Updates in Small Cell Lung Carcinomas

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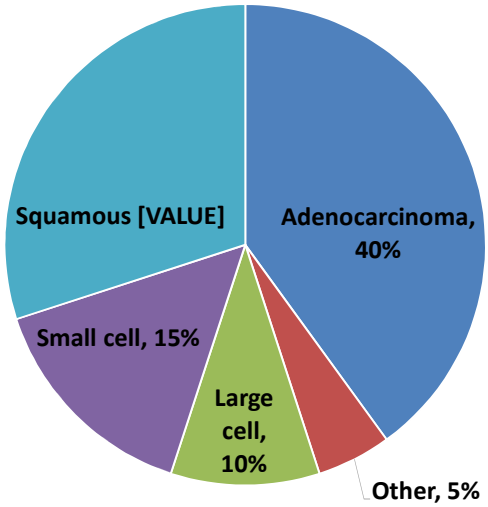
Saint Luke's HEALTH SYSTEM

Disclosures

- Research funding: Novartis, Merck, CanStem, Helsinn, Biocept, Incyte, Genetech & Paradigm
- Advisory role: Astra Zeneca, Boehringer Ingelheim, Novartis, Eli Lilly & Pfizer
- Speakers bureau: Astra Zeneca & Boehringer Ingelheim

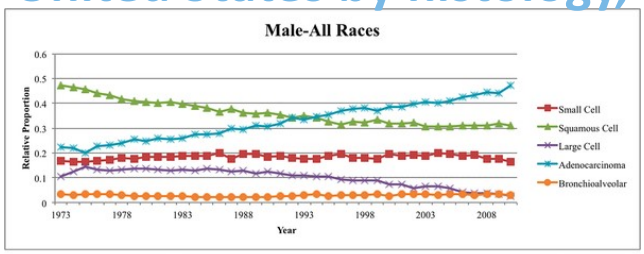
Hanahan D & Weinberg RA et al. Cell 2000

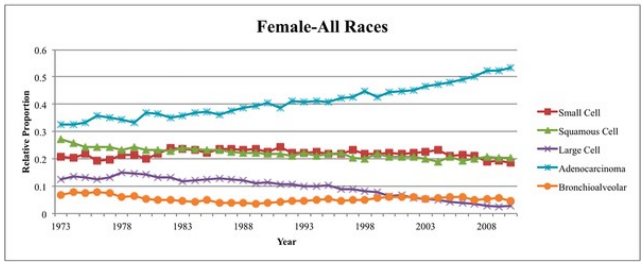
Distribution of Lung Cancer Histologies



Adapted from https://https://lungevity.org/for-patients-caregivers/lung-cancer-101/types-of-lung-cancer

Relative proportions of lung cancer cases in the United States by histology, 1973–2010.



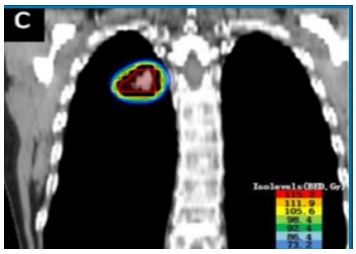


- Small cell cancer rates decline over time.
- Declining rates driven by changes in tobacco smoking habit and type of cigarettes.
- Constitute 40% - 45% of all lung cancers.
- Approximately 80-90,000 cases a year in the United States.
- Both strongly correlate with cigarette smoking.

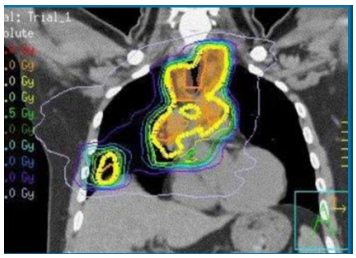
Meza R,et al PLOS ONE 2015

Limited Stage Small Cell Lung Cancer (SCLC)

- Limited stage: 1/3 of all cases
- Defined as disease that can be treated definitively or with curative intent. Corresponds to Stage I to III of NSCLC
- Standard of care
  - Stage I : resection followed by adjuvant chemotherapy
  - Stage I – III: Concurrent chemo-radiation
    - Cis/Etop x 4 cycles
    - RT: QD or BID
  - Prophylactic cranial irradiation (PCI)
    - 5 year survival benefit (5.4% benefit)
  - Outcomes
    - ORR: 70%-90%; 5yr survival at ~ 26%
    - Most (~75%) recur



Stage I



Stage III

Yang et al JCO 2016, Li et al PLoS One 2017, Huo et al, Clin Adv Radio Tech 2016

Extensive Stage (ES) SCLC

- 2/3rds of all SCLC cases
- **Between 1980 – 2006 no major advances beyond platinum doublet**

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Twenty-Seven Years of Phase III Trials for Patients with Extensive Disease Small-Cell Lung Cancer: Disappointing Results

Isao Oze, Katsuyuki Hotta*, Katsuyuki Kiura, Nobuaki Ochi, Nagio Takigawa, Yoshiro Fujiwara, Masahiro Tabata, Mitsune Tanimoto

Department of Respiratory Medicine, Okayama University Hospital, Okayama, Japan

Frontline Setting

Cisplatin + Etoposide

Carboplatin + Etoposide

Carboplatin + Etoposide + Atezo

Carboplatin + Etoposide + Durva

1985 1990 1995 2000 2005 2010 2015 2020

Second-line Setting

Topotecan IV

Topotecan PO

Third-line Setting

Nivolumab

Extensive Stage (ES) SCLC

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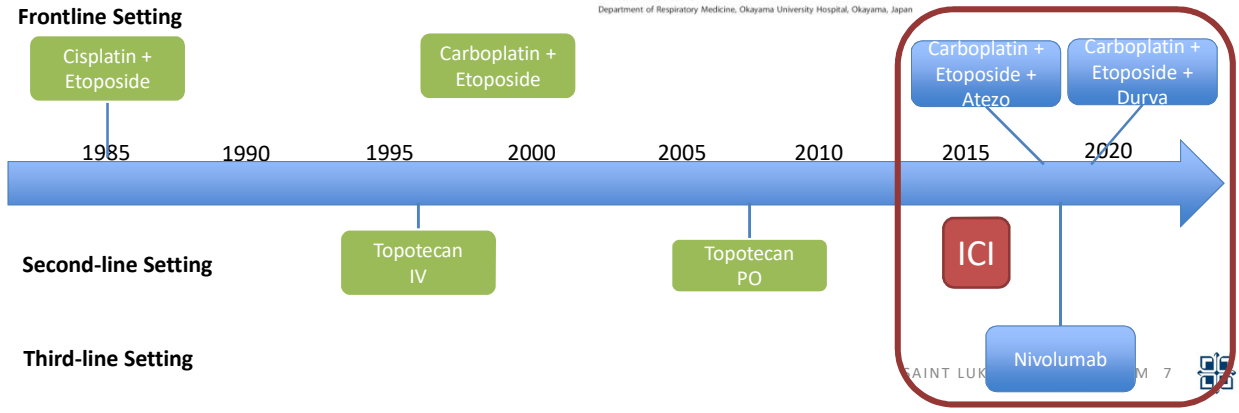
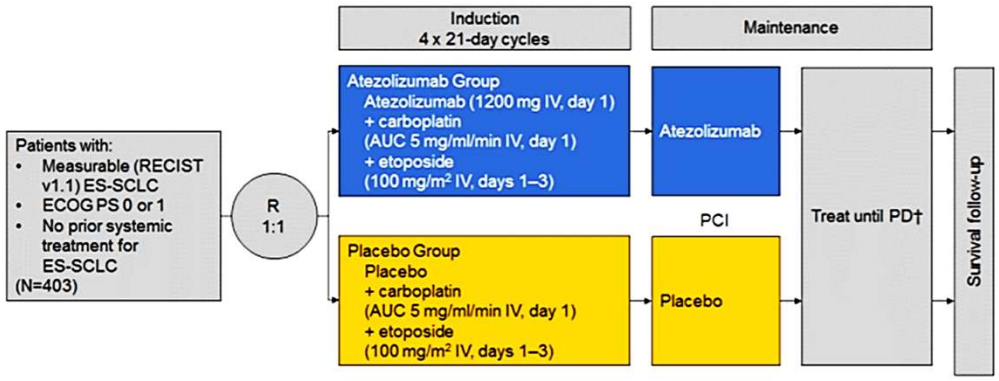


IMpower133: Phase 1/3 double blind, randomized trial evaluating carboplatin, etoposide & atezolizumab



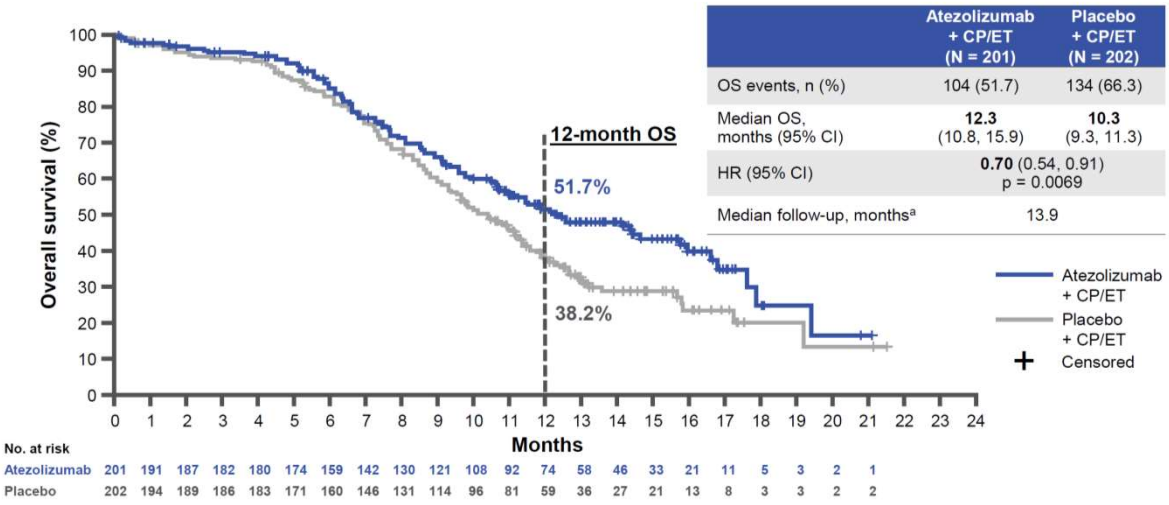
Horn et al NEJM 2018

IMpower133: Baseline Characteristics

Characteristic	Atezo + CP/ET (N = 201)	Placebo + CP/ET (N = 202)
Median age (range)	64 (28-90)	64 (26-87)
Age group – no (%)		
< 65 years	111 (55)	106 (52)
≥ 65 years	90 (45)	96 (48)
Male sex – no (%)	129 (64)	132 (65)
Smoking status		
Current smoker	74 (36.8)	75 (37.1)
Former Smoker	118 (58.7)	124 (61.4)
Race – no (%)		
White	163 (81)	159 (79)
ECOG PS – no (%)		
0	73 (36)	67 (33)
1	128 (64)	135 (67)
Brain metastasis – no (%)		
Yes	17 (8)	18 (9)

Horn et al NEJM 2018

IMpower133: Overall Survival

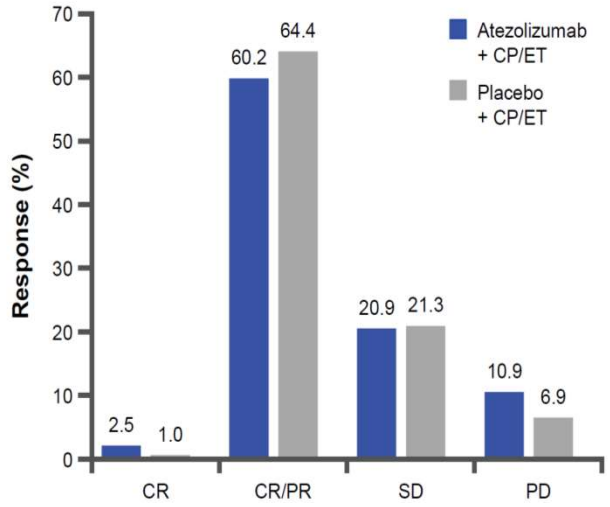


	Atezolizumab + CP/ET (N = 201)	Placebo + CP/ET (N = 202)
OS events, n (%)	104 (51.7)	134 (66.3)
Median OS, months (95% CI)	**12.3** (10.8, 15.9)	**10.3** (9.3, 11.3)
HR (95% CI)	**0.70** (0.54, 0.91) p = 0.0069	
Median follow-up, months[a]	13.9	

[a] Clinical data cutoff date: April 24, 2018, 11 months after the last patient was enrolled. CI, confidence interval; HR, hazard ratio; CP/ET, carboplatin + etoposide.

Horn et al NEJM 2018

IMpower133: ORR and DoR



Duration of response	Atezolizumab + CP/ET (N = 121)	Placebo + CP/ET (N = 130)
Median duration, months (range)	4.2 (1.4[a] to 19.5)	3.9 (2.0 to 16.1[a])
HR (95% CI)	0.70 (0.53, 0.92)	
6-month event-free rate — %	32.2	17.1
12-month event-free rate — %	14.9	6.2
Patients with ongoing response — no. (%)[b]	18 (14.9)	7 (5.4)

Horn et al NEJM 2018

IMpower133: Adverse Events

Treatment-related AEs — no. (%) > 5% Grade 3–4 AEs in either treatment group	Atezolizumab + CP/ET (N = 198)			Placebo + CP/ET (N = 196)		
	Grade 1–2	Grade 3–4	Grade 5	Grade 1–2	Grade 3–4	Grade 5
Neutropenia	26 (13.1)	45 (22.7)	1 (0.5)	20 (10.2)	48 (24.5)	0
Anemia	49 (24.7)	28 (14.1)	0	41 (20.9)	24 (12.2)	0
Neutrophil count decreased	7 (3.5)	28 (14.1)	0	12 (6.1)	33 (16.8)	0
Thrombocytopenia	12 (6.1)	20 (10.1)	0	14 (7.1)	15 (7.7)	0
Leukopenia	15 (7.6)	10 (5.1)	0	10 (5.1)	8 (4.1)	0
Febrile neutropenia	0	6 (3.0)	0	0	12 (6.1)	0

Immune-related AEs — no. (%) > 1% Grade 3–4 AEs in either treatment group	Atezolizumab + CP/ET (N = 198)			Placebo + CP/ET (N = 196)		
	Grade 1–2	Grade 3–4	Grade 5	Grade 1–2	Grade 3–4	Grade 5
Rash	33 (16.7)	4 (2.0)	0	20 (10.2)	0	0
Hepatitis	11 (5.6)	3 (1.5)	0	9 (4.6)	0	0
Infusion-related reaction	7 (3.5)	4 (2.0)	0	9 (4.6)	1 (0.5)	0
Pneumonitis	3 (1.5)	1 (0.5)	0	3 (1.5)	2 (1.0)	0
Colitis	1 (0.5)	2 (1.0)	0	0	0	0
Pancreatitis	0	1 (0.5)	0	0	2 (1.0)	0

Horn et al NEJM 2018

IMpower133: Adverse Events

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Pneumonitis	3 (1.5)	1 (0.5)	0	3 (1.5)	2 (1.0)	0
Colitis	1 (0.5)	2 (1.0)	0	0	0	0
Pancreatitis	0	1 (0.5)	0	0	2 (1.0)	0

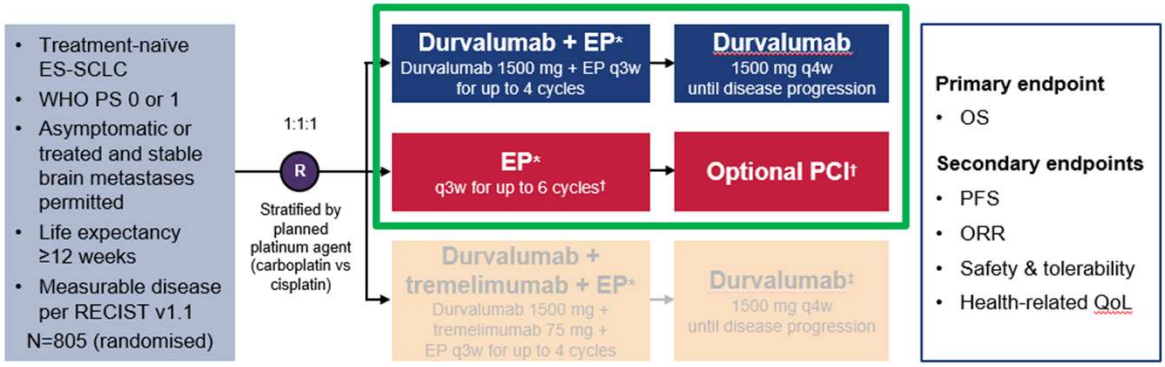
Horn et al NEJM 2018

IMpower133: Results

- IMpower133 shift's the paradigm of managing ES-SCLC after almost 30 years
- Addition of atezolizumab improves both OS and PFS
  - mOS 12.3 months vs 10.3 months
  - mPFS 5.2 months vs 4.3 months
- Atezolizumab plus Carbo/Etop has an acceptable safety profile
  - Hematologic toxicity not significantly different, slightly higher rates of anemia
  - Increased risk for imAEs

Horn et al NEJM 2018

CASPIAN: Phase 3 randomized, open label trial evaluating carboplatin, etoposide & durvalumab



The durvalumab + tremelimumab + EP versus EP comparison continues to final analysis

*EP consists of etoposide 80–100 mg/m² with either carboplatin AUC 5–6 or cisplatin 75–80 mg/m²
†Patients could receive an additional 2 cycles of EP (up to 6 cycles total) and PCI at the investigator's discretion
‡Patients received an additional dose of tremelimumab post-EP

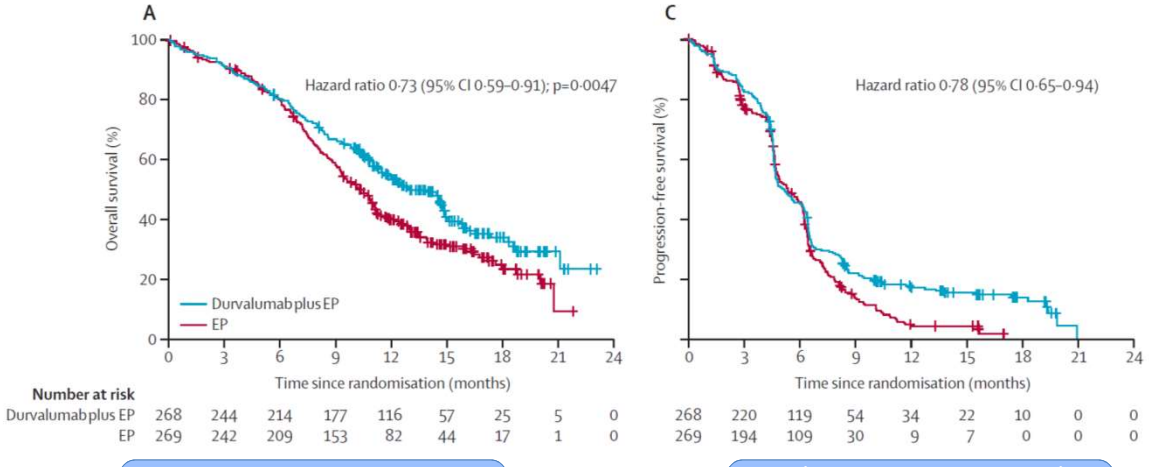
Paz-Ares et al Lancet 2019

CASPIAN: Baseline Characteristics

Characteristic	Durva+ CP/ET (N = 268)	CP/ET (N = 269)
Median age (range)	62 (58-68)	63 (57-68)
Age group – no (%)		
< 65 years	167 (62)	157 (58)
≥ 65 years	101 (38)	112 (42)
Male sex – no (%)	190 (71)	184 (68)
Smoking status		
Current smoker	120 (45)	126 (46)
Former Smoker	126 (47)	128 (48)
Race – no (%)		
White	229 (85)	221 (82)
ECOG PS – no (%)		
0	99 (37)	90 (33)
1	169 (63)	179 (67)
Brain metastasis – no (%)		
Yes	28 (10)	27 (10)

Horn et al NEJM 2018

CASPIAN: Survival

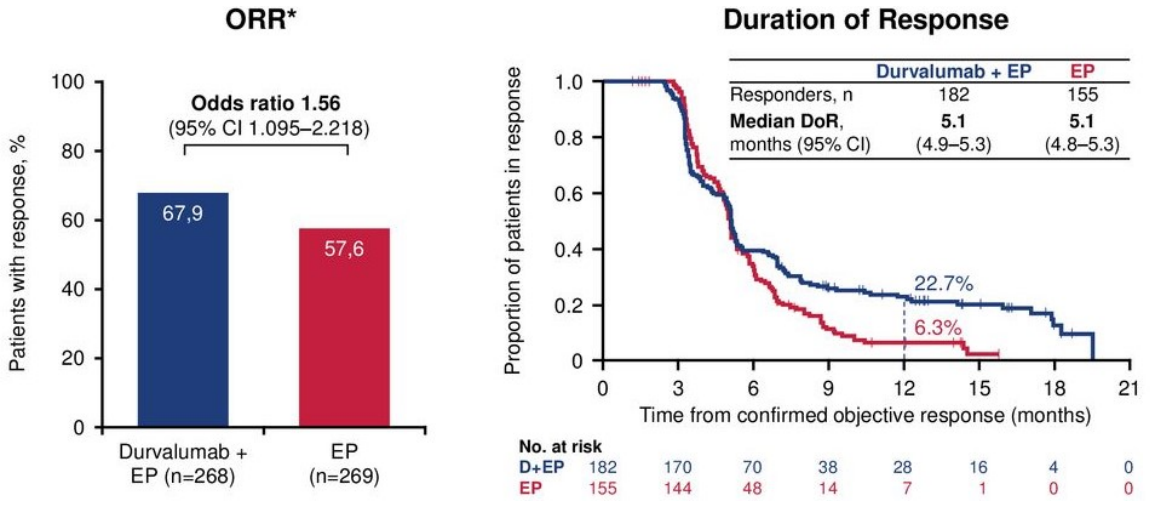


Median OS 13.0 vs 10.3 months
1 year survival 54% vs 40%

Median PFS 5.1 vs 5.4 months
6 month PFS 45% vs 46%
12 month PFS 18% vs 5%

Paz-Ares et al Lancet 2019

CASPIAN: ORR



Paz-Ares et al Lancet 2019

CASPIAN: Safety

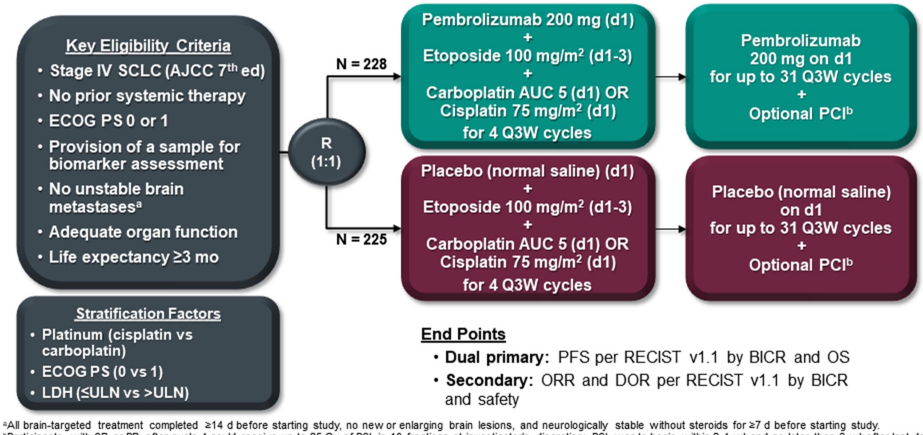
	Durva+ CP/ET (N = 265)	CP/ET (N = 266)
Any grade all cause AEs, n (%)	260 (98.1)	258 (97.0)
Grade 3/4 AEs	163 (61.5)	166 (62.4)
Serious AEs	82 (30.9)	96 (36.1)
AEs leading to treatment discontinuation*	25 (9.4)	25 (9.4)
Immune-mediated AEs†	52 (19.6)	7 (2.6)
AEs leading to death	13 (4.9)	15 (5.6)
Treatment related AEs leading to death	5 (1.9)	2 (0.8)

* Includes patients who discontinued atleast one drug.
† An event that is associated with drug exposure and consistent with an immune-mediated mechanism of action, where there is not clear alternate etiology and the event required the treatment with systemic corticosteroids and immunosuppressants and/or for specific endocrine events, endocribe therapy; majority of imAEs were low grade and thyroid related.

Paz-Ares et al Lancet 2019
Horn et al NEJM 2019

Rudin KN604 ASCO 2020

KEYNOTE-604 Study Design

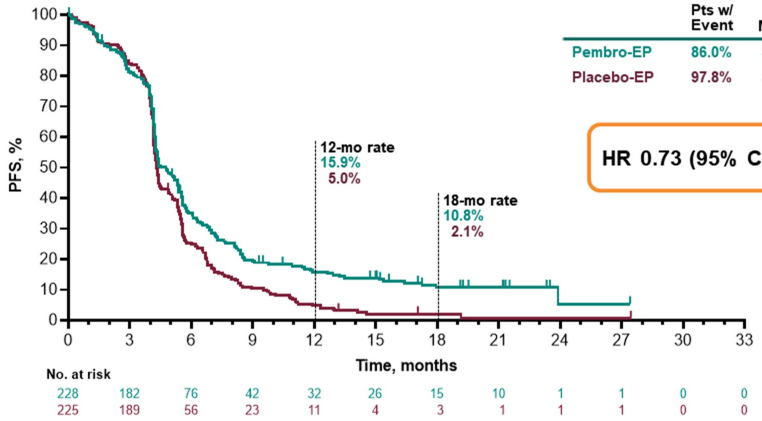


[a]All brain-targeted treatment completed ≥14 d before starting study, no new or enlarging brain lesions, and neurologically stable without steroids for ≥7 d before starting study. [b]Participants with CR or PR after cycle 4 could receive up to 25 Gy of PCI in 10 fractions at investigator's discretion; PCI was to begin within 2-4 wk and no later than 6 wk after last dose of cycle 4; study treatment could continue during PCI. KEYNOTE-604 ClinicalTrials.gov identifier, NCT03066778. BICR, blinded independent central review.

Presented By Charles Rudin at TBD

Rudin KN604 ASCO 2020

Progression-Free Survival, ITT: FA



	Pts w/ Event	Median (95% CI)
Pembro-EP	86.0%	4.8 mo (4.3-5.4)
Placebo-EP	97.8%	4.3 mo (4.2-4.5)

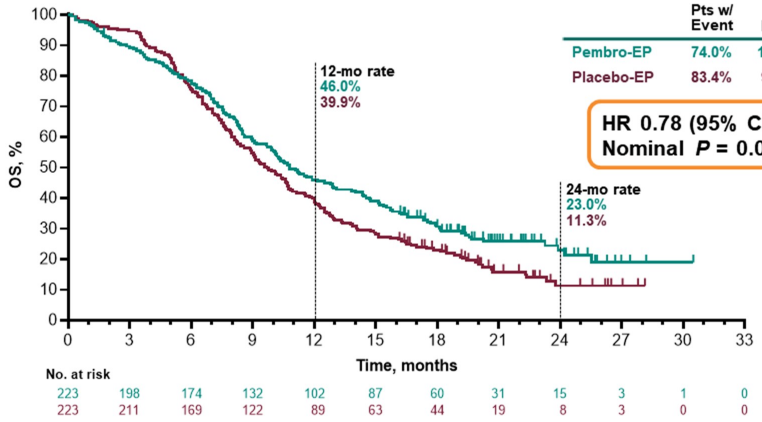
HR 0.73 (95% CI 0.60-0.88)

Data cutoff date: Dec 2, 2019.

Presented By Charles Rudin at TBD

Rudin KN604 ASCO 2020

Overall Survival, As Treated: FA



	Pts w/ Event	Median (95% CI)
Pembro-EP	74.0%	10.8 mo (9.7-12.9)
Placebo-EP	83.4%	9.7 mo (8.6-10.7)

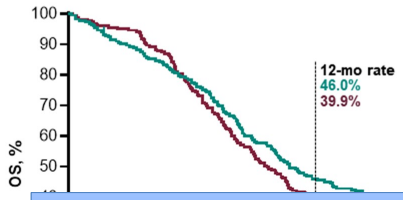
HR 0.78 (95% CI 0.63-0.97)
Nominal *P* = 0.0124

Data cutoff date: Dec 2, 2019.

Presented By Charles Rudin at TBD

Rudin KN604 ASCO 2020

Overall Survival, As Treated: FA



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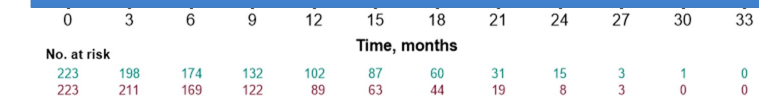
HR 0.78 (95% CI 0.63-0.97)
Nominal *P* = 0.0124

24-mo rate

HR for OS favored Pembro-EP but the significant threshold was missed (HR 0.80; p = 0.0164, significance threshold p = 0.128)



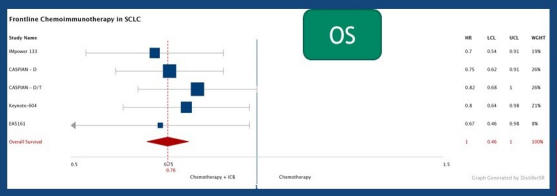
No. at risk

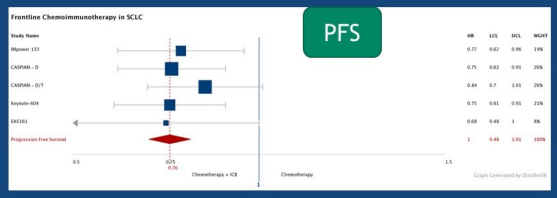
223	198	174	132	102	87	60	31	15	3	1	0
223	211	169	122	89	63	44	19	8	3	0	0

Data cutoff date: Dec 2, 2019.

Presented By Charles Rudin at TBD

Efficacy Summary: Chemo-Immunotherapy in SCLC





	IMpower133	Caspian D	Caspian D/T	KN-604	EA5161
Median PFS	5.2	5.1	4.9	4.5	5.5
Median OS	12.3	13	10.4	10.8	11.3
12-month OS	**51.7**	**52.8**	**43.8**	**45.1**	**≈48**
24-month OS	**≈22**	**22.2**	**23.4**	**22.5**	**NR**
HR PFS 95% CI	0.77 0.62-0.96	0.78 0·65-0·94	0.84 0.70-1.01	0.75 0.61-0.91	0.68 0.48-1.0
HR OS 95% CI	0.70 0.54-0.91	0·73 0·59-0·91	0.82 0.68-1.00	0.80 0.64-0.98	0.67 0.46-0.98

PRESENTED AT: 2020ASCO ANNUAL MEETING #ASCO20

PRESENTED BY: Taofeek K. Owonikoko, MD, PhD

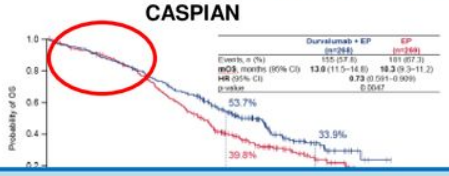
4

IASLC
2019 World Conference on Lung Cancer
September 7–10, 2019 | Barcelona, Spain
wclc2019.iaslc.com | #WCLC19
Conquering Thoracic Cancers Worldwide

1. Maintenance effect or Delayed effect of IO?

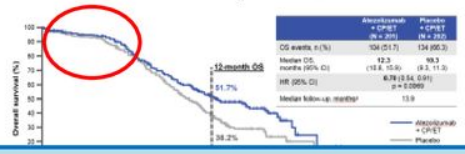
CASPIAN

OS



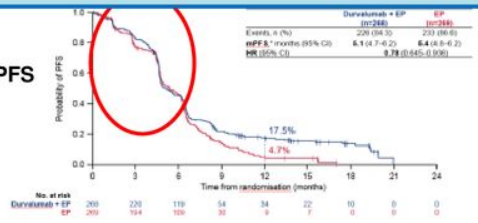
IMpower133

OS

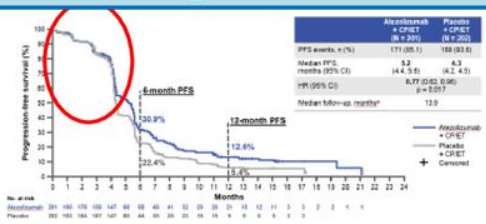


Nivolumab, Nivolumab + Ipilimumab (CM-451), and Pembrolizumab failed in the maintenance setting

PFS



PFS



Paz-Ares L et al WCLC 2019
Horn L et al NEJM 2018

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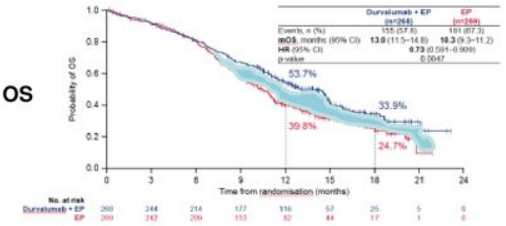
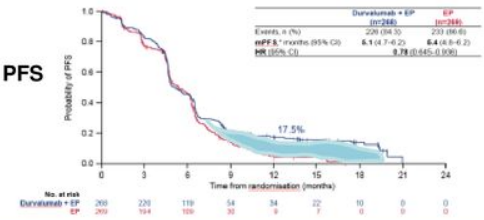
2. Predictive Biomarker to Select Patients Benefit from IO?

CASPIAN

OS

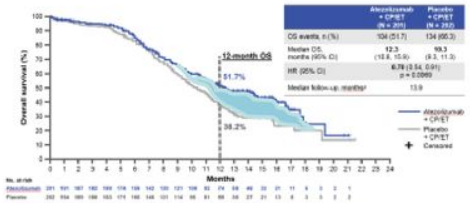


PFS

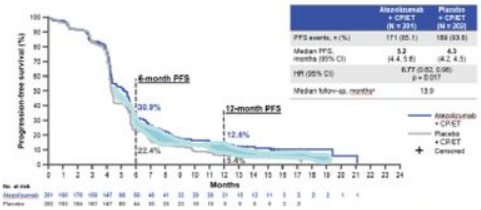


IMpower133

OS



PFS



Paz-Ares L et al WCLC 2019
Horn L et al NEJM 2018

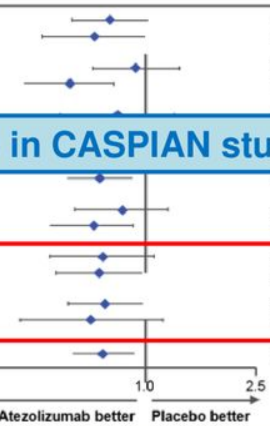
IASLC

2019 World Conference on Lung Cancer
September 7–10, 2019 | Barcelona, Spain

wclc2019.iaslc.com | #WCLC19
Conquering Thoracic Cancers Worldwide

bTMB did not differentiate benefit of atezolizumab in IMpower133

Population	Median overall survival (months): Atezolizumab + CP/ET	Median overall survival (months): Placebo + CP/ET	OS hazard ratio[a] (95% CI)
Male (n = 261)	12.3	10.9	0.74 (0.54, 1.02)
Female (n = 142)	12.5	9.5	0.65 (0.42, 1.00)
< 65 years (n = 217)	12.1	11.5	0.92 (0.64, 1.32)
≥ 65 years (n = 186)	12.5	9.6	0.53 (0.36, 0.77)
ECOG PS 0 (n = 140)	16.6	12.4	0.79 (0.49, 1.27)
No brain metastases (n = 368)	12.6	10.4	0.68 (0.52, 0.89)
Liver metastases (n = 149)	9.3	7.8	0.81 (0.55, 1.20)
No liver metastases (n = 254)	16.8	11.2	0.64 (0.45, 0.90)
bTMB < 10 mut/mb (n = 139)	11.8	9.2	0.70 (0.45, 1.07)
bTMB ≥ 10 mut/mb (n = 212)	14.6	11.2	0.68 (0.47, 0.97)
bTMB < 16 mut/mb (n = 271)	12.5	9.9	0.71 (0.52, 0.98)
bTMB ≥ 16 mut/mb (n = 80)	17.8	11.9	0.63 (0.35, 1.15)
ITT (N = 403)	12.3	10.3	0.70 (0.54, 0.91)

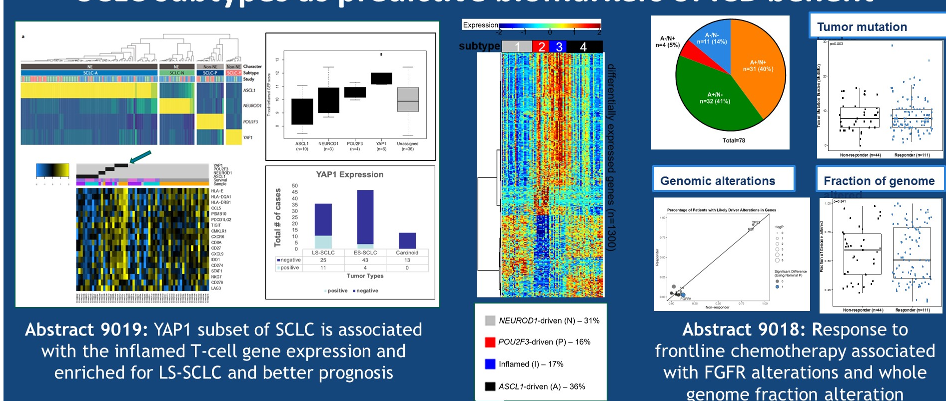


Biomarker study is not available in CASPIAN study !

Clinical data cutoff date: April 24, 2018. bTMB (blood tumor mutational burden) assessed as reported in Gandara DR, et al. *Nat Med*, 2018.
[a] Hazard ratios are unstratified for patient subgroups and stratified for the ITT.

Horn L et al NEJM 2018

SCLC subtypes as predictive biomarkers of ICB benefit



Abstract 9019: YAP1 subset of SCLC is associated with the inflamed T-cell gene expression and enriched for LS-SCLC and better prognosis

Rudin et al., Nat Rev Cancer, 2019; Owonikoko et al. Abs #9019; ASCO 2020.

Gay C et al. WCLC 2019

Abstract 9018: Response to frontline chemotherapy associated with FGFR alterations and whole genome fraction alteration

Lai W. V et al. ASCO 2020.

PRESENTED AT: 2020 ASCO ANNUAL MEETING #ASCO20 Slides are the property of the author, permission required for reuse.

PRESENTED BY: Taofeek K. Owonikoko, MD, PhD

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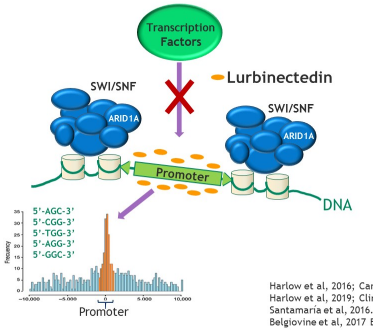
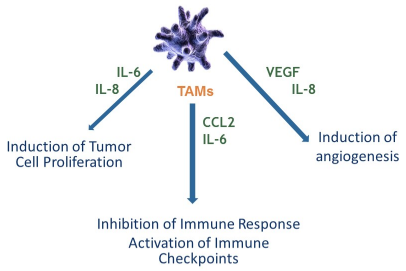
Presented By Taofeek Owonikoko at TBD

Lurbinectedin - a Selective Inhibitor of Oncogenic Transcription

CANCER IS FREQUENTLY A TRANSCRIPTIONAL DISEASE CAUSED BY DEREGULATED ONCOGENIC TRANSCRIPTION FACTORS



BY INHIBITING ACTIVE TRANSCRIPTION IN TUMOR ASSOCIATED MACROPHAGES (TAMS), LURBINECTEDIN DOWNREGULATES IL-6, IL-8, CCL2 AND VEGF



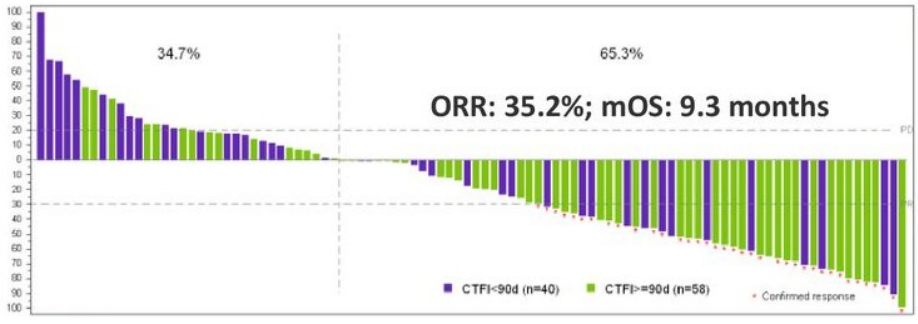
Harlow et al, 2016; Cancer Res 72: 6657-68
Harlow et al, 2019; Clin Cancer Res doi: 10.1158/1078-0432.CCR-18-3511
Santamaria et al, 2016. Mol Cancer Ther 15:2399-412
Belgiovine et al, 2017 Br J Cancer 117:628-38

PRESENTED BY: Dr. Luis Paz Ares

Presented By Luis Paz-Ares at 2019 ASCO Annual Meeting

Phase II: Single agent Lurbinectidin in 2nd line SCLC

Sensitive disease: ORR = 45.0%
Refractory disease: ORR = 22.2%

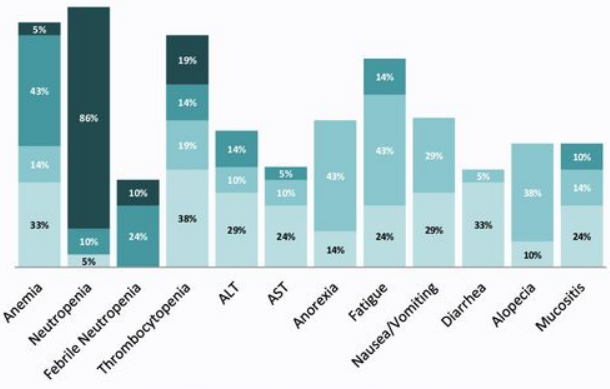


Paz-Ares ASCO 2019

IASLC
INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER

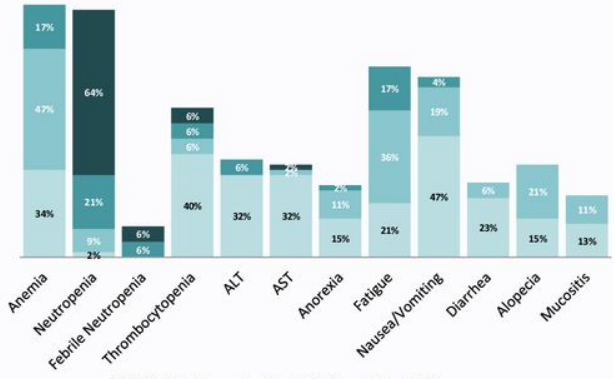
IASLC 18TH WORLD CONFERENCE ON LUNG CANCER
October 15–18, 2017 | Yokohama, Japan
WWW.IASLC.ORG

Safety: Cohort A Combination (n=21)
Myelosupression Most Common AE



GCSF 71%, Dose reduction 33% Dose delays 38%

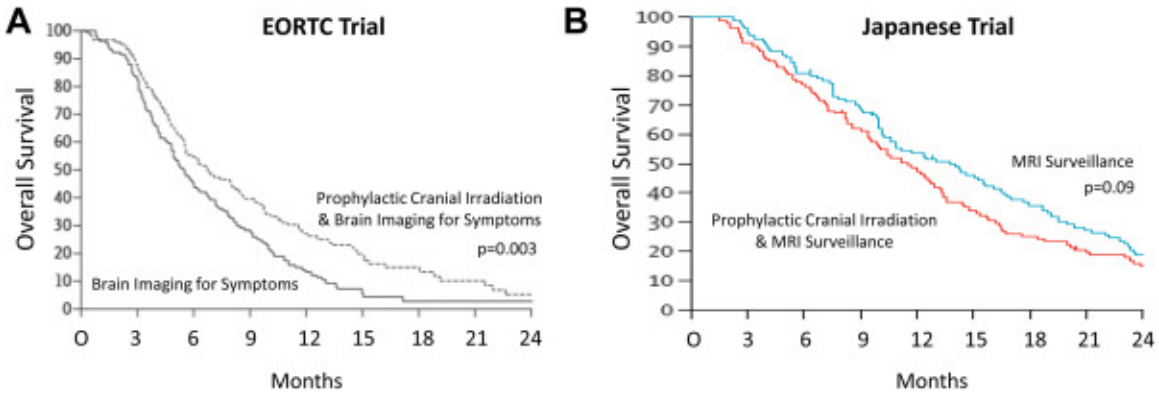
Safety: Cohort B Combination (n=27)
Myelosupression Most Common AE



GCSF 43%, Dose reduction 21% Dose delays 39%

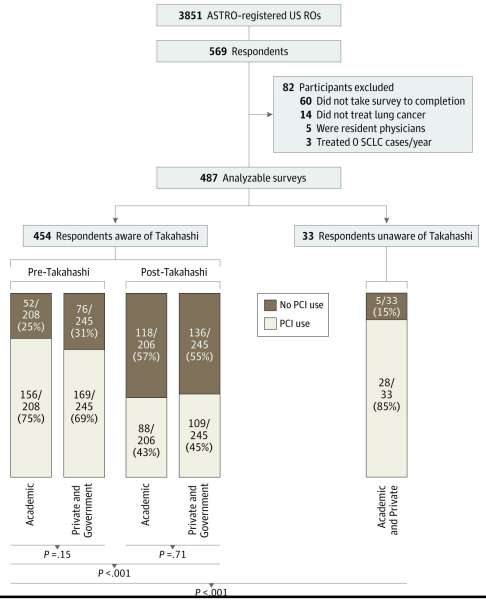
Grade 1 Grade 2 Grade 3 Grade 4

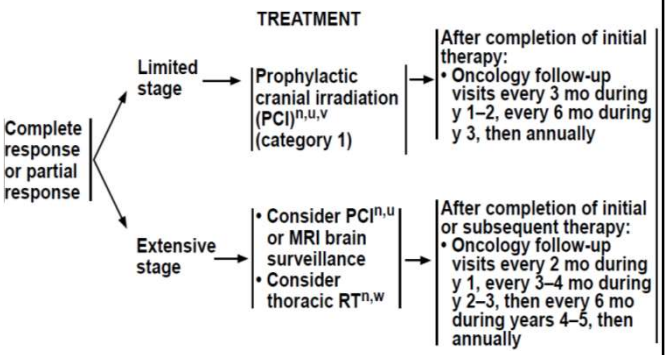
Role of Prophylactic Cranial Irradiation (PCI) in ES-SCLC



Slotman et al NEJM 2007
Takahashi et al Lancet Oncol 2017

PCI in the Community & Guidelines





Conclusions

- ICI plus chemotherapy is the SOC for ES-SCLC
- ICI maintenance not effective
- Evolving role for PCI
  - ? Role for SRS in brain mets.
- 2nd line treatment of SCLC - an unmet need
  - Lurbinectedin has shown promise.
  - Liposomal irinotecan - data awaited.
  - ?DLL3 based Antibody-Drug Conjugate (ADC)?
  - 2nd or 3rd line role for ICI in relapsed/refractory limited stage SCLC

EASY FIX FOR LUNG SMALL CELL LUNG CARCINOMAS.

EASY FIX FOR LUNG SMALL CELL LUNG CARCINOMAS.
SAVE A CIGARETTE