EUROPEAN LUNG CANCER
CONFERENCE 2016

WHAT IS NEW IN SMALL CELL LUNG CANCER?

NOVEL TARGETS IN SCLC

Enriqueta Felip
Vall d'Hebron University Hospital
Barcelona, Spain

SCLC, where are we?

- Accounts for ~15% of newly diagnosed lung cancer
- Predominately associated with tobacco smoking
- Rapid doubling times and early propensity to metastasize
- Initial sensitivity to CT with 60-80% RR

SCLC, where are we?

- 1st-line treatment for both LD and ED: platinum/etoposide x 4-6 cycles
- For patients with LD
  - ✓ Early TRT (<30 days from CT start) should be added to CT
  - ✓ PCI for patients with CR/PR
- 2nd-line: topotecan or re-induction
- No new agents approved in over 20 years
- No targeted agents approved

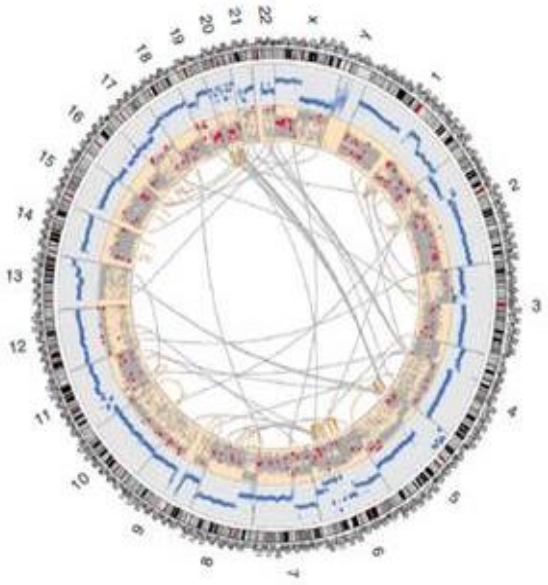
Novel targets in SCLC

- Review paper:
  - *Bunn PA Jr et al.* Small cell lung cancer: can recent advances in biology and molecular biology be translated into improved outcomes? *J Thorac Oncol. 2016*

- I will not cover immunotherapy

Genomic Analysis of SCLC

- **Hot spot mutations**
  - *TP53, RB1, PIK3CA, CDKN2A, PTEN*
  - RAS family regulators (*RAB37, RASGRF1, RASGRF2*)
  - Chromatin modifiers (*EP300, DMBX1, MLL2, MED12*, etc.)
- **Hot spot mutations *PLUS* q-score**
  - *RUNX1T1, CDYL, RIMS2*
- **Gene families and pathways**
  - PI3K pathway, Notch and Hedgehog, glutamate receptor family, DNA repair/checkpoint, SOX family
- **Focal amplifications**
  - *MYC, SOX2, SOX4, KIT*
- **Recurrent translocations and fusion genes**
  - Recurrent: *RLF–MYCL1*
  - Kinase fusions



Circos plot whole genome SCLC
22 significantly mutated genes

Peifer, M et al: Nature Genetics 44:1104-1110, 2012
Rudin CM et al: Nature genetics 44:1111-1116, 2012

Published in final edited form as:
Nat Genet. 2012 October ; 44(10): 1111–1116. doi:10.1038/ng.2405.

Comprehensive genomic analysis identifies *SOX2* as a frequently amplified gene in small-cell lung cancer

Charles M Rudin[1,8], **Steffen Durinck**[2,3,8], **Eric W Stawiski**[2,3,8], **John T Poirier**[1,8], **Zora**

Published in final edited form as:
Cancer Discov. 2012 September ; 2(9): 798–811. doi:10.1158/2159-8290.CD-12-0112.

Proteomic Profiling Identifies Dysregulated Pathways in Small Cell Lung Cancer and Novel Therapeutic Targets Including PARP1

Lauren Averett Byers[1], **Jing Wang**[2], **Monique B. Nilsson**[1], **Junya Fujimoto**[3], **Pierre**

SCLC: comprehensive mutation analysis program at MSKCC

- Prospectively testing of SCLC biopsies genotyping with Sequenom and NGS
- Sequenom (n=32 samples): AKT1E17-mut (n=1) and PIK3CA E542K-mut (n=1)
- NGS (n=25 samples): loss of RB1 (N=18 mutations; N=4 deletions); TP53-mut (N=24), MLL3 (N=9), and EPHA 5 (N=9); and amplifications of CDKN2C (N=5), MYCL1 (N=3), SOX2 (N=2), and FGFR1 (N=1, confirmed by FISH)

Krug ESMO 14

Clinical correlation of extensive-stage SCLC genomics

- 50 SCLC tumors examined
- TP53 (86%) and RB1 (58%), the two most frequently mutated genes
- Other mutated genes (>10% pts), involved in epigenetic regulation / mTOR pathway
- Low-frequency of targetable mutations, including RICTOR, FGFR1, KIT and RET

Comprehensive genomic profiles of SCLC

- 110 SCLC genomes sequenced
- Nearly all tumors analyzed had inactivation of TP53 and RB1
- Uncommonly, SCLC tumors exhibited kinase gene mutations
- Inactivating mutations in NOTCH family genes found in 25% of SCLC
  - ✓ Activation of NOTCH signaling in SCLC mouse model reduced the number of tumors and extended the survival

George Nature 15

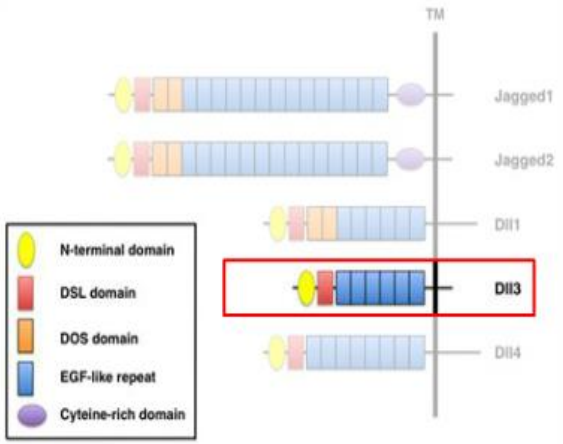
NOTCH pathway

- Delta-like ligand 3 (DLL3)
  - ✓ Inhibits NOTCH pathway activation
  - ✓ One of several NOTCH ligands possibly associated with neuroendocrine phenotype and contribute to neuroendocrine tumorigenesis

- Rovalpituzumab tesirine is an antibody drug conjugate that targets the atypical Notch ligand DLL3 on the cell surface and then delivers the DNA-damaging agent pyrrolobenzodiazepine dimer toxin

Rovalpituzumab tesirine, a delta-like protein 3 (DLL3)-targeted antibody drug conjugate (ADC), in SCLC. Phase I Trial in recurrent pts after 1 or 2 previous lines

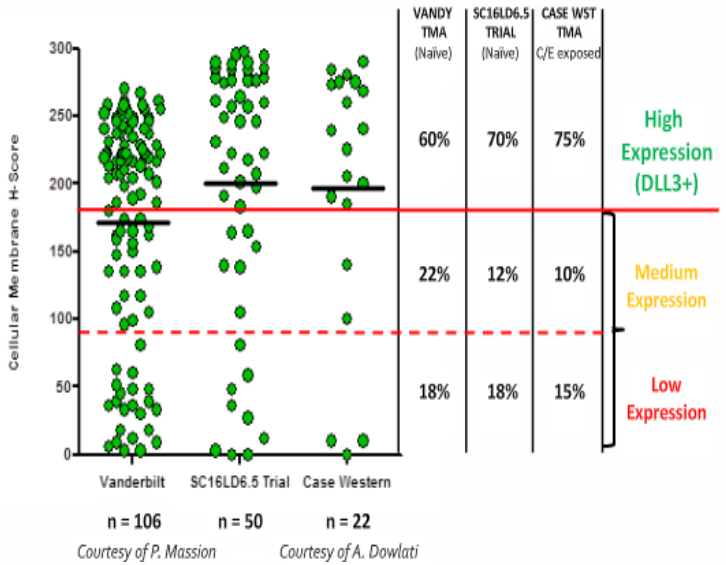
DLL3 is a dominant inhibitor of Notch signaling



- Normally expressed during development in the Golgi
- Aberrantly expressed in SCLC tumor-initiating cells
- Interacts with and inhibits Notch1 in *cis*
- May mediate Notch inhibition downstream of ASCL1

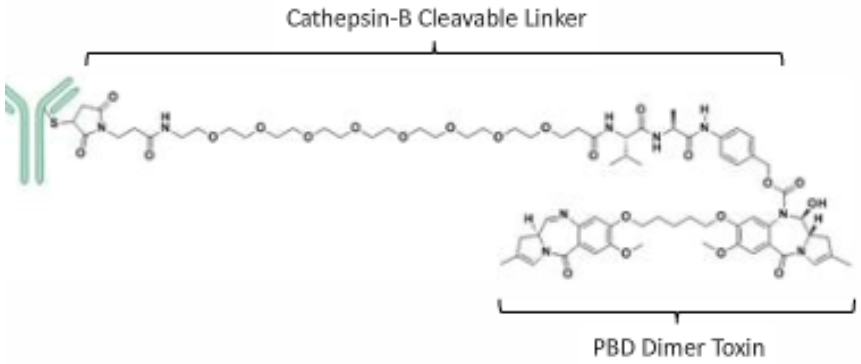
Kume *et al., J Angiogen Res* 2009

DLL3 expression by IHC in SCLC



Courtesy of P. Massion *Courtesy of A. Dowlati*

Drug-to-Antibody Ratio (DAR) = 2



Pietanza et al. Ann Oncol 2015; 26 (suppl 6): abstr 7LBA

Phase I study of a delta-like protein 3 (DLL3)-targeted antibody drug conjugate, rovalpituzumab tesirine, in pts with relapsed and refractory SCLC

Study population: 73 SCLC pts enrolled

Baseline Characteristic (SCLC)		Total (%) or Median (Range)
Demographics	Age	61 (44-81)
	Male	41 (56%)
Disease Characteristics	ECOG 0/1	19 (26%) / 53 (73%)
	Refractory/"Resistant"/"Sensitive"*	9 (12%) / 23 (32%) / 39 (53%)
	Prior CNS metastases	20 (27%)
Prior Therapies	Prior therapies: 1/2	40 (55%) / 33 (45%)
	Cisplatin/Carboplatin + Etoposide	45 (62%) / 28 (38%)
	Topotecan	8 (11%)
	Prior Radiation	60 (82%)

* "Resistant" = Clinical benefit on 1L; began 2L in < 90 days
"Sensitive" = Clinical benefit on 1L; began 2L in ≥ 90 days

Related AEs occurring in > 10% of patients

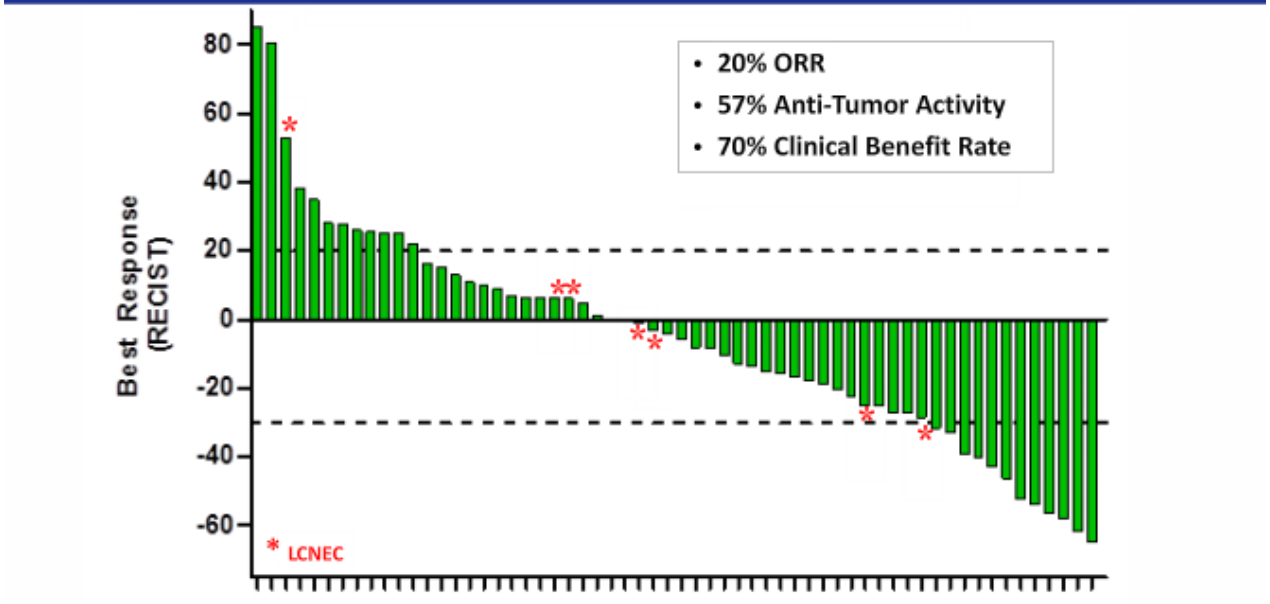
Phase 1b Expansion Cohorts (7/6/15 cutoff)

# Patients Enrolled	25		40	
Dose/Schedule	0.2 Q3W		0.3 Q6W	
	All	Gr 3/4	All	Gr 3/4
Fatigue	24%	4%	28%	5%
Thrombocytopenia	4%	0%	23%	15%
Decreased Appetite	0%	4%	18%	0%
Rash Maculo-Papular	12%	0%	13%	5%
Oedema Peripheral	16%	0%	13%	3%
Anaemia	12%	0%	13%	0%
Erythema	8%	4%	13%	0%
Serosal Effusions	16%	12%	10%	0%
Nausea	20%	0%	10%	0%
Vomiting	8%	0%	5%	0%

RP2D

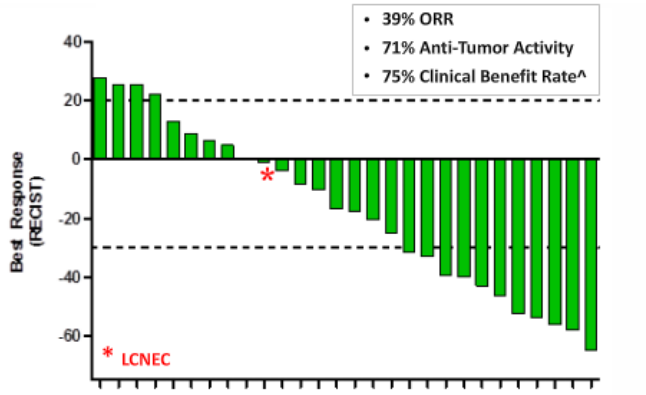
Rova-T: best response data in evaluable patients

0.2 mg/kg q3w and 0.3 mg/kg q6w cohorts (n=60)



Rova-T: best response data in evaluable DLL3+ patients

0.2 mg/kg q3w and 0.3 mg/kg q6w cohorts (n=28)

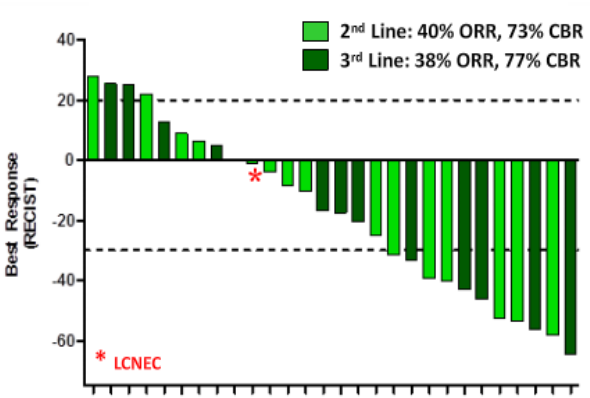


DLL3+ = H-score ≥ 180 on scale of 300

^3 Pts whose target lesions were noted as SD or better by RECIST had clinical progression

Rova-T: best response data in evaluable DLL3+ patients

0.2 mg/kg q3w and 0.3 mg/kg q6w cohorts (n=28)



DLL3+ = H-score ≥ 180 on scale of 300

Results support biomarker-guided phase II studies

Overall response rates

	Topotecan†	Rova-T; SC16LD6.5	
		All Pts & dose levels	DLL3+ Ph 1b Cohorts
2nd Line	17%	22%	40%
3rd Line	No Approved Drug	17%	38%
Sensitive to C/E	23%	24%	62%
Resistant to C/E	9%	14%	20%

Durability of Response at RP2D (0.3 mg/kg q6w): 182+ days

†Tabulated from published trial data with Topotecan: von Pawel (2014) JCO, Jotte (2011) JCO, O'Brien (2006) JCO, Huber (2006) Eur Respir J, von Pawel (1999) JCO, and Ardizzoni (1997) JCO

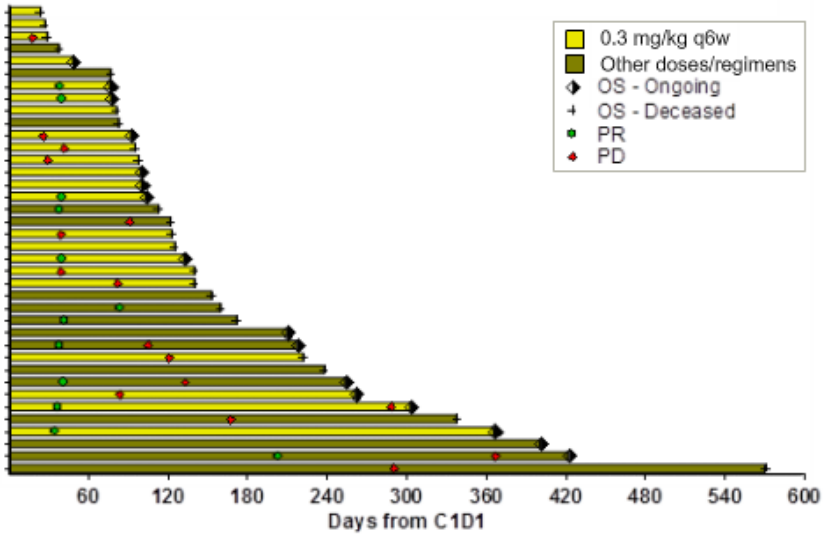
Duration of response by dosing cohort

Dose & Regimen	Objective Responses	# Remaining Progression Free	Mean DOR (Range)	# Alive	Mean OS (Range)
0.2q3w	5	0	88 (68-130)	1	184+ (113-255)
0.3q6w	7	6	182+ (50-332)†	7	227+ (104-367)†
0.4q3w	2	0	164‡	1	437+
Total	*14*	*6*		*9*	

†DOR and OS excluding 3 new responses observed within last 30 days that have not yet been confirmed

‡1 patient censored due to subsequent chemo prior to signs of progression

Rova-T swimmer plot for DLL3+ patients



An open-label, single-arm, phase 2 Study evaluating the efficacy, safety and pharmacokinetics of Rovalpituzumab Tesirine (SC16LD6.5) for third-line and later treatment of subjects with relapsed or refractory delta-like protein 3-expressing SCLC (TRINITY)

- Histologically confirmed SCLC with documented PD after at least 2 prior systemic regimens, including at least one platinum-based regimen
- DLL3-expressing SCLC based on central IHC assessment of banked or otherwise representative tumor tissue. Positive is defined as staining in ≥ 1% of tumor cells
- ECOG PS of 0 or 1
- Estimated enrollment, 154 pts

NOTCH inhibitors in SCLC

- OMP-59R5, a fully human IgG2 antibody, inhibits signaling of NOTCH 2 / 3 receptors

- Phase Ib/II study of OMP-59R5 in combination with etoposide/platinum in untreated ED-SCLC showed promise with 13/16 (81%) attaining a PR and 3 achieving SD

PARP pathway

- Treatment for SCLC relies on DNA-damaging agents (CT, RT); inhibition of DNA damage repair, logical approach
- PARP inhibition, activity in preclinical models and in a subset of SCLC pts
- Single activity of veliparib and synergy with platinum/etoposide demonstrated in cell lines and animal models
  - ✓ Phase II trial of platinum/etoposide +/- veliparib ongoing
- Randomized phase II trial of olaparib *vs* placebo as maintenance after CT, recruitment closed
- Talazoparib, single agent activity in SCLC in a phase I trial

Temozolomide/veliparib

- SCLC, characterized by frequent aberrant methylation and epigenetic silencing of the MGMT gene

- Temozolomide phase II in 62 pts with relapsed SCLC ***(Pietanza, CCR 12)***
  - 20% ORR (23%, sensitive group / 13%, refractory cohort)
  - Pts with tumor demonstrating MGMT promoter methylation responded better to treatment

- Phase II comparing temozolomide/veliparib *vs* temozolomide/placebo, ongoing

Hedgehog pathway

- Hedgehog signaling pathway frequently disrupted in SCLC
  - ✓ Occurs in cell-autonomous manner, independent of the lung microenvironment
  - ✓ May play a significant role in the development and proliferation of SCLC
  - ✓ Inhibition of hedgehog pathway decreases cell growth

- Ongoing trials of hedgehog inhibitors in SCLC, GDC-0449, IPI-926, LDE225

Aurora kinases

- Aurora kinases comprise a family of protein kinases that play a critical role in the mitotic process

- Aurora kinase inhibitors effective in SCLC cell lines bearing MYC amplification, which occurs in 3-7% of SCLC pts

- Phase II of alisertib in SCLC
  - RR 21%, 19% in sensitive relapse and 27% in resistant relapse
  - PFS 2.6 mo in the sensitive and 1.4 mo in the resistant relapse
  - Ongoing randomized phase II trial comparing paclitaxel alone to paclitaxel/alisertinib in SCLC pts who progress after etoposide/platinum (NCT02038647)

Fibroblast growth factor receptor signaling pathway

- FGFR1 gene amplified in 5-6% of pts with SCLC
- High levels of serum FGF2 associated with poor prognosis in SCLC
- Efficacy of ponatinib being studied in a biomarker-driven trial (NCT01935336)
- Phase II trial to analyze lucitanib in pts with lung cancer, ongoing (NCT02109016)

PIK3CA

- Whole exon sequencing and copy number analysis on Japanese pts with SCLC detected genetic alterations in the PI3K/AKT/mTOR pathway in 36% of the tumors

Transcriptional addictions of SCLC

- High-throughout cellular screen of a diverse chemical library discovered that SCLC is sensitive to THZ1, a covalent inhibitor of CDK7
  - ✓ THZ1 may represent a prototype drug for tailored SCLC therapy

- In SCLC, evaluation of online databases and cell lines showed 30-40% have copy number gain for JAK1/2
  - ✓ AZD1480 (which targets JAK1/2/3) has single-agent activity / synergy with CT

RET

- An activating M918T RET somatic mutation identified in a metastatic SCLC tumor specimen ***(Davir JTO 14)***

- A subpopulation of pts with SCLC may derive benefit from TKIs targeting RET

Novel targets in SCLC: summary

- Nearly uniform loss of function of TP53 and RB1
  - ✓ Not targetable at present
- Too many genetic alterations/pathways (mostly tumor suppressor genes)
- A number of potentially targetable molecular pathways have been identified
  - ✓ NOTCH most promising target
- GENOMICS and IMMUNOTHERAPY investigation required also in SCLC!!

Thanks!!

efelip@vhebron.net