

1L EXTENSIVE-STAGE SCLC

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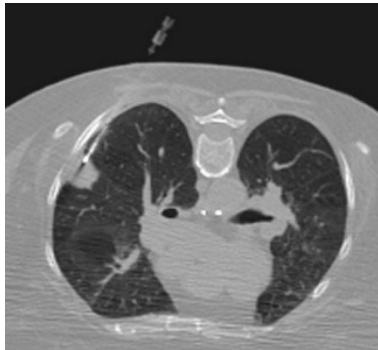




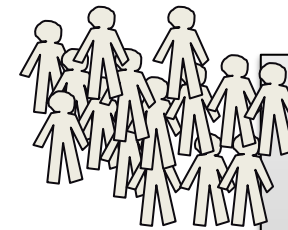
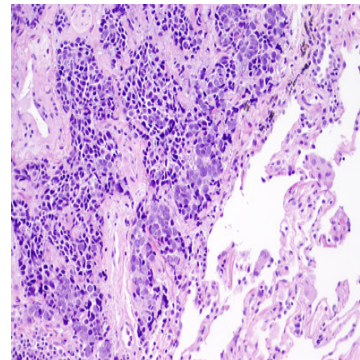
Adapted from *Carpool Karaoke* (courtesy of Simon Heeke)

Urgent need for **personalized, biomarker-driven** therapies for Small Cell Lung Cancer (SCLC)

Tumor Biopsy

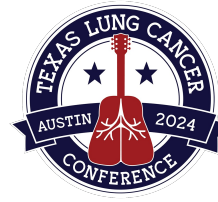


SCLC Diagnosis



“One-size-fits-all”
Standard Treatment
(no biomarkers)

Chemo-Immunotherapy is the standard for 1L ES-SCLC

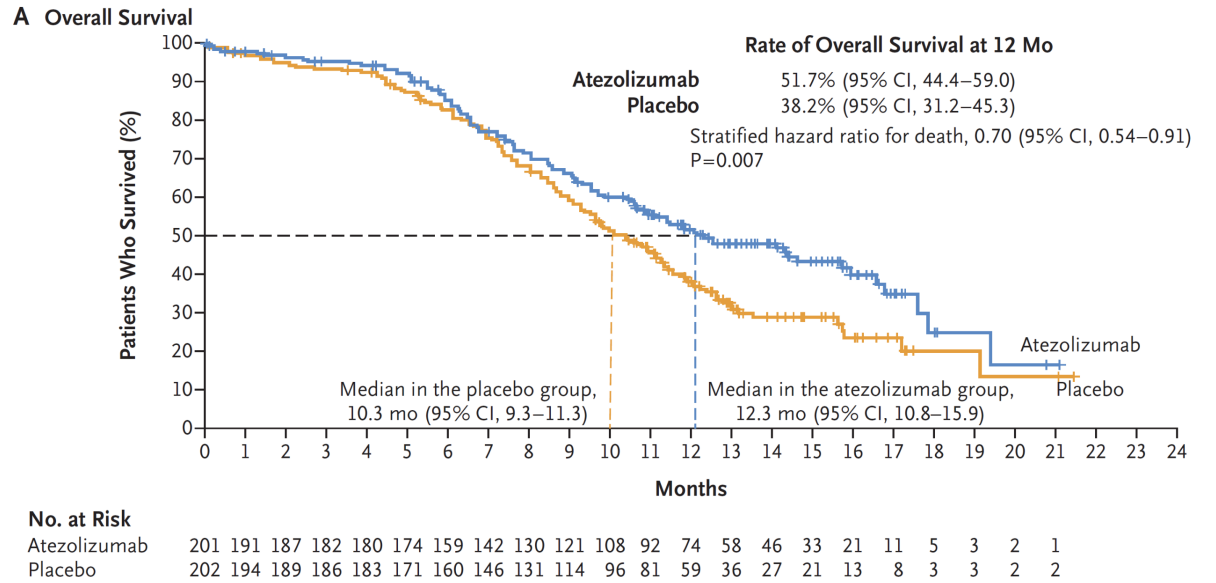


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

First-Line Atezolizumab plus Chemotherapy in Extensive-Stage Small-Cell Lung Cancer

L. Horn, A.S. Mansfield, A. Szczęсна, L. Havel, M. Krzakowski, M.J. Hochmair, F. Huemer, G. Losonczy, M.L. Johnson, M. Nishio, M. Reck, T. Mok, S. Lam, D.S. Shames, J. Liu, B. Ding, A. Lopez-Chavez, F. Kabbinar, W. Lin, A. Sandler, and S.V. Liu, for the IMpower133 Study Group*



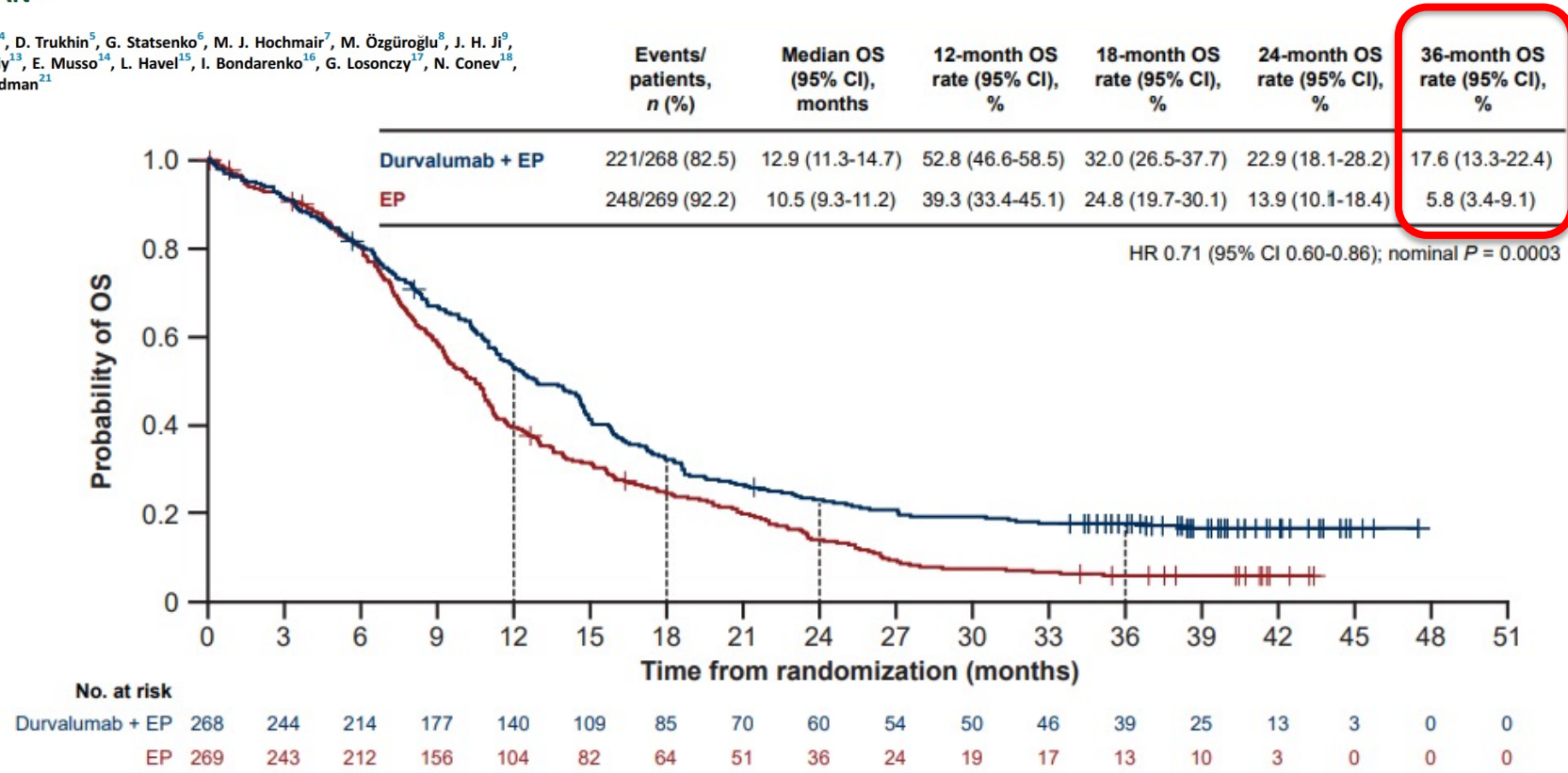
Horn et al, NEJM 2018

(March 2019 – FDA approval of EP-atezolizumab)

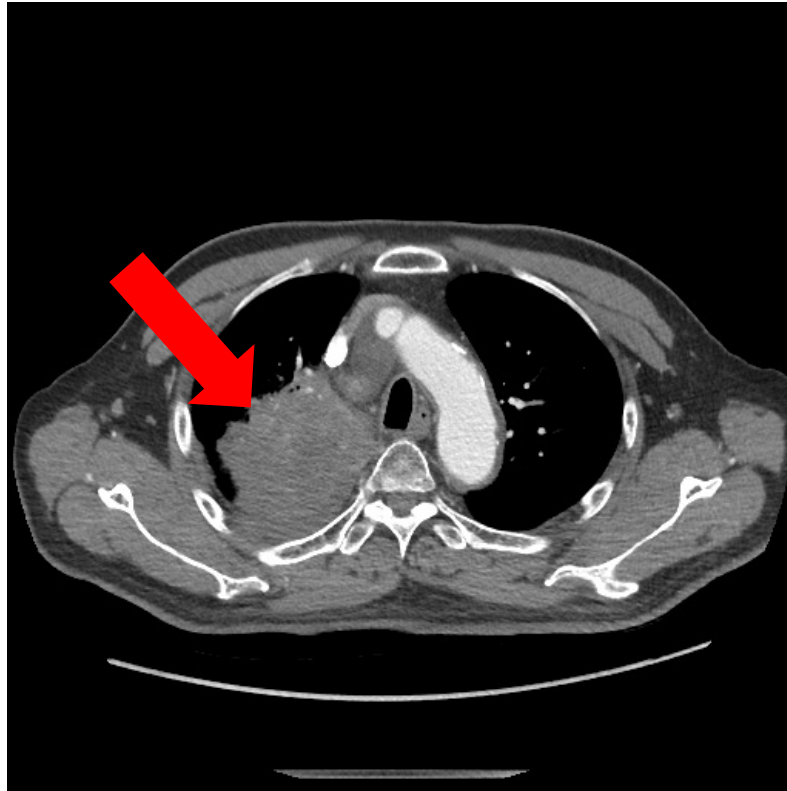
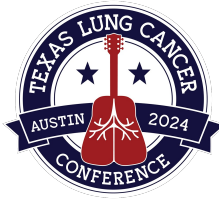
ORIGINAL RESEARCH

Durvalumab, with or without tremelimumab, plus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer: 3-year overall survival update from CASPIAN[☆]

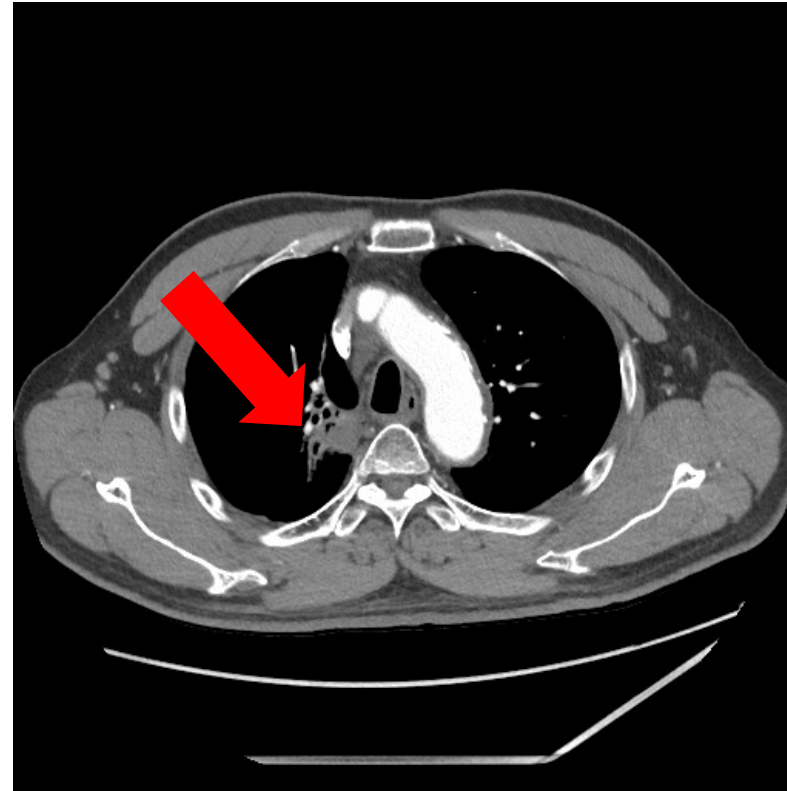
L. Paz-Ares^{1*}, Y. Chen², N. Reinmuth³, K. Hotta⁴, D. Trukhin⁵, G. Statsenko⁶, M. J. Hochmair⁷, M. Özgüroğlu⁸, J. H. Ji⁹, M. C. Garassino^{10,11}, O. Voitko¹², A. Poltoratskiy¹³, E. Musso¹⁴, L. Havel¹⁵, I. Bondarenko¹⁶, G. Losonczy¹⁷, N. Conev¹⁸, H. Mann¹⁹, T. B. Dalvi²⁰, H. Jiang²⁰ & J. W. Goldman²¹



Some SCLC are especially responsive to immunotherapy

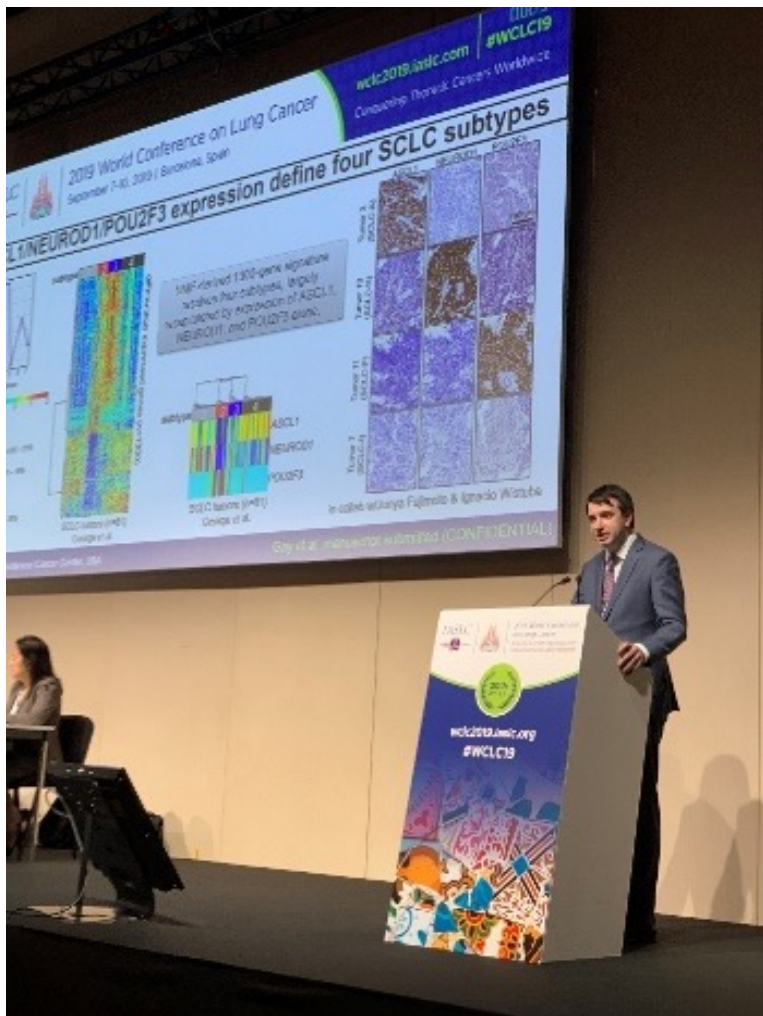


Baseline
(3rd line SCLC)

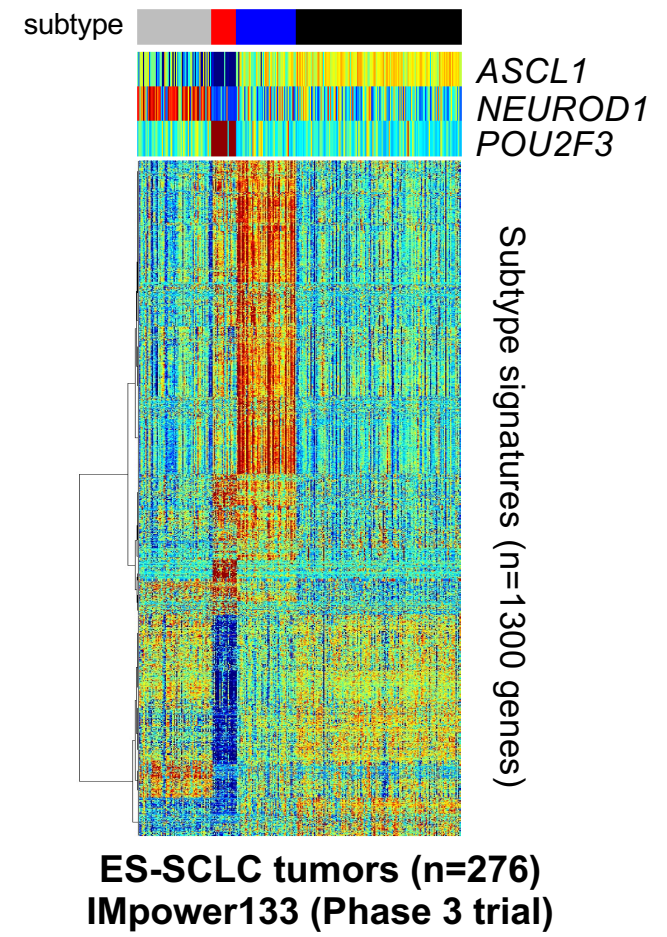
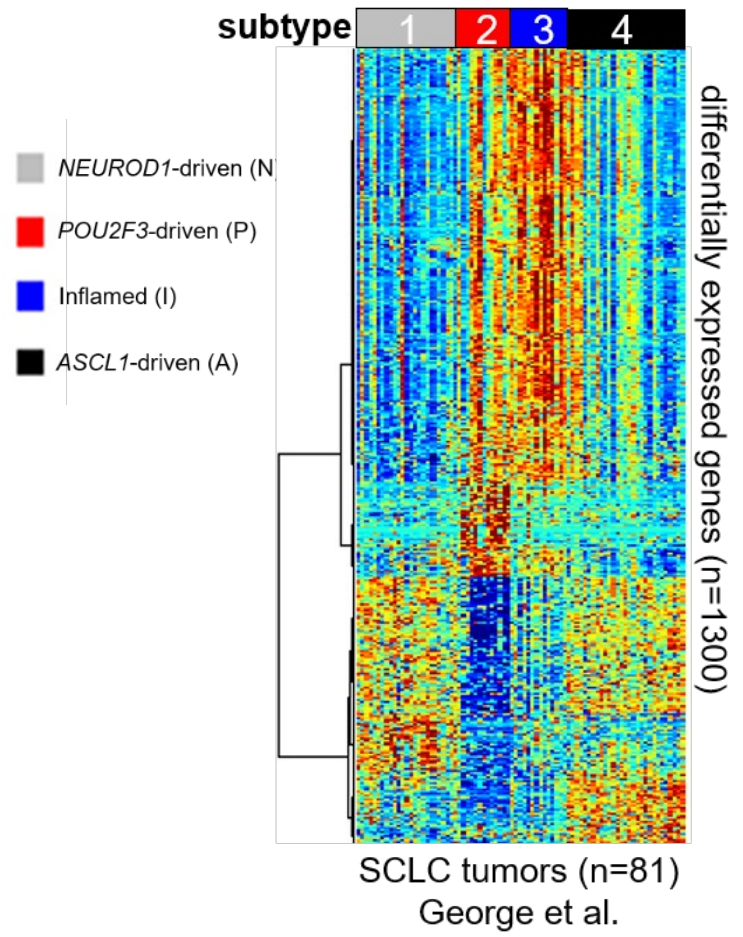


2 years on nivo/ipi

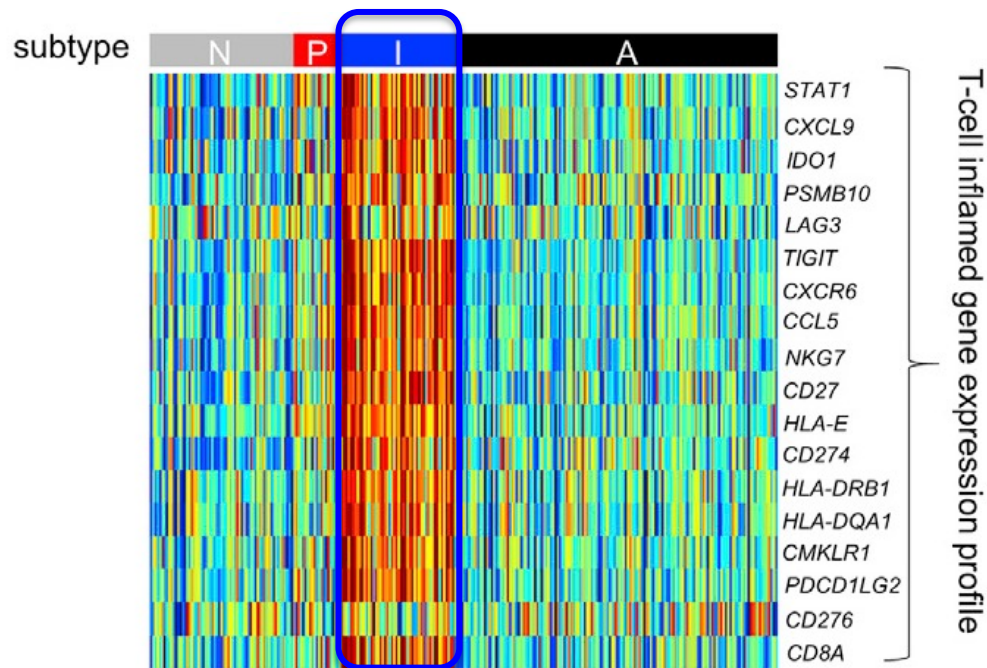
Unsupervised mRNA analysis identified transcriptional subtypes of SCLC: ASCL1, NEUROD1, **POU2F3**, and **Inflamed**



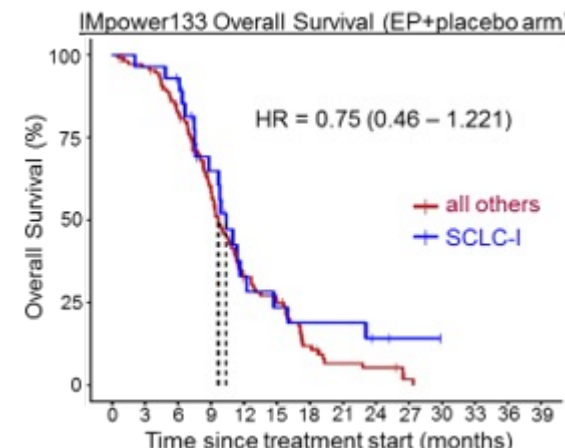
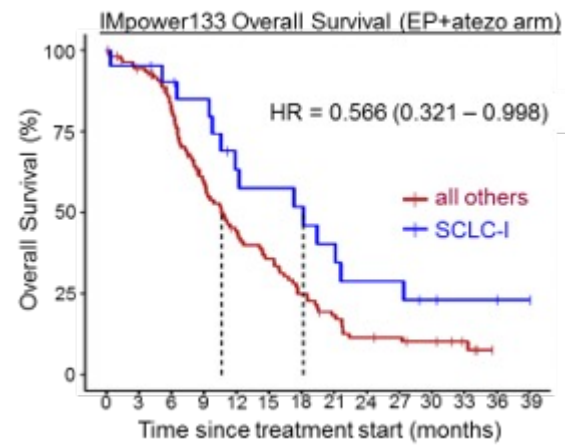
Carl Gay et al, WCLC 2019
Gay et al, Cancer Cell 2021



Immunotherapy improved overall survival in patients with **SCLC-Inflamed subtype (SCLC-I)**



- NEUROD1-driven (N)
- POU2F3-driven (P)
- Inflamed (I)
- ASCL1-driven (A)

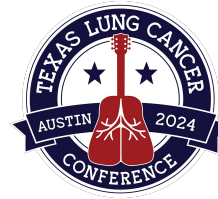


IMpower133
SCLC-Inflamed subtype: 18.2 (EP-atezo) vs 10.4mo (EP)

CASPIAN - SCLC-Inflamed subtype: mOS 17.6 (EP-durva) vs 11.3mo (EP)

IMPower133 - Gay et al, Cancer Cell, 2021
 CASPIAN - Shrestha et al, AACR, 2022

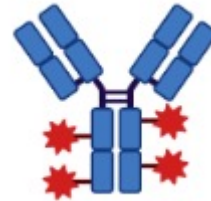
Emerging therapies targeting SCLC cell surface antigens



T cell engagers
(e.g., BiTEs)



Antibody Drug
Conjugates (ADC)

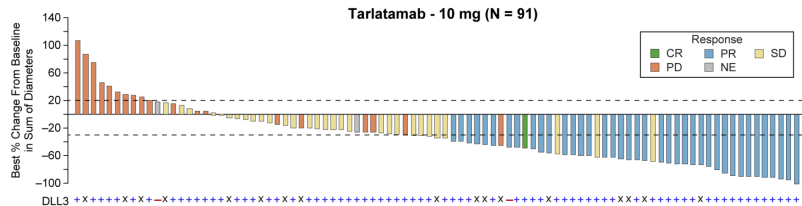


CAR T



Tarlatamab (DLL3/CD3)

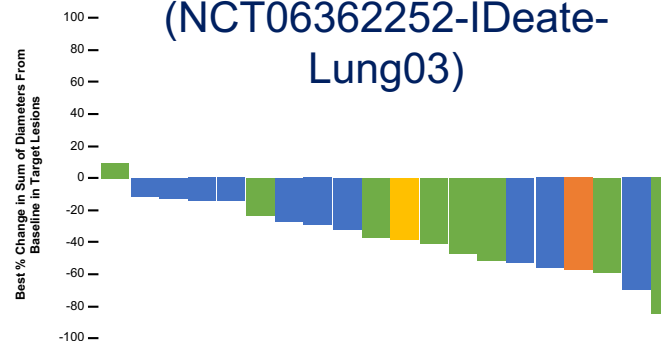
**1L ES-SCLC Trials
(NCT06211036)**



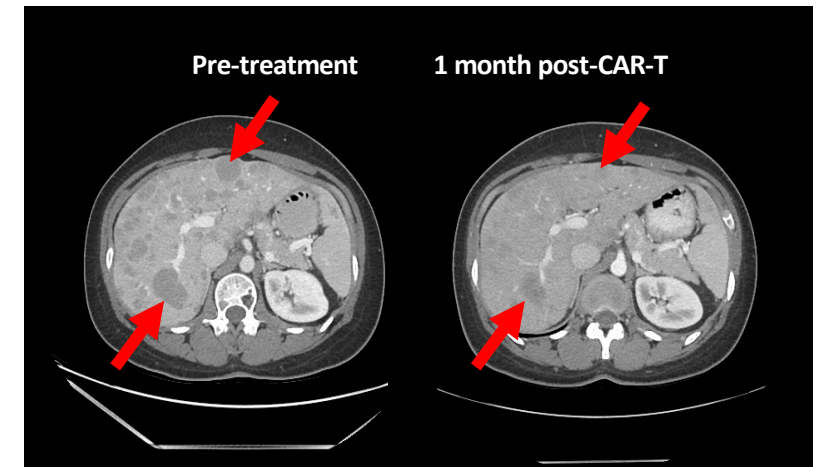
Ifinatamab Deruxtecan

(I-DXd; DS-7300)
(B7-H3 ADC)

**1L ES-SCLC Trials
(NCT06362252-IDeate-
Lung03)**



AMG119 (DLL3)



Ahn, NEJM 2024

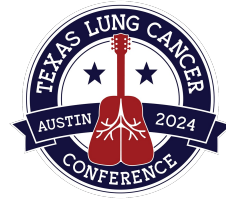
DLL3 T-cell engagers: selected ongoing and future trials



Agent	Disease Setting	NCT	Notes
Tarlatamab	LS-SCLC; 1L-maint.	NCT06117774	Tarlatamab vs placebo following chemoRT
Tarlatamab	ES-SCLC; 1L-maint.	NCT06211036	Tarlatamab + durva vs durva following EP+PDL1
RO7616789	R/R SCLC and NECs	NCT05619744	Tri-specific, incl. CD137 Ab
QLS31904	R/R SCLC and NECs	NCT05461287	
BI 764532	ES-SCLC; 1L-maint.	NCT06077500	Combo w/EP+PDL1
BI 764532	R/R SCLC	NCT05990738	Combo w/topotecan

Adapted from IASLC TTLC24 (Carl Gay, MD, PhD)

Just like not all cows are the same, not all SCLC is the same...



Angus



Charolais



Limousin



Red Brahman

SEZ6
ADC

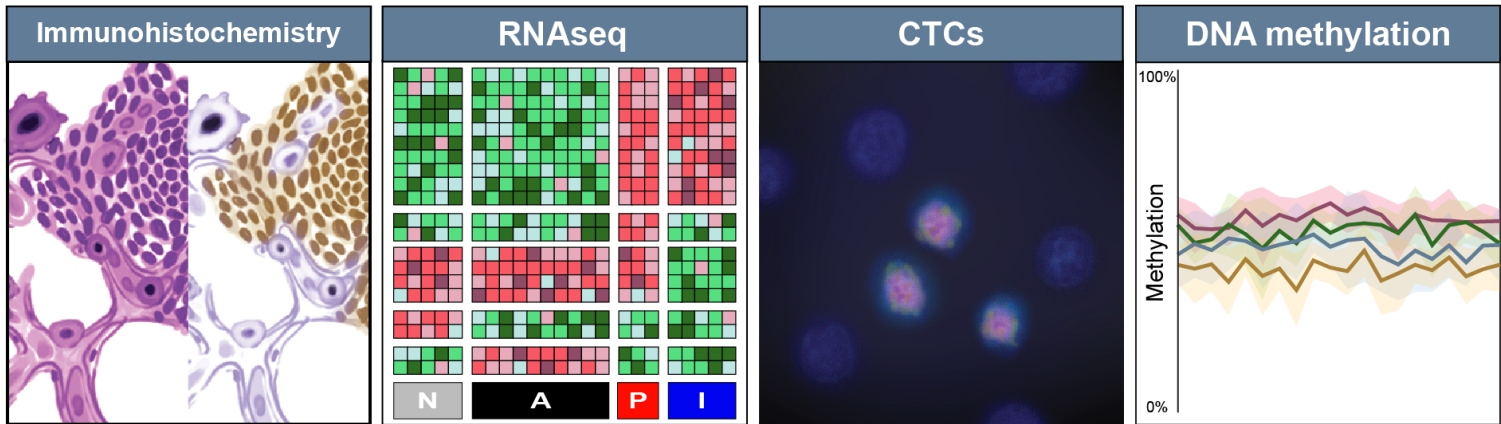
B7-H3
ADC

Tarlatamab
(DLL3)

Anti-PDL1



SCLC Subtypes and Drug Specific Biomarkers (biopsy or blood)

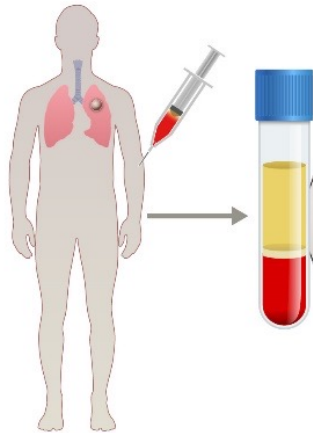


Biomarker testing in SCLC is feasible in ES-SCLC
 (e.g., SWOG 1929 - SLFN11 IHC in >300 pts at MD Anderson with 7 day turn around – accruing ahead of schedule)

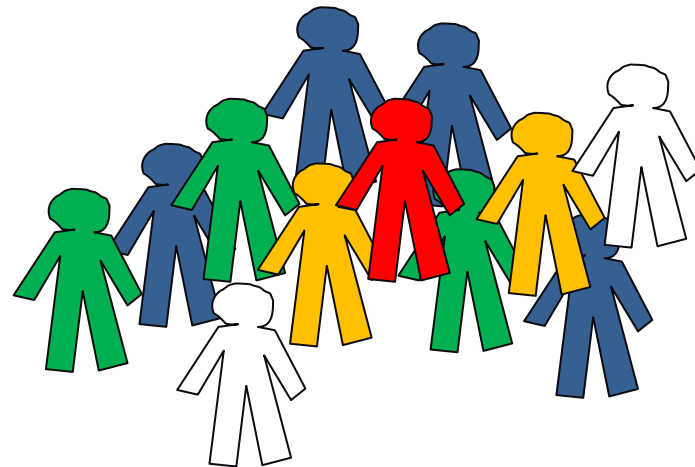
Gay et al, Cancer Cell 2021, Heeke et al, Cancer Cell 2024

Personalizing SCLC Treatment: *Clinical Trials*

Collect patient blood



Profile patient tumor or ctDNA and assign to treatment



Treatment Regimen 1
SCLC-A (**ASCL1**)

Treatment Regimen 2
SCLC-N (**NEUROD1**)

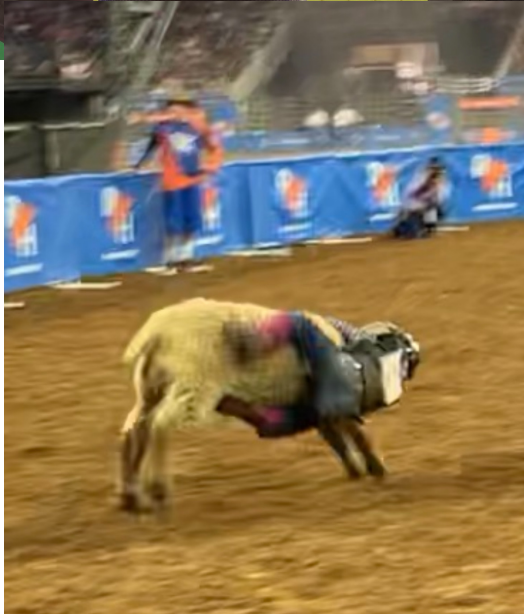
Treatment Regimen 3
SCLC-P (**POU2F3**)

Treatment Regimen 4
SCLC-I (**Inflamed**)

Treatment Regimen 5
Drug-specific biomarker

Conclusions

- Immune checkpoint blockade (e.g., anti-PDL1) provides **durable responses in only ~15% of 1L ES-SCLC patients (primarily SCLC-Inflamed)**.
- More effective treatments are needed in 1L ES-SCLC
- **Promising Surfaceome Targets** (e.g., *DLL3*, *B7H3*, etc) via ADCs, T-cell engagers, etc are now in trials for 1L ES-SCLC, with potential to transform the therapeutic landscape.
- As with NSCLC, biomarkers will be key to personalizing SCLC treatments and improving patient outcomes.



Acknowledgements

Byers Lab

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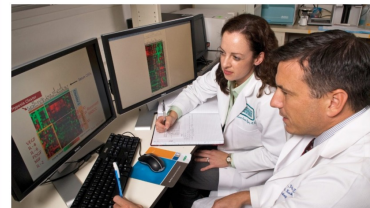
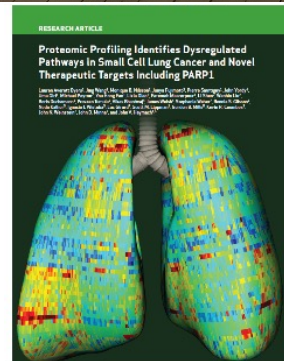
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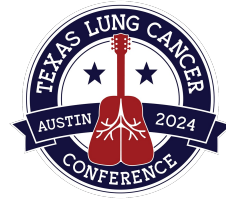
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