# Translational Studies in Small Cell Lung Cancer

Martin J.Edelman, MD

University of Maryland Greenebaum Cancer Center

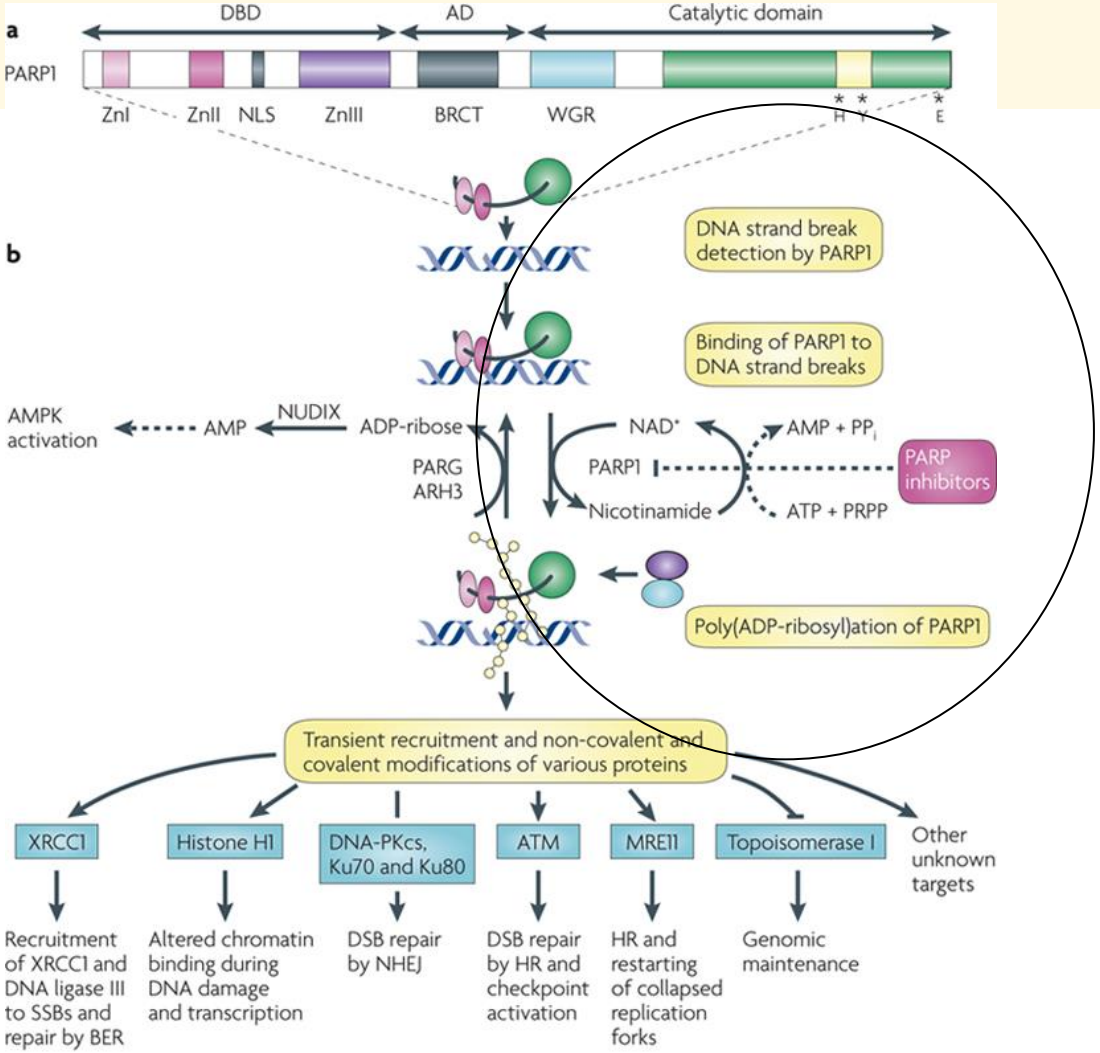
# Disclosures

- Research Funding
  - Lilly Oncology
  - Oncomed
- Stock
  - Andarix
- “Borrowed Slides”
  - Charlie Rudin
  - Lee Krug
  - Cathy Pietenza
  - Host of others

# Overview

- DNA damage repair
  - PARP
  - Chk 1
- Notch
- Immunotherapy
  - Checkpoint inhibitors
  - Vaccines
  - CAR-T

# DNA DAMAGE




Nature Reviews | Cancer

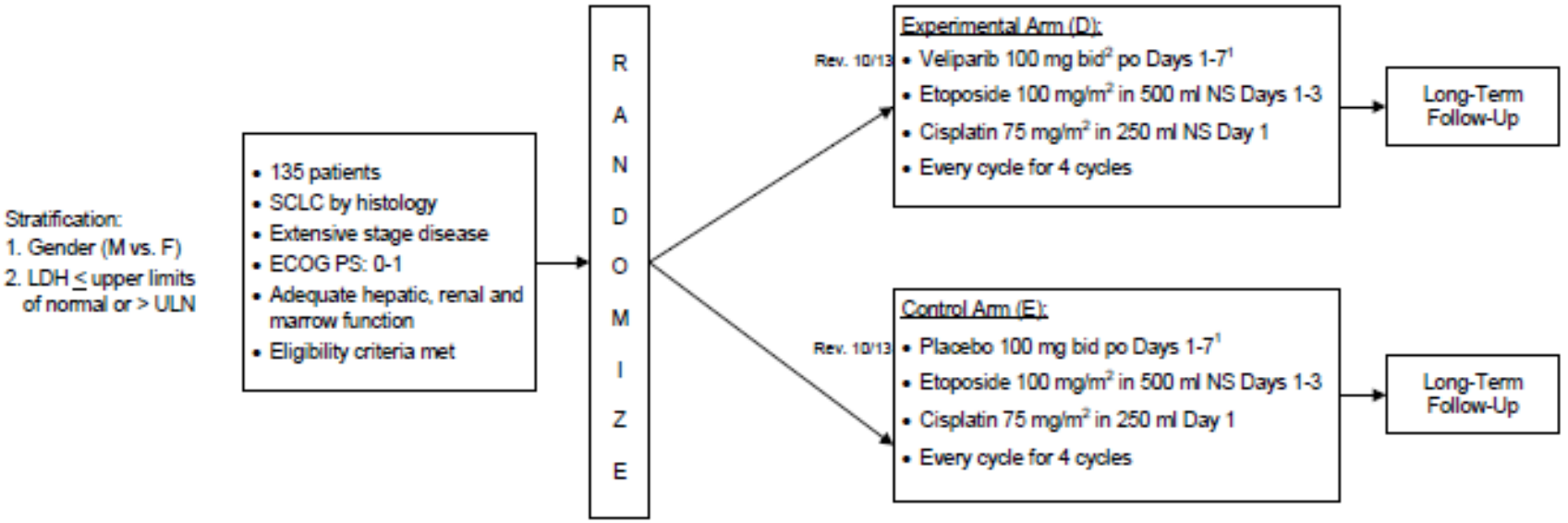
Rouleau et al. Nature Reviews Cancer 2010

# DNA Repair: PARP Inhibitors

**Eastern Cooperative Oncology Group**

**E2511**
**Version Date: October 1, 2013**
**NCI Update Date: November 7, 2012**

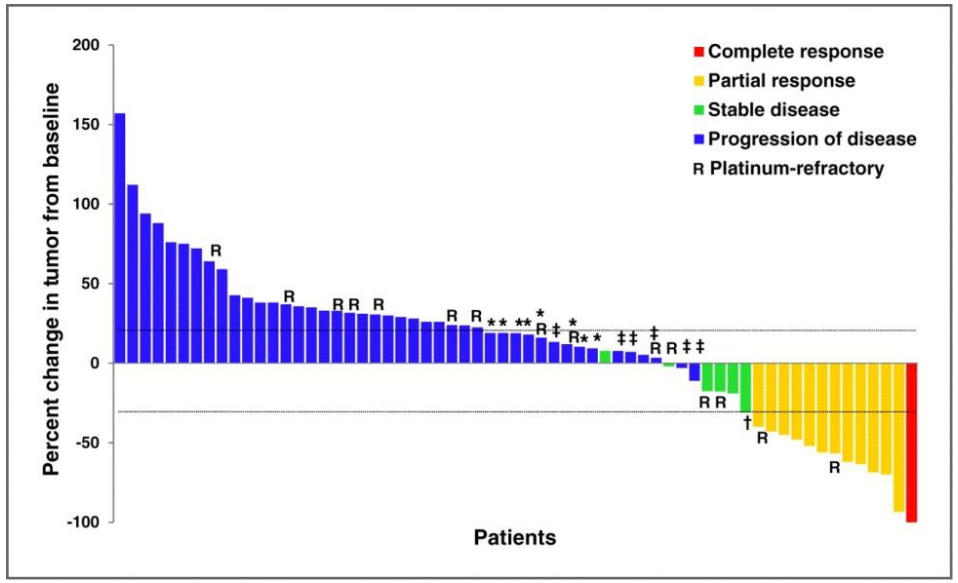
## Phase II Schema




Phase II Accrual Goal = 150
Cycle = 3 weeks (21 days)
IV doses are based on actual weight

1. On days of chemotherapy, the morning veliparib/placebo dose is to be administered AFTER premedications for etoposide, prior to etoposide IV.
2. Recommended Phase II Dose (RP2D) - dose for Phase II was determined in Phase I portion of the study.

# Temozolamide and PARP inhibitor for relapsed SCLC




**Increased response observed with MGMT promoter methylation in tumors (38% vs. 7%; P = 0.08)**

Pietanza M C et al. Clin Cancer Res 2012;18:1138-1145

Relapsed SCLC
1 or 2 prior lines of therapy

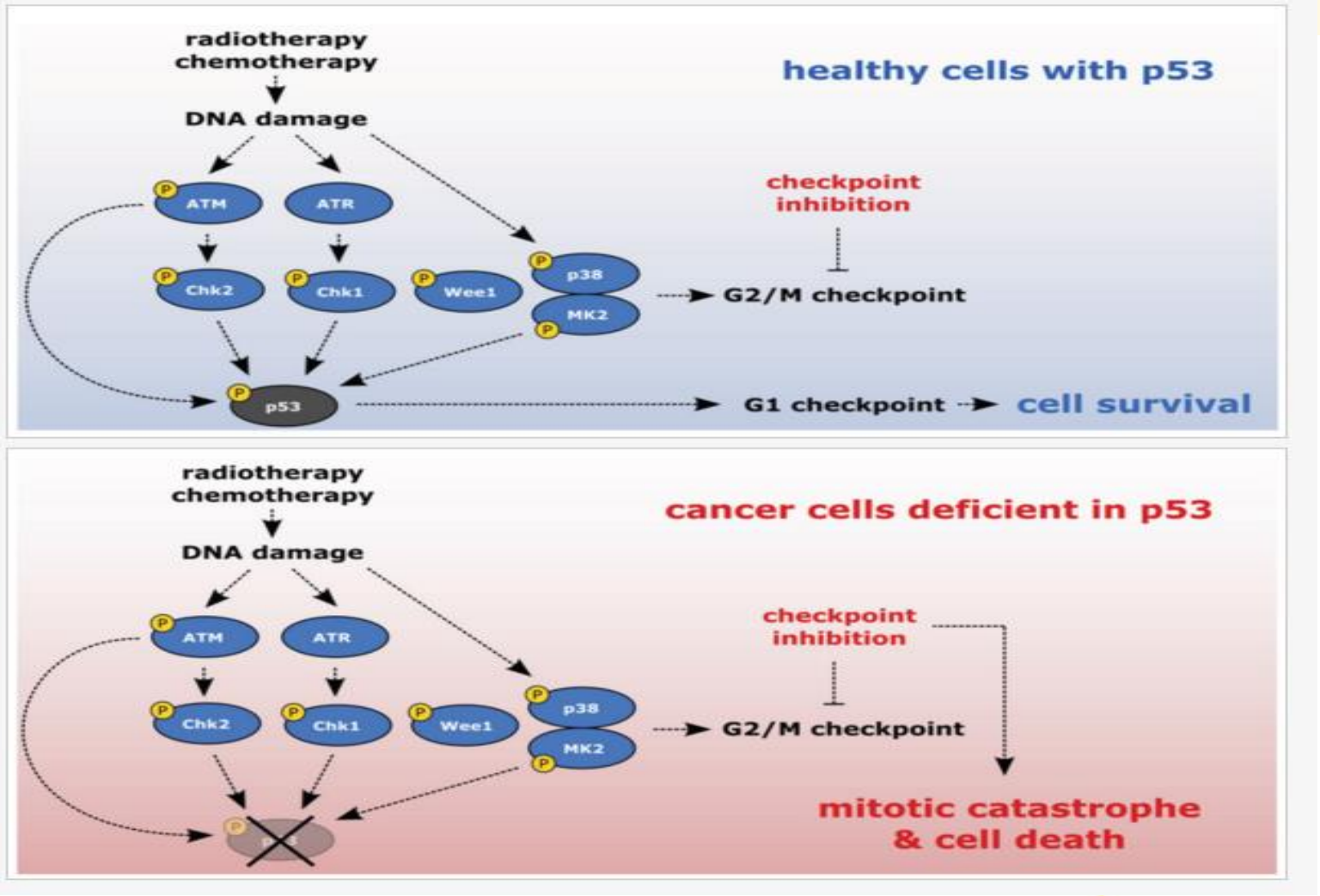
- Temozolamide + Placebo
- Temozolamide + Veliparib

**NCT01638546**
**PI: Pietanza M**

NCI·CC
A Cancer Center Designated by the National Cancer Institute

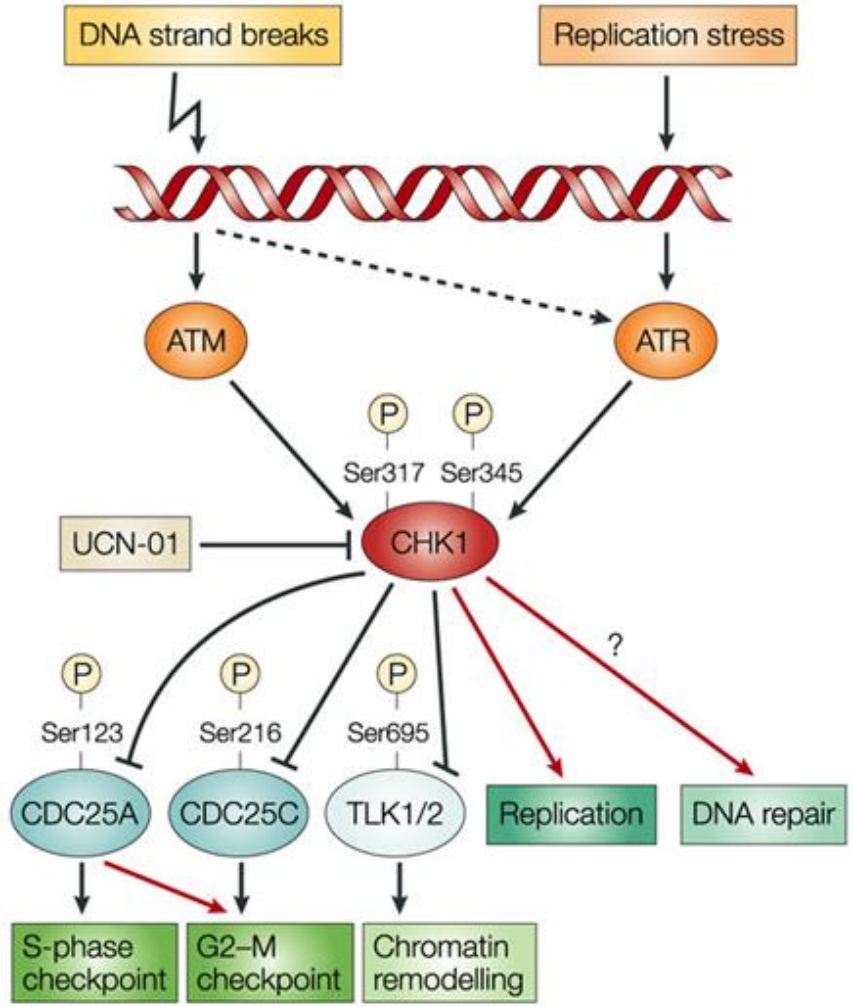
UNIVERSITY of MARYLAND
MARLENE AND STEWART GREENEBAUM CANCER CENTER

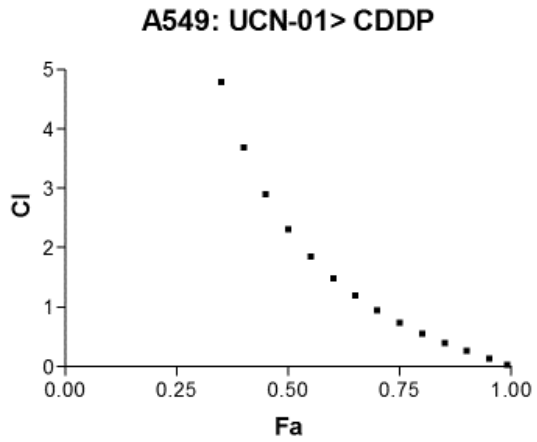
# DNA Repair: CHK1 Inhibition

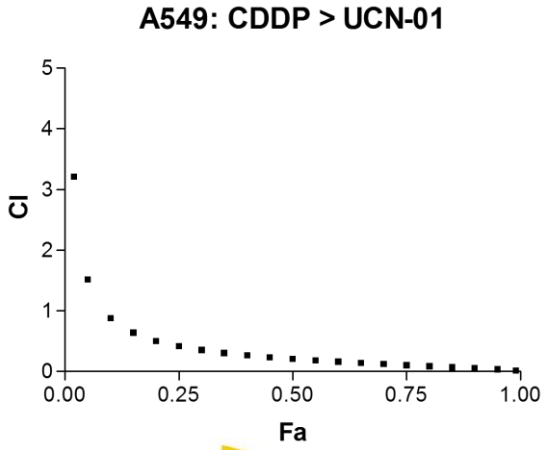



*Biomolecules* **2015**, *5*(3), 1912-1937; doi:10.3390/biom5031912

# Nothing new under the sun…



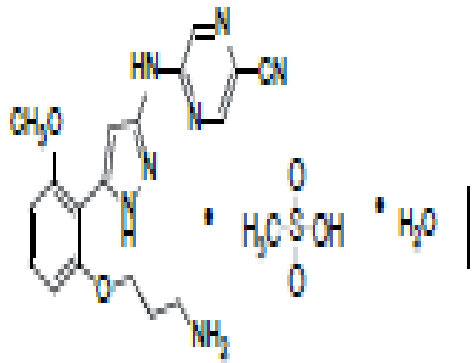

NCI·CC
A Cancer Center Designated by the National Cancer Institute

UNIVERSITY of MARYLAND
MARLENE AND STEWART GREENEBAUM
CANCER CENTER

# LY2606368 in SCLC

**LY2606368**

- $IC_{50}$ values for enzymatic inhibition[9,12]
  - CHK1 = <1 nM
  - CHK2 = 4.7 nM
  - RSK1-3 = 2-7 nM
  - Other targets = >35 nM



LY2606368 monomesylate monohydrate
(referred to herein as LY2606368)

Abbreviations: CHK=checkpoint kinase; $IC_{50}$=half maximal inhibitory concentration; RSK 1-3=ribosomal S6 kinase 1-3.

SCLC
-2nd
-3rd line
PS 0-1
Measurable disease

Platinum responsive → LY2606368

Platinum resistant → LY2606368

Objectives: Pt sensitive H0 = 20%, H1 = 35%
Pt refractory H0 = 5%, H1= 15%

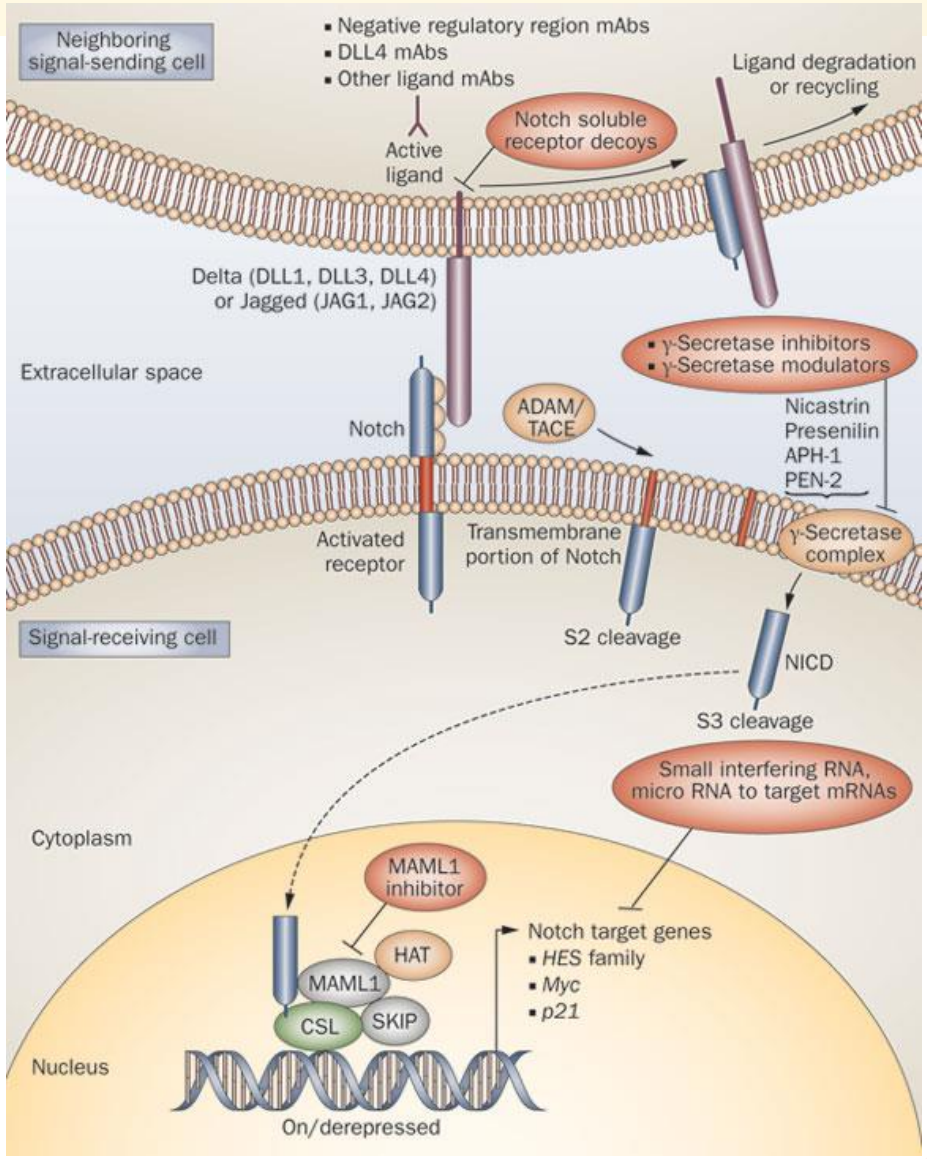
NCI·CC
A Cancer Center Designated by the National Cancer Institute

UNIVERSITY of MARYLAND
MARLENE AND STEWART GREENEBAUM
CANCER CENTER

# NOTCH

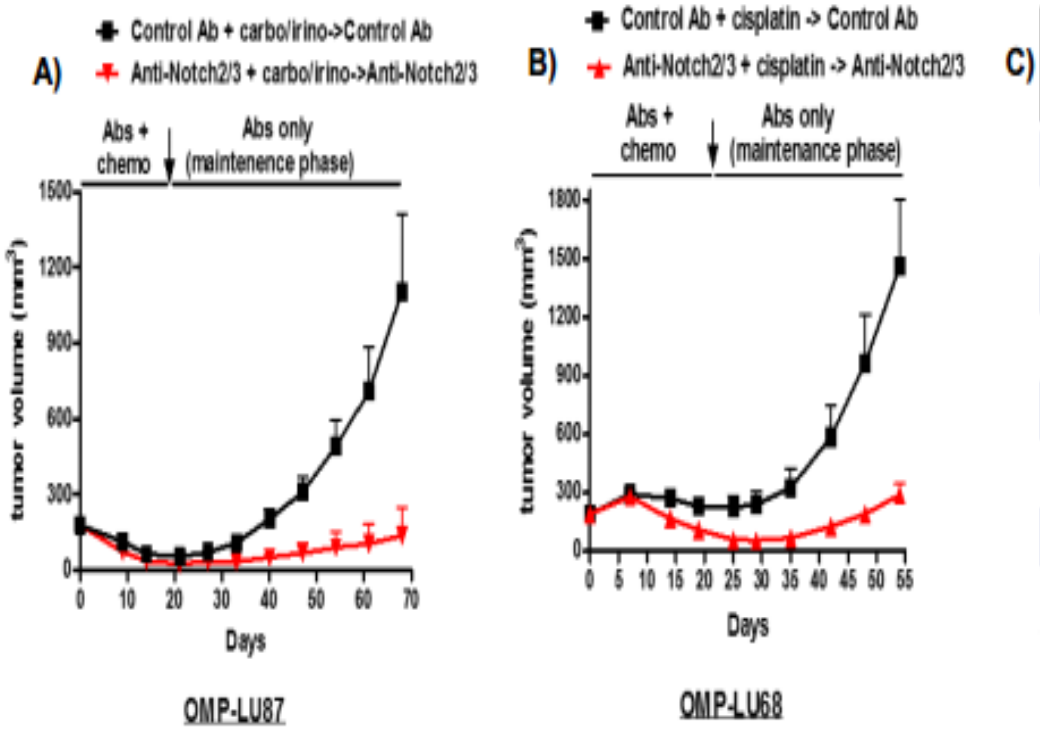
# Notch

- Complicated, multifaceted pathway. Involved in multiple aspects of differentiation and cellular function, including neuronal development.
- Notch receptors modified by addition of sugars. “fringe effect” : lunatic, manic and radical.
- Ligands: Delta (DLL1,3,4); Jagged
- Target:
  - Function
  - expression



# Tarextumab: Anti-Notch2/3

- Tarextumab (TRXT, OMP-59R5, anti-Notch2/3) is a fully human IgG2 that was originally identified by binding to Notch2.
- Inhibits the signaling of both Notch2 and Notch3 receptors
- Excellent preclinical activity in combination with platinum




C)

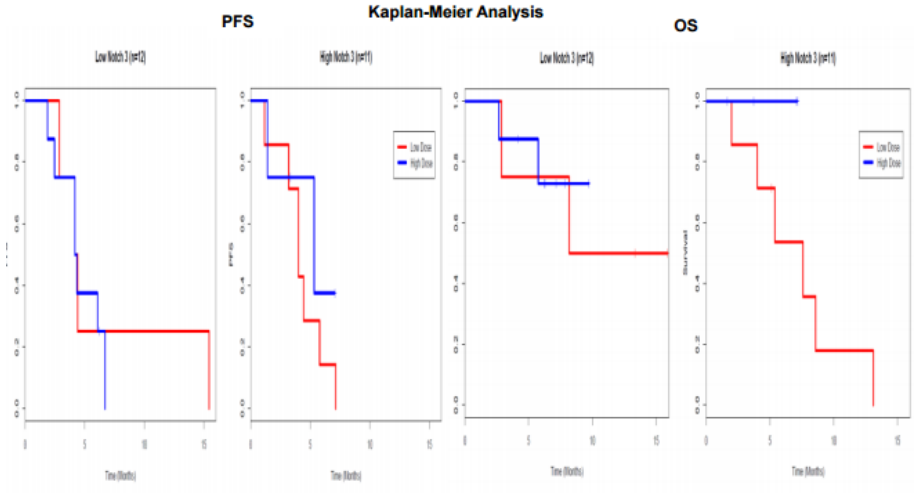
| SCLC Tumor | OMP-59R5 Activity |
|---|---|
| LU40 | + |
| LU61 | + |
| LU65 | + |
| LU66 | + |
| LU67 | - |
| LU68 | + |
| LU87 | + |
| LU90 | - |

NCI·CC
A Cancer Center Designated by the National Cancer Institute

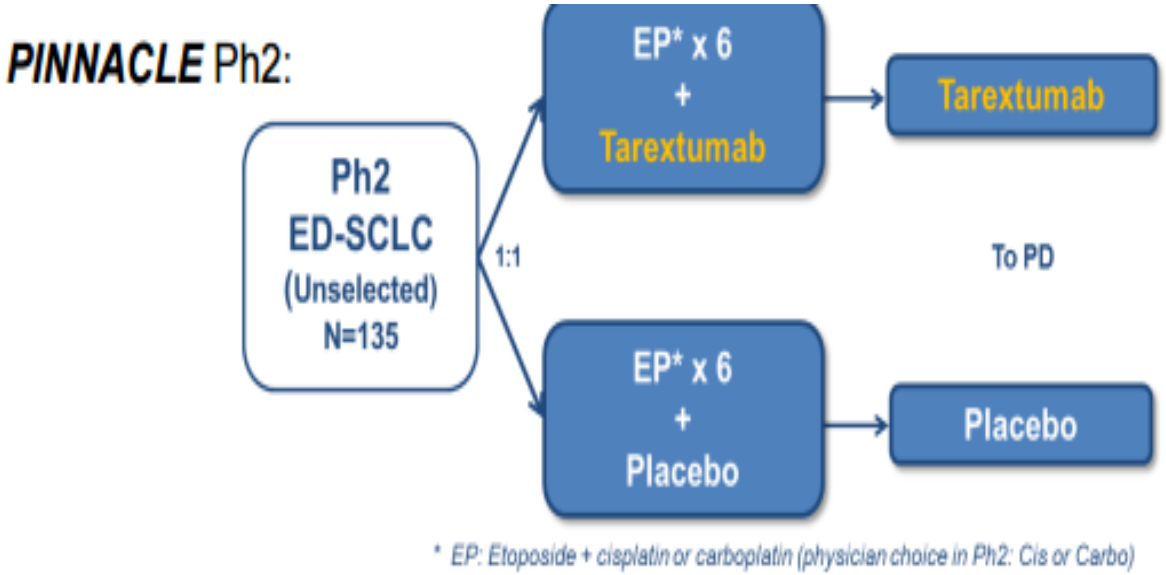
UNIVERSITY of MARYLAND
MARLENE AND STEWART GREENEBAUM CANCER CENTER

# Notch 2/3 targeting

- Phase I reported at ASCO 2015
- Longer survival in pts with elevated Notch 3 expresson
- Randomised Phase II trial in progress.




Potentially longer survival in tumor Notch3 high pts receiving doses of TRXT ≥ 12.5 mg/kg in combination with EP. More follow-up is needed .



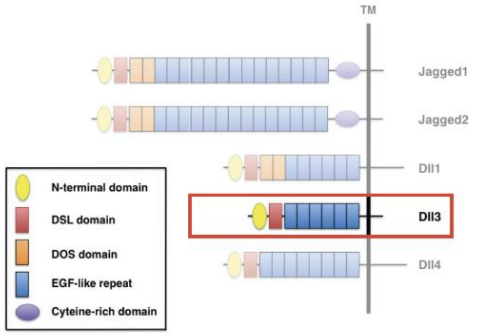

* EP: Etoposide + cisplatin or carboplatin (physician choice in Ph2: Cis or Carbo)

NCI·CC
A Cancer Center Designated by the National Cancer Institute

UNIVERSITY of MARYLAND
MARLENE AND STEWART GREENEBAUM
CANCER CENTER

# Antibody-Drug Conjugate: Targeting DLL3

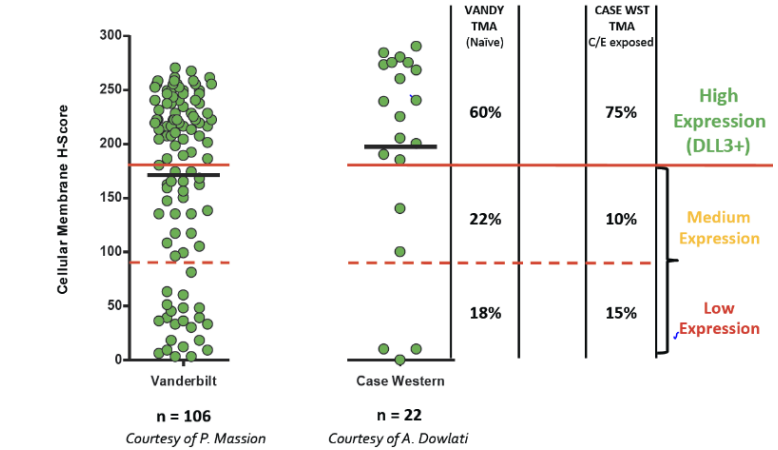
## DLL3 is a dominant inhibitor of Notch signaling




- 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

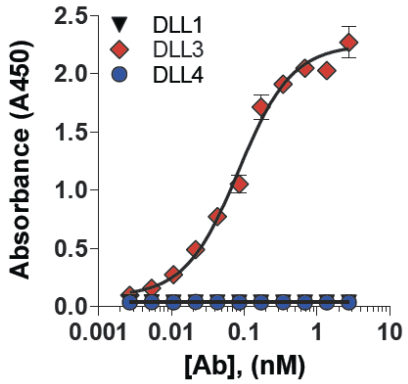
Kume *et al., J Angiogen Res* 2009

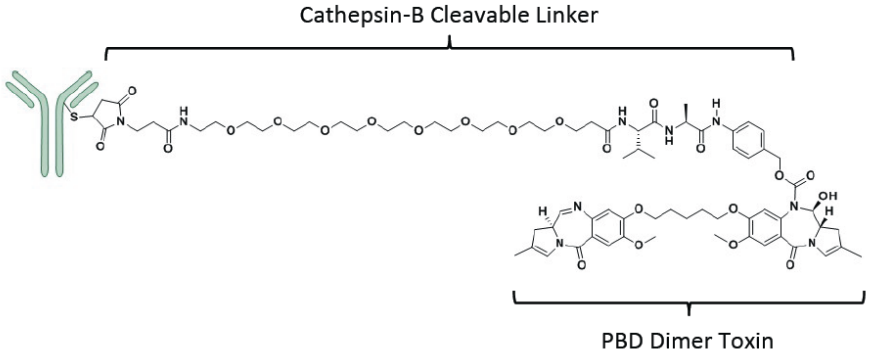
## DLL3 expression in SCLC by IHC




## Rovalpituzumab Tesirine (Rova-T; SC16LD6.5)

Drug-to-Antibody Ratio (DAR) = 2




Rudin WCLC 2015

NCI·CCC
A Cancer Center Designated by the National Cancer Institute

UNIVERSITY of MARYLAND
MARLENE AND STEWART GREENEBAUM CANCER CENTER

# RovaT: Phase I/II Trial

80 pts enrolled

- 73 (91%) SCLC, 7 (9%) LCNEC
- 41 (51%) 2nd line, 39 (49%) 3rd line
- 1st line response: 45 (58%) sensitive, 33 (42%) resistant *
- Mean age 62 yr; 59% male/41% female; ECOG 0/1: 27%/73% *
- 50 (63%) provided archived tumor sample; 70% with "high" DLL3
- 68 (85%) pts in expansion cohorts
  - 0.3 mg/kg q6w
  - 0.2 mg/kg q3w

* Information unavailable for 2 Pts

**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**

NCI·CC
A Cancer Center Designated by the National Cancer Institute

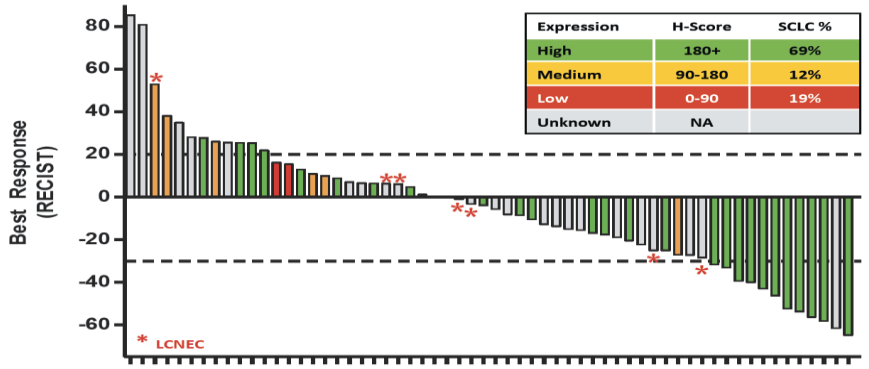
Rudin, WCLC 2015

UNIVERSITY of MARYLAND
MARLENE AND STEWART GREENEBAUM CANCER CENTER

# RovaT: Response

## Rova-T: best response data in evaluable patients

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



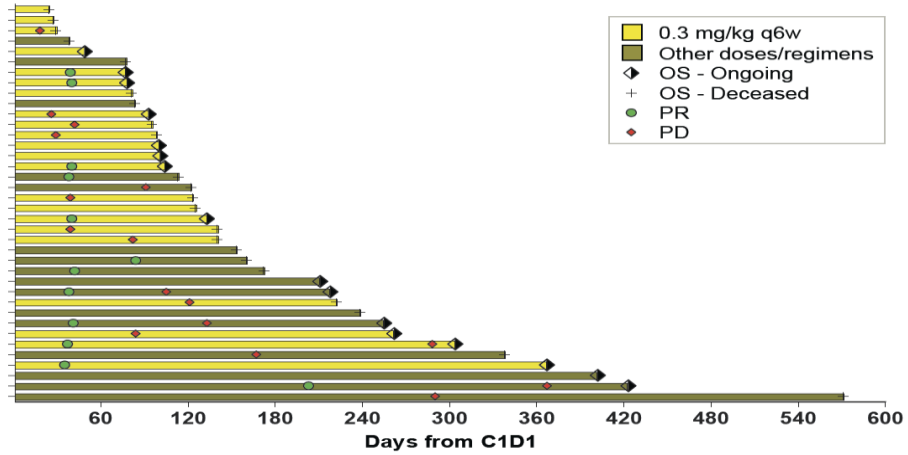

| Expression | H-Score | SCLC % |
|---|---|---|
| High | 180+ | 69% |
| Medium | 90-180 | 12% |
| Low | 0-90 | 19% |
| Unknown | NA | |

## 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 plots for DLL3+ patients




## Overall response rate

| | Topotecan† | Rova-T; SC16LD6.5 All Pts & dose levels | Rova-T; SC16LD6.5 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

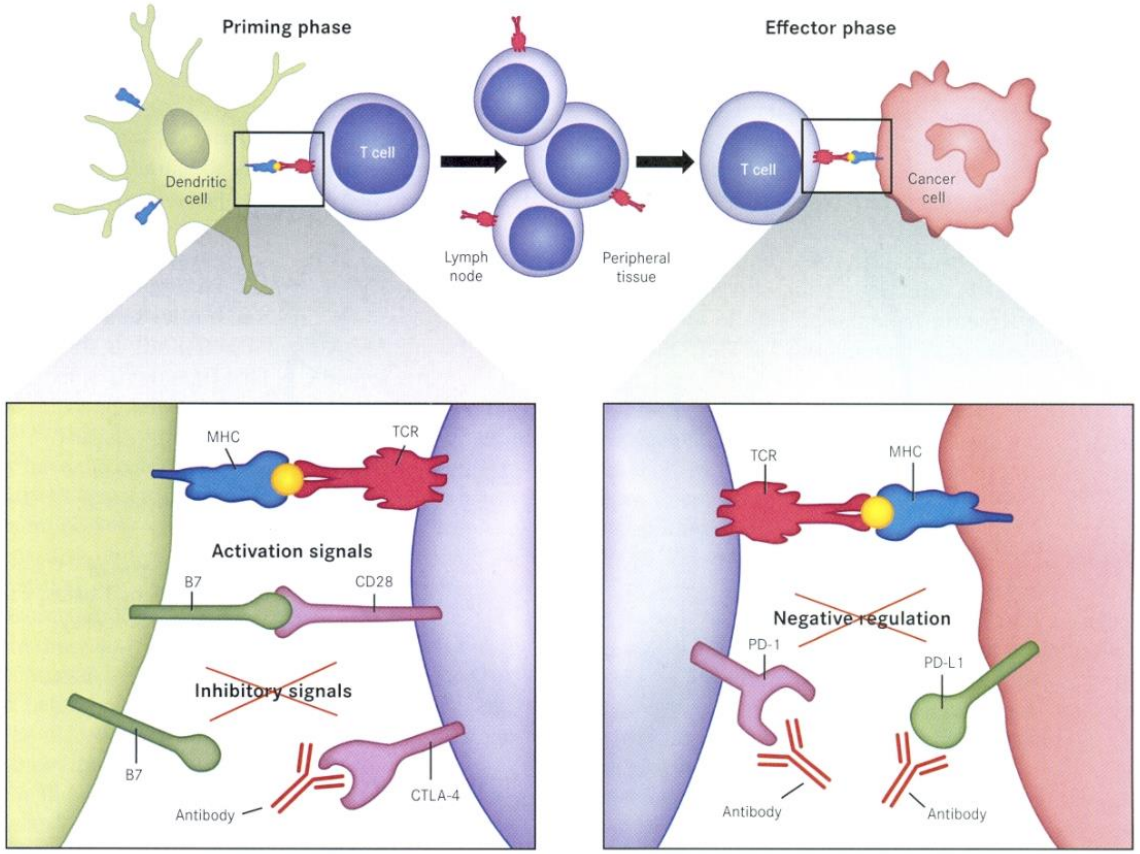
NCI·CC
A Cancer Center Designated by the National Cancer Institute

Rudin, WCLC 2015

UNIVERSITY of MARYLAND
MARLENE AND STEWART GREENEBAUM CANCER CENTER

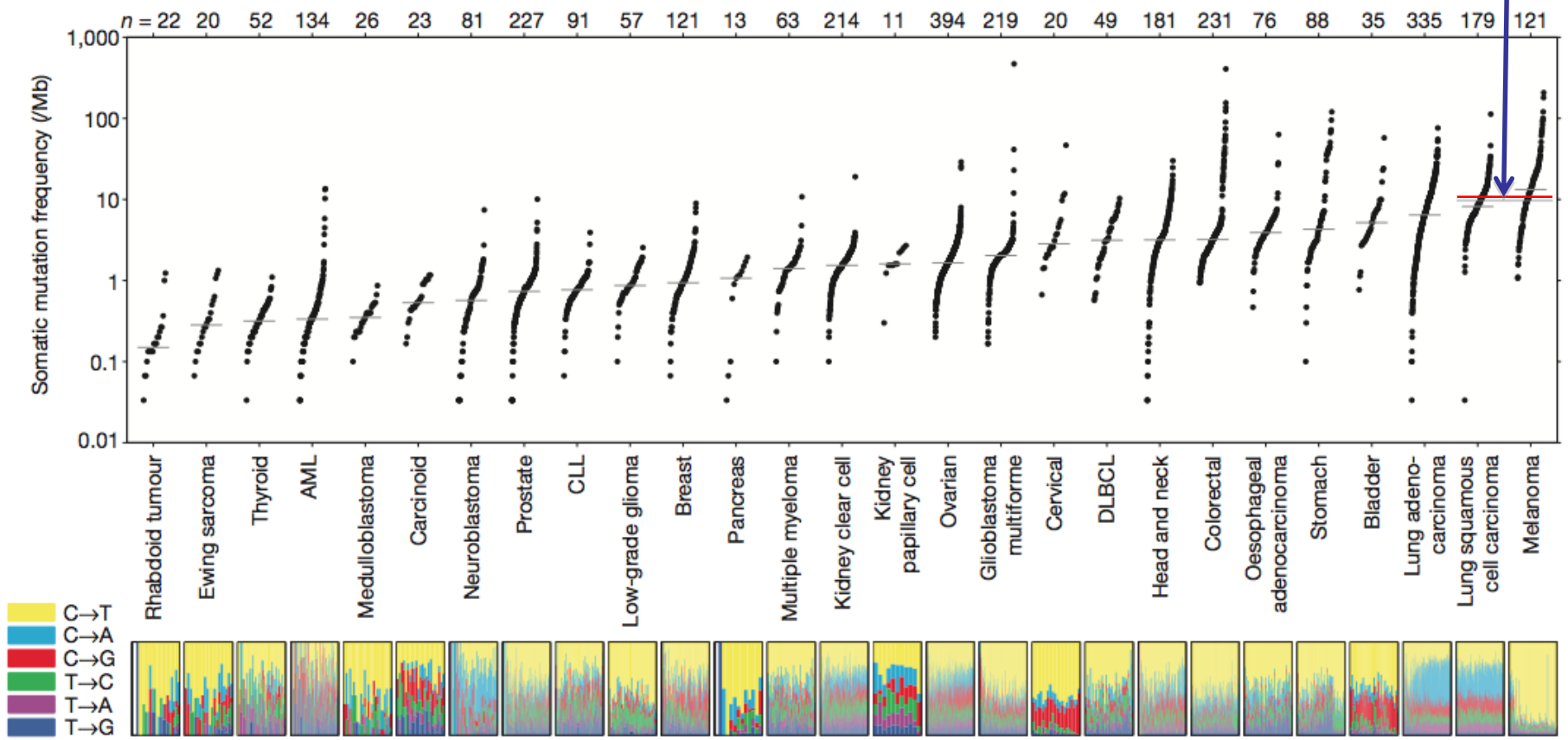
# IMMUNOTHERAPY

# Regulation of immune response



# Global Mutational Spectrum of SCLC

**SCLC**
8.88 mutations/Mb
(7.4 mutations/Mb in protein changing genes)

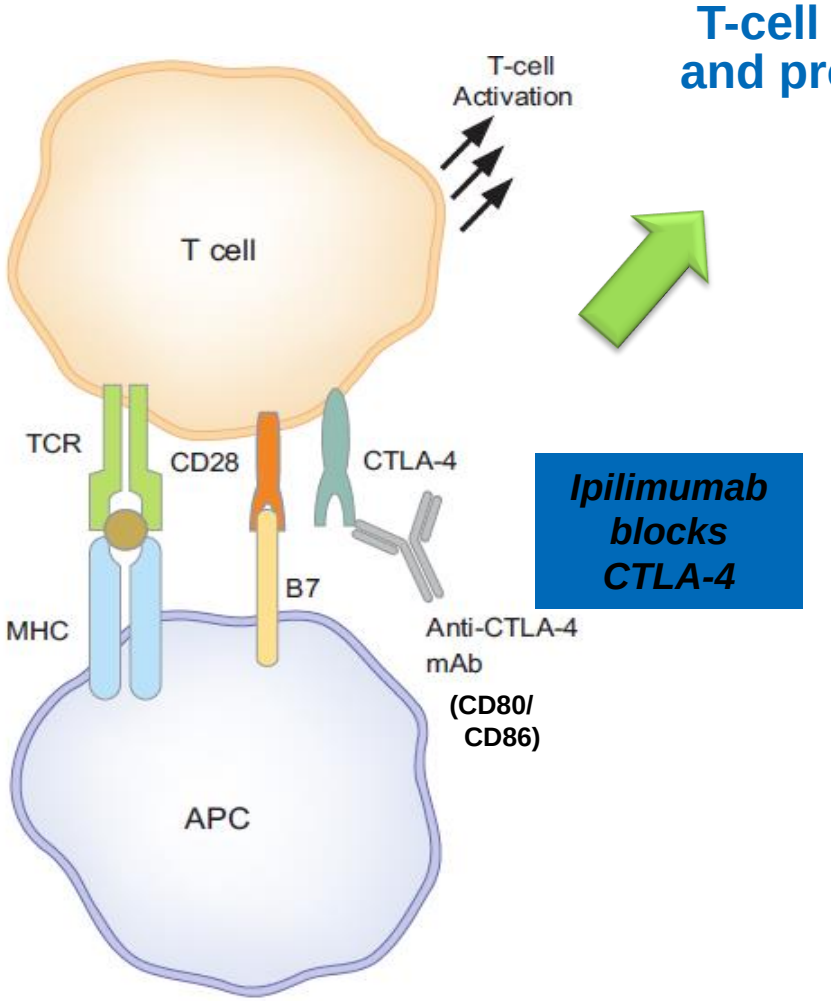




Rudin C, et al. *Nature Genetics*. 2012;44:1111.
Peifer M, et al. *Nature Genetics.* 2012;44:1104.
Lawrence MS, et al. *Nature*. 2013;499:214.

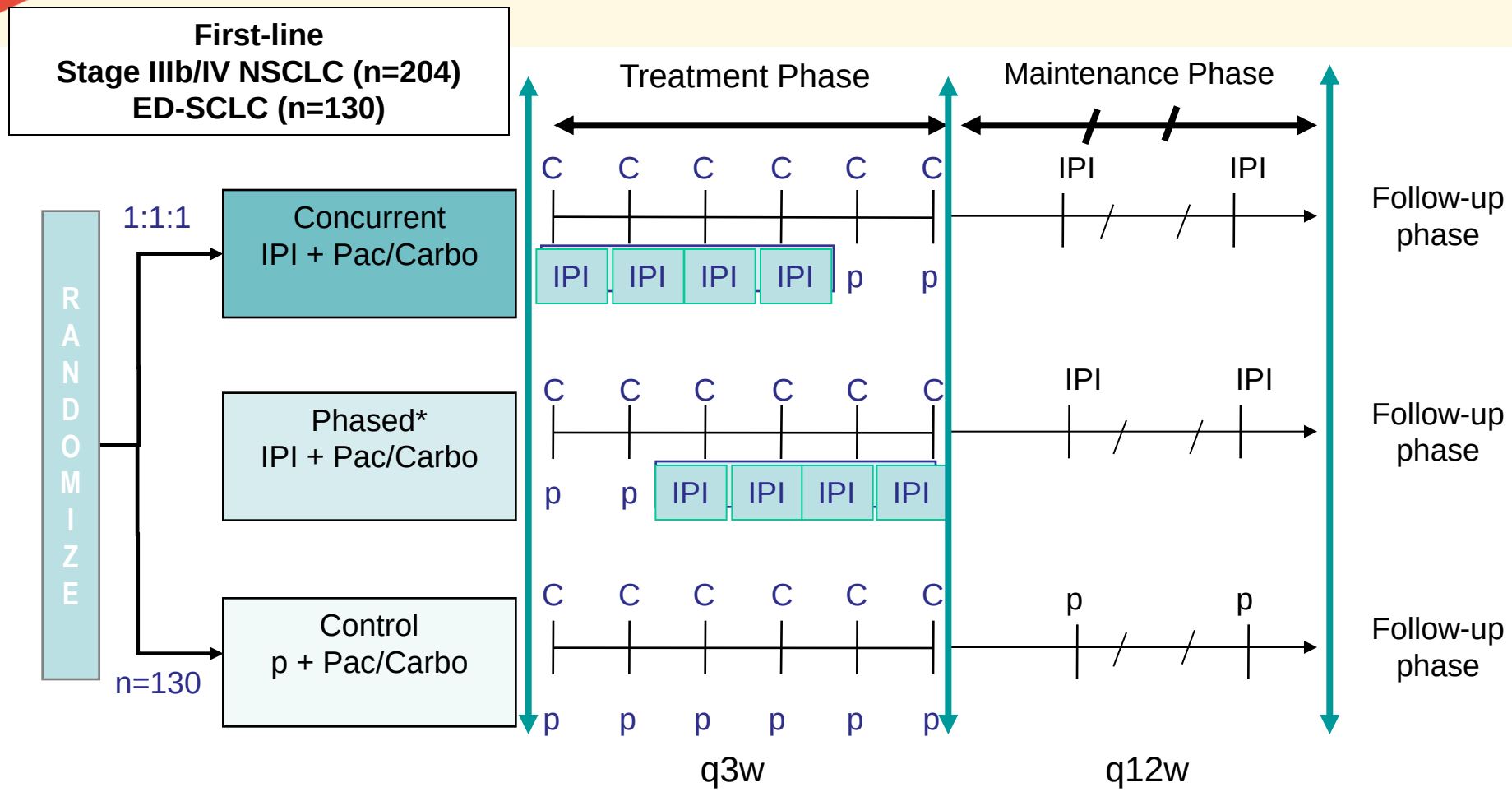
# CTLA-4 Inhibitor: Ipilimumab

- Ipilimumab is a humanized IgG1 monoclonal antibody against CTLA-4
- By blocking the inhibitory signal provided by CTLA-4, this class of antibodies can prolong the activation and proliferation of tumor-directed cytotoxic T cells, thus promoting an anti-tumor immune response




Pardoll DM. *Nat Rev Ca*. 2012; 12:252.
Spigel DR & Socinski MA. *JTO*. 2013;8:587.

# Phase II Study of Ipilimumab in Lung Cancer

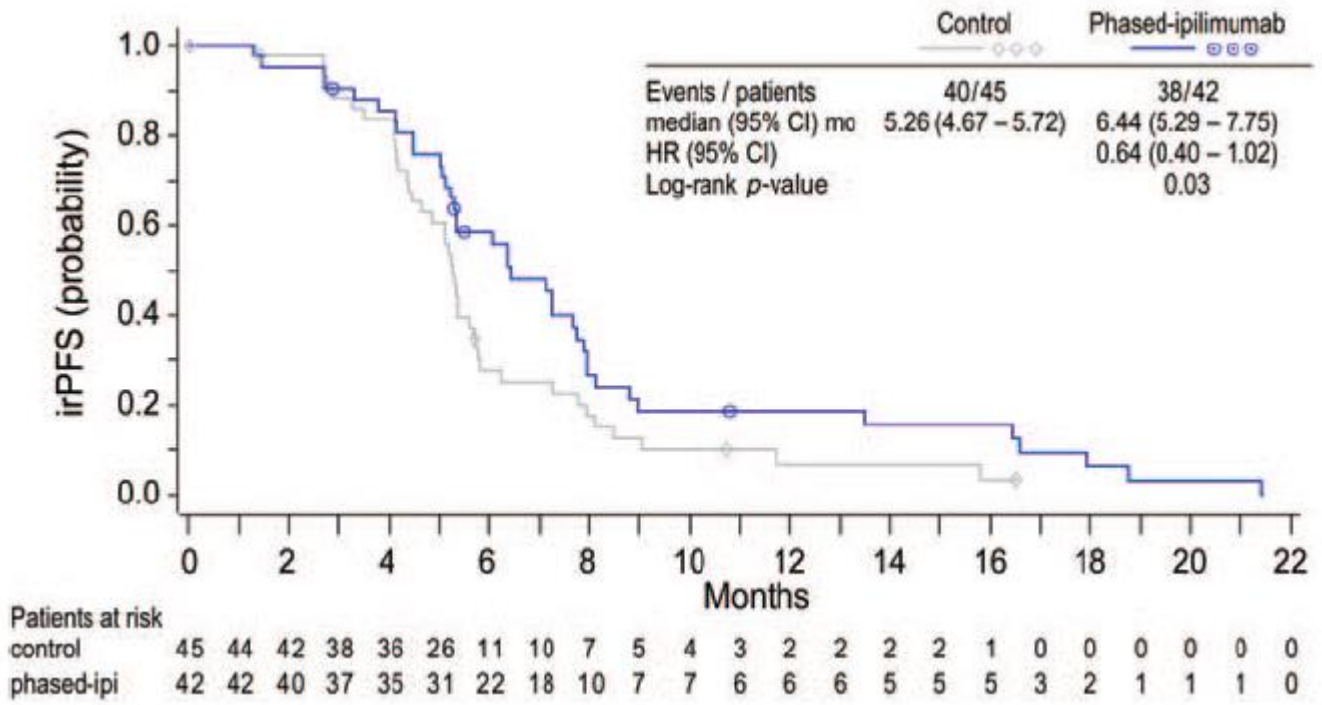



C: chemotherapy doublet (Pac 175mg/m$^2$)/Carbo (AUC=6); IPI: Ipilimumab (10 mg IV); p: Placebo
*Phased : 2 doses of paclitaxel /carboplatin given prior to start of ipilimumab
Note: Steroids were given as premedication for chemotherapy
Adopted from BMS.
Lynch TJ, et al. JCO. 2012;30:2046.

NCI·CC
A Cancer Center Designated by the National Cancer Institute

University of Maryland
Marlene and Stewart Greenebaum Cancer Center

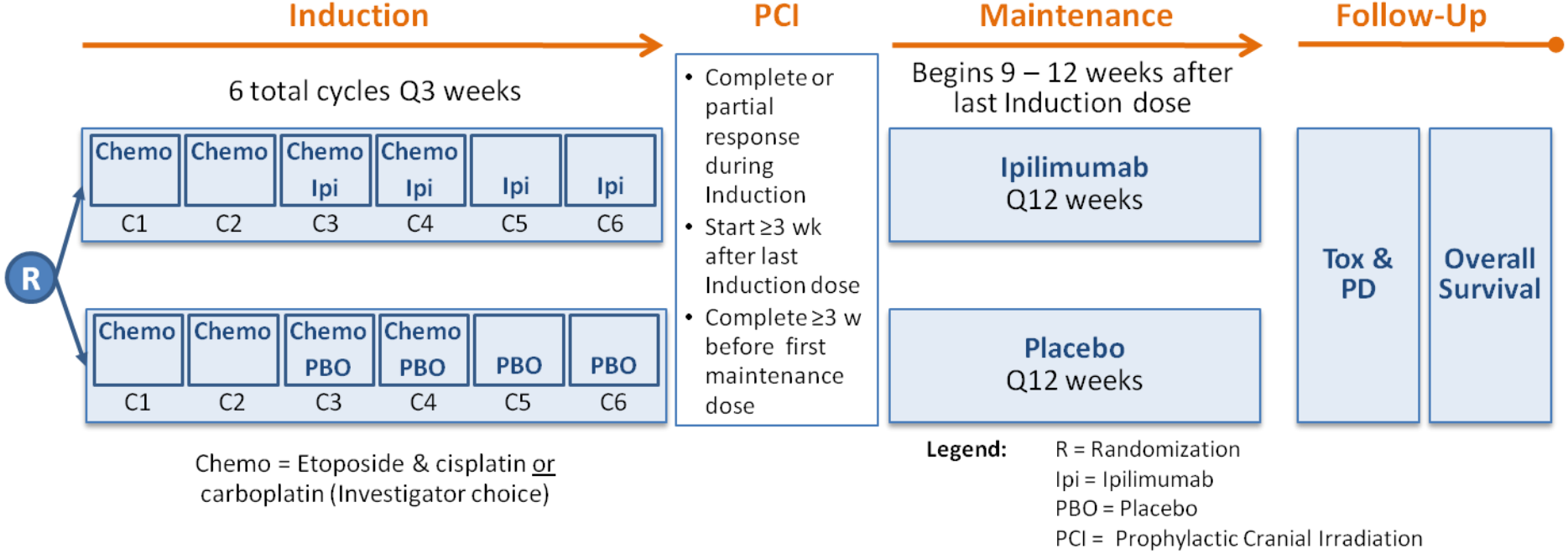
# Phase II Study of Ipilimumab in SCLC




- Phased schedule:
  - Significantly improved irPFS
  - Trend for improved OS
- No trend for concurrent schedule

Reck M, et al. *Ann Oncol*. 2013;24:75.

# Phase III Study of Ipilimumab in SCLC (NCT01450761)




Primary end-point: OS

Study population:
- ED SCLC
- Brain mets allowed if stable
- Measurable disease not required

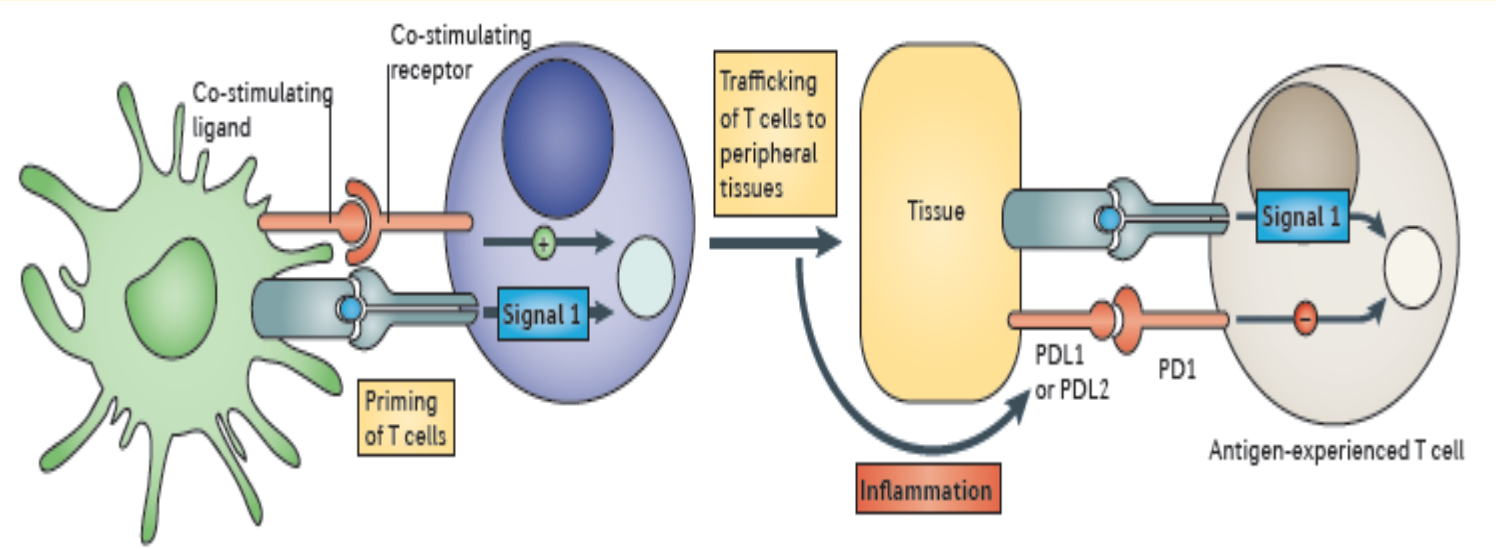
Approximately 210 sites
33 countries
1100 subjects

NCI·CC
A Cancer Center Designated by the National Cancer Institute

Sponsored by BMS.

University of Maryland
Marlene and Stewart Greenebaum Cancer Center

# Programmed Cell Death Protein (PD-1)

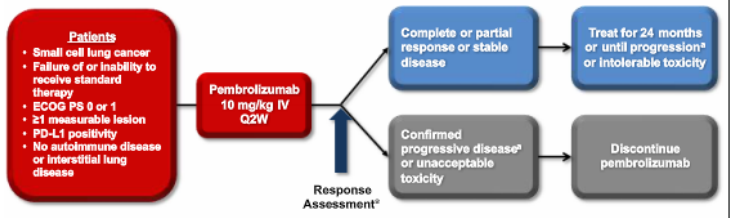



- Inhibitory receptor induced when T cells are activated
- Limits activity of T cells in peripheral tissue during an inflammatory response to infection
- Limits autoimmunity
- Ligands are PDL-1 and PDL-2
- Blocking PD-1 prevents interaction with PD-L1 and PD-L2, restoring antitumor T-cell function



Pardoll DM. *Nature Rev Ca*. 2012;12:252.

## KEYNOTE-028 (NCT02054806): Phase 1b Multicohort Study of Pembrolizumab for PD-L1+ Advanced Solid Tumors




*Response assessment: Every 8 weeks for the first 6 months; every 12 weeks thereafter

Primary end points: ORR per RECIST v1.1 and safety

Secondary end points: PFS, OS, duration of response

*If clinically stable, patients are to remain on pembrolizumab until progressive disease is confirmed on a second scan performed ≥4 weeks later.

3285 – Patrick A. Ott

## Baseline Characteristics

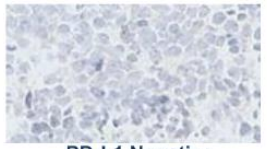
| Characteristic, n (%) | N = 24 |
|---|---|
| Median age, years (range) | 60.5 (41–80) |
| Male | 14 (58.3) |
| Race | |
| White | 13 (54.2) |
| Asian | 3 (12.5) |
| Not specified | 8 (33.3) |
| ECOG performance status | |
| 0 | 7 (29.2) |
| 1 | 17 (70.8) |
| Stable brain metastases | 3 (12.5) |

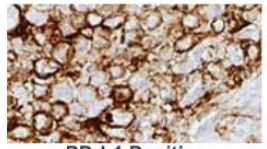
| Characteristic, n (%) | N = 24 |
|---|---|
| Histology | |
| Small cell | 23 (95.8) |
| Neuroendocrine | 1 (4.2) |
| Type of prior therapy[a] | |
| Chemotherapy | 24 (100) |
| Radiotherapy | 1 (4.2) |
| Investigational TKI | 1 (4.2) |
| Other investigational therapy | 1 (4.2) |
| Specific prior therapies[a,b] | |
| Cisplatin/carboplatin + etoposide | 24 (100) |
| Irinotecan or topotecan | 11 (45.8) |
| Taxane | 7 (29.2) |

## Analysis of PD-L1 Expression

- Samples: archival or newly obtained core or excisional biopsy of a nonirradiated lesion
- Immunohistochemistry: performed at a central laboratory using a prototype assay and the 22C3 antibody clone (Merck)
- Positivity: membranous PD-L1 expression in ≥1% of tumor and associated inflammatory cells or positive staining in stroma
- SCLC cohort: of 147 evaluable samples, 42 PD-L1 positive (28.6%)

**Examples of PD-L1 Staining in SCLC Specimens from KEYNOTE-028**


PD-L1 Negative


PD-L1 Positive

## Antitumor Activity[a] (RECIST v1.1, Investigator Review)

| Best Overall Response | n | % | 95% CI |
|---|---|---|---|
| Complete response | 0 | 0 | 0.0-14.2 |
| Partial response | 7 | 29.2 | 12.6-51.1 |
| Stable disease | 1 | 4.2 | 0.1-21.1 |
| Progressive disease | 10 | 41.7 | 22.1-63.4 |
| No assessment[b] | 6 | 25.0 | 9.8-46.7 |

**Objective response rate: 29.2% (95% CI, 12.6–51.1)**

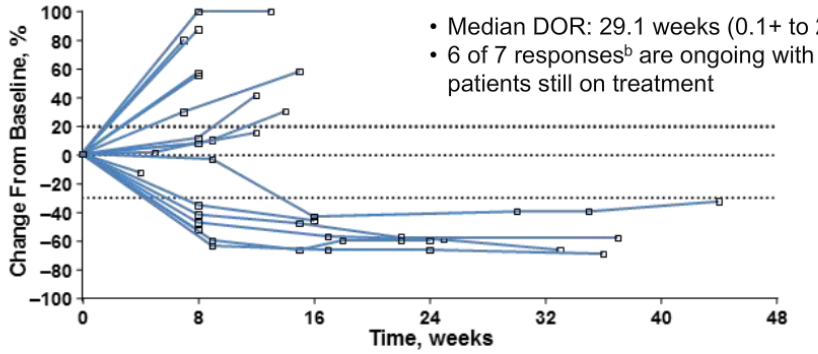
**Disease control rate[c]: 33.3% (95% CI, 15.6–55.3)**

NCI·CC
A Cancer Center Designated by the National Cancer Institute

Ott, WCLC 2015

UNIVERSITY of MARYLAND
MARLENE AND STEWART GREENEBAUM CANCER CENTER

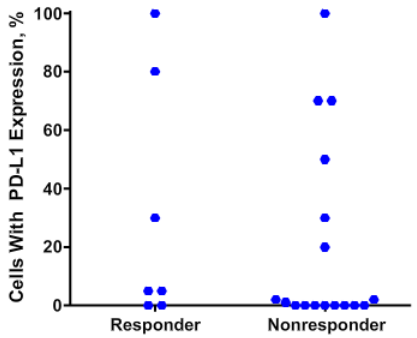
## Change From Baseline in Tumor Size Over Time[a]




- Median DOR: 29.1 weeks (0.1+ to 29.1)
- 6 of 7 responses[b] are ongoing with patients still on treatment

## Level of PD-L1 Expression and Response

- Using prototype IHC assay, no relationship between level of PD-L1 expression on tumor and immune cells within tumor nests and frequency of response
  - One-sided $P = 0.235$ by logistic regression




## Comments

- Anti-PD-1/L1 therapies have clear activity in SCLC. Other trials reported at ASCO with nivolumab +/- Ipilumumab.

*No relationship between PD-L1 and response (at least In this small series and with this assay).

NCI·CC
A Cancer Center Designated by the National Cancer Institute

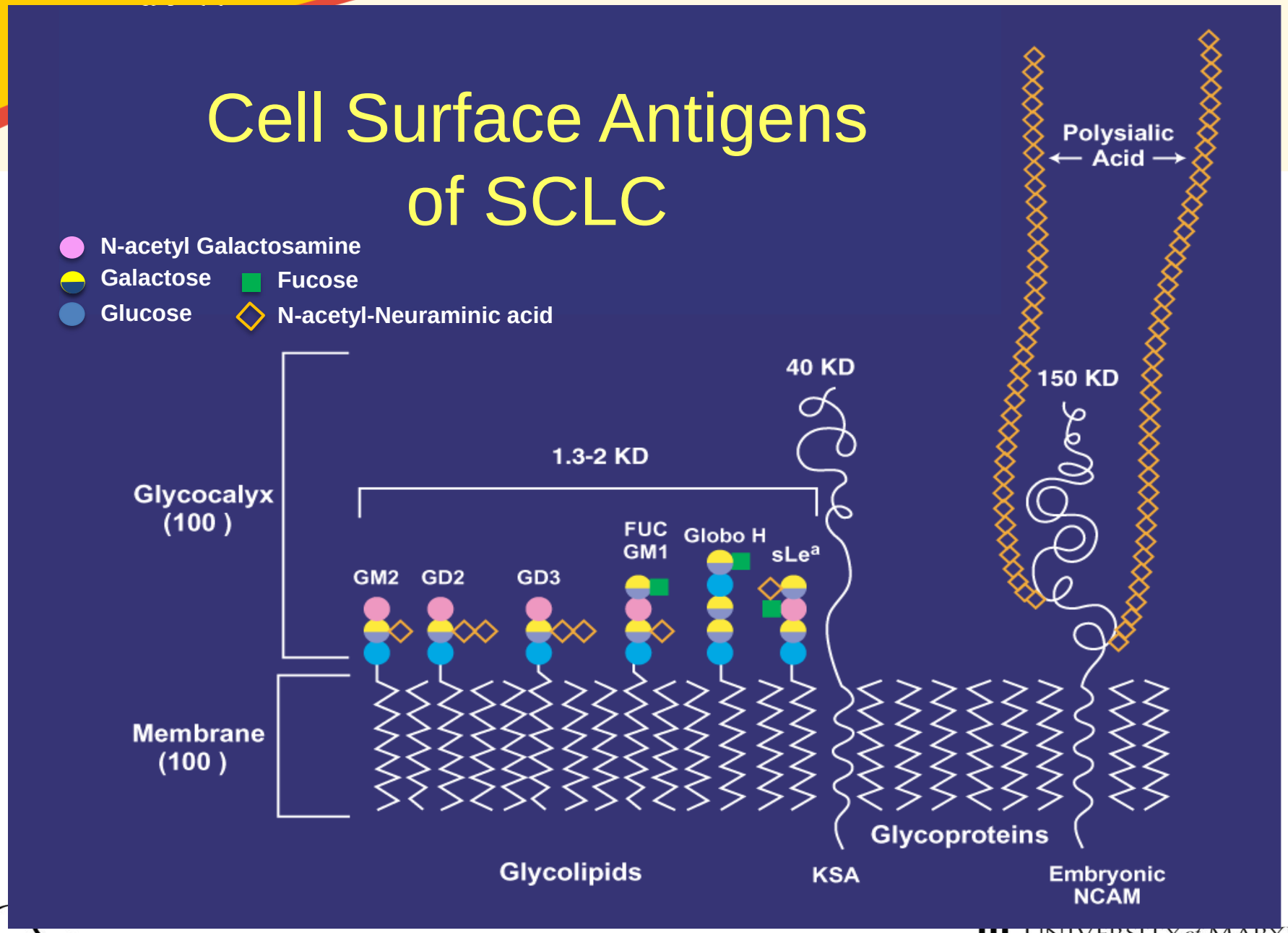
UNIVERSITY of MARYLAND
MARLENE AND STEWART GREENEBAUM CANCER CENTER

# Checkpoint Inhibition Studies in SCLC

- A Phase 1/2, Open-label Study of Nivolumab Monotherapy or Nivolumab Combined with Ipilimumab in Subjects with Advanced or Metastatic Solid Tumors [NCT01928394]
- A Phase I/2 Study to Evaluate MEDI4736 [NCT01693562]
- A Phase I Study of MEDI4736 (Anti-PD-L1 Antibody) in Combination With Tremelimumab (Anti-CTLA-4 Antibody) in Subjects With Advanced Solid Tumors [NCT02261220]
- Phase I Trial of MK-3475 and Concurrent Chemo/Radiation for the Elimination of Small Cell Lung Cancer [NCT02402920]
- Pembrolizumab in Treating Patients With Extensive Stage Small Cell Lung Cancer After Completion of Combination Chemotherapy [NCT02359019]

# VACCINES

# Cell Surface Antigens of SCLC

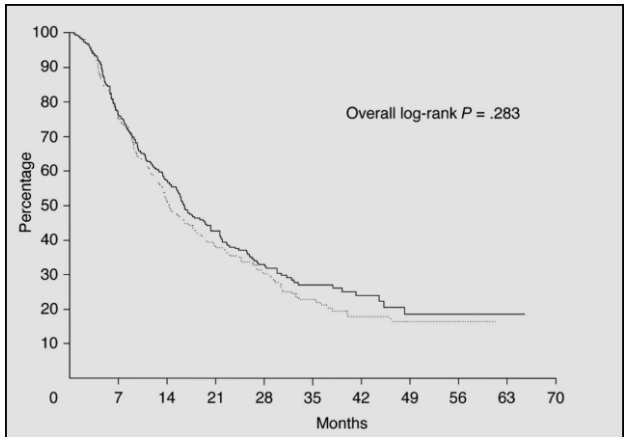


# Past Failures: SILVA Trial

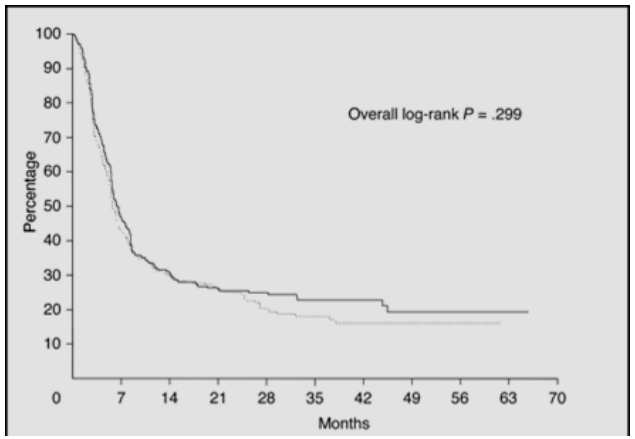
Limited SCLC
PR or CR after chemo/RT
PCI optional

N=258 → Observation

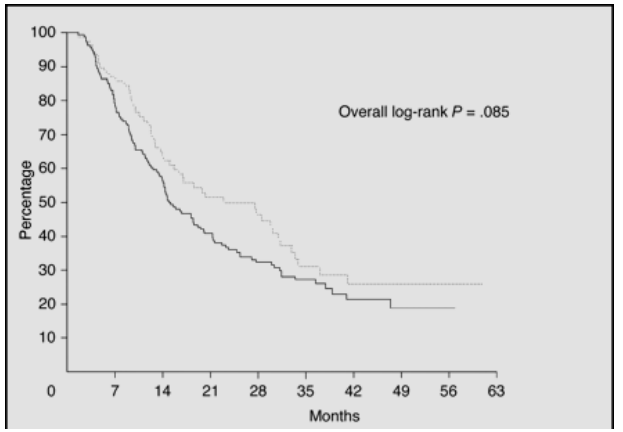
N=257 → BEC-2 (2.5 mg) + BCG intradermal injections weeks 0, 2, 4, 6, 10




OS




PFS




Surv Based on Imm Resp

NCI·CC
A Cancer Center Designated by the National Cancer Institute

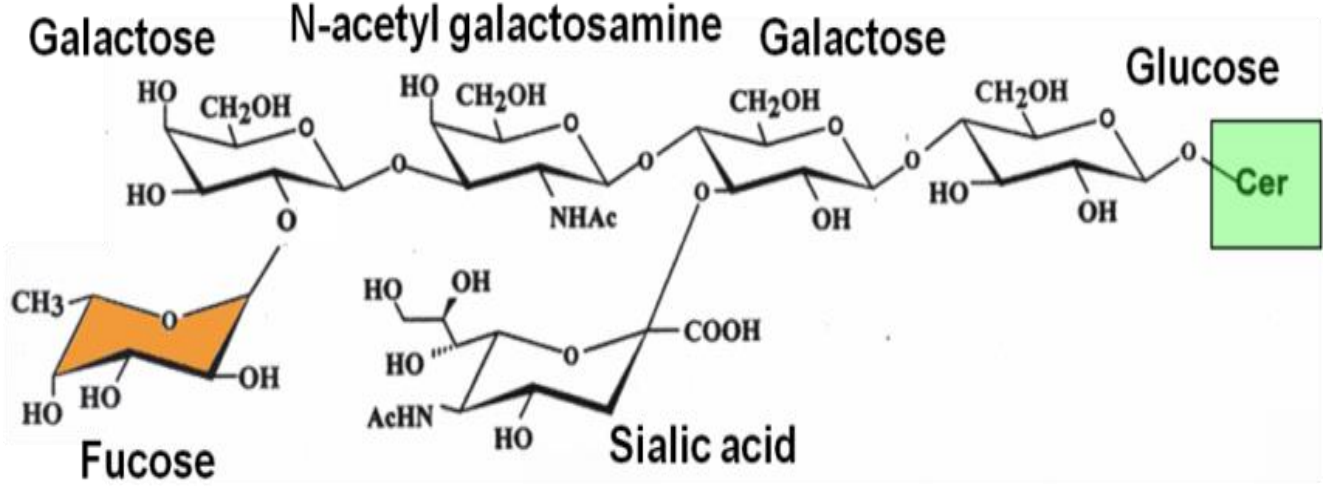
Giaccone et al, J Clin Oncol 2005

University of Maryland
Marlene and Stewart Greenebaum Cancer Center

## Gangliosides in SCLC

# Fucosyl-GM1: Background

- Ganglioside isolated from bovine thyroid gland.
- Identified by immunofluorescence using the monoclonal antibody F12 in 19/21 human SCLC tumors.
- Detected in culture media from SCLC cell lines, and in tumor extracts and serum of nude mouse xenografts.
- Detected in the serum of 6/20 patients with extensive stage SCLC but not in NSCLC patients or volunteers.




Courtesy of L. Krug

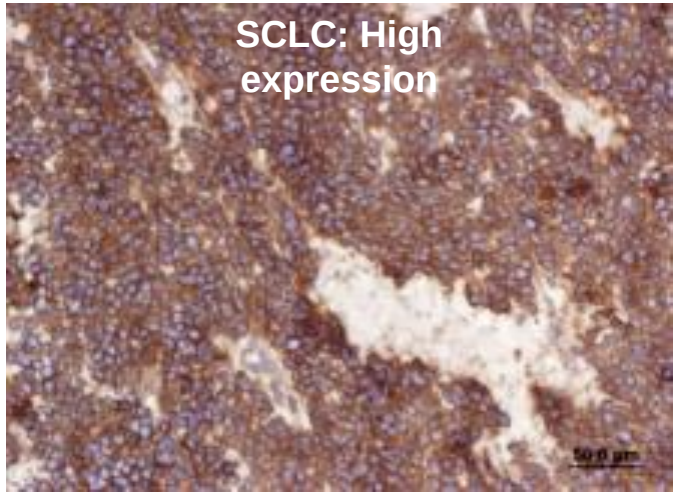


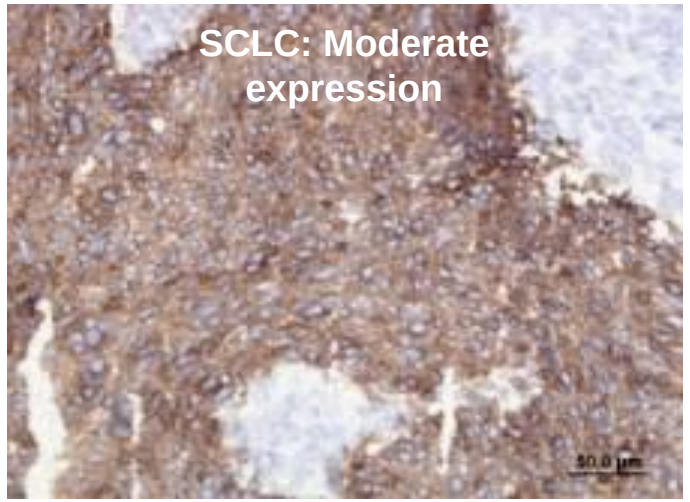
Macher, Biochim Biophys Acta, 1979
Brezicka, Cancer Res, 1989
Vangsted, Cancer Res, 1991

# Fucosyl GM1 Trial IHC Results

Prevalence of fucosyl GM1 by IHC (BMS analyses)

- ~50% (12 positive/24 total samples)



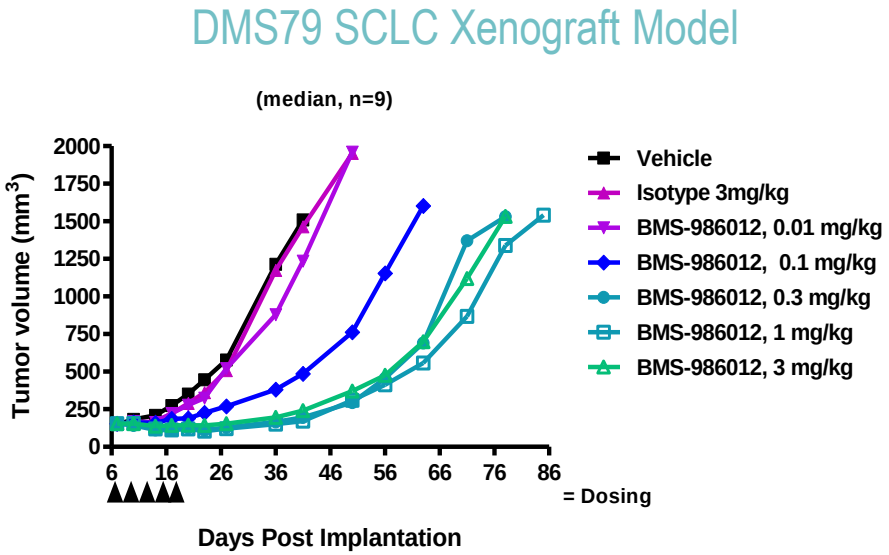




Prevalence of fucosyl GM1 in SCLC in the literature

- ~ 70% (89 positive/124 total samples)

# Anti-FucGM1 mAB BMS-986012

- First-in-class fully human IgG1 mAb
- High affinity and dose-dependent saturable binding to FucGM1 -- No binding to GM1
- Optimized for enhanced ADCC by elimination of fucosylation on Fc domain



Gangliosides in SCLC

# Phase I/II Trial with BMS-986012

## Phase I Dose Escalation

Eligibility: Ext or limited SCLC
At least 1 prior chemo regimen

Primary endpoint: Safety

| Dose level | BMS-986012 IV Q3W |
|---|---|
| 1 | 70 |
| 2 | 160 |
| 3 | 400 |
| 4 | 1000 |

## Phase II Expansion

Eligibility: Relapsed SCLC
One prior chemo regimen

Primary Endpoint: Response rate

| Cohort | Group | N |
|---|---|---|
| A | Refractory, MTD | 22 |
| B | Refractory, dose below MTD | 22 |
| C | Sensitive, MTD | 28 |
| D | Sensitive, dose below MTD | 28 |

Participating sites: MSKCC, Duke, Cross Cancer Institute, Monash Cancer Centre

NCI·CC
A Cancer Center Designated by the National Cancer Institute
Supported by Bristol-Myers Squibb

University of Maryland
Marlene and Stewart Greenebaum Cancer Center

# CAR-T CELLS

# CAR Rationale

**If endogenous T cell elicitation is difficult to due immunosuppressive microenvironment, then ex vivo T cell culture expansion should be considered**

Chimeric antigen receptor T cells provide advantages:

- HLA-independent
- Does not require stimulation by host immune system
- Targets SCLC antigens

Adapted from J. Heymach

# Potential CARs for SCLC

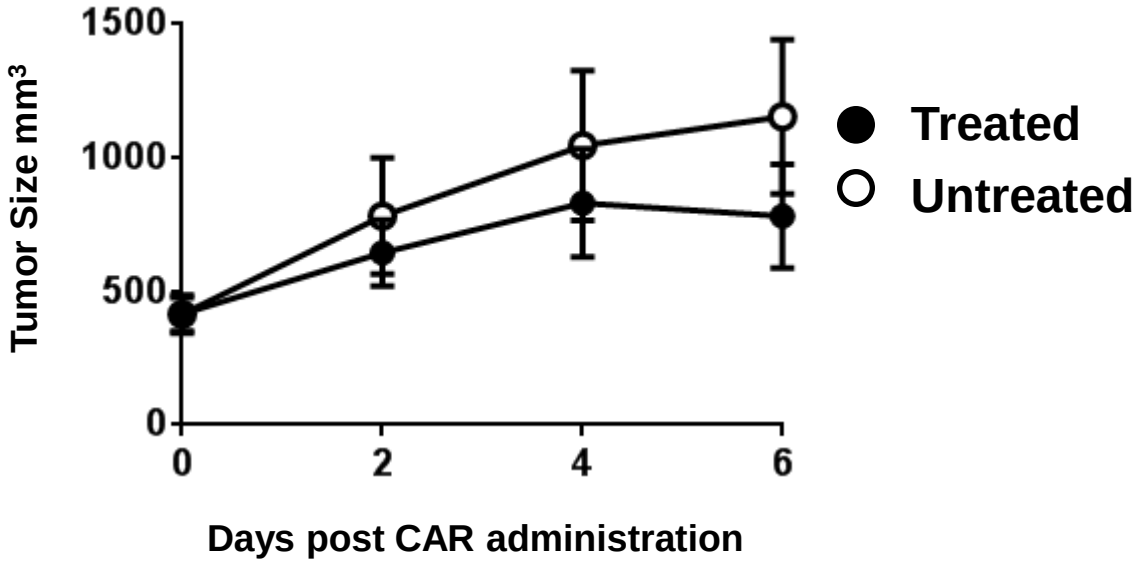
- 50% of patients detectable auto-antibodies to at least 1 target (e.g. p53, NY-ESO-1,CD56, SOX-2 etc).
- CD56 (NCAM) selected as initial candidate for CARs
  - highly expressed in SCLC and other malignancies
  - also expressed in neuronal tissue, lower expression in skeletal muscle, NK cells, and Tcells (potential fratricide)
  - ADCs have been tested with CD56

Distribution of NCAM in malignant tissues

| Malignoma | % NCAM positive |
|---|---|
| Neuroblastoma | ≈100% |
| Rhabdomyosarkoma | ≈100% |
| Glioma | ≈100% |
| Astrocytoma | ≈100% |
| Small cell lung cancer | ≈100% |
| Multiple myeloma | 78% |
| Acute myeloid leukemia | 53% |

Robertson et. al. CCR. 2011

# CD56R-CAR T cells control SCLC growth *in vivo*




**Early experiments (low dose CARs, 1 CAR: 20 tumor cells) indicate CAR T cells may control even well established tumors**



(Denning unpublished data) 2015, presented MSKCC

# Concerns

**CD56 is expressed on WT tissues (on target, off tissue)**
*Damage to the brain and other neural tissue possible similar to autoimmune already displayed in some SCLC patients.*

**Natural Killer cells loss**
*Would patient become more susceptible to viral infections or NK cells act as a "decoy" reducing CD56R-CAR killing at tumor site.*

**Antigen loss**
*Intense selection by CAR T cells may allow rapid generation of tumor escape variants most likely due to antigen loss*

# General Comments: Clinical Trial Design Issues

- Traditional designs
  - Combination with existing regimens: PE vs. PE + X (front line)
  - Second line in combination or against: Topo vs. Topo + X or Topo vs. X
- Problems
  - Requires excellent PS
  - Fails to recognize the real world presentation (very sick)
  - Fails to exploit the value of current therapy (high RR)
- Suggest
  - Consolidaton design:
  - PE -> X vs. PE

# Conclusions

- Improved understanding of SCLC biology has led to the identification of new targets/strategies.
- Notch targeting and immunotherapy are most advanced.
- Clinical trial design should be optimized for this disease