Neuroendocrine Tumors of the Lung
"A Spectrum of Clinical Challenges "

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Neuroendocrine Tumors of the Lung

- 20% of lung neoplasms
  - Small Cell Lung Cancer (SCLC) 15%
  - Large Cell Neuroendocrine Cancer (LCNEC) 3%
  - Typical Carcinoid (TC) 2%
  - Atypical Carcinoid (AC) 0.2%
- Indolent to very aggressive clinical behavior
- Distinctive cytological features
- Neuroendocrine markers – chromogranin-A, synaptophysin, CD56 (neural cell adhesion molecule)

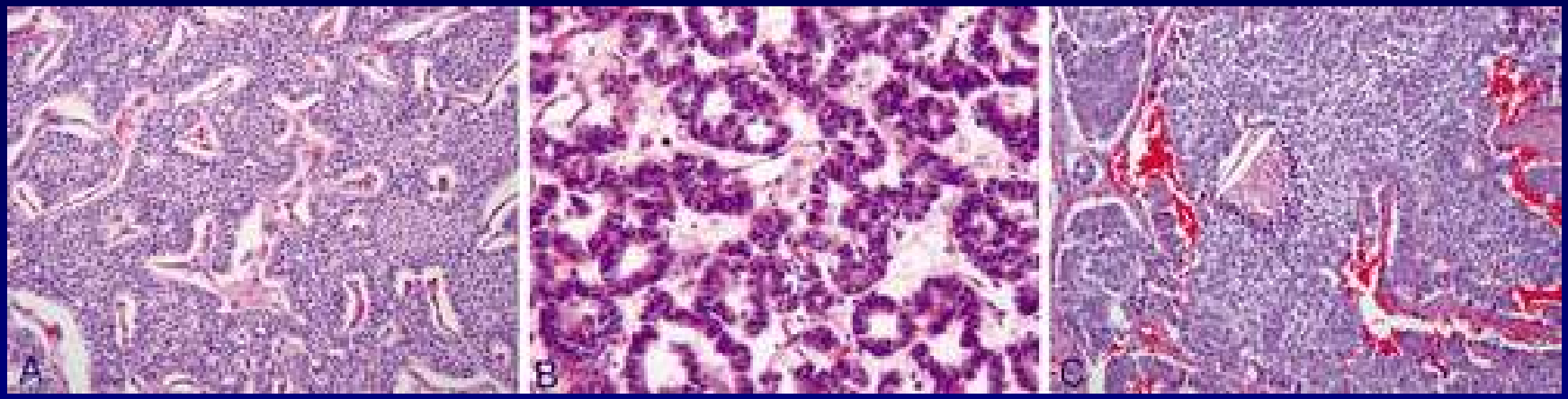
2015 WHO Classification: Lung Neuroendocrine Tumors

	Typical Carcinoid	Atypical Carcinoid	Large Cell Neuroendocrine Carcinoma	Small Cell Carcinoma
Grade	Low	Intermediate	High	High
Morphology	Well-Differentiated	Well-Differentiated	Poorly Differentiated	Poorly Differentiated
Mitoses per 2 mm^2	<2	2-10	>10 (median, 70)	>10 (median,80)
Necrosis	None	Present (focal punctate)	Present (extensive)	Present (extensive)
Ki-67	$\leq$ 5%	$\leq$ 20%	> 40%	>40%

Travis WD et al: IARC Press; 2004, Vol 10; Rekhtman N: Arch Pathol Lab Med, Vol 134, 2010;

Travis WD et al: IARC Press; 2015, 4th edition

Carcinoid: Typical and Atypical



Typical carcinoid | Glandular Variation | Atypical carcinoid

- Correlation with smoking is uncertain
- Symptoms: cough, hemoptysis, post-obstructive pneumonia
- Carcinoid sydrome rare (1-3%)
  - Hepatic metastases – 2-5%
  - Cushing's syndrome 1-6%
  - MEN 5-6%

Carcinoid: Staging

- TNM classification as in NSCLC
- CT/MRI routine – May appear hyperdense because often vascular
- FDG-PET of limited benefit
  - Sensitivity (14-100%)
  - Most useful for LCNC and SCLC
- Somatostatin receptor scintigraphy (Octreotide scan)
  - 80% express SSTRs
    - SSTR2 most common
  - Unknown benefit for staging
  - NCCN – not routinely recommended but can be useful
  - ^{68}Ga-DOTATATE/TOC PET
    - Improved resolution and shorter scanning
    - ↑ SSTR binding affinity
    - Estimation of receptor density and functionality

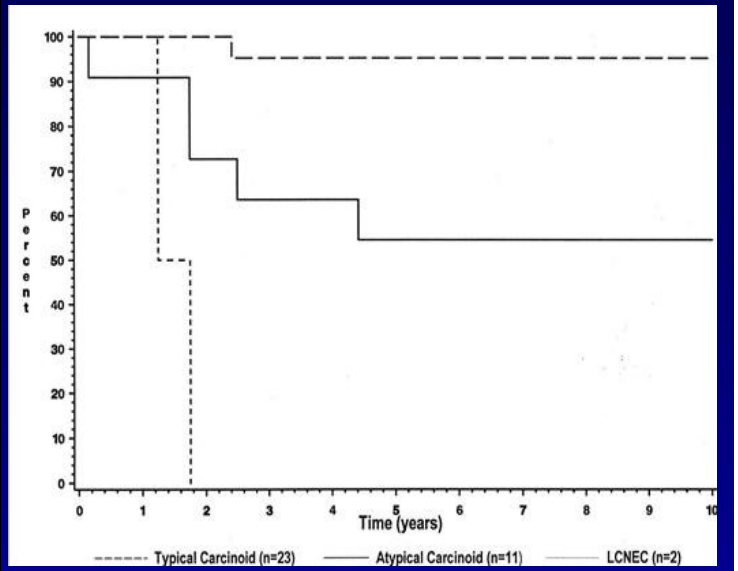
Treatment: Early Stage

- Surgery is the Mainstay of Treatment
- Typical carcinoid
  - Limited resections are preferred
    - Results with radical resections are similar
    - Endoscopic treatment can be considered in select patients
- Atypical carcinoid
  - Lobectomy preferred
- Mediastinal lymph nodes
  - Sampling to establish stage in clinical N0
  - Dissection for central tumors and clinical N positive

Ducrocq et al: Ann Thorac Surg, 65:1410, 1998; Stamatis et al: Eur J Cardio-Thorac Surg 4:527, 1990; Fox et al: Amer J Surg 205:200, 2013

Post Surgery Treatment

	Typical	Atypical
Survival 5yr,10yr (all)	>90%	70%, 50%
N0	>90%	85%, 70%
N1/N2	90%, 75%	60%, 50%
Recurrence	3-5%	25%



- **Adjuvant Treatment**
  - Not well studied
  - Not recommended for Typical Carcinoids
  - Consider in node positive Atypical Carcinoids
- **Surveillance**
  - Probably not warranted in node neg typical carcinoid
  - Consider yearly CT in node positive and atypical histology
  - NCCN – at 3-12 mo post resection then Q1-2 yrs

Thomas et al: Chest 119: 1143, 2001; Lou et al: Ann Thorac Surg, 96:1156, 2013.

Metastatic Carcinoid: ISSUES

- 25% metastatic at diagnosis (SEER)
  - 16 mo median survival
- No randomized trials
- Indolent nature of the disease can make survival difficult to interpret
- Pulmonary carcinoids are often included in trials of all NE tumors

Yao et al: J Clin Oncol 26:3063, 2008

Treatment of Metastatic Carcinoid: Chemotherapy

- Platin/etoposide in pts with intermediate grade tumors
- Temozolomide 31% RR, 7mo TTP in small trial
  - Capecitabine-temozolomide 65% DCR 19 pts
- Hepatic artery embolization w/wo chemotherapy in liver metastases
- Surgery can be considered in patients with limited sites of disease
- **NO STANDARD TREATMENT ESTABLISHED**

Gridelli et al: Cancer Treat Rev 39:466, 2013; Ekeblad et al: Clin Cancer Res 13:2986, 2007; Papaxoinis G et al: Eur NE Tumor Soc Conference, 2016.

Somatostatin Analogues

- Improves symptoms of carcinoid syndrome
- Prolongation of survival (PFS) only established in mid-gut tumors
- Octreotide or Lanreotide recommended for pts with carcinoid/Cushing's symptoms or octreotide+ scans
- SPINET Phase III trial: Lanreotide vs. Observation – completed awaiting results
- Radiolabelled somatostatin analogues
  - Some responses are being seen
  - Very little experience with bronchial carcinoids

Rinke et al: J Clin Oncol 27:4656, 2009; Sideris et al: Oncologist 17:747, 2012

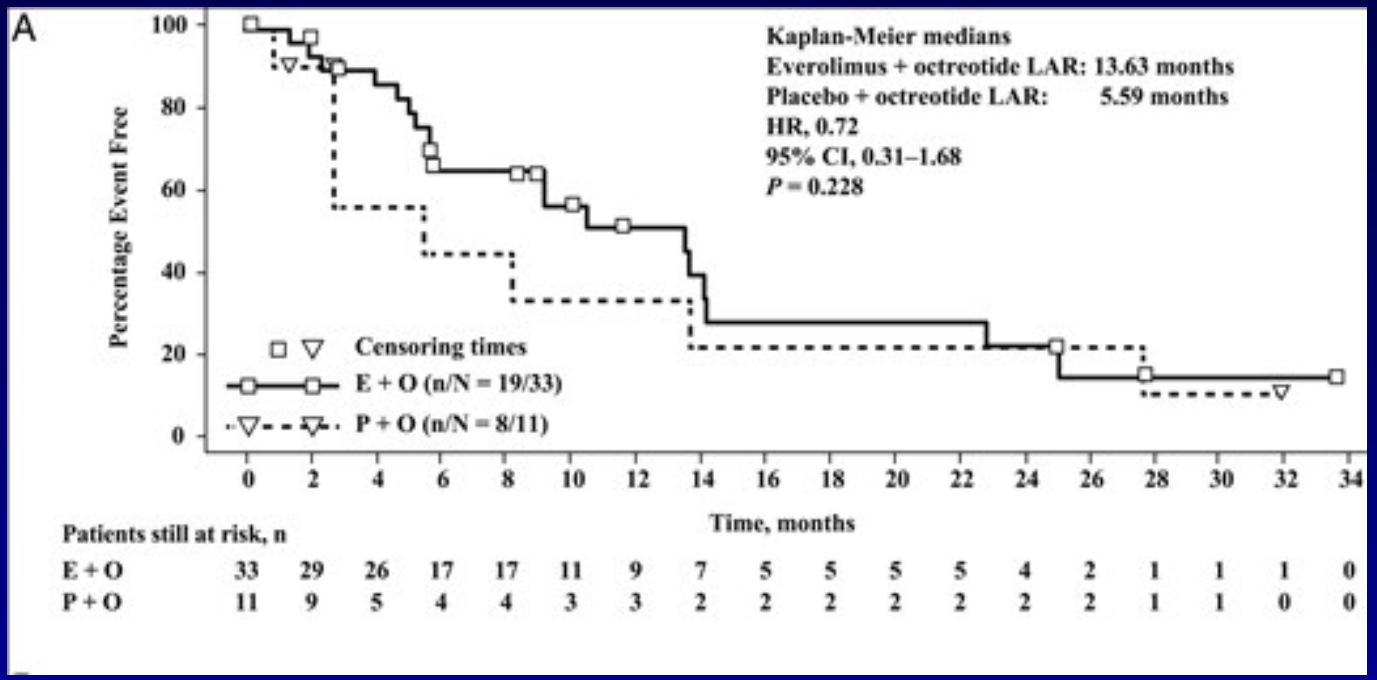
Hendifar AE et al: J Thorac Oncol 12:425, 2017

mTOR

- **mTOR** pathway may be involved in pathogenesis of NE tumors
  - Phase III RADIANT-4: Everolimus vs. Placebo
  - 90 lung; 9.2 v 3.6mo PFS HR=0.50
  - Approved for progressive well-differentiated NETS of GI/lung origin
- **Octreotide** reduces IGF-1→ potential for synergy
- **Phase II trial**: Everolimus + Octreotide LAR
  - 22% PR, 60 weeks PFS, 78% 3-yr survival
  - Only 4 pulmonary carcinoids

O'Reilly et al: Cancer Res 66:1500, 2006; Pollak at et : Anticancer Res 9:889, 1989; Yao et al: J Clin Oncol 26:4311, 2008; Pavel et al: Lancet 378:2005, 2011.; Yao JC et al: Lancet 387:968, 2016; Yao JC et al J Clin Oncol 34:4090, 2016.

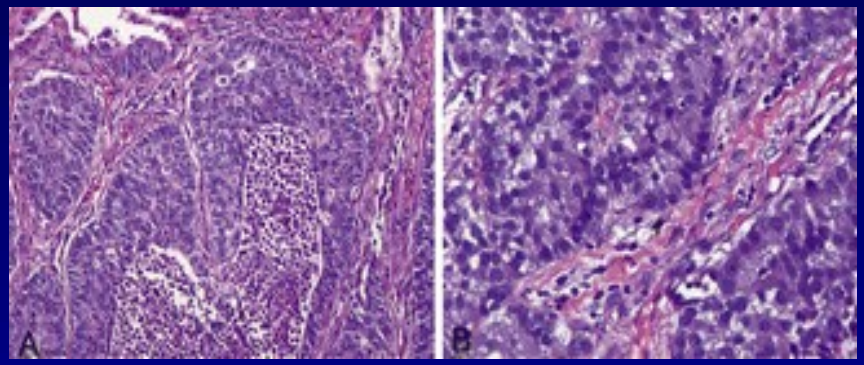
RADIANT-2: Lung Carcinoids



- Octreotide LAR + Everolimus (33 pt) or Placebo (11 pt)
- PFS 13.63 vs 5.59 mo, HR 0.72
- Not definitive but intriguing
- LUNA – Lung or thymus NE tumors (% progression-free)
  - Pasireotide LAR (39%) vs everolimus (33.3%) vs both (58.5%)
- Peptide receptor radionucleotide therapy may be promising
- NCI NE tumor task force
  - Tumors from different sites should be studied separately
  - Well and poorly differentiated tumors should be studies separately

Fazio et al: Chest 143:955, 2013; Kulke et al: J Clin Oncol 29:934, 2011; Ferolla P et al: Ann Oncol 27:4160,

Large Cell Neuroendocrine Cancer (LCNEC)



Low Power **High Power**

- Incidence 1- 3.5%
- Pathology
  - High grade, necrosis, IHC +
  - Overlap with other histologies
  - Most have nuclear and cytoplasmic features distinctive from SCLC
  - Can be difficult to distinguish from NSCLC
  - Requires IHC confirmation

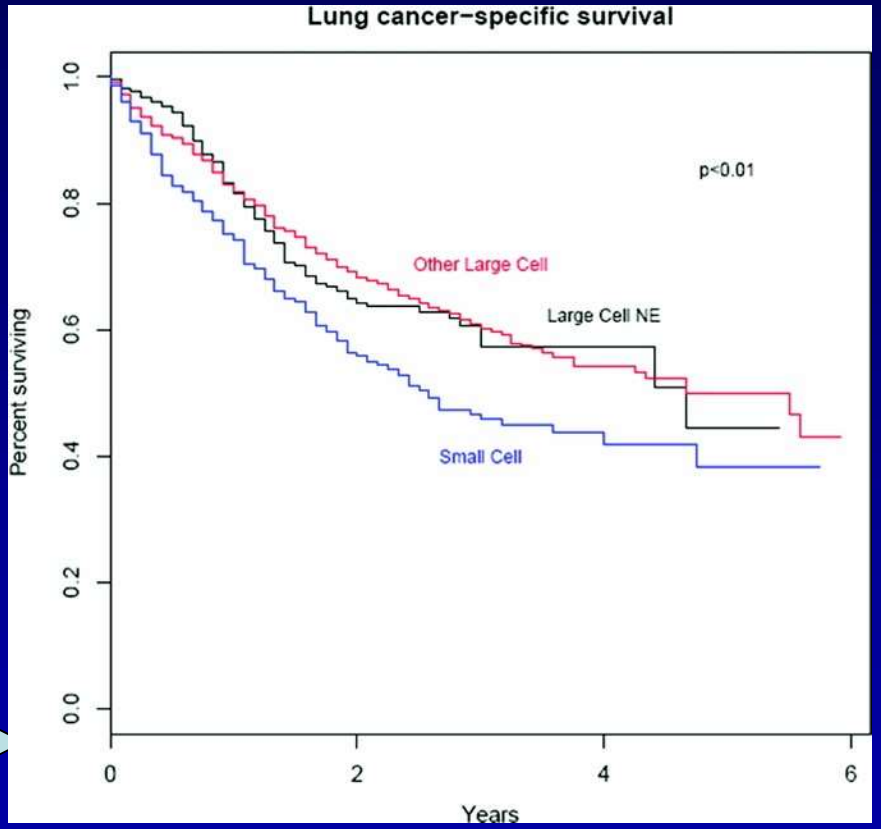
	(+) NE Markers by IHC	(−) NE Markers by IHC
(+) NE morphology[a]	LCNEC	NSCLC-NEM[b]
(−) NE morphology[a]	NSCLC-NED[c]	NSCLC, NOS[d]

Abbreviations: IHC, immunohistochemistry; LCNEC, large cell neuroendocrine carcinoma; NE, neuroendocrine; NED, neuroendocrine differentiation; NEM, neuroendocrine morphology; NOS, not otherwise specified; NSCLC, non–small cell carcinoma.

Rekhtman: Arch Pathol Lab Med 134:1628, 2010; Bakker et al: J Clin Pathol 00:1, 2013

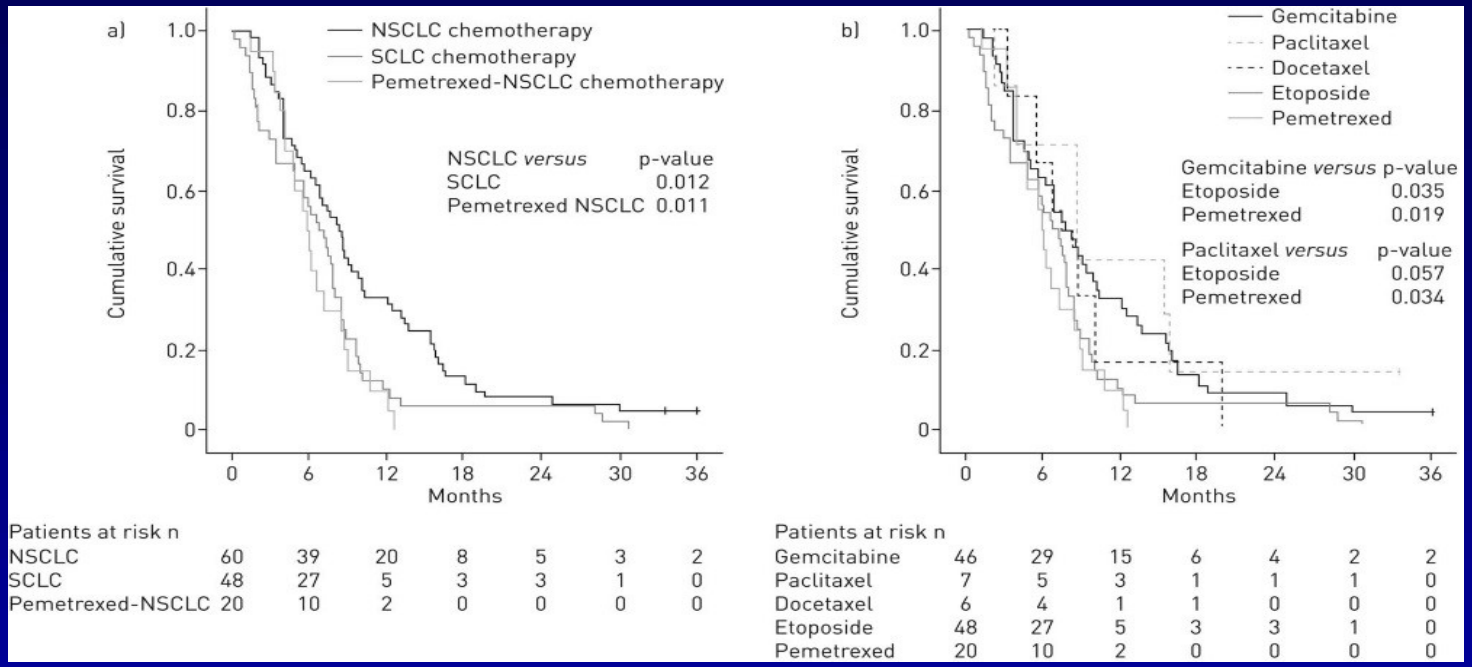
Treatment of LCNEC

- Early stage - Surgery
- ?Adjuvant chemo in early stage
  - Small patient numbers
  - Pathology may include other histologies
  - Different chemo and different timing
  - Large retro analysis suggests no benefit
  - Recent retro analysis shows benefit for chemo in stage I
- Should LCNEC be treated like SCLC???
  - ??Biologically similar to LCLC
- **NCCN guidelines recommend to treat like SCLC**



Grand et al: Lung Cancer 81:404, 2013;
Varlotto et al: J Thorac Oncol 6:1050, 2011;
Kujtan et al: J Thorac Oncol13(5):707, 2018.

Does the Chemotherapy Regimen Matter?

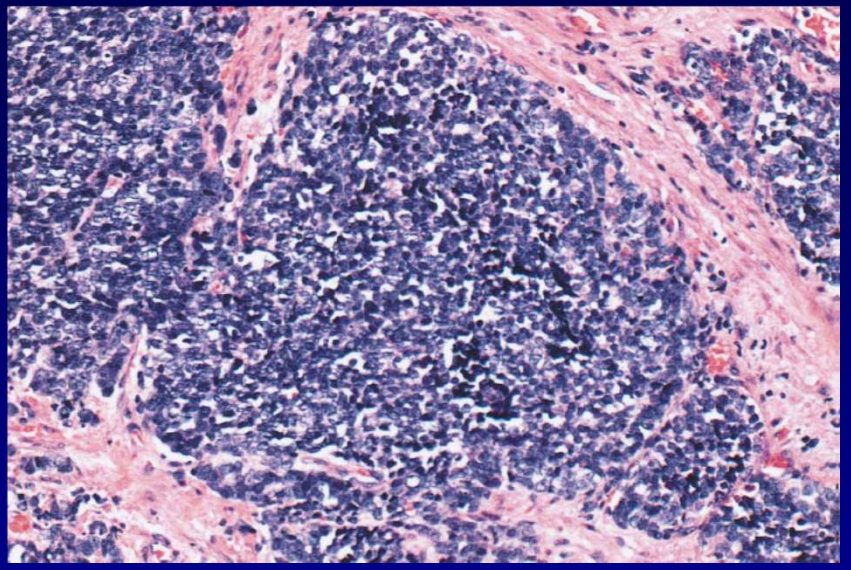


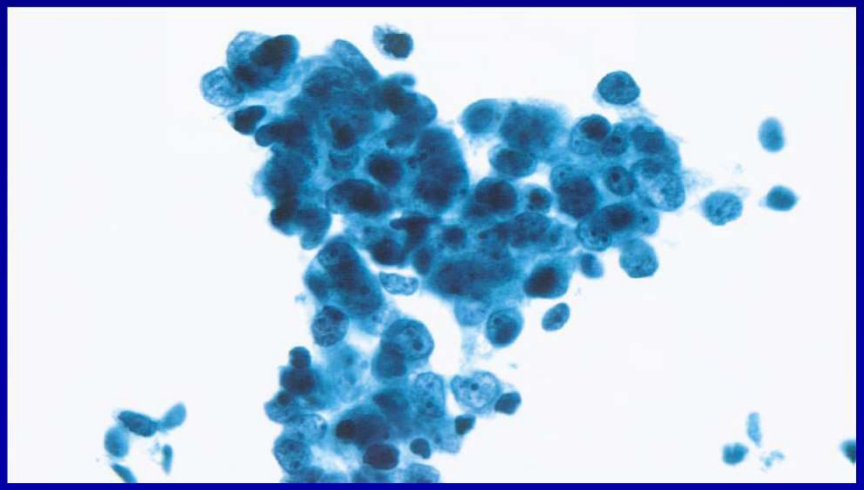
- 128 pts with LCNEC
- Platinum-based doublets
  - Gem, Doc, Pac, Vnr – median OS 8.5 mo
  - Etop – median OS 6.7 mo
  - Pem – Median OS 5.9 mo
- DON'T USE PEMETREXED

Derks JL et al: Eur Respir J, 2017

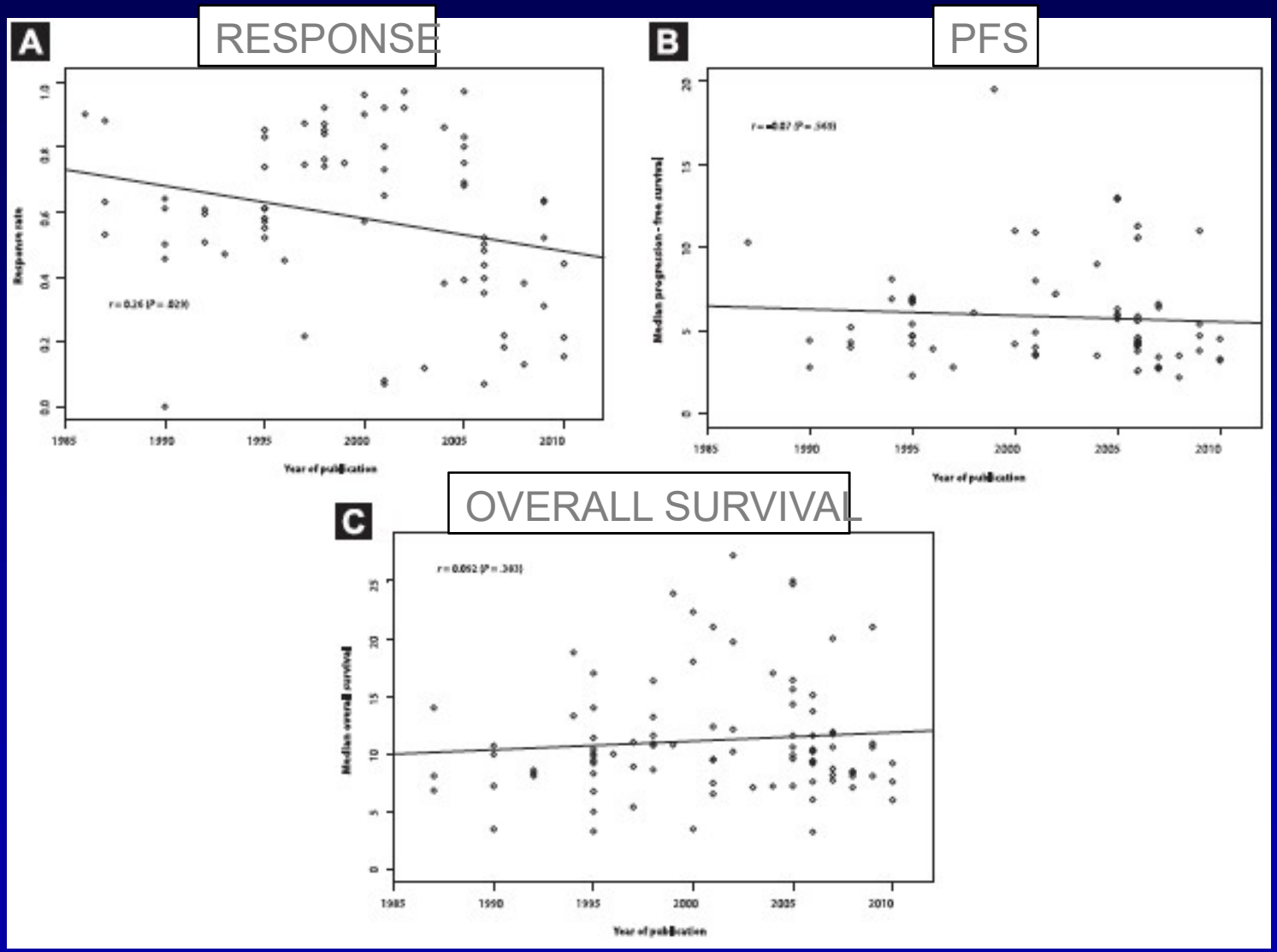
Natural History and Chemosensitivity of SCLC

- 15% of lung cancers
  - 31,000 cases/yr
- Fast growing and aggressive
- Screening (NLST) – no impact
- Surgery has a minor role
- Chemotherapy and radiation responsive
  - 60-70% chemotherapy response rate
- Relapse in all but a minority of SCLC patients
- 5-year survival 6%
- Usually diagnosed with minimal tissue
  - Lack of adequate tissue has limited identification of therapeutic targets





Absence of Change in Survival in SCLC



Nickolich Clin Lung Cancer 2014

SCLC: Chemotherapy Strategies

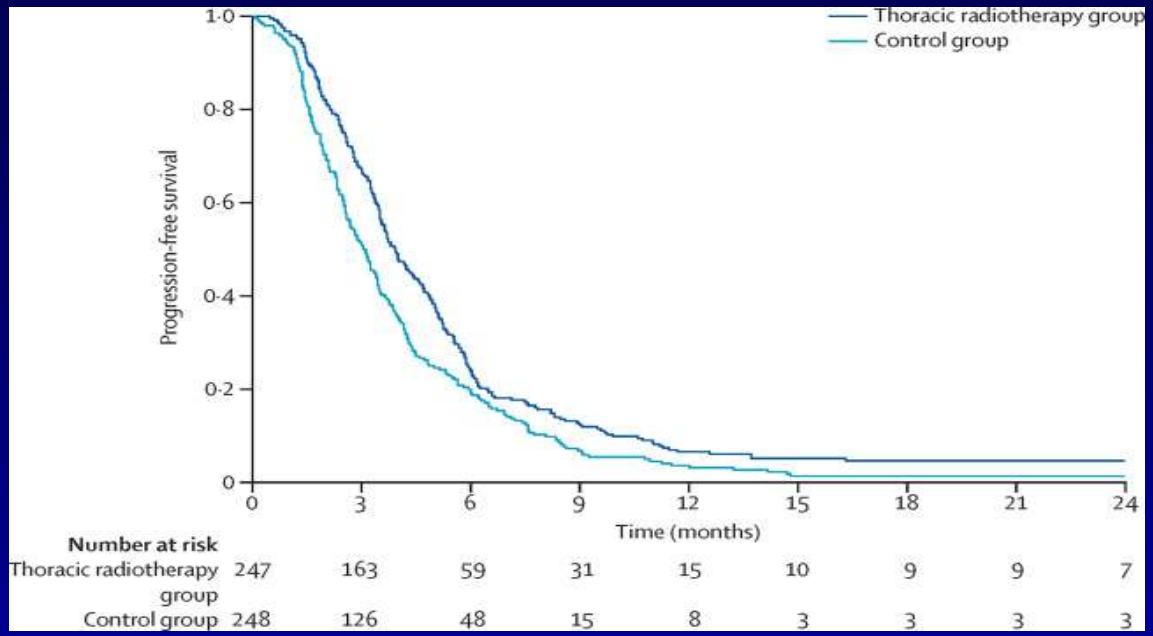
- Alternating regimens - no consistent benefit
- Maintenance therapy - no benefit beyond 4-6 cycles
- Consolidation chemo - no benefit
- 'Triplet' regimens - no benefit + excessive toxicity
- Dose-intensification - no benefit + excessive toxicity
- Dose-dense chemo - no benefit + excessive toxicity

Thoracic Radiotherapy

- Standard of care in LS-SCLC
  - Meta-analysis – 5.4% survival benefit
  - Better local control
  - Concurrent chemoradiotherapy is superior
- Timing – earlier is probably better
- Hyperfractionated radiotherapy – Yes or No?
  - Lack of shoulder on the SCLC RT response curve
  - Decreased delayed toxicity; increased esophagitis
  - TRIALS
    - 45Gy once daily v bid - 26% v 16% 5-yr survival
    - CONVERT 45Gy bid v 66Gy once daily – No difference
    - NCT00632853 45Gy bid v 70Gy once daily – Ongoing
- May have some benefit in extensive disease

Turrisi et al: NEJM 340:265, 1999; Faivre-Finn et al: Lancet Oncol 18:1116, 2017; Slotman et al: Lancet 385:38, 2015

Thoracic Radiaiton in Extensive SCLC



- 498 pts who responded to chemotherapy were randomized to receive thoracic RT (30Gy in 10 fx) v obs
- All received PCI
- OS not significantly different but at 2-yr OS 13% v 3% (p=0.001)
- Some pts may benefit from thoracic RT

Slotman al: Lancet 385:36,2015

SCLC: Prophylactic Cranial Irradiation

- Incidence: 67% brain relapse; 45% as 1st site
- Meta-analysis: 5% survival advantage at 3 yr
- EORTC randomized trial
  - Significant reduction in brain mets
  - Improvement in survival – 27.1% v 13.3% at one yr
  - Routine MRIs not done
- Japanese randomized trial (224 pts)
  - No survival difference (HR=1.27 favoring OBS)
  - Routine MRIs

Auperin et al. NEJM 341:476, 1999; Slotman et al: NEJM 357:664, 2007;
Takahashu et al: Lancet Oncol 18:663, 2017


I'LL BE BACK!

Randomized Second Line Therapy Trials for SCLC

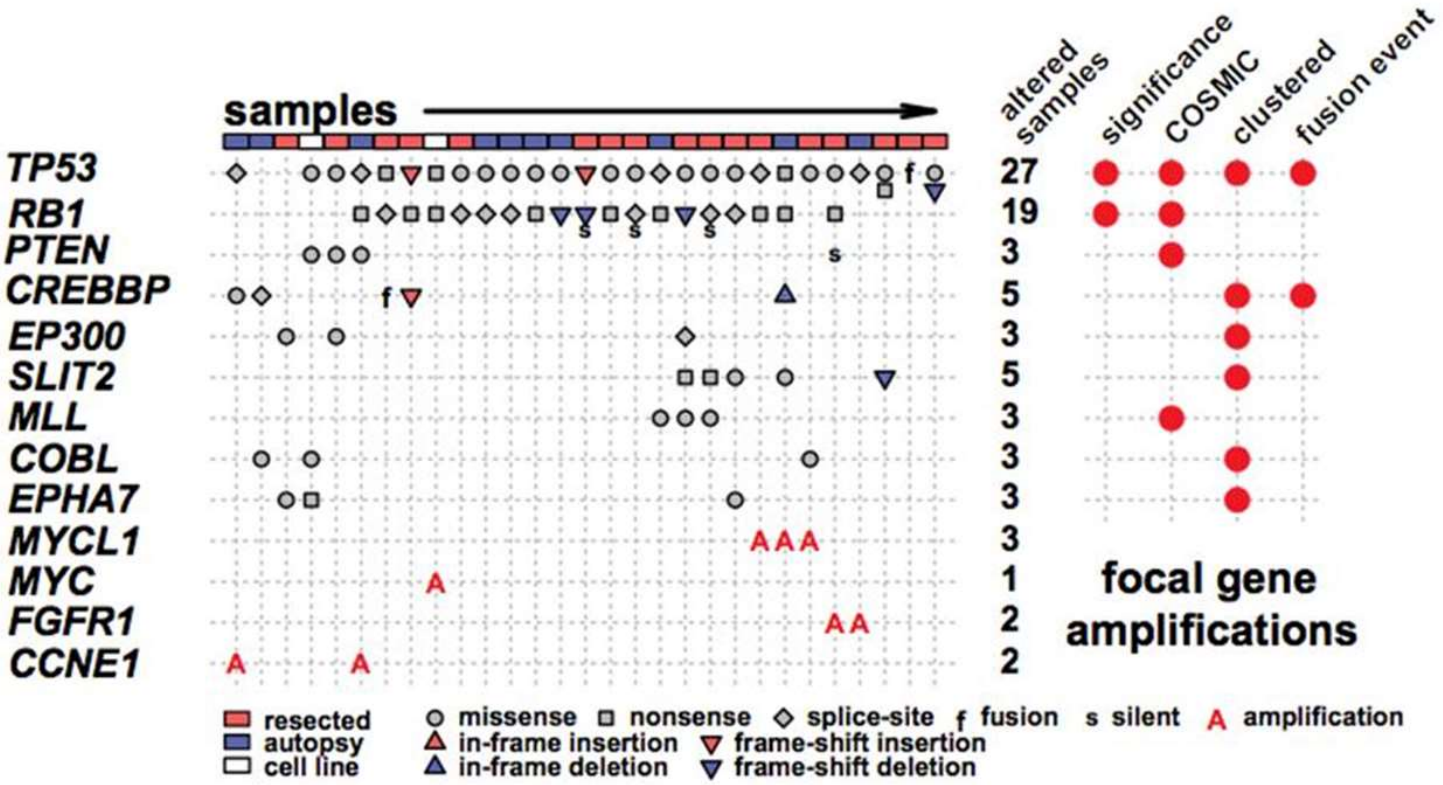
Study	No. of Patients	Results Primary endpoint	Population Studied
Topotecan vs CAV	211	Equivalent	Sensitive
Toptecan vs Best Supportive Care	141	Superior	Refractory and Sensitive
IV Topotecan vs PO Topotecan	309	Equivalent	Sensitive
Toptecan vs Amrubicin	637	Equivalent	Refractory and Sensitive

TopoteCAN'T

SCLC: Ineffective Targeted Therapy

- Matrix metalloproteinase inhibitors
  - Marimastat, BAY-12-9566
- Angiogenesis inhibitors
  - Thalidomide, vandetanib, sunitinib, sorafenib, cediranib
- Immuno-targeted vaccine
  - BEC2
- Growth-factor pathway inhibitors
  - Imatinib, CI-779, R11577, exisulind, tamoxifen, dasatinib
- Anti-apoptotic inhibitors
  - Oblimersen, AT-101
- Histone deacetylase (HDAC) inhibitors
  - Romidepsin

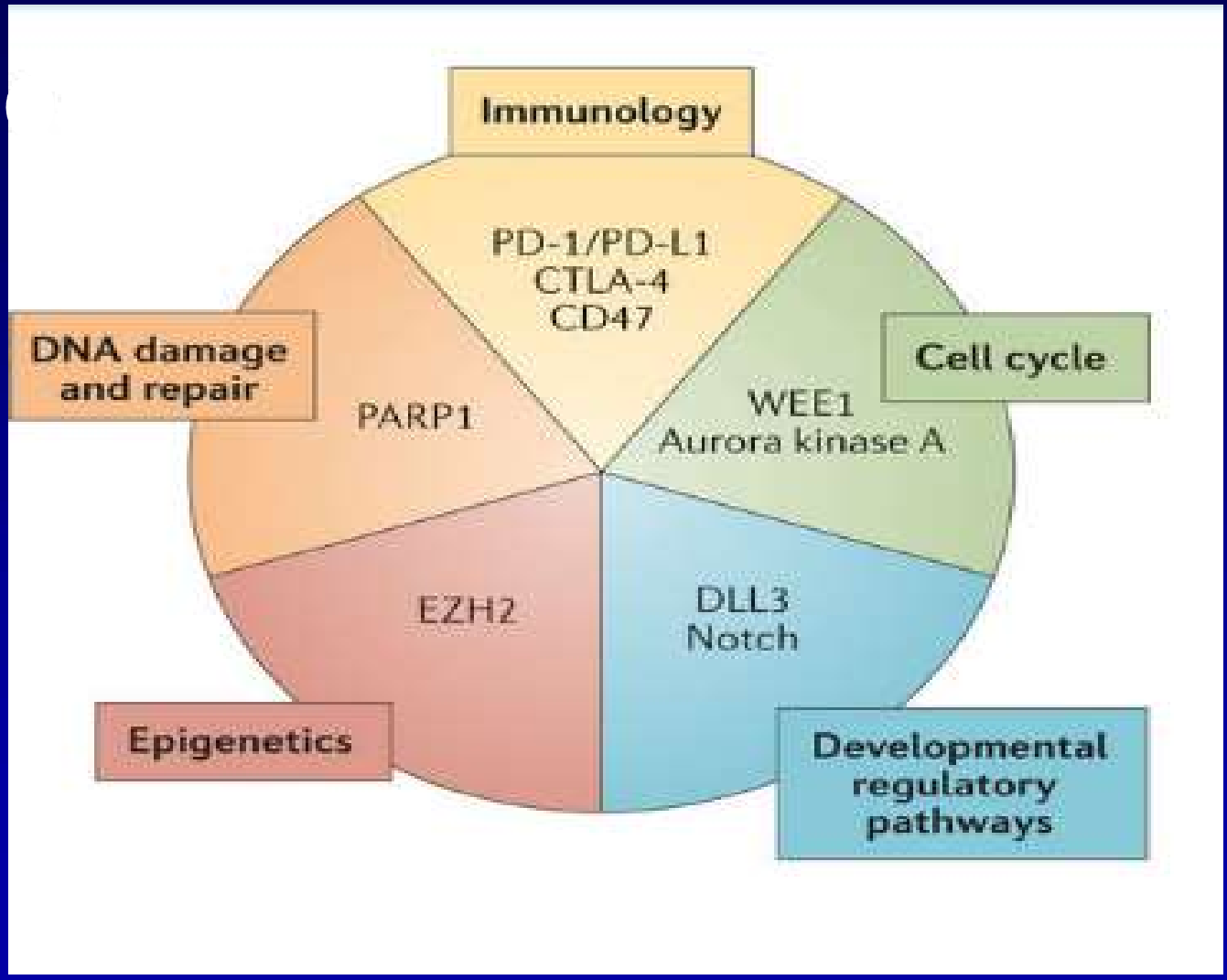
Mutations in small cell lung cancer



Peifer et al., Nat Genet 2012

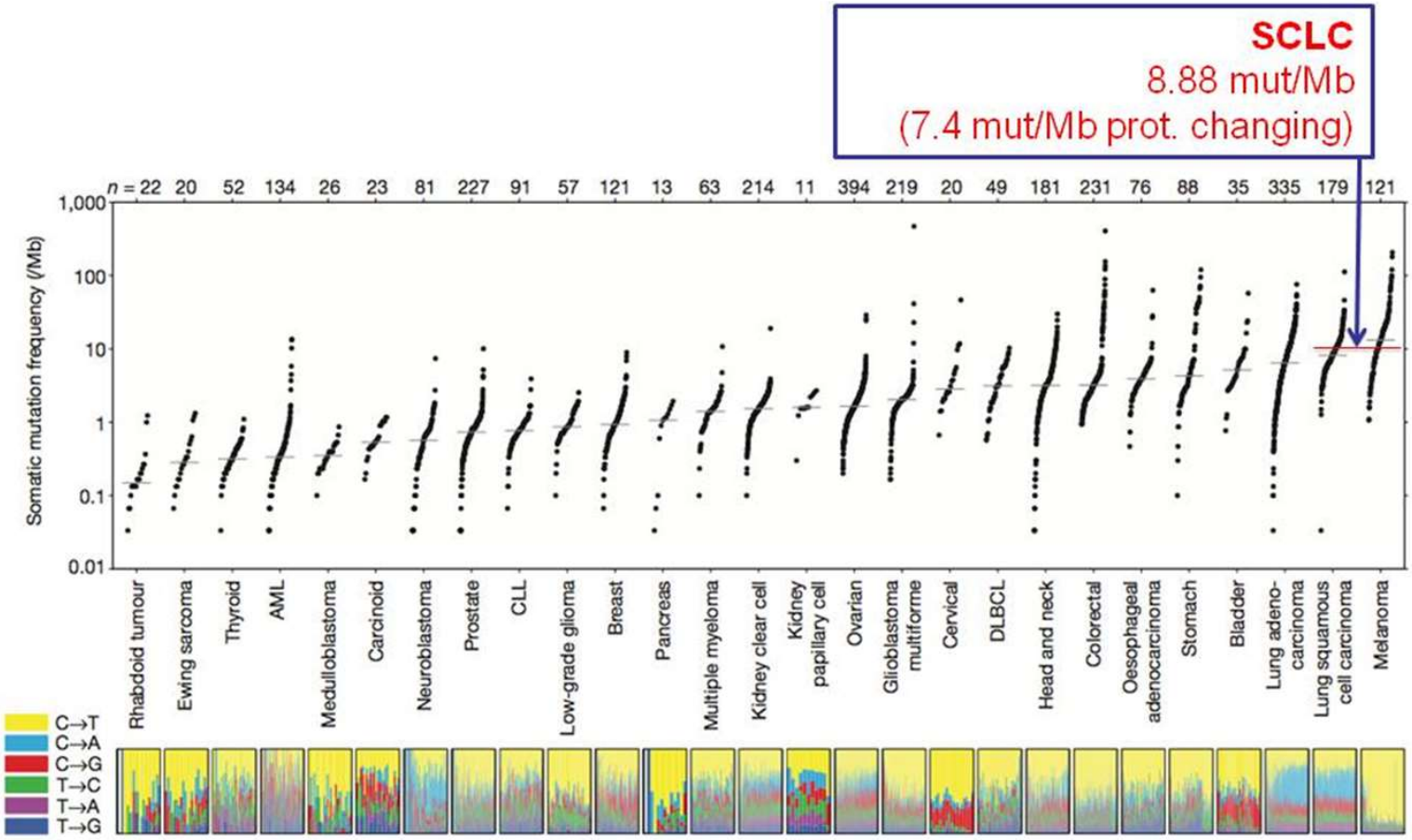
P53 loss and Rb1 loss almost universal. No dominant ‘driver’ mutation. No alteration that explains disease characteristics.

Novel Targeted Therapeutics for SCLC



Sabari JK et al: Nature Rev Clin Oncol, 14:549, 2017

Somatic mutation frequency in lung cancer

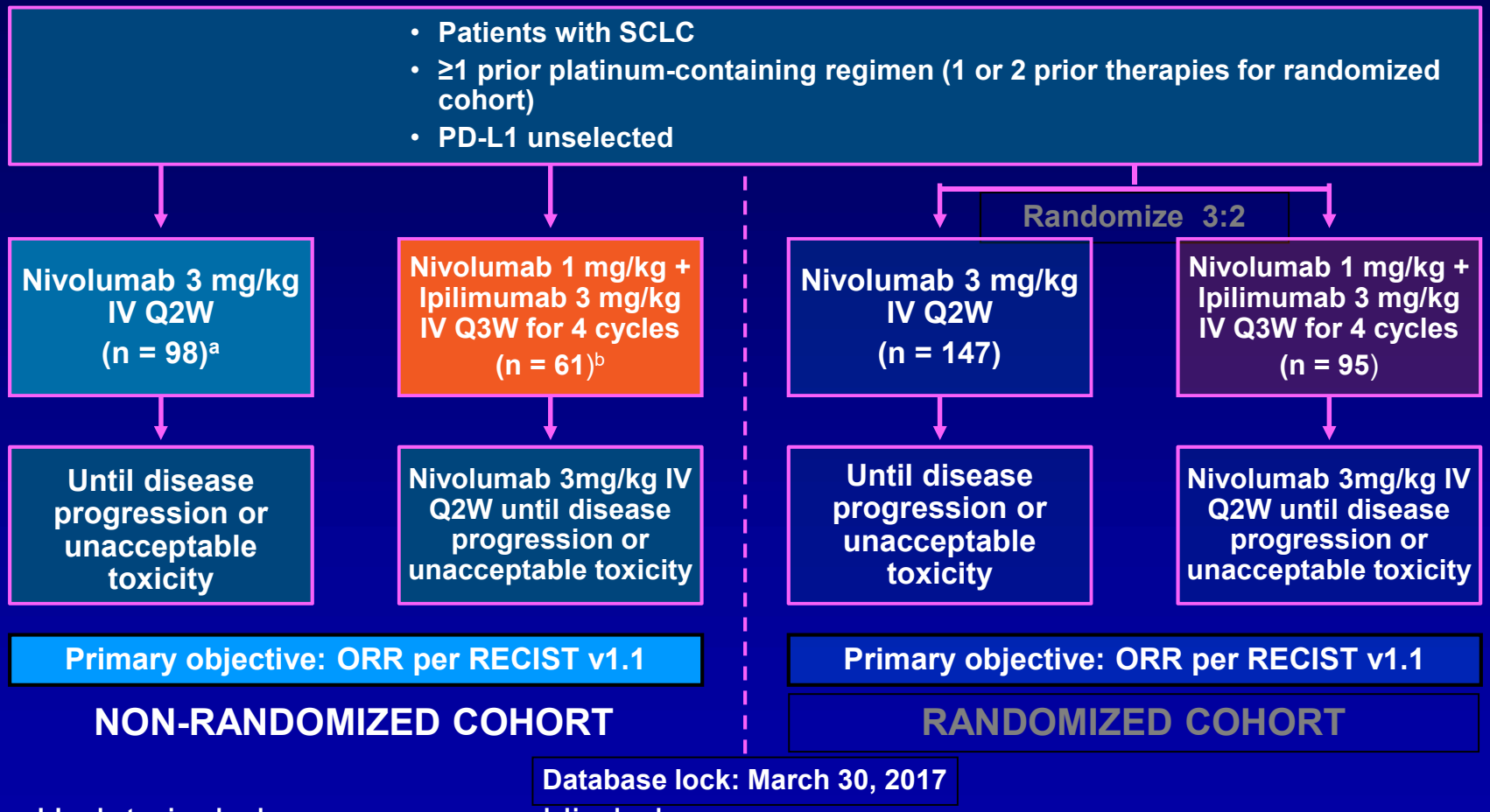


Lawrence et al. *Nature* (2013)
Peifer et al., Nat Genet (2012)

Data from NSCLC suggests smokers have a higher probability of benefit from anti-PD-L1 inhibitor- Soria, et al ESMO 2013.

CheckMate 032: Nivolumab ± Ipilimumab in Advanced SCLC

Phase I/II CheckMate 032 Study Design – Non-Randomized Cohort

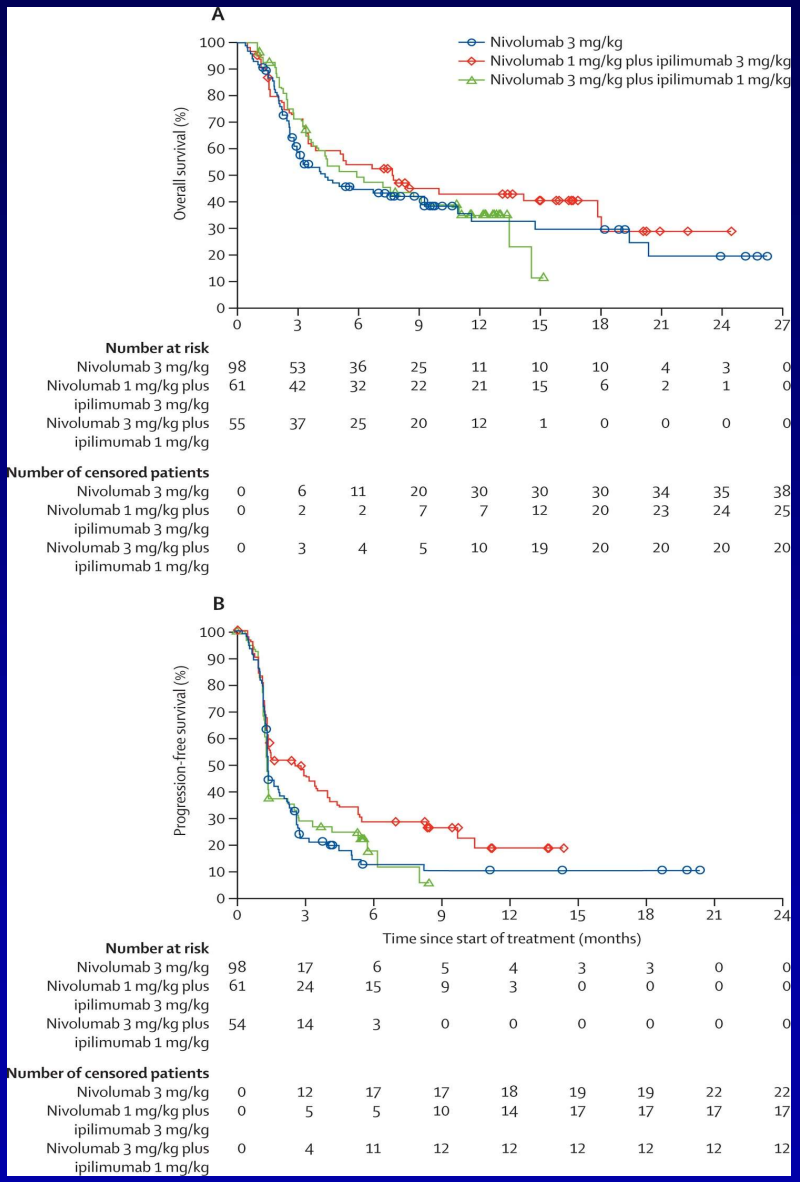


- Update includes response per blinded independent central review (BICR)
  - Additional follow-up of ~6 months from prior disclosure[8]

[a]Median follow-up 23.3 mo; [b]Median follow-up 28.6 mo
Follow-up was calculated as time from first dose to database lock

Antonia et al, The Lancet Oncology 2016 17, 883-895DOI: (10.1016/S1470-2045(16)30098-5

Checkmate 032 Results



- Nivo monotherapy
  - RR 10%, DOR 17.9 mo, 12mo 28.3%
- Nivo + ipi
  - RR 19-23%
  - Survival better but more toxic
- PD-L1 expression did not correlate with response
- Enhanced efficacy of nivo ± ipi in high TMB
- **FDA approved nivo as third-line treatment of SCLC August 2018**

Antonia et al: Lancet Oncol, 2016;17(7):883; Ready et al: J Thorac Oncol, 2019;14(2):237; Hellman et al: Cancer Cell, 2018;33(5):853

CheckMate 331: Nivolumab vs. Chemotherapy in relapsed SCLC

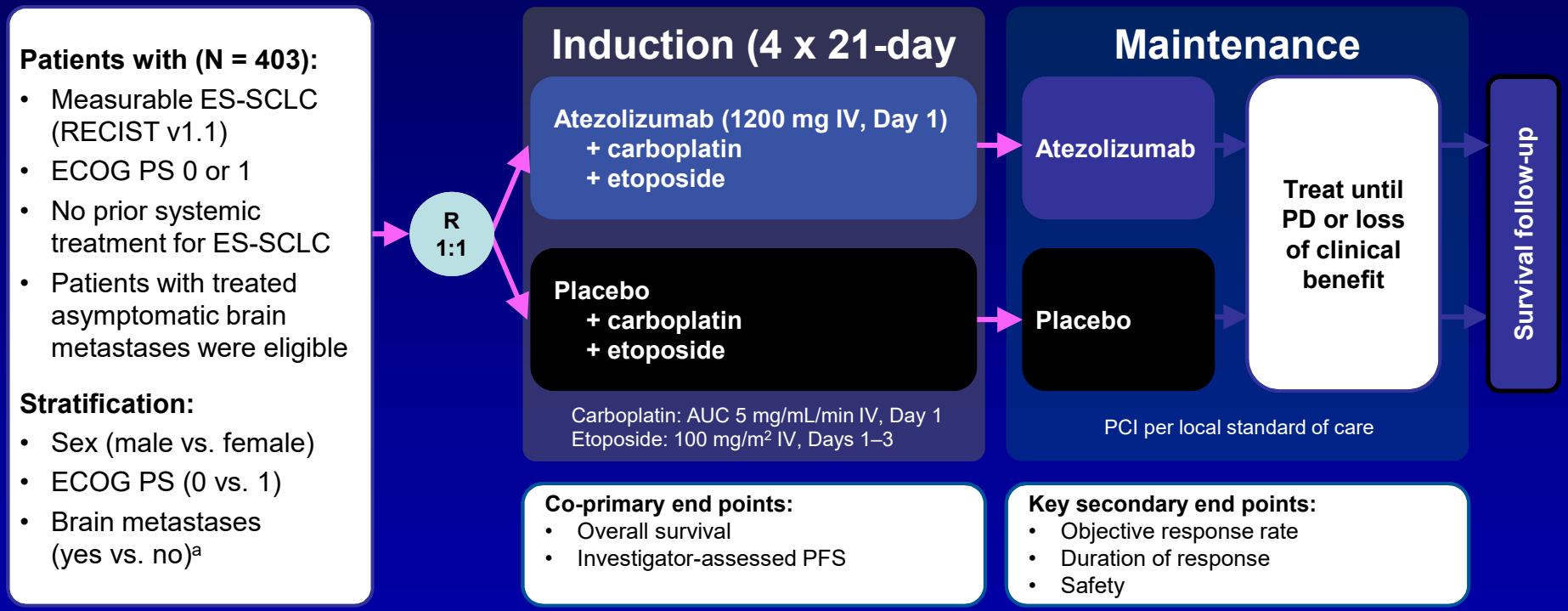
- Disease progression or recurrence after first-line chemotherapy or chemoradiation therapy
- ECOG performance status 0-1
- The primary endpoint is OS
- Randomized 1:1 to nivolumab or chemotherapy (topotecan in the US or EU, and topotecan or amrubicin in Japan)

October 12, 2018 Press Release

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

Horn et al, ASCO JCO.2016.34.15

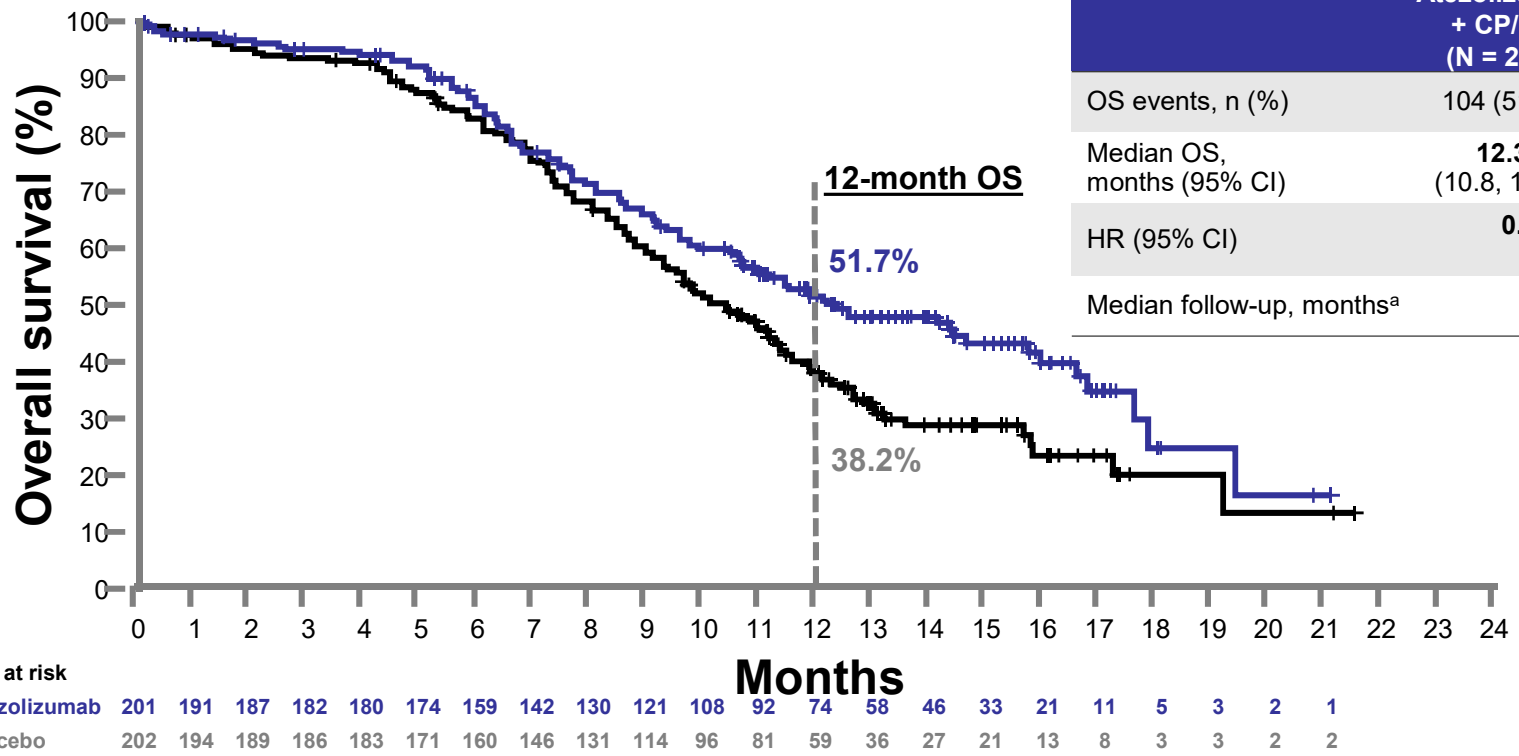
IMpower133: Global Phase 1/3, double-blind, randomized, placebo-controlled trial evaluated atezolizumab + carboplatin + etoposide in 1L ES-SCLC



[a] Only patients with treated brain metastases were eligible. ECOG PS, Eastern Cooperative Oncology Group Performance Status; IV, intravenous; PCI, prophylactic cranial irradiation; PD, progressive disease; PFS, progression-free survival; R, randomized; RECIST, Response Evaluation Criteria In Solid Tumors.

Horn et al: N Engl J Med, 2018;379(23):2220

Overall survival



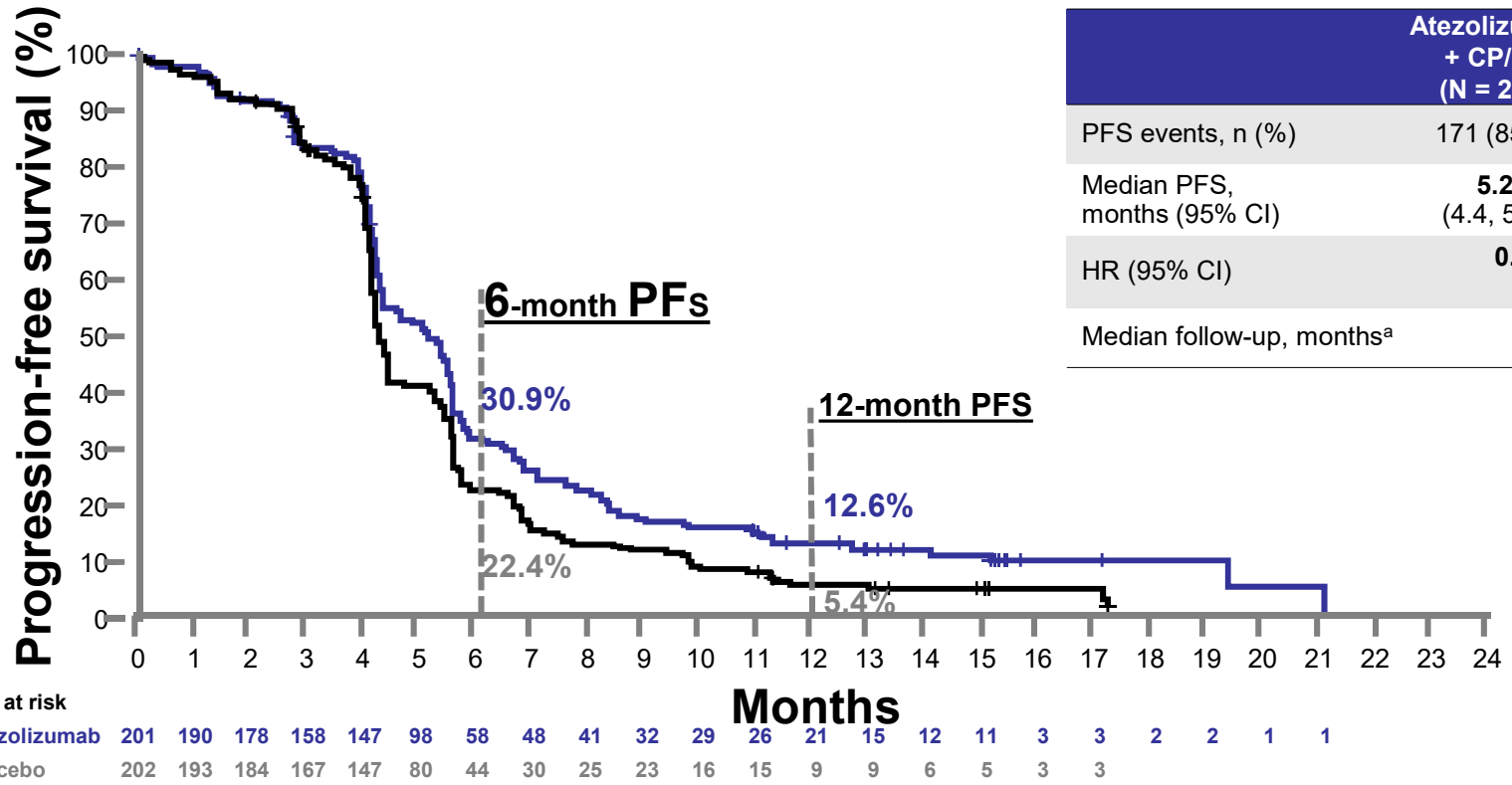
	Atezolizumab + CP/ET (N = 201)	Placebo + CP/ET (N = 202)
OS events, n (%)	104 (51.7)	134 (66.3)
Median OS, months (95% CI)	**12.3** (10.8, 15.9)	**10.3** (9.3, 11.3)
HR (95% CI)	**0.70** (0.54, 0.91) p = 0.0069	
Median follow-up, months[a]	13.9	

No. at risk

Atezolizumab	201	191	187	182	180	174	159	142	130	121	108	92	74	58	46	33	21	11	5	3	2	1
Placebo	202	194	189	186	183	171	160	146	131	114	96	81	59	36	27	21	13	8	3	3	2	2

[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.

Investigator-assessed progression-free survival



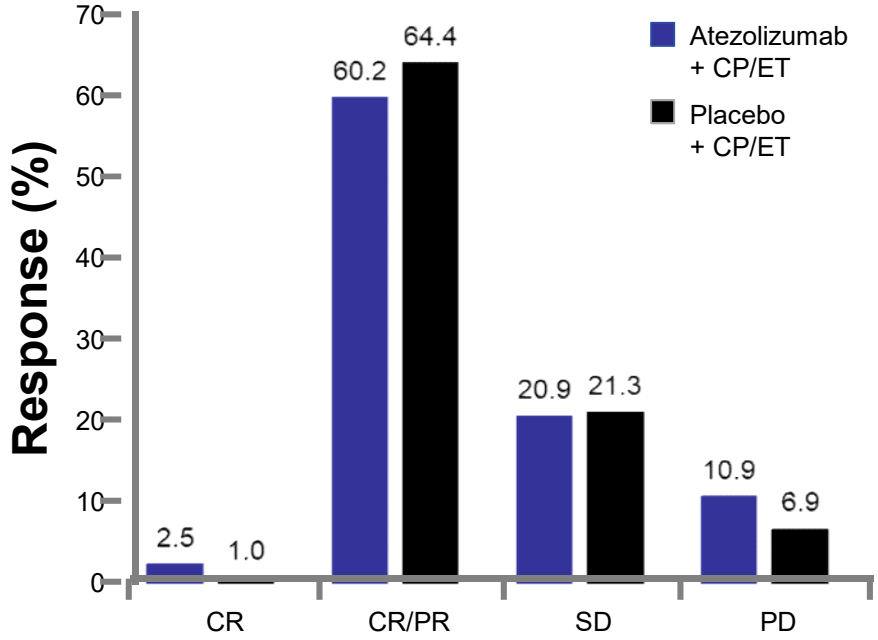
	Atezolizumab + CP/ET (N = 201)	Placebo + CP/ET (N = 202)
PFS events, n (%)	171 (85.1)	189 (93.6)
Median PFS, months (95% CI)	**5.2** (4.4, 5.6)	**4.3** (4.2, 4.5)
HR (95% CI)	**0.77** (0.62, 0.96) p = 0.017	
Median follow-up, months[a]	13.9	

No. at risk

Atezolizumab	201	190	178	158	147	98	58	48	41	32	29	26	21	15	12	11	3	3	2	2	1	1	
Placebo	202	193	184	167	147	80	44	30	25	23	16	15	9	9	6	5	3	3					

[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.

Confirmed objective response and duration of response

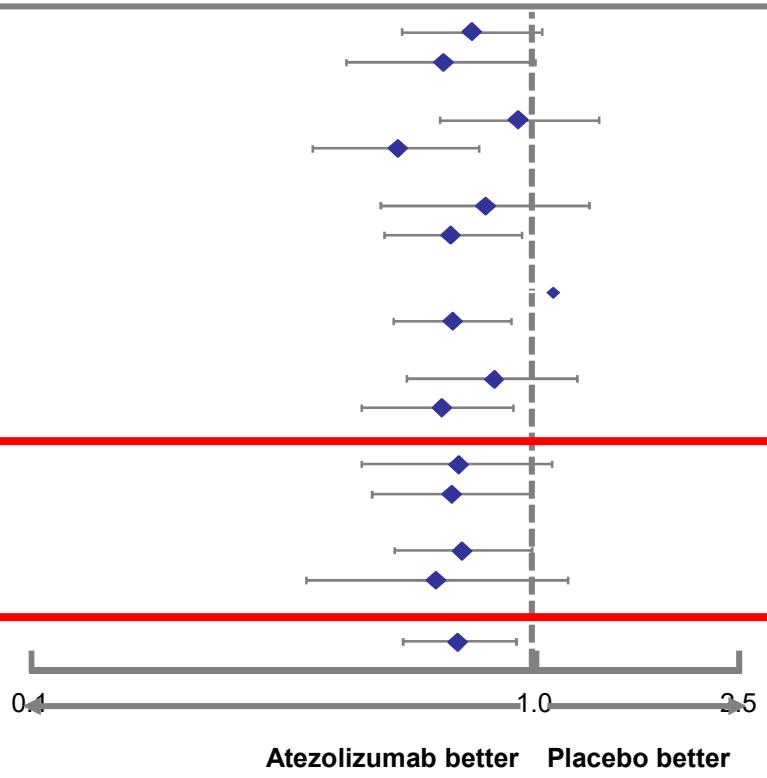


Duration of response	Atezolizumab + CP/ET (N = 121)	Placebo + CP/ET (N = 130)
Median duration, months (range)	4.2 (1.4[a] to 19.5)	3.9 (2.0 to 16.1[a])
HR (95% CI)	0.70 (0.53, 0.92)	
6-month event-free rate — %	32.2	17.1
12-month event-free rate — %	14.9	6.2
Patients with ongoing response — no. (%)[b]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

[a] Censored. [b] At clinical cutoff date: April 24, 2018. CR, complete response; EFS, event-free survival; PD, progressive disease; PR, partial response; SD, stable disease.

Overall survival in key subgroups

Population	Median overall survival (months) Atezolizumab + CP/ET	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)
ECOG PS 1 (n = 263)	11.4	9.3	0.68 (0.50, 0.93)
Brain metastases (n = 35)	8.5	9.7	1.07 (0.47, 2.43)
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)



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.

Most frequently observed AEs

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.

Immunotherapy in SCLC

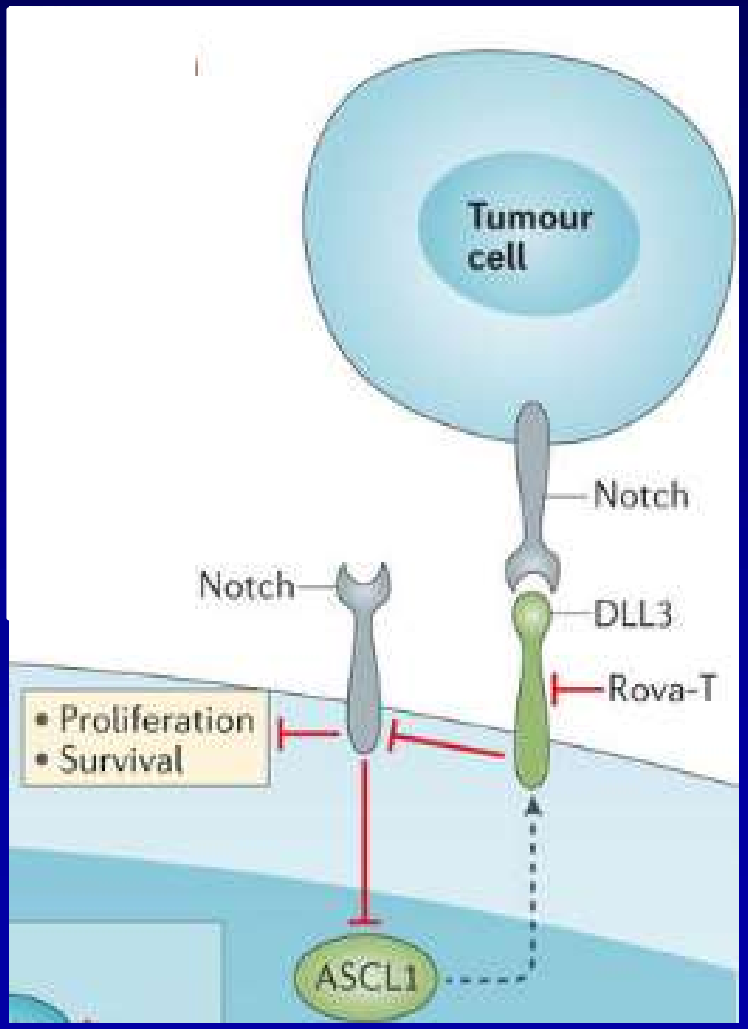
- Not a 

but works sometimes
- Low expression of PD-L1 – 16.5%
  - PD-L1 expression was not predictive of response in CheckMate 032
  - Role of Tumor Mutational Burden????
- Immune microenvironment may be different in SCLC
- Paucity of lymphocytes in SCLC tumors may suggest immune incompetency of the host
- More work is needed
  - IO combos

Yu H et al: J Thorac Oncol 12:110, 2017; Antonia S et al: Lancet Oncol 17:883, 2016

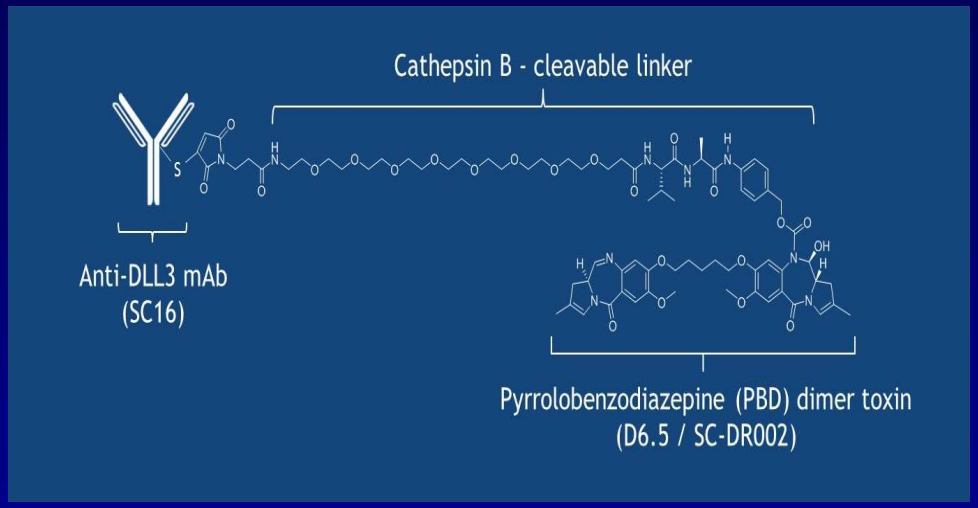
Notch Ligand DLL3

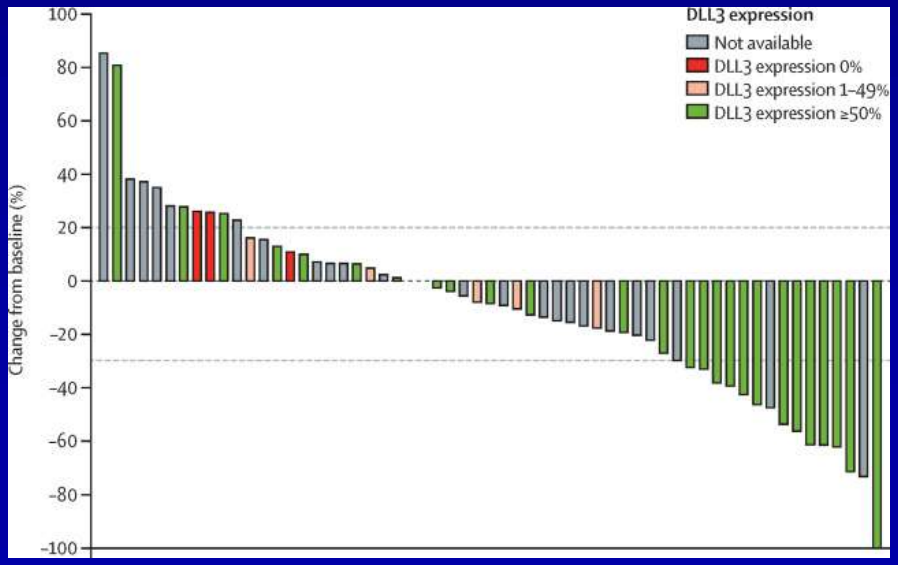
- Notch pathway is involved in regulating neuroendocrine differentiation
- Notch signaling suppresses oncogenesis and tumor growth in NE tumor cells
- DLL3 is upregulated and aberrantly expressed in high grade NE tumors
- DLL3 is a potential target



Kunnimalaiyaan M et al: Oncologist 12:535, 2007; Chapman G et al: Hum Mol Genet 20:905, 2011; Sabari JK et al: Nature Rev/Clin Oncol 14:549, 2017

Rovalpituzumab Teserine





- Drug antibody conjugate directed against delta-like protein 3 (DLL3)
  - Expressed in 80%
- Phase I – 18% RR; 38% in high expressors
- Toxicities – thrombocytopenia, edema, ↑LFTs, rashes
- Trinity Phase II trial complete

Rudin CM et al: Lancet Oncol 18:42, 2017

TRINITY: A Phase 2, Single-Arm Study of Rova-T in DLL3-Expressing, Relapsed/Refractory SCLC

Key Eligibility Criteria
- DLL3-positive* SCLC
- Relapsed or refractory disease
- ≥ 2 previous regimens
- ≥ 1 platinum-based regimen
- ECOG Performance Status 0-1
- Stable CNS metastases allowed

→

N = 339
Rova-T
0.3 mg/kg IV
q6w x 2[a]

→

Primary Endpoints
- Objective response rate (ORR)
- Overall survival (OS)

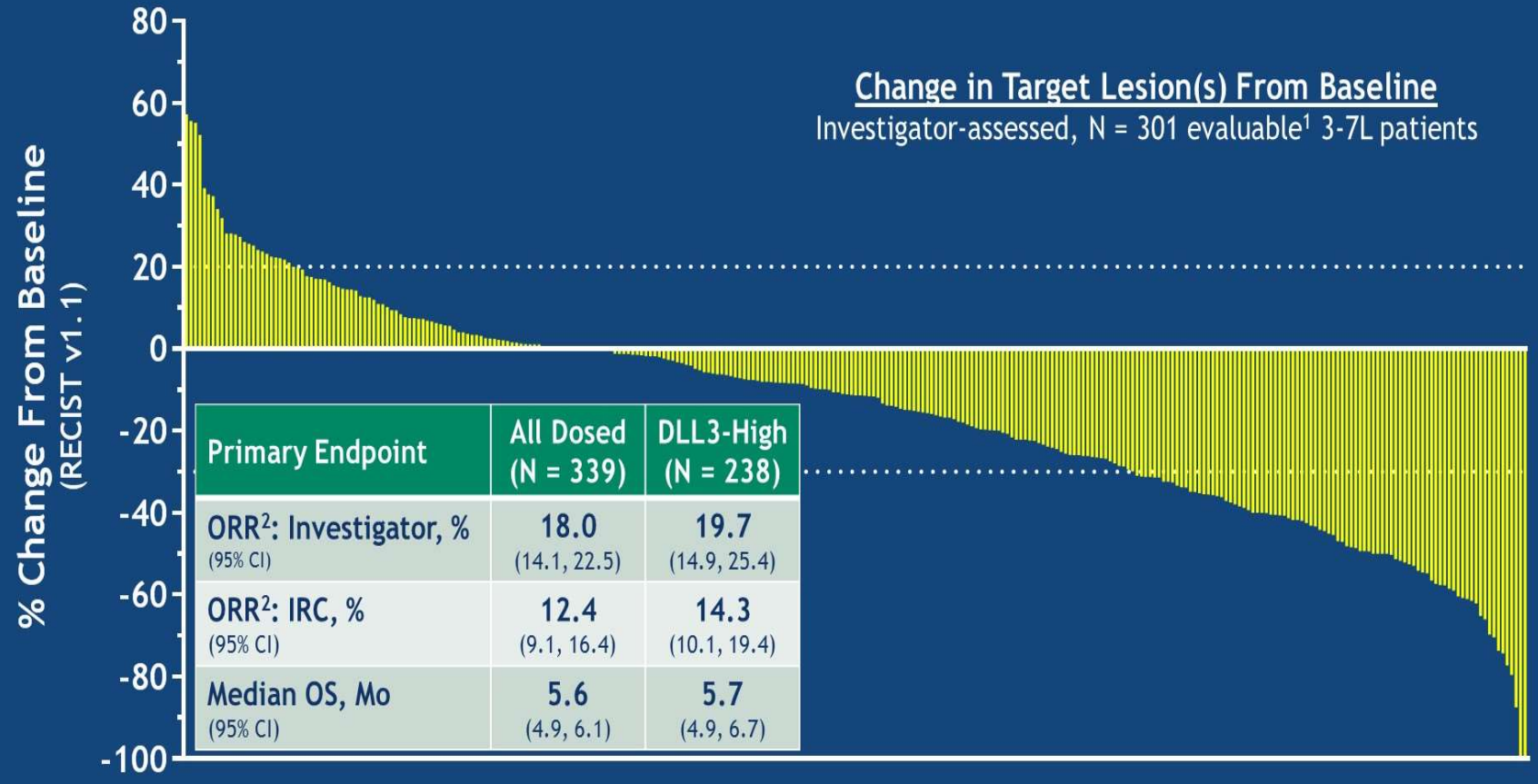
Secondary Endpoints
- Duration of response (DOR)
- Clinical benefit rate (CBR)
- Progression-free survival (PFS)

- Re-treatment was permitted at progression
- Study was powered to detect a 25% best overall response rate in DLL3-high Pts with a Simon's two-stage design
- Study size was increased to ensure adequate enrollment of 3L Pts

*Clinical trial mouse antibody-based immunohistochemistry assay.
[a]Re-treatment with 2 cycles of Rova-T was permitted for patients who tolerated the initial 2 doses, exhibited SD or better, received no other systemic anticancer therapy after Rova-T, and progressed ≥ 12 weeks after the 2nd initial dose.
CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; IHC, immunohistochemistry; IV, intravenous; q6w, every 6 weeks.

Carbone at 2018 ASCO, Abst 8507

TRINITY: Primary Endpoint Analyses



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)

1. Patients who had a baseline scan and at least 1 follow-up scan with an evaluable response.
2. Confirmed CR+ PR per RECIST v1.1

Carbone at 2018 ASCO, Abst 8507

Summary of TEAEs

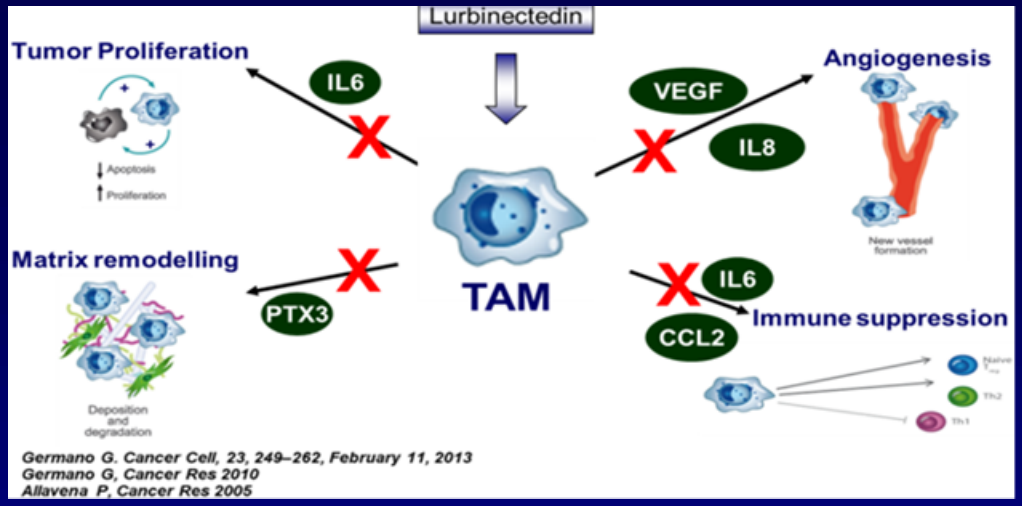
TEAEs, Any Grade ≥ 15% Patients	All Patients, N = 339	
	Any n (%)	Drug-Related n (%)
Fatigue	130 (38%)	96 (28%)
Photosensitivity reaction	123 (36%)	120 (35%)
Pleural effusion	109 (32%)	95 (28%)
Peripheral edema	104 (31%)	89 (26%)
Decreased appetite	103 (30%)	53 (16%)
Nausea	88 (26%)	55 (16%)
Dyspnea	84 (25%)	33 (10%)
Thrombocytopenia	83 (25%)	74 (22%)
Constipation	75 (22%)	15 (4%)
Vomiting	59 (17%)	28 (8%)
Anemia	58 (17%)	44 (13%)
Cough	55 (16%)	7 (2%)
Hypoalbuminemia	53 (16%)	40 (12%)
Pericardial effusion	50 (15%)	42 (12%)
Abdominal pain	49 (15%)	18 (5%)
Asthenia	49 (15%)	40 (12%)

TEAEs, Grade 3/4 ≥ 10 Patients	All Patients, N = 339	
	Any n (%)	Drug-Related n (%)
Thrombocytopenia	38 (11%)	37 (11%)
Photosensitivity reaction	23 (7%)	23 (7%)
Anemia	16 (5%)	12 (4%)
Fatigue	15 (4%)	12 (4%)
Pleural effusion	15 (4%)	14 (4%)

- Serosal effusions were managed primarily through standard drainage procedures; steroids, NSAIDs, and colchicine also used
- History of effusions may be identified risk factor for Gr3+ Rova-T-related effusions

Carbone at 2018 ASCO, Abst 8507

Lurbinectedin



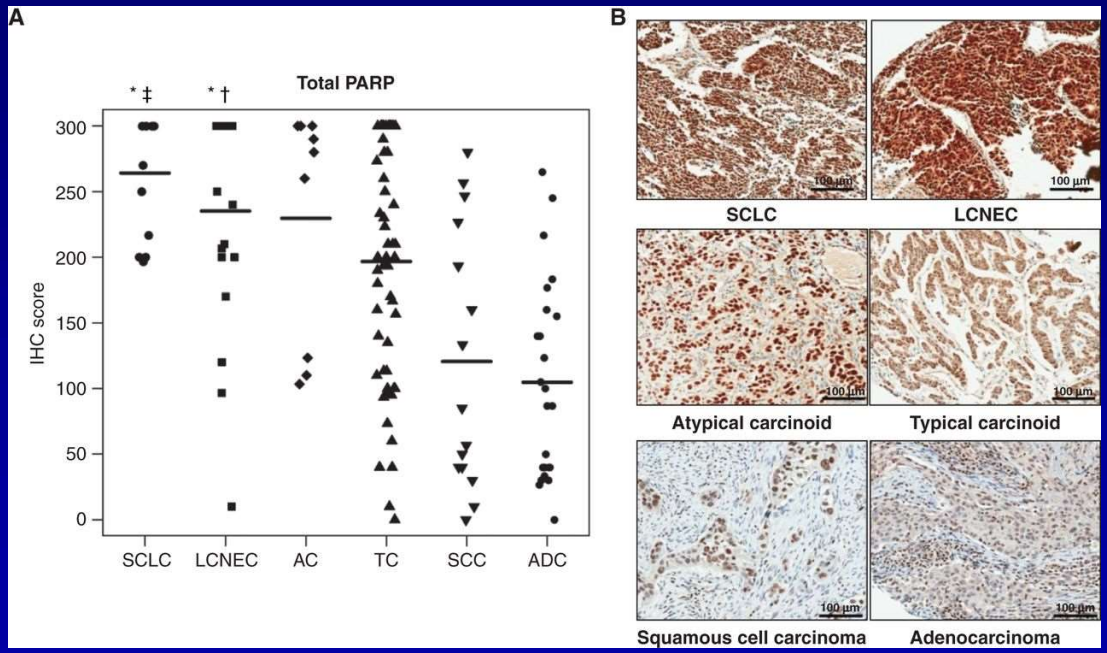
- **Inhibits RNA polymerase II, structurally related to trabectedin, a marine-derived agent FDA approved in liposarcoma or leiomyosarcoma**
- **Efficacy and safety of Lurbinectedin in SCLC**
  - 68 patients were treated , 1-2 prior lines of therapy
  - 39.3% PR rate, Median PFS was 4.1 months, MST 11.8 months
  - Myelosuppression was most common adverse event
  - FDA granted Orphan Drug Status
- **Lurbinectedin + doxorubicin as second-line therapy in SCLC**
  - 26/28 patients were treated and evaluable for efficacy response rate (RR)
  - Confirmed RR was 58%
    - 86% Grade 4 neutropenia
- **ATLANTIS: Global, randomized phase III study of lurbinectedin (L) with doxorubicin (DOX) vs. CAV or topotecan (T) in SCLC after platinum therapy**

Perez et al, ASCO 2018, abst 8570;
Forster et al, ASCO 2018, abst 7509;
Farago et al, ASCO 2018, TPS 8587;
Calvo et al, Ann Oncol 28:2559, 2017.

PARP Inhibitor in SCLC

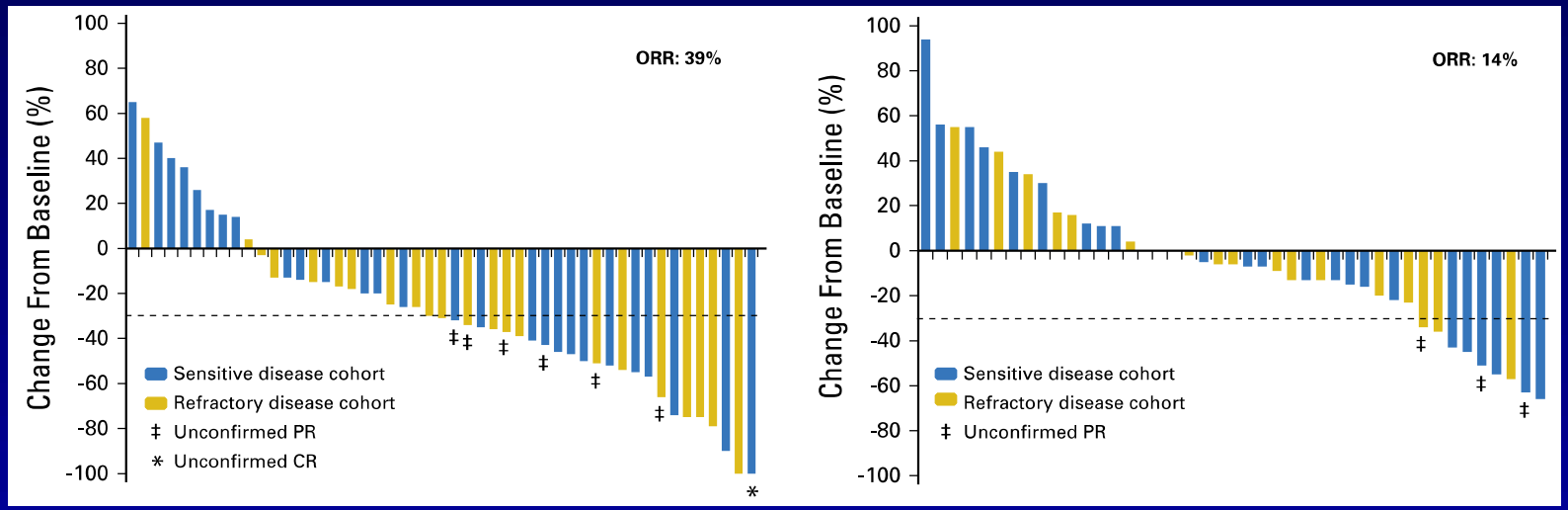
- Rb regulates E2F1. One target of E2F1 is PARP1. PARP1 in turn activates E2F1
- The addition of PARP inhibitor to DNA damaging agents (cisplatin and etoposide) will result in enhanced cytotoxicity and improved clinical outcome

High PARP expression in SCLC and other neuroendocrine cancers



Byers L A et al. Cancer Discovery 2012;2:798-811

Phase II randomized placebo-controlled trial evaluating temozolomide + veliparib in relapsed SCLC



- RR 39% v 14%
- No significant difference in PFS and OS
- Schlafen11 regulates response to DNA damage
- SLFN11+ significantly prolonged PFS and OS
- PARP-1 expression – no association with clinical outcomes

Pietanza et al., JCO 2018

Ongoing or recently completed PARP inhibitor trials in SCLC

Regimen	Phase	Setting and Location	Identifier
Cisplatin Etoposide ± Veliparib	Phase I/II RCT	1st-line, USA	NCT01642251*
Carboplatin Etoposide ± Veliparib	Phase I/II RCT	1st-line, International	NCT02289690
Olaparib maintenance	Phase II RCT	1st line maintenance, UK	ISRCTN 73164486*
Niraparib maintenance	Phase II RCT	1st line maintenance, China	NCT03516084
Temozolomide + Niraparib maintenance	Phase Ib/II RCT	1st line maintenance, USA (UCLA)	NCT03830918
Cediranib (**VEGF**)+ Olaparib maintenance	Phase II RCT	1st line maintenance, USA	NCT02899728
Temozolomide ± Veliparib	Phase II RCT	Relapsed, USA	NCT01638546*
Temozolomide + Olaparib	Phase I/II	Relapsed, USA (Boston)	NCT02446704
Temozolomide + Talazoparib	Phase II	Relapsed, USA (UCLA)	NCT03672773
Topotecan + Veliparib	Phase I/II	Relapsed, Germany	NCT03227016
CRLX101 (nano-CPT) + Olaparib	Phase I/II	Relapsed, USA (NCI)	NCT02769962
AZD6738 (**ATR**) + Olaparib	Phase II	Relapsed, South Korea (Samsung Med. Ctr.)	NCT03428607
AZD6738 (ATR) + Olaparib	Phase II	Relapsed platinum resistant/refractory, Europe	NCT02937818
AZD1775 (**WEE1**) + Olaparib	Phase Ib	Relapsed, USA & Canada	NCT02511795
Low-dose thoracic radiation + Olaparib	Phase I	Relapsed, USA (MSKCC)	NCT03532880
Olaparib monotherapy	Phase II	Relapsed + HR mut., South Korea (Samsung Med. Ctr.)	NCT03009682
Talazoparib monotherapy	Phase I	Adv./recurrent solid tumors, USA & UK	NCT01286987*
Cediranib + Olaparib	Phase II	Adv./recurrent solid tumors, USA & Canada	NCT02498613
Durvalumab (**PD-L1**)+ Olaparib	Phase I/II	Adv./recurrent solid tumors, International	NCT02734004

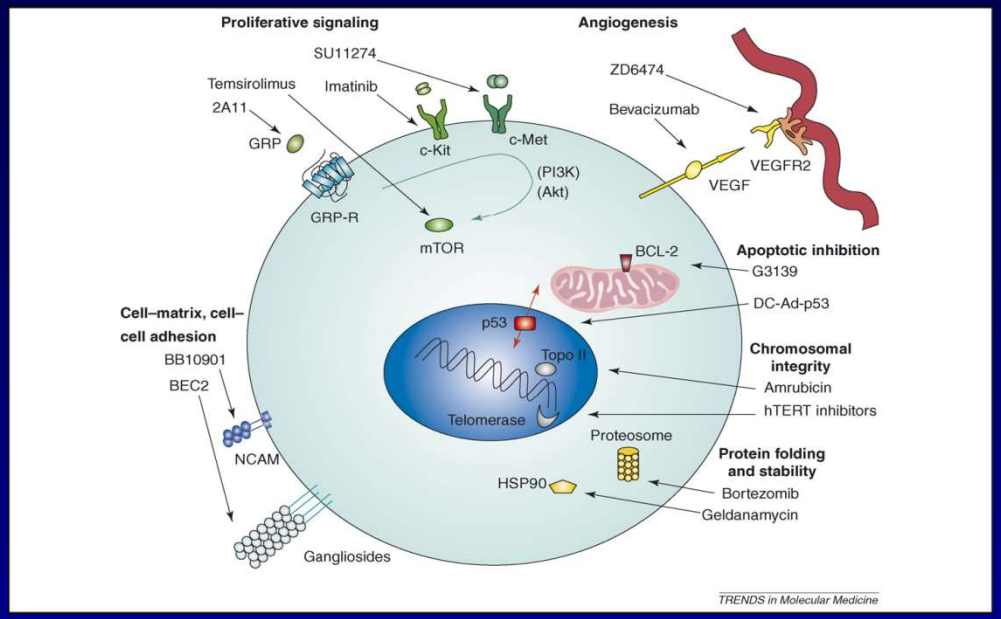
Inno et al., Transl. Lung Cancer Res 2018

* Completed and reported

Ongoing Research

- IO combos
  - Cytotoxics
  - Novel agents
- Epigenetic modulators
  - LSD1
  - EZH-2 inhibitors – may help with emergence of resistance
  - RRx-001
- DLL3
  - AMG 757
- CDK4/6 inhibitors
- Cytotoxics
  - Liposomal irinotecan
- Co-Argl-PEG

FUTURE DIRECTIONS



- Empiric chemotherapy is unlikely to further improve outcomes
- Identify molecular targets that drive survival, proliferation, resistance, and metastasis
- Identify and characterize lung cancer progenitor (“stem”) cells
- Identifying biomarkers is key for future discovery
- Subgroups of SCLC may exist that may be targeted by specific therapies

Hann & Rudin. Trends Mol Med 13:150, 2007

APPLAUSE