Small Cell Lung Cancer and Mesothelioma

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January 10-12, 2025.

Icahn School of Medicine at Mount Sinai

OVERVIEW

- Mesothelioma- Molecular Alterations and Altered Pathways

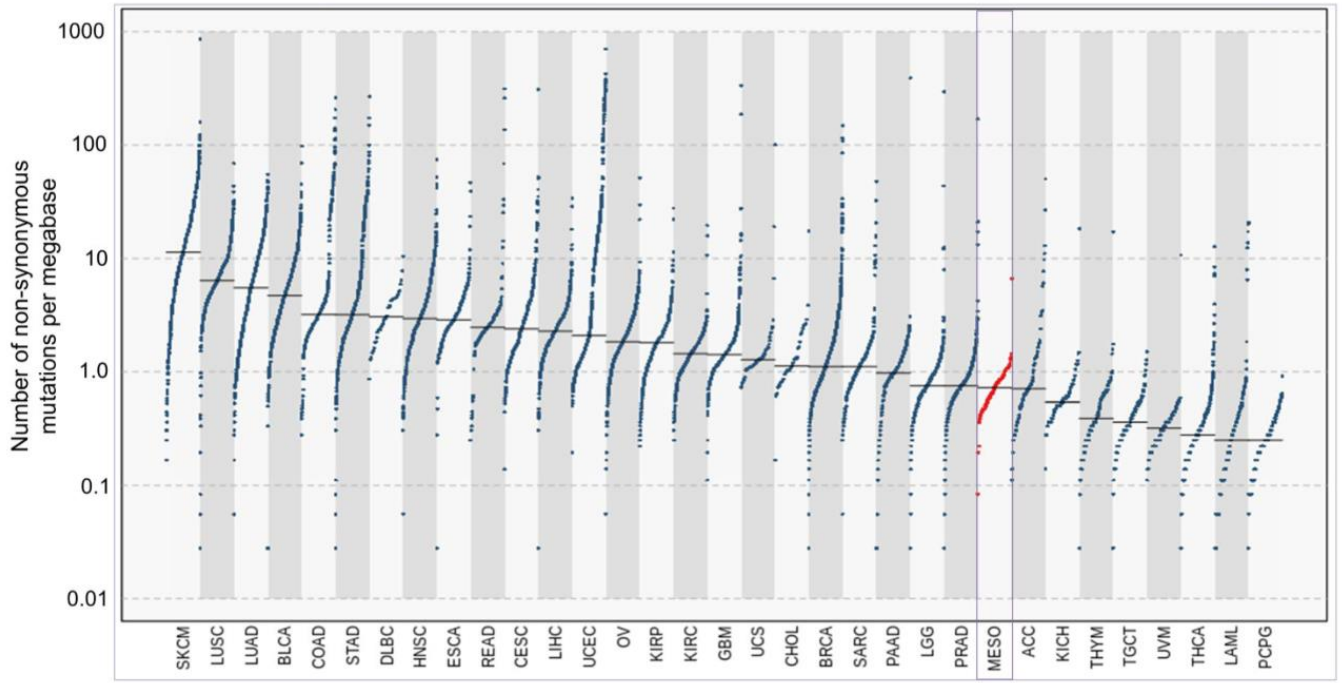
Small Cell Lung Cancer

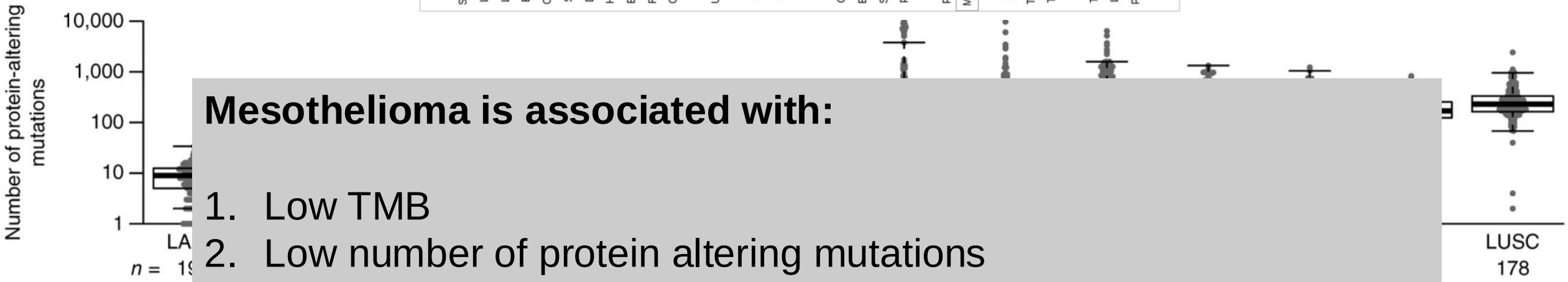
- Recent Advancements in Treatment
    - Limited-Stage
    - Extensive-Stage
- Emerging Trials & Novel Targets
- Biology & Biomarkers in SCLC

Mesothelioma- Background

- Often aggressive tumor arising from pleura, peritoneum, pericardium, tunica vaginalis
- 3 major histologic types: epithelioid, biphasic, sarcomatoid
- Asbestos is the primary implicated carcinogen
- Latency period 3-5 decades after exposure
- Average life expectancy is 1.5 years with standard therapies (chemo, immunotherapy)
- Substantial need for efficacious therapies!

Mutation Burden in Mesothelioma



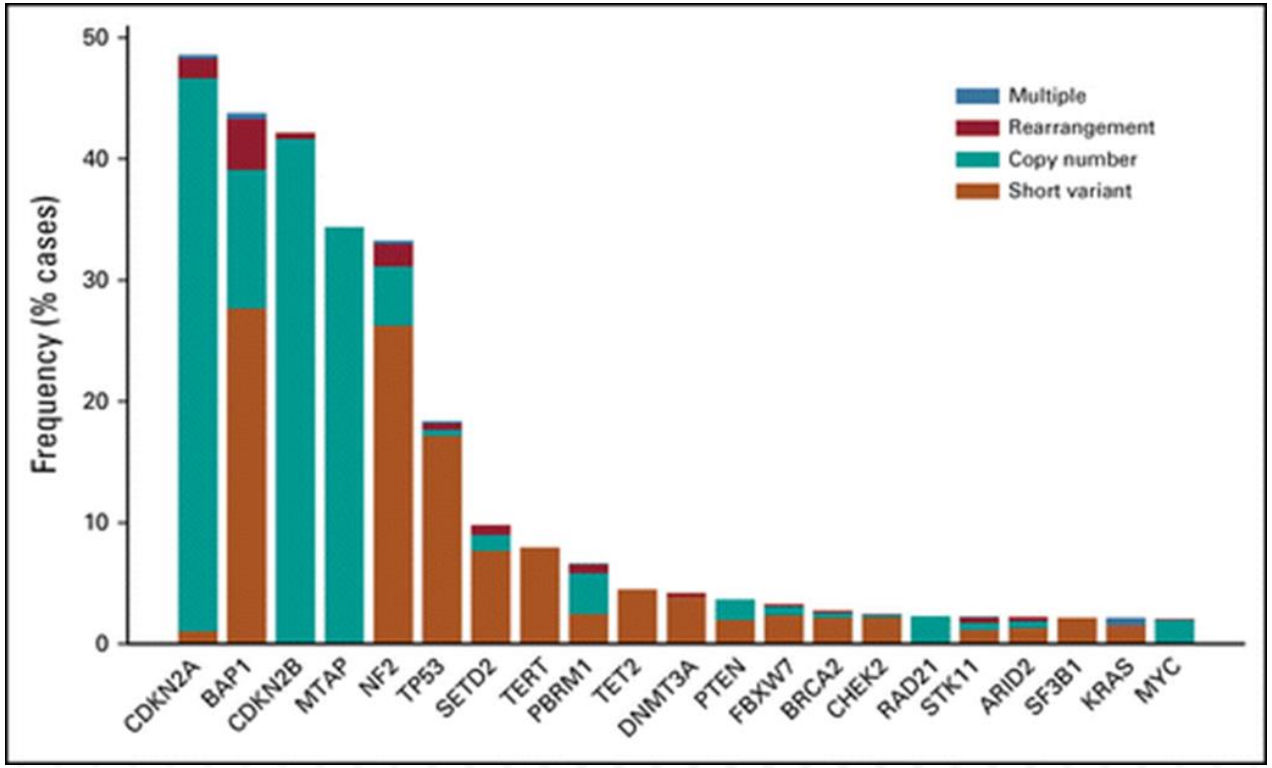


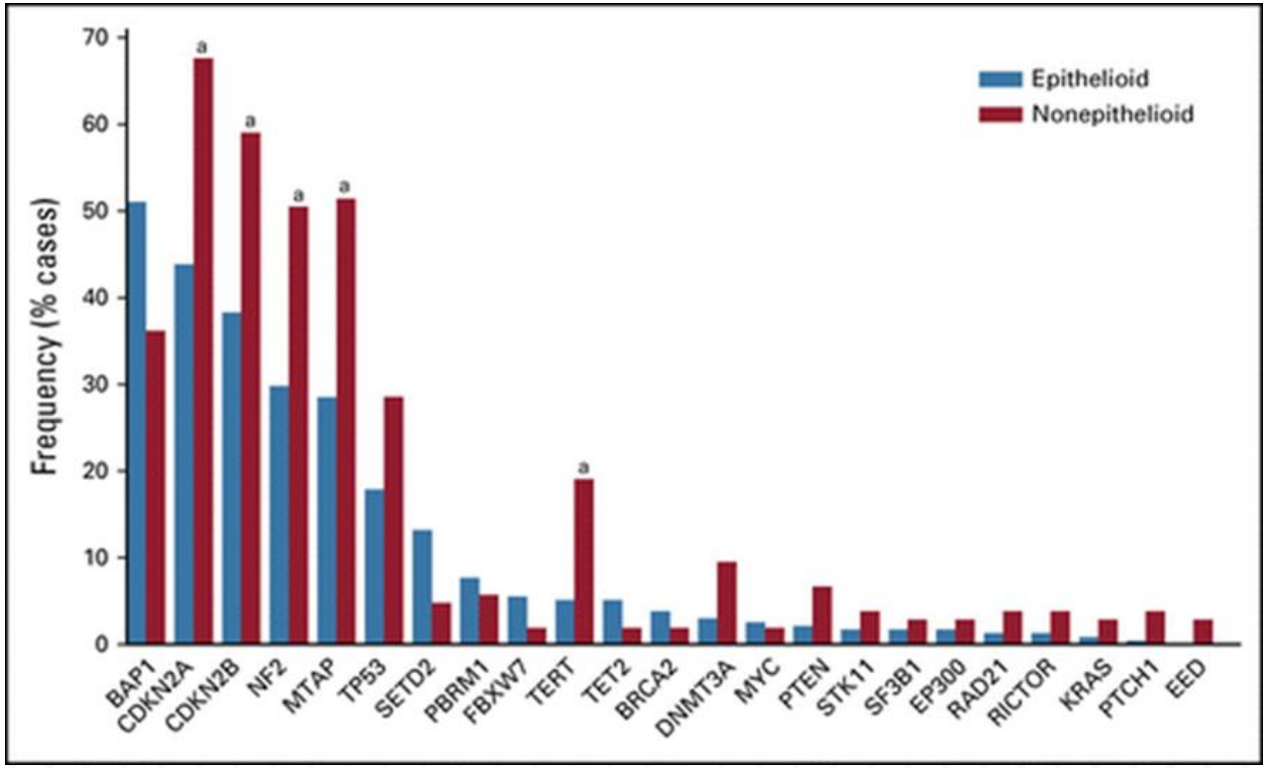
Mesothelioma is associated with:

1. Low TMB
2. Low number of protein altering mutations
3. Enriched for structural variants and deletions

ure Comm 2021

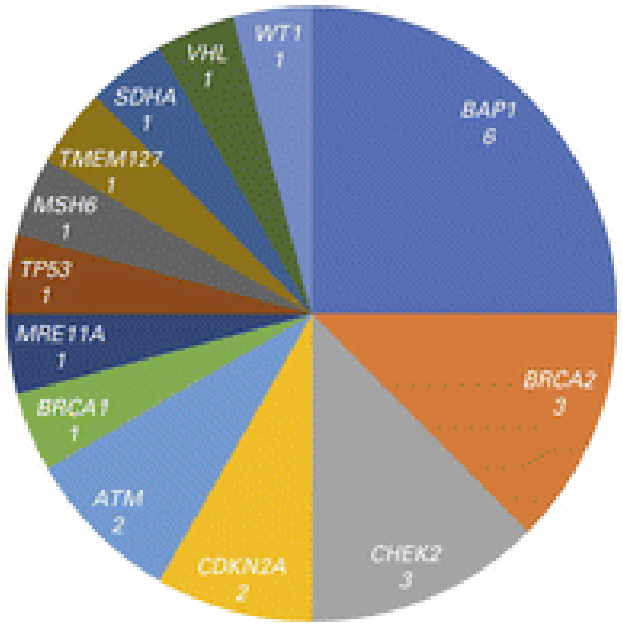
Molecular Alterations in Mesothelioma

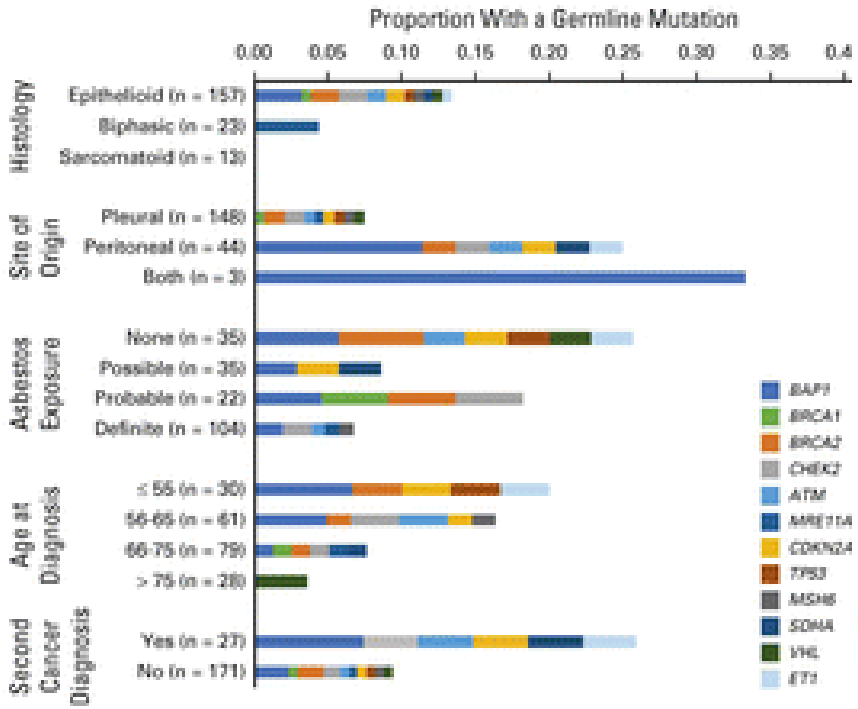


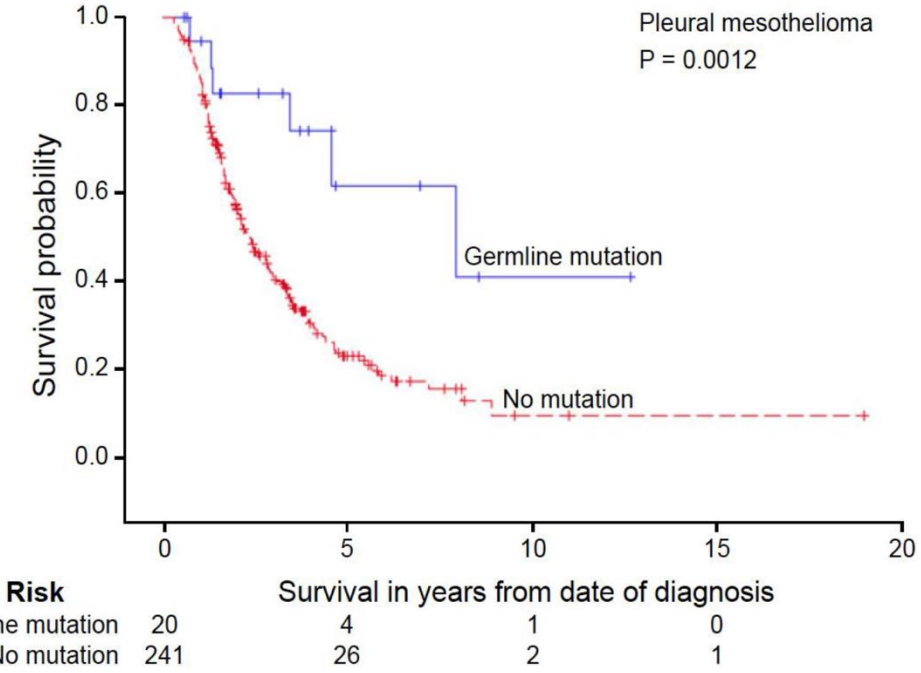


Dagogo-Jack JCO Precision Oncology 2022

Germline Mutation in Mesothelioma



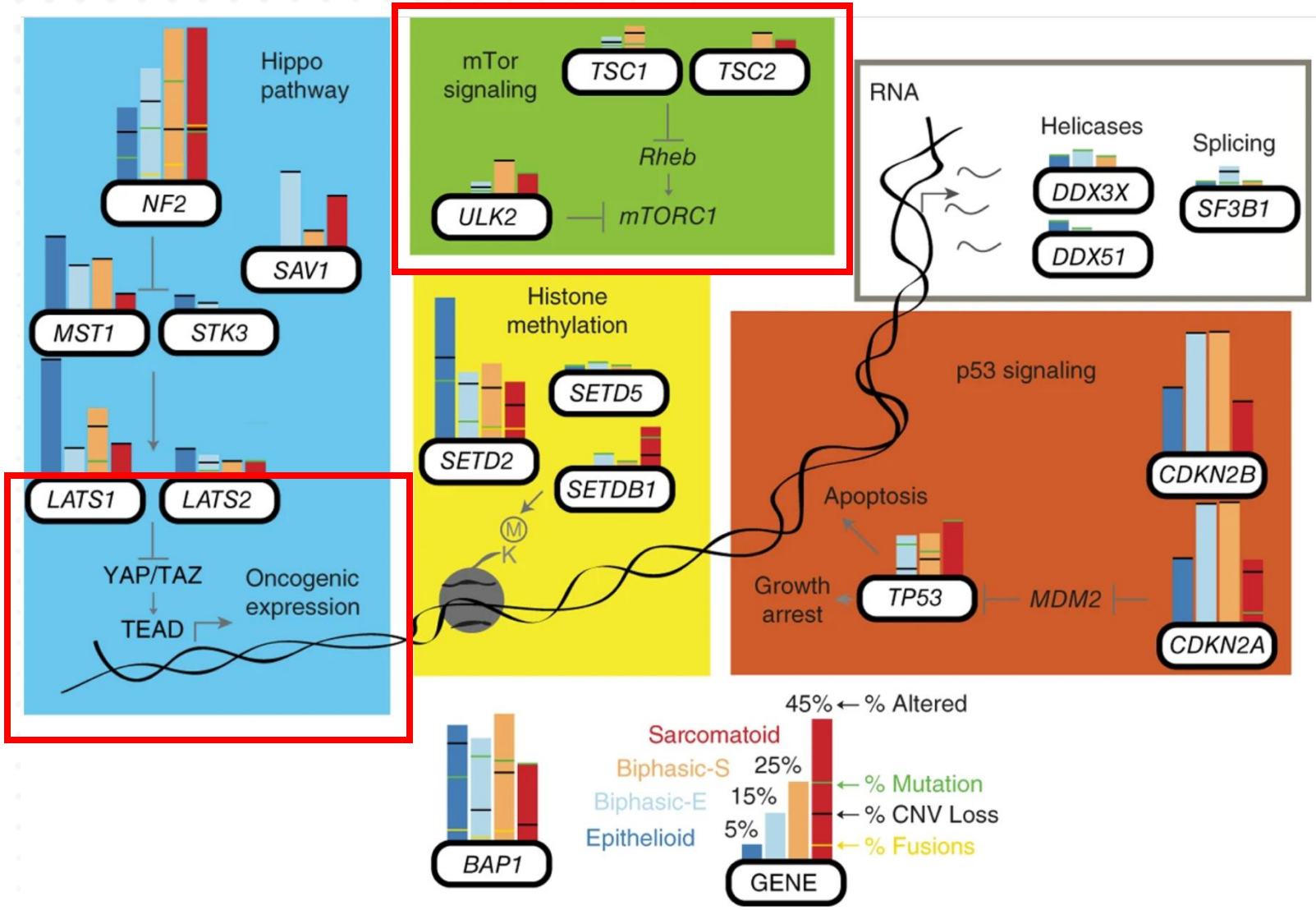


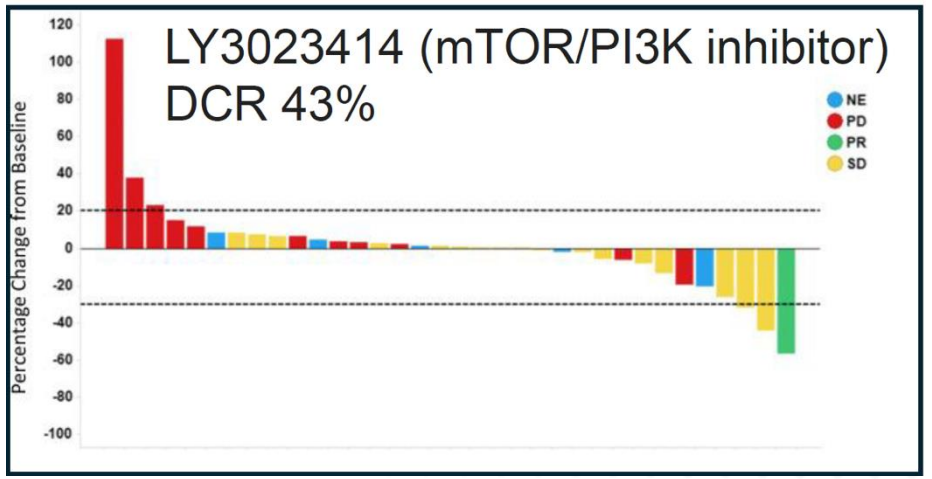


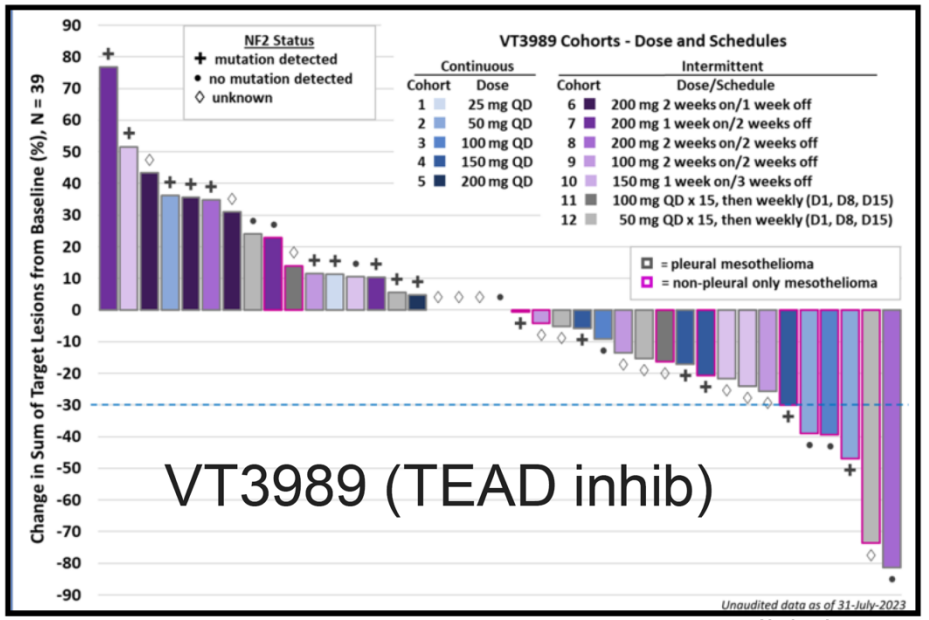
- 9-12% of pleural mesotheliomas harbor germline alterations in cancer susceptibility genes
  - genes include *BAP1*, *CHEK2, PALB2, BRCA2, MLH1, POT1, TP53, MSH3, BARD1, MRE11A*
- Germline *BAP1* mutations are seen in 1-2% of pleural mesotheliomas

Fennell ASCO Education Book 2023, PanouJCO 2018, Hassan PNAS 2019

Recurrently Altered Pathways in Mesothelioma







Bueno Nature Genetics 2016, Carbone CA: A Cancer Journal for Clinicians 2019, ZaudererInvest New Drugs 2021 , Kwiatkowski WCLC 2023

Conclusion and Future Directions

- Mesothelioma is characterized by low mutational burden but frequent structural variants.
- Frequent inactivation of tumor suppressor genes.
- Germline alterations in ~10% of tumors.
- Frequently altered pathways include major oncogenic signaling.

- **Successful therapeutic options should incorporate molecular alterations, histological characteristics and signaling pathways.**

SCLC- Leading causes of US cancer mortality

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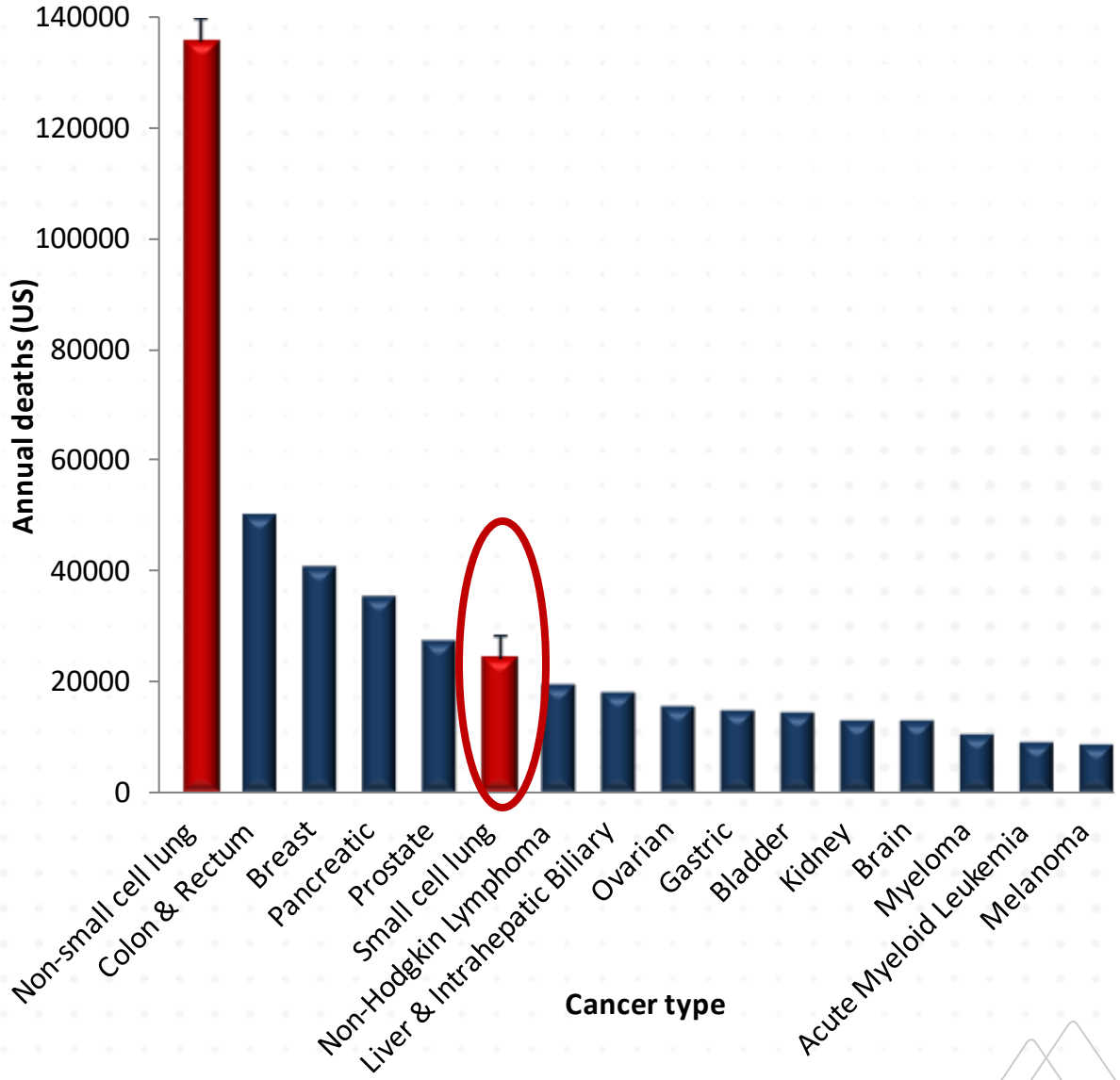
- SCLC accounts for approximately 15% of all lung cancer diagnoses worldwide
- High-grade neuroendocrine tumor
- Majority of patients metastatic at diagnosis

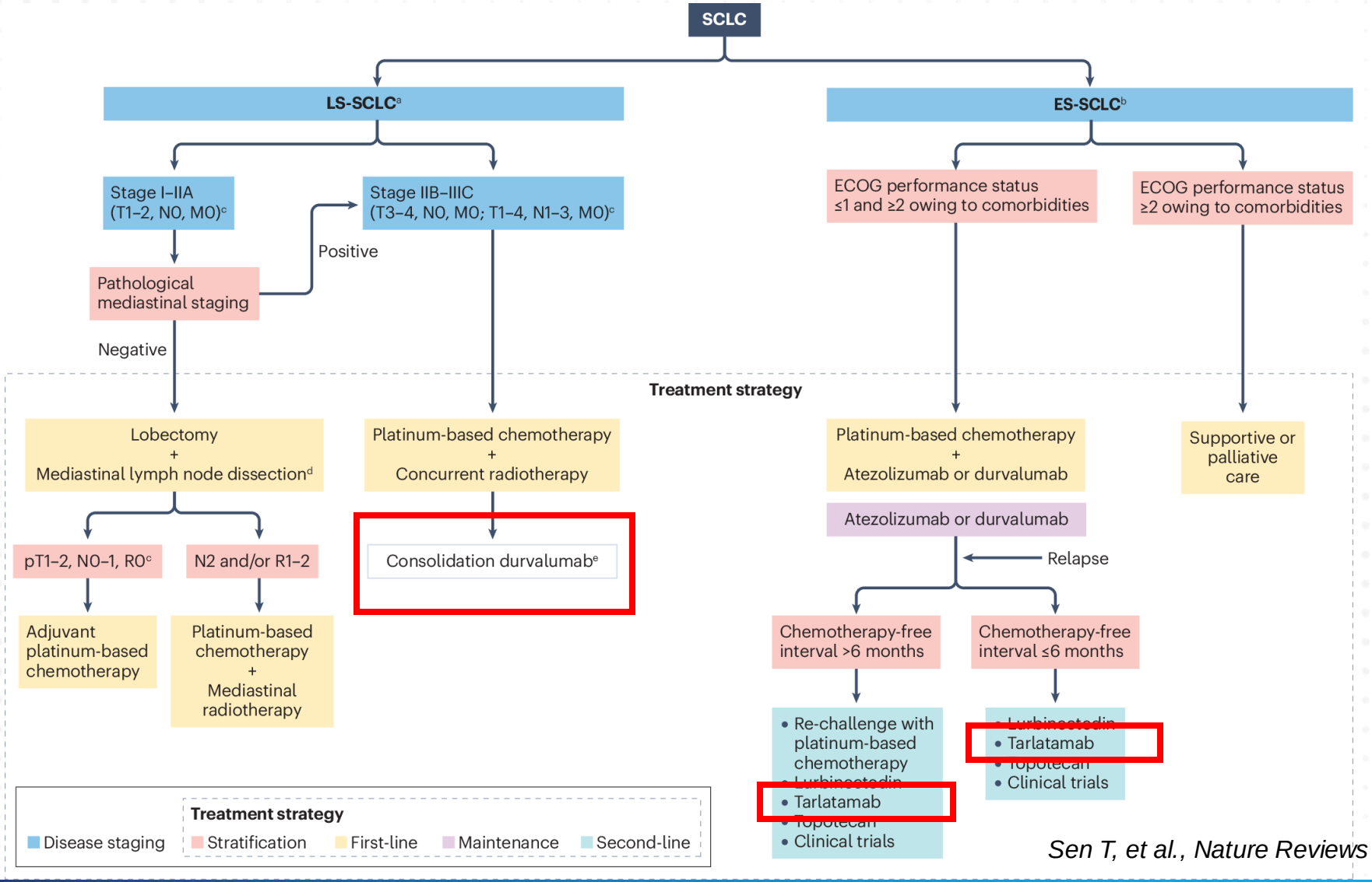
Far too many patients succumb to SCLC



Sen T, et al., Nature Reviews Clinical Oncology, 2024

Management of patients with small-cell lung cancer (SCLC) as of 2024

Promising changes but still limited progress



Sen T, et al., Nature Reviews Clinical Oncology, 2024

Consolidation Durvalumab after Concurrent ChemoXRT

ADRIATIC study design

Phase 3, randomized, double-blind, placebo-controlled, multicenter, international study (NCT03703297)

- Stage I–III LS-SCLC (stage I/II inoperable)
- WHO PS 0 or 1
- Had not progressed following cCRT*
- PCI* permitted before randomization

N=730

R‡

Durvalumab
1500 mg Q4W
N=264

Placebo
Q4W
N=266

Durvalumab + tremelimumab
D 1500 mg Q4W + T 75 mg Q4W for 4 doses, followed by D 1500 mg Q4W
N=200

cCRT components
- Four cycles of platinum and etoposide (three permitted†)
- RT: 60–66 Gy QD over 6 weeks or 45 Gy BID over 3 weeks
- RT must commence no later than end of cycle 2 of CT

Stratified by:
Disease stage (I/II vs III)
PCI (yes vs no)

Treatment until investigator-determined progression or intolerable toxicity, or for a **maximum of 24 months**

Dual primary endpoints:
- Durvalumab vs placebo
  - OS
  - PFS (by BICR, per RECIST v1.1)

Key secondary endpoints:
- Durvalumab + tremelimumab vs placebo
  - OS
  - PFS (by BICR, per RECIST v1.1)

Other secondary endpoints:
- OS/PFS landmarks
- Safety

*cCRT and PCI treatment, if received per local standard of care, must have been completed within 1–42 days prior to randomization.
†If disease control was achieved and no additional benefit was expected with an additional cycle of chemotherapy, in the opinion of the investigator.
‡The first 600 patients were randomized in a 1:1:1 ratio to the 3 treatment arms; subsequent patients were randomized 1:1 to either durvalumab or placebo.

BICR, blinded independent central review; BID, twice daily; CT, chemotherapy; D, durvalumab; PCI, prophylactic cranial irradiation; PS, performance status; Q4W, every 4 weeks; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors; RT, radiotherapy; T, tremelimumab; WHO, World Health Organization.

Consolidation Durvalumab Post-CCRT Improves PFS and OS

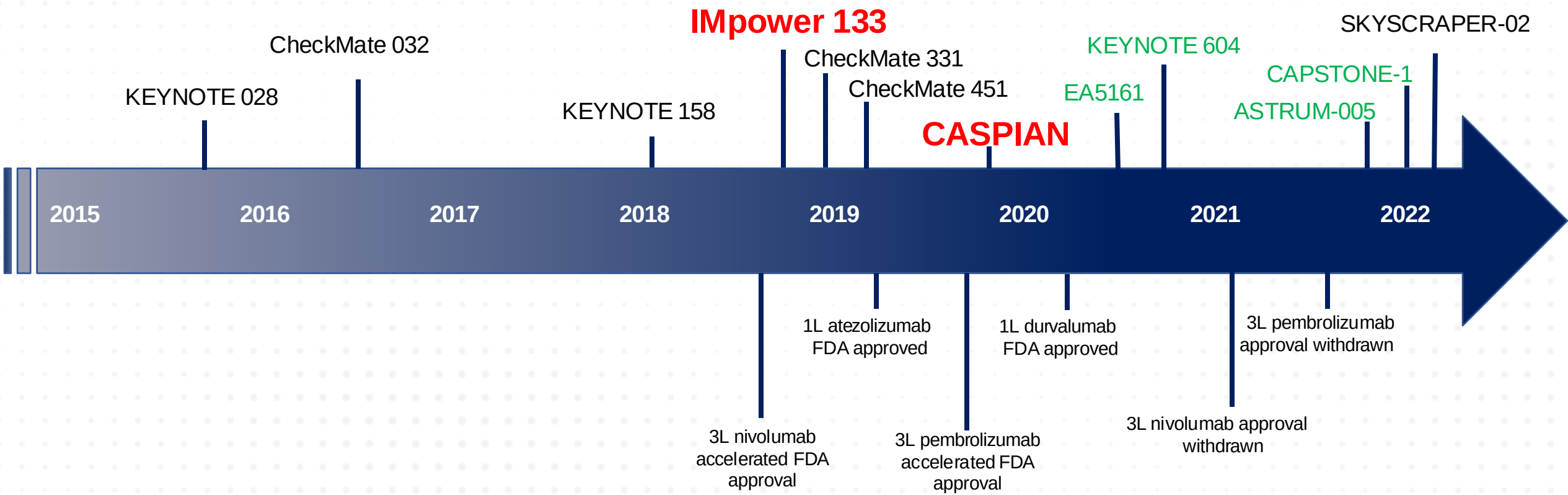
Imfinzi approved in the US as first and only immunotherapy regimen for patients with limited-stage small cell lung cancer

PUBLISHED
5 December 2024

Based on ADRIATIC Phase III trial results which showed a 27% reduction in the risk of death versus placebo

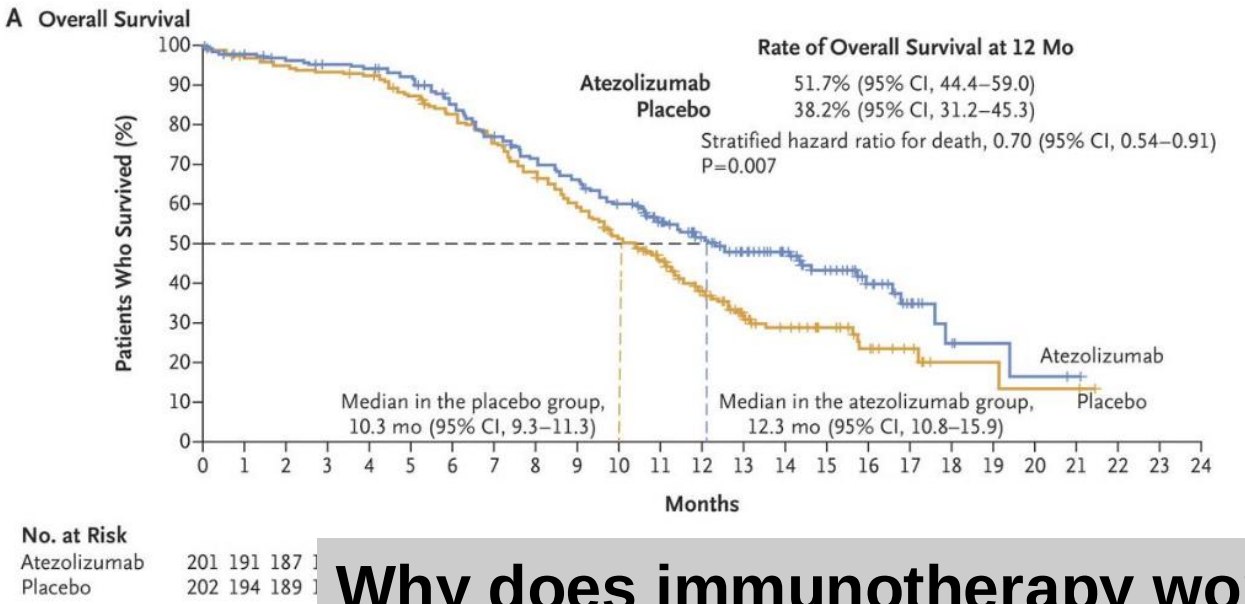
Cheng, Ying et al. The New England journal of medicine vol. 391,14 (2024).

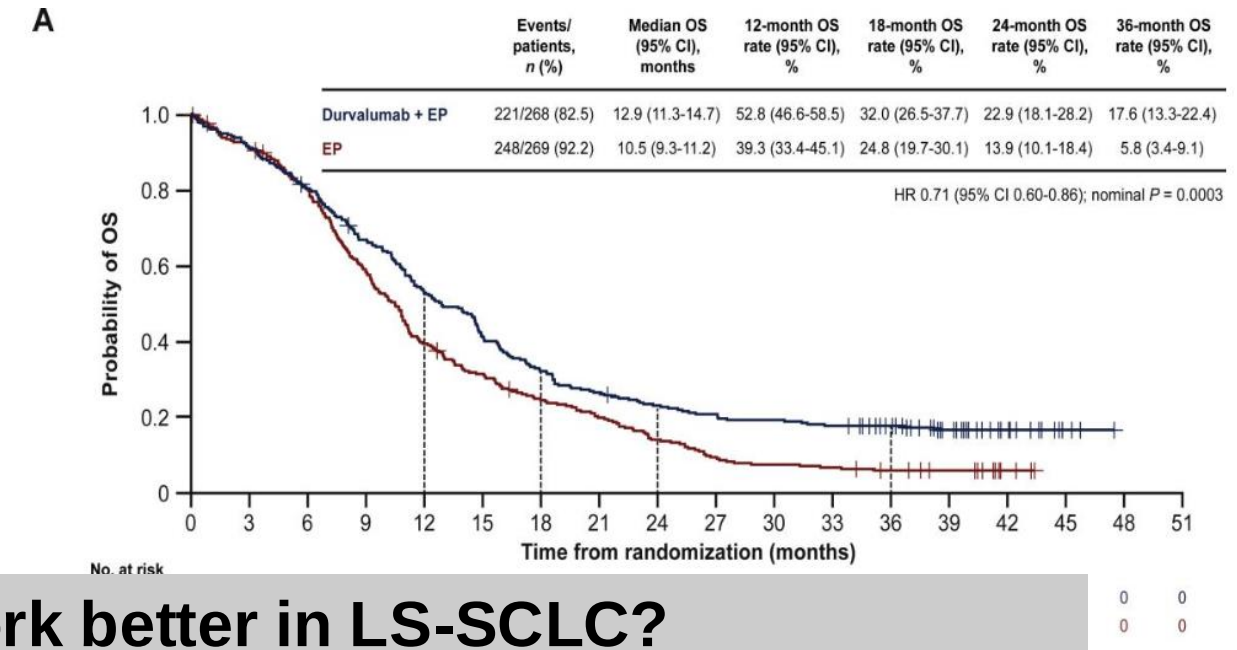
Checkpoint Inhibitors and SCLC



Adapted from Sen T, et al., Nature Reviews Clinical Oncology, 2024

Chemoimmunotherapy in ES-SCLC





Why does immunotherapy work better in LS-SCLC?

- Abscopal effect?
- Upregulation of MHC Class I?
- Enrichment for a particular NE subtype?
- Tumor-immune co-evolution…

Horn, et al. *NEJM* 2018; Paz-Ares, et al. *Lancet* 2019/ESMO Open 2022.

Lurbinectedin as a second line therapy for SCLC

- Selective inhibitor of transcription & TME
- **Phase 2 single-arm basket trial**
  - 105 pts with relapsed SCLC (2 or 3L)
  - 3.2 mg/m^2 dose IV q3weeks
  - 1° endpoint: Overall response rate = **35.2%**
  - Platinum-response: **45.0%** (S) vs **22.2%** (R)
- **Accelerated FDA approval (June 2020)**

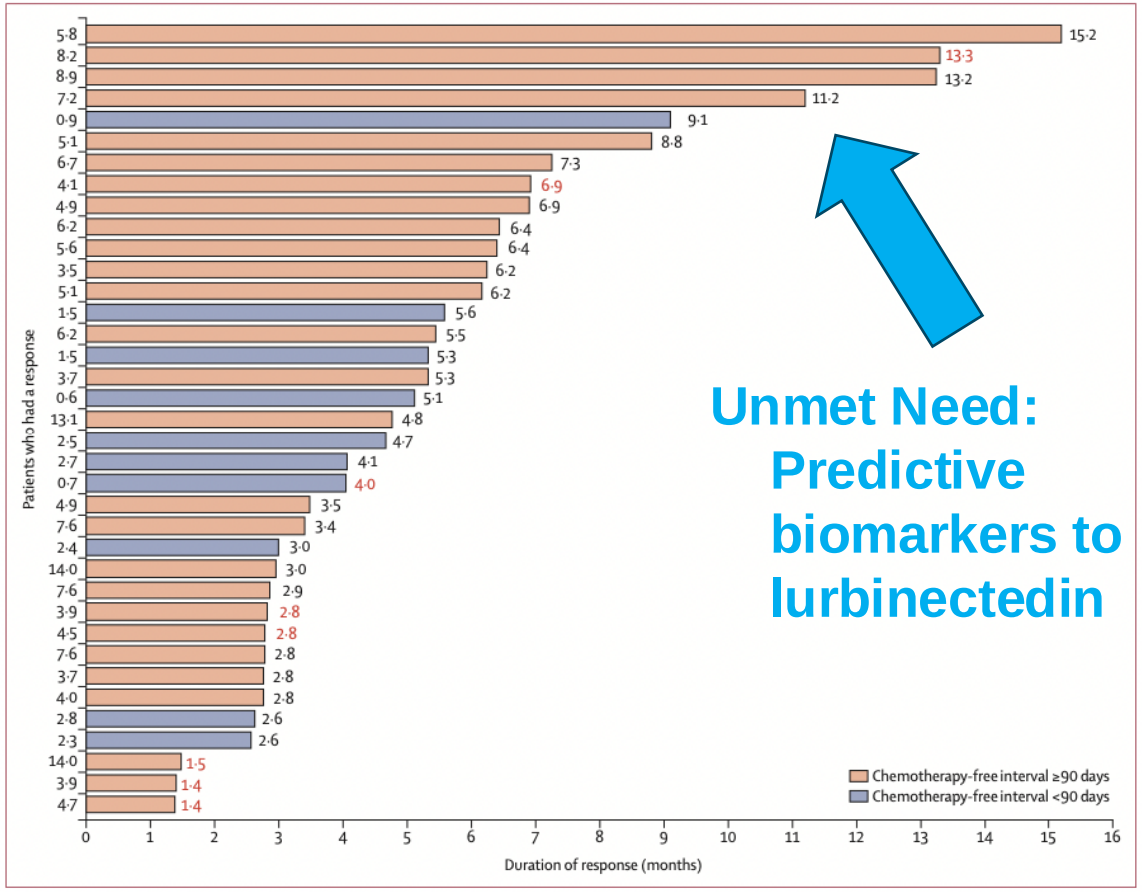


Figure 1: **Duration of response by investigator assessment**
Each bar represents a patient with SCLC who responded to treatment (n=37). Data shown on the left of each bar are the chemotherapy-free interval (months); data shown on the right of each bar are the duration of response (0 is the time of starting response). Data in red font refer to eight patients censored at the cutoff date: seven with no documented progression (under follow-up) and one who discontinued treatment due to an investigator's decision and then received further therapy. SCLC=small-cell lung cancer.

Trigo, et al. *Lancet Oncol.* 2020.

IMforte: Addition of Lurbinectedin to Atezolizumab Maintenance

Statistically Significant Overall Survival and Progression-Free Survival Results for lurbinectedin and Atezolizumab Combination in First-Line Maintenance Therapy for Extensive-Stage Small Cell Lung Cancer was announced

October 15, 2024

Lurbinectedin augments the anti-tumor effect of osimertinib in transformed SCLC

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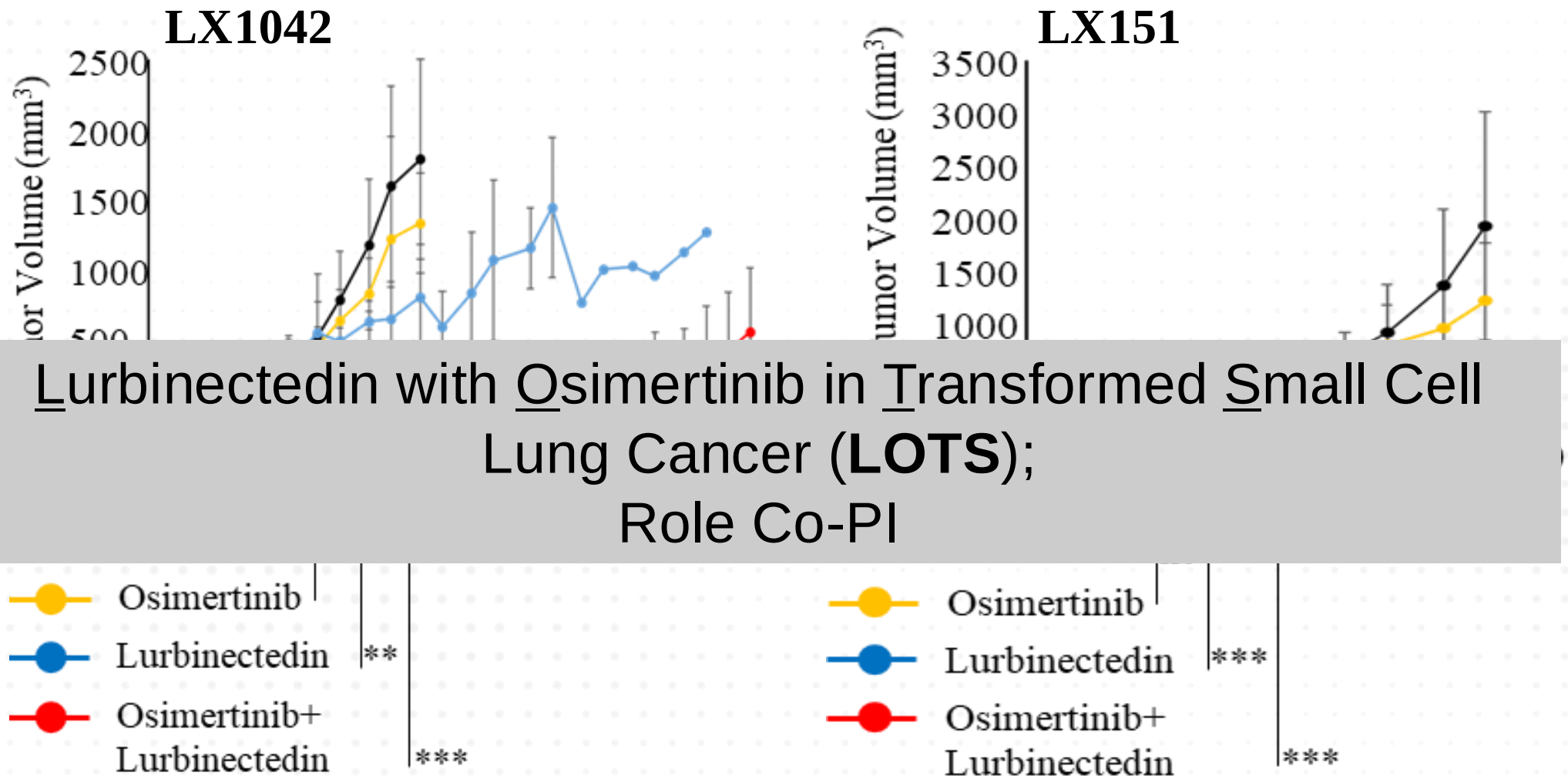
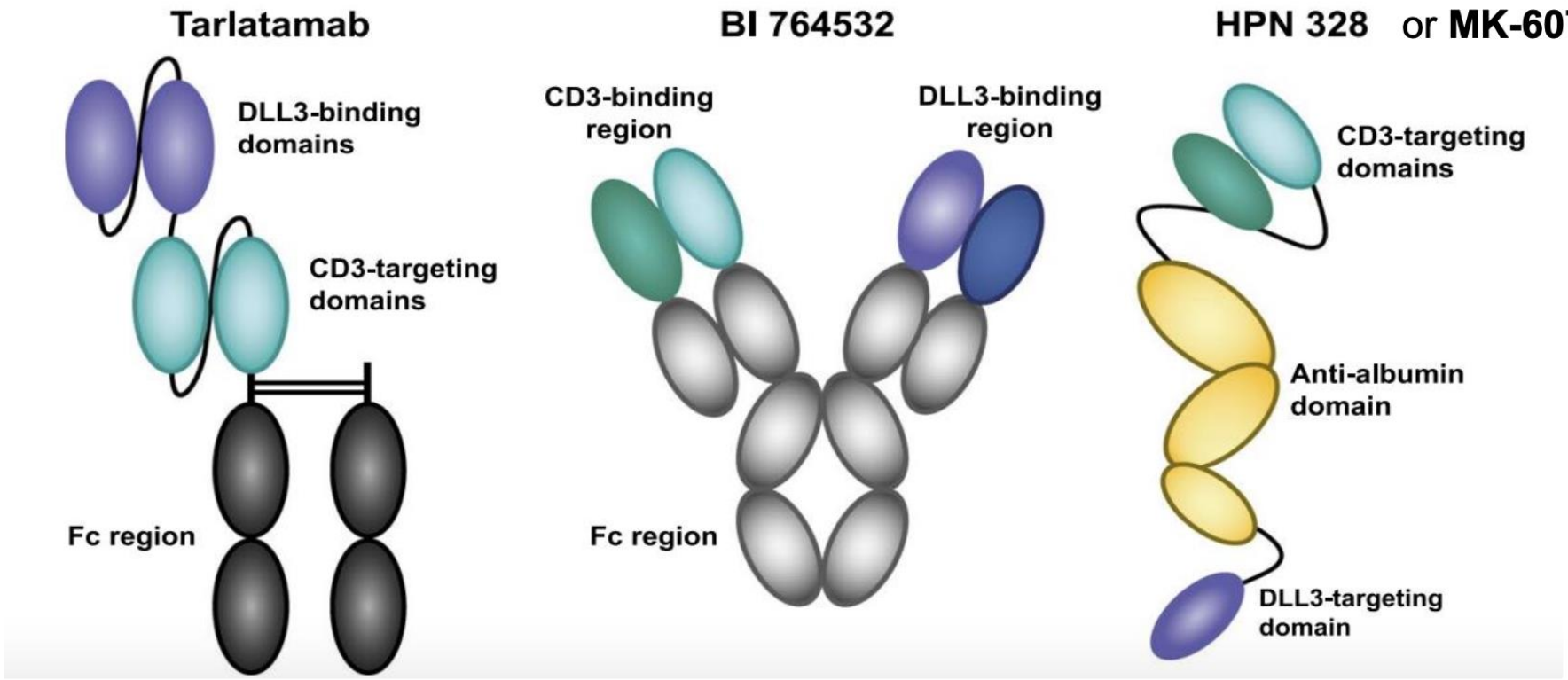


Lurbinectedin with Osimertinib in Transformed Small Cell Lung Cancer (**LOTS**);
Role Co-PI

Chakraborty et al., Clinical Cancer Research, 2023

DLL3 BiTE/TriTEs in ES-SCLC

Structure of DLL3-targeting TCEs in development



Rudin et al. Journal of Hematology & Oncology (2023) 16:66

Tarlatamab as a second line therapy for SCLC

FDA APPROVES TARLATAMAB-DLLE , THE FIRST AND ONLY T-CELL ENGAGER THERAPY FOR THE TREATMENT OF EXTENSIVE-STAGE SMALL CELL LUNG CANCER

Breakthrough DLL3-Targeting Therapy Regimen for a Major Solid Tumor

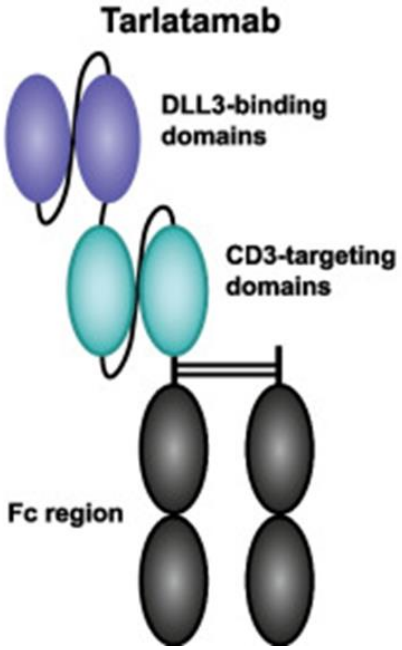
Tarlatamab-Dlle Demonstrated Impressive 40% Objective Response Rate, 9.7 Month Median Duration of Response and 14.3 Month Median Overall Survival in Pivotal DeLLphi-301 Study

Ahn, et al. *NEJM*. 2023.

Tarlatamab Addition to 1L ChemoIO Maintenance

DeLLphi-303: Tarlatamab with PD-L1 Inhibitor as 1LM

DeLLphi 303



- Phase 1b, multicenter, open-label study (NCT05361395)

1L Chemo-IO

Platinum-etoposide + PD-L1 inhibitor

(4-6 cycles)

Enrollment

Key Inclusion Criteria

- No disease progression following 4-6 cycles of platinum-etoposide + PD-L1 inhibitor
- Eligible if no access to 1L PD-L1 inhibitor
- Prior treatment for LS-SCLC permitted
- ECOG PS 0-1
- Treated and asymptomatic brain metastases allowed
- DLL3 positivity not required

1L Maintenance

Non-randomized

Switching to different PD-L1 inhibitor permitted

- **Tarlatamab (10 mg IV Q2W)* + Atezolizumab (1680 mg IV Q4W)**
- **Tarlatamab (10 mg IV Q2W)* + Durvalumab (1500 mg IV Q4W)**

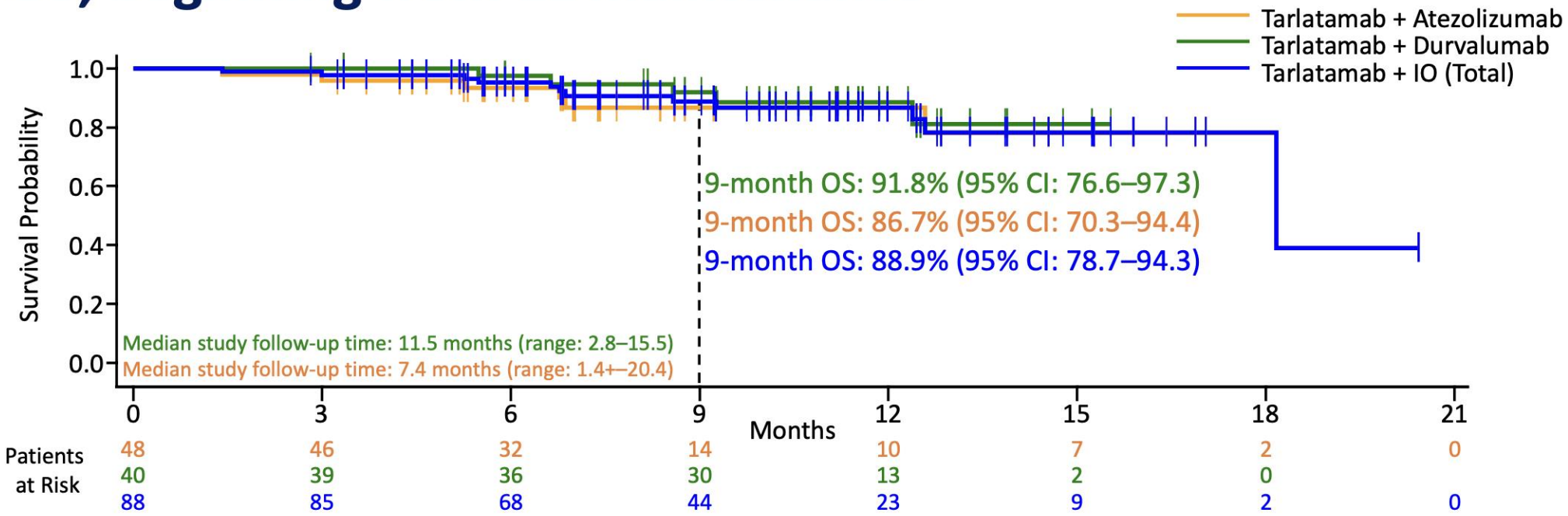
- Must initiate C1D1 of maintenance phase within 8 weeks of the start of the last cycle of 1L chemo-immunotherapy
- Median follow-up time (N = 88): 10.0 months (range: 1.4+–20.4)

Primary Endpoints†: Dose-limiting toxicities, treatment-emergent / treatment-related adverse events (TEAEs, TRAEs)
Secondary Endpoints‡: Disease control and PFS per local RECIST 1.1 assessment, OS

Data cutoff was May 31, 2024. *Tarlatamab was initiated with step dosing: 1 mg on Day 1, followed by 10 mg on Days 8, 15, and Q2W thereafter. †Also includes vital signs, electrocardiograms, and clinical laboratory tests. ‡Also includes objective response, duration of response, and serum concentrations of tarlatamab. **+,** censored; **1L,** first-line; **1LM,** first-line maintenance; **C1D1,** cycle 1 day 1; **chemo,** chemotherapy; **DLL3,** delta-like ligand 3; **ECOG PS,** Eastern Cooperative Oncology Group performance status; **IO,** immuno-oncology agent; **IV**, intravenous; **LS**, limited-stage; **OS,** overall survival; **PD-L1**, programmed death-ligand 1; **Q2W**, once every two weeks; **Q4W**, once every four weeks; **RECIST,** response evaluation criteria in solid tumors; **SCLC**, small cell lung cancer.

Tarlatamab Addition to 1L ChemoIO Maintenance

OS, beginning from 1L maintenance



After a median time from 1L chemoimmunotherapy to 1LM of 3.6 months, tarlatamab with a PD-L1 inhibitor as 1LM showed a 9-month OS of 89%.

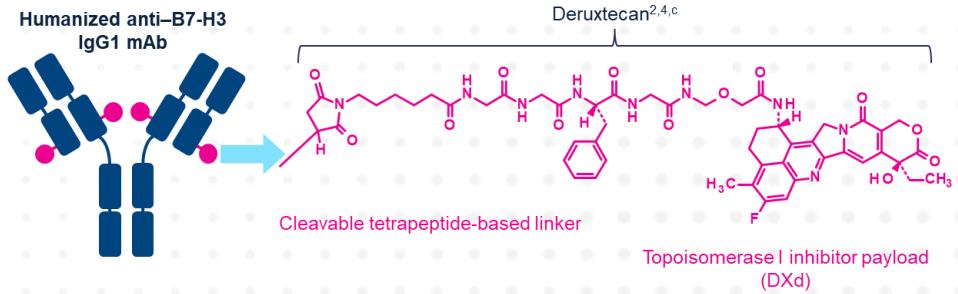
+, censored; **1L,** first-line; **1LM,** first-line maintenance; **CI,** confidence interval; **IO,** immuno-oncology agent; **OS,** overall survival; **PD-L1,** programmed death-ligand 1.

Antibody Drug Conjugates in ES-SCLC

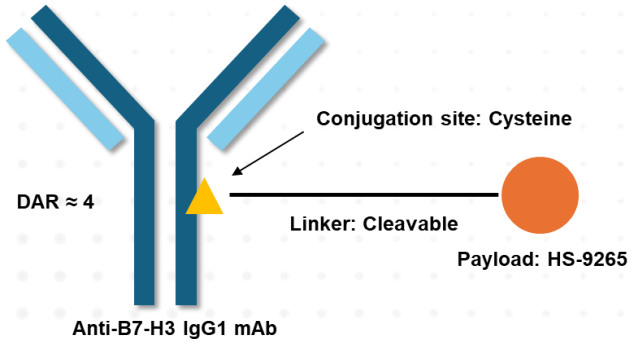
Target	Drug	Phase	NCT number
B7-H3	Ifinatamab deruxtecan	III	NCT06203210
		I/II	NCT04145622
	MGC018	II	NCT06227546
	HS-20093	I	NCT05276609
B7-H3	Mirzotamab clezutoclax plus paclitaxel or docetaxel	I	NCT03595059
TROP2, ATR	Sacituzumab govitecan plus berzosertib	I/II	NCT04826341
TROP2	SKB264	I/II	NCT04152499
	Dapotomab deruxtecan	I	NCT03401385
SEZ6	ABBV-706, cisplatin, carboplatin and budigalimab	I	NCT05599984
	ABBV-011 ± budigalimab	I	NCT03639194

Sen T, et al., Nature Reviews Clinical Oncology, 2024

Ifinatamab deruxtecan (I-DXd)



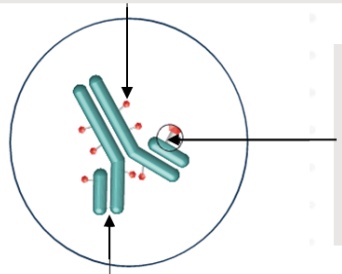
Sacituzumab govitecan



- High permeability
- High potency of tumor cell killing
- High clearance in vivo
- Good bystander effect

HS-20093 (B7-H3-directed ADC)

SN-38 payload
- SN-38 is more potent than the parent compound, irinotecan (Topo-1 inhibitor)
- SN-38 is rapidly internalized and efficiently released to the tumor with minimized effect on healthy tissues



Linker for SN-38
- pH-sensitive, hydrolyzable linker for SN-38 release in targeted tumor cells and tumor microenvironment, allowing bystander effect
- High drug-to-antibody ratio (7.6:1)[4]

Humanized anti–Trop-2 antibody
- Binds with high (K_D = 0.3 nM) affinity to Trop-2, an epithelial antigen expressed on many solid tumors[5]

Ifinatamab Deruxtecan (I-DXd) in ES-SCLC

Phase 2 IDeate-Lung01 study (NCT05280470)

Patient eligibility:

- Histologically or cytologically documented ES-SCLC
- Age ≥18 years[a]
- ≥1 prior line of PBC and ≤3 prior lines of systemic therapy
- Radiologically documented PD on or after most recent prior systemic therapy
- ECOG PS 0–1
- ≥1 measurable lesion per RECIST 1.1[b]
- Patients with asymptomatic brain metastases (untreated or previously treated) are eligible

R 1:1

Arm 1: I-DXd 8 mg/kg Q3W (n≈40)

Arm 2: I-DXd 12 mg/kg Q3W (n≈40)

Extended enrollment at RP3D (n≈70 3L+)

Stratification:

- 2L CTFI <90 days, 2L CTFI ≥90 days, 3L or 4L
- Prior anti–PD-(L)1 treatment (yes or no)

Primary endpoint:

- ORR by BICR[c]

Secondary endpoints:

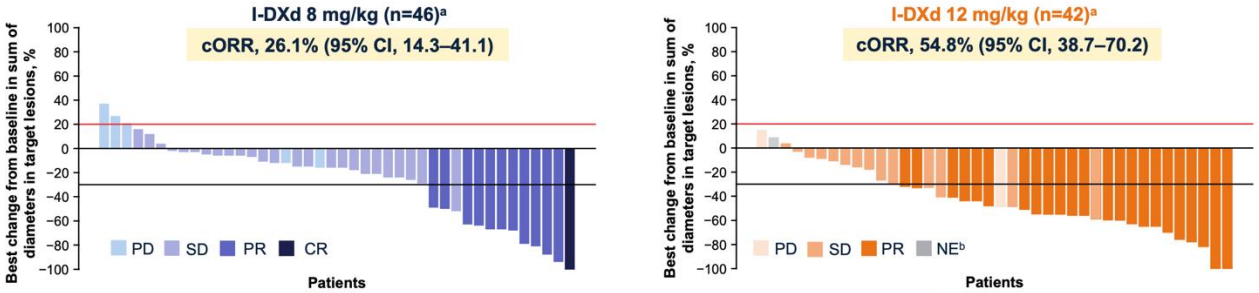
- DOR by BICR and inv[c]
- PFS by BICR and inv[c]
- OS
- DCR[c]
- TTR by BICR and inv[c]
- ORR by inv[c]
- Safety
- Pharmacokinetics
- Immmunogenicity

Exploratory analysis:

- Intracranial ORR by BICR[d]

[a]Or local legal age of consent. [b]Patients must also have ≥1 lesion that has not been irradiated and is amenable to biopsy. [c]Per RECIST 1.1. [d]Per CNS RECIST.
2L, second-line; 3L+, third-line and beyond; 4L, fourth-line; BICR, blinded independent central review; CTFI, chemotherapy treatment-free interval; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; ES-SCLC, extensive-stage small cell lung cancer; inv, investigator; ORR, objective response rate; OS, overall survival; PBC, platinum-based chemotherapy; PD, progressive disease; PD-(L)1; programmed death (ligand) 1; PFS, progression-free survival; Q3W, every 3 weeks; R, randomization; RECIST 1.1, Response Evaluation Criteria in Solid Tumors, version 1.1; RP3D, recommended Phase 3 dose; TTR, time to response.

I-DXd has promising antitumor activity; patients treated with 12 mg/kg had a higher ORR than those treated with 8 mg/kg



Confirmed response by BICR[c]	I-DXd 8 mg/kg n=46	I-DXd 12 mg/kg n=42
ORR, % (95% CI)	26.1 (14.3–41.1)	54.8 (38.7–70.2)
CR, n (%)	1 (2.2)	0
PR, n (%)	11 (23.9)	23 (54.8)
DCR, % (95% CI)	80.4 (66.1–90.6)	90.5 (77.4–97.3)

Data cutoff: April 25, 2024. The median follow-up for 8-mg/kg and 12-mg/kg cohorts was 14.6 months (range, 0.6–17.0) and 15.3 months (range, 0.8–20.3) respectively.
[a]Only patients with measurable disease at baseline and ≥1 post-baseline tumor scan were included in the waterfall plot: in the I-DXd 8-mg/kg cohort, n=42; 2 patients died and 2 patients withdrew consent before the Week 6 assessment; in the 12-mg/kg cohort, n=40; 1 patient died before the Week 6 assessment and 1 patient did not have target lesions at baseline. [b]This patient has a BOR of NE because the only post-baseline tumor scan was conducted outside the designated time window; the timepoint response was SD. [c]Per RECIST 1.1.
BICR, blinded independent central review; BOR, best overall response; cORR, confirmed ORR; CR, complete response; DCR, disease control rate; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST 1.1, Response Evaluation Criteria in Solid Tumors, version 1.1; SD, stable disease.

- I-DXddemonstrated promising efficacy in patients with pretreated ES-SCLC; 12 mg/kg had improved efficacy compared with the 8-mg/kg dose:
  - ORR was 54.8% vs 26.1%
  - Median PFS was 5.5 months vs 4.2 months
  - Median OS was 11.8 months vs 9.4 months
- The observed safety profile was generally manageable, with a higher frequency of TEAEs in the 12-mg/kg cohort than in the 8-mg/kg cohort; the safety profile was consistent with previous reports.
- I-DXd12 mg/kg has been selected as the RP3D for further clinical development, including in an ongoing Phase 3study in patients with relapsed SCLC following only 1 prior line of therapy (IDeate-Lung02; NCT06203210)

Sacituzumab Govitecan as Second-Line Treatment in Patients With Extensive-Stage Small Cell Lung Cancer

2024 World Conference on Lung Cancer | SEPTEMBER 7-10, 2024 SAN DIEGO, CA USA #WCLC24 wclc2024.iaslc.org

TROPiCS-03 Study Design

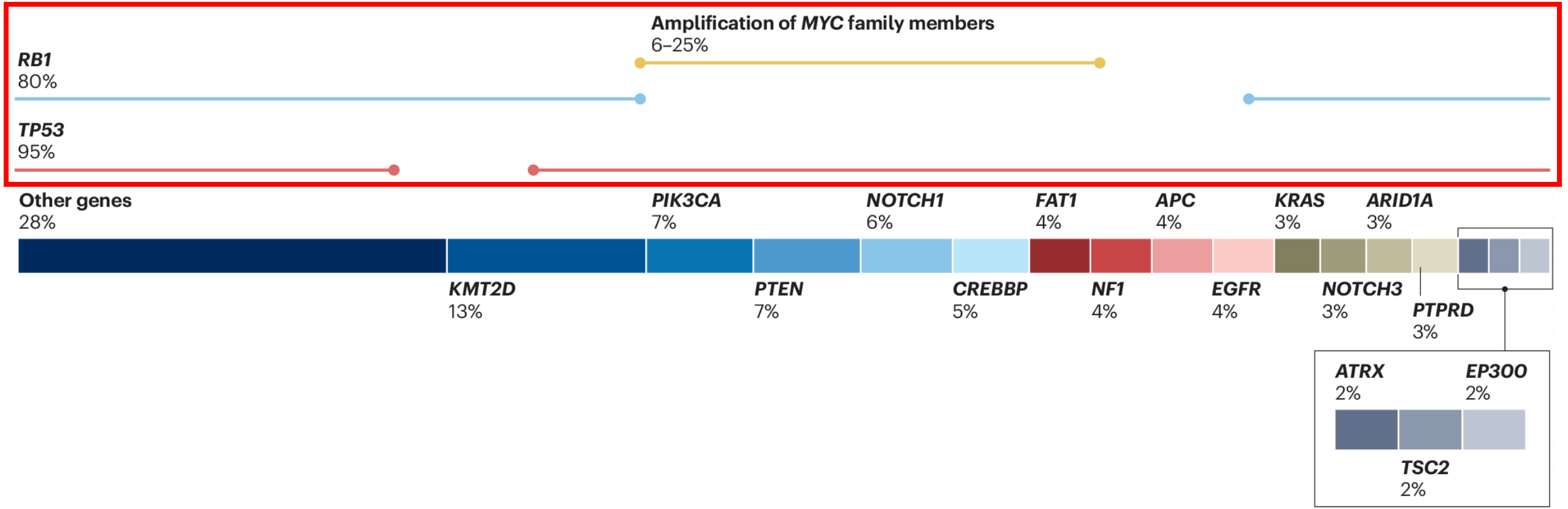
Efficacy Analyses

December 17, 2024

U.S. FDA Grants Breakthrough Therapy Designation to [redacted] sacituzumab govitecan-hziy for Second-Line Treatment of Extensive-Stage Small Cell Lung Cancer

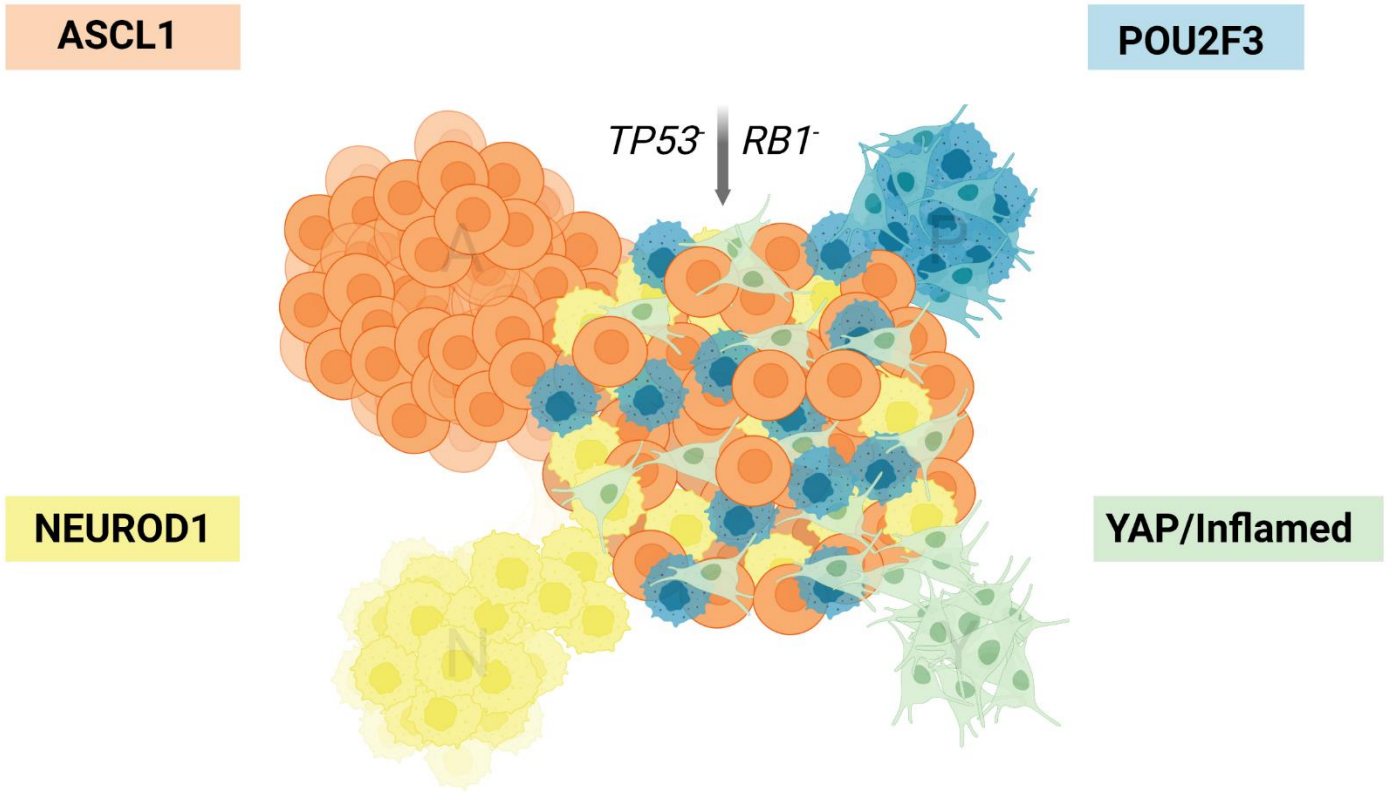
- SG showed promising efficacy as a second-line treatment for patients with ES-SCLC
  - —ORR was 41.9% (95% CI, 27.0–57.9); DOR rate at 6 months was 48.2% (95% CI, 23.9–68.9)
  - —Median PFS was 4.4 months (95% CI, 3.81–6.11) and median OS was 13.6 months (95% CI, 6.57–14.78)
- SG demonstrated antitumor activity in patients with both platinum-resistant (ORR, 35.0%; 95% CI, 15.4–59.2) and platinum-sensitive (ORR, 47.8%; 95% CI, 26.8–69.4) disease

SCLC genetics:
major genomic aberrations; LOF mutations



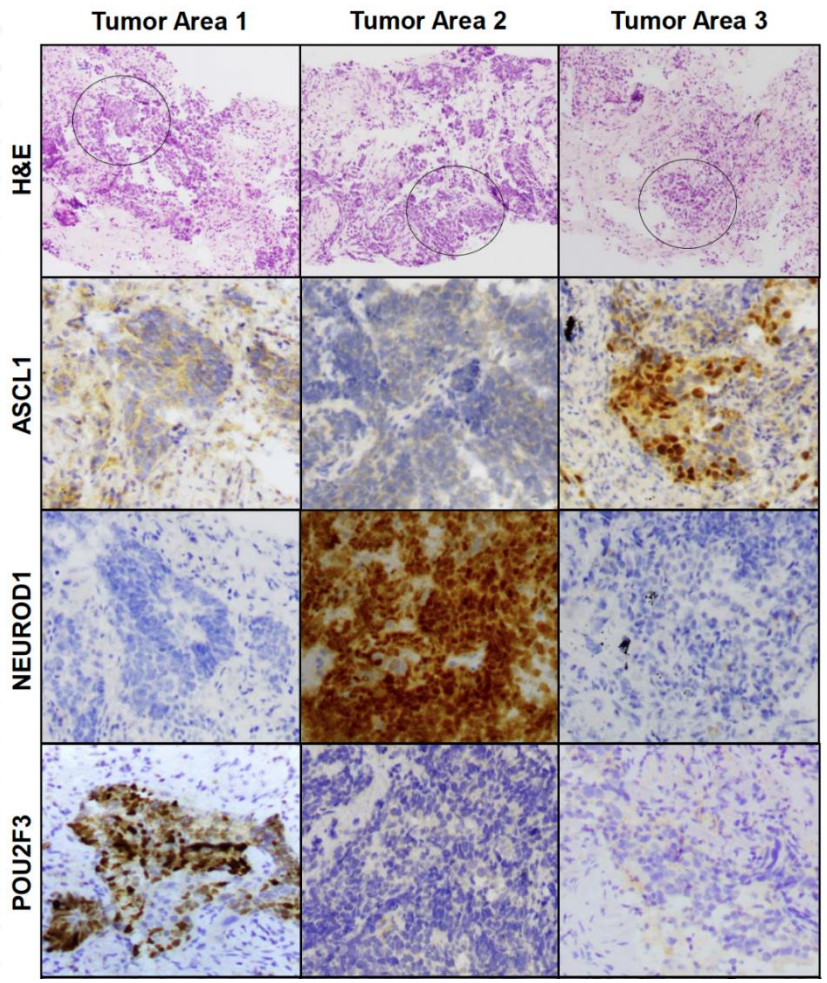
Sen T, et al., Nature Reviews Clinical Oncology, 2024

Biological significance of SCLC subtypes

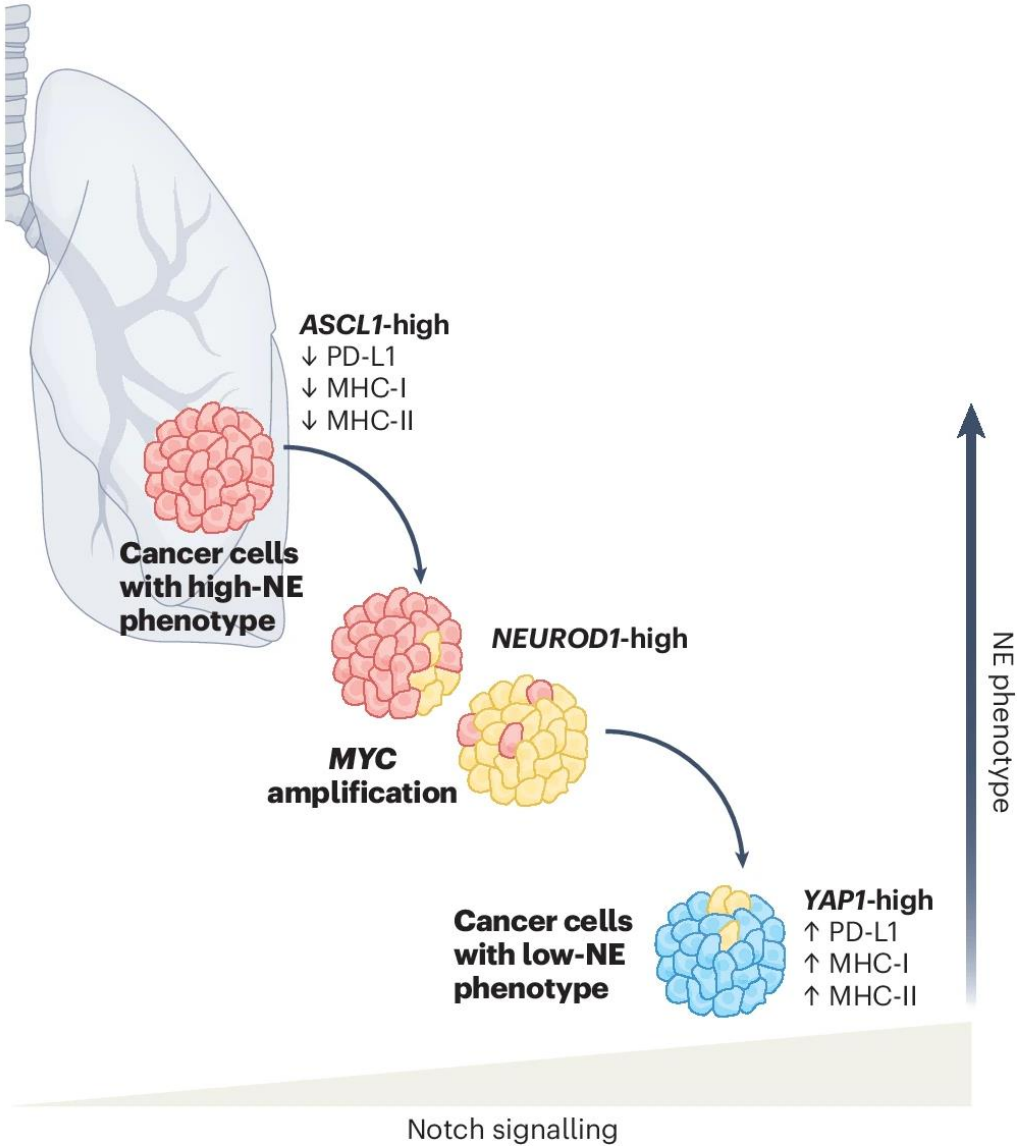


Modified from Sen T, et al., Nature Reviews Clinical Oncology, 2024

SCLC subtypes are heterogeneous and plastic



Baine et al., JTO 2020

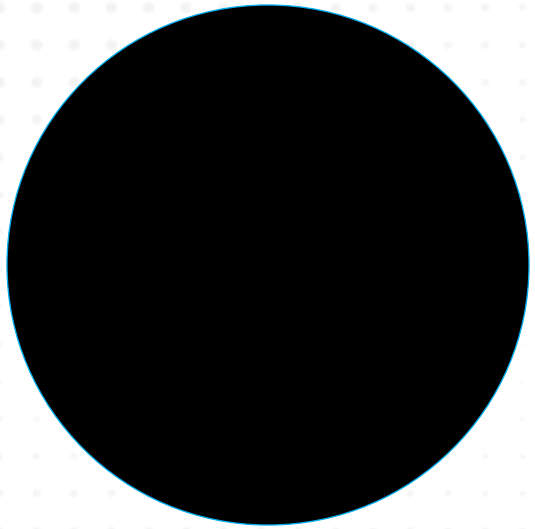


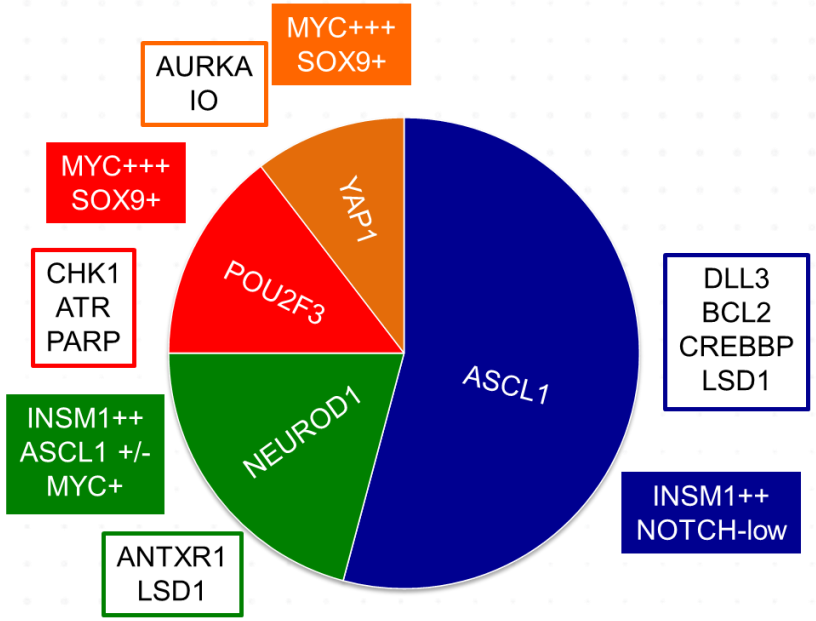
Sen et al., Nature Reviews Clinical Oncology, 2024

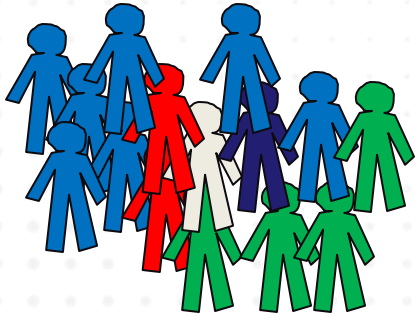
174 SCLC cases

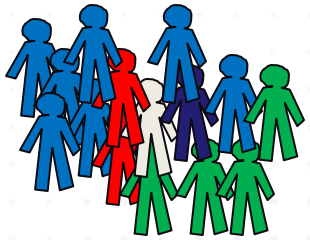
- Expression more heterogeneous in models
  - High prevalence of ASCL1/NEUROD1 co-expression

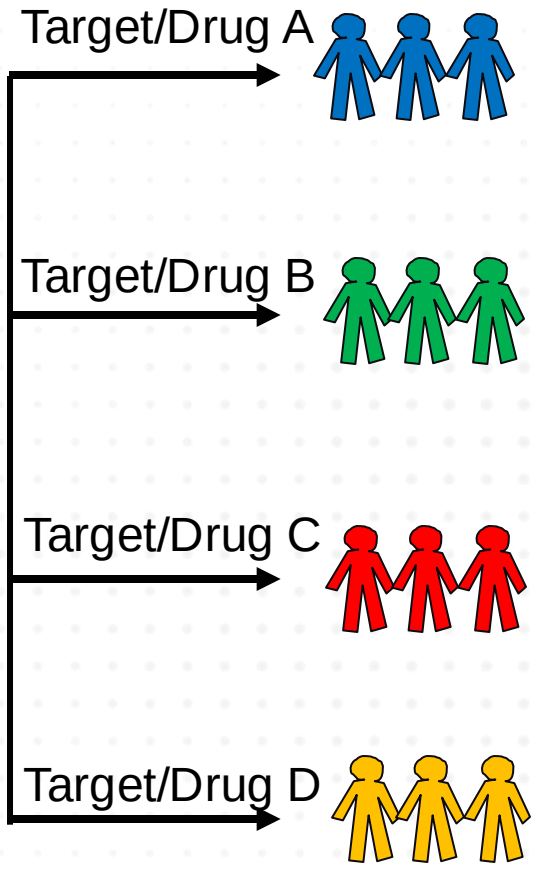
Evolving landscape of biomarkers in SCLC











Profiling of CM032 cohort reveals unanticipated promise (CD8/MHC-I as a biomarker)

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Clinical Benefit From Immunotherapy in Patients With SCLC Is Associated With Tumor Capacity for Antigen Presentation

Charles M. Rudin, MD, PhD • David Balli, PhD • W. Victoria Lai, MD • Allison L. Richards, PhD • Evelyn Nguyen, BA • Jacklynn V. Egger, BS • Noura J. Choudhury, MD • Triparna Sen, PhD • Andrew Chow, MD, PhD • John T. Poirier, PhD • William J. Geese, PhD • Matthew D. Hellmann, MD • Ann Forslund, PhD • Show less

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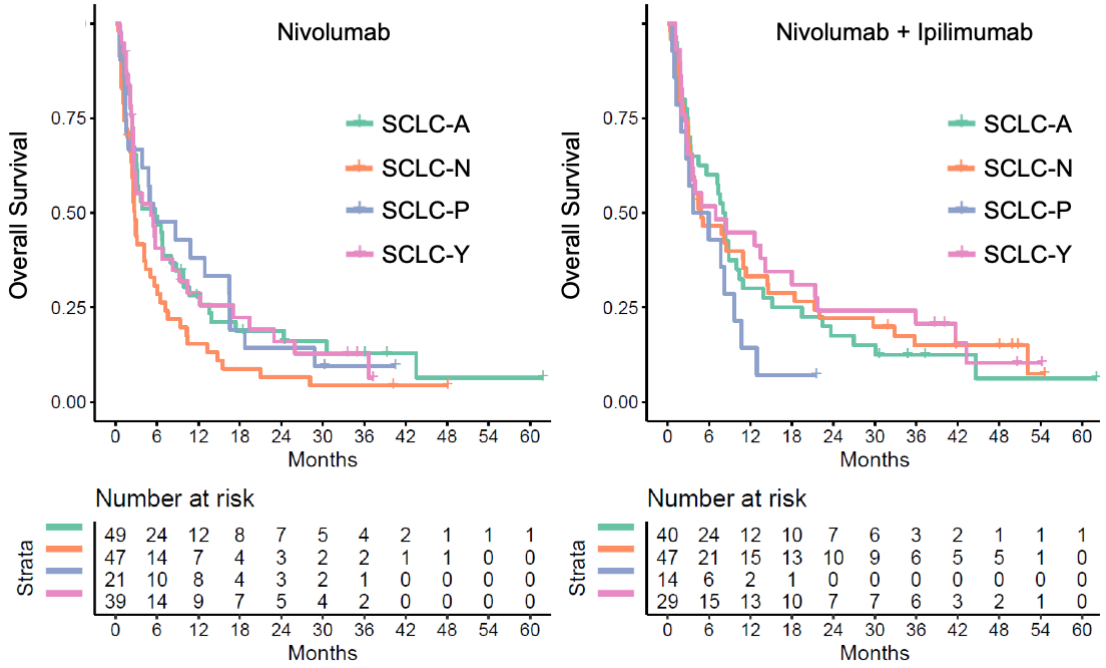
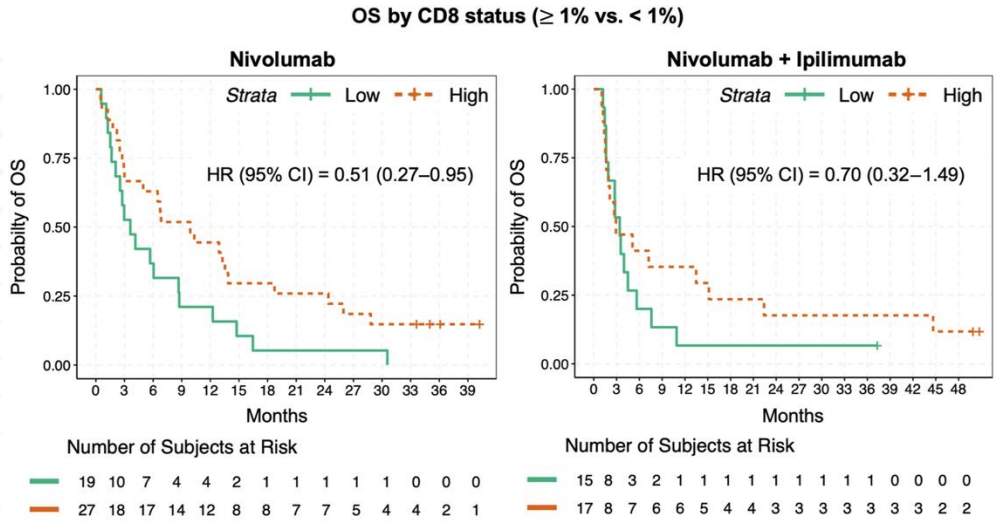
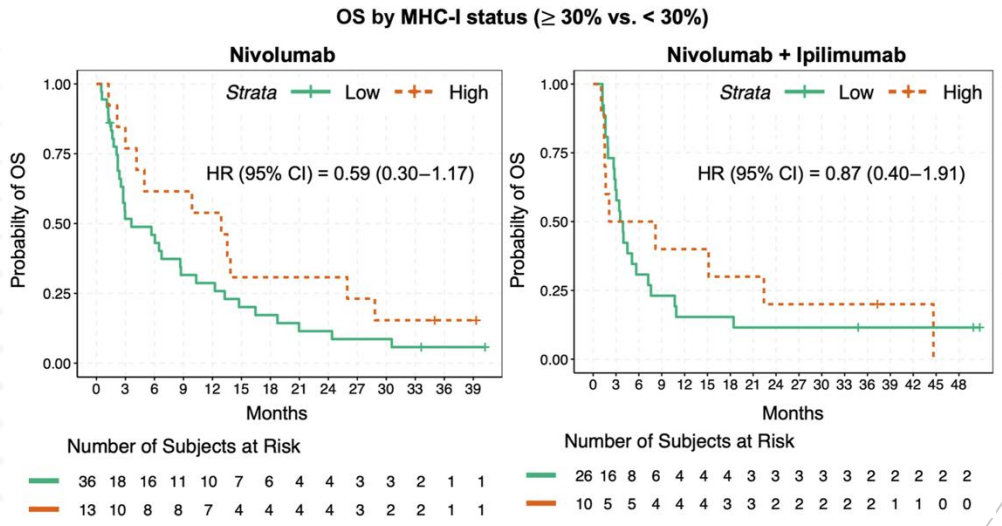
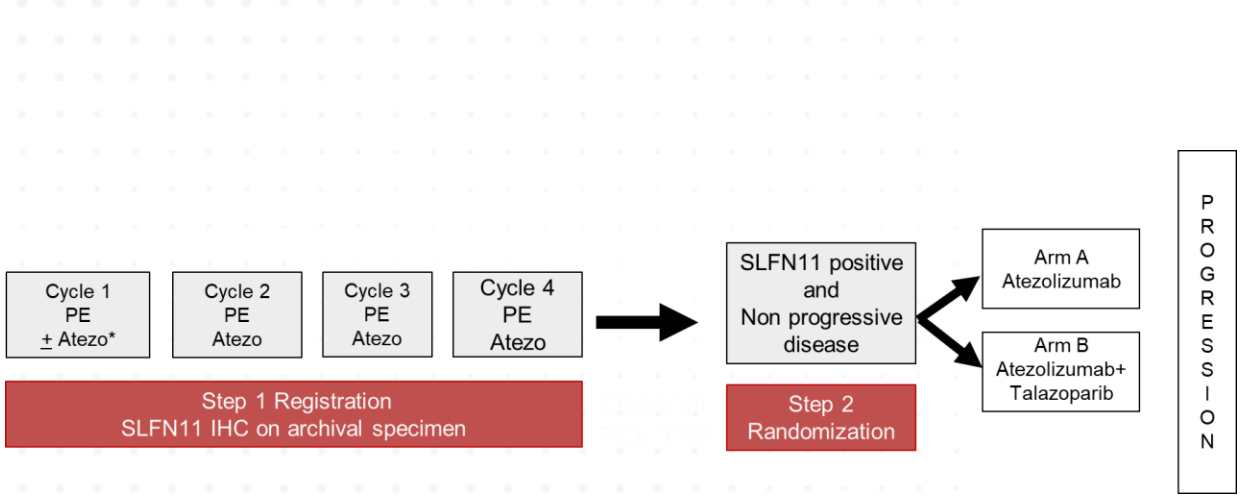
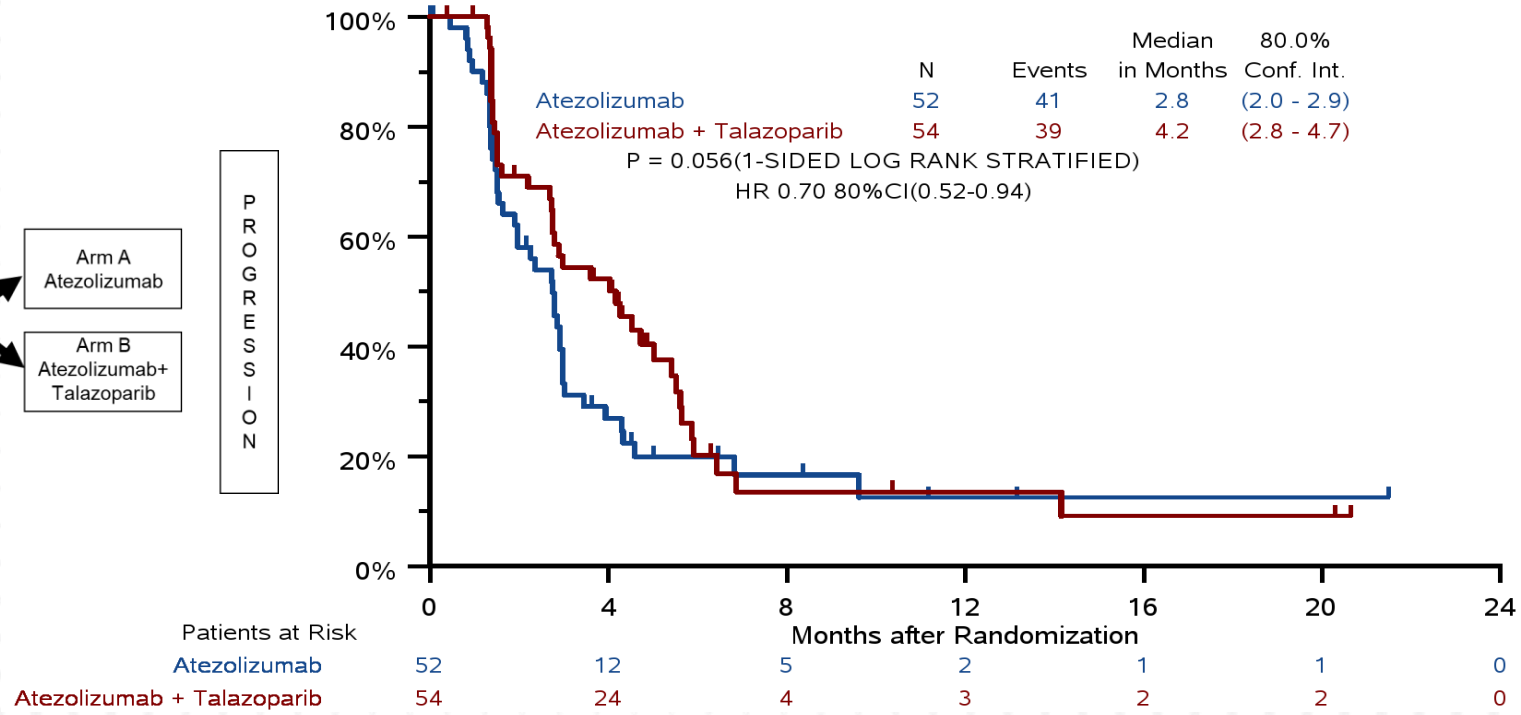






S1929: Phase II Study of Maintenance Atezolizumab Versus Atezolizumab in Combination with Talazoparib in Patients with SLFN11 Positive Extensive Stage Small Cell Lung Cancer (ES-SCLC) NCT04334941





Maintenance Atezo+Tal improved PFS in SLFN11-positive patients with ES-SCLC.

Karim et al., JTO, 2024

Conclusions and Next Steps

THE SEN LAB

- There is a cohort of SCLC patients, small but real, who have durable benefit from immunotherapy
  - Strategies to improve the response to immunotherapy
  - Defining determinants of durable benefit

Acknowledgments

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Patients and their families!