BEST PRACTICES FOR EXTENSIVE STAGE SCLC

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MD Anderson Cancer Center

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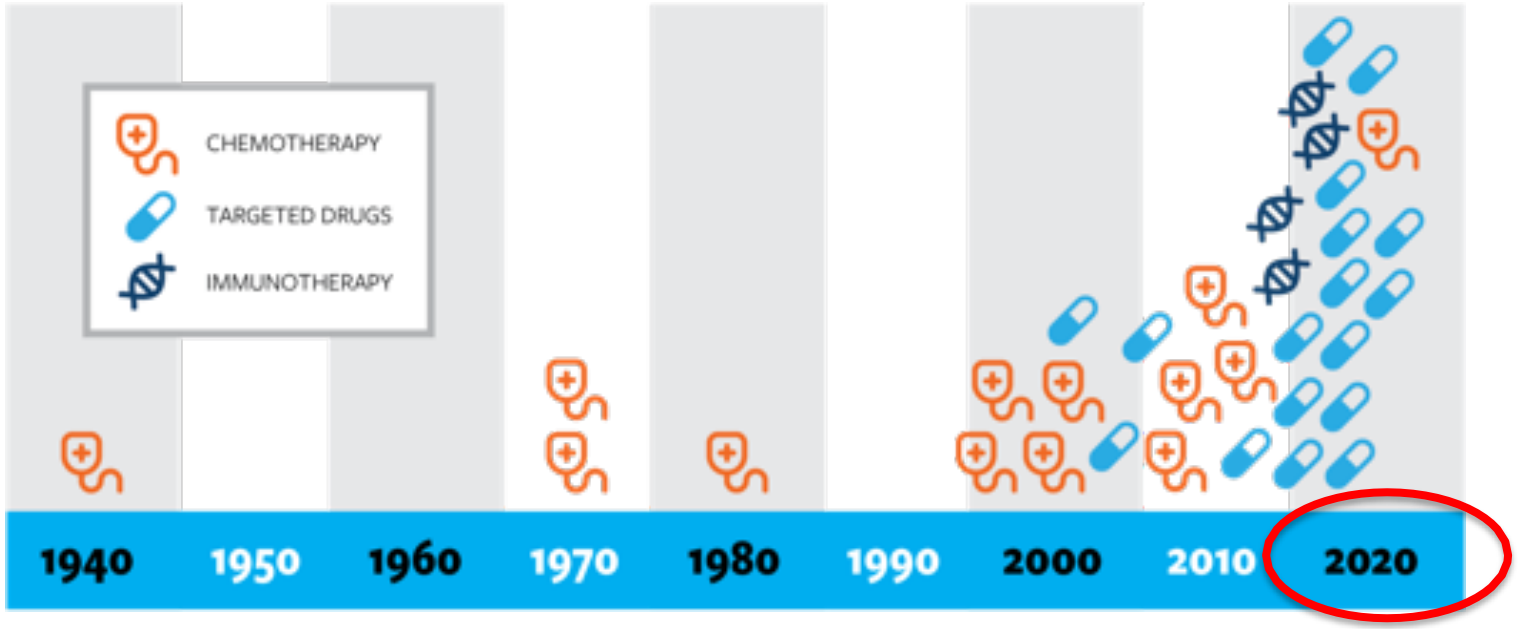
Drug approvals for lung cancer are accelerating

*Since 2020, **>15 new drugs approved for lung cancer**, including new drug classes of targeted therapy (KRAS, Her2 targeting, etc)*



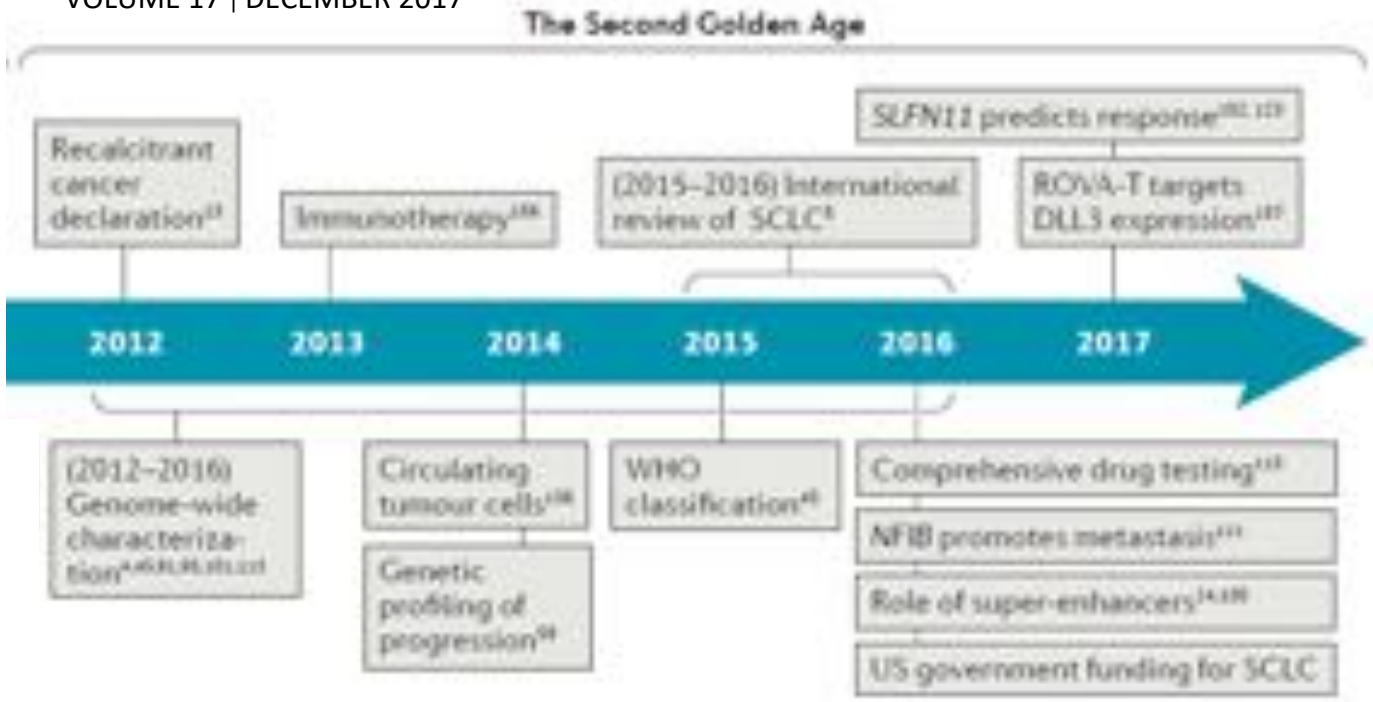
History of lung cancer treatment advances (updated 5/20); Lung Cancer Research Foundation

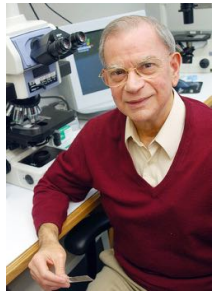
Adapted from Carpool Karaoke (courtesy of Simon Heeke)

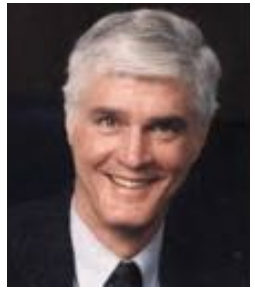
Small-cell lung cancer: what we know, what we need to know and the path forward

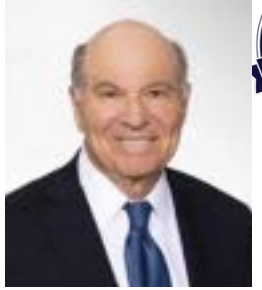
Adi F. Gazdar[1,2], Paul A. Bunn[5] and John D. Minna[1,4]

NATURE REVIEWS | CANCER
VOLUME 17 | DECEMBER 2017





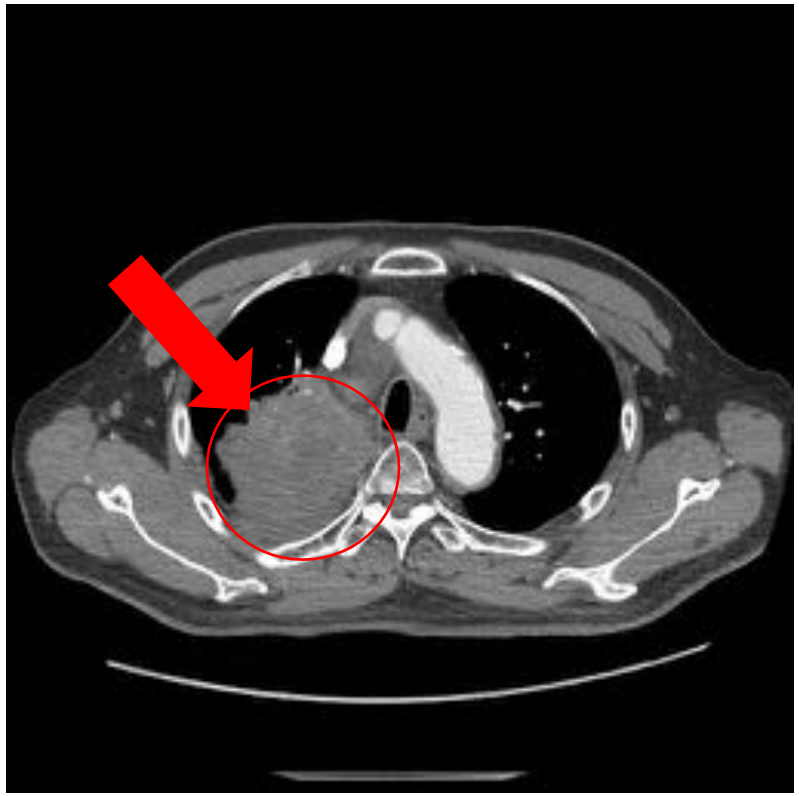




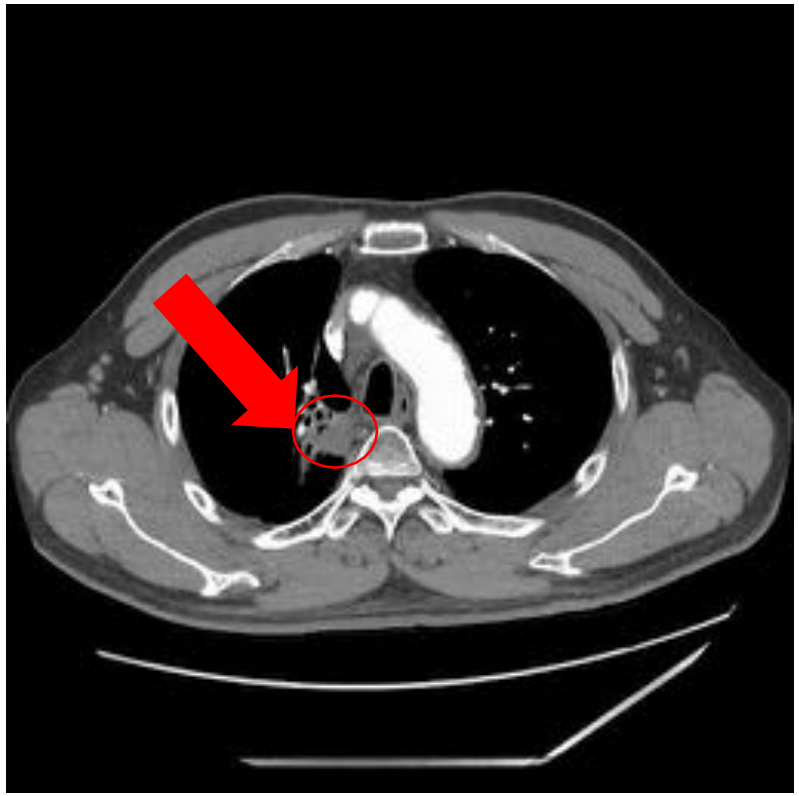
"…while the past has been bleak, the future offers great promise"

- Adi Gazdar, Paul Bunn, John Minna

A radical new way to fight cancer -- Immunotherapy



Relapsed SCLC
Before treatment



After immunotherapy
(nivo/ipi third line)

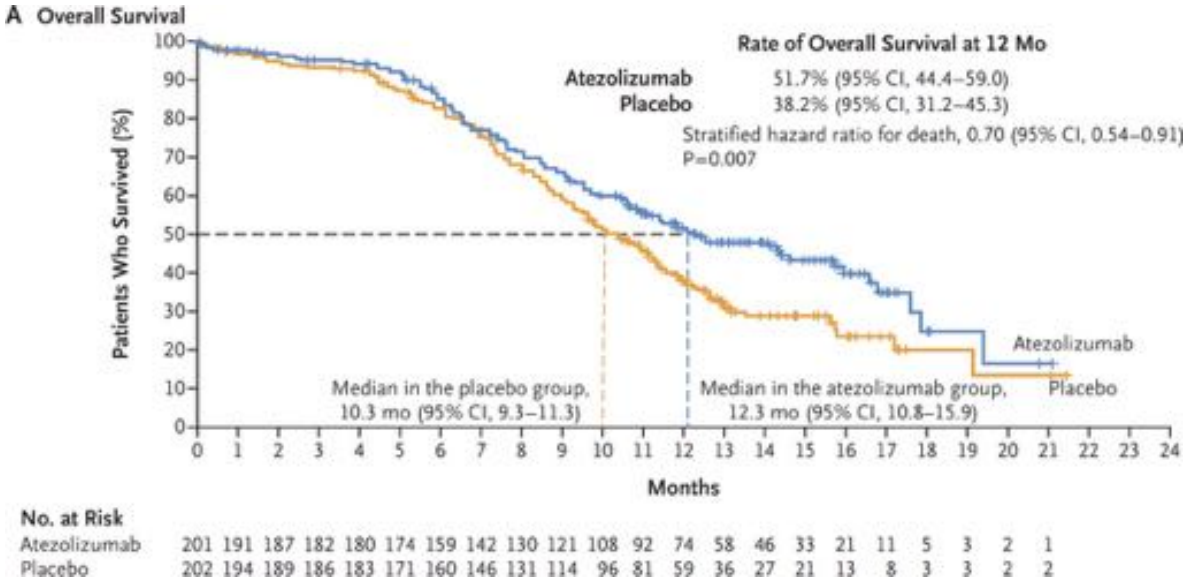
Immunotherapy is a new standard of care for SCLC

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. 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 *(March 2019 – FDA approval of EP-atezolizumab)*

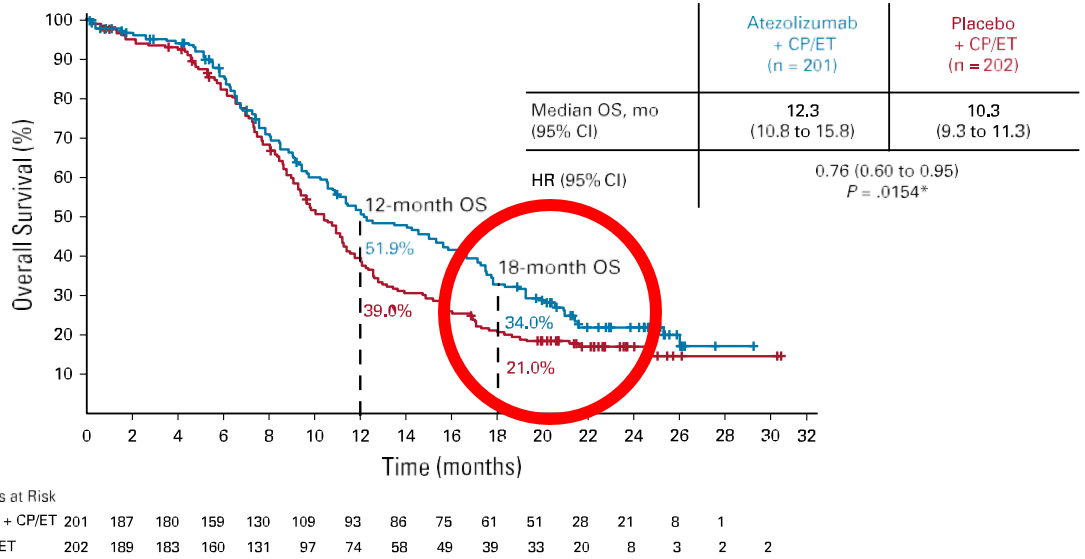
original reports

Updated Overall Survival and PD-L1 Subgroup Analysis of Patients With Extensive-Stage Small-Cell Lung Cancer Treated With Atezolizumab, Carboplatin, and Etoposide (IMpower133)

Stephen V. Liu, MD[1]; Martin Reck, MD, PhD[2]; Aaron S. Mansfield, MD[3]; Tony Mok, MD[4]; Arnaud Scherpereel, MD, PhD[5]; Niels Reinmuth, MD, PhD[6]; Marina Chiara Garassino, MD[7]; Javier De Castro Carpeno, MD[8]; Raffaele Califano, MD[9]; Makoto Nishio, MD[10]; Francisco Orlandi, MD[11]; Jorge Alatorre-Alexander, MD[12]; Ticiana Leal, MD[13]; Ying Cheng, MD[14]; Jong-Seok Lee, MD[15]; Sivuonthanh Lam, PharmD[16]; Mark McCleland, PhD[16]; Yu Deng, PhD[16]; See Phan, MD[16]; and Leora Horn, MD[17]

Overall survival at 18 months:

34% Atezo + chemo
21% Placebo + chemo



Liu et al, JCO 2021

ESMO OPEN CANCER HORIZONS

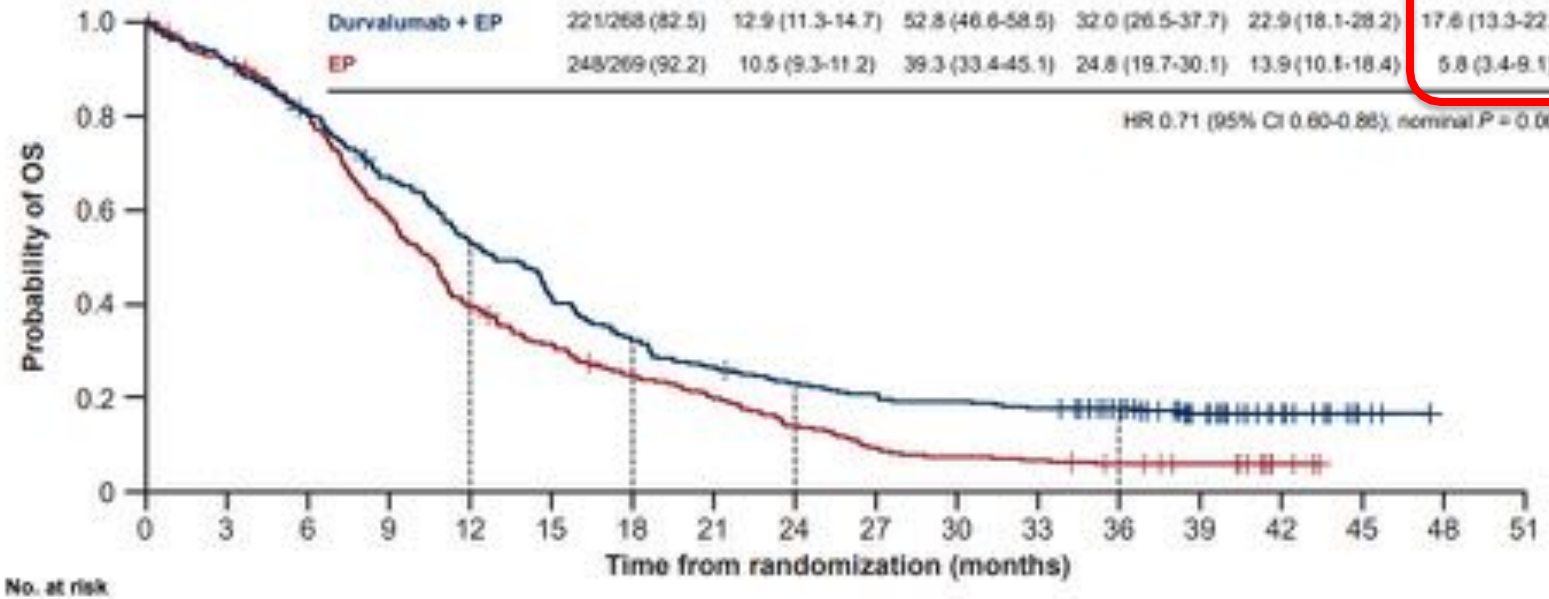
ORIGINAL RESEARCH

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. Chen[2], N. Reinmuth[3], K. Hotta[4], D. Trukhin[5], G. Statsenko[6], M. J. Hochmair[7], M. Özgüroğlu[8], J. H. Ji[9], M. C. Garassino[10,11], O. Voitko[12], A. Poltoratskiy[13], E. Musso[14], L. Havel[15], I. Bondarenko[16], G. Losonczy[17], N. Conev[18], H. Mann[19], T. B. Dalvi[20], H. Jiang[20] & J. W. Goldman[21]

	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 $P = 0.0003$



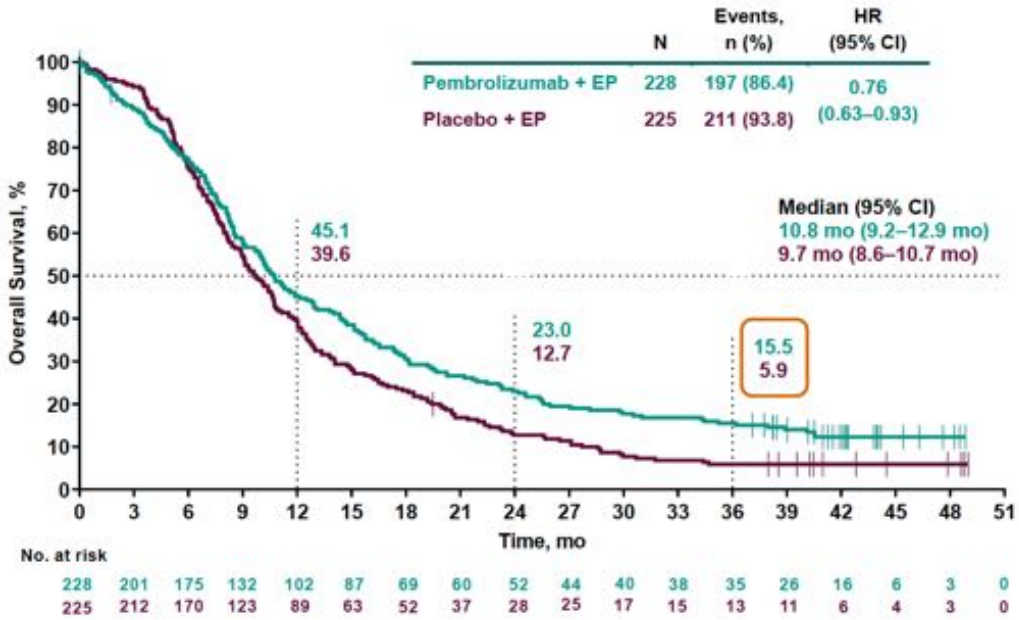
No. at risk

Durvalumab + EP	268	244	214	177	140	109	85	70	60	54	50	46	39	25	13	3	0	0
EP	269	243	212	156	104	82	64	51	36	24	19	17	13	10	3	0	0	0

Paz-Ares et al, ESMO OPEN 2022

First-Line Pembrolizumab or Placebo Combined With Etoposide and Platinum for ES-SCLC: KEYNOTE-604 Long-Term Follow-Up Results

C.M. Rudin[1]; H.R. Kim[2]; A. Navarro[3]; M. Gottfried[4]; S. Peters[5]; T. Csőszi[6]; P.K. Cheema[7]; D. Rodriguez-Abreu[8]; M. Wollner[9]; G. Czyżewicz[10]; J.C.-H. Yang[11]; J. Mazieres[12]; F.J. Orlandi[13]; A. Luft[14]; M. Gümüş[15]; T. Kato[16]; G.P. Kalemkerian[17]; W. Fu[18]; B. Zhao[18]; H. El-Osta[18]; M.M. Awad[19]



Keynote-604 - Patients who <u>completed</u> all 35 cycles of pembrolizumab (and then monitored WITHOUT treatment) had <u>durable responses</u>.

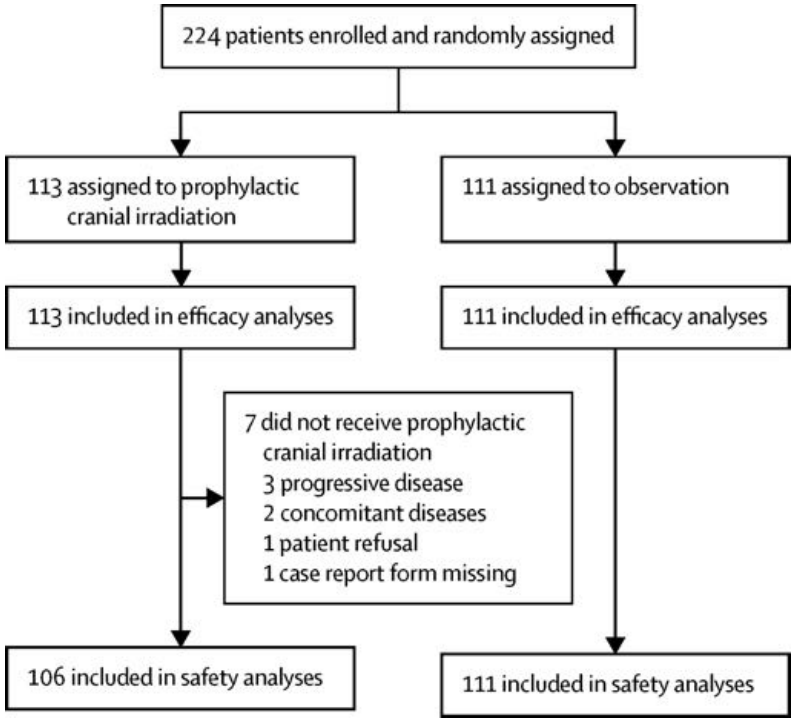
Majority alive 4 years after randomization

(i.e., 2 years after <u>completing</u> pembro maintenance)

Rudin, WCLC 2022

Prophylactic cranial irradiation versus observation in patients with extensive-disease small-cell lung cancer: a multicentre, randomised, open-label, phase 3 trial

Toshiaki Takahashi, Takeharu Yamanaka, Takashi Seto, Hideyuki Harada, Hiroshi Nokihara, Hideo Saka, Makoto Nishio, Hiroyasu Kaneda, Koichi Takayama, Osamu Ishimoto, Koji Takeda, Hiroshige Yoshioka, Motoko Tachihara, Hiroshi Sakai, Koichi Goto, Nobuyuki Yamamoto



Phase 3 trial in Japan, 47 centers

Inclusion:

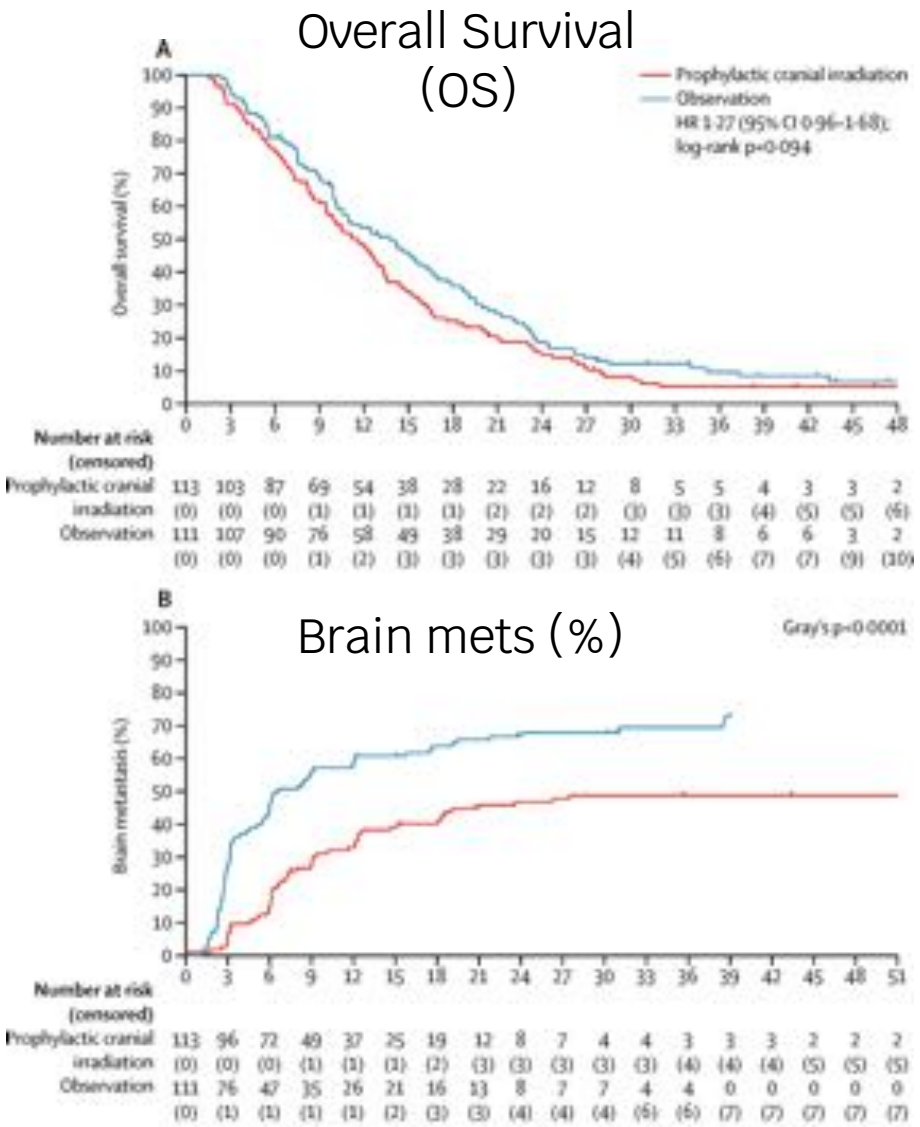
- -ED-SCLC with any response to platinum-based chemo
- -No brain mets on baseline MRI

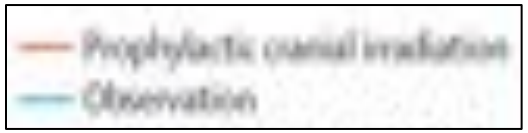
1:1 randomization to PCI (25Gy/10Fx) vs. Observation

MRI brain at 3, 6, 9, 12, 18, 24 months

Primary Endpoint – Overall Survival

Takahashi, et al. Lancet Oncology 2017





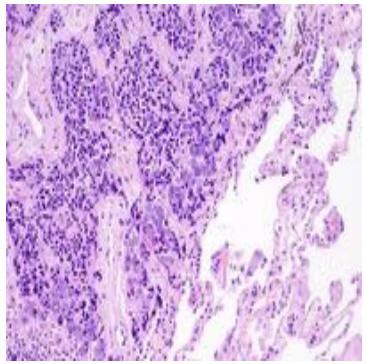
- ***Trial CLOSED early for futility of PCI***
- *No improvement in OS with PCI*
- *Longer survival in observation arm (13.7mo vs 11.6mo) –more 3L and 4L systemic treatment in pts w observation*
- *High rate of brain mets in both arms (48% PCI, 69% Obs) → supports need for MRI surveillance for all pts*

Takahashi, et al. Lancet Oncology 2017

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)

Just like not all cows are the same,

not all SCLC is the same…

JUNIOR BREEDING BEEF HEIFER SHOW ____ 195
Angus Beef Heifers ____ 199
Beefmaster Beef Heifers ____ 201
Brangus Beef Heifers ____ 202
Charolais Beef Heifers ____ 203
Chianina Beef Heifers ____ 204
Grey Brahman Beef Heifers ____ 205
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Maine-Anjou Beef Heifers ____ 208
Polled Hereford Beef Heifers ____ 209
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American Registered Breeds Beef Heifers ____ 217
Other Registered Breeds Beef Heifers ____ 218

2023 Houston Livestock Show and Rodeo

Angus

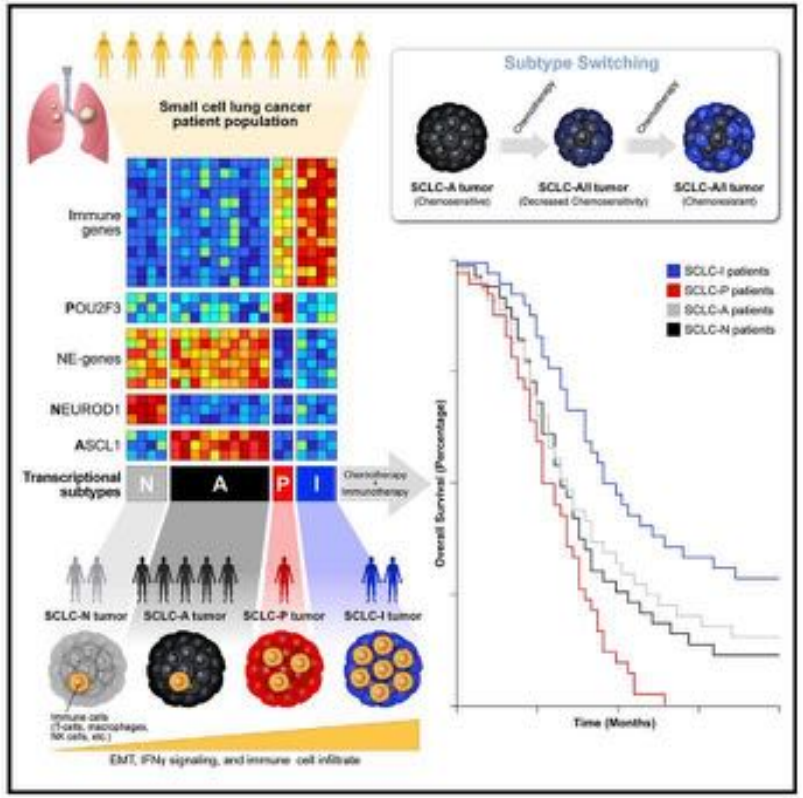
Charolais

Limousin

Red Brahman

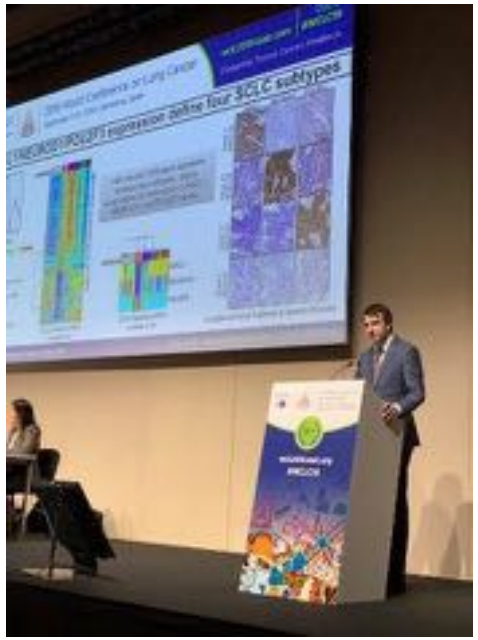
Cancer Cell

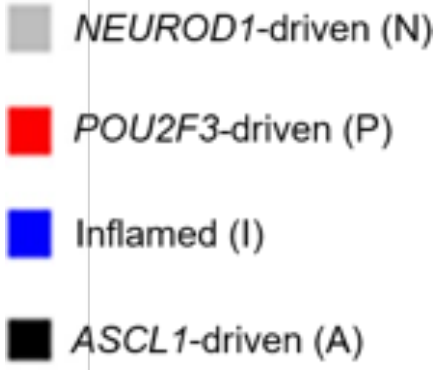
Patterns of transcription factor programs and immune pathway activation define four major subtypes of SCLC with distinct therapeutic vulnerabilities

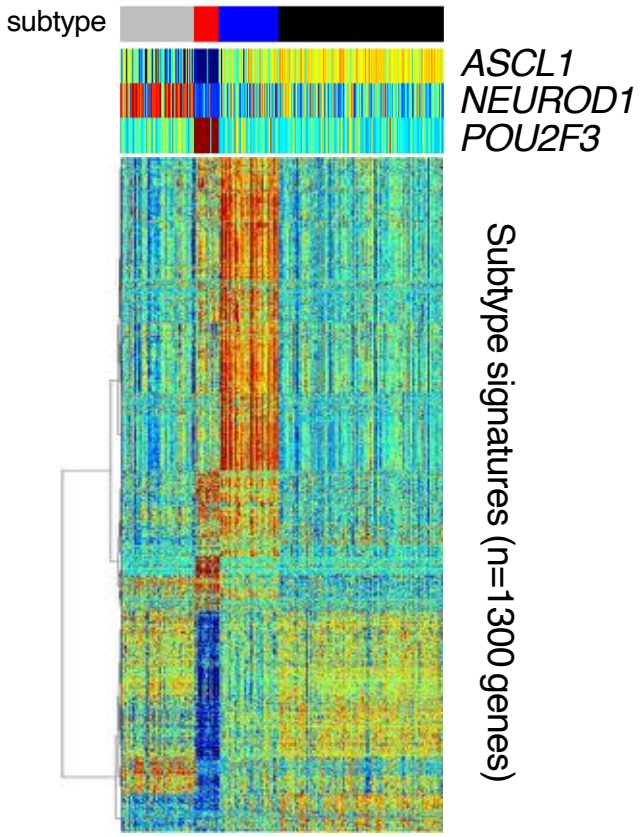


Gay, et al, Cancer Cell 2021

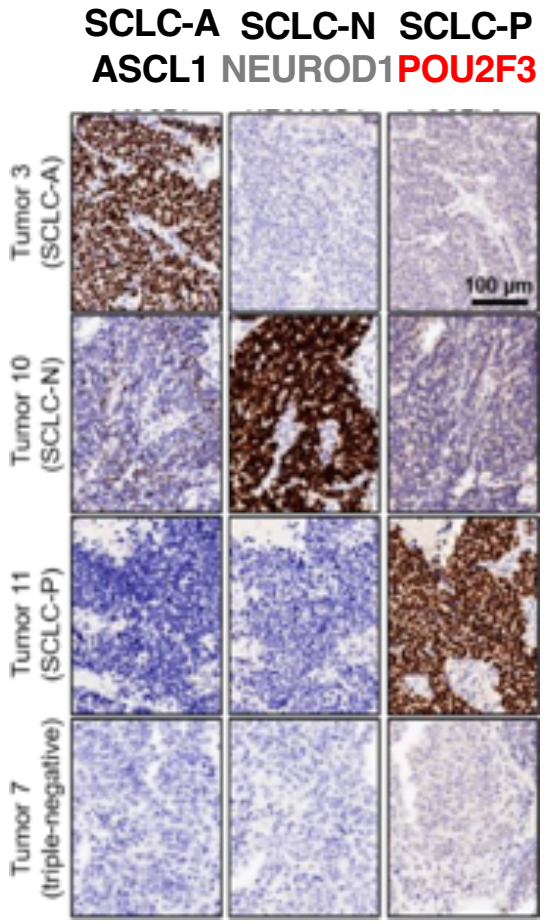
Unsupervised mRNA analysis identified four major transcriptional subtypes of SCLC: ASCL1, NEUROD1, POU2F3, and Inflamed







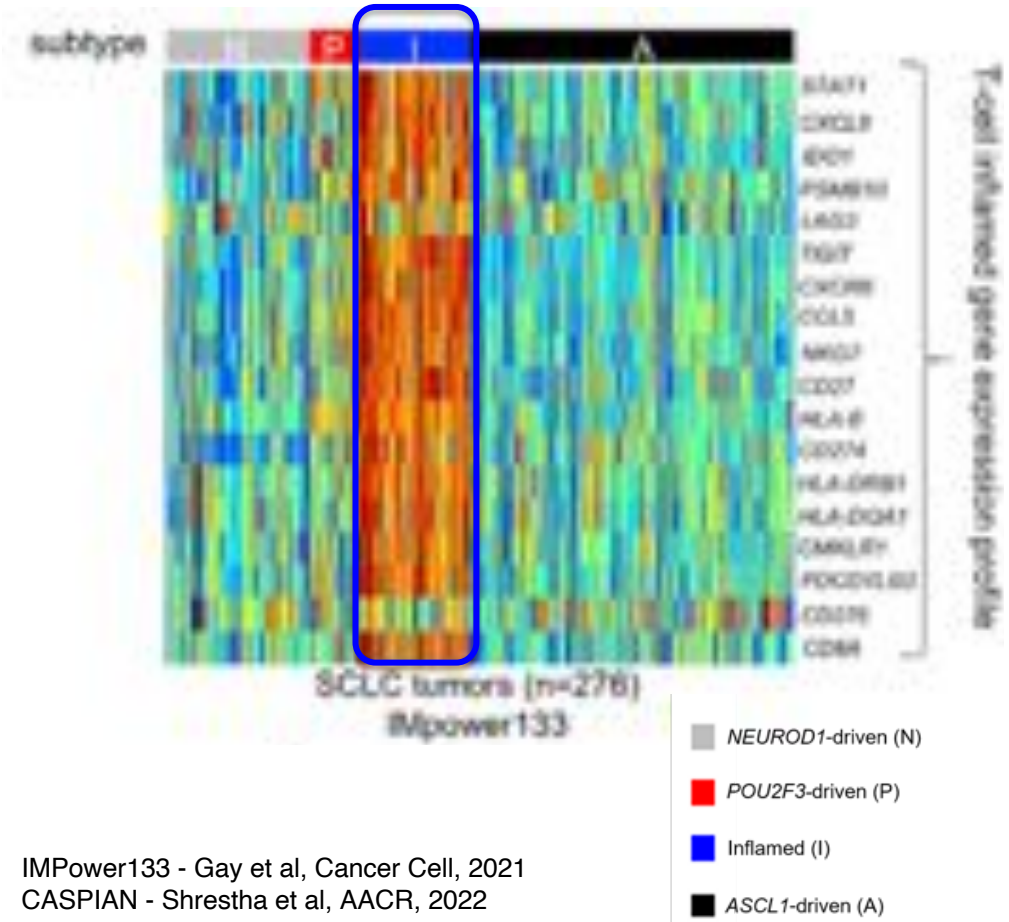
ES-SCLC tumors (n=276)
IMpower133



SCLC Subtype	Limited stage	Extensive Stage
SCLC-A	36%	51%
SCLC-N	31%	23%
SCLC-P	17%	7%
SCLC-Inflamed	16%	18%

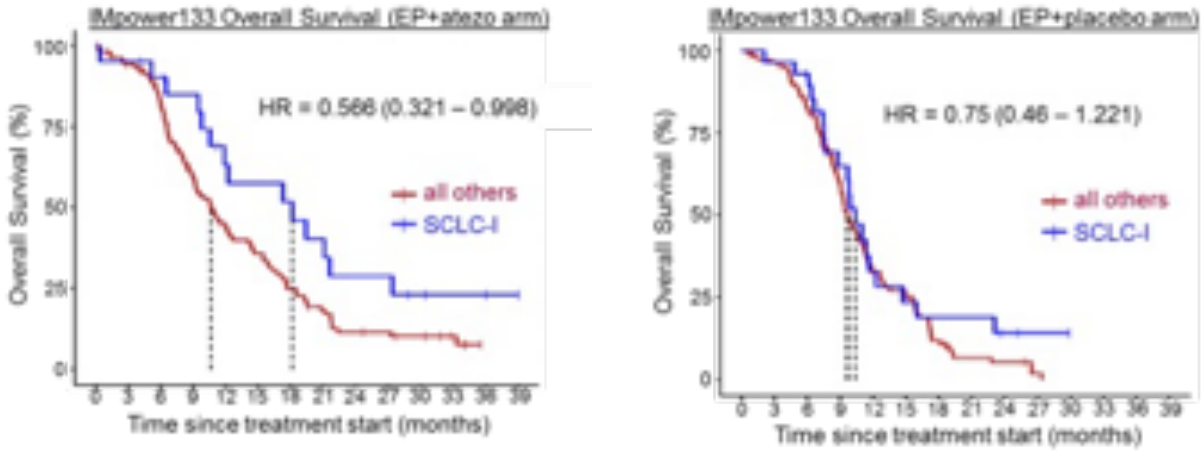
Carl Gay et al, WCLC 2019
Gay et al, Cancer Cell 2021

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



IMpower133

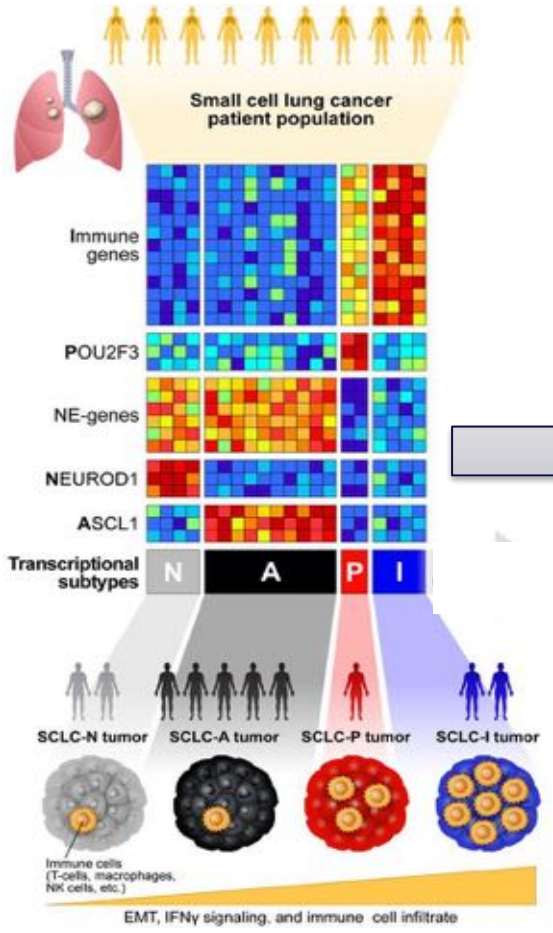
SCLC-Inflamed: 18.2 vs 10.4mo

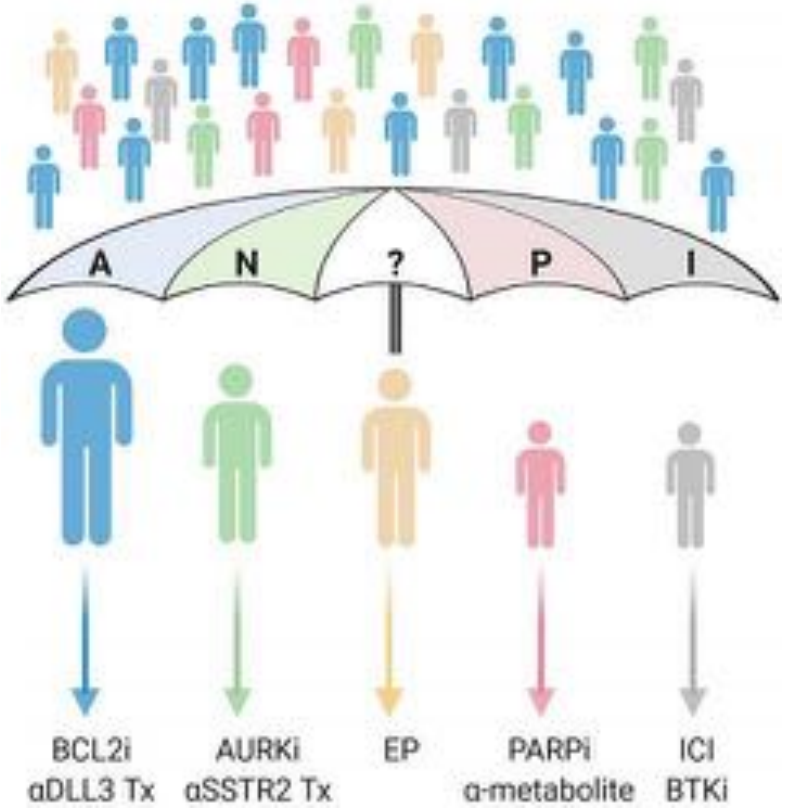


CASPIAN - SCLC-Inflamed subtype: mOS 17.6 (EP-durva) vs 11.3mo (EP)

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

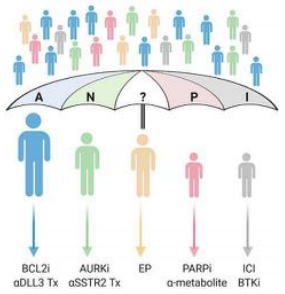
Distinct therapeutic vulnerabilities in molecular subtypes of Small Cell Lung Cancer

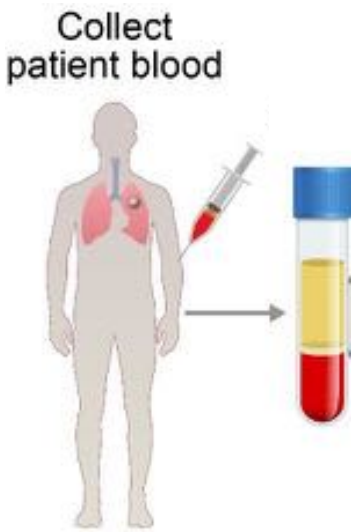




Gay, Stewart, Park et al, Cancer Cell 2021
Frese, Simpson, *Dive, "SCLC enters the era of precision medicine,"* Cancer Cell 2021

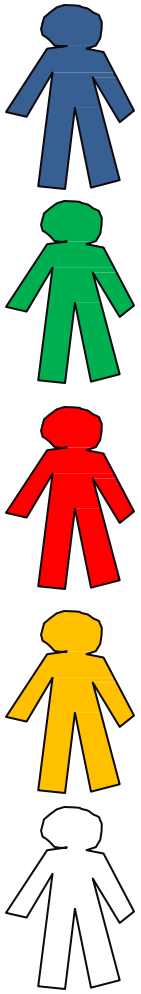
Personalizing SCLC Treatment: *Clinical Trials*





Profile for SCLC subtype or drug specific biomarker and assign to treatment

(Repeat upon relapse)



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

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

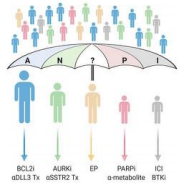
Treatment Regimen 3
SCLC-P (**POU2F3**)

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

Treatment Regimen 5
Drug-specific biomarker

	Neuroendocrine		Non-Neuroendocrine	
Subtype	SCLC-A (36-51%)	SCLC-N (23-31%)	SCLC-P (7-17%)	SCLC-Inflamed (16-18%)
Targets	DLL3 BCL2 CD56 EZH1 LSD1	AURKA DLL3 MYC GD2	PARP1	AXL CD274 CD38 CTLA4 PD1/PDL1 BTKi

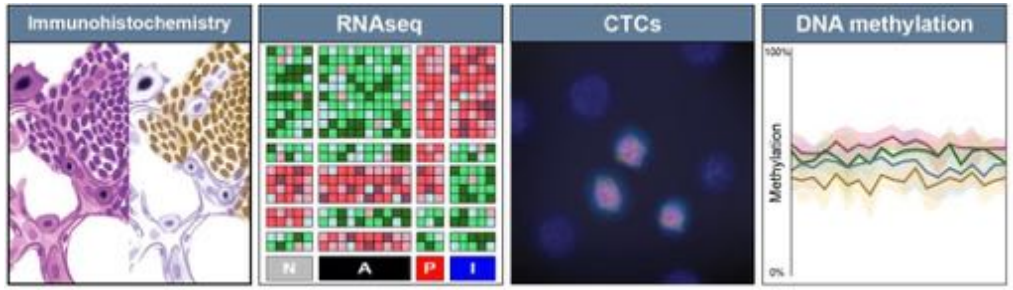
Conclusions and Next Steps

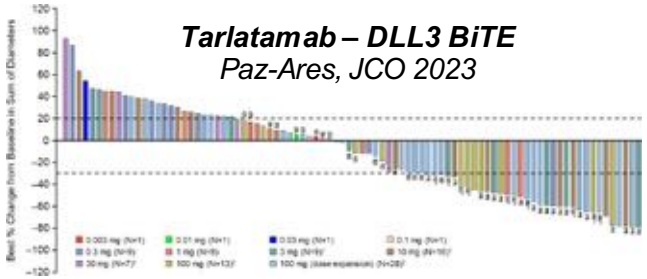


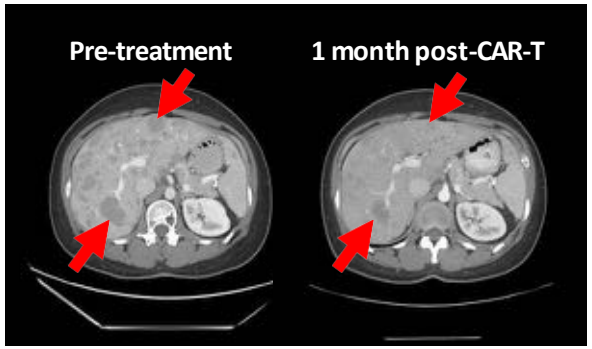
- **Chemo-immunotherapy now the gold standard frontline treatment of Extensive Stage disease (ES-SCLC)** (EP-atezo or EP-durva)

- **Despite addition of immunotherapy, most SCLC patients need more effective treatments.**

- **Recent discoveries enable biomarker-driven clinical trials.**
  - **Molecular subtypes of SCLC** *(SCLC-ASCL1, NEUROD1, POU2F3, Inflamed)*
  - **Novel surface targeting therapeutics** *(BiTE, CAR-T, DLL3, etc)*
  - **Blood-based biomarkers** *(e.g., ctDNA/methylation)*







Liquid biopsy feasible for SCLC
(SCLC sheds huge amount of ctDNA, CTCs)

Acknowledgements

Byers Lab

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Adi Gazdar
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Giulia Fabbri
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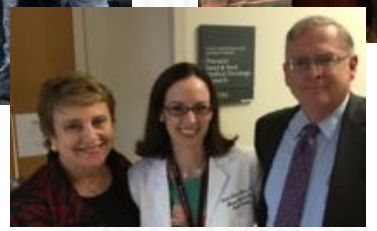
IASLC INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER
Conquering Thoracic Cancers Worldwide



Cancer Prevention & Research Institute of Texas

MD Anderson Moon Shots Program

LUNGEVITY Find it. Treat it. Live.

LUNG CANCER RESEARCH FOUNDATION Living. Breathing. Science.

NIH NATIONAL CANCER INSTITUTE

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Thank you!