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Small Cell and Neuroendocrine Carcinoma of the Lung

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Disclosures

- Advisory Board – AbbVie, Ascentage, Bristol-Myers Squibb, Genentech/Roche
- Research Funding (to institution) - AbbVie, Amgen, Bristol-Myers Squibb, GlaxoSmithKline, Merrimack pharmaceuticals

Overview

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- Briefly review large cell neuroendocrine carcinoma of the lung
- Review the standard of care for the management of small cell lung cancer (SCLC)
- Discuss ongoing immunotherapy and novel agents under evaluation in SCLC

WHO Classification of neuroendocrine neoplasms (NENs)

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Table 1 NEN 2018 WHO proposed classification of selected NEN by site, category, family, and tumor type

Site	Category	Family	Type	Grade	Current terminology
Lung	Neuroendocrine neoplasm (NEN)	Neuroendocrine tumor (NET)	Pulmonary neuroendocrine tumor (NET)[a]	G1 G2	Carcinoid Atypical carcinoid[a]
		Neuroendocrine carcinoma (NEC)	Small cell lung carcinoma (Pulmonary NEC, small cell-type)[b]		Small cell lung carcinoma
			Pulmonary NEC, large cell-type		Large cell NE carcinoma
Uterus (corpus and cervix)	Neuroendocrine neoplasm (NEN)	Neuroendocrine tumor (NET)	Uterine neuroendocrine tumor (NET)	G1 G2 G3	Carcinoid Atypical carcinoid Atypical carcinoid
		Neuroendocrine carcinoma (NEC)	Uterine NEC, small cell-type		Small cell carcinoma
			Uterine NEC, large cell-type		Large cell NE carcinoma
Pancreas	Neuroendocrine neoplasm (NEN)	Neuroendocrine tumor (NET)	Pancreatic neuroendocrine tumor (NET)	G1 G2 G3	PanNET G1 PanNET G2 PanNET G3
		Neuroendocrine carcinoma (NEC)	Pancreatic NEC, small cell-type		Small cell NE carcinoma
			Pancreatic NEC, large cell-type		Large cell NE carcinoma

Rindi et al., Mod Path, 2018

Large Cell NEC of the Lung

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- A high grade neuroendocrine carcinoma with non–small cell cytologic features
- 1 - 3% of all lung cancers and is associated with a poor prognosis
- Diagnosis requires assessment of morphology and neuroendocrine differentiation
  - Distinguishing characteristics for SCLC are high nuclear-to-cytoplasmic ratio and paucity of nucleoli in SCLC

Chemotherapy for metastatic LCNEC varies between from SCLC and NSCLC regimens

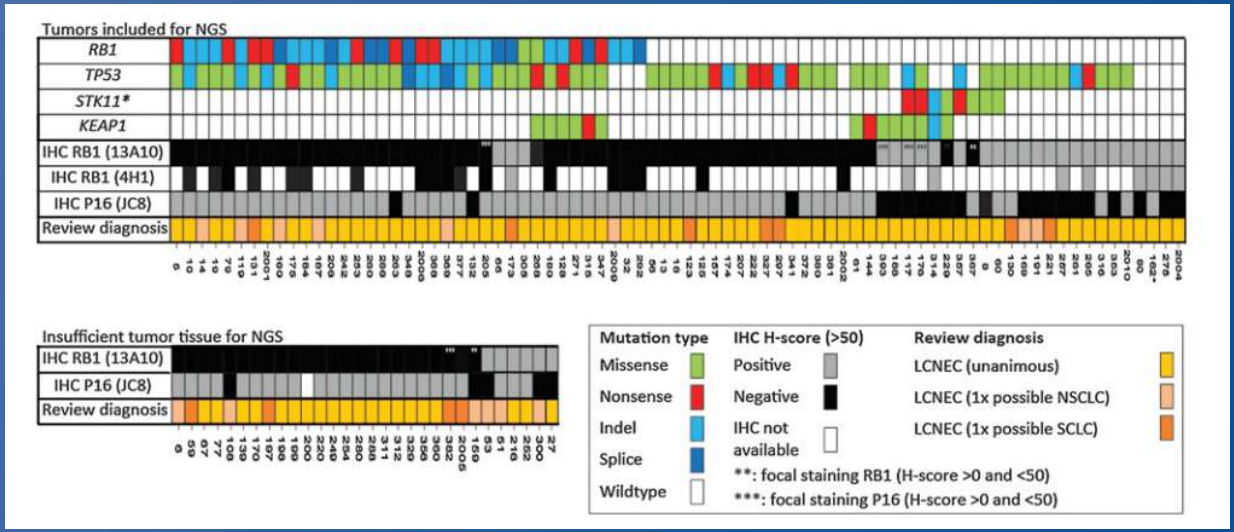
- Netherlands Cancer Registry and Netherlands Pathology Registry (PALGA) reported on 128 LCNEC patients who received first-line platinum-based chemotherapy
  - NSCLC-t (n=60; 46%): gemcitabine, docetaxel, paclitaxel or vinorelbine; 8.5mos
  - NSCLC-pt (n = 20; 16%): pemetrexed; 5.9 mos
  - SCLC-t (n= 48; 38%): etoposide; mOS 6.7 mos

  In patients with LCNEC, NSCLC-t chemotherapy results in longer overall survival compared to NSCLC-pt and SCLC-t chemotherapy.

Rindi et al., Mod Path, 2018; Derks et al, Eur Resp J 2017

LCNEC: genomics

NGS studies of LNCEC have demonstrated two major genomic signatures
- "SCLC-like" with coalterations of *TP53* and *RB1*, MYC (40%)
- "NSCLC-like" with mutations KRAS, STK11, KEAP1



How to manage is still unclear, but data such as this may be able to help with decisions on front-line treatment

Rekhtman, Clin Can Res 2016; Derks, Clin Can Res 2018

Small Cell Lung Cancer (SCLC): General

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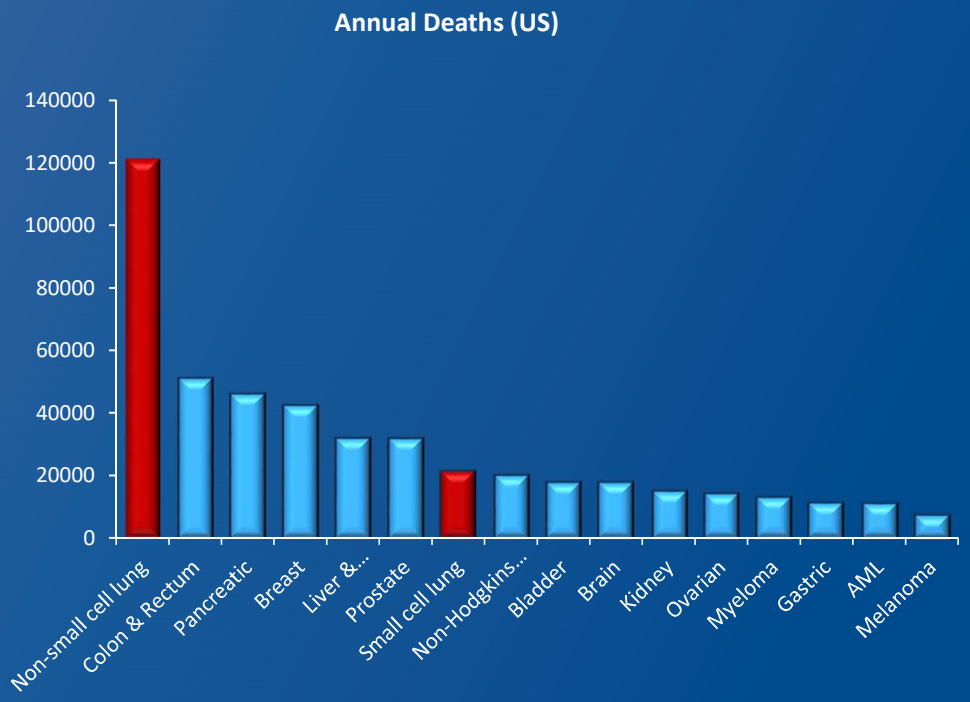
- Epithelial malignancy hallmarked by
  - early metastatic behavior
  - therapy resistance
  - one of the highest case-fatality rates among cancers
- ~13-15% of lung cancer diagnoses
- a major cause of cancer-related mortality
  - ~ 22,000 cancer related deaths
  - > 200,000 worldwide
- Strongly correlated with cigarette smoking



American Cancer Society. Cancer Facts & Figures 2019

SCLC: Pathology

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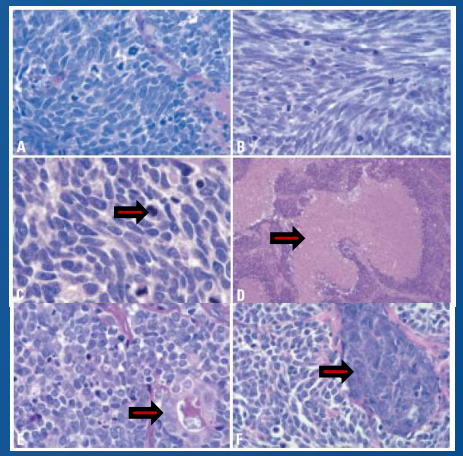
- A malignant epithelial tumor consisting of small cells with scant cytoplasm, ill defined borders, finely granular nuclear chromatin, inconspicuous nucleoli, high mitotic count and necrosis is often present
- Combined SCLC –mixed with any histologic subtype of NSCLC

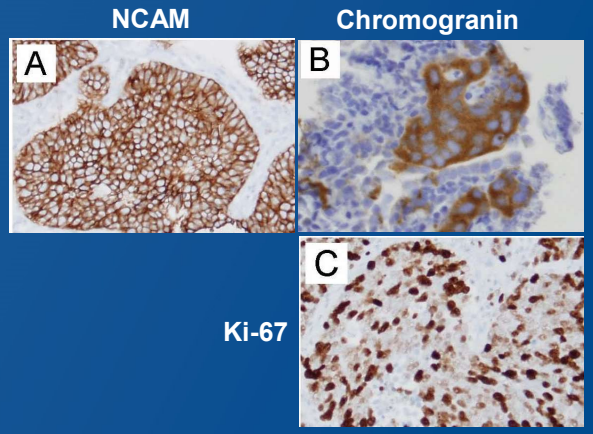
Tumor markers:

- Epithelial: AE1/3, EMA
- Neural/neuroendocrine: > 1 positive in 75% of cases
  - NSE
  - Neural cell adhesion molecule (NCAM)
  - Chromogranin
  - Synaptophysin
  - Gastrin releasing peptide
  - insulin-like growth factor (IGF-1)

- Diagnosis is based on H&E

- Ki-67 can help distinguish HG NE carcinoma from intermediate grade (atypical carcinoid)
  - Consider additional review for SCLC diagnosed in a never-smoker





Souhami RL et al., JNCI 1991; Guinee DG, Am J Clin Path 1994; Junker K J Can Res Clin Onc 2000

Limited Stage (LS) SCLC: definition and treatment

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1/3 of SCLC cases at diagnosis

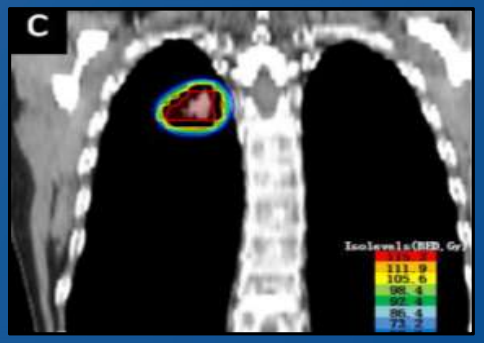
Definition: Disease that can be safely treated with definitive radiation therapy. Corresponds to Stage I-III disease

Standard of Care

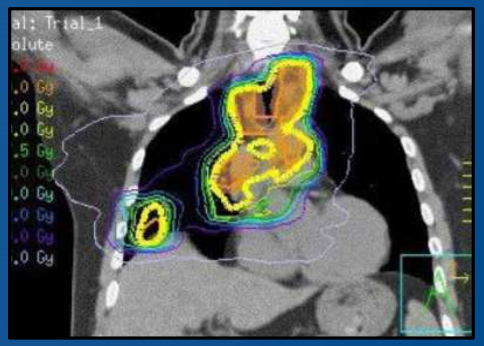
- Stage I: Resection followed by chemotherapy
- Stage I-III: Concurrent chemoradiotherapy
  - Etoposide/Cisplatin x 4 cycles
  - Radiation: BID or qD *(studies are ongoing)*
- Prophylactic Cranial Irradiation (PCI)
  - 5 year survival benefit (5.4% improvement)

Outcomes:

- ORR: 70 – 90%; 5 yr survival ≤ 26%
- Most (>75%) recur



Stage I



Stage III

Li et al., *PLoS One* 2017; Huo et al., *Clin Adv in Radio Tech* 2016

Is TRT to 66Gy qD superior to 45Gy BID?

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INTERGROUP 0096: 45Gy BID TRT is superior to 45 Gy qD

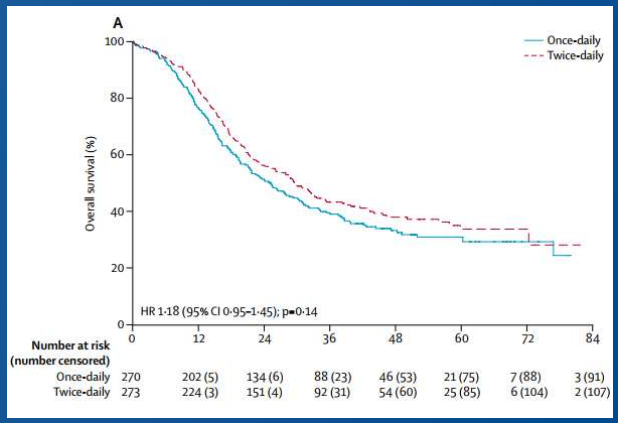
CONVERT STUDY: Open label, randomized Ph3 study (n = 547):

- TRT (45Gy) BID in 30 x 1.5Gy fractions
- TRT (66Gy) in 33 x 2Gy fractions
- With Cisplatin plus etoposide (4-6 cycles)

**Designed as a superiority study thus could not confirm equivalence

No significant difference in survival or toxicity

- 5 yr OS 31% (qD) and 34% (BID)
- G4 esophagitis 19%
- Increased G4 neutropenia in BID



Turrisi AT III et al. *N Engl J Med*. 1999;340:265-271; Faivre-Finn et al., Lancet Oncology; Aug. 2017

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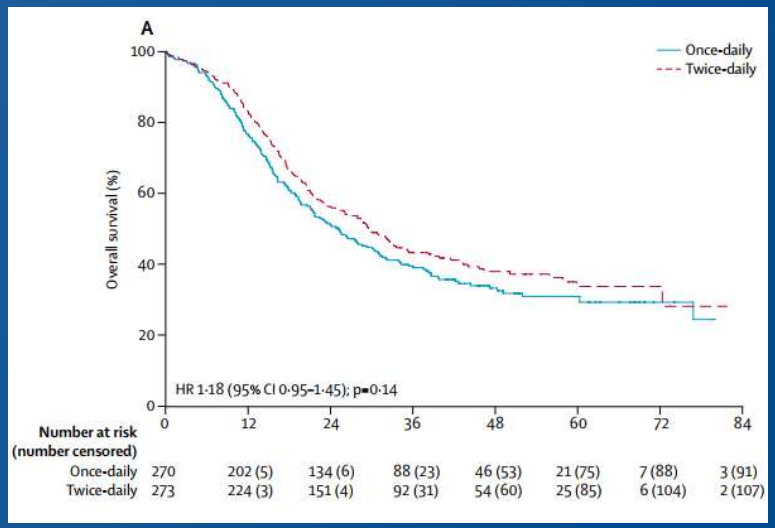

RTOG 0538/CALGB-30610 (NCT00632853) is ongoing

- Initially a RP3 study of 3 fractionation schedules **(A) 45Gy BID, (B) 70Gy qD** and (C) 61.2Gy with delayed accelerated hyperfractionation.
- Arm C was discontinued and this study is enrolling to compare 2 arms

Turrisi AT III et al. *N Engl J Med*. 1999;340:265-271; Faivre-Finn et al., Lancet Oncology; Aug. 2017

Studies of Immune Checkpoint Inhibitors in LS SCLC

ChemoRT + plus ICI				
NRG-LU005 (NCT03811002)	2/3	1) **ChemoRT** + **atezolizumab** followed by 1 year of atezolizumab 2) ChemoRT followed by observation	206	PFS (Ph 2) OS (Ph 3) Correlative study: bTMB *Recruiting*
ICI consolidation after chemoRT				
ADRIATIC (NCT03703297)	3	1) **Durvalumab** plus placebo x 4 cycles followed by durvalumab q4W x 2 years 2) **Durvalumab plus tremelimumab** x 4 cycles followed by durvalumab q4W x 2 years 3) Placebo for 4 cycles followed by placebo maintenance	600	PFS, OS Open Est completion: 6/1/21
ACHILES (NCT03540420)	RP2	1) **Atezolizumab** x 12 months 2) Observation	212	2 year survival 7/31/18 Est compl: 12/23
STIMULI (NCT02046733)	RP2	1) **Nivolumab plus ipilimumab** x 4 followed by nivolumab x 12 months 2) Observation	260	OS, PFS Opened:1/28/14 Est compl: 10/19

Extensive Stage SCLC: Initial management

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2/3 of SCLC cases at diagnosis

Definition: Stage IV or volume too large to be encompassed in a tolerable RT plan

Standard of Care:
- 4-6 cycles of platinum doublet
- PCI and/or TRT – non consensus

<u>SOC Regimen (US)</u> 1980s - Sept 2018
- **Platinum plus etoposide**
- ORR ~60%
- OS 8-10 months
- mPFS 2.3 months
- 5 yr OS < 2%

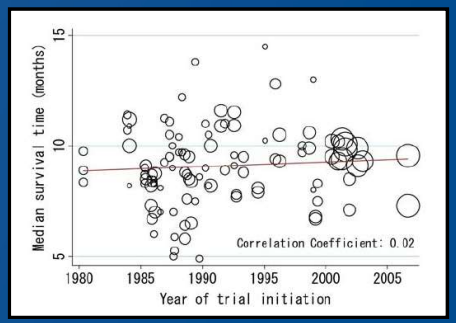
98% relapse ES SCLC +
75% relapse LS SCLC →
> 90% case-fatality rate

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

- Data from
- 52 first-line RCTs
- From 1980 - 2006
- including 10,262 patients
- 110 chemotherapy arms
- No difference in outcomes/survival

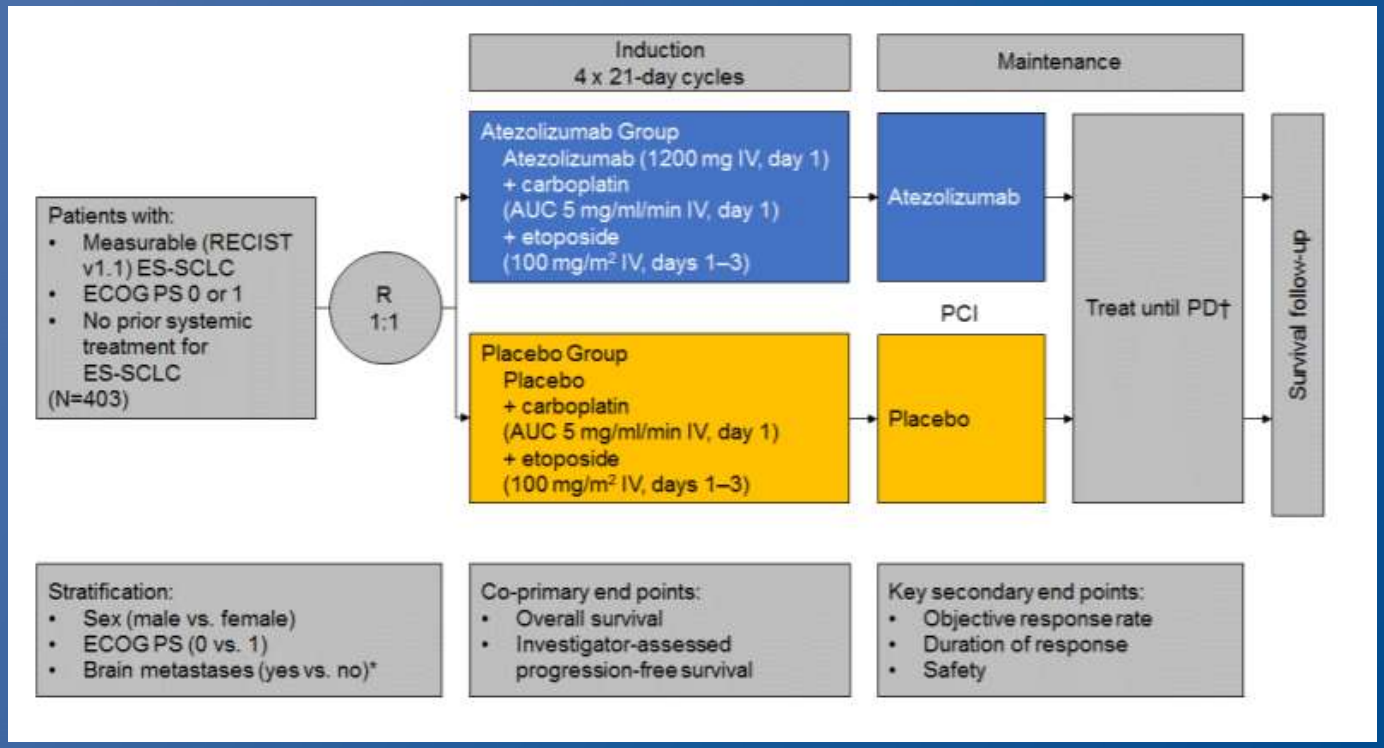


Oze, et al., *PLoS One* 2009

FRONT-LINE SETTING FOR ES SCLC

- Atezolizumab + First-line chemotherapy (IMpower133)
- Nivolumab +/- ipilimumab maintenance after induction chemotherapy

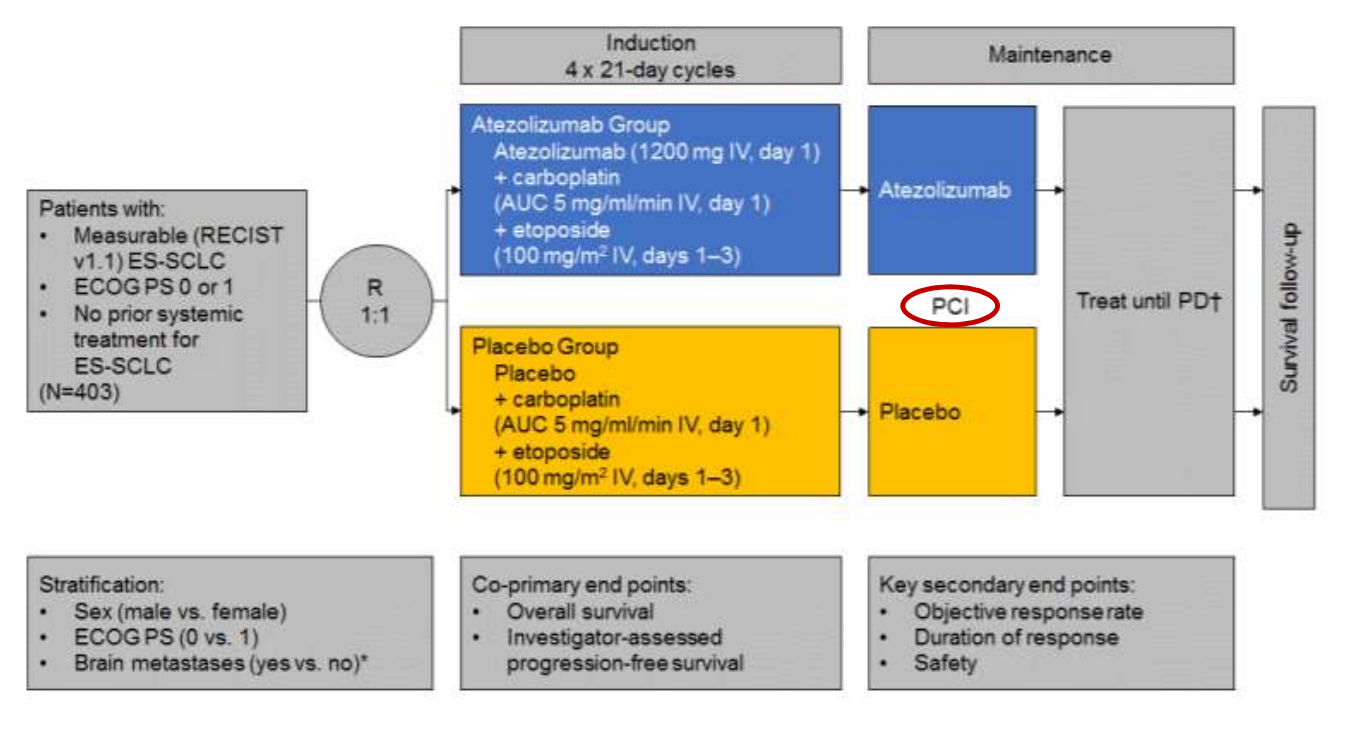
IMpower133: RPh 1/3 Study of Carboplatin/Etoposide + atezolizumab or placebo



403 patients were enrolled between June 6, 2016, and May 31, 2017

Horn L et al. *N Engl J Med*. 2018

IMpower133: RPh 1/3 Study of Carboplatin/Etoposide + atezolizumab or placebo

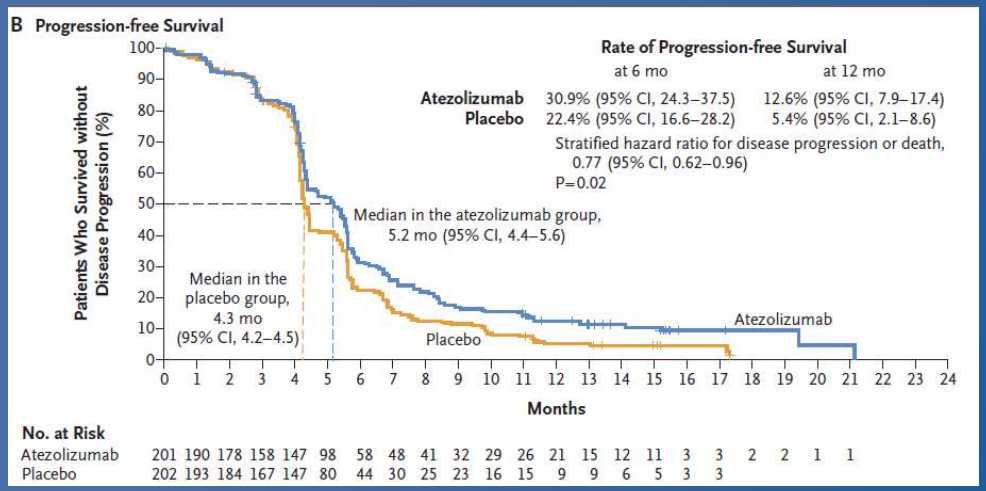


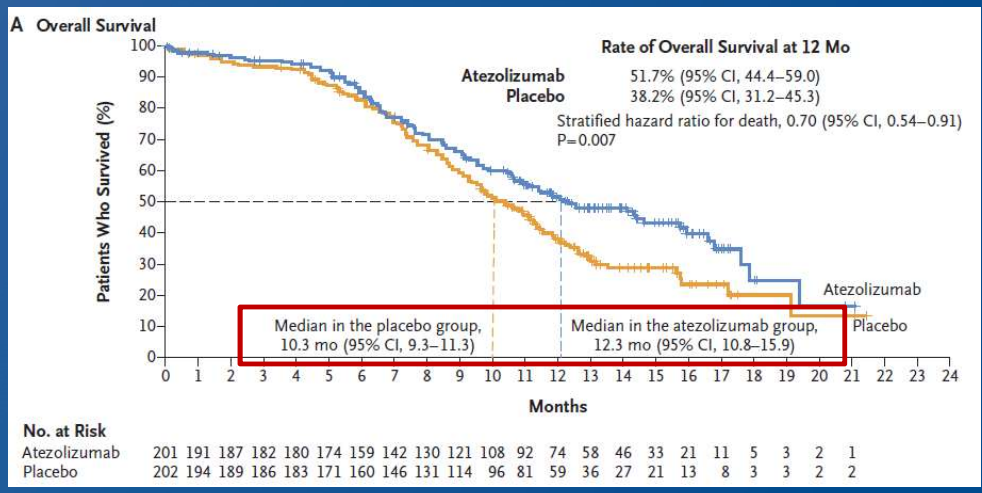
403 patients were enrolled between June 6, 2016, and May 31, 2017
Correlative study: bTMB

Horn L et al. *N Engl J Med*. 2018

IMpower133: OS and PFS

OS and PFS Improved with the addition of Atezolizumab





Median follow-up of 13.9 mos

ORR	60.2% vs 64.4%
mDOR	4.2 vs 3.9 mos
SD	20.9% vs 21.3%

Horn L et al. *N Engl J Med*. 2018

IMpower133: OS and baseline characteristics

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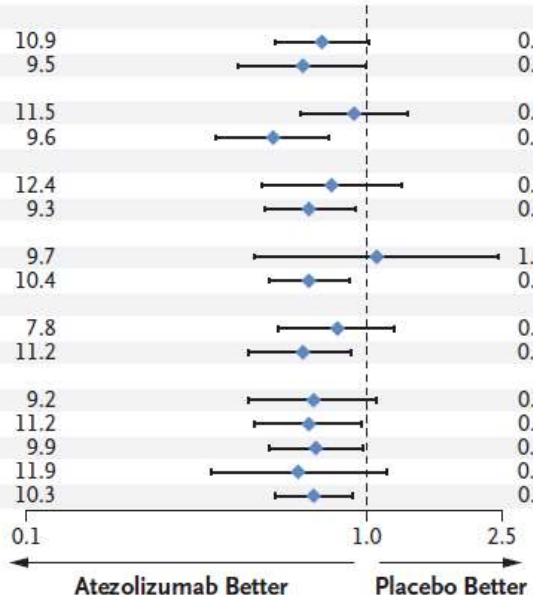
C Overall Survival According to Baseline Characteristics

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)



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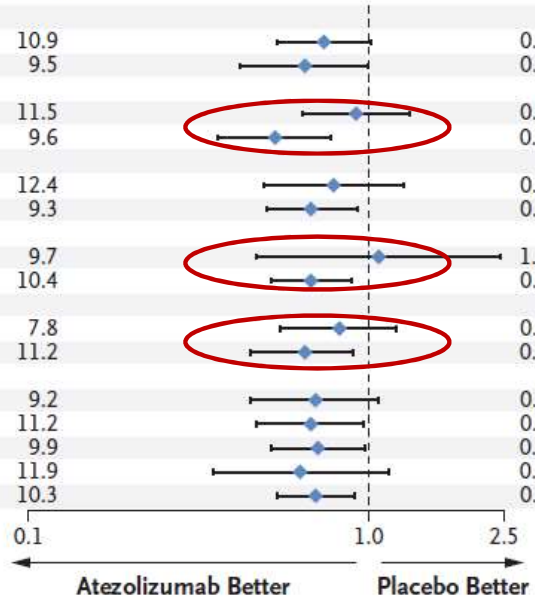
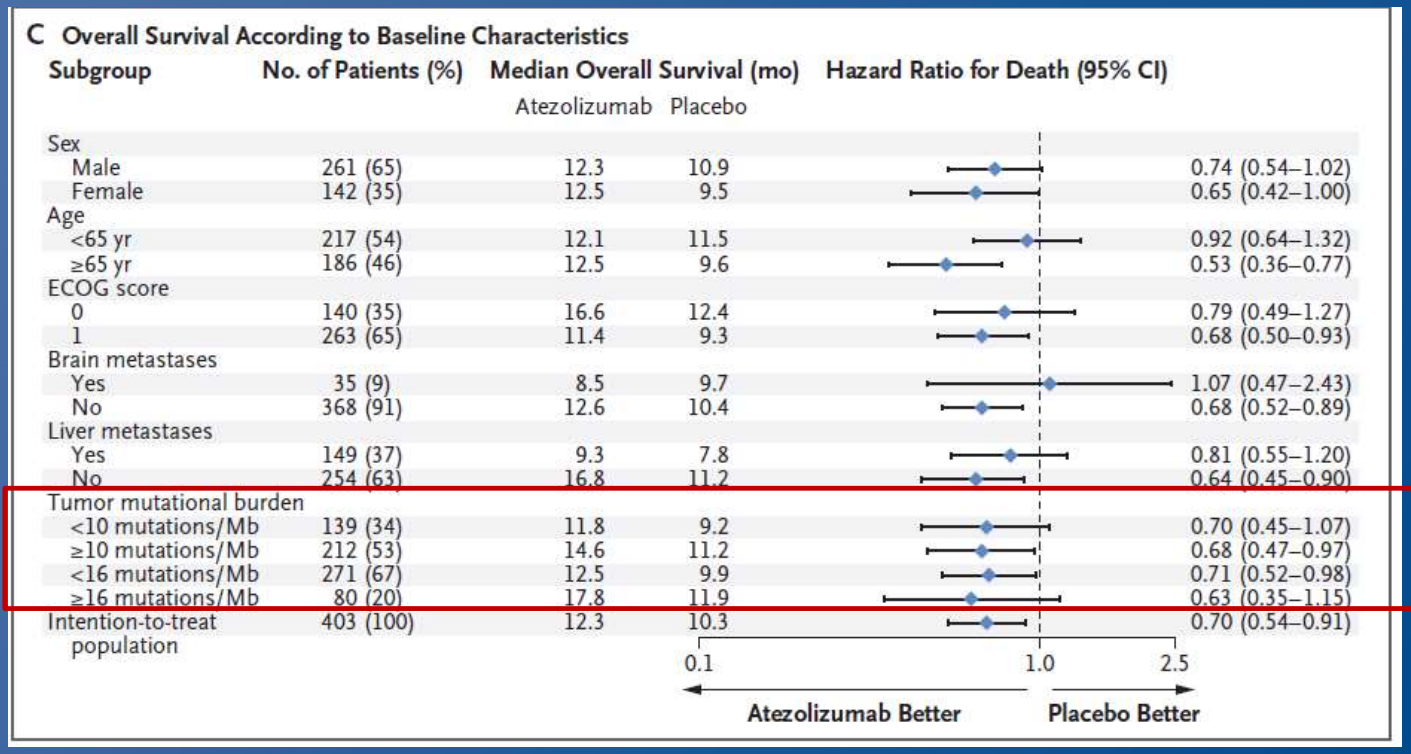


Horn L et al. *N Engl J Med*. 2018

IMpower133: OS and baseline characteristics



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Horn L et al. *N Engl J Med*. 2018

IMpower133: Adverse Events

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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

Clinical data cutoff date: April 24, 2018.

Presented by Stephen Liu at WCLC 2018; Horn L et al., NEJM 2018

First-Line Systemic SCLC Therapy: 2019

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NCCN 2019

Systemic therapy as primary or adjuvant therapy:

- Limited stage (maximum of 4–6 cycles):
  - Cisplatin 75 mg/m^2 day 1 and etoposide 100 mg/m^2 days 1, 2, 3[1]
  - Cisplatin 25 mg/m^2 days 1, 2, 3 and etoposide 100 mg/m^2 days 1, 2, 3[1]
  - Cisplatin 60 mg/m^2 day 1 and etoposide 120 mg/m^2 days 1, 2, 3[2]
  - Carboplatin AUC 5–6 day 1 and etoposide 100 mg/m^2 days 1, 2, 3[3]
  - During systemic therapy + RT, cisplatin/etoposide is recommended (category 1).
  - The use of myeloid growth factors is not recommended during concurrent systemic therapy plus radiotherapy (category 1 for not using GM-CSF).[4]
- Extensive stage (maximum of 4–6 cycles):
  - Carboplatin AUC 5 day 1 and etoposide 100 mg/m^2 days 1, 2, 3 and atezolizumab 1,200 mg day 1 every 21 days x 4 cycles followed by maintenance atezolizumab 1,200 mg (category 1, preferred)[§,5]
  - Carboplatin AUC 5–6 day 1 and etoposide 100 mg/m^2 days 1, 2, 3[†,6]
  - Cisplatin 75 mg/m^2 day 1 and etoposide 100 mg/m^2 days 1, 2, 3[†,7]
  - Cisplatin 80 mg/m^2 day 1 and etoposide 80 mg/m^2 days 1, 2, 3[†,8]
  - Cisplatin 25 mg/m^2 days 1, 2, 3 and etoposide 100 mg/m^2 days 1, 2, 3[†,9]
  - Carboplatin AUC 5 day 1 and irinotecan 50 mg/m^2 days 1, 8, 15[†,10]
  - Cisplatin 60 mg/m^2 day 1 and irinotecan 60 mg/m^2 days 1, 8, 15[†,11]
  - Cisplatin 30 mg/m^2 days 1, 8 and irinotecan 65 mg/m^2 days 1, 8[†,12]

Atezolizumab was given priority review in Dec. 2018
FDA approved in March 2019

Ongoing studies of ICIs in Front-line ES SCLC

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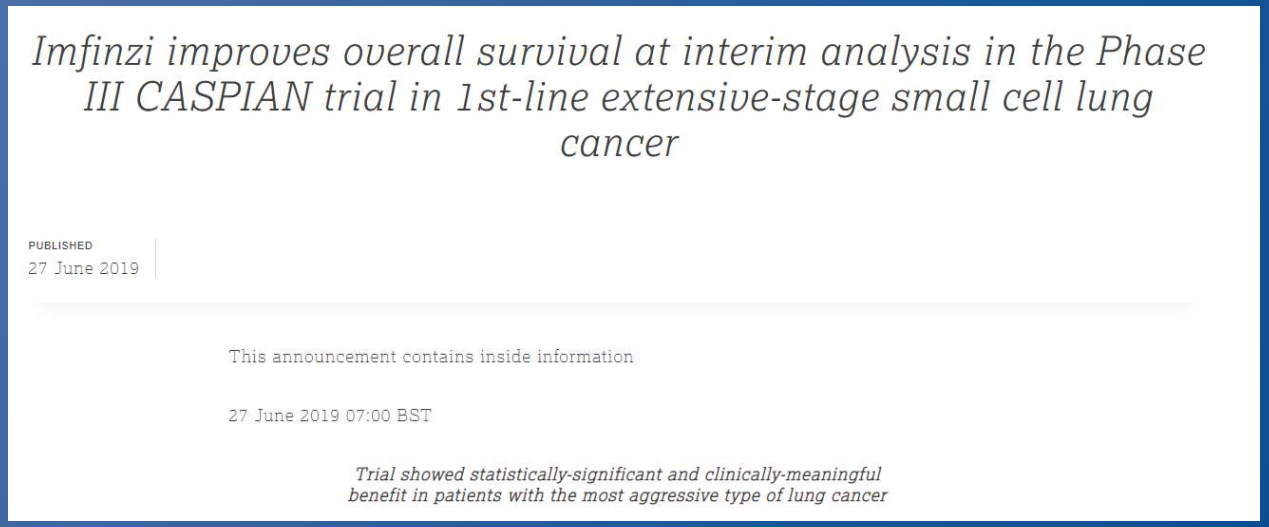
CASPIAN (NCT03043872)	RP3	1) EP + durvalumab + tremelimumab x 4 cycles followed by durvalumab maintenance 2) EP + durvalumab x 4 cycles followed by durvalumab maintenance 3) EP x 4-6 cycles followed by observation	795	OS and PFS Completed accrual Press release
KEYNOTE-604 (NCT03066778)	RP3	1) EP plus pembrolizumab x 4 cycles followed by pembrolizumab maintenance 2) EP plus placebo x 4 cycles followed by placebo	453	PFS by BICR and OS Active not accruing
EA5161 (NCT03382561)	Ph2	1) EP plus nivolumab x 4 cycles followed by nivolumab maintenance up to 2 years 2) EP plus placebo x 4 cycles	156	PFS Completed Accrual

CASPIAN Study – press release



Imfinzi improves overall survival at interim analysis in the Phase III CASPIAN trial in 1st-line extensive-stage small cell lung cancer

PUBLISHED
27 June 2019

This announcement contains inside information

27 June 2019 07:00 BST

Trial showed statistically-significant and clinically-meaningful benefit in patients with the most aggressive type of lung cancer

https://www.astrazeneca.com/media-centre/press-releases/2019/imfinzi-improves-overall-survival-at-interim-analysis-in-the-phase-iii-caspian-trial-in-1st-line-extensive-stage-small-cell-lung-cancer-27062019.html

CASPIAN Study – press release

Imfinzi improves overall survival at interim analysis in the Phase III CASPIAN trial in 1st-line extensive-stage small cell lung cancer

A planned interim analysis conducted by an Independent Data Monitoring Committee concluded that the trial has met its primary endpoint by showing a statistically-significant and clinically-meaningful improvement in OS in patients treated with *Imfinzi* in combination with standard-of-care etoposide and platinum-based chemotherapy options vs. chemotherapy alone. The safety and tolerability for this *Imfinzi* combination was consistent with the known safety profiles of these medicines.

This announcement contains inside information

27 June 2019 07:00 BST

Trial showed statistically-significant and clinically-meaningful benefit in patients with the most aggressive type of lung cancer

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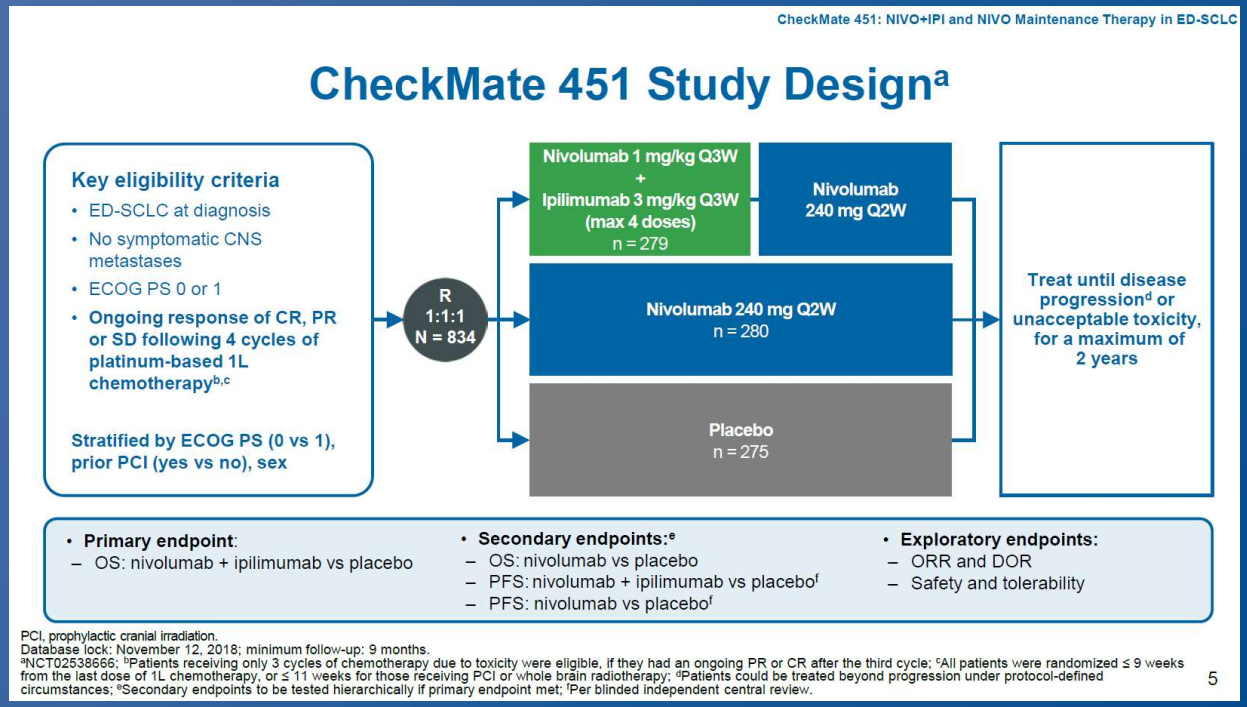
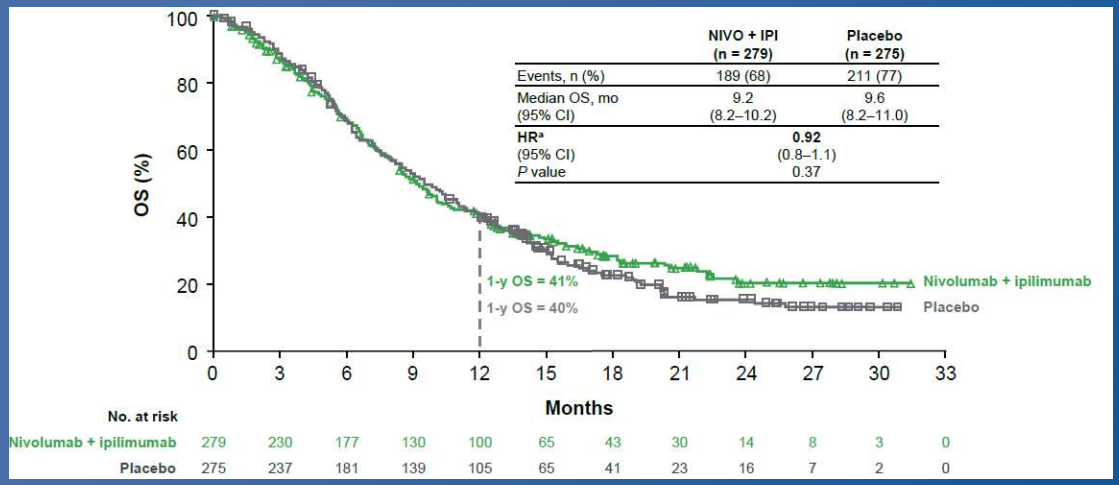
CheckMate 451: Maintenance Nivolumab ± Ipilimumab vs. Placebo in 1L SCLC



Expected average HR (N/I) vs placebo was 0.72
Arms were well-balanced

Owonikoko TK et al., presented at ELCC 2019

Checkmate 451: OS Nivolumab ± Ipilimumab vs. Placebo



TRAE's: Nivo + ipilimumab: 52% Any G3/4 TRAEs
Serious TRAEs: 31% G3/4
25% TRAEs leading to treatment discontinuation

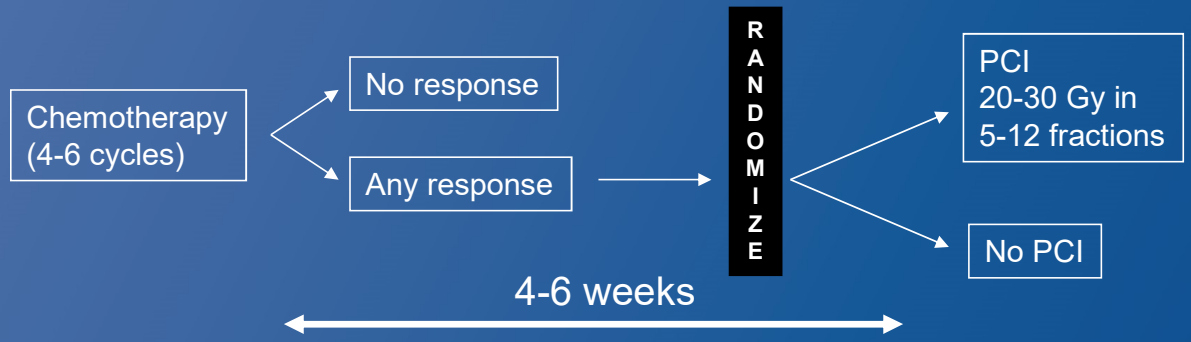
- did not meet its primary endpoint of significantly prolonged OS with nivolumab plus ipilimumab vs placebo as maintenance therapy after platinum-based 1L chemotherapy
- The safety profiles of nivolumab plus ipilimumab and nivolumab were consistent with previous reports at this dose/schedule

Owonikoko TK et al., presented at ELCC 2019

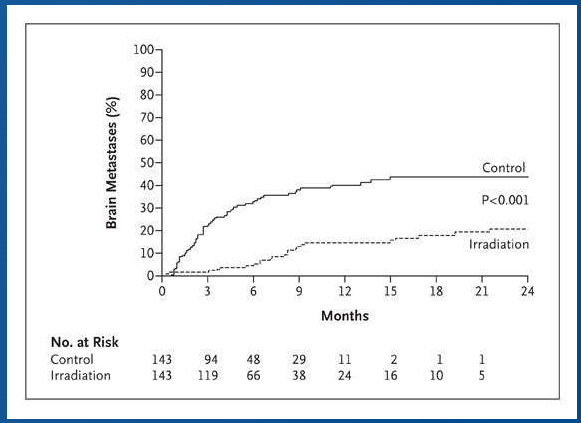
RADIATION FOR ES SCLC

- Prophylactic Cranial Irradiation
- Thoracic Radiotherapy

PCI in ES-SCLC: EORTC Study

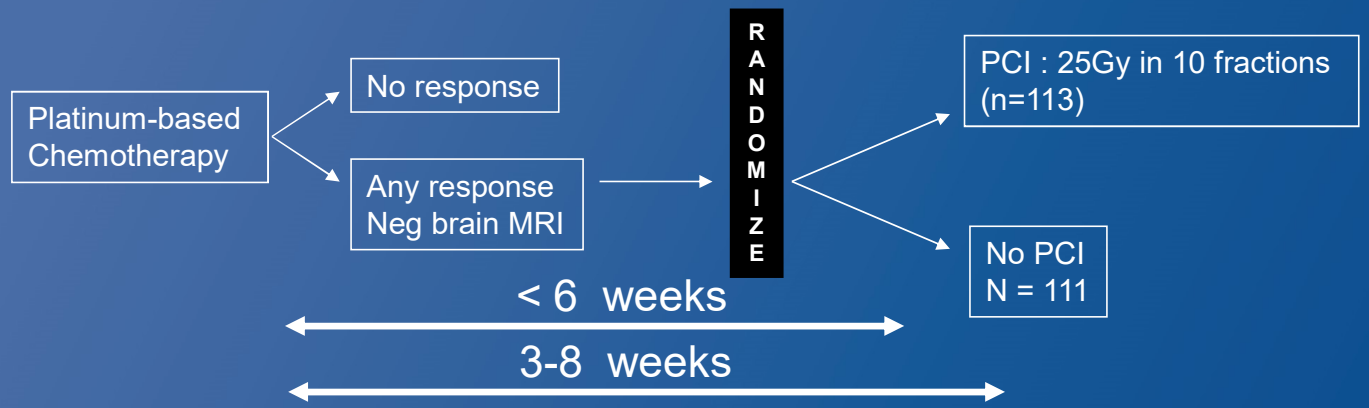


- 286 ES SCLC with response to chemotherapy randomized to PCI
- Primary EP: time to symptomatic brain metastases
- **Outcome:** symptomatic brain mets: ↓ at 1 year from 40 vs. 15%
  - Median OS: 6.7 vs. 5.4 months
  - 1 yr survival 27 vs. 13% (HR 0.68; CI 0.52-0.88)

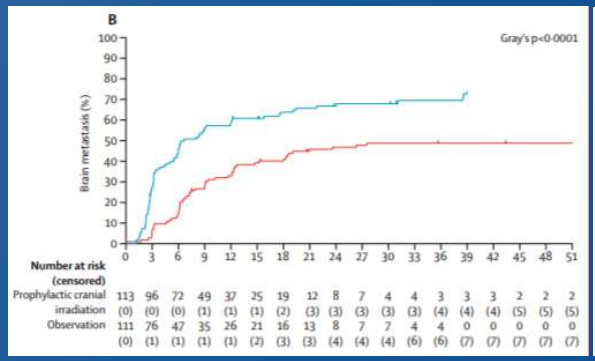


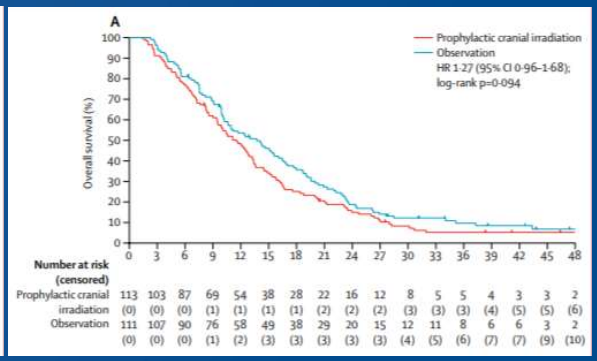
Slotman et al., *NEJM* 2007; 357(7):664-72

PCI in ES-SCLC: Takahashi et al. 2017



- RP3 study – designed to assess superiority of PCI
- Primary endpoint: OS
- Secondary: Time to BM, PFS
- **Closed early due to futility at 1st interim analysis**





Takahashi et al., Lancet Oncology March 2017

TRT in ES SCLC: CREST Trial

ES-SCLC
- No brain- /leptomeningeal mets
- No pleural mets
- No previous RTX brain/thorax
- Any response after 4-6 cycles of platinum-based chemotherapy
- WHO 0-2
- Age 18+
- Encompassable volume

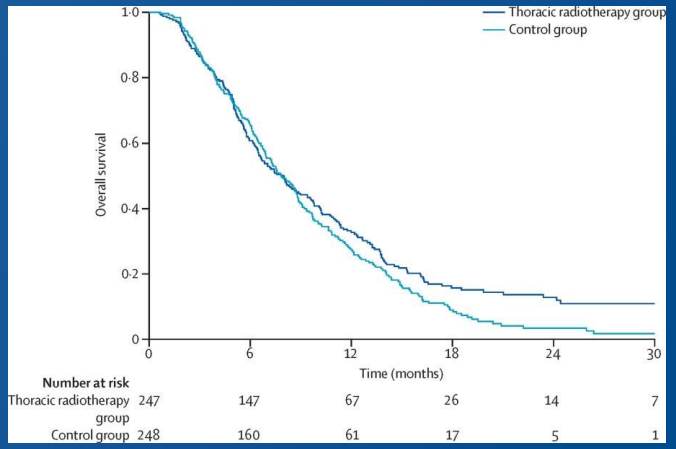
RANDOMIZE

PCI + TRT (10 x 3Gy)

PCI

2-7 weeks

- Primary Endpoint: OS at 1 year
- Secondary: PFS, local control
- 498 patients
- Results:
  - **1 year OS was not significantly different**
  - 2 year OS was 13% vs. 3% (secondary analysis)
  - Improvement restricted to those with RITD



Slotman et al., *Lancet* 2015

Summary: First-line Management for ES SCLC

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- **Carboplatin, etoposide plus atezolizumab is the SOC in the US**
  - CASPIAN study – interim analysis (+) for durvalumab
  - Awaiting presentation of CASPIAN and KEYNOTE-604 studies
- No data to support ICIs initiated as maintenance
  - **CheckMate 451 did not meet its primary endpoint**
- **The use of PCI and/or TRT** – non consensus
  - reasonable to decide on a case-by-case basis

Relapsed SCLC

JOHNS HOPKINS MEDICINE

Initial response > 6 months

- reinduction with EP

FDA-APPROVED OPTIONS

Initial response < 6 months

Topotecan is the only FDA-approved option as second-line

- ORR: 18-24%; PFS: 3mo; OS: 6mo
- Toxicities are substantial
- Approved based on improvement in symptoms
- Approved for sensitive-relapse

Third-line

- Nivolumab – accelerated approval in Aug 2018
- Pembrolizumab – accelerated approval June 2019

Off-label options

- temozolomide
- nivolumab + ipilimumab
- taxanes
- irinotecan
- gemcitabine
- bendmustine

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-pembrolizumab-metastatic-small-cell-lung-cancer; NCCN SCLC 2019 Guidelines

RECENT STUDIES IN RELAPSED SCLC

- Pembrolizumab (KEYNOTE-028, -158 studies)
- Nivolumab +/- ipilimumab (CheckMate-032)
- Nivolumab vs Topotecan (CheckMate-331)
- Lurbinectidin
- PARP-inhibitors

Relapsed SCLC: ICI studies

JOHNS HOPKINS MEDICINE

Study	N	ORR (%)	mDOR (mo)	mPFS (mo)	OS (mo)	TRAE (G3/4)
KEYNOTE-028 PD-L1(+)	20	33.3 (15.6-55.3)	19.4 (3.6-20+)	1.9	9.7 (4.1 – NR)	
KEYNOTE-158 (all)	107	18.7 (11.8-27.4)	NR (2.1+ - 18.7+)	2.0 (1.0-2.1)	8.7 (5.6-12.0)	12%
PD-L1 (CPS) ≥ 1	42	35.7 (21.6-52.0)		2.1 (2.0-8.1)	14.9 (5.6 – NR)	
PD-L1 (CPS) < 1	50	6.0 (1.3-16.5)		1.9 (1.6-2.0)	5.9 (3.3-10.1)	
CheckMate-032 (initial)						
Nivo 3mg/kg q2	98	10 (5-18)	NR (4.4-NR)	1.4 (1.4-1.9)	4.4 (3.0-0.3)	12%
Nivo 1+ Ipi3	61	23 (13-36)	7.7 (4.0-NR)	2.6 (1.4-4.1)	7.7 (3.6-18.0)	37%* * *Pooled data*
Nivo3 + Ipi1	54	19 (9-31)	4.4 (3.7-NR)	1.4 (1.2-2.2)	6.0 (3.6-11.0)	

Ott et al., J Clin Oncol 2017; Chung AACR Meeting 2019; Antonia Lancet Oncology 2017; Hellmann ASCO Meeting 2017

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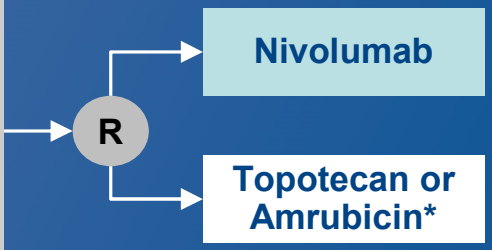
CheckMate 331: RP3 study of Nivolumab vs Chemotherapy 2L SCLC

JOHNS HOPKINS MEDICINE

N=798

Key Eligibility Criteria

- Limited or extensive-stage SCLC
- Recurrence/PD after 1L PLT-CT or CRT
- ECOG PS ≤1
- No symptomatic CNS metastases
- No prior therapy with anti–CTLA-4, anti–CD137, anti–PD-1/PD-L1/PD-L2



Primary Outcome Measure: OS
Secondary Outcome Measures: PFS, ORR

Presented by Reck et al., ESMO 2018

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R → **Nivolumab**

R → **Topotecan or Amrubicin***

mOS: 7.5 vs 8.4 mo
1 y OS: 37% vs 34%

Primary Outcome Measure: OS
Secondary Outcome Measures: PFS, ORR

Bristol-Myers Squibb
Press Release
FRIDAY, OCTOBER 12, 2018

Bristol-Myers Squibb Announces Phase 3 CheckMate -331 Study Does Not Meet Primary Endpoint of Overall Survival with Opdivo Versus Chemotherapy in Patients with Previously Treated Relapsed Small Cell Lung Cancer

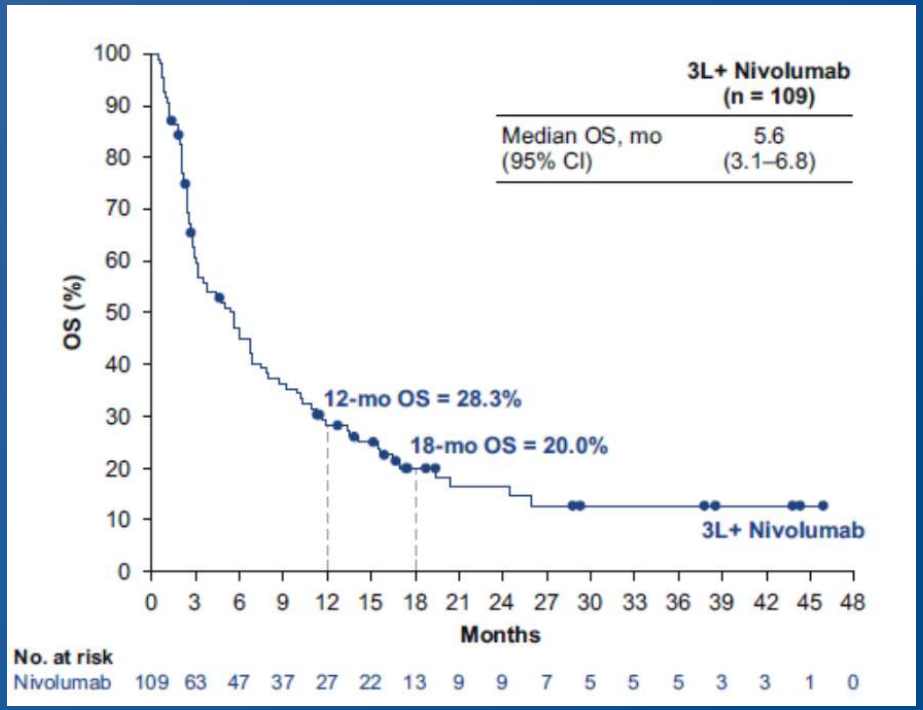
At a min FU of 15.8 months, no statistically significant improvement in OS observed

Presented by Reck et al., ESMO 2018

SCLC 3rd-line setting: CheckMate 032

Table 2. ORRs with Third-or Later-Line Nivolumab Monotherapy

Endpoint	Third-or Later-Line Nivolumab (n = 109)
ORR by BICR[a]	
No. of patients	13
% of patients (95% CI)	11.9 (6.5-19.5)
Best overall response, n (%)	
Complete response	1 (0.9)
Partial response	12 (11.0)
Stable disease	25 (22.9)
Progressive disease	56 (51.4)
Unable to determine	14 (12.8)
Not reported	1 (0.9)
Median time to response, mo	1.6
Duration of response	
≥6 mo, n (%)	10 (76.9)
≥12 mo, n (%)	8 (61.5)
Median (95% CI), mo[b]	17.9 (7.9-42.0)
Range, mo	3.0-42.1



August 2018 Nivolumab received accelerated approval for SCLC after 2 lines of therapy

Ready, et al., JTO 2018

Combined analysis of KEYNOTE-028 and -158

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Exploratory pooled analysis of efficacy and safety of subjects who received ≥ 2 lines of therapy

- Of 131 patients, **83 received ≥ 2 L of therapy**
- mFU 7.7 months (range 0.5-48.mos)
- **ORR 16%**
- **Duration of Response ≥ 18 months**

FDA approves pembrolizumab for metastatic small cell lung cancer

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The main efficacy outcome measures were overall response rate (ORR) and duration of response (modified RECIST v1.1) assessed by blinded independent central review. The ORR was 19% (95% CI: 11, 29); the complete response rate was 2%. Responses were durable for 6 months or longer in 94%, 12 months or longer in 63%, and 18 months or longer in 56% of the 16 responding patients.

randomized, open label trials: KEYNOTE-158 (NCT02628067) Cohort G or KEYNOTE-028 (NCT02054806) Cohort C1. Patients received either pembrolizumab 200 mg intravenously every 3 weeks (n=64) or 10 mg/kg intravenously every 2 weeks (n=19). Treatment continued until documented disease progression, unacceptable toxicity, or a maximum of 24 months.

Chung et al., AACR 2019

Summary – SCLC current options

JOHNS HOPKINS MEDICINE

- **LS SCLC** – definitive chemoRT followed by PCI
- **First-line ES SCLC: Carboplatin, etoposide plus atezolizumab is the SOC in the US**
  PCI and TRT are non-consensus
- **Maintenance/Consolidation after EP: No**
- **2nd line:** topotecan is still the only FDA-approved treatment
  - Remission > 2 months after initial chemo
- **3rd line:** Nivolumab and pembrolizumab have received FDA approval in the 3rd line setting but unclear how to use IO post-chemo-IO

SCLC - Future Directions

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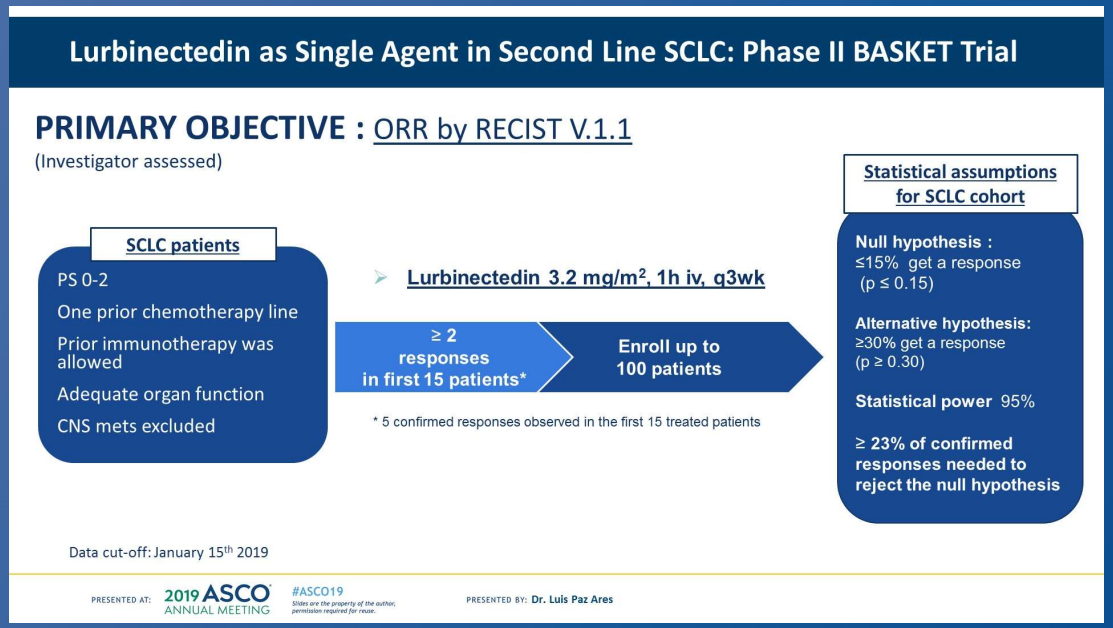
- Biomarkers are need to help select patients
  - IMpower 133 bTMB did not correlate with benefit
  - PD-L1
  - TMB need to be validated and harmonized
- Other novel approaches/combinations –
  - Lurbinectidin
  - Targeted therapies
    - DLL3/T cell–redirecting immunotherapy with BiTE or CAR-T
    - Other targets emerging from preclinical efforts in SCLC: MYC, SFLN11, DDR, PARP-inhibitors

Lurbinectedin

- DNA minor groove binder
- Acts as an inhibitor of oncogenic transcription with various effects including
  - DS DNA breaks
  - Downregulation of IL-6, IL-8, VEGF



Paz-Ares et al., ASCO 2019

Lurbinectedin Ph 2 results

	Overall (n=105)
ORR, % (95% CI)	35.2 (26.2-45.2)
Best response	n (%)
- PR (confirmed)	37 (35.2) #
- SD	35 (33.3)
- PD	28 (26.7)
- NE* (non- evaluable)	5 (4.8)
Disease Control Rate,% (95% CI)	68.6 (58.8-77.3)

5 of 8 patients who failed prior immunotherapy had confirmed response

Treatment Related (or Unknown) Adverse Events (AEs)
Events in >5% of patients or Gr 3-4

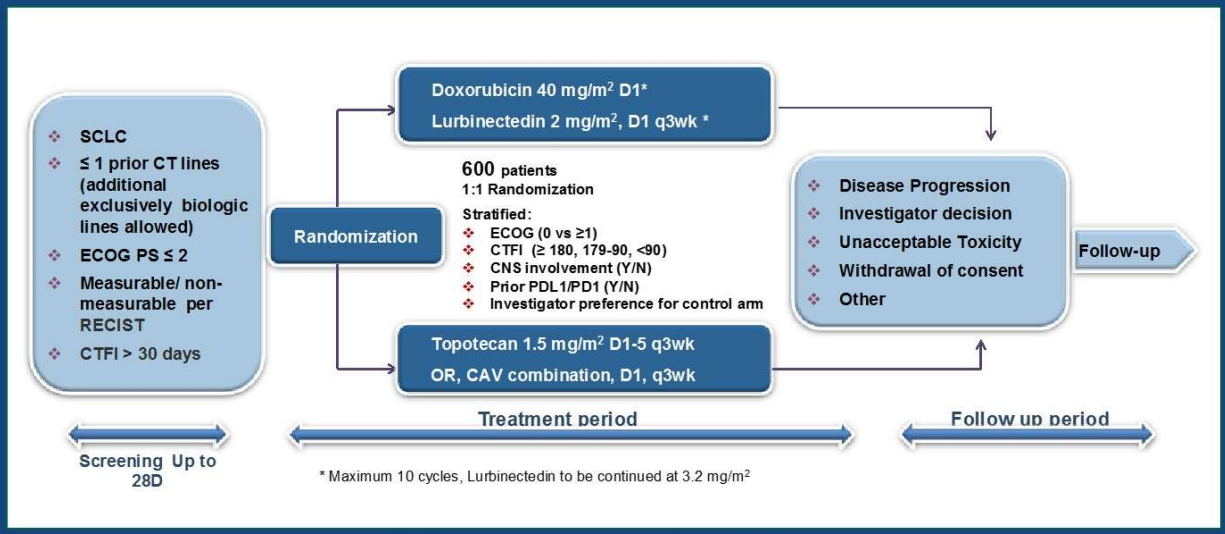
	n=105	Gr 1-2 n (%)	Gr 3-4 n (%)
Hematological AEs *	Neutropenia	6 (5.7)	24 (22.9)
	Anemia	2 (1.9)	7 (6.7)
	Thrombocytopenia	2 (1.9)	5 (4.8)
	Febrile neutropenia	.	5 (4.8)
Non-Hematological AEs	Fatigue	54 (51.4)	7 (6.7)
	Nausea	34 (32.4)	.
	Decreased appetite	22 (21.0)	.
	Vomiting	19 (18.1)	.
	Diarrhea	13 (12.4)	1 (1.0)
	Constipation	10 (9.5)	.
	Pneumonia	.	2 (1.9)
	Alanine aminotransferase increased *	.	2 (1.9)
	Skin ulcer	.	1 (1.0)

Paz-Ares et al., ASCO 2019

Lurbinectidin – ongoing Phase 3 study

JOHNS HOPKINS MEDICINE

ATLANTIS:
Phase 3 global randomized study in relapsed SCLC

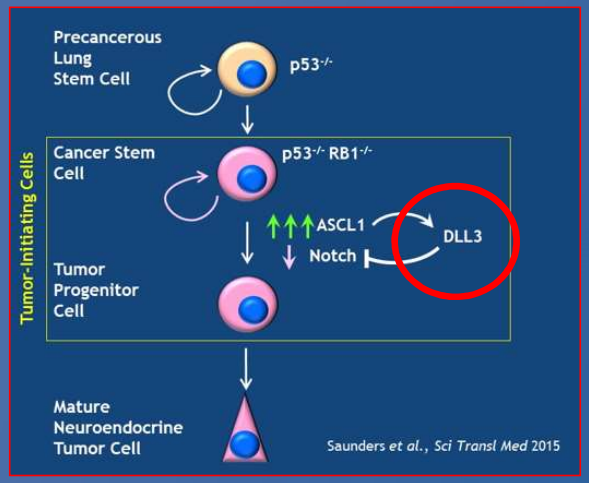


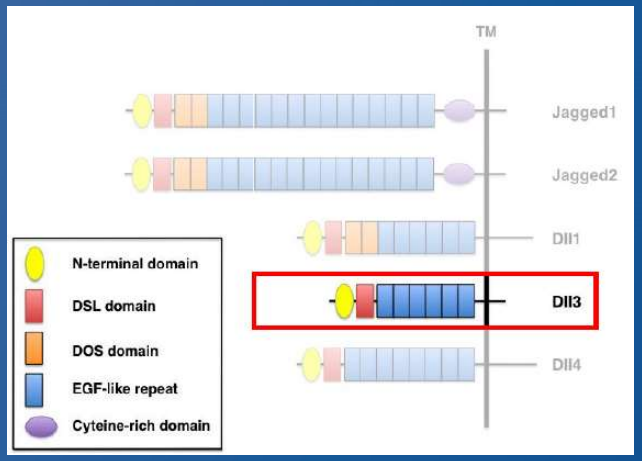
Primary endpoint: OS

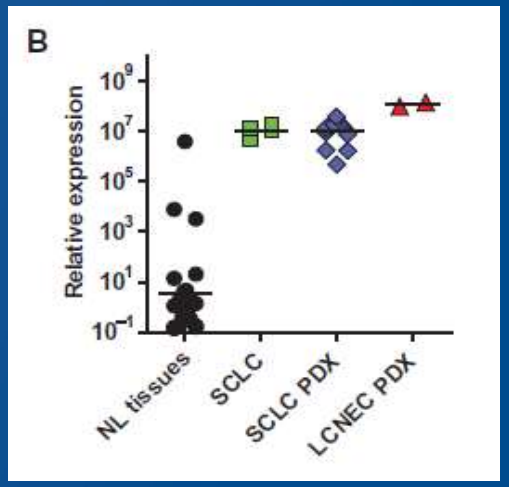
Presented by A Farago, ASCO 2019

Delta-like ligand 3 (DLL3) as a target

- DLL3 is an inhibitory notch protein
- Highly expressed in SCLC
- No expression in normal adult tissues







Saunders et al., Sci Trans Med 2015

Targeting DLL3: Rova-T experience

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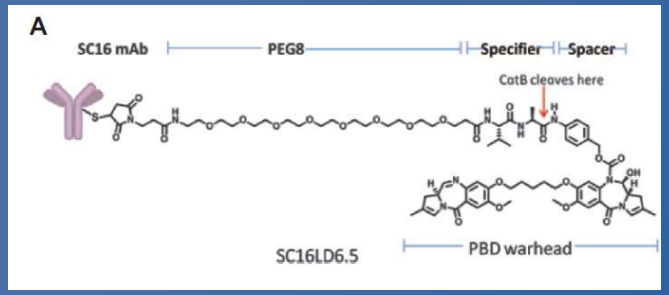
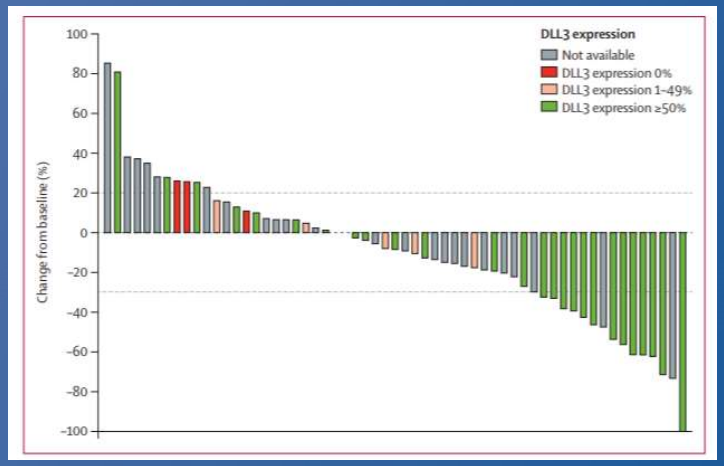
Rova-T



Promising Phase 1 data:
38% ORR in DLL3 high SCLC



TRINITY: Ph2 Third-line Study in SCLC

Primary Endpoint	All Dosed (N = 339)	DLL3-High (N = 238)
ORR[2]: Investigator, % (95% CI)	18.0 (14.1, 22.5)	19.7 (14.9, 25.4)
ORR[2]: IRC, % (95% CI)	12.4 (9.1, 16.4)	14.3 (10.1, 19.4)
Median OS, Mo (95% CI)	5.6 (4.9, 6.1)	5.7 (4.9, 6.7)

Toxicities: rash, pleural effusion, pericardial effusion

Additional studies:

- TAHOE: 2nd line vs. Topotecan – stopped early
- Maintenance – results pending
- Future direction – unknown
- First-line +/- EP – present at ESMO

Saunders et al., Sci Trans Med 2015; Rudin et al., Lancet Oncol 2016; Carbone et al., ASCO 2018

Using DLL3 as a T-cell redirecting therapy

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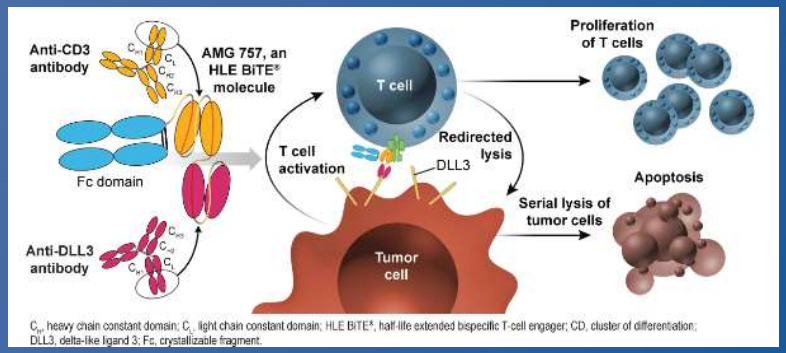
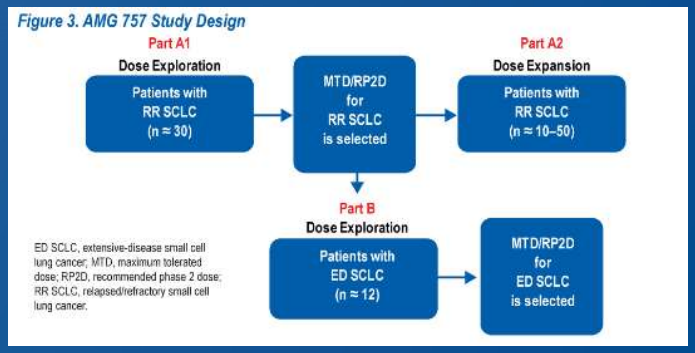
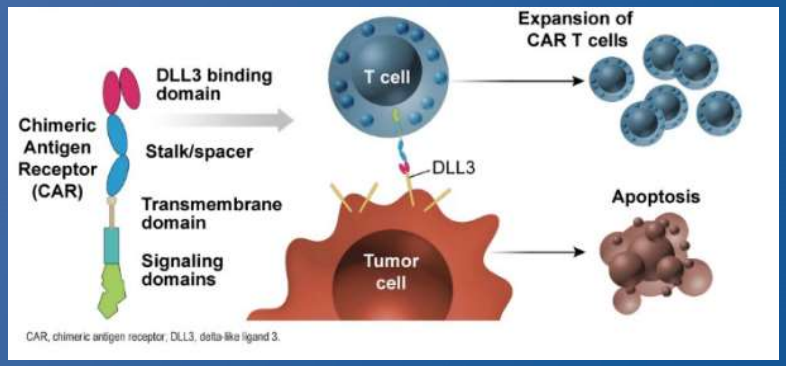
DLL3-BiTE (AMG-757)



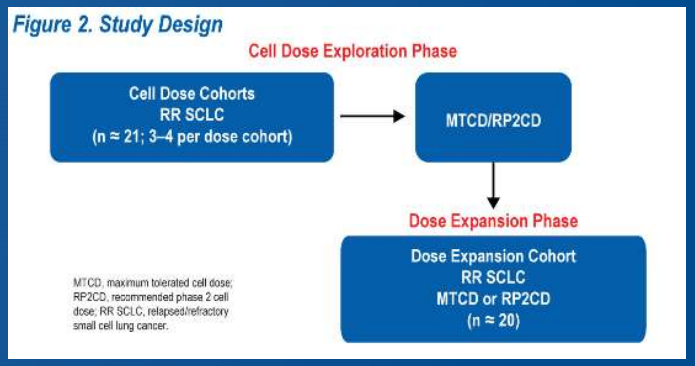
C_H, heavy chain constant domain; C_L, light chain constant domain; HLE BiTE®, half-life extended bispecific T-cell engager; CD, cluster of differentiation; DLL3, delta-like ligand 3; Fc, crystallizable fragment.



DLL3-CAR T (AMG-199)

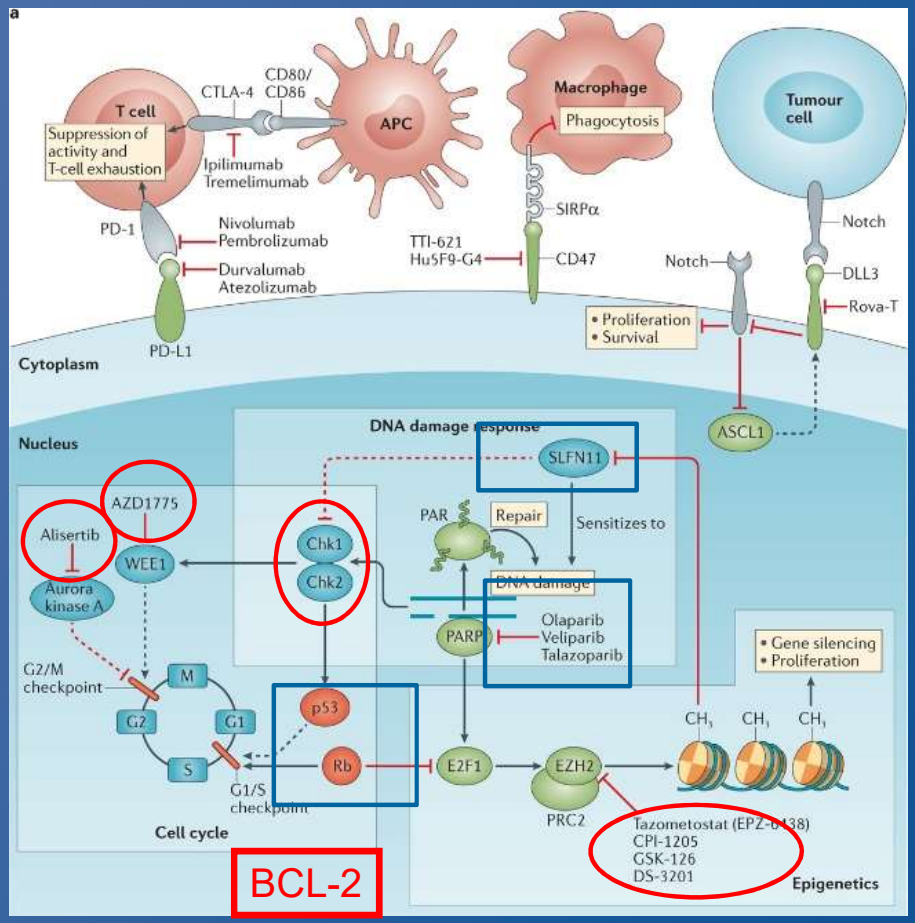


CAR, chimeric antigen receptor; DLL3, delta-like ligand 3.



Smit et al., ASCO 2019; Byers et al, ASCO 2019

Many potential vulnerabilities in SCLC



Ph 2 Temozolomide/Olaparib (Farago AACR)

Sunitinib maintenance (Ready 2015)

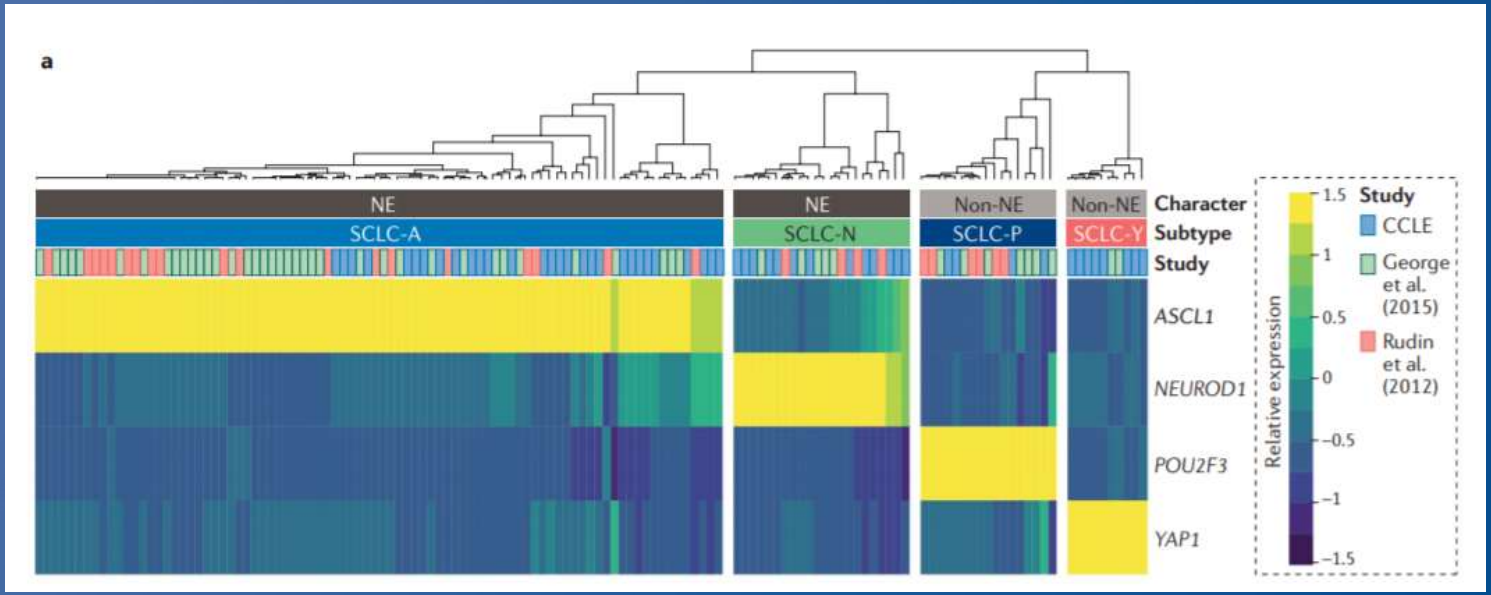
SLFN11 – associated with therapy resistance, can be targeted with EZH2 inhibitors

MYC amplified tumors are sensitive to AurK inhibtors

BCL-2/xL directed therapies

SCLC: subsets and targetable vulnerabilities

Genomic, epigenomic, proteomic, animal model data - supports further classification of SCLC into subsets – ASCL1 (A), NeuroD1 (N), Pou2F3 (P) and YAP1 (Y)



Rudin et al., Nat Rev Cancer 2019

Summary – SCLC current options

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- **LS SCLC** – definitive chemoRT followed by PCI
- **First-line ES SCLC: Carboplatin, etoposide plus atezolizumab is the SOC in the US**
  PCI and TRT are non-consensus
- **Maintenance/Consolidation after EP: No**
- **2nd line:** topotecan is still the only FDA-approved treatment
  - Remission > 2 months after initial chemo
- **3rd line:** Nivolumab and pembrolizumab have received FDA approval in the 3rd line setting but unclear how to use IO post-chemo-IO

ICI Approvals in 2018-19
BUT MUCH MORE TO COME!