INSTITUT JULES BORDET

ONCODISTINCT NETWORK

BSMO

14th Belgian Symposium on the Integration of Molecular Biology Advances into Oncology Clinical Practice

Metastatic SCLC : new therapeutic developments from biologicals to new cytotoxics

Virtual, 27- 28 november 2020

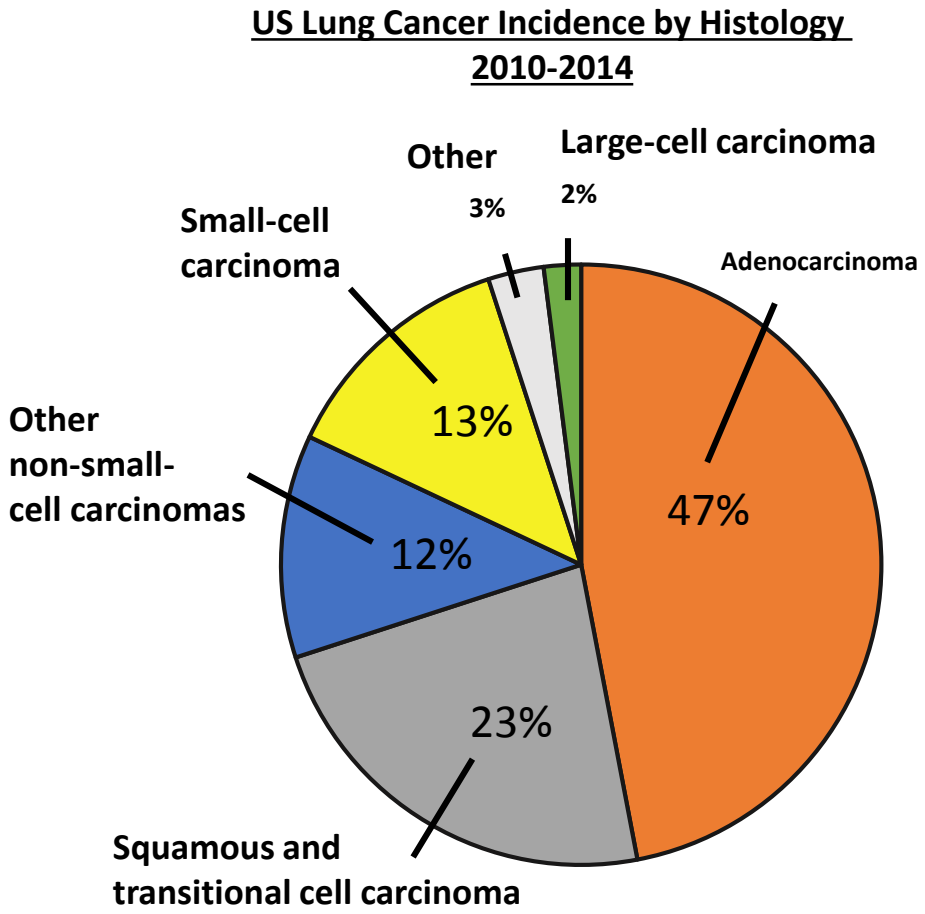
CHL Centre Hospitalier de Luxembourg

Prof. Guy Berchem MD, PhD

Oncologie Médicale
Centre Hospitalier de Luxembourg

Small-Cell Lung Cancer

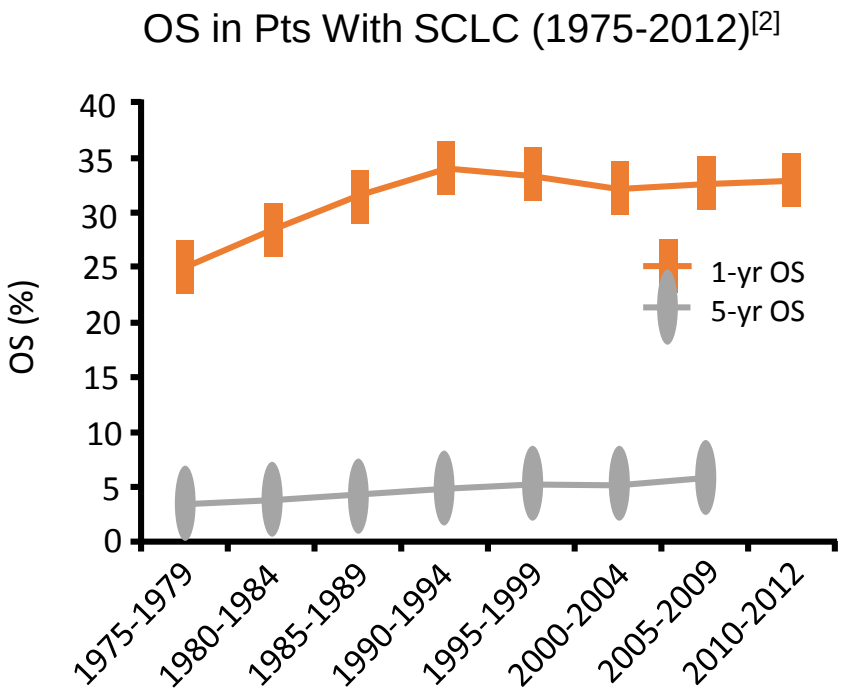
- SCLC 13% of all lung cancers
- Neuroendocrine high-grade features
- Strong association to tobacco (only 2% are never smokers) formerly almost only men…
- Unique biology: rapid proliferation, large (bulky) central tumors, hematogeneous metastase
- 70% of cases with metastatic disease at diagnosis
- High response rates with 1st line chemotherapy (~75%)
- Rapid emergence of resistance and poor long-term survival rates



Oronsky B, et al. Neoplasia. 2017;19:842-847. Alvarado-Luna G, et al. Transl Lung Cancer Res. 2016;5:26-38. Howlander N, et al. SEER Cancer Statistics Review, 1975-2014.

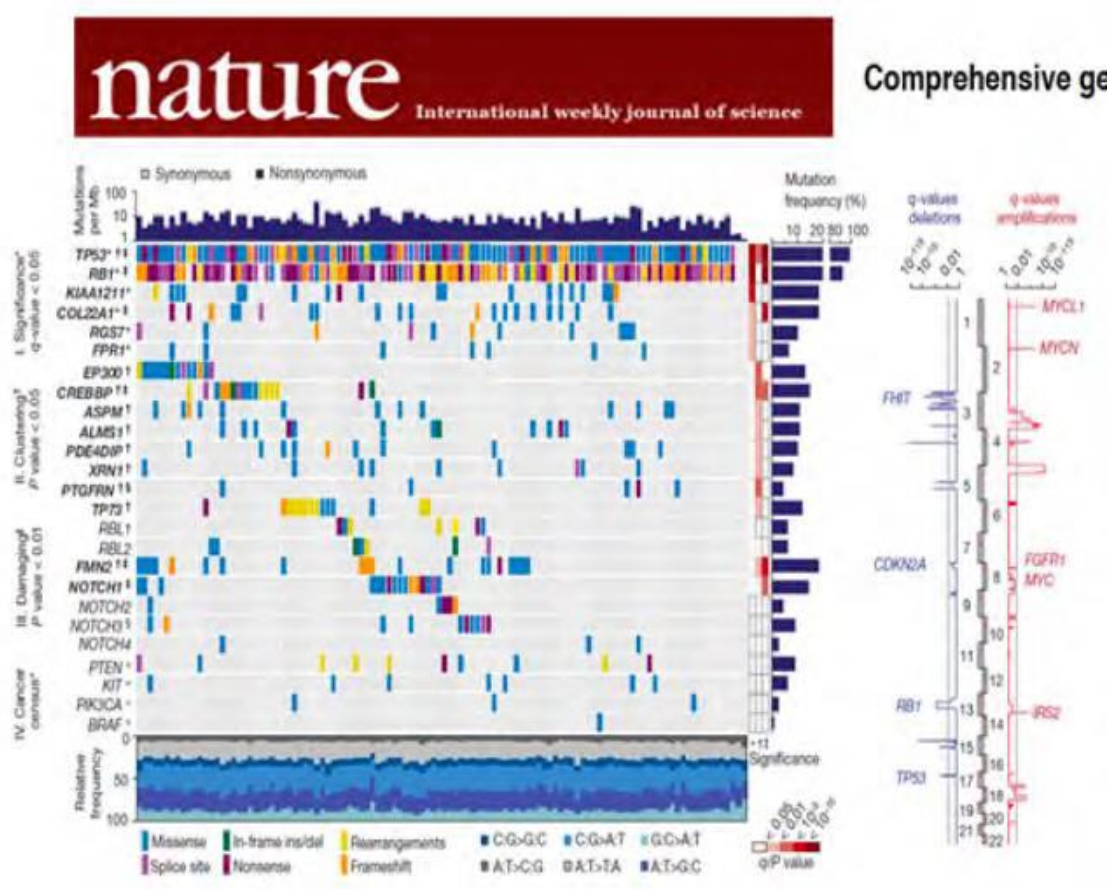
Treatment outcomes of SCLC

- Very little progress has been made in the treatment of SCLC during the last 30 yrs[1,2]
- Poor outcomes dependant on disease extent[1]
  - LS-SCLC: (radiochemotherapy)
    - median OS 15-20 mos
    - 3-yr survival of 40% (CONVERT trial)[3]
  - ES-SCLC: (chemotherapy +/- PCI)
    - median OS 9-11 mos
    - 2 year survival 5-10% (20% best immuno trials)



1. Koinis F, et al. Transl Lung Cancer Res. 2016;5:39-50. 2. Waqar SN, et al. Pharmacol Ther. 2017;[Epub ahead of print]. 3. Faivre Finn et al.; Vol 18, 8, p1116-1125, Aug 01, 2017.

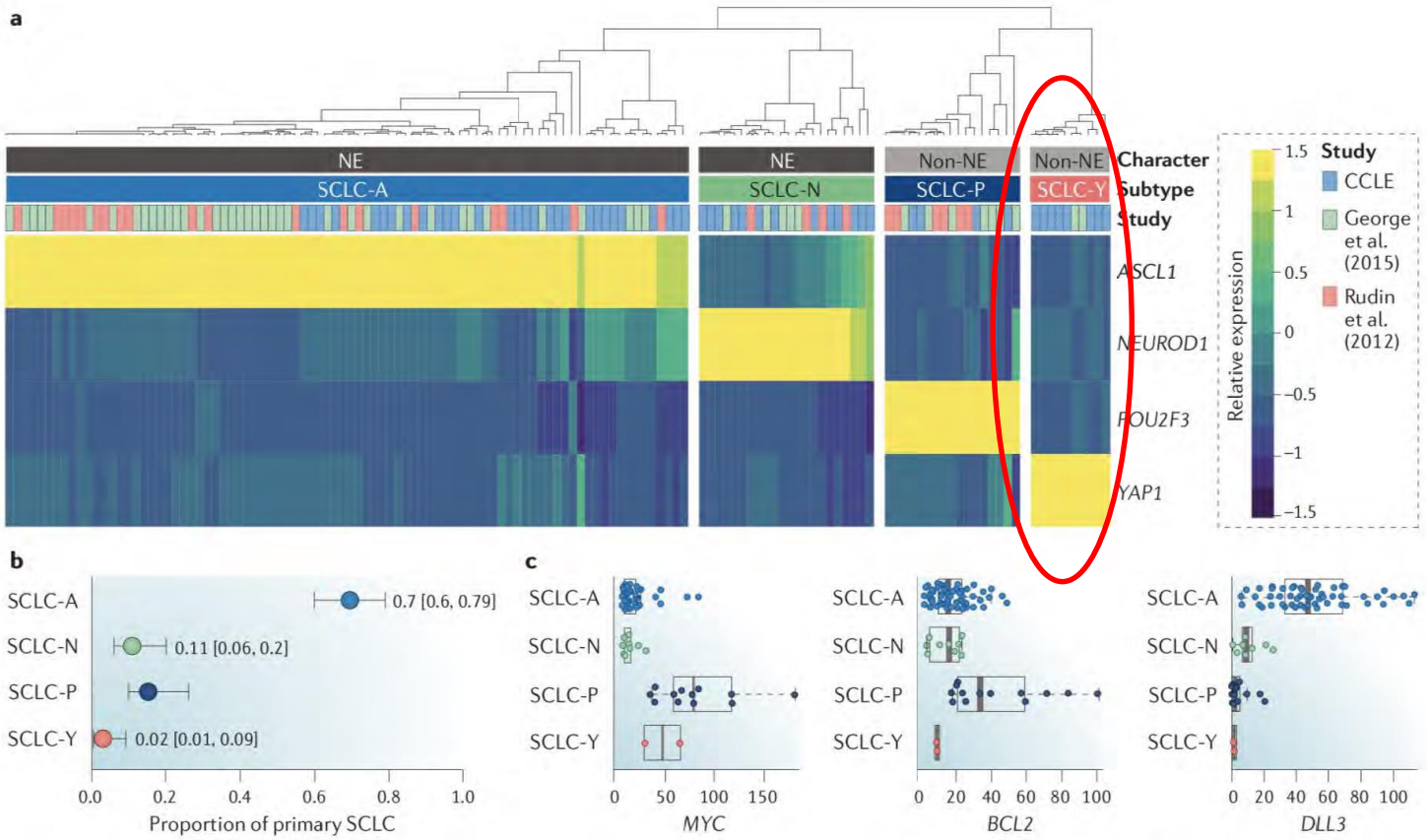
Genetic alterations in SCLC



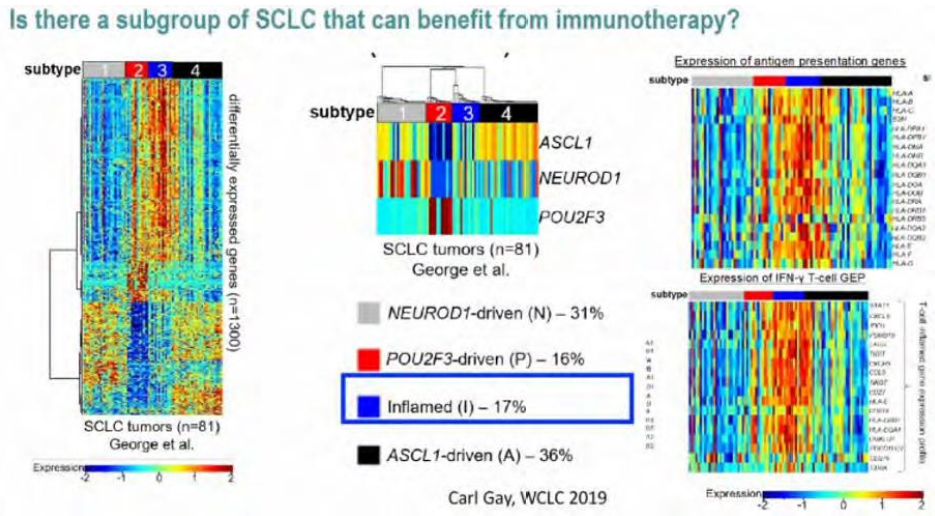
- High mutational burden (8.6 mutmut/Mb)
- Universal loss of function mutations in TP53 and RB1
- Few targetable driver oncogene to date
  - KIT, PIK3CA, BRAF
  - Inactivating mutations in *NOTCH* (25%)[2]
  - Amplification of FGFR1, SOX2 and MYC [1-4]
  - *MYC-L1* > *N-MYC* > *C-MYC*[1]
  - *Fusions RFL-MYCL1* have been described

1. Peifer M, et al. Nat Genet. 2012;44:1104-1110. 2
2. George J, et al. Nature. 2015;524:47-53.
3. Sabari JK, et al. Nat Rev Clin Oncol. 2017;14:549-561.
4. Rudin CM, et al. Nat Genet. 2012;44:1111-1116.

SCLC is not a uniform disease



- SCLC subtypes defined by differential expression of 4 key transcription regulators: ASCL1, NeuroD1, YAP1 and POU2F3
- Correlations with sensitivity to treatment are underway
- One of the subtypes seems to correspond to an “inflamed” phenotype



Rudin, Charles M et al. “Molecular subtypes of small cell lung cancer: a synthesis of human and mouse model data.” *Nature reviews. Cancer* vol. 19,5 (2019): 289-297.

SCLC therapeutic advances in:

1

Small cell lung cancer limited disease

- The always recurring question of RxT fractioning and PCI
- Does Immunotherapy maintenance have a role in this setting

2

Small cell lung cancer extensive disease

- Immunotherapy + chemo, are all ICI antibodies equal?
- Irinotecan vs etoposide with platinum

3

Further line treatments

- Immunotherapy
- Lurbinectedin
- Other molecules

SCLC therapeutic advances in:

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Small cell lung cancer extensive disease 1st line

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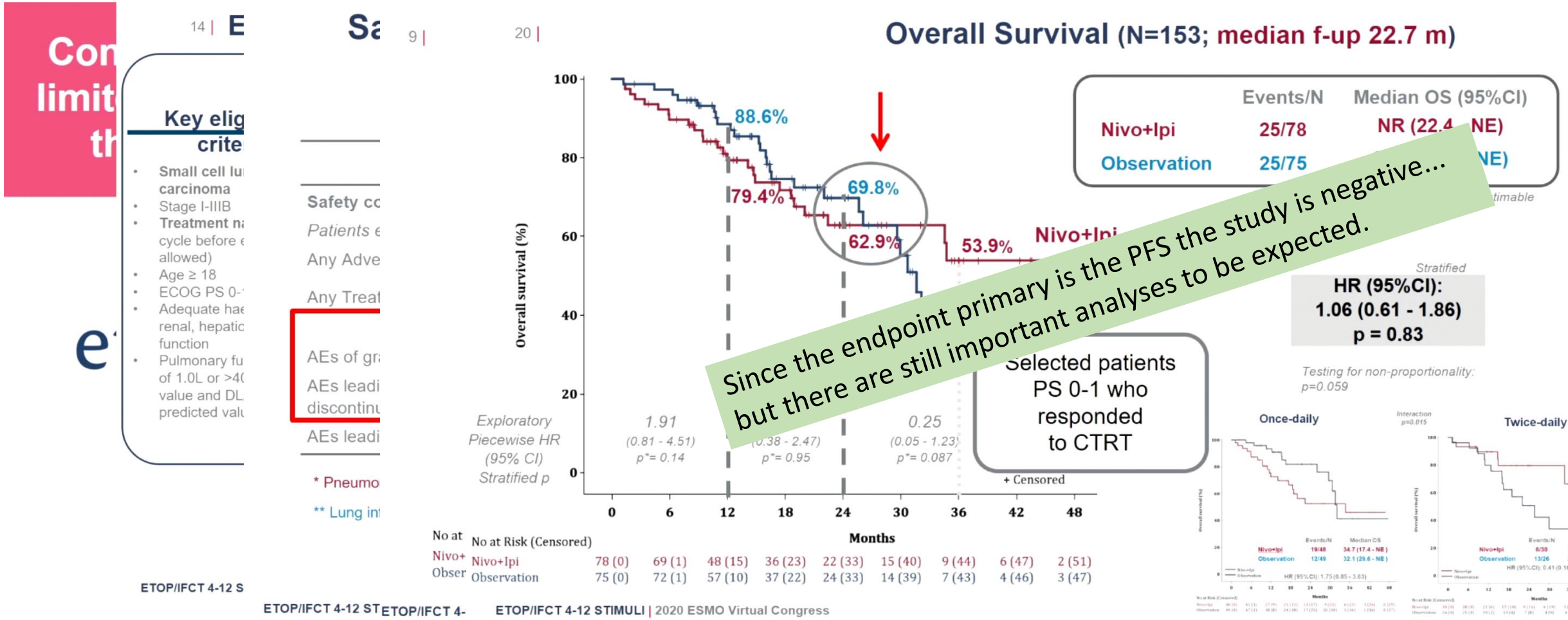
Ipi-Nivo consolidation for limited stage SCLC



Other studies are underway

IMMUNOTHERAPY FOR SCLC LIMITED DISEASE

Immunotherapy for LD-SCLC	Study name	Study phase	Number of patients	Primary endpoints	Estimated completion
ICI Consolidation after chemoradiation					
Nivolumab + ipilimumab -> nivolumab vs observation	STIMULI	II	260	PFS, OS	
Durvalumab ± tremelimumab vs placebo	ADRIATIC	III	600	PFS, OS	January 2022
Atezolizumab	ACHILES	II	212	2-year OS	December 2023
ICI + concurrent chemoradiation					
Atezolizumab + cisplatin/etoposide vs CRT	NRG-LU005	II/III	506	PFS, OS	? Opened end 2019
Pembrolizumab + CRT (EP/ECb)	NCI-2015-00598	I	80	Safety	
Durvalumab ± tremelimumab + CRT (EP)	CLOVER	I	30	Safety	End 2022
Durvalumab + CRT (EP)	2018-01-103	II	51	PFS	

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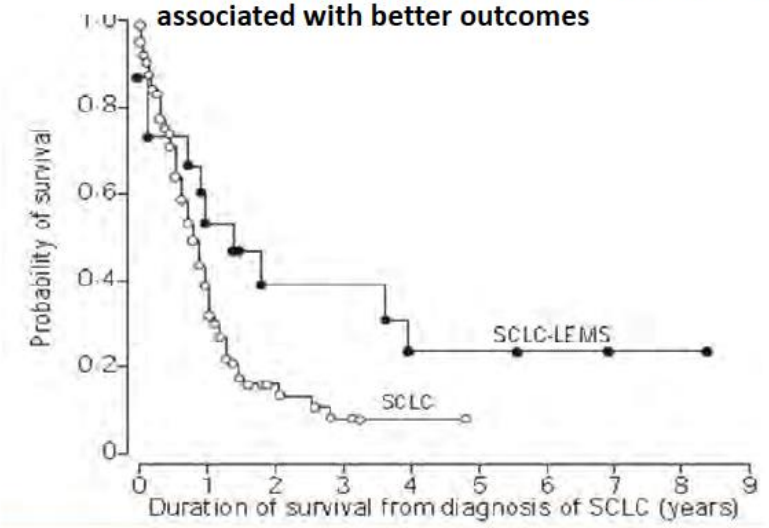
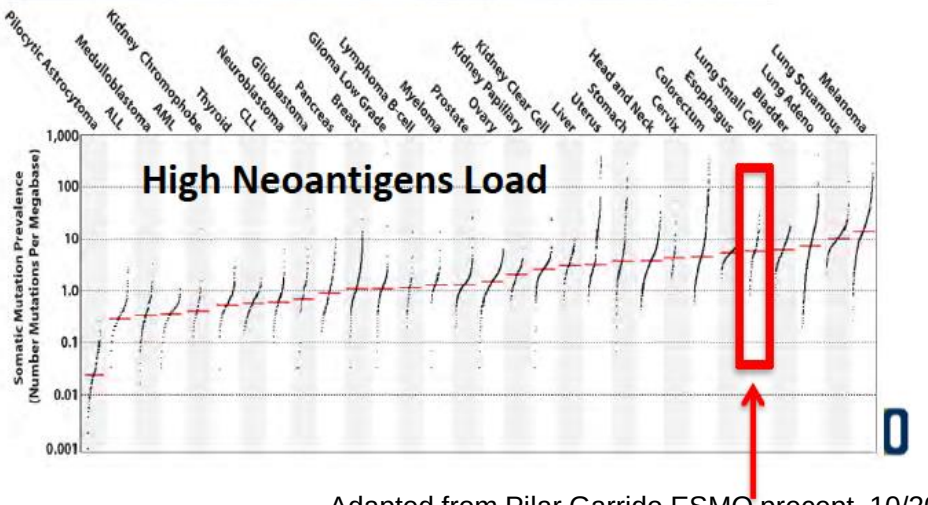
IMMUNOTHERAPY IN SCLC

- Immune check point inhibitors represent a paradigm shift in oncology
- Standard of care in NSCLC
- Clear rationale in SCLC
  - Remarkable **high number of somatic non-synonymous mutations** related to tobacco smoking exposure
  - Immunogenic disease
    - 15%-20% of newly diagnosed SCLC have clinical evidence of some **paraneoplastic syndromes**
    - Paraneoplastic syndromes are associated with longer survival.
  - SCLC induces an **immune suppressive phenotype**

Immune mediated paraneoplastic syndrome (LEMS) associated with better outcomes





Gelsomino F. Cancer Treat Rev 2019

Adapted from Pilar Garrido ESMO precept. 10/2020

CT-IO NEW STANDARD OF CARE IN FIRST LINE SCLC

	Phase III **IMpower133**	Phase III **CASPIAN**	Phase III **KEYNOTE 604**	Phase II ECOG-ACRIN EA51611 study
SCHEME	CARBOPLATIN + ETOPOSIDE +/- **ATEZOLIZUMAB**	PLATINUM + ETOPOSIDE +/- **DURVALUMAB +/- TREMELIMUMAB**	PLATINUM + ETOPOSIDE +/- **PEMBROLIZUMAB**	PLATINUM + ETOPOSIDE +/- **NIVOLUMAB**
RESULT	*POSITIVE*	*POSITIVE FOR DURVALUMAB*	*POSITIVE PFS* ***NEGATIVE OS***	*POSITIVE PFS (POSITIVE OS)* underpowered

Adapted from Pilar Garrido ESMO precept. 10/2020

Impower 133

IMpower133: Phase 1/3, of carboplatin + etoposide +/- atezolizumab in first line extensive stage SCLC

Patients with
(N = 403):

- Measurable ES-SCLC (RECIST v1.1)
- ECOG PS 0 or 1
- No prior systemic treatment for ES-SCLC
- Patients with treated asymptomatic brain metastases were eligible

Stratification:

- Sex (male vs. female)
- ECOG PS (0 vs. 1)
- Brain metastases (yes vs. no)[a]

R 1:1

Induction (4 x 21-day

- **Atezolizumab (1200 mg IV, Day 1) + carboplatin + etoposide**
- **Placebo + carboplatin + etoposide**

Carboplatin: AUC 5 mg/mL/min IV, Day 1
Etoposide: 100 mg/m^2 IV, Days 1–3

Maintenance

- **Atezolizumab**
- **Placebo**

Treat until PD or loss of clinical benefit

PCI per local standard of care

Survival follow-up

Co-primary end points:

- Overall survival
- Investigator-assessed PFS

Key secondary end points:

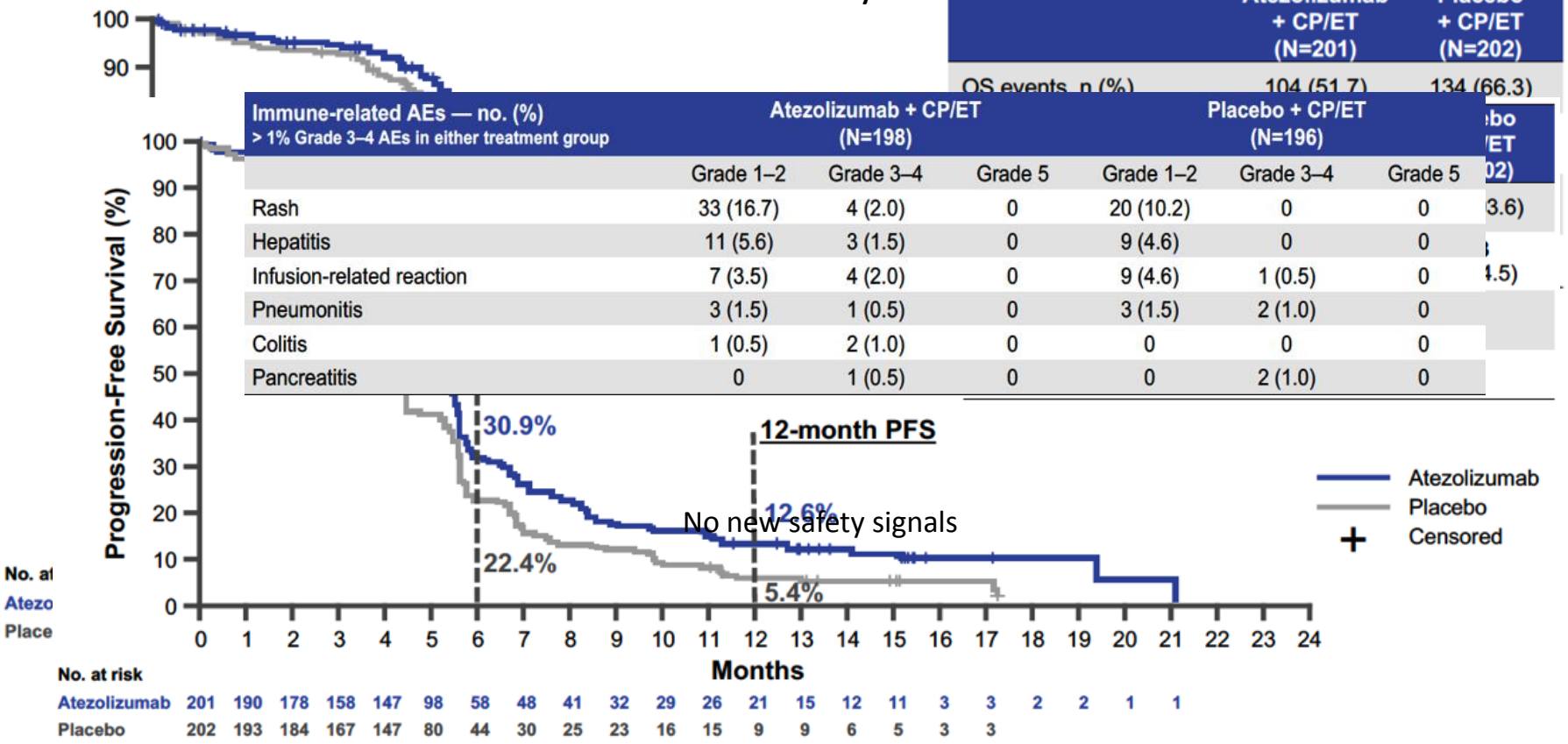
- Objective response rate
- Duration of response
- Safety

Impower 133

Safety

	Atezolizumab + CP/ET (N=201)	Placebo + CP/ET (N=202)
OS events, n (%)	104 (51.7)	134 (66.3)

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



No new safety signals

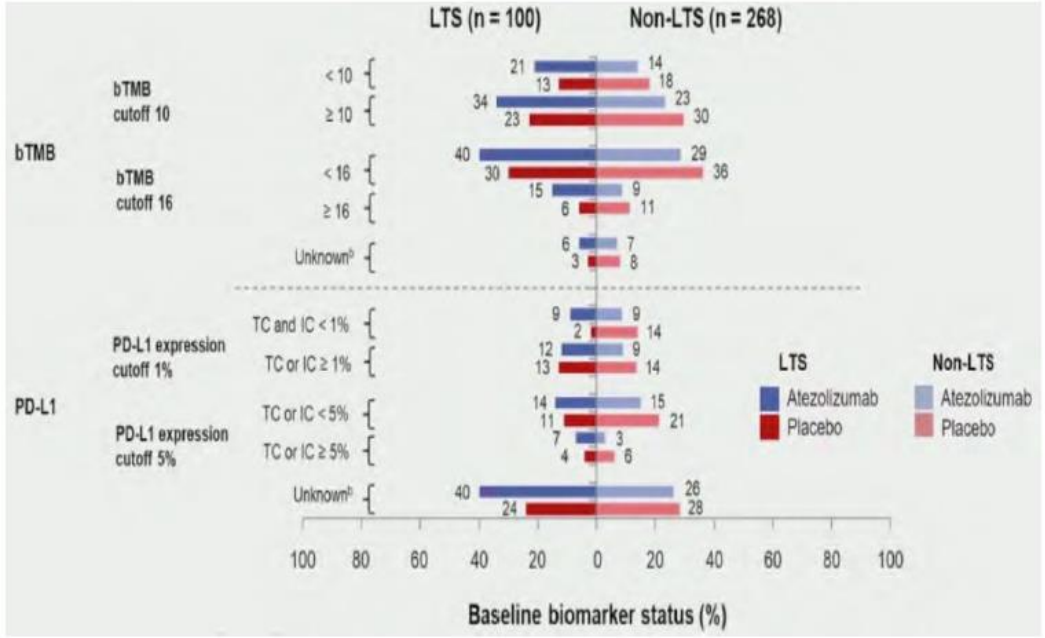
Liu SV, et al. WCLC 2018. Abstract PL02.07. Horn L, et al. N Engl J Med. 2018;379

IMPOWER 133: LONG TERM SURVIVAL

More than one half of the patients treated with atezolizumab plus chemotherapy were still alive at the 12-month landmark analysis compared with fewer than 40% of patients treated with chemotherapy alone.

Covariate	Univariate		Multivariate	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Treatment arm (ref: atezolizumab)	0.76 (0.61, 0.96)	0.02	0.71 (0.56, 0.90)	< 0.01
Sex (ref: male)	1.11 (0.88, 1.41)	0.38	1.21 (0.94, 1.54)	0.13
Age (ref: ≥ 65 y)	1.17 (0.93, 1.47)	0.17	1.18 (0.93, 1.50)	0.17
ECOG PS (ref: 1)	1.64 (1.29, 2.10)	< 0.01	1.43 (1.11, 1.85)	0.01
Metastatic sites (ref: ≥ 3)	1.53 (1.18, 1.97)	< 0.01	1.22 (0.93, 1.61)	0.15
LDH (ref: > ULN)	1.53 (1.21, 1.94)	< 0.01	1.30 (1.01, 1.66)	0.04
SLD (ref: ≥ 111 mm)	1.69 (1.34, 2.12)	< 0.01	1.56 (1.22, 2.00)	< 0.01

- Treatment by covariate interactions were tested, but no significant interactions were observed at the 5% level



ESMO 2020 UPDATE (N=373):

- OS ≥18 months in atezolizumab arm vs placebo arm
- No association between biomarker (bTMB, PD-L1) status and OS ≥18 months

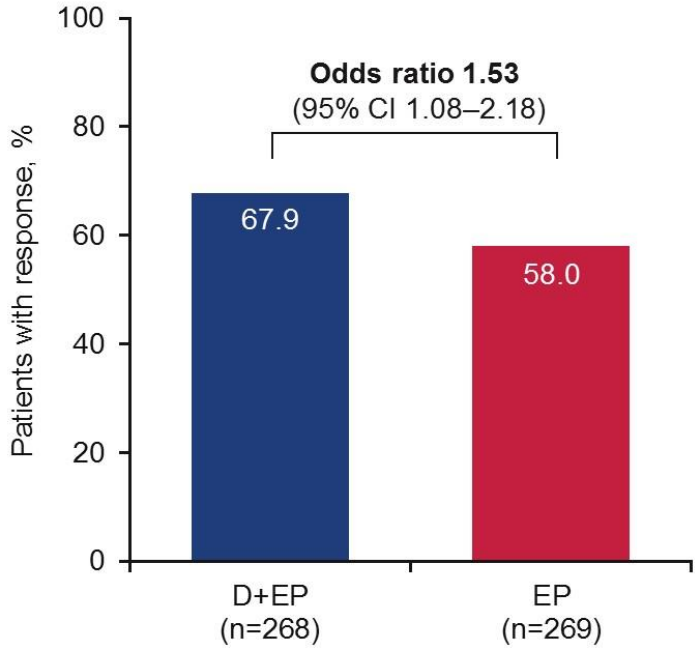
Liu S, ESMO 2020

Adapted from Pilar Garrido ESMO precept. 10/2020

CASPIAN

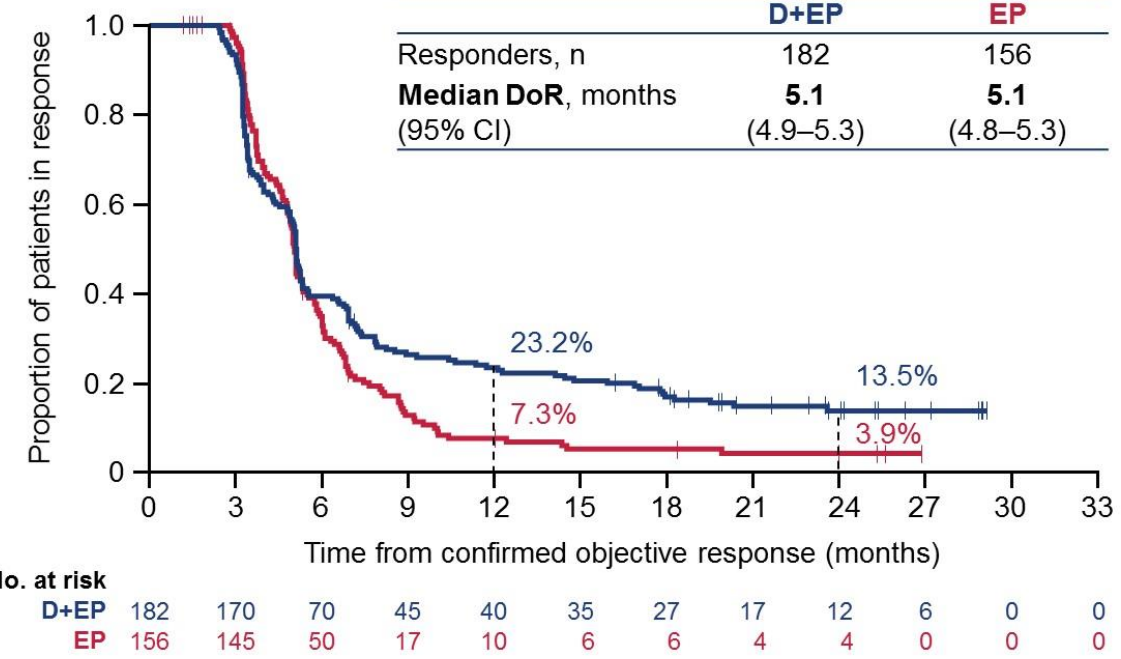
Updated Confirmed Objective Response: D+EP vs EP

ORR*



Duration of Response

	D+EP	EP
Responders, n	182	156
Median DoR, months	**5.1**	**5.1**
(95% CI)	(4.9–5.3)	(4.8–5.3)



No. at risk

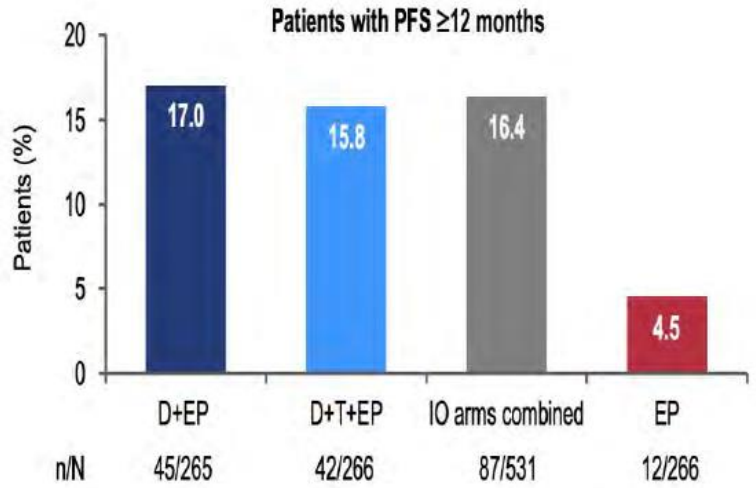
D+EP	182	170	70	45	40	35	27	17	12	6	0	0
EP	156	145	50	17	10	6	6	4	4	0	0	0

*Investigator assessed per RECIST v1.1

CASPIAN: LONG-TERM SURVIVAL, EXPLORATOY ANALYSIS

Exploratory Subgroup Analyses

- Exploratory subgroup analyses were conducted to characterise patients deriving long-term benefit
  - PFS ≥12 months was used as a preliminary threshold to identify potential predictive parameters in treated patients
  - D+EP and D+T+EP arms were also combined for the analyses to increase the sample size of the subgroup, given the consistent overlap in PFS throughout the Kaplan-Meier curves



IO, immuno-oncology

Overall Survival (PFS ≥12 & <12m Subgroups)

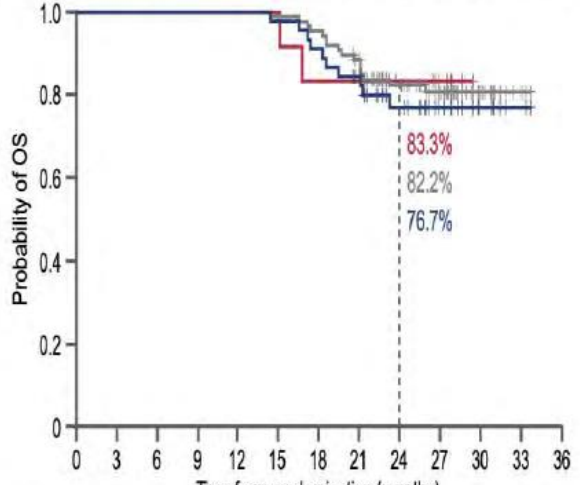
Due to potential post-randomisation selection bias, cross-treatment comparisons should be considered with caution

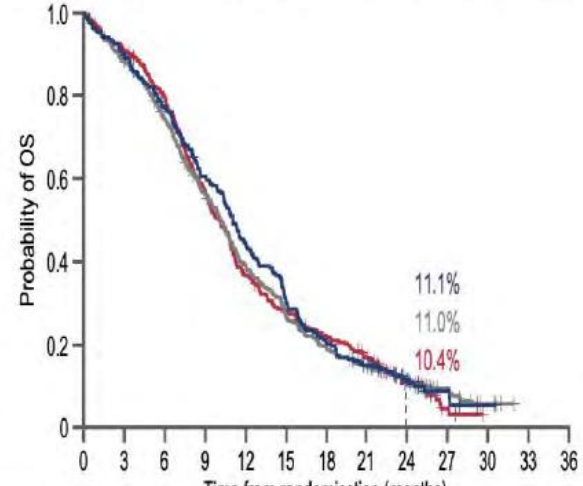
PFS ≥12 months

	D+EP	IO arms combined	EP
Patients, n (% of treated)	**45 (17)**	**87 (16)**	**12 (5)**
Events, n/N (%)	10/45 (22)	16/87 (18)	2/12 (17)
mOS, months (95% CI)	**NR** (NE–NE)	**NR** (NE–NE)	**NR** (16.8–NE)

PFS <12 months

	D+EP	IO arms combined	EP
Patients, n (% of treated)	**220 (83)**	**444 (84)**	**254 (95)**
Events, n/N (%)	197/220 (90)	397/444 (89)	228/254 (90)
mOS, months (95% CI)	**11.0** (9.9–12.0)	**10.1** (9.2–10.8)	**10.0** (9.0–10.8)





In CASPIAN, >3 times more patients derived long-term benefit when treated with durvalumab + EP vs EP alone

Patients in all arms with PFS ≥12m had improved ORR, DoR and OS vs the PFS 75% –

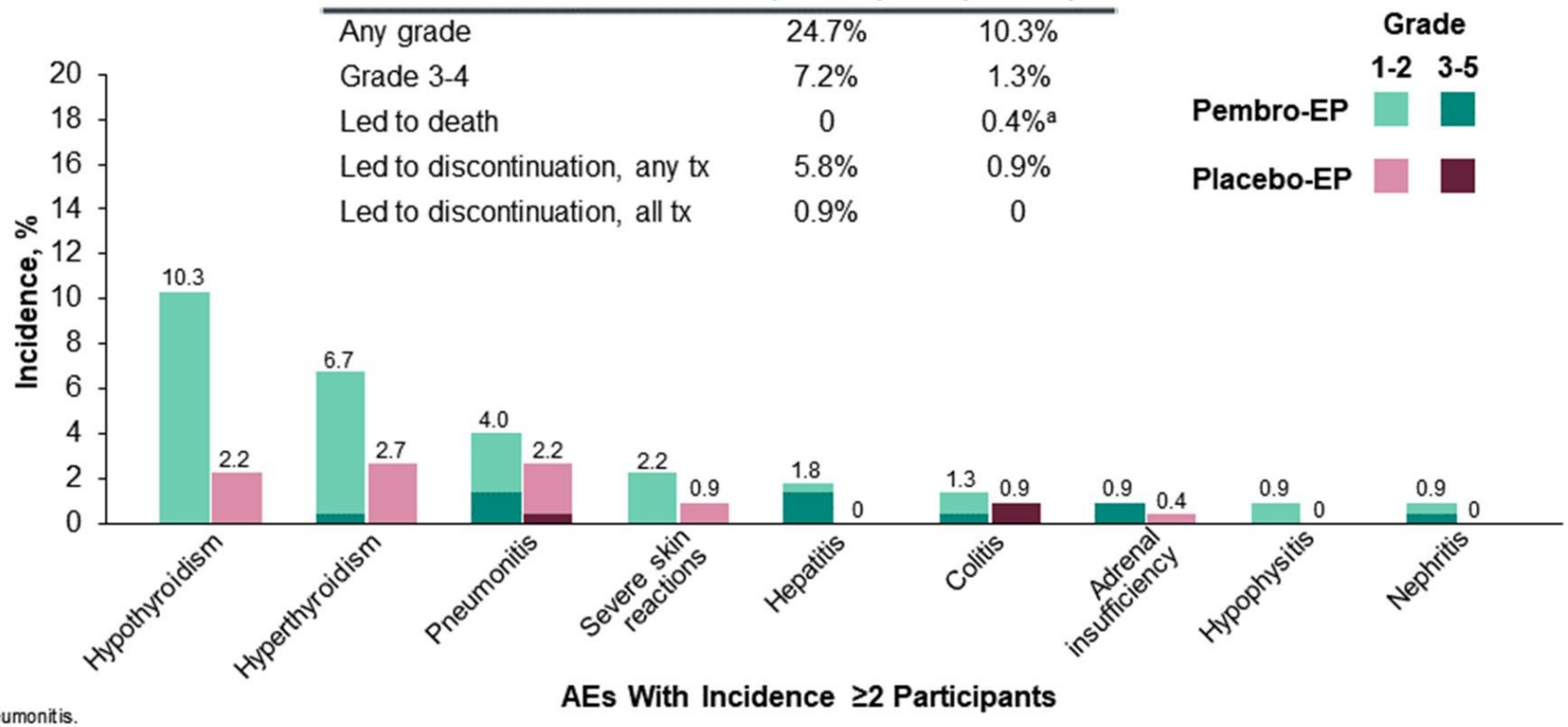
Adapted from Pilar Garrido ESMO precept. 10/2020

KEYNOTE-604

Rudin KN604 ASCO 2020

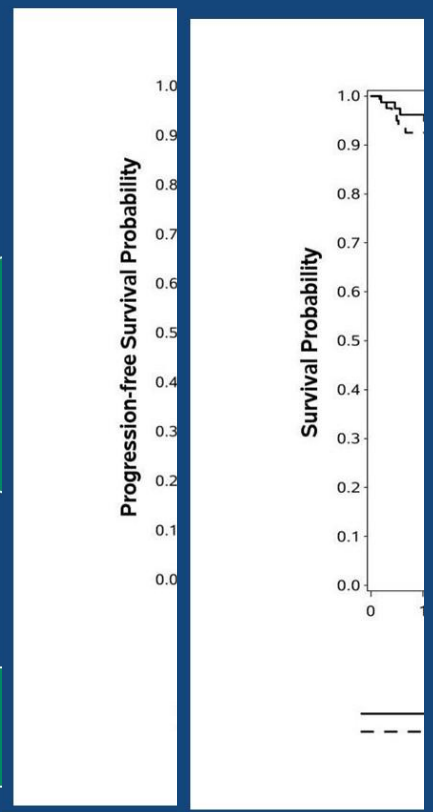
Immune-Mediated AEs, As Treated: FA

All AEs	Pembro-EP (n = 223)	Placebo-EP (n = 223)
Any grade	24.7%	10.3%
Grade 3-4	7.2%	1.3%
Led to death	0	0.4%[a]
Led to discontinuation, any tx	5.8%	0.9%
Led to discontinuation, all tx	0.9%	0

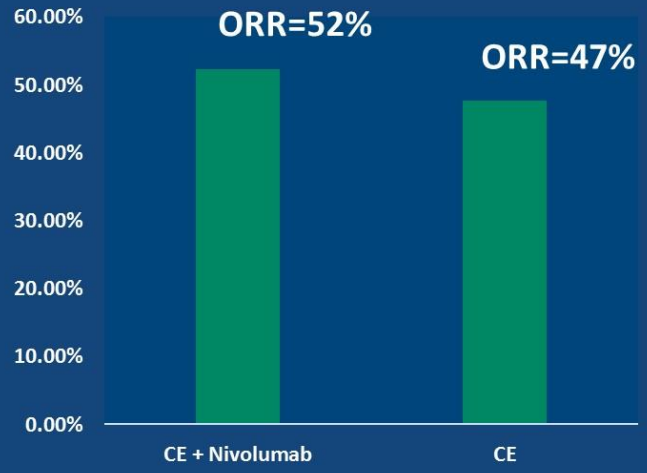


[a]Pneumonitis.
Data cutoff date: Dec 2, 2019.

ECOG-ACRIN EA5161



Objective Response Rate



Efficacy

	Nivolumab + CE	CE
Median duration of response (months)	5.6	3.3

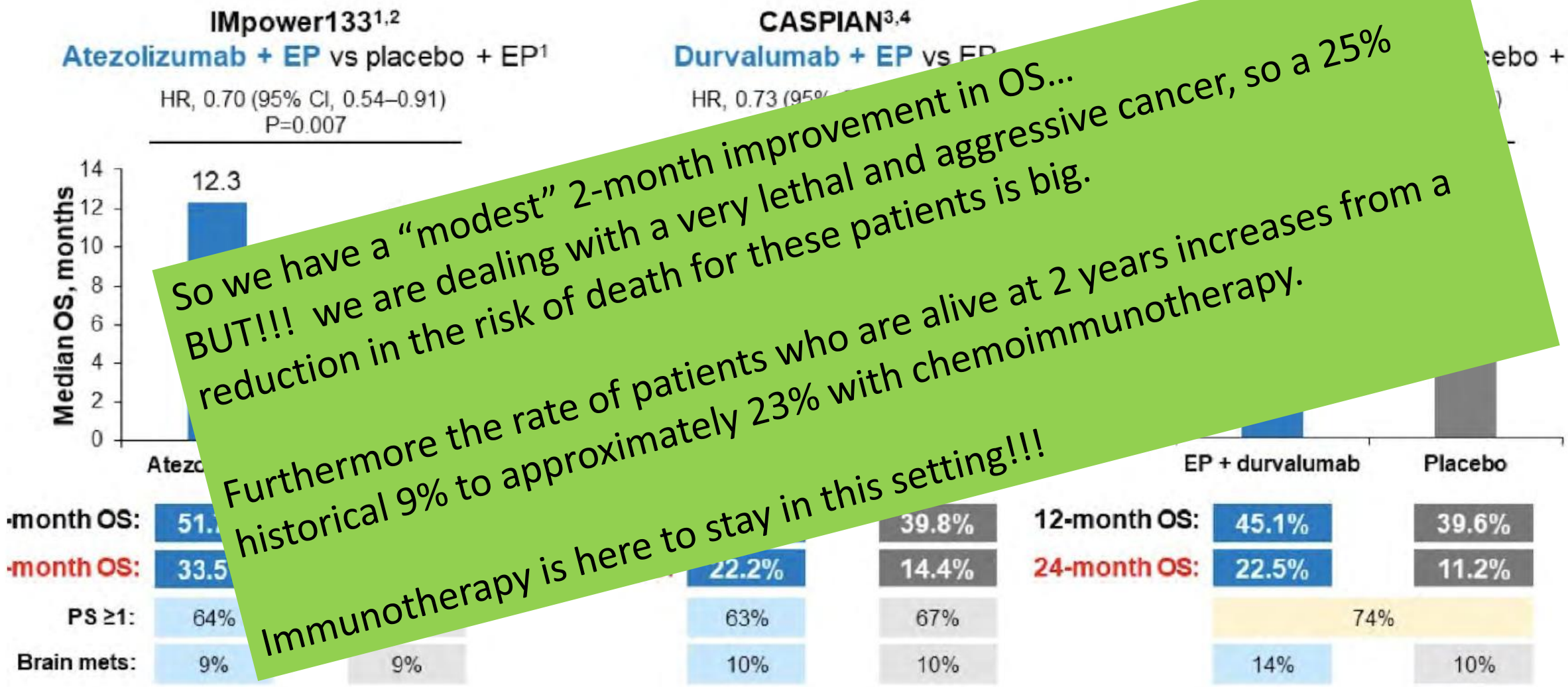
COMPARISON OF IO + CT TRIALS IN FIRST LINE SCLC-ED

Phase III

	IMpower133	CASPIAN	KEYNOTE 604
Placebo	X		X
Untreated Brain Metastases		X	
PCI allowed in control arm	X	X	X
PCI allowed in experimental arm	X		X
Up to 6 cycles of CT (control arm)		X	
Cisplatin/Carboplatin	Only Carboplatin	X	X
IO Maintenance	q3w	q4w	q3w
Primary Endpoints PFS/OS	X	Only OS	X
Only Investigator Assessed PFS	X	X	

Adapted from Pilar Garrido ESMO precept. 10/2020

COMPARISON OF IO + CT TRIALS IN FIRST LINE SCLC-ED (II)



So we have a "modest" 2-month improvement in OS…
BUT!!! we are dealing with a very lethal and aggressive cancer, so a 25% reduction in the risk of death for these patients is big.

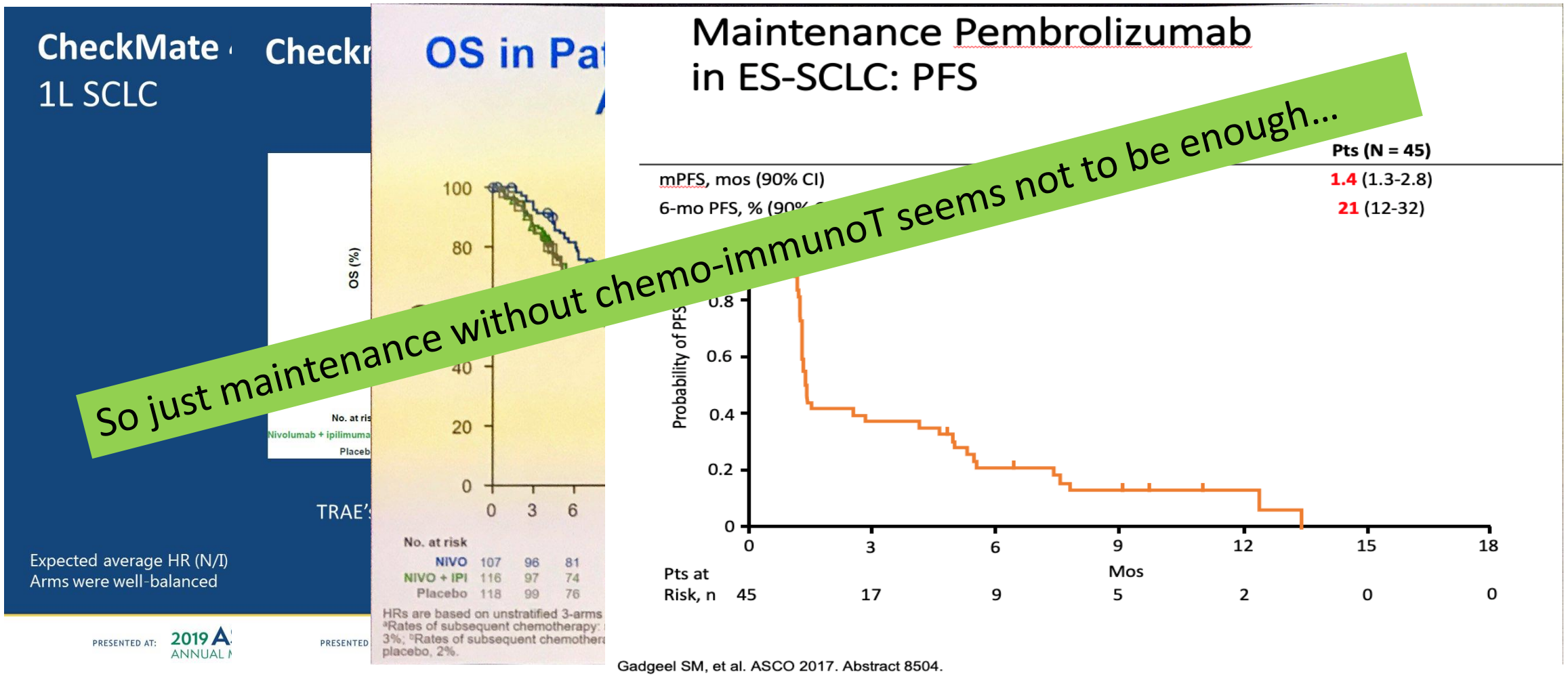
Furthermore the rate of patients who are alive at 2 years increases from a historical 9% to approximately 23% with chemoimmunotherapy.

Immunotherapy is here to stay in this setting!!!

1. Horn L, et al. N Engl J Med 2018;379:2220–29; 2. Liu SV, et al. ESMO 2020; Abstract 1781MO; 3. Paz-Ares L, et al. Lancet 2019;394:1929–39;
4. Paz-Ares L, et al. ASCO 2020; Abstract 9002; 5. Rudin CM, et al. J Clin Oncol 2020; 38:2369–79; 6. Rudin CM, et al. ASCO 2020; Abstract 9001.

Adapted from Pilar Garrido ESMO precept. 10/2020

Is maintenance immuno a good idea?



Gadgeel SM, et al. ASCO 2017. Abstract 8504.

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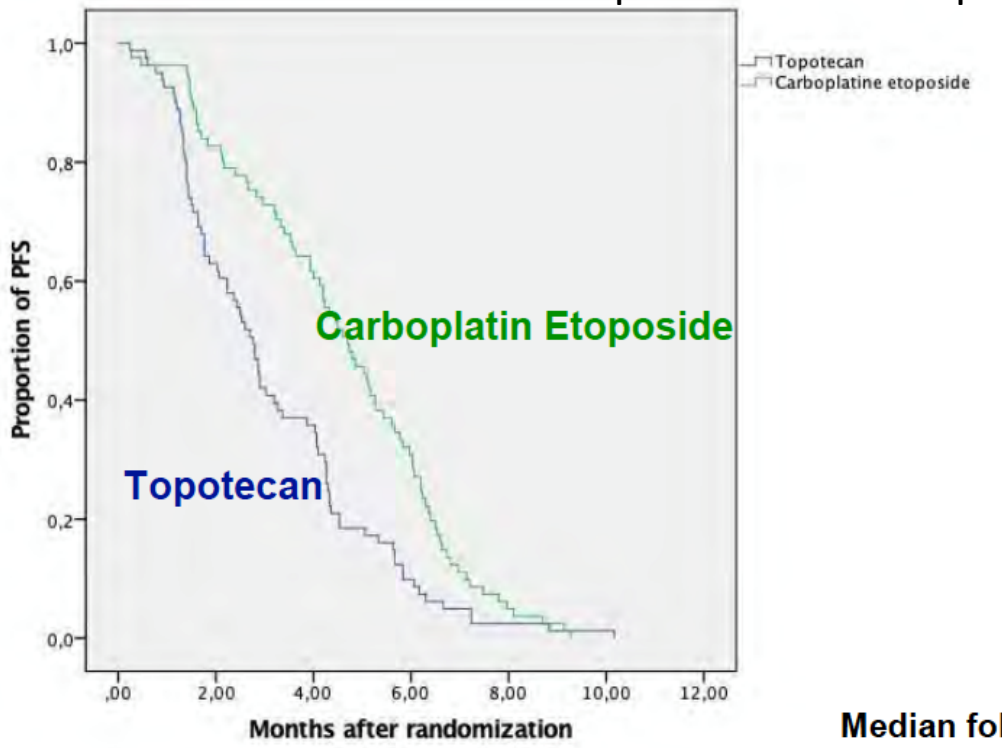
- Other molecules

Second line Topotecan

"chemosensitive" patients with relapse > 90 days after 1st line



	Topotecan	Carboplatine Etoposide
Events	81	81
mPFS	2.7 mo	4.7 mo
(95%CI)	(2.3-3.2)	(3.9-5.5)

One sided p< 0.001

By stratified log-rank test

Hazard ratio, 0.6; 95% CI 0.4-0.8

Median follow-up: 16 months

ORR: 25% (topotecan) vs. 49%, (carbo/etoposid), p= 0.002
more neutoropenia (36% vs. 23%), p=0.035, 2 deaths with topotecan arm

Is another combination chemo an option?

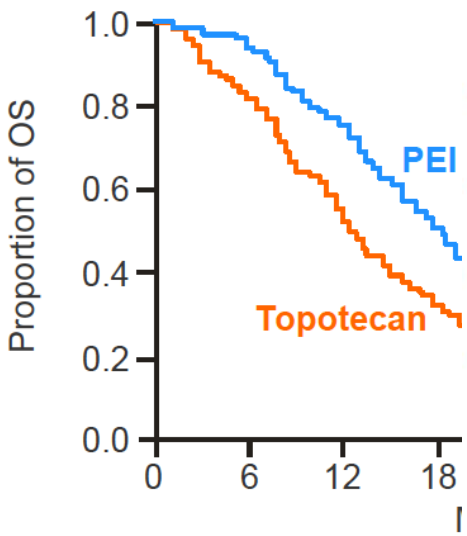
Higher D

OS benef

Key patient inclusion
- SCLC
- Responded to first treatment
- Relapse/PD ≥90 d treatment
- ECOG PS 0–2

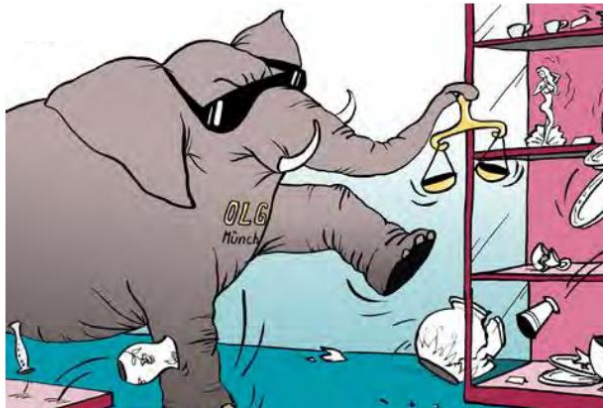
(n=180)

Primary endpoint
- OS



PEI: Too much?

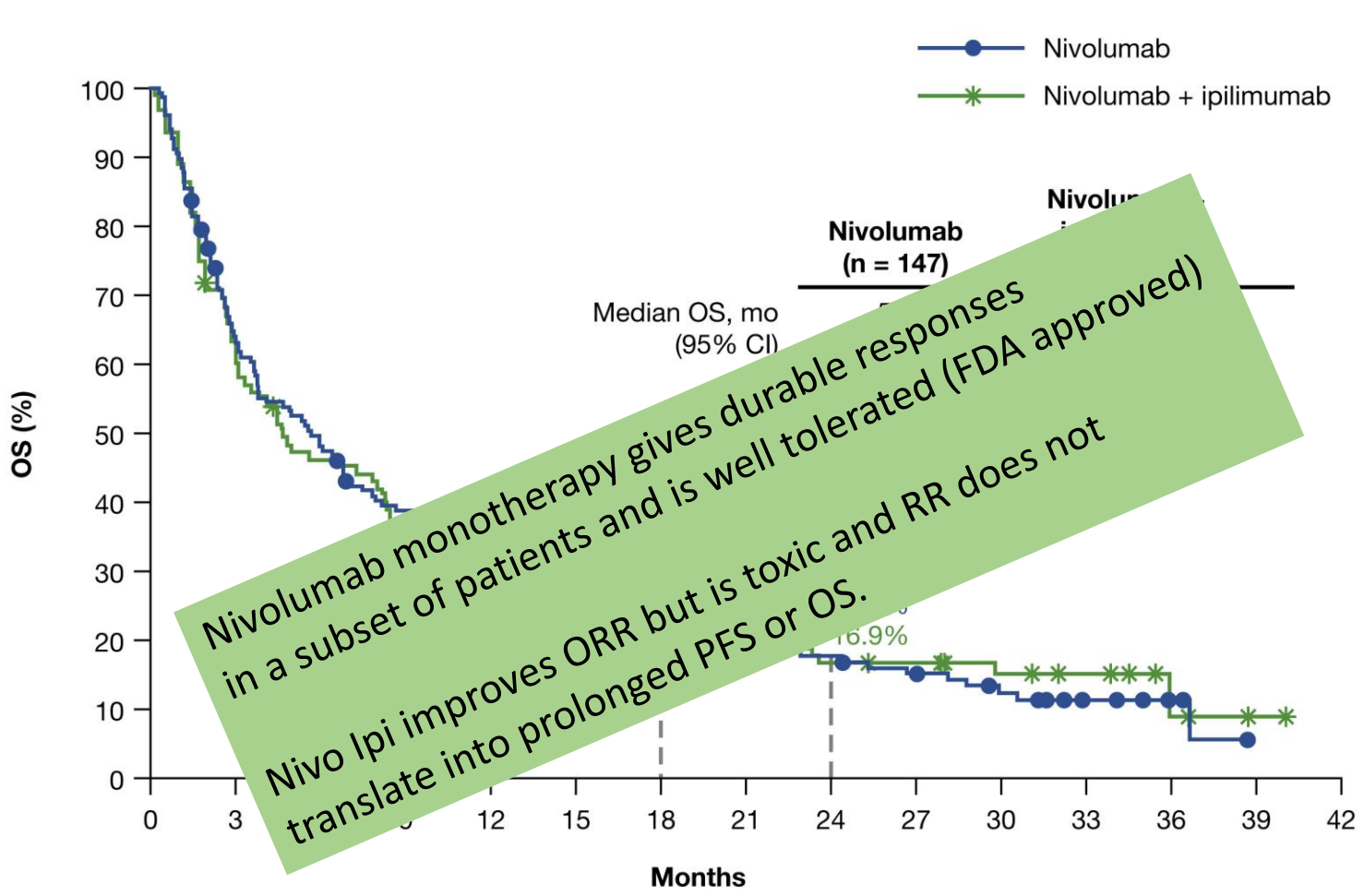
- Hematol. grade 3-4 tox.
  - >80% neutropenia/anemia,
  - >40% tc-penia
  - >30% febrile neutropenie (1 pt grade 5)
- 50% dose reduction
- NO QoL
- Comparator arm?
- Western population?



Goto Lancet Oncol 2016

Adapted from Martin Früh ESMO precept. 10/2020

What about immunotherapy in second line?

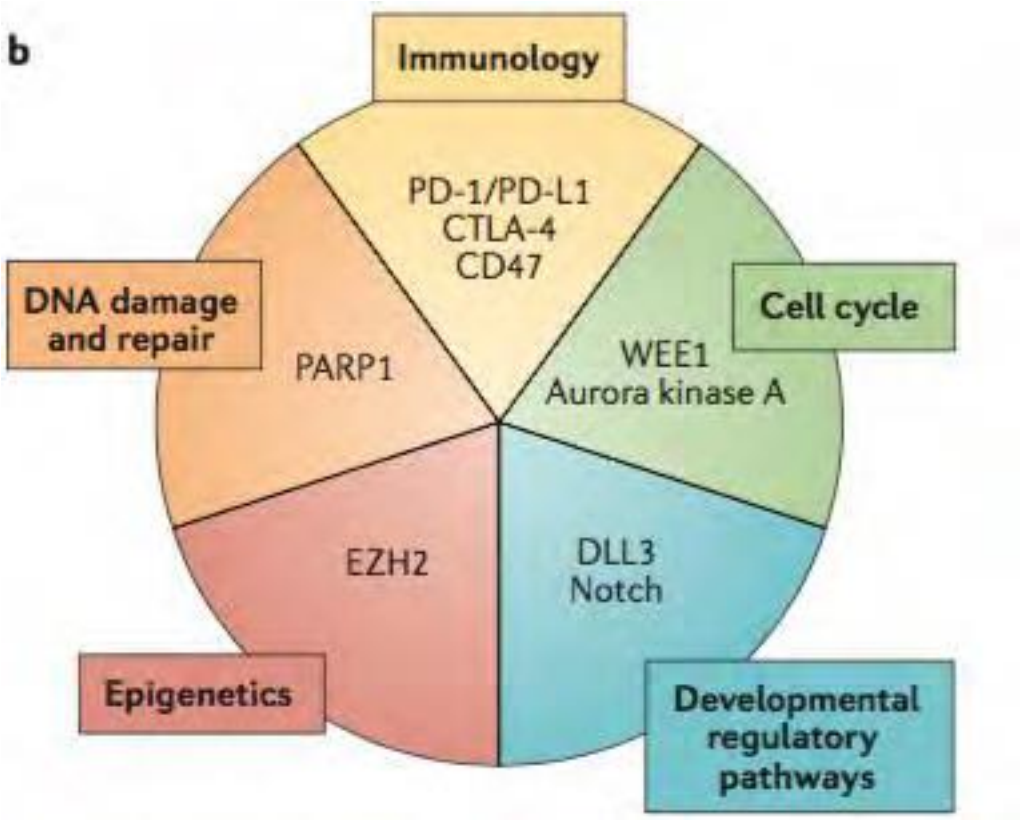


Nivolumab monotherapy gives durable responses in a subset of patients and is well tolerated (FDA approved)

Nivo Ipi improves ORR but is toxic and RR does not translate into prolonged PFS or OS.

Ready N et al: JTO; Vol 15, 3 P 426-435 (March 2020)

Potential therapeutic opportunities for SCLC

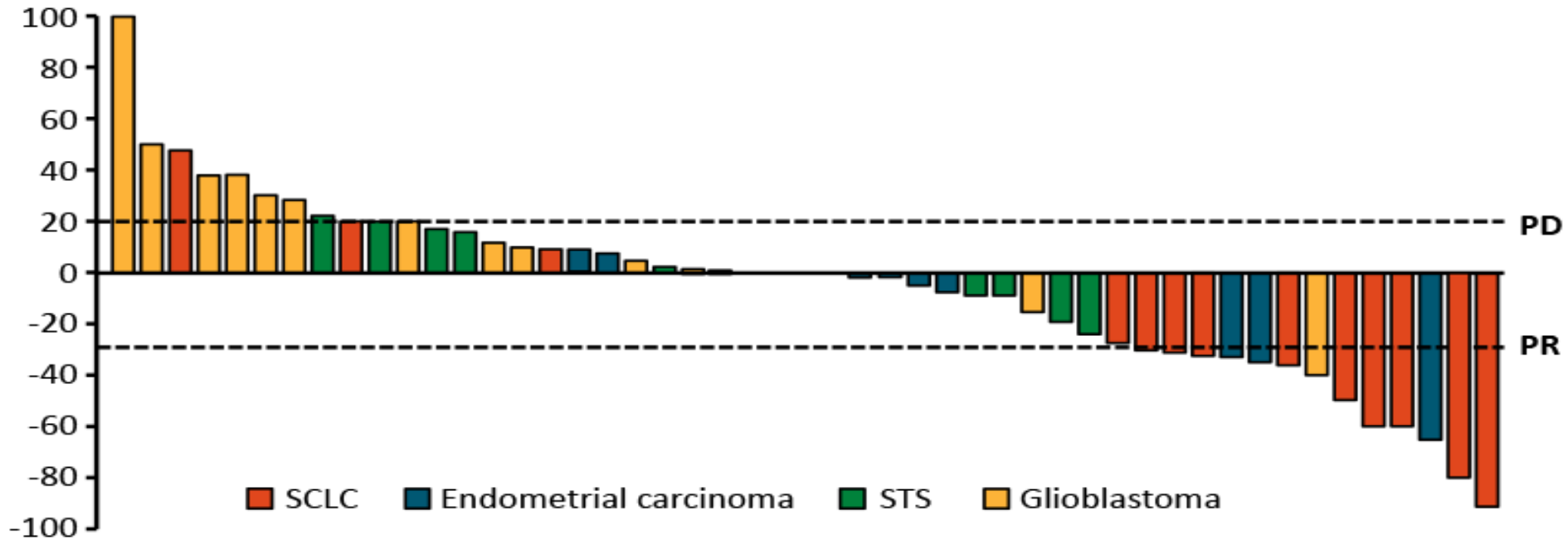


- NOTCH pathway
  - Rovalpituzumab
- Cell cycle and DNA damage repair pathway
  - Aurora kinase A inhibitors
  - PARP inhibitors
  - Lurbinectedin
  - Irinotecan liposome injection
- •TKIs
  - Apatinib
  - Anlotinib

Sabari, Joshua K et al. “Changing the Therapeutic Landscape in Non-small Cell Lung Cancers: the Evolution of Comprehensive Molecular Profiling Improves Access to Therapy.” *Current oncology reports* vol. 19,4 (2017)

Lurbinectidin

Lurbinectedin + Irinotecan in Advanced Solid Tumors: Tumor Size Decrease at Recommended Dose



Aix. ASCO 2020. Abstr 3514. Reproduced with permission.

Slide credit: clinicaloptions.com

Rovalpituzumab Tesirine (Rova-T)

Antibody-Drug conjugate

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- Rova-
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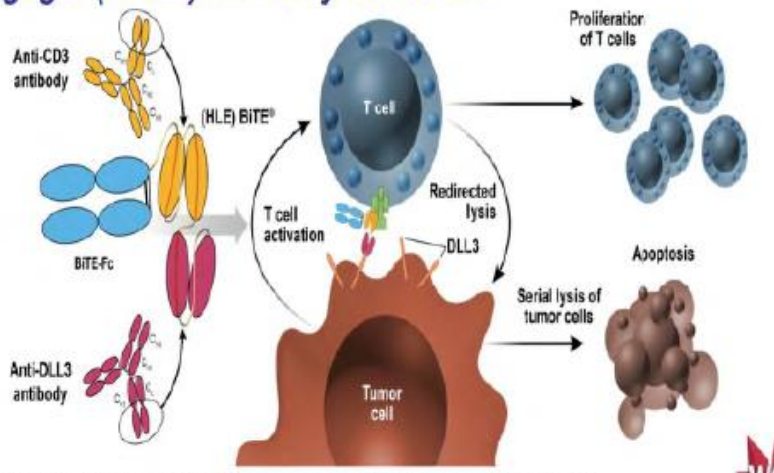
Table 3: A

Morgensztern

Two novel immunotherapy agents targeting DLL3 in SCLC: AMG757 & AMG 119

IASLC 19th World Conference on Lung Cancer
September 23–26, 2018 Toronto, Canada
WCLC2018.IASLC.ORG #WCLC2018

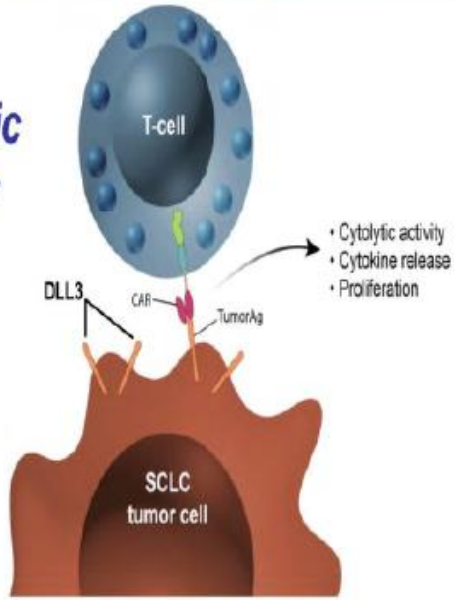
AMG 757 is a half-life extended (HLE) bi-specific T cell engager (BiTE®) antibody construct



BiTE®, bispecific T cell engager; CD, cluster of differentiation; Fc, crystallizable fragment; HLE, half-life extended.

WCLC 2018

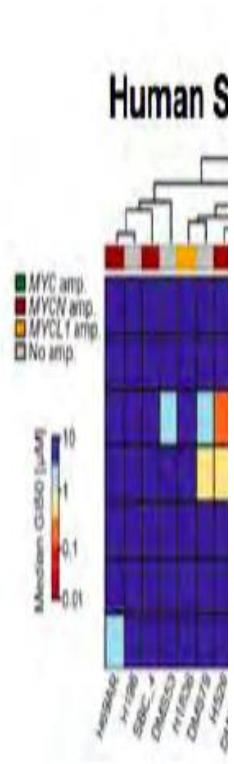
AMG 119 is an adoptive chimeric antigen receptor (CAR) T cell therapy



WCLC 2018

Owonikoko WCLC 18

Aurora Kinase Inhibitor : Alisertib



MYC-

Ranc

Randomized phase II of paclitaxel/alisertib or

n ED-SCLC

PFS in all patients

expression

0.12–0.72

300

Aliserti

Placeb

MY

by

IHC analysis of MYC (only 46/178 patients)

- 1+, 2+ or 3+ score: MYC positive
- 0+ score: MYC negative

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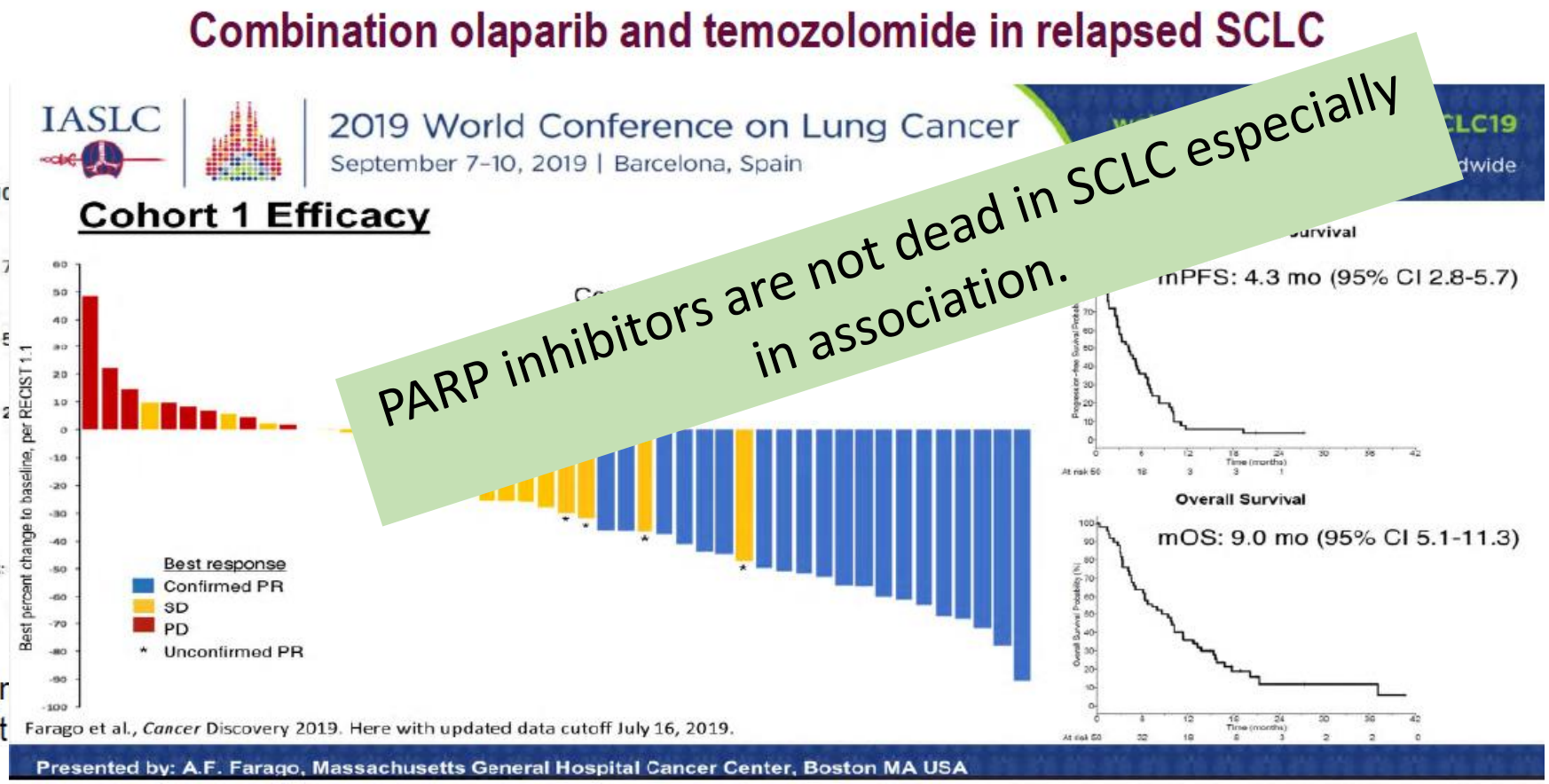
Volume 2020 | Article ID 8026849 | https://doi.org/10.1155/2020/8026849

Show citation

Deep and Prolonged Response to Aurora A Kinase Inhibitor and Subsequently to Nivolumab in MYCL1-Driven Small-Cell Lung Cancer: Case Report and Literature Review

Bhaskar C. Kolla,[1] Emilian Racila,[2] and Manish R. Patel[1]

PARP Inhibitors



PARP inhibitors are not dead in SCLC especially in association.

Anti-angiogenesis TKIs in SCLC
Anlotinib and Apatinib

- ALT
  -
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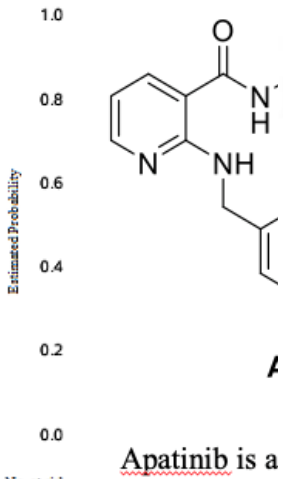

Apatinib is a
kinase inhibi
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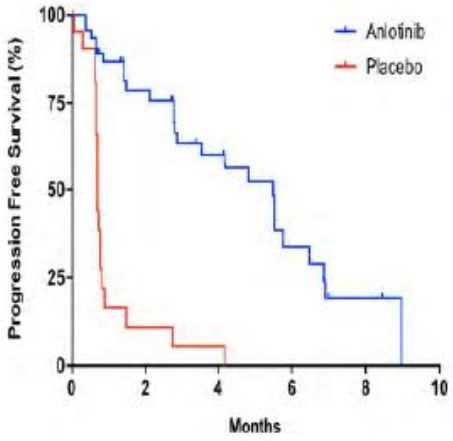
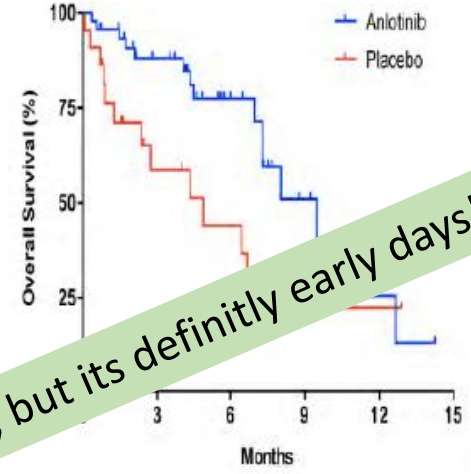


	Anlotinib group	Placebo group
mPFS	5.49 months	0.69 months
P value	<0.0001	
HR (95% CI)*	0.13 (0.06-0.28)	

*HR was adjusted for clinical stage and pattern of relapse.

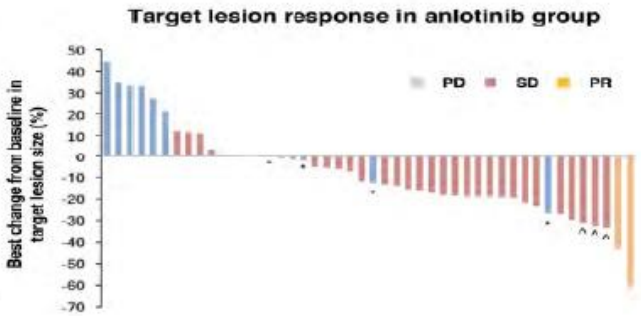


	Anlotinib group	Placebo group
mOS	9.49 months	4.89 months
P value	0.0388	
HR (95% CI)*	0.47 (0.22-0.98)	

*HR was adjusted for clinical stage and pattern of relapse.

			P
Complete Response, n(%)		0 (0.0)	-
Partial Response, n	(4.35)	0	
Stable Disease, n(%)	32 (69.57)	2 (9.09)	
Progression Disease, n(%)	10 (21.74)	14 (63.64)	
NE, n(%)	2 (4.35)	6 (27.27)	
Objective Response Rate(%)	2 (4.35)	0	0.454
95% CI	(0.53, 14.84)	-	
Disease Control Rate(%)	34 (73.91)	2 (9.09)	<0.001
95% CI	(58.87, 85.73)	(1.12, 29.16)	

Interesting developments, but its definitly early days!!!

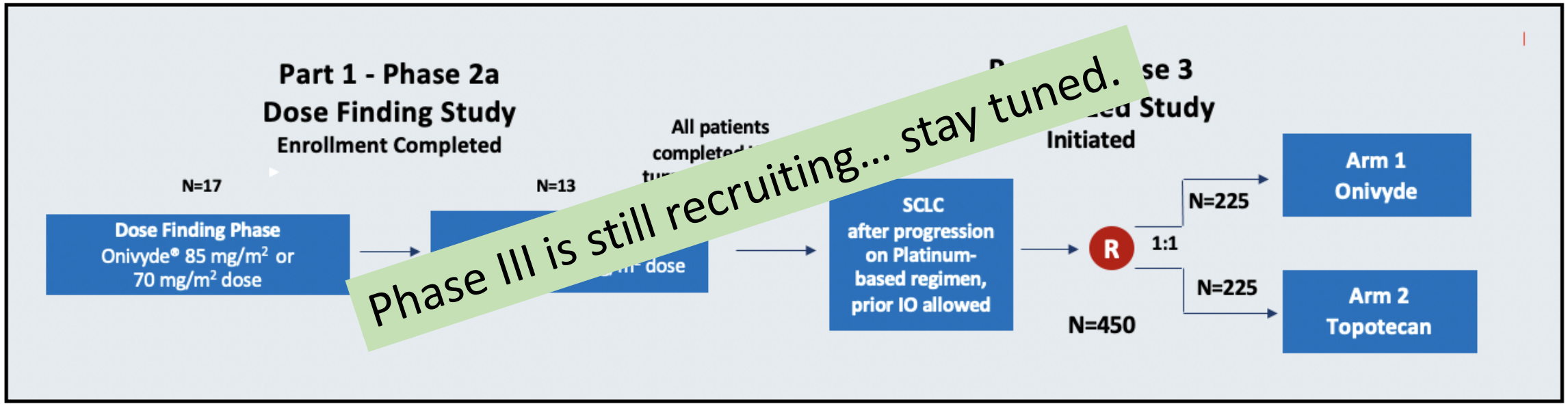


Quiming Wang, WLCC 2019

Liposomal irinotecan (nal-IRI)

RESILIENT Phase 2/3 Study Seamless Design

A **R**andomized, Op**e**n Label Phase 3 **S**tudy of **I**rinotecan **L**iposome **Inj**ection (ONIVYDE®) versus **T**opotecan in Patients with Small Cell Lung Cancer Who Have Progressed on or after Platinum-based First-Line Therapy



INSTITUT JULES BORDET

ONCODISTINCT NETWORK

BSMO

14th Belgian Symposium on the Integration of Molecular Biology Advances into Oncology Clinical Practice and Post-MASCC

CHL Centre Hospitalier de Luxembourg

Thank you very much !