IRE
ISTITUTO NAZIONALE TUMORI
REGINA ELENA

CARCINOMA POLMONARE: QUALI NOVITÀ NEL 2022?

20 Maggio 2022

IRCCS "Sacro Cuore - Don Calabria"
Negrar di Valpolicella
Sala Perez

Coordinatore Scientifico: **Dr.ssa Stefania Gori**

SESSIONE IV
SCLC: dalla pratica clinica attuale alle prospettive future
Moderatori:
FILIPPO ALONGI - EMILIO BRIA

NUOVI TARGET E PROSPETTIVE FUTURE

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IRCCS IFO Istituto Nazionale Tumori
Regina Elena

CONFLITTI DI INTERESSE

- Speaker/adv board
  Astra Zeneca/Novartis/Amgen

- PI Studi Clinici
  Spectrum/Roche/Pfizer/Merck/Blueprint/BMS/Novartis/Astrazeneca

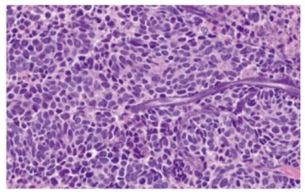
AGENDA

- GENOMIC AND GENE EXPRESSION SUBTYPES
- POTENTIAL THERAPEUTIC IMPLICATIONS OF MOLECULAR CLASSIFICATION
- NOVEL SYSTEMIC THERAPEUTIC APPROACH

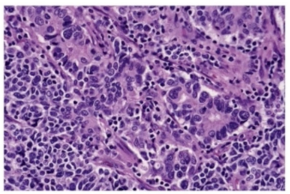
SCLC

HISTOLOGIC SUBTYPES

Pure SCLC (~80% cases)



Combined SCLC (~20% cases)



e.g., Adenocarcinoma

Travis et al., Clin Chest Med, 2020

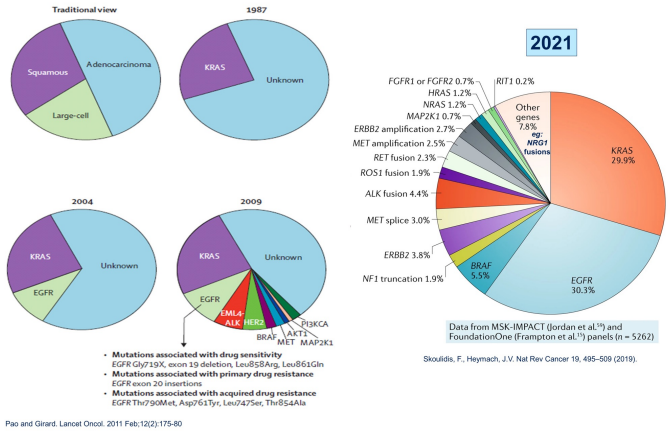
WHO Classification of Tumors 5th Edition, 2021

Less frequent
Only in smokers
Frail and comorbid patients
Older age
Lack of surgical tissue
Rapid course

NSCLC

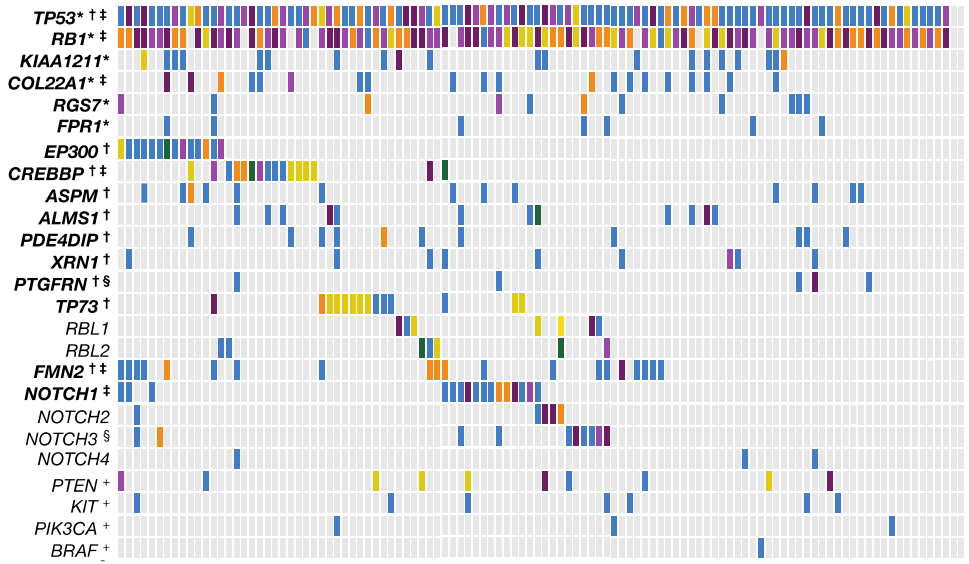
MOLECULAR ALTERATIONS

Evolution of Knowledge About 'Driver Mutations' in Non-Small Cell Lung Cancer



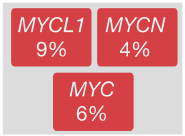
Pao and Girard. Lancet Oncol. 2011 Feb;12(2):175-80

FEW MUTUALLY EXCLUSIVE ONCOGENIC DRIVERS



- ~Universal loss of *RB1* and *TP53*
- *NOTCH* family 10-25%
- *PTEN, PIK3CA* 10-15%
- *CREBBP, EP300* 20-30%
- *KMT2D* 13%

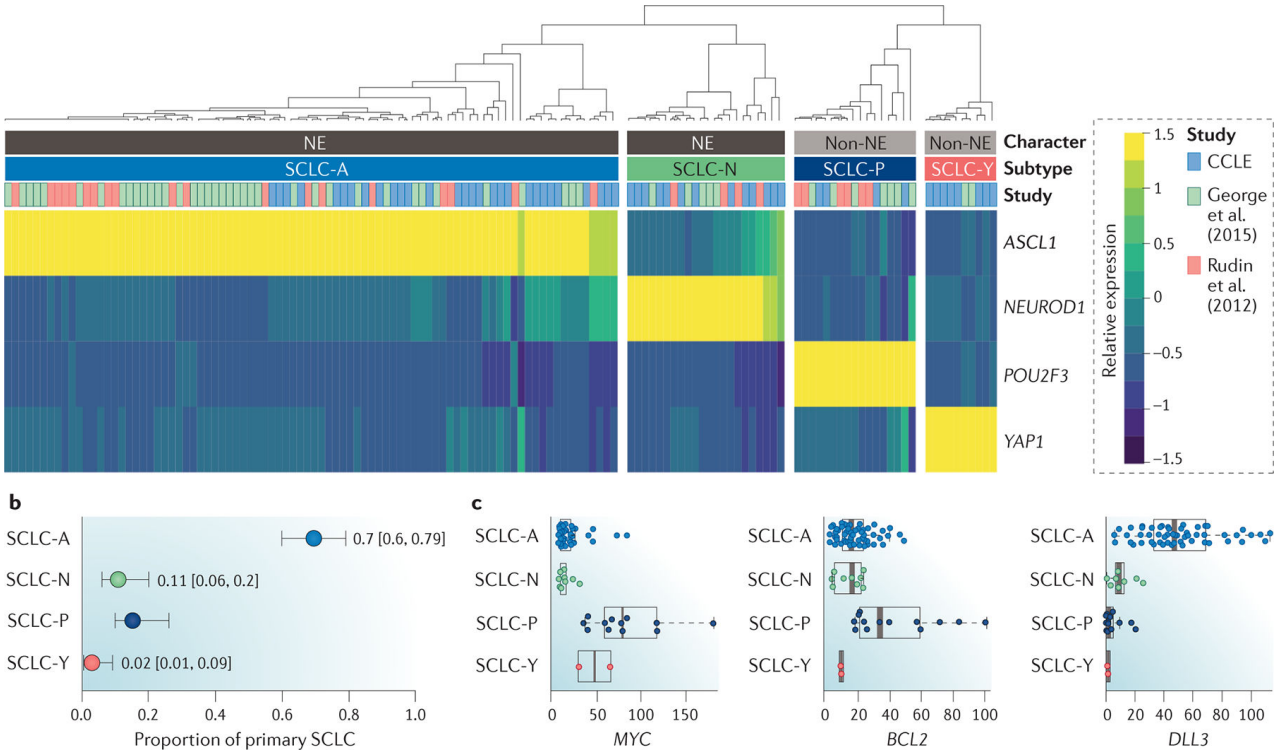
MYC family amplification 20-30%



George et al., Nature 2015

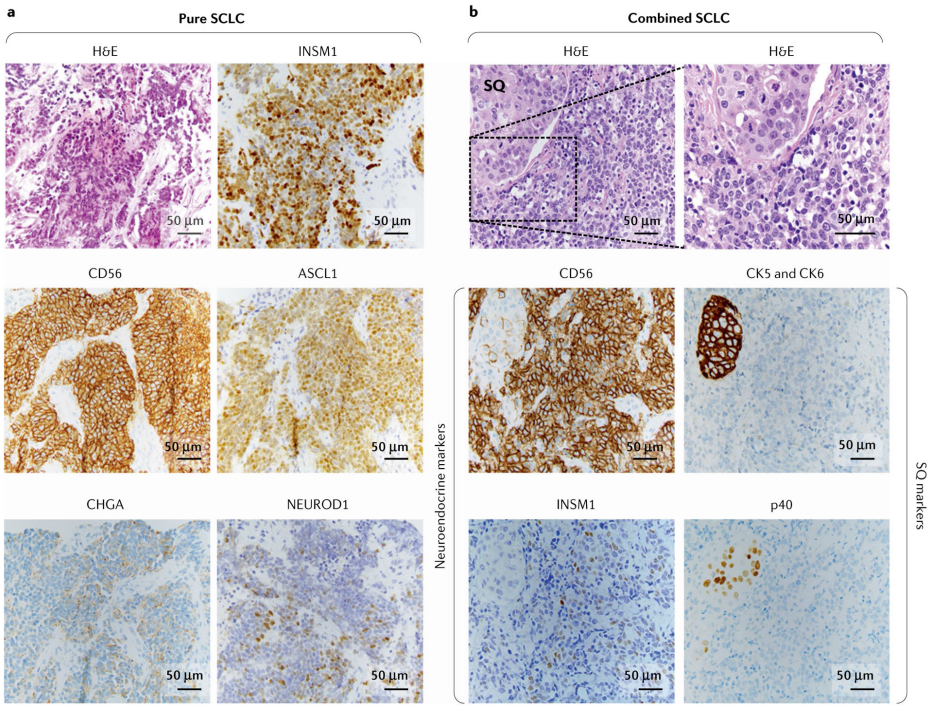
Rudin et al., Nature Reviews 2021

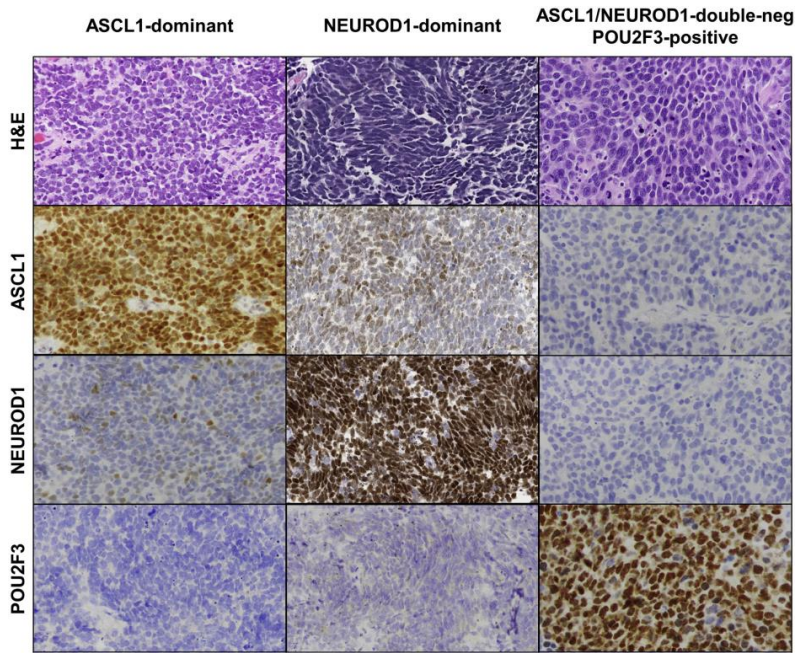
ANPY MOLECULAR SUBTYPES



Rudin et al Nat review cancer 2019

CAN BE IHC ASSESSED





Bain et al., JTO 2020

Rudin et al., Nat Rev Cancer 2019

GENE EXPRESSION: CHALLENGES

- Plasticity
- Heterogeneity

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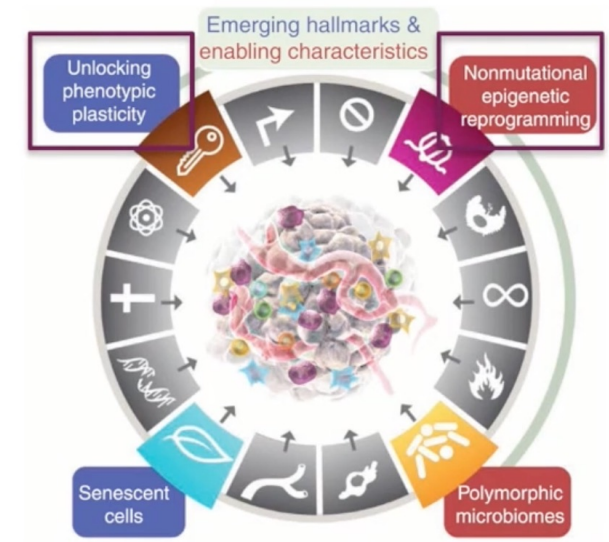
- Plasticity
- Heterogeneity

Hallmarks of Cancer: New Dimensions

Douglas Hanahan



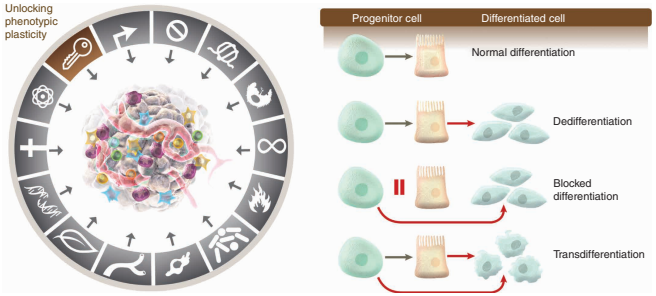
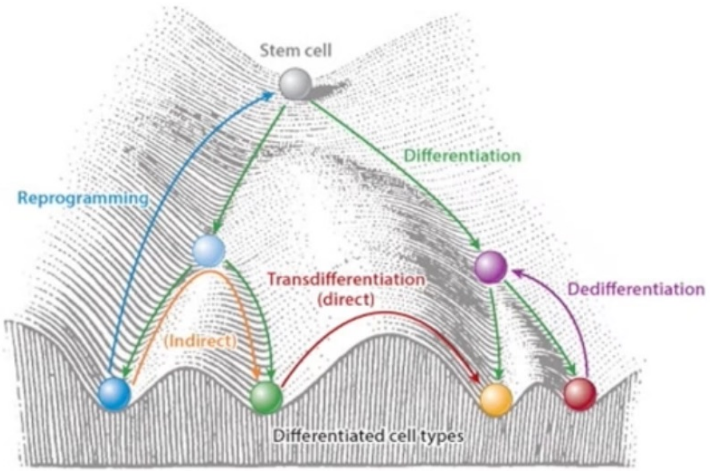
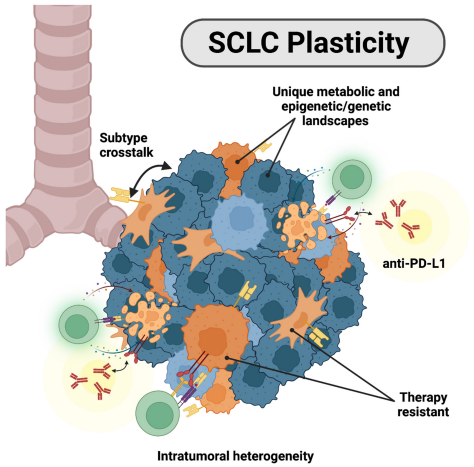


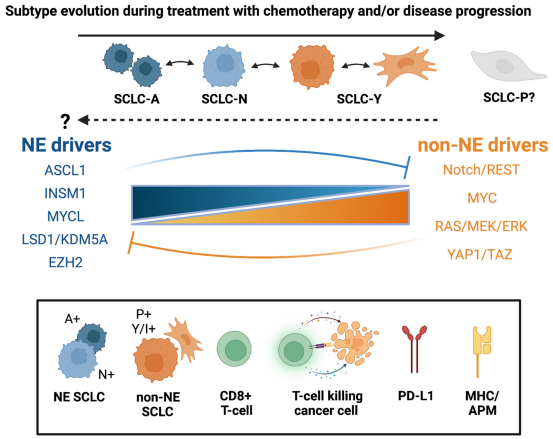
Figure 2. Unlocking phenotypic plasticity. Left, phenotypic plasticity is arguably an acquired hallmark capability that enables various disruptions of cellular differentiation, including (i) dedifferentiation from mature to progenitor states, (ii) blocked (terminal) differentiation from progenitor cell states, and (iii) transdifferentiation into different cell lineages. Right, depicted are three prominent modes of disrupted differentiation integral to cancer pathogenesis. By variously corrupting the normal differentiation of progenitor cells into mature cells in developmental lineages, tumorigenesis and malignant progression arising from cells of origin in such pathways is facilitated.

Hanahan, Cancer Discovery, 2022

Lineage plasticity is a property of normal cells and encompasses many cellular processes including trans-differentiation, dedifferentiation, and cellular reprogramming.



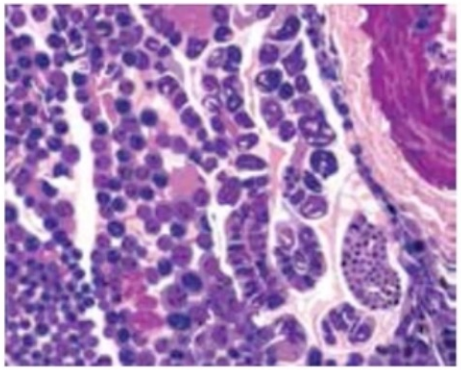




Sutherland et al. Genes & Development 2022

Lineage plasticity as a mechanism of targeted drug resistance

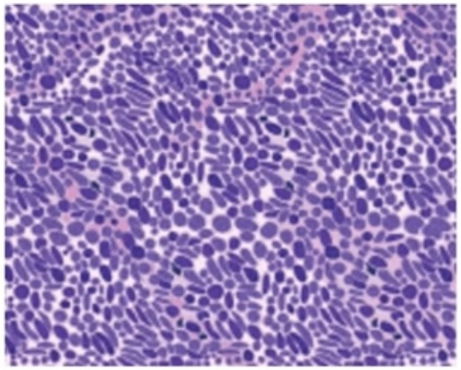
EGFR-mutant lung adenocarcinoma



TKI

— ? - ? →

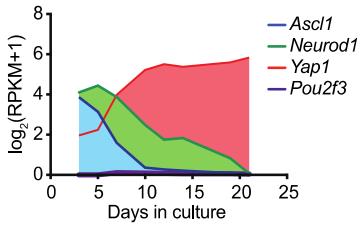
Small cell lung cancer



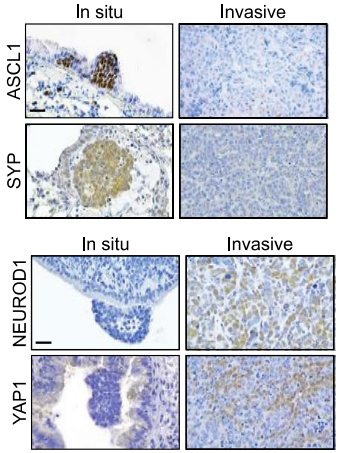
ESMO 2021

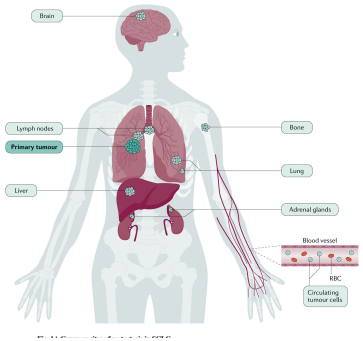
TEMPORAL HETEROGENEITY

In vitro:



In vivo:





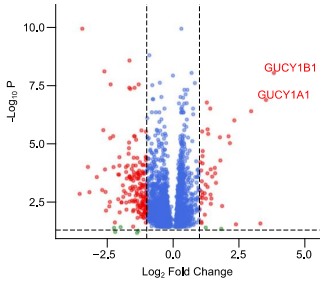
Mouse model of *MYC*^{high} variant SCLC evolves throughout tumorigenesis

- In culture premalignant cells change dominant TF expression over time
- Same occurs in the mouse, transitioning from *ASCL1*^{high} to mixed expression of *NEUROD1* and *YAP1*
- These subtypes may not be stable tumor features

Ireland et al., Cancer Cell 2020

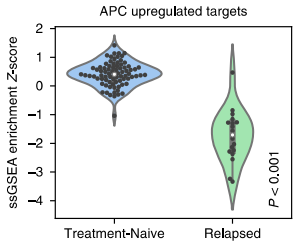
CHANGES IN RELAPSED RESISTANT SCLC

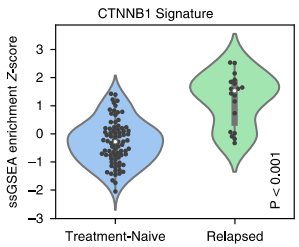
6 isogenic pairs of PDX models from CTCs derived pre-treatment and post-relapse



- Loss of SLFN11 expression
- Gain of EMT markers
- Loss of inflammatory markers
- Gain of MYC activity
- Gain of soluble guanylate cyclase (sGC)

Paired biopsy samples from patients before and after 1st line therapy

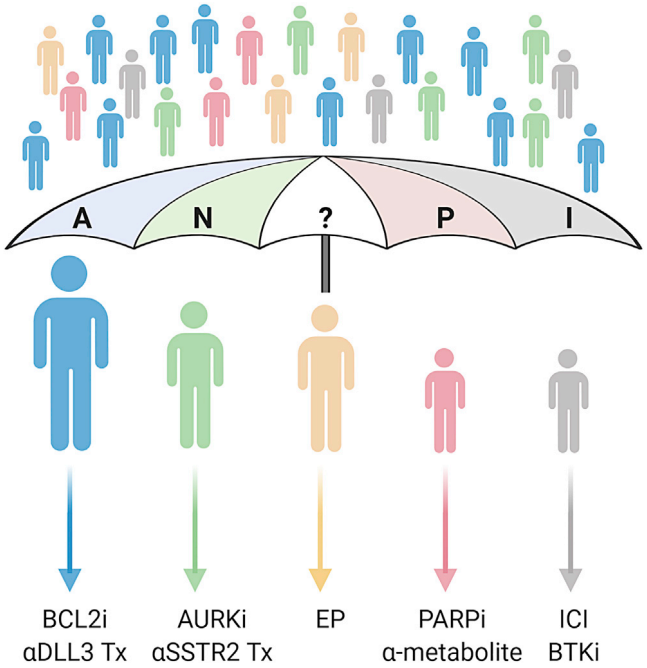


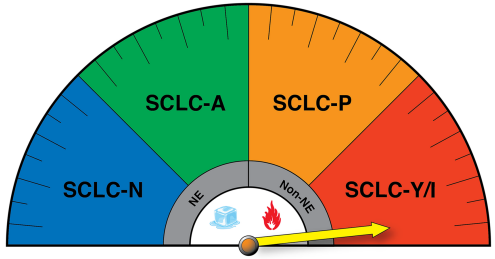


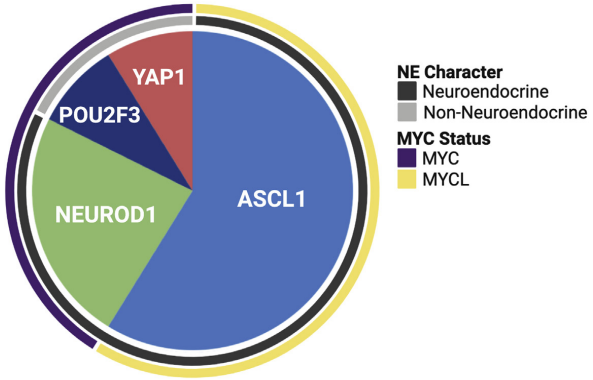
- Loss of SLFN11 expression
- Gain of EMT markers
- Loss of inflammatory markers
- Gain of MYC activity
- Gain of soluble guanylate cyclase (sGC)
- Gain of WNT signaling

Wagner et al Nature Communications, 2018
Schenk et al Nature Communications, 2022

POTENTIAL THERAPEUTIC IMPLICATIONS OF MOLECULAR CLASSIFICATION



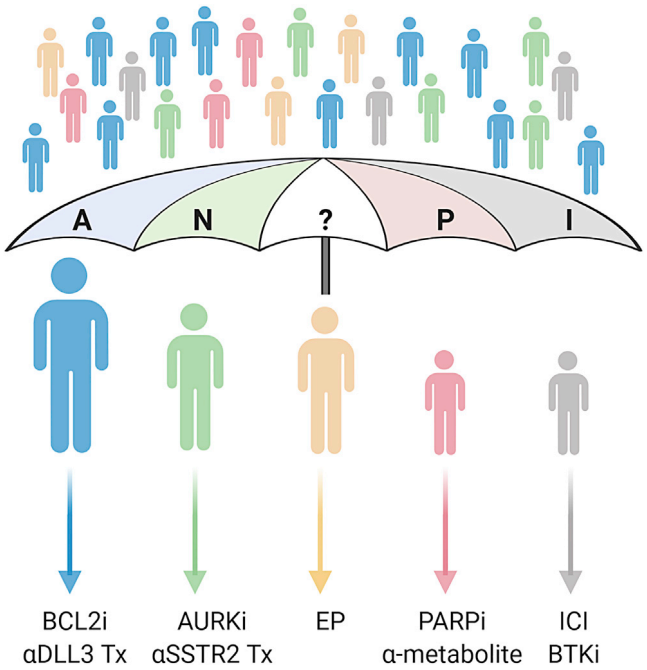


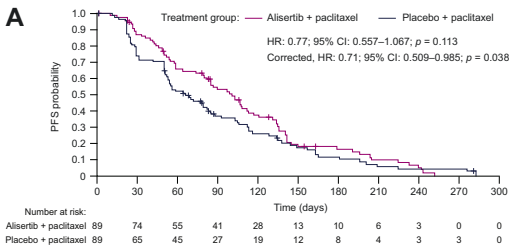


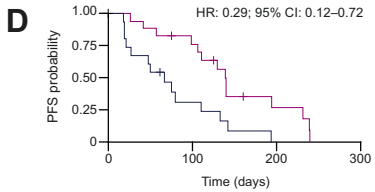
	ASCL1	NEUROD1	POU2F3	YAP1
Targeted Therapies	BCL2 CREBBP DLL3 LSD1	Arginine Deprivation AURKA/B CHK1 IMPDH LSD1	Arginine Deprivation AURKA/B CHK1 IGF-R1 IMPDH	Arginine Deprivation AURKA/B CHK1 IMPDH IO

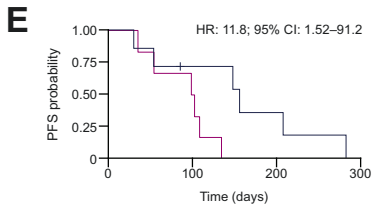
Frese cancer cell 2021
Suterland 2022
Poirier Nat Gen 2021

POTENTIAL THERAPEUTIC IMPLICATIONS OF MOLECULAR CLASSIFICATION





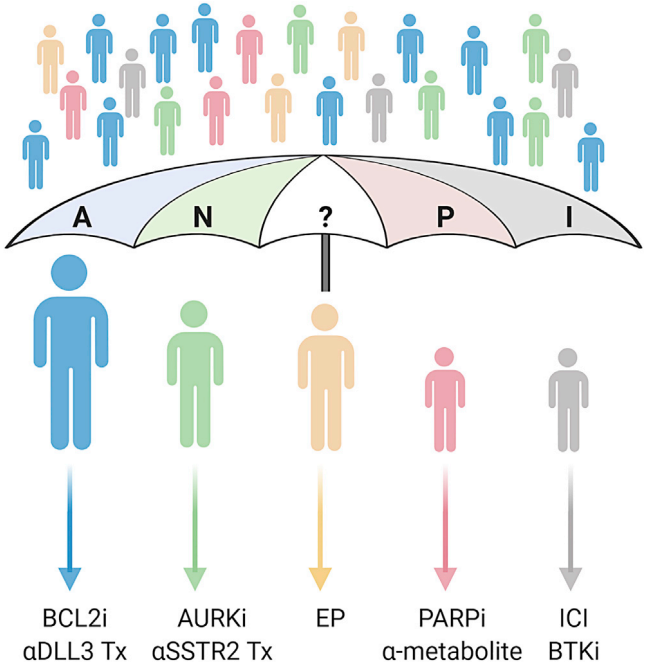


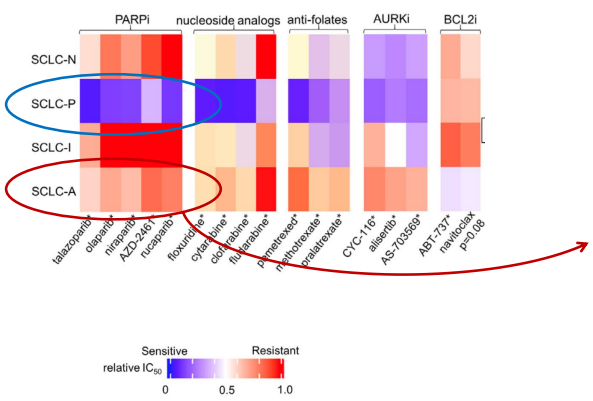


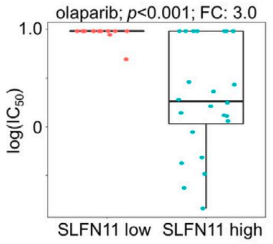
- Alisertib (AAK inhibitor)
- 178 patients randomized to paclitaxel + alisertinib/placebo
- • No difference in PFS (primary endpoint)
  • Among patients with mutations in cell cycle regulators, alisertib superio
- Improved PFS (HR 0.395)
- Improved OS (HR 0.427)

Frese cancer cell 2021
Owonikoko JTO 2020

POTENTIAL THERAPEUTIC IMPLICATIONS OF MOLECULAR CLASSIFICATION



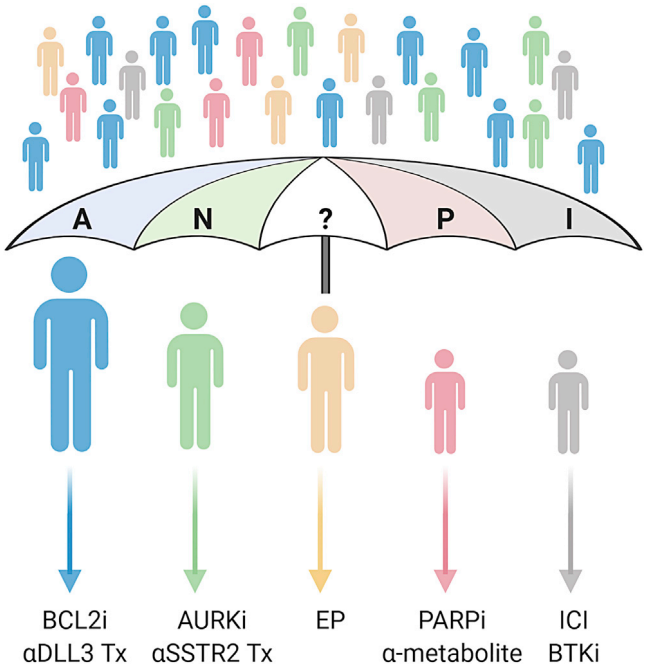


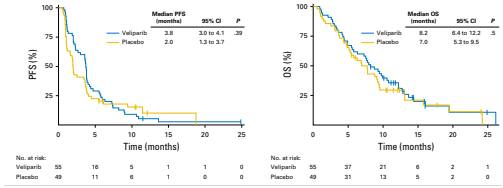


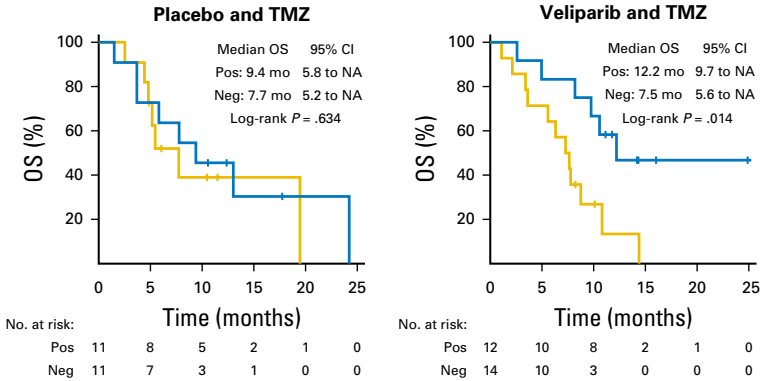
Gay et al., *Cancer Cell* 2021

Frese cancer cell 2021

POTENTIAL THERAPEUTIC IMPLICATIONS OF MOLECULAR CLASSIFICATION





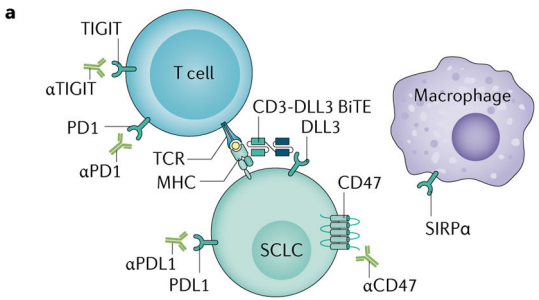


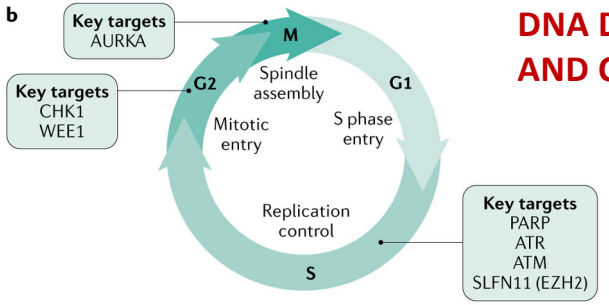
- Modest activity of PARP inhibitors in SCLC
- Schlafen-11 (SLFN11)
- Expression can sensitize cells to DNA-damaging agents
- Veliparib added to temozolomide improved outcomes in SLFN11+
- Not seen in SLFN-11 negative

Frese cancer cell 2021
Pietanza JCO 2019

Representative therapeutic targets of interest in SCLC

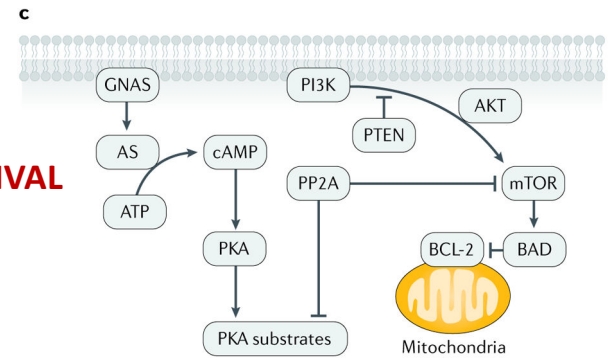
IMMUNOTHERAPY

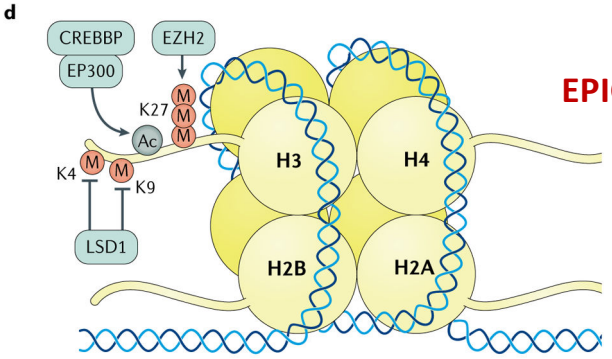




DNA DAMAGE REPAIR AND CELL CYCLE CHECKPOINT

GROWTH AND SURVIVAL SIGNALING





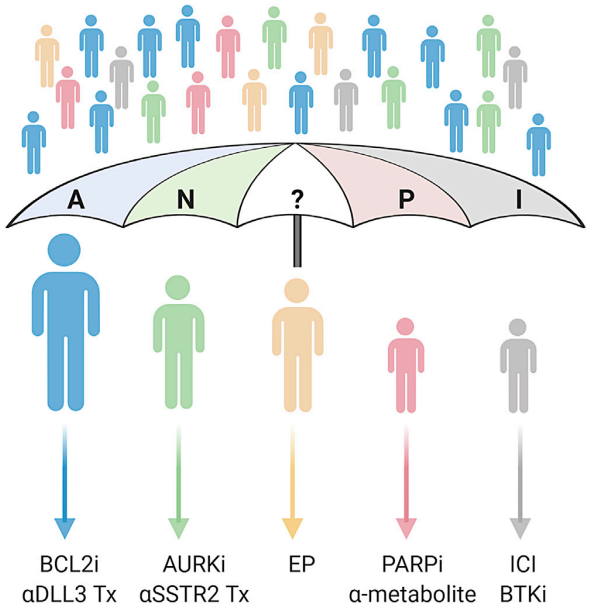
EPIGENETIC REGULATORS

Rudin , Nat Rev Dis Primers 2021

NOVEL SYSTEMIC THERAPEUTIC APPROACH

- Biomarker-based treatment
- Improve immunotherapy in first line(combinations-immunomodulation-antiagiogenic drugs)
- Early adoption of immunotherapy in Limited Disease
- New drug development (salvage therapy)

BIOMARKER-DRIVEN



Pathway	Target	Functional description	NCT#	References
Proliferation and survival	AURKA/B	Kinase, microtubule formation and spindle stabilization	03898791	81, 82
			04525391	
	PI3K	Oncogene Kinase inhibited by PTEN	02194049	83
	mTOR	TORC1 and TORC2 regulate growth	01737502	84, 85
	PP2A	Serine/threonine phosphatase, regulates Raf, MET and AKT	04560972	76
	BCL-2	Inhibitor of apoptosis	00005032	86
			03387332	
			03080311	
			03366103	
DNA damage and repair	ATR	DNA damage checkpoint kinase	04514497	87
			04768296	
			02487095	
	CHK1	Cell cycle checkpoint Kinase	02735980	88
	WEE1	Cell cycle check point kinase	02593019	89
	PARP1	ssDNA damage repair	01286987	42, 90
			01638546	
			01642251	
	CDK7	Link transcription to cell cycle, DNA repair, transcription		91
Epigenetic regulator	EZH2	Transcriptional repression of genes	03460977	77, 78
	LSD1 (KDM1A)	Gene silencing by demethylation	02034123	92, 93
Immune Checkpoint	PD-1	Immune check point	multiple	
	PD-L1	Immune checkpoint	multiple	
	TIGIT	Immune checkpoint	04256421	
	CD47	Leukocyte surface antigen, receptor for SIRPa, inhibits production of cytokine by DC		94
Others (ADC or SMDC)	DLL3	Counteract NOTCH1 function	04471727	35
			03319940	
	TROP-2		01631552	46
	SSTR2		02936323	48

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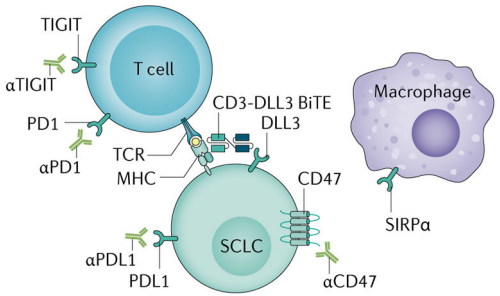
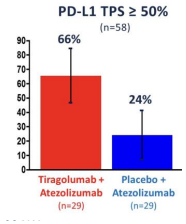
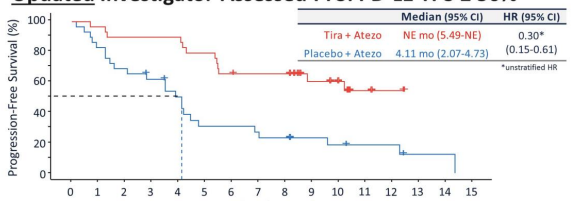


CITYSCAPE NSCLC





Phase III trial： Tiragolumab: Anti-TIGIT antibody

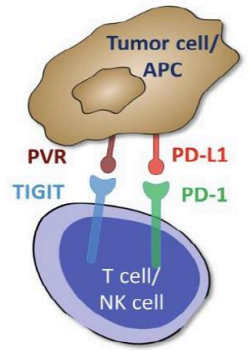


Figure adapted from Manieri et al.
Trends Immunology 2017

ES-SCLC

Key eligibility

- All-comer
- Untreated metastatic measurable ES-SCLC
- ECOG PS 0 or 1
- No prior systemic treatment
- Treated or untreated asymptomatic brain metastases are eligible

N≈400

R 1:1

Induction (4 x 21 day cycles)

Day 1: Tiragolumab 600mg IV Q3W + atezolizumab 1200mg IV Q3W + carboplatin IV AUC 5mg/mL/min

Day 1–3: Etoposide IV 100mg/mg²

Day 1: Placebo 600mg IV Q3W + atezolizumab 1200mg IV Q3W + carboplatin IV AUC 5 mg/mL/min

Day 1–3: Etoposide IV 100mg/m²

Maintenance (21 day cycles)

Tiragolumab 600mg IV Q3W + atezolizumab 1200mg IV Q3W

Placebo 600mg IV Q3W + atezolizumab 1200mg IV Q3W

Treat until progression, loss of clinical benefit, or unacceptable toxicity

No crossover

Stratification: ECOG PS (0 vs 1); LDH (≤ULN vs >ULN); brain metastases (yes vs no)

For the first 24 randomised patients (approximately 12 per arm), safety and tolerability data will be assessed by an independent Data Monitoring Committee

Co-primary endpoints

- PFS by investigator assessment according to RECIST v1.1
- OS

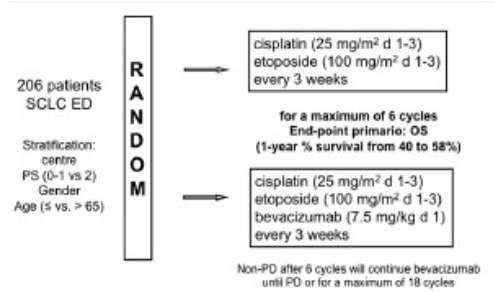
NCT04256421

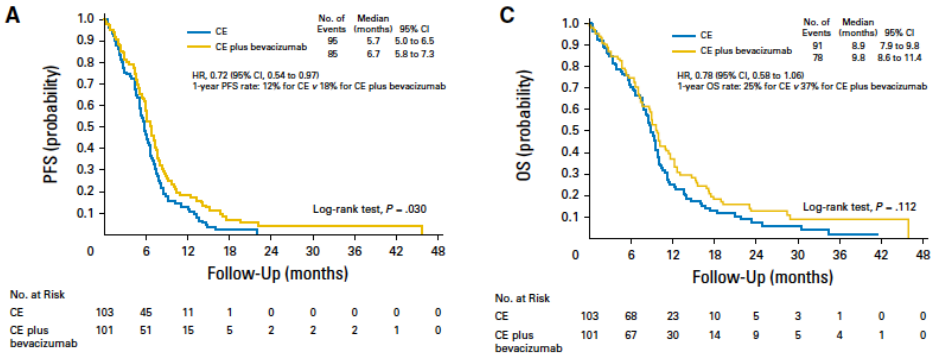
UNIVERSITÀ DI PARMA

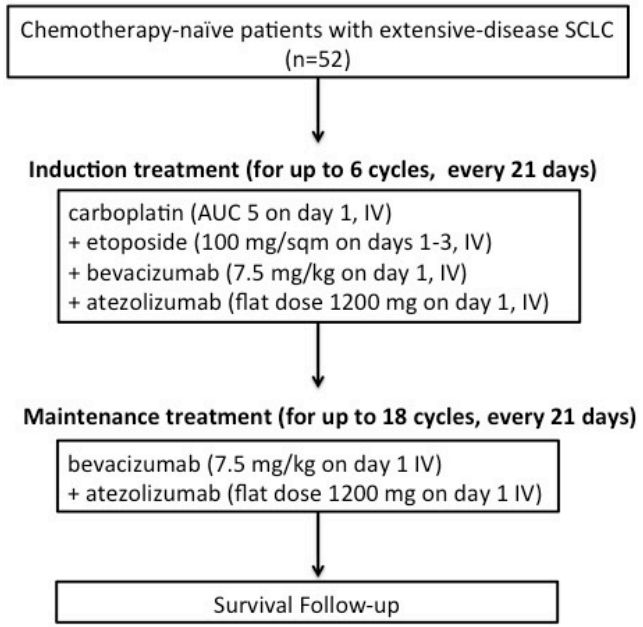
SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Parma

A phase II study of CarbopLatin plus Etoposide with Bevacizumab and Atezolizumab in patients with exTEnded-disease small-cell lung cancer (SCLC) CeLEBrATE trial

GOIRC
GRUPPO ONCOLOGICO ITALIANO DI RICERCA CLINICA







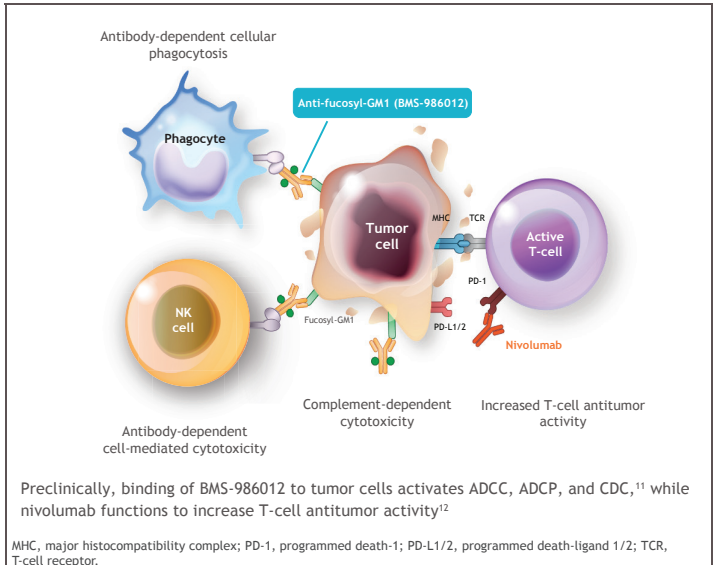
AUC = area under the concentration-time curve; IV = intravenous; SCLC = small-cell lung cancer

Tiseo et al, J Clin Oncol 2017

FUCOSYL-GM1

- Fucosyl-GM1 highly expressed on SCLC
  - Inhibition of fucosylation associated with NK binding and ADCC
- BMS-986012 is an anti-fucosyl-GM1 IgG1 mAb
- Phase I/II of BMS-968012 + Nivolumab: RR in SCLC 38% (11/29), mDOR 26.2m

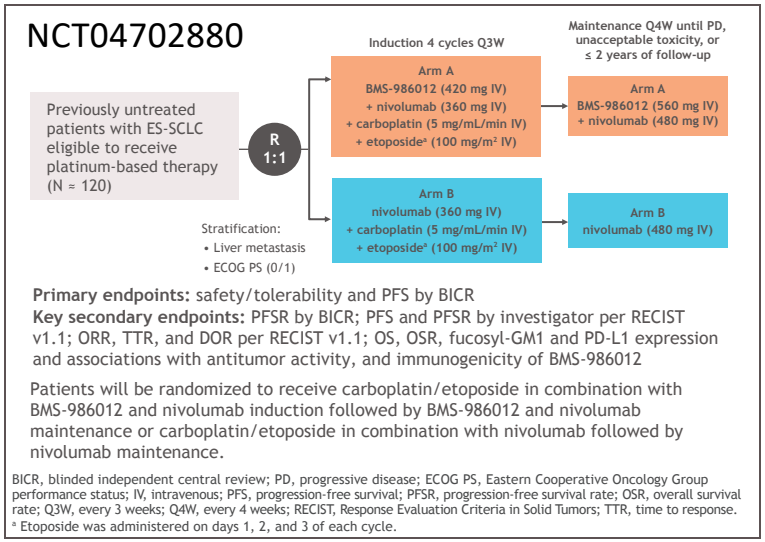
Figure 1. BMS-986012 and nivolumab mechanism of action



Preclinically, binding of BMS-986012 to tumor cells activates ADCC, ADCP, and CDC,[11] while nivolumab functions to increase T-cell antitumor activity[12]

MHC, major histocompatibility complex; PD-1, programmed death-1; PD-L1/2, programmed death-ligand 1/2; TCR, T-cell receptor.

Figure 2. Study design

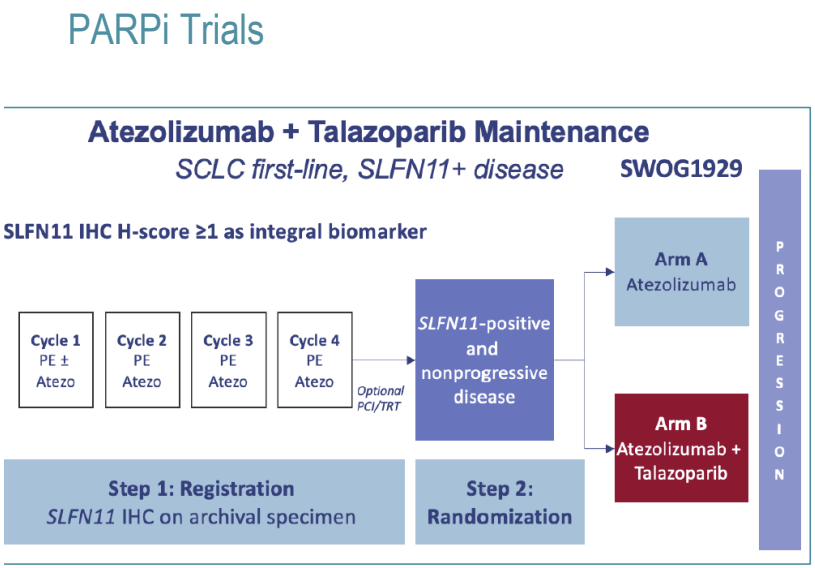


Primary endpoints: safety/tolerability and PFS by BICR
Key secondary endpoints: PFSR by BICR; PFS and PFSR by investigator per RECIST v1.1; ORR, TTR, and DOR per RECIST v1.1; OS, OSR, fucosyl-GM1 and PD-L1 expression and associations with antitumor activity, and immunogenicity of BMS-986012

Patients will be randomized to receive carboplatin/etoposide in combination with BMS-986012 and nivolumab induction followed by BMS-986012 and nivolumab maintenance or carboplatin/etoposide in combination with nivolumab followed by nivolumab maintenance.

BICR, blinded independent central review; PD, progressive disease; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenous; PFS, progression-free survival; PFSR, progression-free survival rate; OSR, overall survival rate; Q3W, every 3 weeks; Q4W, every 4 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; TTR, time to response.
[a] Etoposide was administered on days 1, 2, and 3 of each cycle.

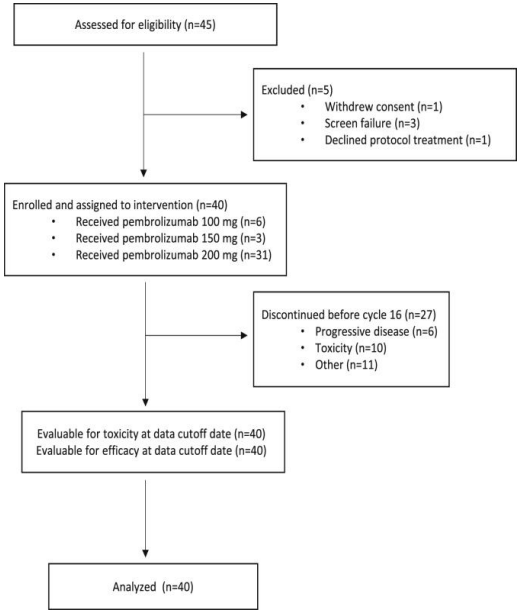
ONGOING TRIALS IN ADVANCED DISEASE: PARPi and anti-PD1

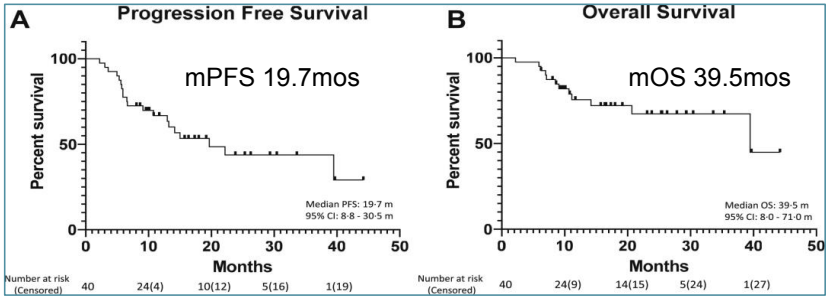


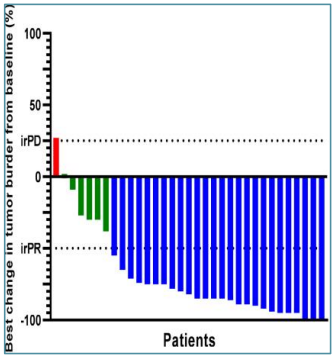
IO + PARPi	R Ph II Maintenance Atezo +/- Talazoparib in SLFN11+ ES SCLC NCT04334941
	Ph II Niraparib + Dostarlimab in SCLC/HGNEC NCT04701307
RT + PARPi	Ph I/II PARPi + RT + IO in ESCLC: PRIO trial NCT04728230
	Ph I Talazoparib + Consolidative TRT in ES SCLC NCT04170946
	Maintenance TRT+Durva vs. Durva/Treme vs Durva/Olaparib in ES SCLC after 1st-line NCT03923270

IMMUNOTHERAPY IN LIMITED DISEASE

Phase 1/2 Trial of Pembrolizumab and Concurrent Chemoradiation Therapy for Limited-Stage SCLC







- MTD could not be determined
  - 200mg dose selected ph II portion
- ORR 79% (3 CRs; 23 PRs)
- Phase 1 portion: 1 DLT
- 3 grade 4 events
- Incidence of pneumonitis: 15%

Welsh et al JTO 2020

IMMUNOTHERAPY CONCURRENT TO CT/RT

ONGOING TRIALS

Agent	ICI class	Phase	n	Primary Endpoint
Atezolizumab (LU005)	PD-L1	II/III	506	PFS or OS
Durvalumab	PD-L1	II	51	2 yr OS
Durvalumab (DOLPHIN)	PD-L1	II	105	PFS
Sintilimab	PD-1	II	140	PFS
Pembrolizumab (concurrent); pembro + Olaparib consolidation (KEYLYNK-013)	PD-1 + PARPi	III	672	PFS, OS

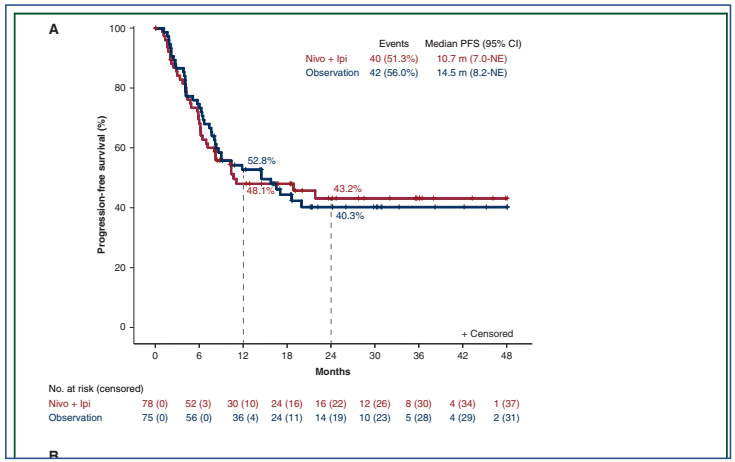
CONSOLIDATION IMMUNOTHERAPY AFTER CT/RT

ONGOING TRIALS

Agent	ICI class	Phase	n	Primary Endpoint
Ipilimumab + Nivolumab (STIMULI)	PD-1 + CTLA-4	II	174	PFS
Atezolizumab (ACHILLES)	PD-L1	II	212	2 yr OS
Atezolizumab +/- Tiragolumab	PD-L1 + TIGIT	II	150	PFS
Durvalumab +/- Tremelimumab (ADRIATIC)	PD-L1+ CTLA-4	III	724	PFS, OS
SHR 1613	PD-1	II	60	PFS
Toripalimab	PD-1	II	170	PFS

Consolidation nivolumab and ipilimumab versus observation in limited-disease small-cell lung cancer after chemo-radiotherapy — results from the randomised phase II ETOP/IFCT 4-12 STIMULI trial

ANNALS OF ONCOLOGY
driving innovation in oncology



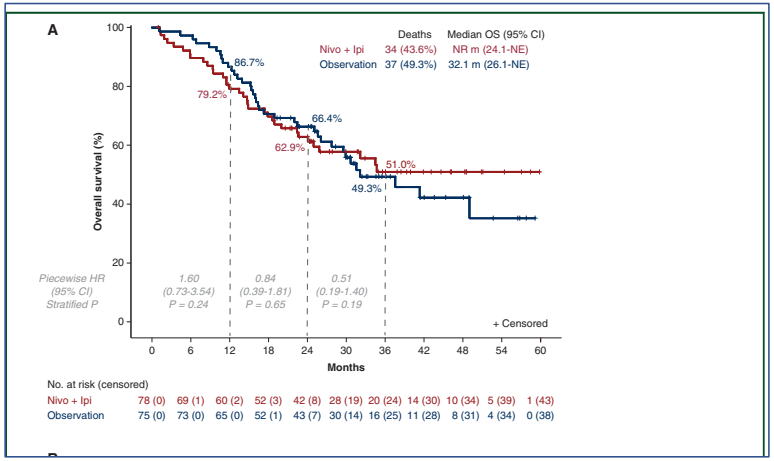
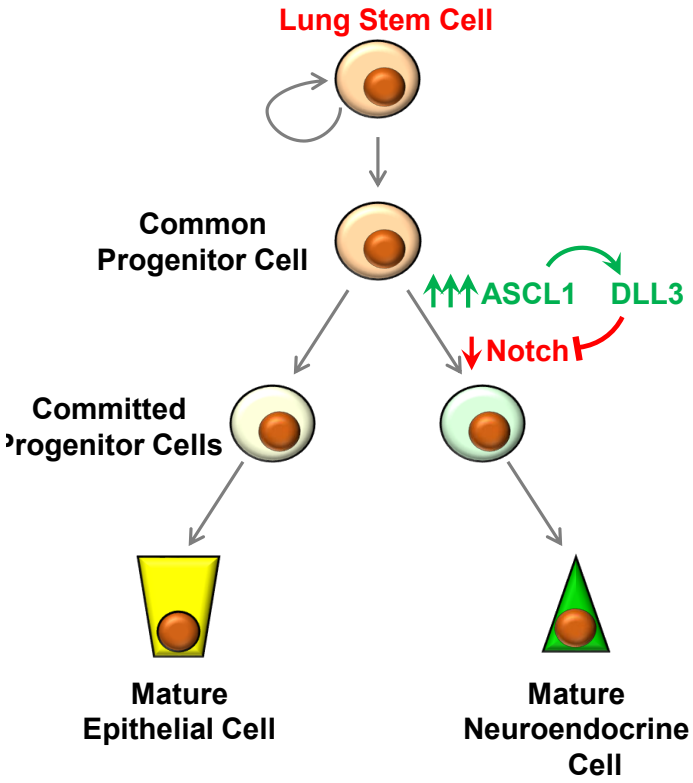
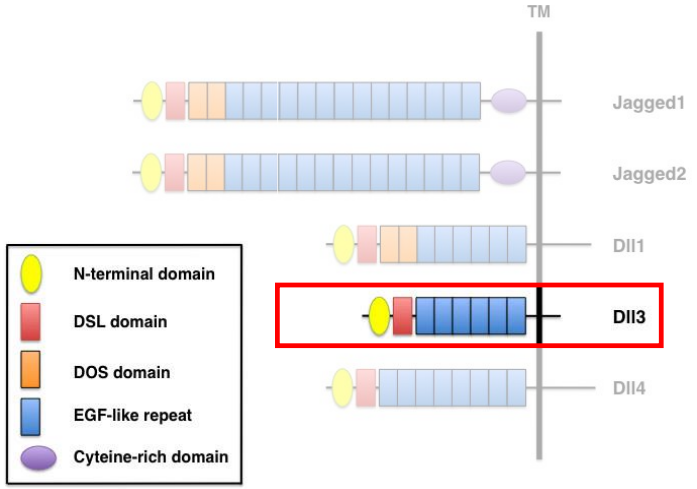


Table 2. Safety information of the as-treated cohort

	Nivo + Ipi (n = 78)		Observation (n = 75)	
	Number of patients (%)			
Any adverse event	77 (98.7)		65 (86.7)	
Treatment related adverse events	75 (96.2)		—	
Adverse events of grade ≥3	48 (61.5)		19 (25.3)	
Adverse events leading to treatment discontinuation	43 (55.1)		—	
Adverse events leading to death	4[a] (5.1)		1[b] (1.3)	
AEs occurring in ≥15% of the patients in either arm	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**
Fatigue	38 (48.7)	7 (9.0)	21 (28.0)	—
Anorexia	25 (32.1)	5 (6.4)	12 (16.0)	—
Diarrhoea	22 (28.2)	7 (9.0)	6 (8.0)	—
Vomiting	21(26.9)	1 (1.3)	5 (6.7)	—
Pneumonitis	22 (28.2)	7 (9.0)	4 (5.3)	1 (1.3)
Nausea	19 (24.4)	2 (2.6)	6 (8.0)	—
Cough	20 (25.6)	—	5 (6.7)	—
Hyperthyroidism	22 (28.2)	2 (2.6)	1 (1.3)	1 (1.3)
Anaemia	7 (9.0)	1 (1.3)	13 (17.3)	1 (1.3)
Dyspnoea	13 (16.7)	1 (1.3)	6 (8.0)	1 (1.3)
Pruritus	19 (24.4)	1 (1.3)	—	—
Constipation	15 (19.2)	1 (1.3)	3 (4.0)	—
Hypothyroidism	13 (16.7)	—	—	—

DLL3 IS A DOMINANT INHIBITOR OF NOTCH SIGNALING

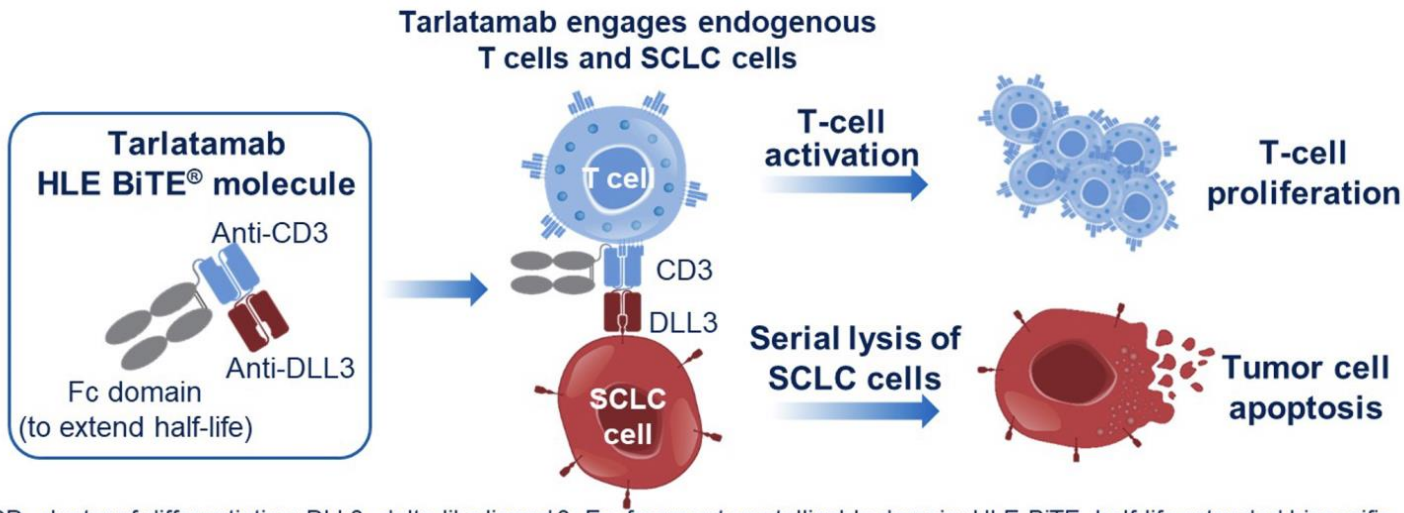




- Normally expressed during development in the Golgi
- Interacts with and inhibits Notch1 in *cis*
- Aberrantly (surface) expressed in SCLC and other NE tumors

Kume *et al.*, *J Angiogen Res* 2009

TARLATAMAB: bispecific T cell engager (BiTE) targeting DDL3 and CD3

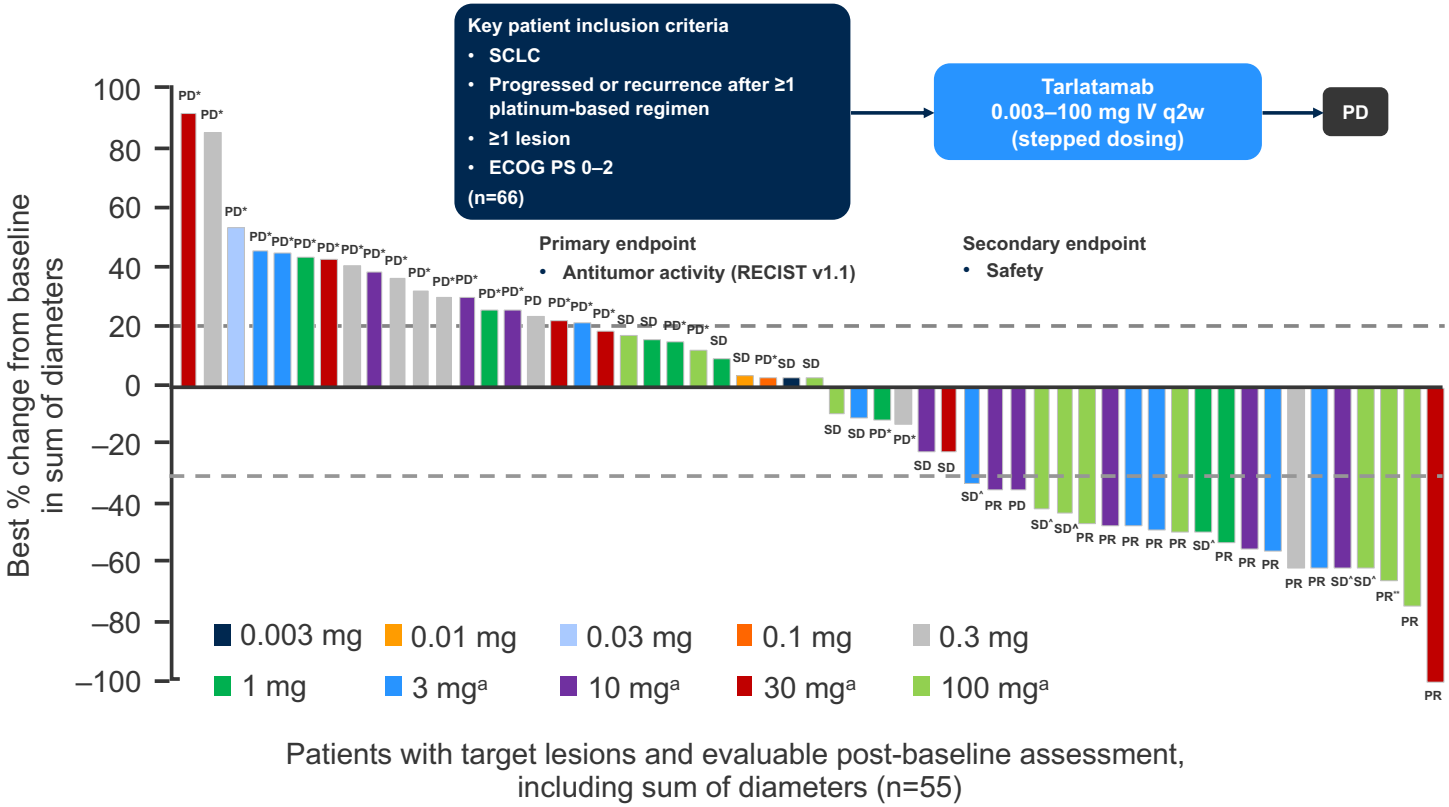


CD, cluster of differentiation; DLL3, delta-like ligand 3; Fc, fragment crystallizable domain; HLE BiTE, half-life extended bispecific T-cell engager; SCLC, small cell lung cancer.

- Single arm Phase I study: RR 20%, mTTR 1.8m, mDOR 8.7m, n=66
- TRAEs leading to discontinuation in only 5%
- CRS in 44% (2% G3)

Owonikoko et al ASCO 2021

TARLATAMAB



Patients with target lesions and evaluable post-baseline assessment, including sum of diameters (n=55)

Response, n/N (%)	Patients (n=64)[a]
PR, confirmed	13 (20)
0.3 mg	1/12 (8)
1 mg	1/8 (13)
3 mg	4/11 (36)
10 mg	3/10 (30)
30 mg	1/8 (13)
100 mg	3/11 (27)
PR, unconfirmed	1 (2)
100 mg	1/11 (9)
SD	17 (27)
DCR, %	30 (47)

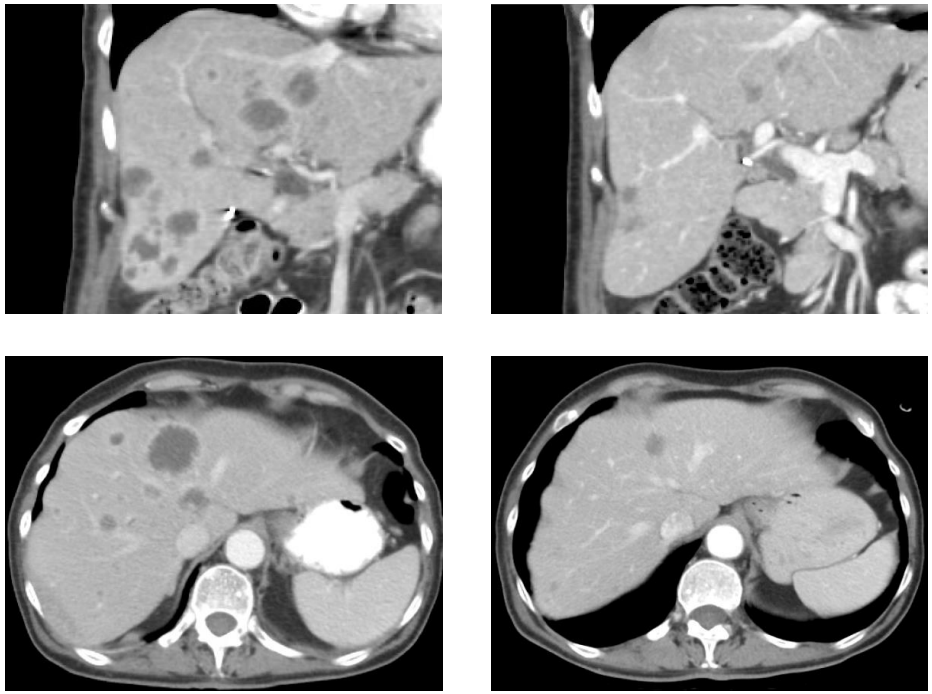
- Single arm Phase I study: RR 20%, mTTR 1.8m, mDOR 8.7m, n=66
- TRAEs leading to discontinuation in only 5%
- CRS in 44% (2% G3)

Owonikoko TK et al, ASCO 2021

AMG 757: EXEPTIONAL RESPONSE IN ADV-SCLC

Pre-treatment

2 cycles DLL3-BiTE



PR > 12 months

Rudin ESMO 2021

Phase 2 Study of Tarlatamab, a Half-Life Extended Bispecific T-cell Engager (HLE BiTE®) Immuno-oncology Therapy Targeting DLL3, in Third-line or Later Small Cell Lung Cancer (DeLLphi-301 Study)

Figure 1. Tarlatamab: A HLE BiTE® Therapy Targeting DLL3

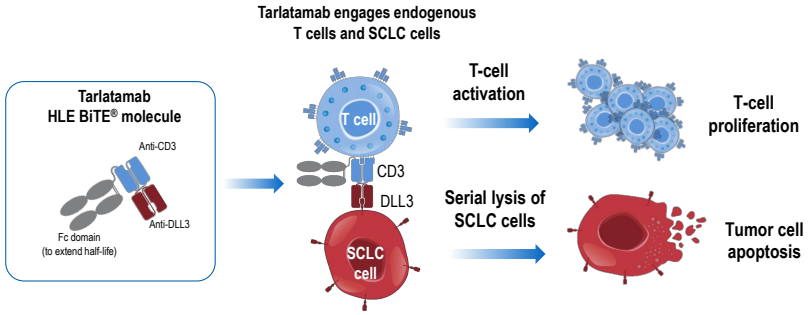
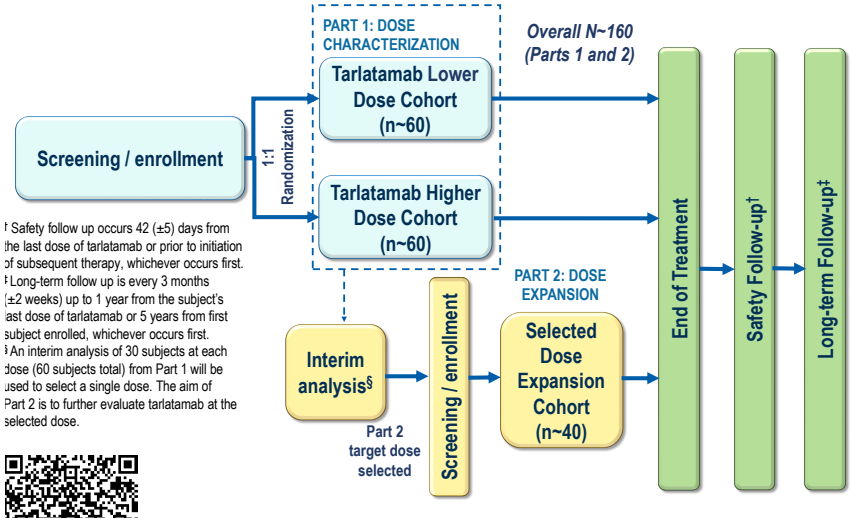
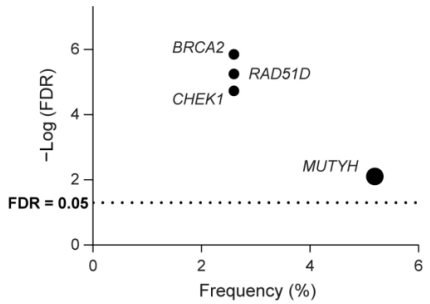


Figure 2. Study Design - Phase 2 Study of Tarlatamab in 3L or Later SCLC (DeLLphi-301 Study)



- Adults with histologically or cytologically confirmed SCLC
- Progressed/recurred after two or more lines of prior treatment including at least 1 platinum-based chemotherapy regimen (including a PD-L1 inhibitor, if standard of care, with certain exceptions per protocol)
- ECOG performance status ≤1
- Treated brain metastases permitted provided defined criteria are met

GERMLINE VARIANTS IN DNA REPAIR GENES



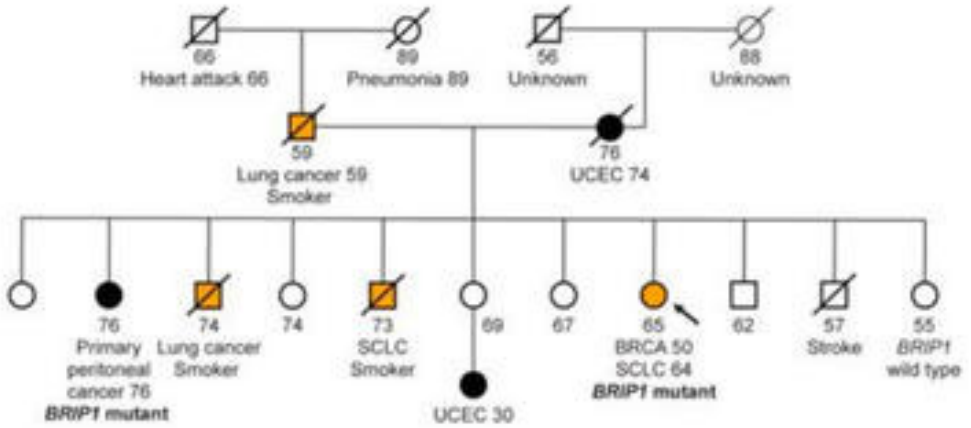
87 patients for discovery, 79 for validation

- ~Universal loss of *RB1* and *TP53*
- *NOTCH* family 10-25%
- *PTEN, PIK3CA* 10-15%
- *CREBBP, EP300* 20-30%
- *KMT2D* 13%
- *MYC* family amplification 20-30%
- *MUTYH* germline ~5%

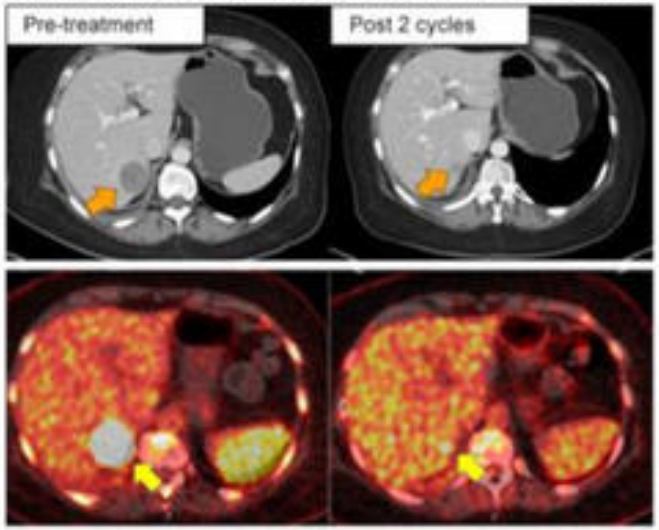
Tlemsani et al., Science Transl Med 2021

Major response to DNA damaging agents in a *BRIP1* germline-mutated SCLC patient

65 yo F ex-smoker, *BRIP1* c.514A>T; p.K172*



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



e-Poster: 1656P

Germline Mutations in DNA Damage Repair Genes in Patients with Small Cell Lung Cancer

- A total of four patients (4/36, 11.1%) hold the pathogenic or likely pathogenic germline variants in genes involved in DDR pathways (Table). The patient with BRCA1 germline mutation was diagnosed with SCLC at the young age of 44.
-
- All patients were treated with first-line standard platinum-based chemotherapy. The 1-year progression-free survival (PFS) rate of all patients with germline variants was 100% (4/4), and 75% (3/4) patients had a more than 23 months' duration of remission time.

Age	Sex	Smoker	Germline Mutation	Cancer in First-Degree Relatives	TMB (Muts/Mb)	Follow Up Time (months)	PFS (months)	Efficacy of Platinum-based Chemotherapy
54	Female	No	MUTYH c.799C>T	None	7.68	17.4	12.6	Partial Response
59	Male	Yes	BLM c.2556-1G>A	None	19.2	23.3	Not Reach	Partial Response
56	Male	Yes	MUTYH c.820C>T	Lung cancer,lung Cancer,brain cancer	0.96	23.3	Not Reach	Partial Response
44	Female	No	BRCA1 c.3897_3904delGTGCAGTG	Cardiac cancer	13.44	23.3	Not Reach	Partial Response

Feng et al ESMO 2021

Quitting Smoking At or Around Diagnosis Improves the Overall Survival of Lung Cancer Patients: A Systematic Review and Meta-Analysis

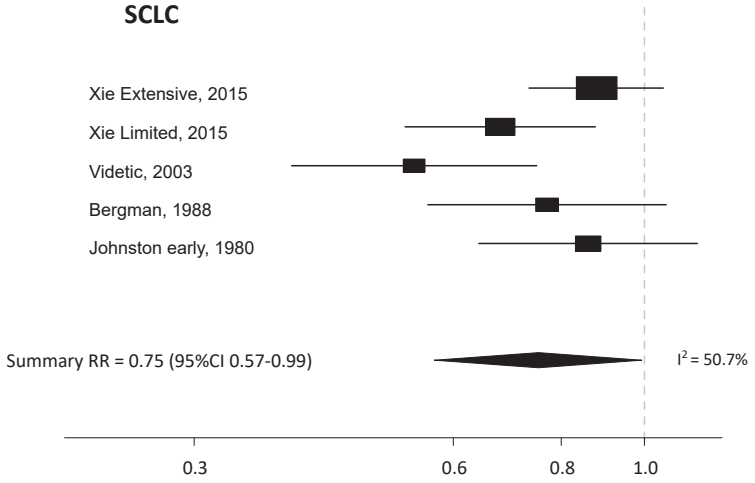
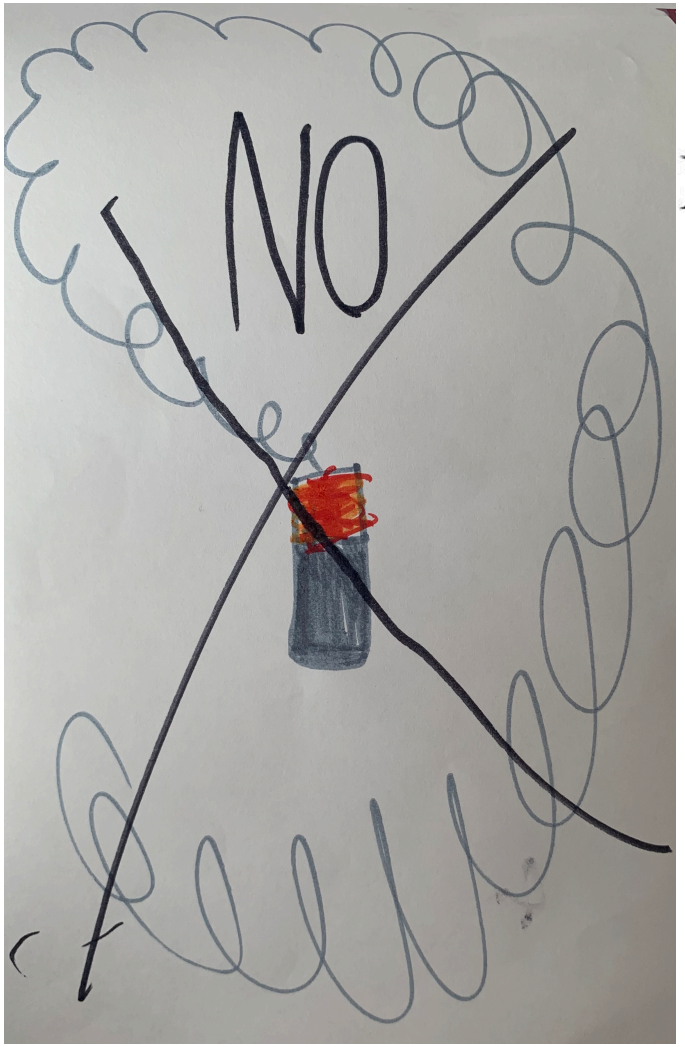


Figure 3. Forest plot for the association between quitting smoking at or around diagnosis and overall survival of patients with SCLC. CI, confidence intervals; RR, relative risk.

Journal of Thoracic Oncology *Vol. 17 No. 5: 623-636*

CONCLUSIONS

- SCLC is a very aggressive disease with limited improvement in prognosis so far
- SCLC can be divided in subgroups based on expression of differential expression of transcriptional regulators
- These subtype may have a therapeutic implications (adoption in clinical trials?)
- Plasticity and heterogeneity play an important role in SCLC (role for liquid biopsy?)
- Combinations and new immunotherapeutic agents and Use of immunotherapy in limited disease are under investigation



IRE
ISTITUTO NAZIONALE TUMORI
REGINA ELENA

GRAZIE!!!

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