Best of WCLC: Small Cell Lung Cancer

Millie Das, MD

Chief, Oncology, VA Palo Alto Health Care System
Clinical Associate Professor, Stanford University

DISCLOSURES

Commercial Interest	Relationship(s)
Novartis, Abbvie, United Therapeutics, Verily, Varian	Research
Jazz Pharmaceuticals	Consulting

SCLC Abstracts

Pathophysiology

- OA11.05 – Whole Exome Sequencing Reveals the Potential Role of Hereditary Predisposition in Small Cell Lung Cancer, a Tobacco-Related Cancer

Early Stage SCLC

- MA12.05 – Is there a Role for Surgery in Stage 1 Small Cell Lung Cancer? A National VA Database Analysis

Therapeutic advances

- OA11.03 – A Phase I Study of AMG 757, Half-Life Extended Bispecific T-Cell Engager (BiTE®) Immune Therapy Against DLL-3, in SCLC
- OA11.04 – Lurbinectedin with Irinotecan in Relapsed Small Cell Lung Cancer. Results from the Expansion Stage of a Phase I-II Trial

Advances in SCLC

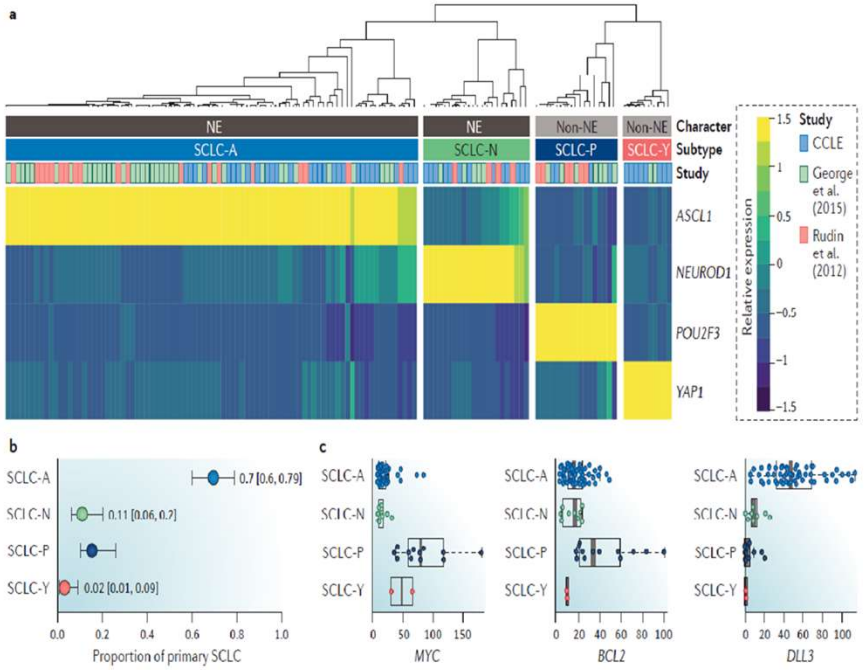
- Accelerated FDA approvals for PD-1 inhibitors as 3rd line in relapsed SCLC
  - Nivolumab (Checkmate 032)→ Checkmate 331/451 negative for OS
  - Pembrolizumab (KEYNOTE 028/158)→ KEYNOTE 604 negative for OS

- FDA approvals for PDL-1 inhibitors in combination with platinum/etoposide as frontline treatment in ES SCLC
  - Atezolizumab (IMpower 133)
  - Durvalumab (CASPIAN)

- Accelerated FDA approval for lurbinectedin
  - Single arm phase II trial (ORR=35%)
  - Phase III ATLANTIS trial press release negative OS

Is there a hereditary predisposition to SCLC?

- Molecular subtypes based upon transcriptional drivers
- Almost all cases of SCLC are linked to tobacco use
- Not all smokers develop lung cancer
- Why do certain smokers develop SCLC while others don't?



Rudin C et al, Nature Reviews Cancer, 2019:19;289-297

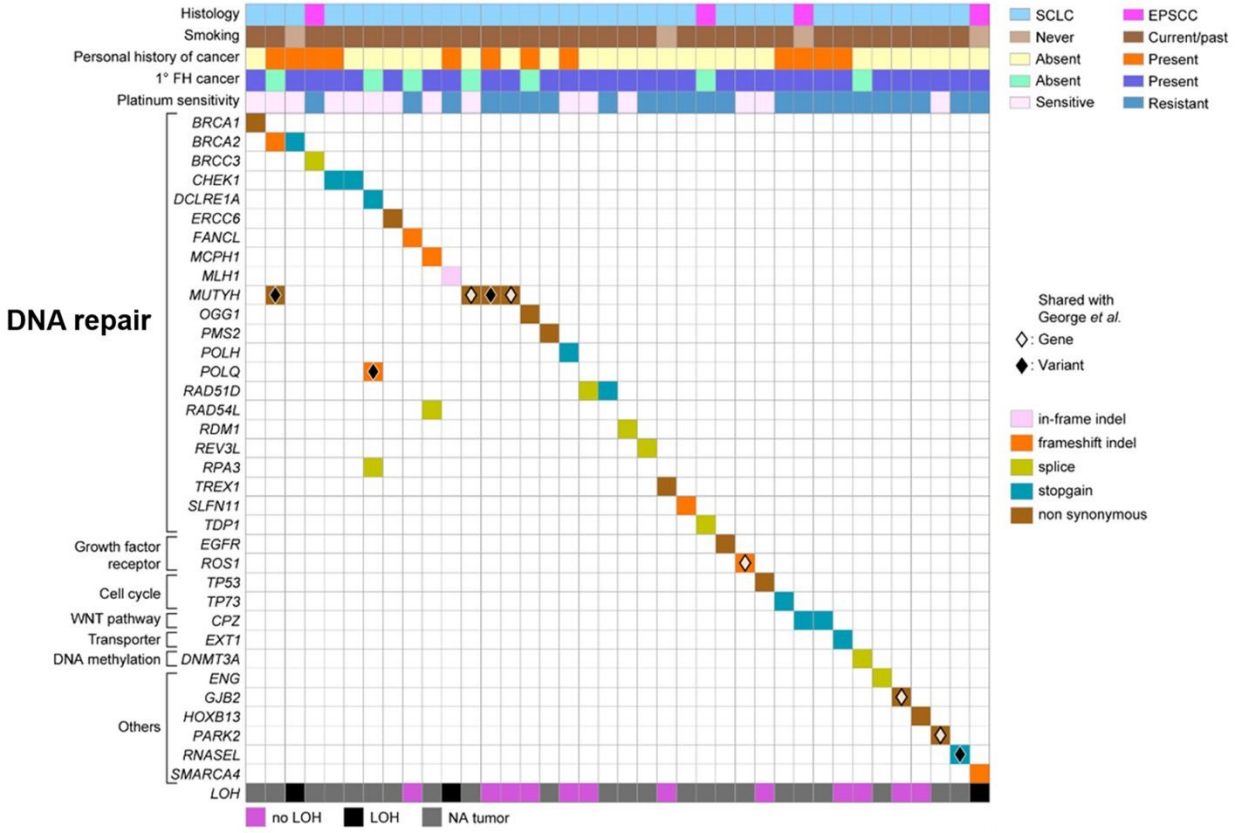
Whole Exome Sequencing Reveals the Potential Role of Hereditary Predisposition in Small Cell Lung Cancer, a Tobacco-Related Cancer

Nobuyuki Takahashi[1], Camille Tlemsani[1], Lorinc Pongor[1], Vinodh N. Rajapakse[1], Manoj Tyagi[1], Xinyu Wen[1], Grace-Ann Fasaye[1], Keith T. Schmidt[1], Chul Kim[2], Arun Rajan[1], Shannon Swift[1], Linda Sciuto[1], Rasa Vilimas[1], Santhana Webb[1], Samantha Nichols[1], William Douglas Figg[1], Yves Pommier[1], Kathleen Calzone[1], Seth M. Steinberg[1], Jun S. Wei[1], Udayan Guha[1], Clesson E. Turner[3], Javed Khan[1], Anish Thomas[1]

[1]Center for Cancer Research, National Cancer Institute, Bethesda, MD, USA
[2]Georgetown University, Washington DC, USA
[3]Walter Reed National Military Medical Center, Bethesda, MD

NIH NATIONAL CANCER INSTITUTE
Center for Cancer Research

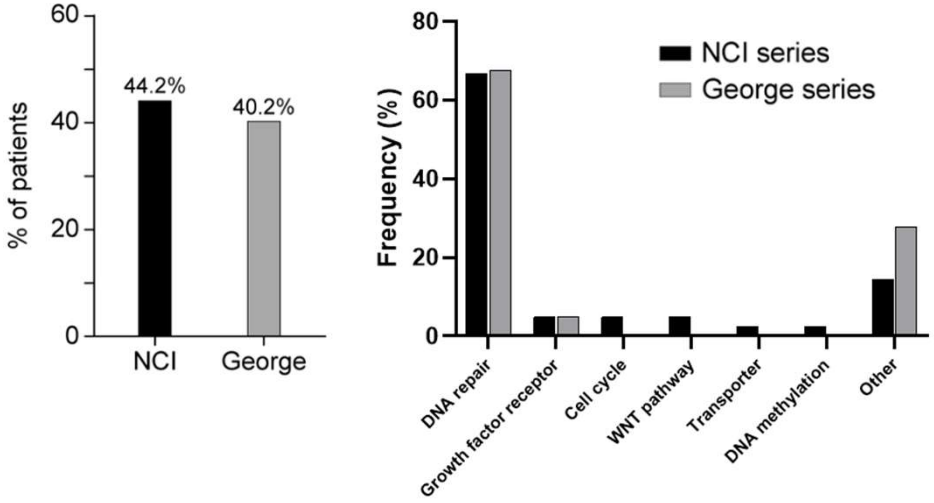
Germline mutations are highly prevalent in patients with SCLC



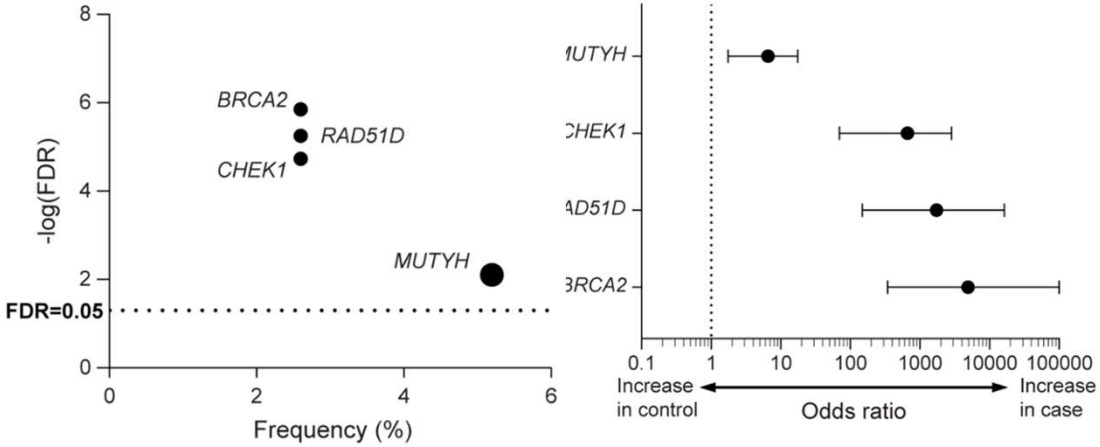
- 34/77 (44.2%) of SCLC patients had a P/LP germline mutation
- 9/77 (11.7%) of SCLC patients had a P/LP germline mutation in ACMG genes
- Most genes were involved in DNA repair (66.7%)
- 3/31 cases with available tumor had loss of heterozygosity (*BRCA2*, *MLH1*, *SMARCA4*)

Frequency of germline mutations are comparable with independent SCLC cohort; more frequent than expected in cancer-free controls

SCLC cohort (n=79)[4]



ExAC cancer free cohort (n=53,105)[5]



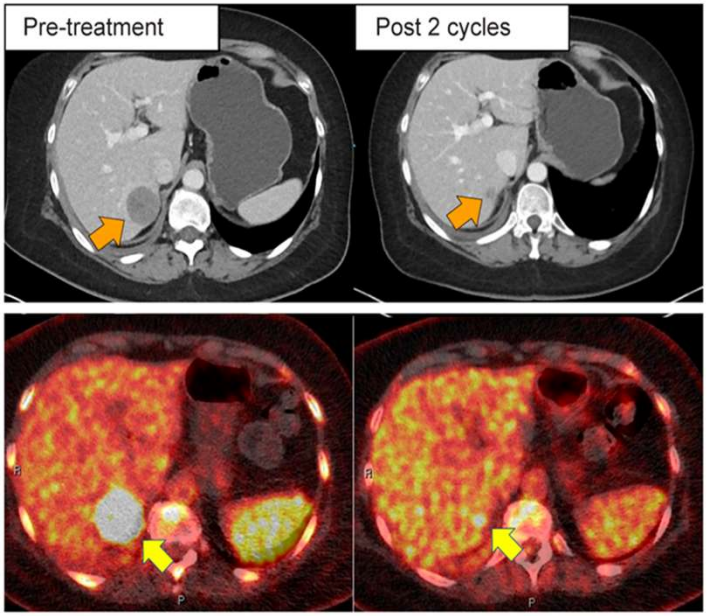
Frequencies of all identified pathogenic mutation: <1%

[4]: George J et al. Nature 2015. 6;524(7563):47-53. [5]: Lek M et al. Nature 2016. 536, 285-291.

Hereditary predisposition?

- Intriguing results from a robust dataset with external validation
- Complements the concept of molecular subtypes
- Potential implications if findings are confirmed
  - Personalize risk assessment and screening practices
  - May influence therapeutic interventions
- Requires further validation

CRLX-101 (nano-particle topoisomerase 1 inhibitor) + olaparib (PARP inhibitor) NCT02769962



Surgery in SCLC

- Role of surgery in SCLC is controversial
- Smoking can increase surgical risk
  - PFTs
  - Tobacco cessation
- Never surgery alone
  - SCLC considered systemic disease
  - Adjuvant platinum/etoposide in resected stage I SCLC patients

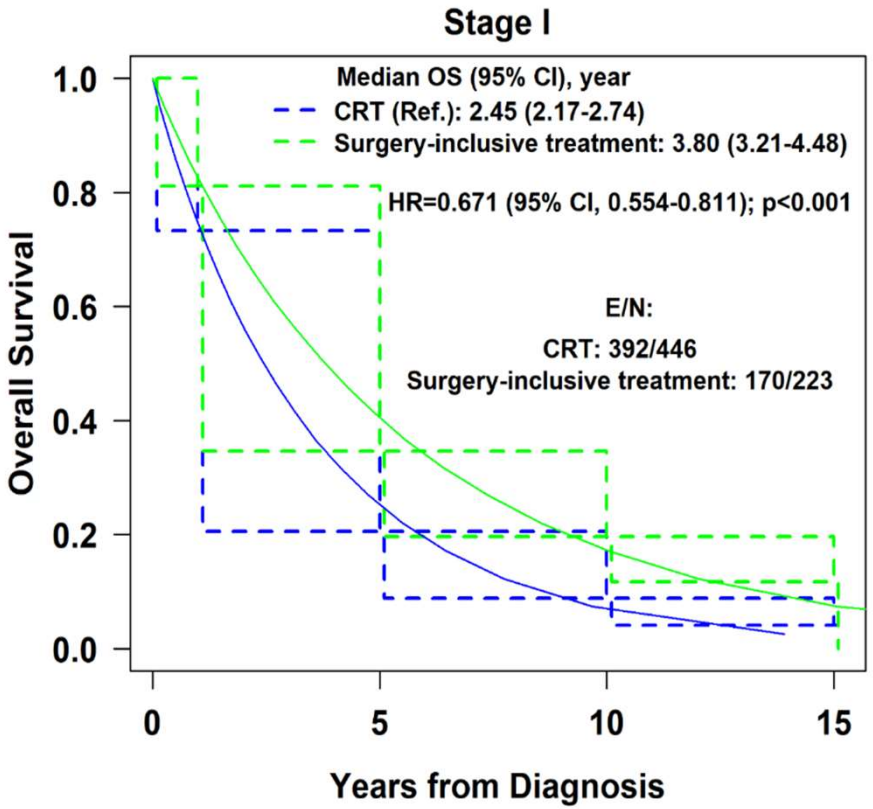
Is There A Role For Surgery In Stage I Small Cell Lung Cancer? A National VA Database Analysis

Ibrahim Azar[1], Adam Austin[2], Hyejeon Jang[1], Seongho Kim[1], Omid Yazpandaneh[3], Amit Chopra[4], Syed Mehdi[5], Hirva Mamdani[1]

[1]Karmanos Cancer Institute, Detroit, MI [2]University of Florida, Gainesville, FL [3]Wayne State University, Detroit, MI
[4]Albany Medical College, Albany, NY [5]Stratton VA Medical Center, Albany, NY

BARBARA ANN Karmanos CANCER INSTITUTE Wayne State University

Results: Surgery is beneficial in early stage SCLC



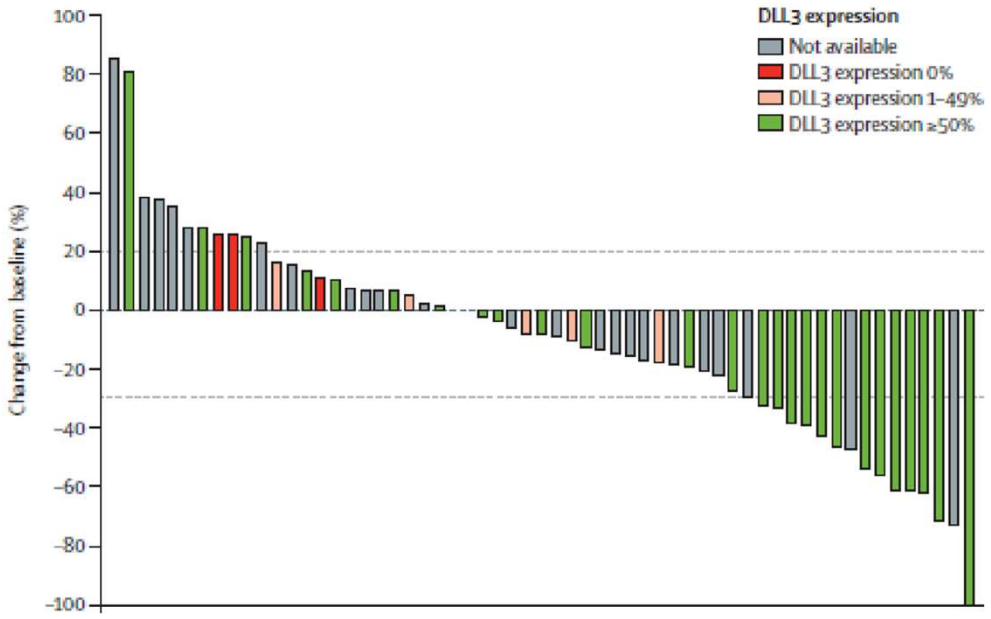
- N=1,037 Stage 1 SCLC patients, included 669 patients who received surgery or chemoradiation
- Less than a third of patients with stage I SCLC who received some form of treatment underwent surgery
- Surgery-inclusive multimodality treatment associated with longer OS vs chemoradiation, independent of age or performance status

Biomarkers in SCLC

- Currently no clinically targetable mutations
- Alterations in p53 and Rb frequently noted
- PDL-1 not highly expressed
- Tumor mutational burden (TMB) not predictive of response to immunotherapies
- Potential biomarkers exist
  - SLFN11 expression and sensitivity to PARP inhibitors

Rova-T and DLL-3

- DLL-3 (inhibitory Notch ligand) is highly expressed in SCLC
- Rovalpituzumab teserine (Rova-T) is an ADC targeting DLL-3



Rudin, Lancet Oncol 2017

Rova-T and DLL3

Phase I with 1L platinum + etoposide

- RR 50%, Grade 3+ AEs in 93%, 2/14 with Grade 5 AEs

TRINITY (Phase II, DLL-3+ SCLC, 3rd line and beyond)

- 339 patients enrolled, RR 12.4%, PFS 3.5m, OS 5.6m
- Grade 3+ AEs in 40%, Grade 5 treatment related AEs in 10% results

TAHOE (Phase III, 2nd line SCLC)

- Negative trial, shorter survival than topotecan control arm

MERU (Phase III, SCLC maintenance)

- No survival benefit over placebo

Rovalpituzumab teserine (Rova-T) no longer in development

- Does not invalidate DLL-3 as a potential target!

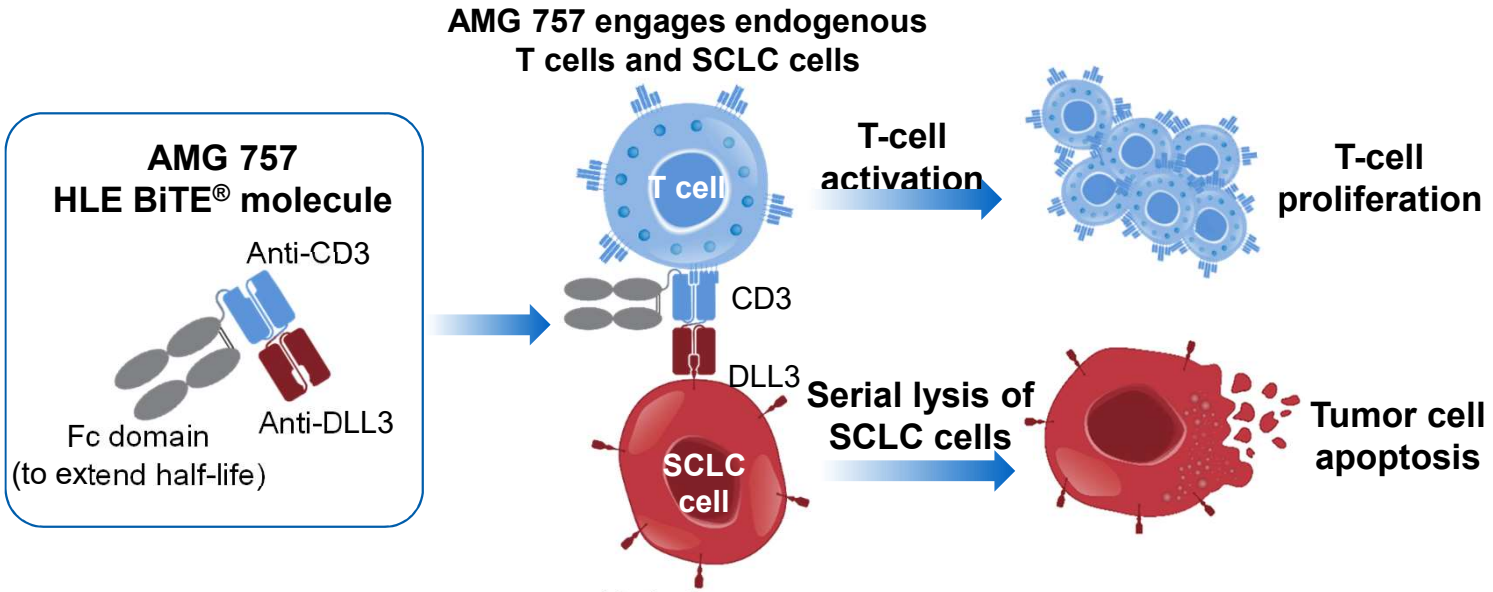
Morgensztern, CCR 2019

A phase 1 study of AMG 757, a half-life extended bispecific T-cell engager (BiTE®) immuno-oncology therapy against DLL3, in SCLC

Taofeek K. Owonikoko,[1] Michael Boyer,[2] Melissa Johnson,[3] Ramaswamy Govindan,[4] Luis Paz-Ares Rodrigues, [5] Fiona H. Blackhall,[6] Rene J. Boosman,[7] Stéphane Champiat,[8] Horst-Dieter Hummel,[9] W. Victoria Lai,[10] Hibiki Udagawa, [11] Anne C. Chiang,[12] Afshin Dowlati,[13] Christine L. Hann,[14] Ravi Salgia,[15] Everett E. Vokes,[16] Mukul Minocha,[17] Nooshin Hashemi Sadraei,[17] Aditya Shetty,[17] Marie-Anne Damiette Smit,[17] Yiran Zhang,[17] Amrita Pati,[17] Sumi Roy,[17] Beate Sable,[17] Hossein Borghaei[18]

[1]Emory University School of Medicine, Atlanta, GA, USA; [2]Chris O'Brien Lifehouse, Camperdown, NSW, Australia; [3]Sarah Cannon Research Institute, Tennessee Oncology, Nashville, TN, USA; [4]Washington University Medical School, St. Louis, MO, USA; [5]Hospital Universitario 12 de Octubre, Universidad Complutense & Ciberonc, Madrid, Spain; [6]The Christie NHS Foundation Trust, University of Manchester, Manchester, UK; [7]The Netherlands Cancer Institute, Amsterdam, Netherlands; [8]Gustave Roussy, Paris-Saclay University, Villejuif, France; [9]Comprehensive Cancer Center Mainfranken, University Hospital Wuerzburg, Wuerzburg, Germany; [10]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [11]National Cancer Center Hospital East, Kashiwa, Chiba, Japan; [12]Yale School of Medicine, New Haven, CT, USA; [13]University Hospitals Seidman Cancer Center and Case Western Reserve University, Cleveland, OH, USA; [14]Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA; [15]City of Hope Hospital, Duarte, CA, USA; [16]University of Chicago Medicine and Biological Sciences, Chicago, IL, USA; [17]Amgen Inc., Thousand Oaks, CA, USA; [18]Fox Chase Cancer Center, Philadelphia, PA, USA

AMG 757: A Half-life Extended Bispecific T-cell Engager (BiTE®) Targeting DLL3 for SCLC

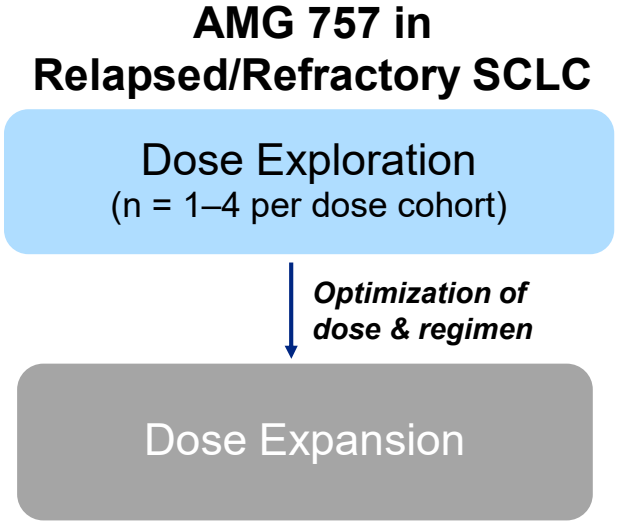


CD, cluster of differentiation; DLL3, delta-like ligand 3; Fc, fragment crystallizable domain; HLE BiTE, half-life extended bispecific T-cell engager; SCLC, small cell lung cancer.

- BiTE molecules engage a patient's own T cells to attack and eradicate cancer cells[1,2]

1. Stieglmaier J, et al. *Expert Opin Biol Ther*. 2015;15:1093-1099.
2. Einsele H, et al. *Cancer*. 2020;126:3192-3201.

First-In Human Dose Exploration Study of AMG 757



Primary Objectives	▪ Evaluate safety and tolerability in SCLC ▪ Determine MTD or RP2D
Secondary Objectives	▪ Characterize PK ▪ Evaluate preliminary antitumor activity
Exploratory Objectives	▪ Evaluate immunogenicity, biomarkers, and target protein & outcomes

- **Study design** – NCT03319940: open-label, multi-center study of AMG 757 (dose escalation ranging from 0.003 mg to 30 mg as of data cutoff [***3 November 2020***]), administered by IV infusion every 2 weeks, with/without step dose
- **Disease assessment** – Antitumor activity assessed using modified RECIST 1.1 every 8 ± 1 weeks

IV, intravenous; MTD, maximum tolerated dose; PK, pharmacokinetics; RP2D, recommended phase 2 dose; SCLC, small cell lung cancer.

Adverse Events (AEs) Summary

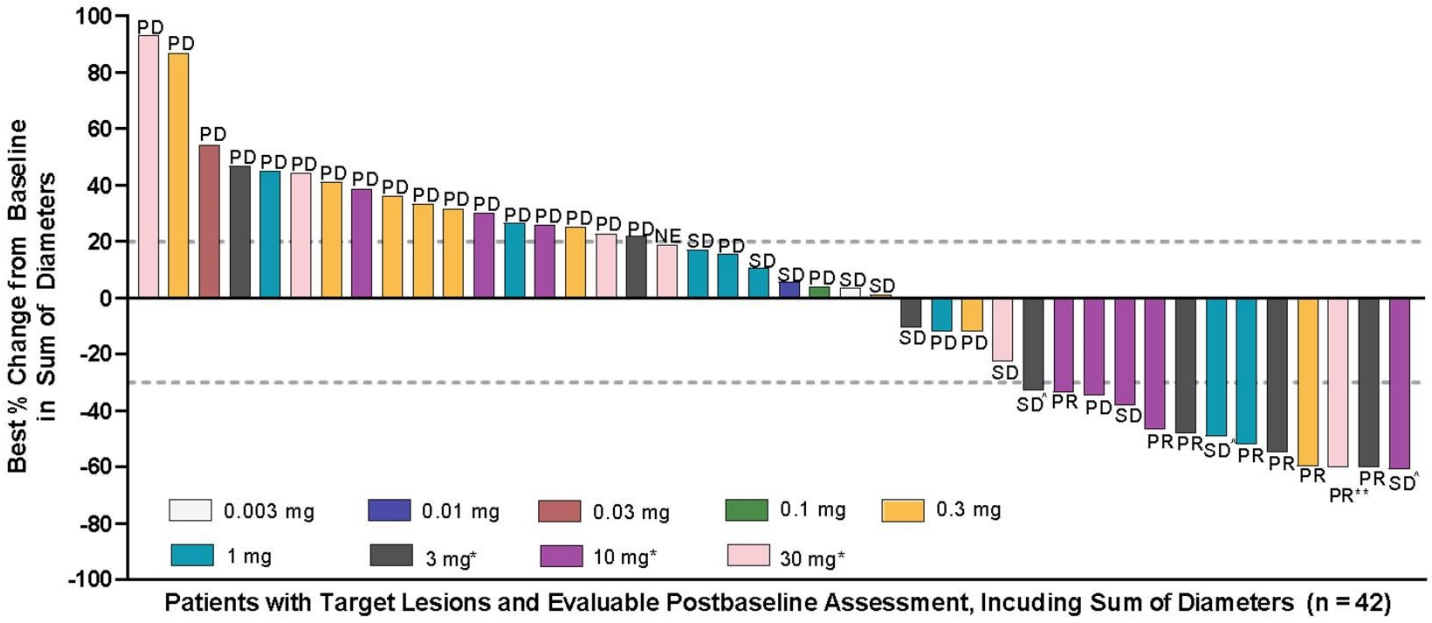
Treatment-related AEs	Patients (N = 52)	
	All Grades, n (%)	Grade ≥ 3, n (%)*
Any treatment-related AE	41 (79)	12 (23)
Treatment-related AEs in ≥ 10% of patients		
CRS	**23 (44)**	**1 (2)†**
Pyrexia	10 (19)	0
Fatigue	7 (14)	0
Anemia	5 (10)	1 (2)
Nausea	5 (10)	0

*Includes one patient with grade 5 pneumonitis; † Grade 3 CRS, more detail presented on next slide.
AE, adverse event; CRS, cytokine release syndrome; DLT, dose limiting toxicity.

- Treatment-emergent AEs occurred in 51/52 (98%) patients
  - Grade ≥ 3 occurred in 27 (52%) patients
- Treatment-related AEs occurred in 41 (79%) patients, resulting in discontinuation in 1 (2%) patient
  - The one DLT was grade 5 pneumonitis and occurred in 1 (2%) patient

AMG 757 monotherapy demonstrated a favorable safety profile

AMG 757 Demonstrates Anti-Tumor Activity in Patients with SCLC

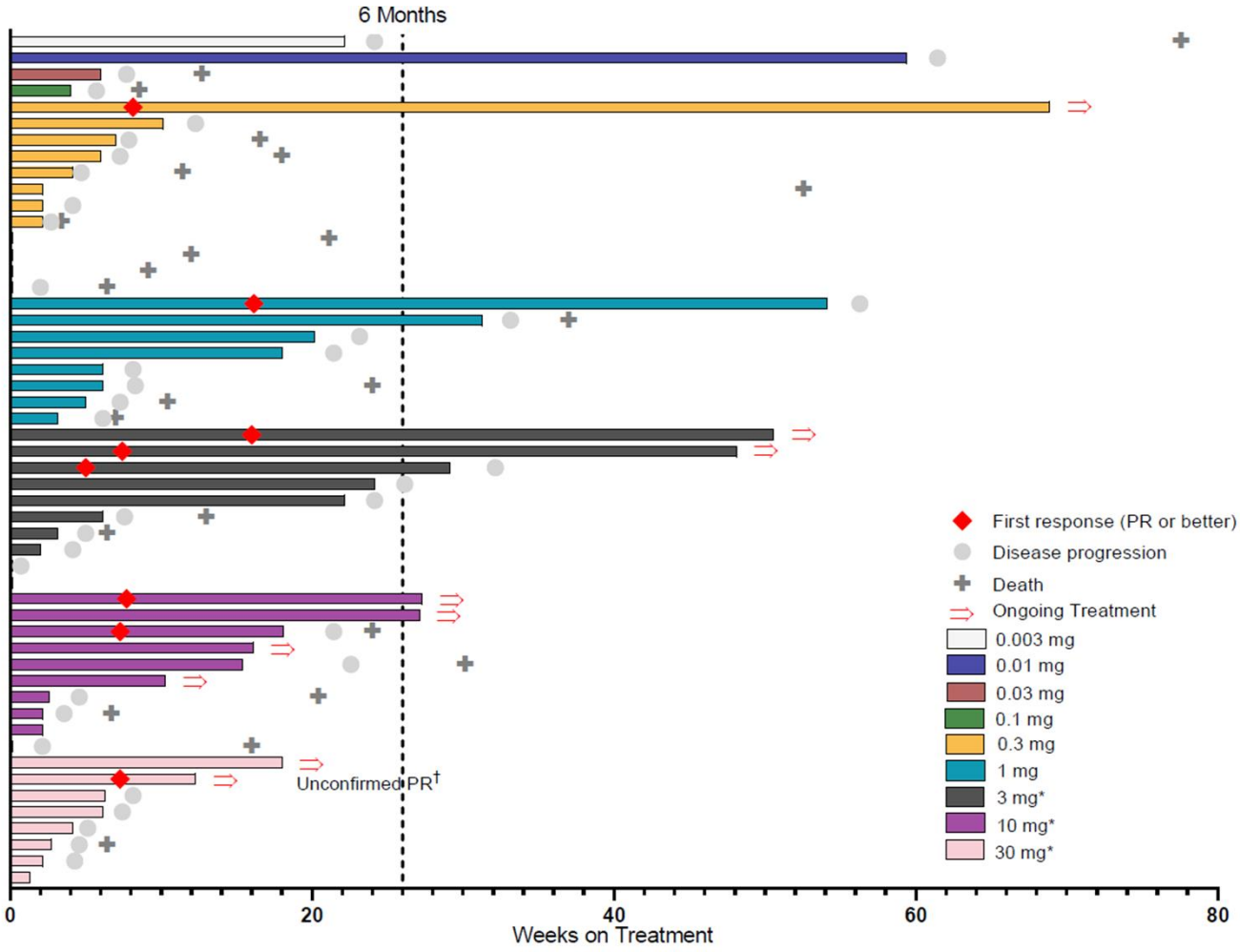


Modified RECIST 1.1 Response, n (%)	Patients† (N = 51)
PR, confirmed	7 (14)
0.3 mg target dose	1/12 (8)
1 mg target dose	1/8 (13)
3 mg target dose	3/9 (33)
10 mg target dose	2/10 (20)
PR, unconfirmed	1 (2)
30 mg target dose	1 (2)
SD	11 (22)
Disease control rate, %	37

PR** indicates the PR is unconfirmed. SD^ indicates patients who had an initial PR, but did not have confirmation of PR on the subsequent scan. NE indicates PD in the post-baseline scan and came off study without further confirmation scan.
*Step dosing. †Includes patients who received ≥ 1 dose of AMG 757 and had at least 8 weeks follow-up. NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

Duration of Treatment and Response

- **10/52 (20%) patients have completed ≥ 6 months (≥ 24 weeks) of treatment**
  - 4/7 patients with confirmed PR are still receiving therapy and have on-going response
- **For patients with confirmed PR (n = 7)**
  - Median time to response was 1.8 months
  - Median duration of response was 6.2 months
  - Median follow-up was 11.5 months



Includes all patients who received ≥ 1 dose of AMG 757. *Step dosing. †No follow-up confirmation scan at cutoff.

AMG-757

- Novel DLL-3 targeting agent
- Clear activity with potential for durable responses
- Relatively well tolerated overall
  - Potential concerns about cytokine release syndrome
  - Can this be administered in community oncology centers?
- Need additional data with larger numbers of patients

EFFICACY AND SAFETY PROFILE OF LURBINECTEDIN-IRINOTECAN IN PATIENTS WITH RELAPSED SCLC

Results from a phase Ib-II trial

Santiago Ponce[1], Gregory M. Coté[2], Alejandro Falcón[3], Elizabeth Jimenez-Aguilar[1], Jessica J Lin[2], Inmaculada Sánchez Simón[3], María José Flor[3], Rafael Núñez[4], Ana M Jiménez[4], Eva Jiménez[4], Sonia Extremera[4], Carmen Kahatt[4], Ali Zeaiter[4], Luis Paz-Ares[1]

[1]Hospital Universitario 12 de Octubre, Madrid, Spain. [2]Massachusetts General Hospital, Boston, MA, U.S.A. [3]Hospital Universitario Virgen del Rocío, Sevilla, Spain. [4]Pharma Mar, S.A., Colmenar Viejo, Madrid, Spain.

Lurbinectidin-Irinotecan shows high response rates in phase I trial

SCLC cohort, waterfall plot (n=21)

Lurbinectidin-Irinotecan associated with significant toxicities

SCLC cohort, Safety (n=21)

Adverse Events and Laboratory abnormalities		Grade 1-2, %	Grade 3-4, %
Treatment-related adverse events	Fatigue	66.7	23.8*
	Nausea	57.1	-
	Vomiting	38.1	4.8
	Diarrhea	33.3	28.6**
	Constipation	19	-
	Abdominal pain	4.8	-
	Anorexia	52.4	-
	Febrile neutropenia	-	9.5
Laboratory abnormalities	Anemia	81	19
	Neutropenia	33.3	61.9***
	Thrombocytopenia	66.7	9.5
	ALT increase	57.1	4.8
	AST increase	61.9	4.8

ALT, alanine aminotransferase; AST, aspartate aminotransferase; IRI, irinotecan; LUR, lurbinectedin.

*1 episode per patient (n=5 pts) **All were grade 3. 1 episode per patient, except in 1 patient (2 episodes of 1 day of duration each)
*** 6/21 pts (28.6 %) neutropenia grade 4

Related AEs summary / dose modifications / supportive treatment	n (%)
Any AE	21 (100)
AE ≥ grade 3	16 (76.2)
SAEs	6 (28.5)
Related AEs leading to death	**0 (0.0)**
Related AEs leading to treatment discontinuation	**0 (0.0)**
Dose delays treatment related	6 (28.6)
Dose reductions	11 (52.4)
Transfusions (red blood)	7 (33.3)

Lurbinectidin-Irinotecan

- Favorable activity seen with this combination in both platinum resistant and sensitive settings
- Toxicities are a potential concern
- Await additional data from larger studies

Summary and Future Directions

- Risk factors beyond smoking
  - Genetic predisposition to developing SCLC
- Early stage
  - Surgery for eligible stage I patients
- Extensive stage
  - Frontline therapy with platinum/etoposide + PDL-1 inhibitor
  - Second line therapies and beyond
    - Topotecan and lurbinectedin are FDA approved options
    - AMG 757 and lurbinectedin-irinotecan show promise
- Further biomarker exploration remains a critical goal
- Prospective trials with selection for molecular subtypes