SCLC BIOMARKERS

Carl M. Gay, M.D., Ph.D.

University of Texas MD Anderson Cancer Center

April 19, 2024

Endorsed by

IASLC International Association for the Study of Lung Cancer — Conquering Thoracic Cancers Worldwide

Accredited by

PIM Postgraduate Institute for Medicine — Professional Excellence in Medical Education

Presented by

IDEOlogy Health — Creating Aha! Moments In Healthcare

A comprehensive list of SCLC biomarkers recommended by international guidelines

Standards of care are one-size-fits-all

IMpower133: Phase 3 – EP + atezolizumab with atezolizumab maintenance in ED- SCLC
(NCT02763579)

- Histologically documented ED-SCLC
- No prior treatment
- ECOG PS 0 – 1
- No autoimmune disease
- No active CNS disease

R 1:1

Carboplatin + Etoposide + Atezolizumab

Carbo (AUC 5) D1+ Etop 100mg/m2 D1-3 + Atezo 1200mg D1 q3W x 4 cycles

Followed by
Atezo 1200mg D1 q3W until PD or unacceptable toxicity

Carboplatin + Etoposide + Placebo

Carbo (AUC 5) D1+ Etop 100mg/m2 D1-3 + Placebo q3W x 4 cycles

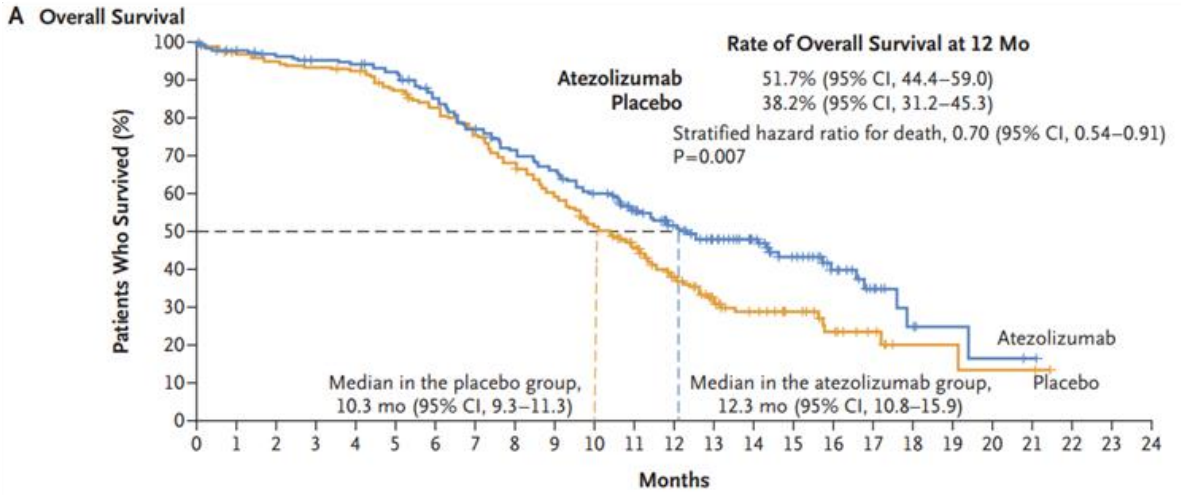
Followed by
Placebo D1 q3W until PD or unacceptable toxicity

Co-primary endpoints: OS, PFS
Secondary endpoints: ORR, DOR, 6-month PFS, QoL
(N=500)

ORIGINAL ARTICLE

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

L. Horn, A.S. Mansfield, A. Szczęsna, 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. Kabbinavar, W. Lin, A. Sandler, and S.V. Liu, for the IMpower133 Study Group*



Horn et al, NEJM 2018

Standards of care are one-size-fits-all

IMpower133: Phase 3 – EP + atezolizumab with atezolizumab maintenance in ED- SCLC
(NCT02763579)

- Histologically documented ED-SCLC
- No prior treatment
- ECOG PS 0 – 1
- No autoimmune disease
- No active CNS disease

R 1:1

Carboplatin + Etoposide + Atezolizumab

Carbo (AUC 5) D1+ Etop 100mg/m2 D1-3 + Atezo 1200mg D1 q3W x 4 cycles

Followed by
Atezo 1200mg D1 q3W until PD or unacceptable toxicity

Carboplatin + Etoposide + Placebo

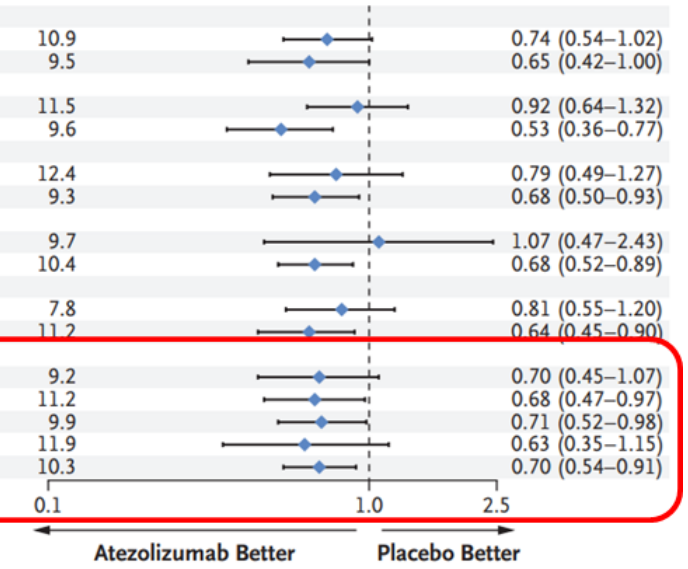
Carbo (AUC 5) D1+ Etop 100mg/m2 D1-3 + Placebo q3W x 4 cycles

Followed by
Placebo D1 q3W until PD or unacceptable toxicity

Co-primary endpoints: OS, PFS
Secondary endpoints: ORR, DOR, 6-month PFS, QoL
(N=500)

C Overall Survival According to Baseline Characteristics

Subgroup	No. of Patients (%)	Median Overall Survival (mo)		Hazard Ratio for Death (95% CI)
		Atezolizumab	Placebo	
Sex				
Male	261 (65)	12.3	10.9	0.74 (0.54–1.02)
Female	142 (35)	12.5	9.5	0.65 (0.42–1.00)
Age				
<65 yr	217 (54)	12.1	11.5	0.92 (0.64–1.32)
≥65 yr	186 (46)	12.5	9.6	0.53 (0.36–0.77)
ECOG score				
0	140 (35)	16.6	12.4	0.79 (0.49–1.27)
1	263 (65)	11.4	9.3	0.68 (0.50–0.93)
Brain metastases				
Yes	35 (9)	8.5	9.7	1.07 (0.47–2.43)
No	368 (91)	12.6	10.4	0.68 (0.52–0.89)
Liver metastases				
Yes	149 (37)	9.3	7.8	0.81 (0.55–1.20)
No	254 (63)	16.8	11.2	0.64 (0.45–0.90)
Tumor mutational burden				
<10 mutations/Mb	139 (34)	11.8	9.2	0.70 (0.45–1.07)
≥10 mutations/Mb	212 (53)	14.6	11.2	0.68 (0.47–0.97)
<16 mutations/Mb	271 (67)	12.5	9.9	0.71 (0.52–0.98)
≥16 mutations/Mb	80 (20)	17.8	11.9	0.63 (0.35–1.15)
Intention-to-treat population	403 (100)	12.3	10.3	0.70 (0.54–0.91)



Higher TMB did not predict benefit with addition of ICI in IMpower133

Horn et al, NEJM 2018

Standards of care are one-size-fits-all

CASPIAN: Phase 3 – EP + durvalumab with durvalumab maintenance in ES-SCLC

- Treatment-naïve ES-SCLC
- WHO PS 0 or 1
- Asymptomatic or treated and stable brain metastases permitted
- Life expectancy ≥12 weeks
- Measurable disease per RECIST v1.1

N=805 (randomized)

1:1:1 (R) Stratified by planned platinum (carboplatin vs cisplatin)

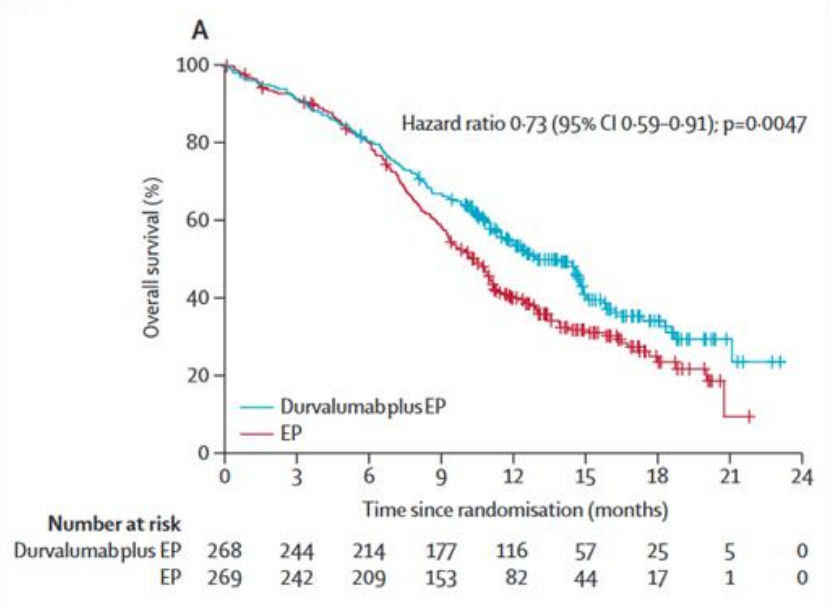
Durvalumab + tremelimumab + EP* q3w for 4 cycles	Durvalumab‡ q4w until PD
Durvalumab + EP* q3w for 4 cycles	Durvalumab q4w until PD
EP* q3w for up to 6 cycles†	Optional PCI†

Primary endpoint
- OS

Secondary endpoints
- PFS§
- ORR§
- Safety & tolerability
- PROs

Durvalumab plus platinum–etoposide versus platinum–etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial

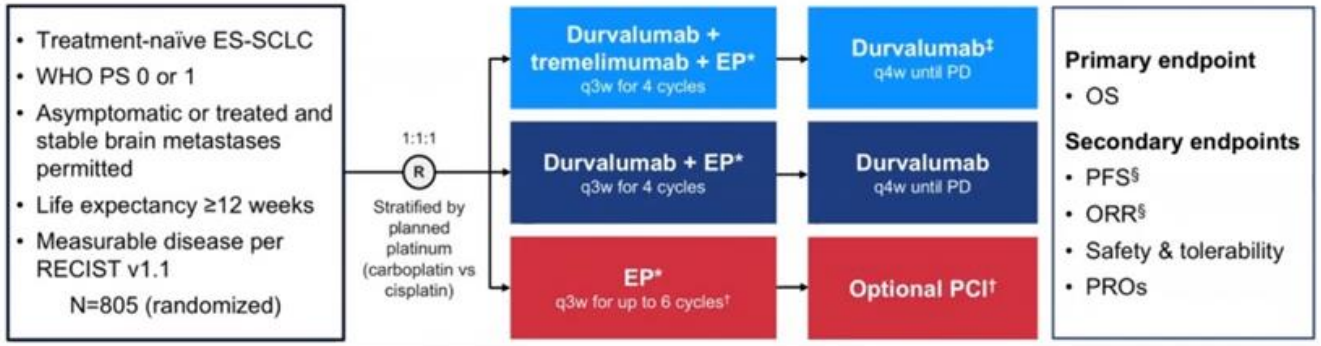
*Luis Paz-Ares, Mikhail Dvorkin, Yuanbin Chen, Niels Reinmuth, Katsuyuki Hotta, Dmytro Trukhin, Galina Statsenko, Maximilian J Hochmair, Mustafa Özgüroğlu, Jun Ho Ji, Oleksandr Voitko, Artem Poltoratskiy, Santiago Ponce, Francesco Verderame, Libor Havel, Igor Bondarenko, Andrzej Kazarnowicz, György Losonczy, Nikolay V Conev, Jon Armstrong, Natalie Byrne, Norah Shire, Haiyi Jiang, Jonathan W Goldman, for the CASPIAN investigators**



Paz-Ares et al, Lancet 2019

Standards of care are one-size-fits-all

CASPIAN: Phase 3 – EP + durvalumab with durvalumab maintenance in ES-SCLC



ESMO 2019 update:

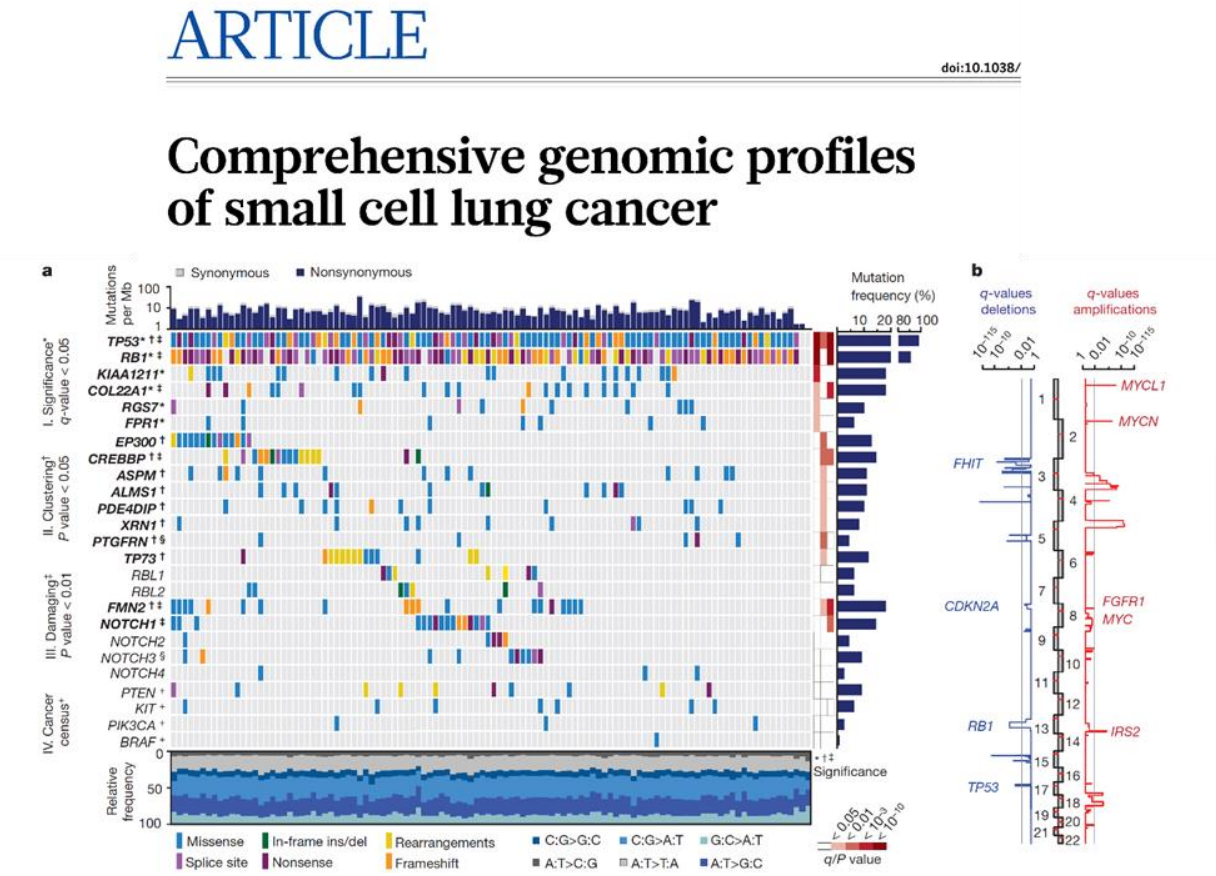
277 with evaluable samples with Ventana PD-L1 (SP263)

- 5% and 22% of pts with expression ≥1% in tumor and immune cells, respectively
- PD-L1 expression as continuous variable had no impact on OS, PFS, or ORR

Similarly, PD-L1 expression was infrequent and had no bearing on outcomes with addition of ICI in CASPIAN.

Paz-Ares et al, Lancet 2019; Paz-Ares et al. ESMO 2019

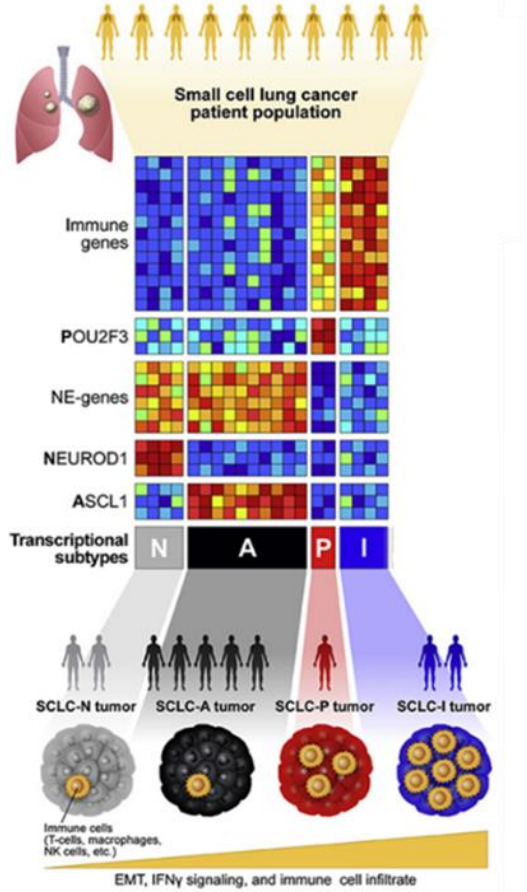
Personalization in SCLC may look different

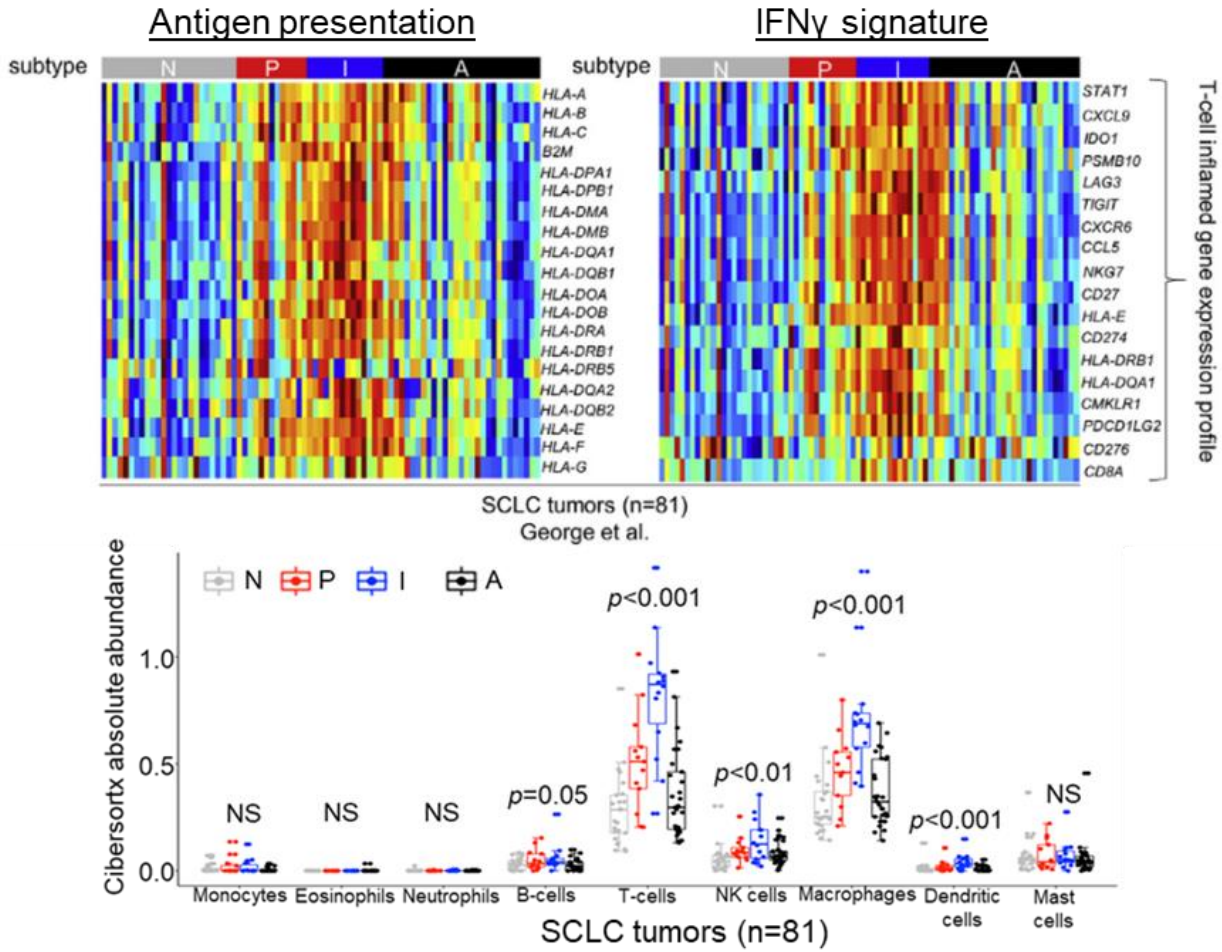


- Ubiquitous bi-allelic loss of tumor suppressor genes *TP53* and *RB1*
- Absence of actionable oncogenic drivers

George et al, Nature 2015

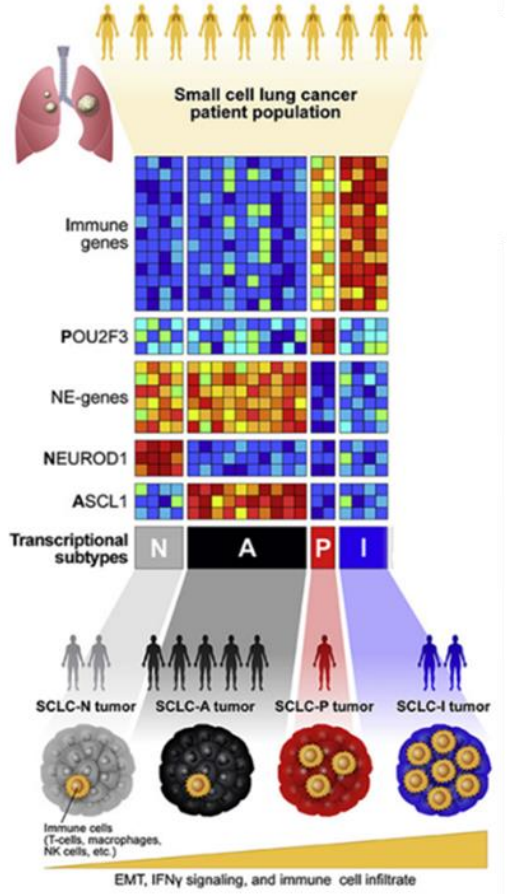
Transcriptional diversity underlies immune phenotypic diversity

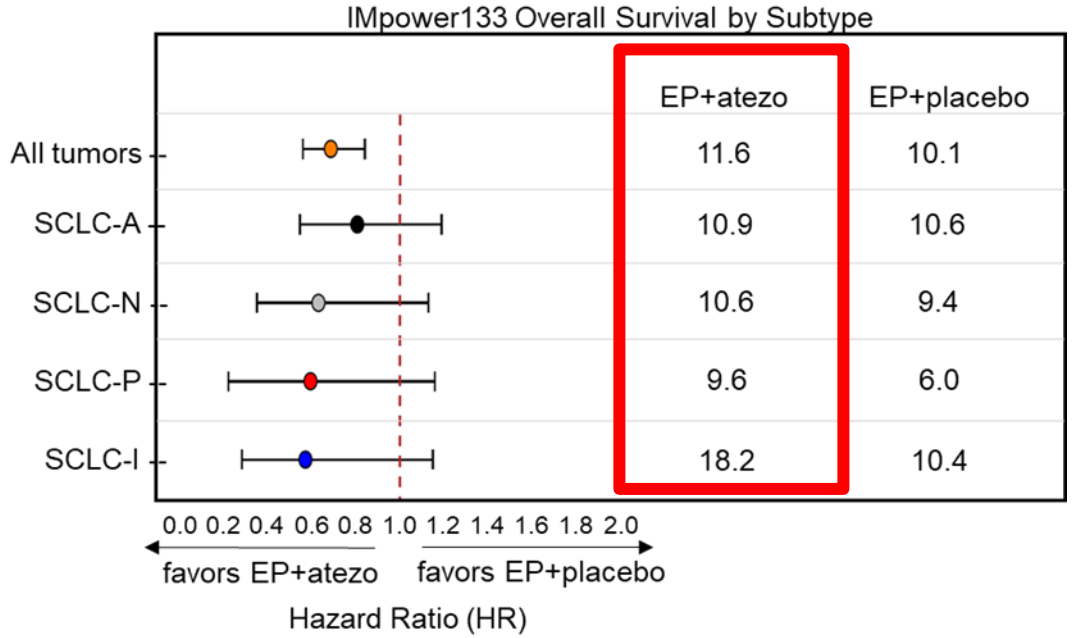




Gay et al. Cancer Cell, 2021

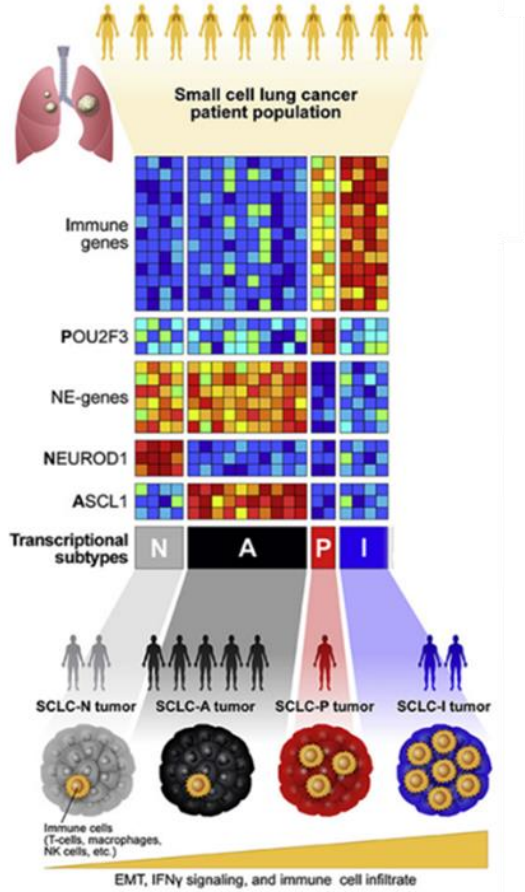
Transcriptional subtype predicts differential benefit of the addition of immunotherapy (IMP133)

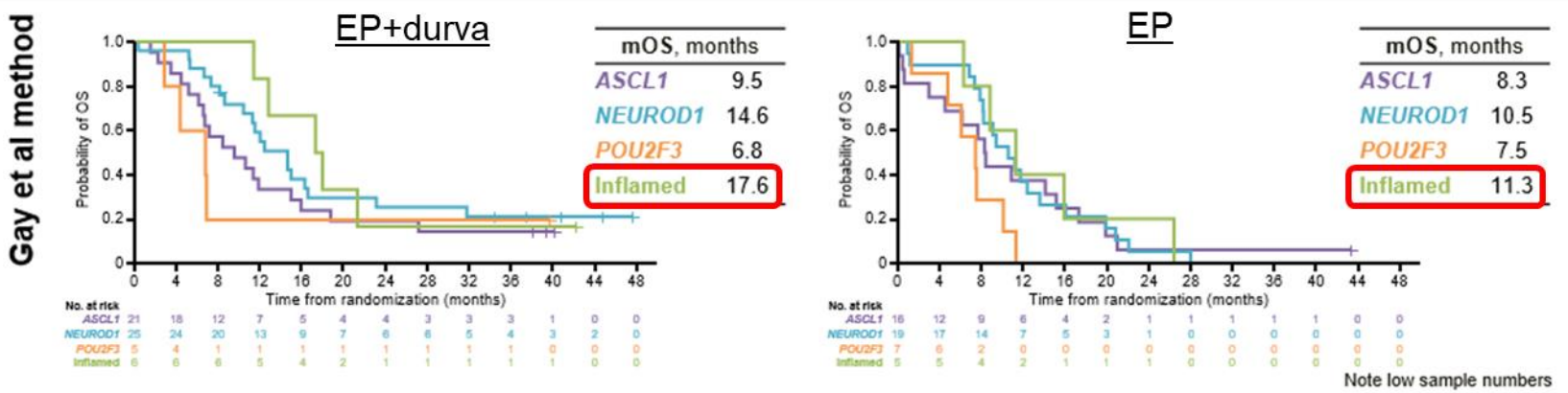




Gay et al. Cancer Cell, 2021

Transcriptional subtype predicts differential benefit of the addition of immunotherapy (CASPIAN)

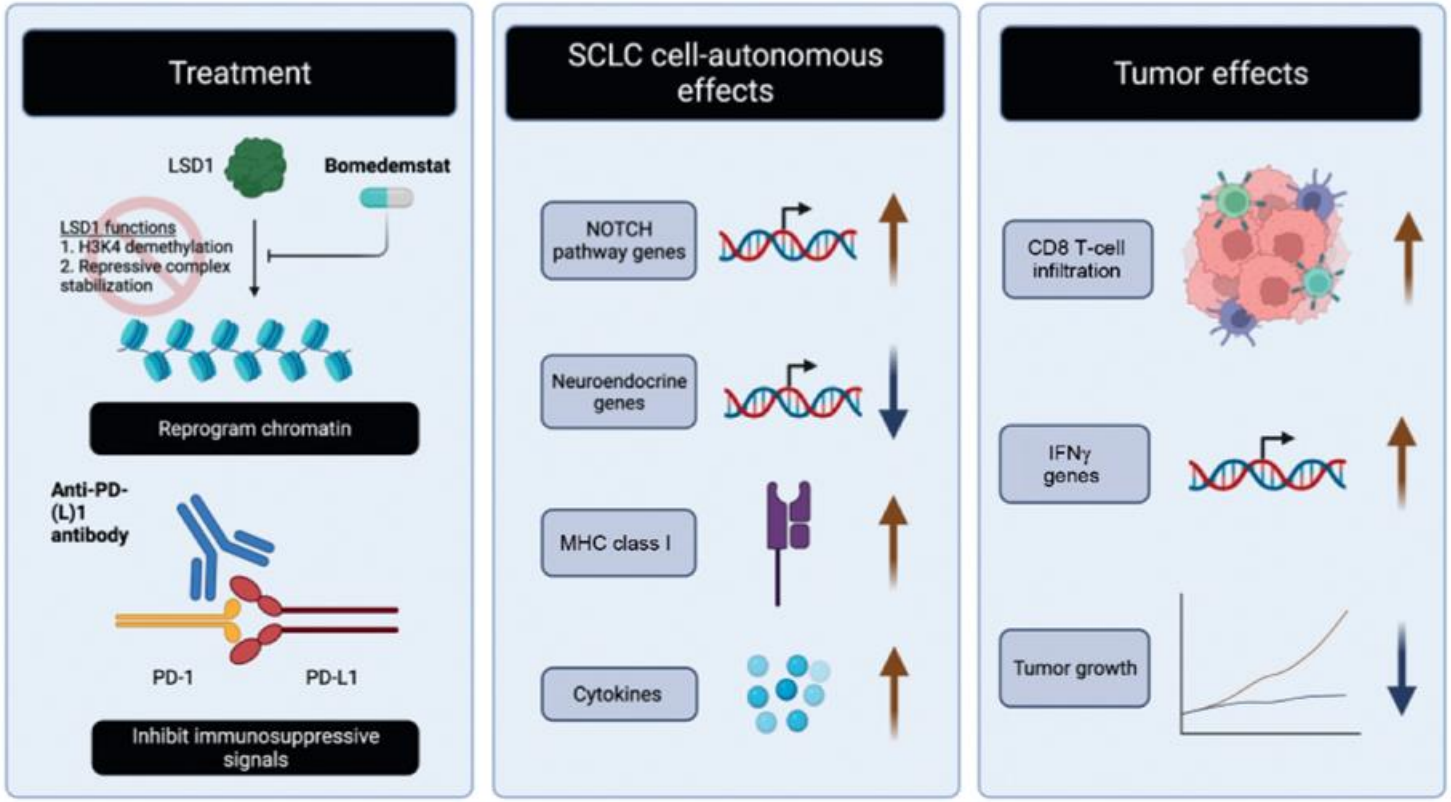




Gay et al. Cancer Cell, 2021

What about the un-inflamed subtypes?

Could we make them all inflamed? Maybe…

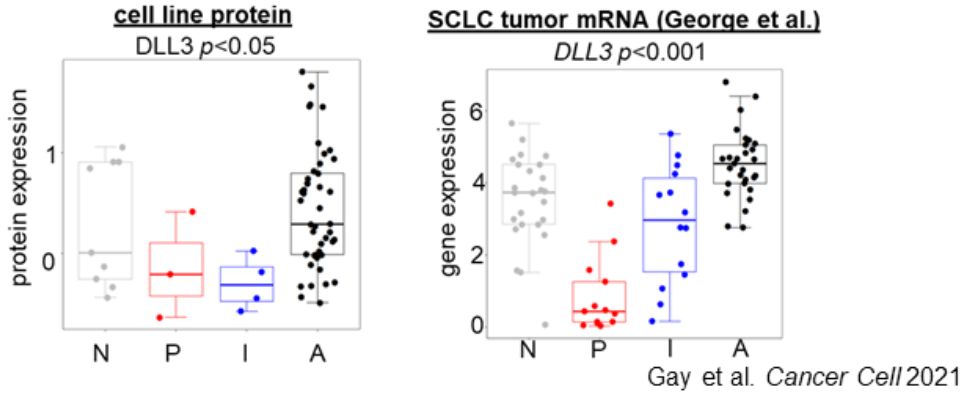


LSD1 inhibition directs neuroendocrine subtypes (e.g. SCLC-A or –N) toward more inflamed states.

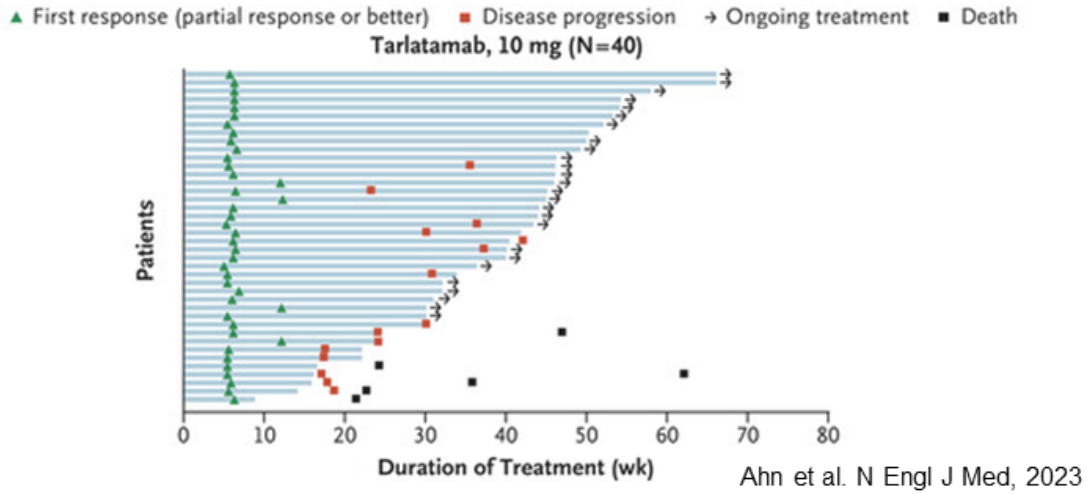
Hiatt et al. Clin Cancer Res, 2022

What about the un-inflamed subtypes?

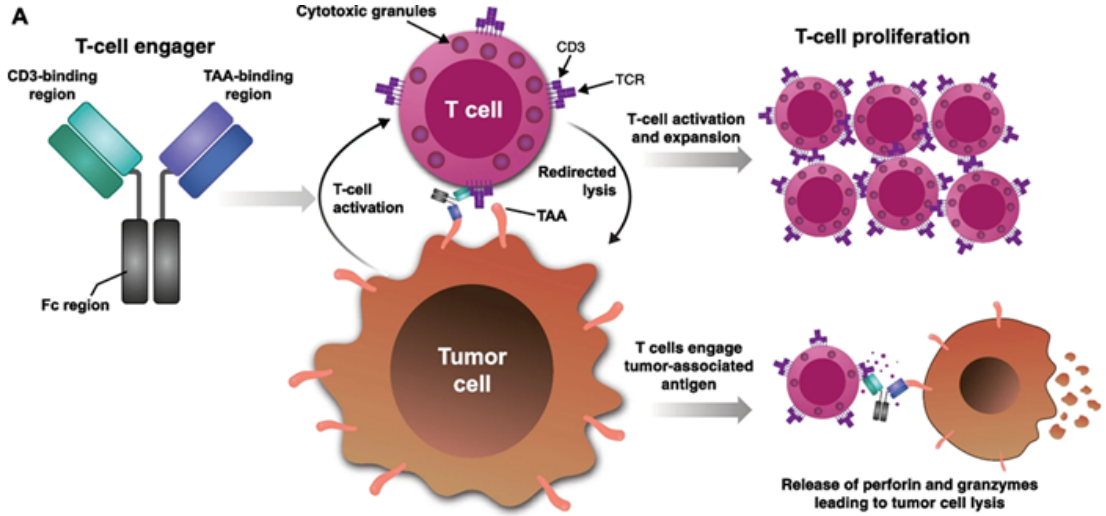
Could we make them all inflamed? Maybe…



Gay et al. *Cancer Cell* 2021



Ahn et al. N Engl J Med, 2023



Modified from Rudin et al. *Journal of Hematology & Oncology*, 2023

T-cell engagers can be directed at subtype-specific targets to deliver anti-tumor immune response.

If subtype, or any biomarker, is needed in SCLC, how might we do that practically?

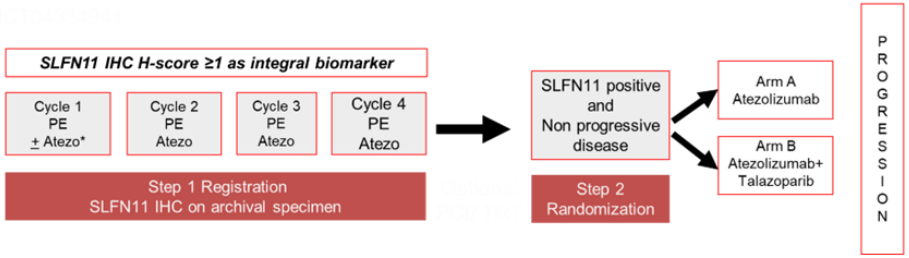
- Perform biomarker analysis in parallel with treatment.

- Plasma-based approaches.

If subtype, or any biomarker, is needed in SCLC, how might we do that practically?

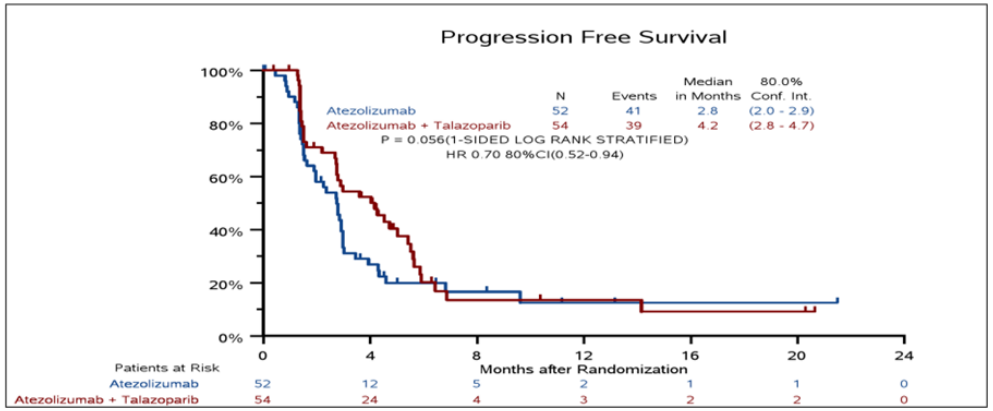
- Perform biomarker analysis in parallel with treatment.

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)



SWOG1929 successfully integrated an IHC for SLFN11 – a predictive biomarker for PARP inhibitor sensitivity in SCLC – into frontline maintenance by performing assay *during* initial therapy.

- 259 pts screened
- Mean assay TAT: 7 days
- Enrollment ahead of schedule

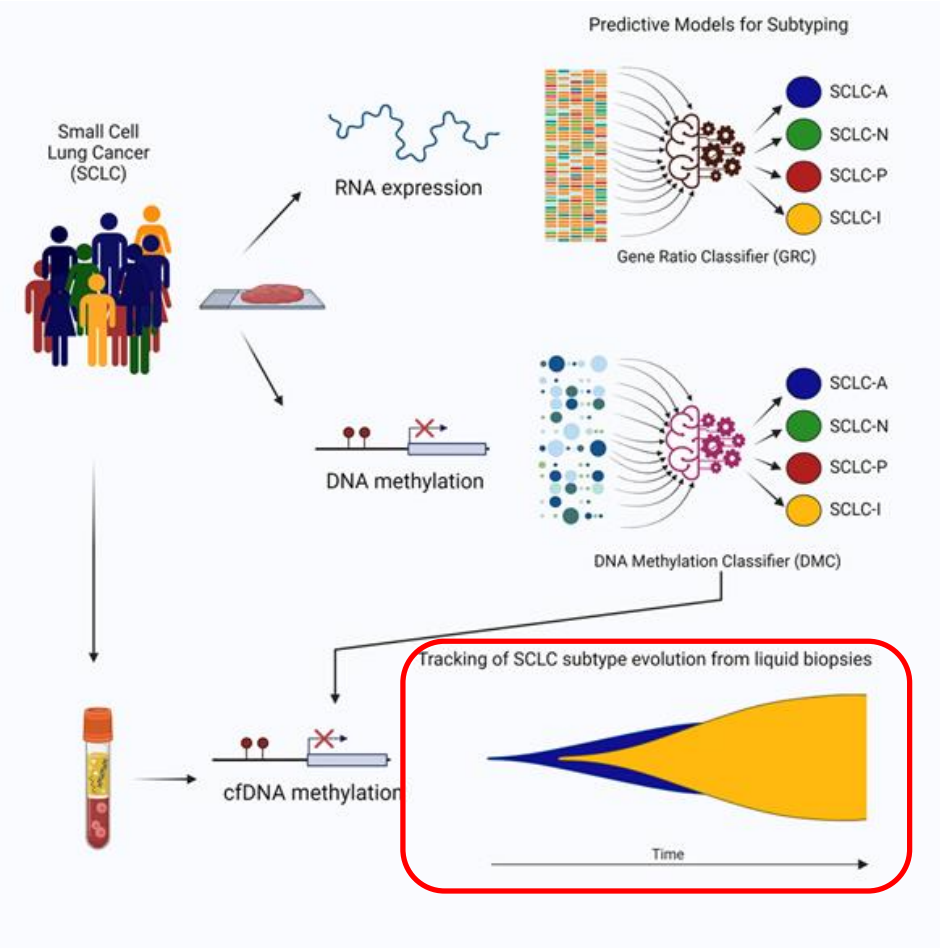


Karim et al., ASCO, 2023

If subtype, or any biomarker, is needed in SCLC, how might we do that practically?

- Plasma-based approaches.

- **Transcriptional subtype, as well as other expression-based features, are epigenetically encoded, including in ctDNA, and can be rapidly and longitudinally collected.**
- **Longitudinal collections highlight the limitations of archival tissue analysis.**



Heeke et al. Cancer Cell 2024

SCLC Biomarkers: Summary

- Genomic biomarkers are out, for now.
- Even established expression-based biomarkers (e.g. PD-L1) are not predictive.
- SCLC transcriptional subtypes delineate tumor diversity.
  - SCLC-I patients experience greatest benefit from ICI.
  - Other subtypes may benefit from intensification or novel immune-based strategies (e.g. BiTEs).
- Aggressive natural history requires creative strategies to assess biomarkers without delaying care.
- Transcriptional biomarkers may evolve with treatment – assess longitudinally?
- Should surface protein targets be integrated into biomarker plans?
  - DLL3 vs. B7H3 vs. SEZ6 vs. TROP2, etc.