mg
3.9m in 100 mg

CRS 51%, 61%
G3 1%, 6%

Ahn et al NEJM 2023 PMID 37861218
Dingemans ASCO 2024

IMPACT

FDA granted accelerated approval for extensive stage SCLC with disease progression on or after platinum-based chemotherapy 5/16/2024; *(C1D1 (1mg) C1D8 (10mg) must be given in hospital then C1D15 (10mg) and every two weeks after okay in clinic

Molecular subtypes in SCLC

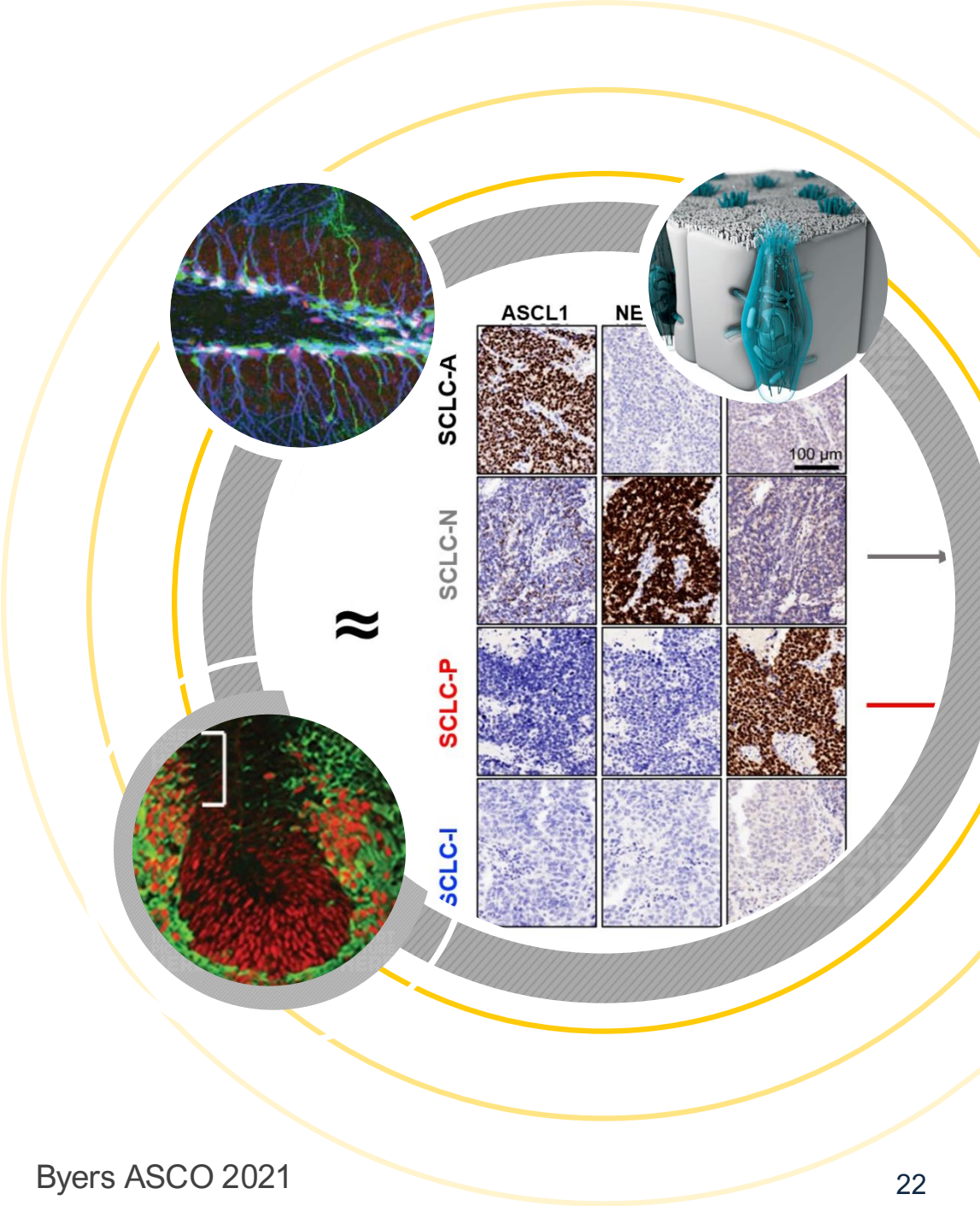
SCLC adapts and escapes rapidly, transcription regulators suggest treatment sensitivity

A Classic: >50% express **ASCL1** (achaete-scute homolog 1), which drives NE differentiation **DLL3** expression (includes **SLFN11** ~ **PARPi**).

N Variant: ~15% express **NEUROD1** (neurogenic differentiation factor 1) associated with MYC, may suggest **novel** tx opportunities

P Tuft cell-like variant: ~12% express **POU2F3** (POU class 2 homeobox 3) suggests response to **Switchniff complex inhibitors** (e.g., IV-255, small molecules that targets BRG catalytic subunit)

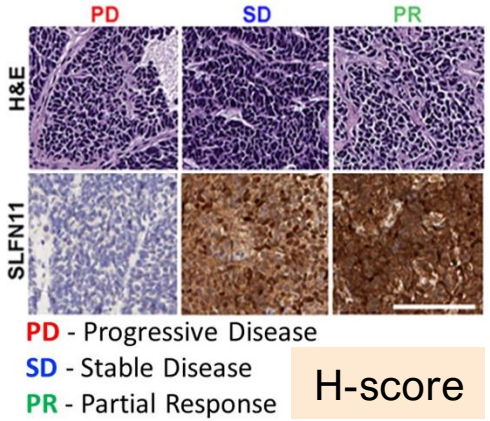
I Inflamed: ~20% express an **inflammatory signature** that may suggest durable responses to **immune-targeting** therapies



Byers ASCO 2021

Velaparib (PARP inhibitor) + temozolomide by SLFN11

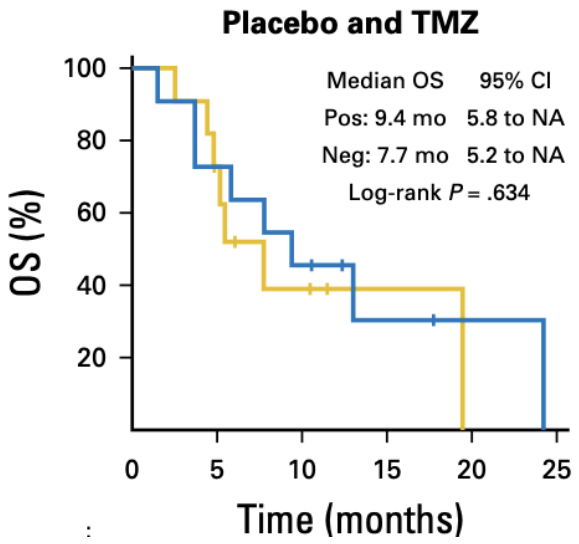
Primary progression-free survival at 4 months

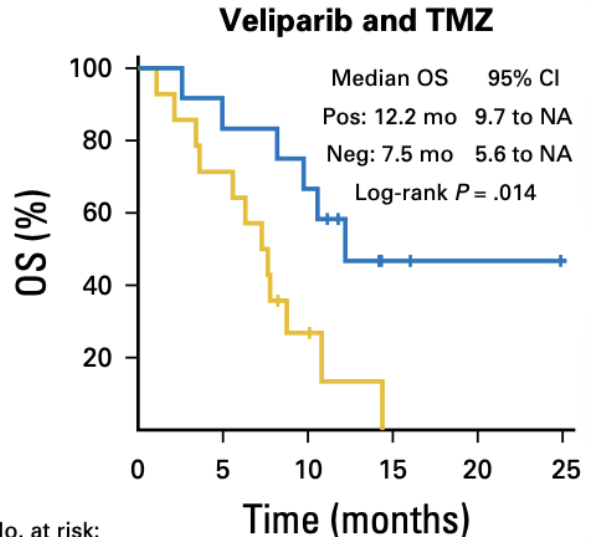


H-score

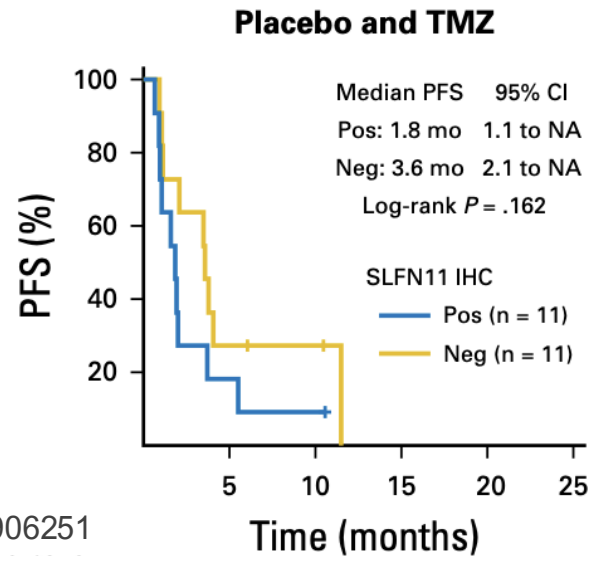
Stewart et al OncoTarget 2017

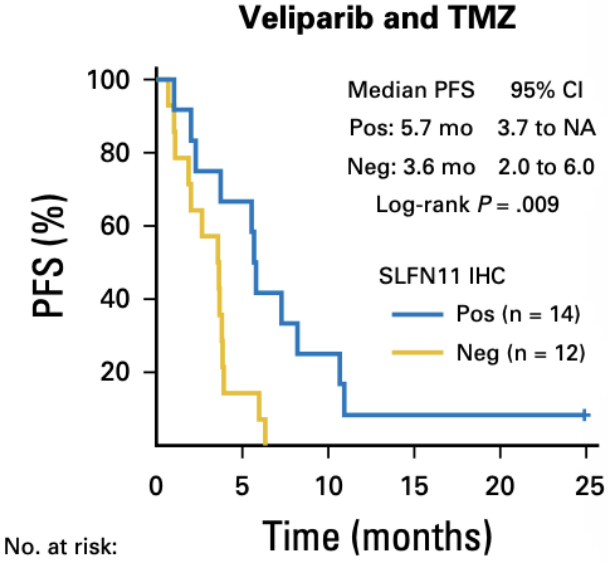
Temozolomide 150-200 mg/m² 40 mg po D1-5 every 28 days + talazoparib 0.75 mg po daily





No. at risk:





No. at risk:

Pietanza et al JCO 2018 PMID 29906251

United States phase 2, randomized, double-blind

104 enrolled
55 V+TMZ
(SLFN+ 23; - 25)

PFS
4m: 36% vs 27%
p=0.19
SLFN+ 5.7 vs 3.6m

OS
8.2 vs 7.0m
p=0.50
SLFN+ 12.2 vs 7.5m

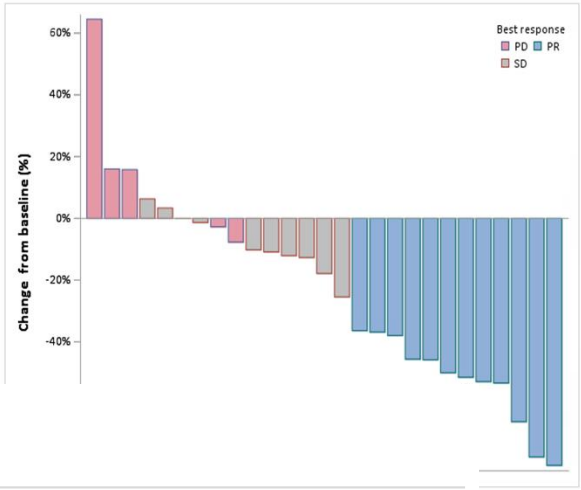
ORR
39% vs 14%
p=0.016

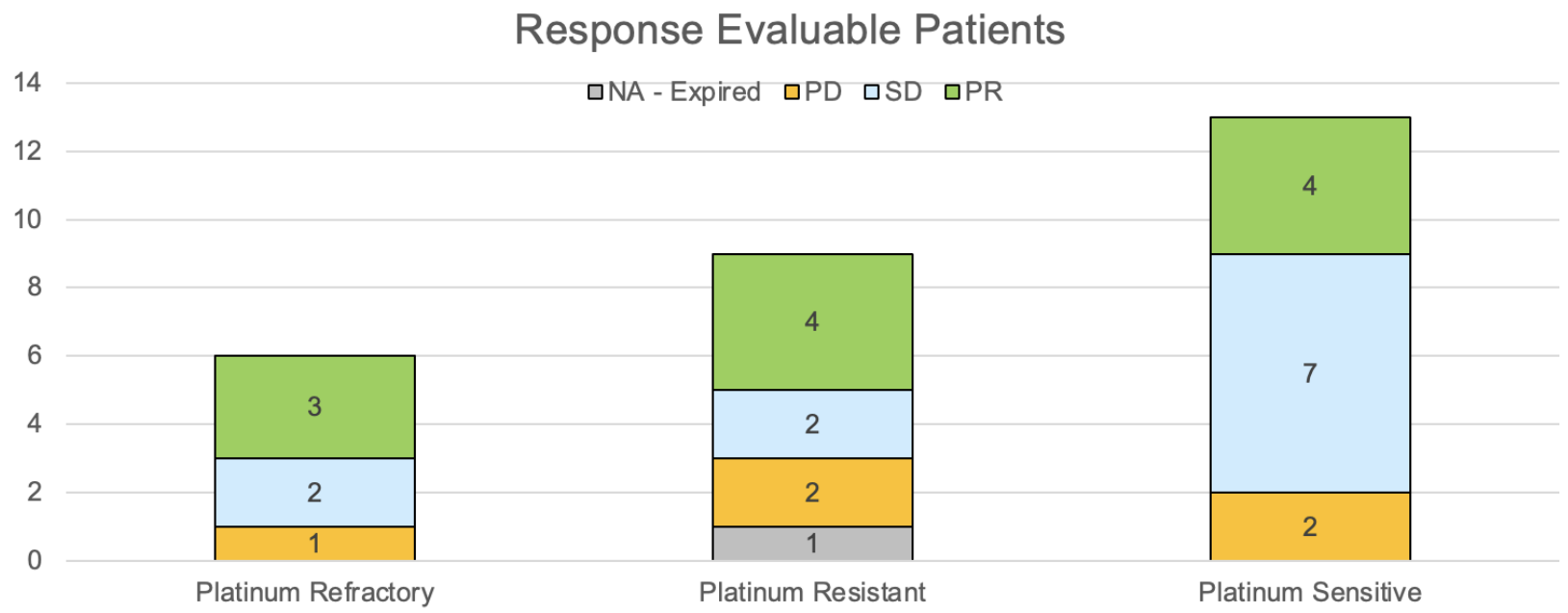
G3+ neutropenia
12.7 vs 4.1%
Thrombocytopenia
18.2 vs 2.0%

TRIO-US L07: talazoparib (PARPi) + temozolomide

Primary progression-free survival

Temozolomide 30-40 mg po D1-5 every 28 days + talazoparib 0.75 mg po daily in patients with previously treated SCLC





United States phase 2, single arm IIT

Enrolled 33

PFS

PFS 4.5m (OS 11.9m)

ORR

39.3% (TTR 51d) DC 78.6%

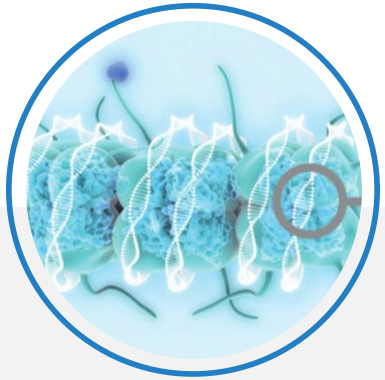
G3+ AE include thrombocytopenia (50%), resolved with hold/TMZ dose reduction

Goldman et al ASCO 2022

IMPACT | **Remains off-label consideration for fragile patients; has acceptable safety data with concurrent anti-PDL1 therapy**

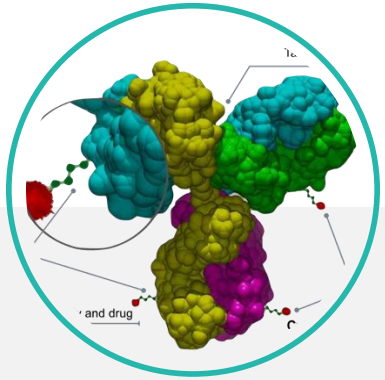
What's next for SCLC

Trials/concepts in progress



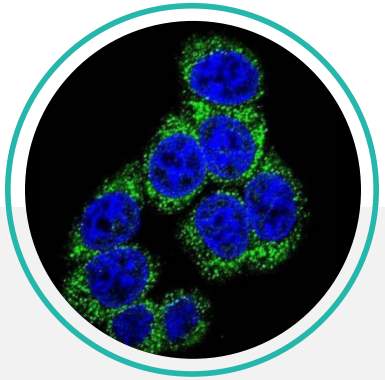
Diagnosis:
Ongoing refinement of **biomarkers** for molecular subtypes; consideration of **ctDNA/ MRD** and **methylation** assays

Dx



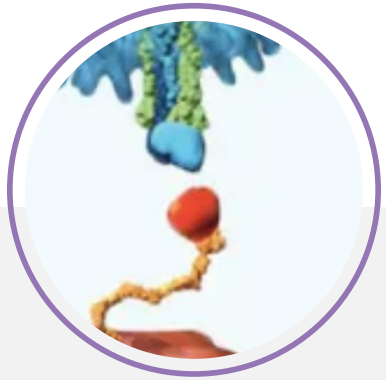
Cytotoxics:
Many **ADC trials ongoing** including sacituzumab govitecan (TROP-2); Ifinatamab derutxecan (B7-H3/CD276); ABBV-706 (SEZ6)

ADCs



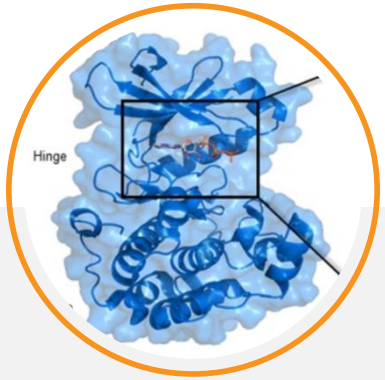
Checkpoint inhibitors:
ASTRIDE (serplulimab vs atezolizumab); **KEYLYNK-013** (pembro+olaparib); nivo+DF6002 (fusion protein IL-12 with Fc NK target)

ICI



Bispecifics:
Many **DeLLphi trials ongoing** including phase 3 (304), first-line (303), limited-stage (306), combinations (303), SC (308)

BiTES



Others:
Lurbinectedin/berzosertib (ATR kinase inhibitor); **BET inhibitors** (JQ1) for SCLC-N; RZY101+SSTR; angiogenic (anlotinib) combinations

TKIs

Conclusion

Small cell lung cancer (SCLC)/high-grade neuroendocrine cancer continues to have a **poor prognosis** – median overall survival for limited stage is <2y; extensive stage ~1y

Molecular subtyping has suggested **treatment opportunities**, although this testing is not provided as standard of care

Advances in targeting the immune system include the **addition of anti-PDL1** first-line and **CD3-DLL3** bispecific T-cell engagers upon PD

Ongoing drug development in SCLC is **crucial to ongoing progress** in cancer-related mortality

THANK YOU!

UCLA Jonsson Comprehensive Cancer Center