LUNG CANCER UPDATES

ESMO HIGHLIGHTS

19-23 DE OCTUBRE 2018, MUNICH

CARCINOMA DE PULMÓN DE CÉLULA PEQUEÑA

Dr. Joaquim Bosch

Iniciativa científica de:

GECP

Grupo Español de Cáncer de Pulmón

Spanish Lung Cancer Group

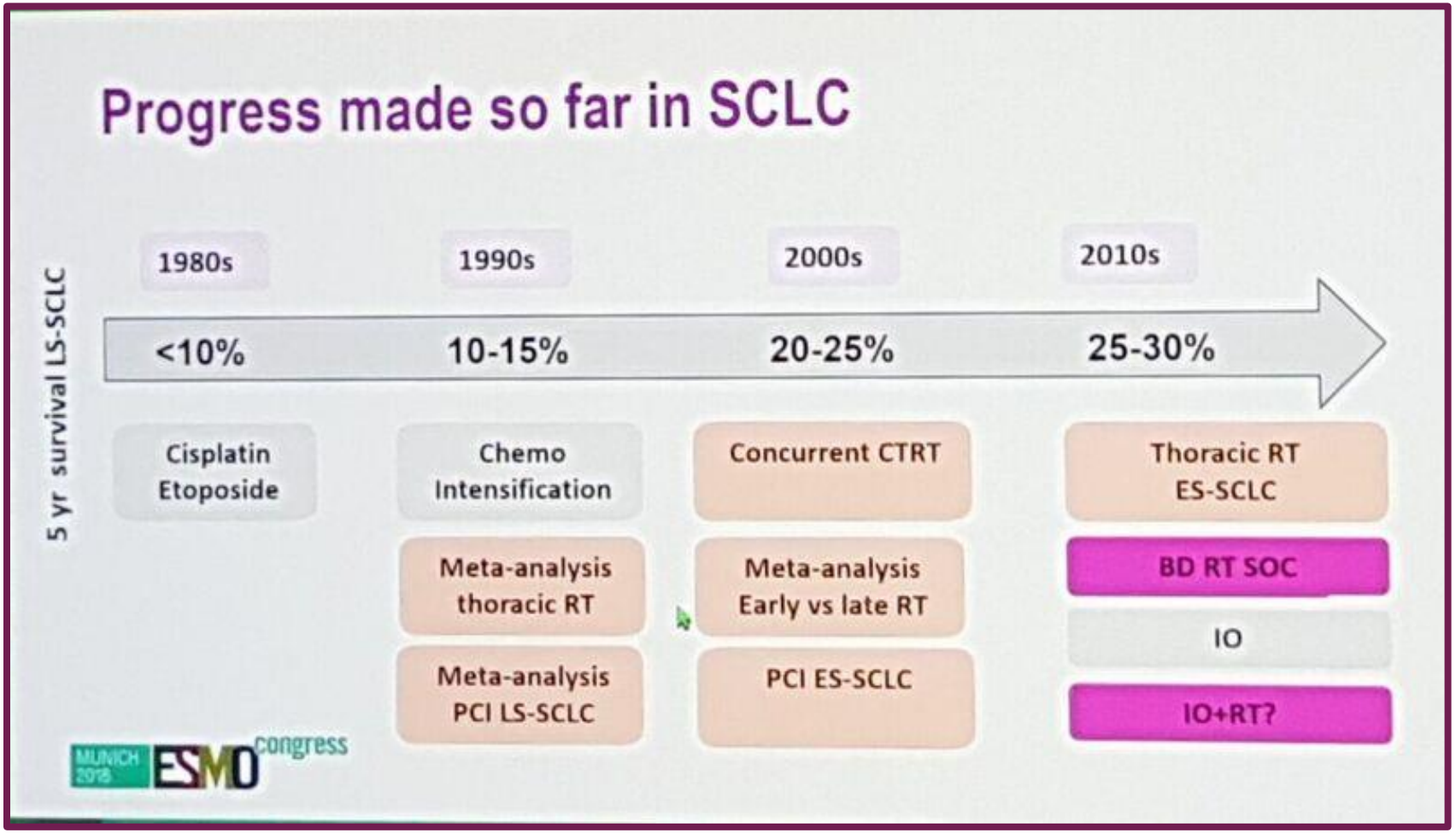
Cáncer de célula pequeña de pulmón

- Alrededor de 13-15% de los cáncer de pulmón son célula pequeña

- Poco papel de la cirugía en estadios no diseminados, 25% de probabilidad de curación con QT-RDT en estadio localizado

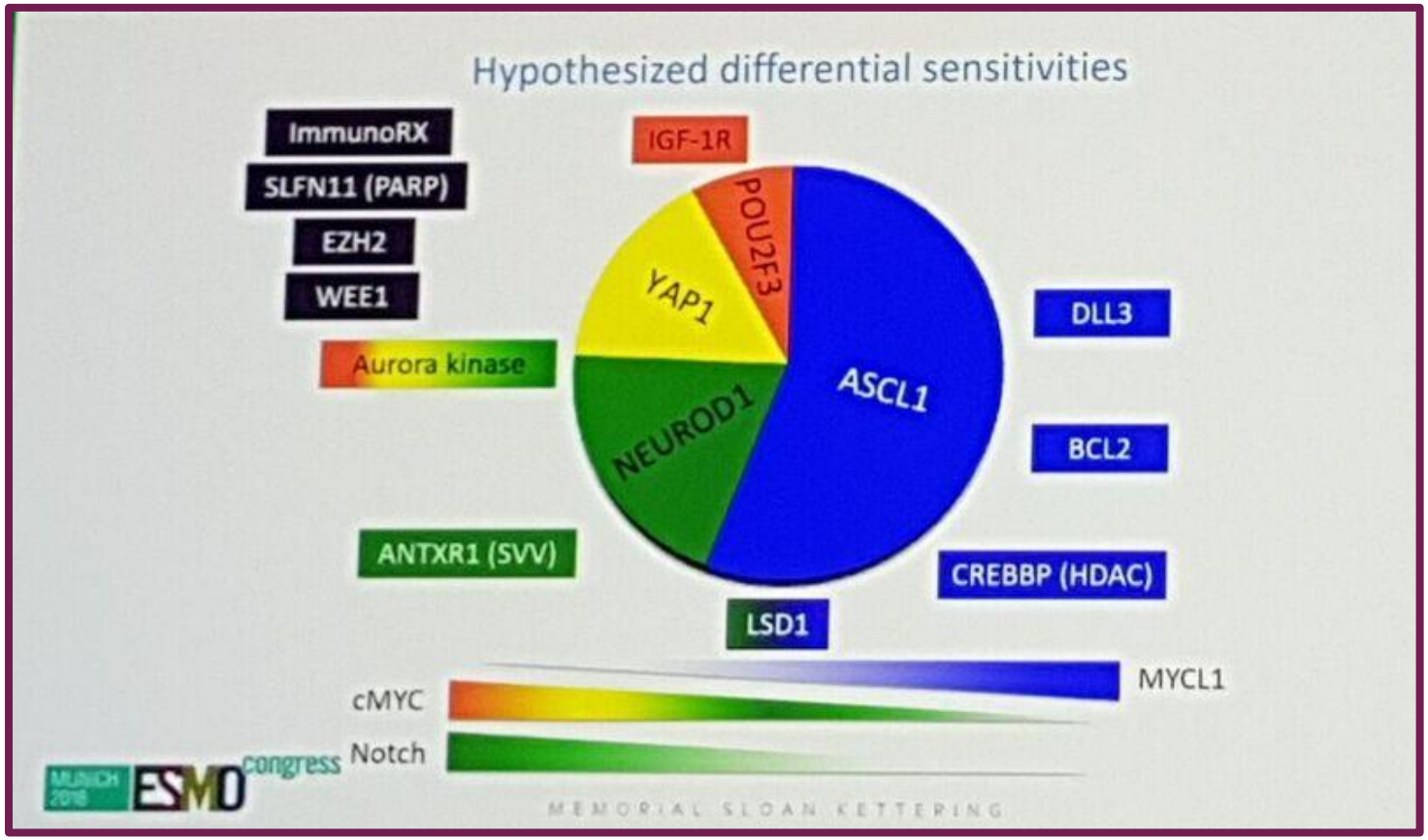
- Estadio diseminado: mal pronóstico, y supervivencia al año del 20-30% y a los 2 años <5%.

Cáncer de célula pequeña de pulmón

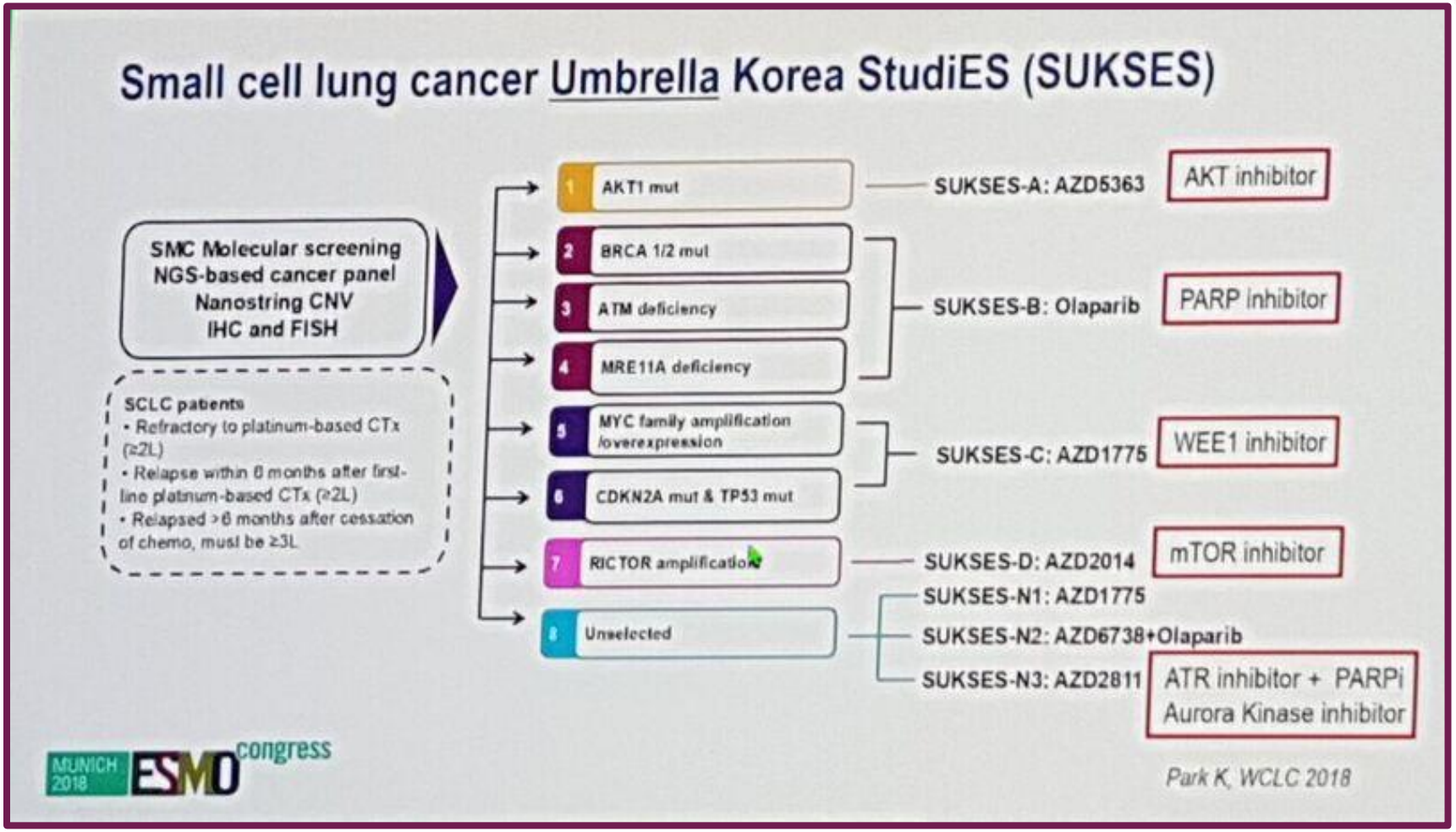


Cáncer de célula pequeña de pulmón

- Determinados marcadores moleculares pueden ayudar a decidir futuras terapias dirigidas



Cáncer de célula pequeña de pulmón



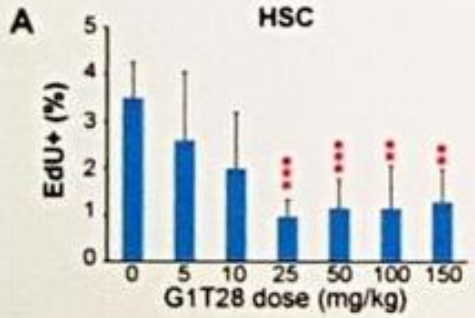
Trilaciclib and prevention of bone marrow exhaustion myelosuppression during small cell lung cancer treatment

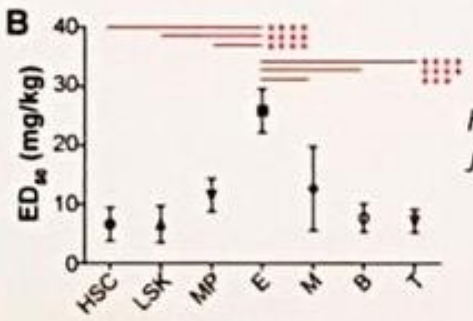
1666- Trilaciclib decreases multi-lineage myelosuppression in extensive-stage SCLC

K.H. Dragnev, T. owonikoko, T. csoszi et al.

Rationale

- Trialaciclib: a small-molecule inhibitor of cyclin-dependent kinases 4 and 6 (CDK4/6).
- Trialaciclib induces transient, reversible G1 cell cycle arrest in both murine and human BM haematopoeitic stem progenitor cell (HSPCs)

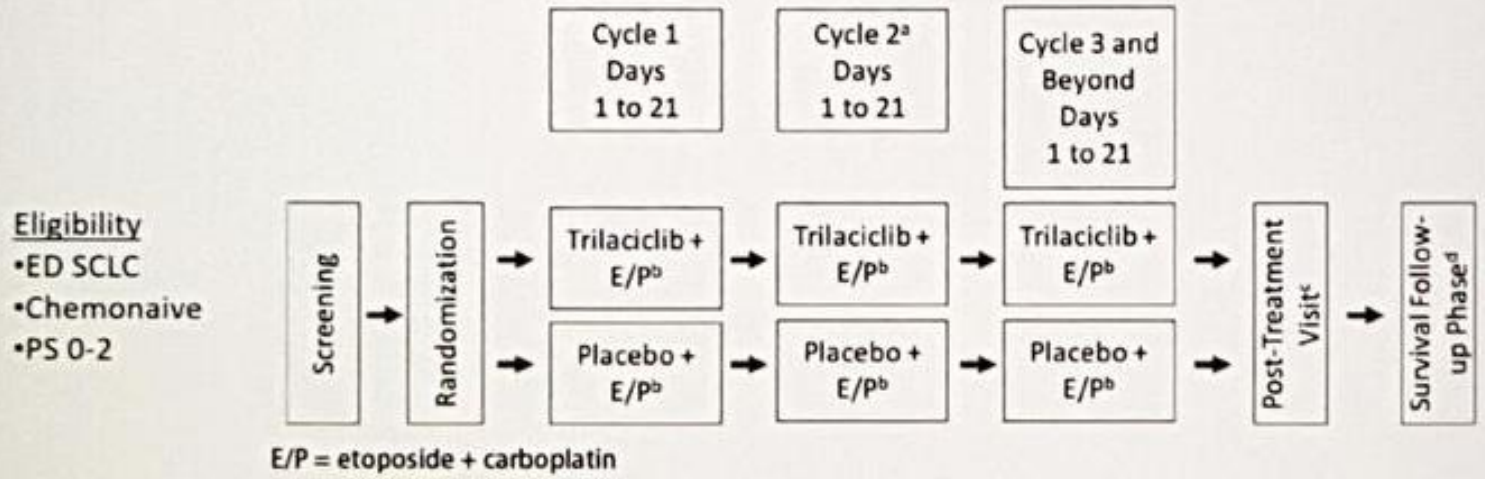




He S, Roberts PJ, Sorrentino JA, Bisi JE, Sci Transl Med. 2017 Apr 26;9

Study design

– Randomized, double-blind, placebo-controlled, multicenter, Phase 1b/2

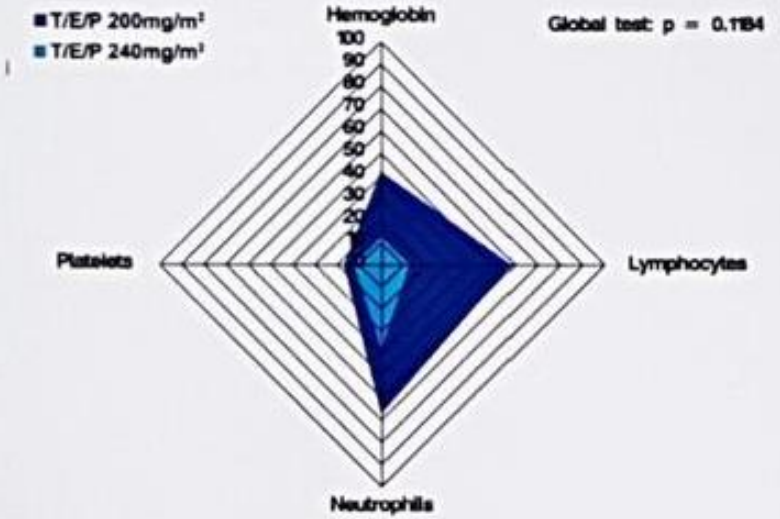


E/P = etoposide + carboplatin

Endpoints for the part 2:
•Multi-lineage Myeolosupression
•Response rate Investigators' assessment
•Overall survival

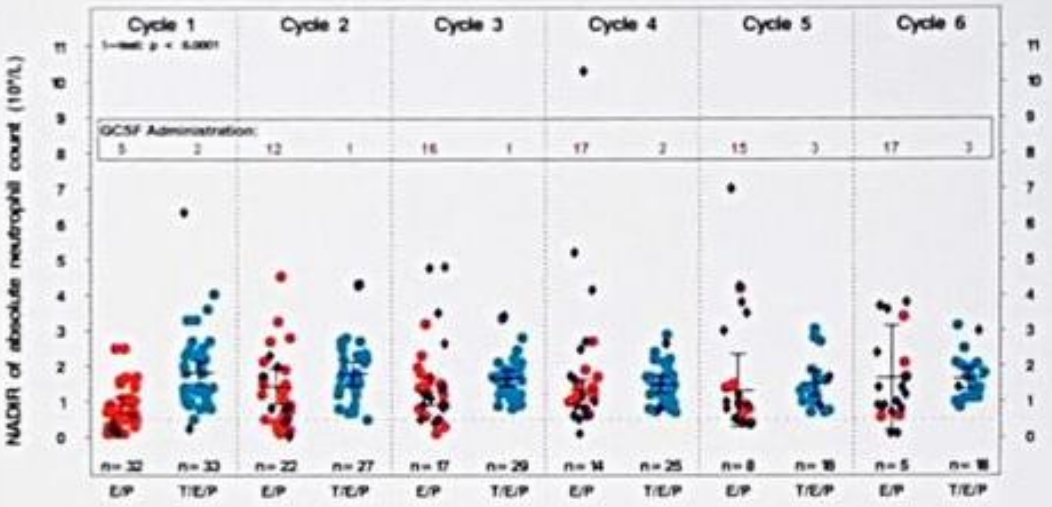
Cáncer de célula pequeña de pulmón

Phase 1 part



This radar chart displays grade 3/4 laboratory abnormalities for hemoglobin, lymphocytes, neutrophils, and platelets. Each axis of the chart represents the proportion (%) of patients with a grade 3/4 abnormality for a hematology laboratory parameter. The shaded area of the whole shape, reflecting the multi-lineage grade 3/4 abnormalities, was compared between treatment groups using a multivariate test to generate the p-value.

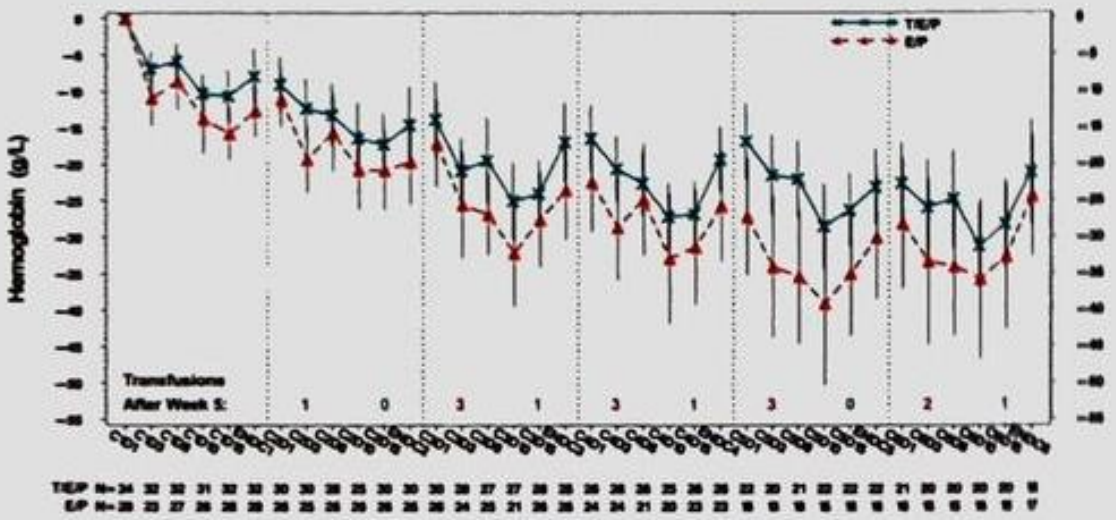
Phase 2 Neutrophil



Endpoint, n (%)	E/P + Placebo (N = 37)	E/P + Trilaciclib (N = 38)	P-value
Patients with Grade 4 ANC	16/37 (43·2%)	2/38 (5·3%)	0·0001
Median duration in days (95%CI)	8 (7, 8)	3 (2, 3)	0.0097
Mean Cycle 1 ANC nadir	0·815 × 10^9/L	1·899 × 10^9/L	<0·0001
Patients with G-CSF administration	24/37 (64·9%)	4/38 (10·5%)	<0·0001
Patients with febrile neutropenia	3/37 (8·1%)	1/38 (2·6%)	0·2773
Cycles with febrile neutropenia	5/190 (2.6%)	1/186 (0.5%)	0.1542

Menor toxicidad en neutrófilos y requerimiento de factores estimuladores, no diferencia en neutropenia febril

Phase 2
RBC



Endpoint, n (%)	E/P + Placebo (N = 37)	E/P + Trilaciclib (N = 38)	P-value
Patients with RBC transfusions	9/37 (24.3%)	4/38 (10.5%)	0.1109
Patients with transfusions after 5 weeks on study	8/37 (21.6%)	2/35 (5.7%)	0.0615
Units transfused per chemotherapy cycle	0.11 (21/190)	0.05 (10/186)	0.0711
Patients with Grade 3/4 hemoglobin	7/37 (18·9%)	4/38 (10·5%)	ND
Patients with ESA administration	2/37 (5·4%)	1/37 (2·6%)	0·5578

Menor toxicidad en serie roja, pero no significativa (salvo número bolsas de transfusión)

Conclusion

- Trilaciclib 240 mg/m2 significantly reduced clinical impacts of carboplatin – etoposide on neutrophils and lymphocytes, and trended to reduce RBC transfusion requirements. Due to the low impact of this chemotherapy in platelet lineage, no significant difference was observed between trilaciclib and placebo.
- Dose reductions and treatment delays affected a lower proportion of patients in the trilaciclib group, resulting in a better response rate and a trend toward longer PFS .
- This trial deserves further studies evaluating trilaciclib with more myelo-suppressive chemotherapy such as topotecan.

IO in SCLC

> IFCT-1603 study, Pujol et al, abstract 1664O

A randomized non-comparative phase II study of anti–PD-L1 atezolizumab or chemotherapy as 2nd line therapy in patients with small cell lung cancer: Results from the IFCT-1603 Trial

J-L. Pujol, L. Greillier, C. Audigier-Valette, D. Moro-Sibilot, L. Uwer, J. Hureaux, L. Thiberville, D. Carmier, J. Madelaine, J. Otto, V. Gounant, P. Merle, P. Mourlanette, O. Molinier, P-A. Renault, J. Mazieres, M. Antoine, M. Denis, A. Langlais, F. Morin, P-J. Souquet.

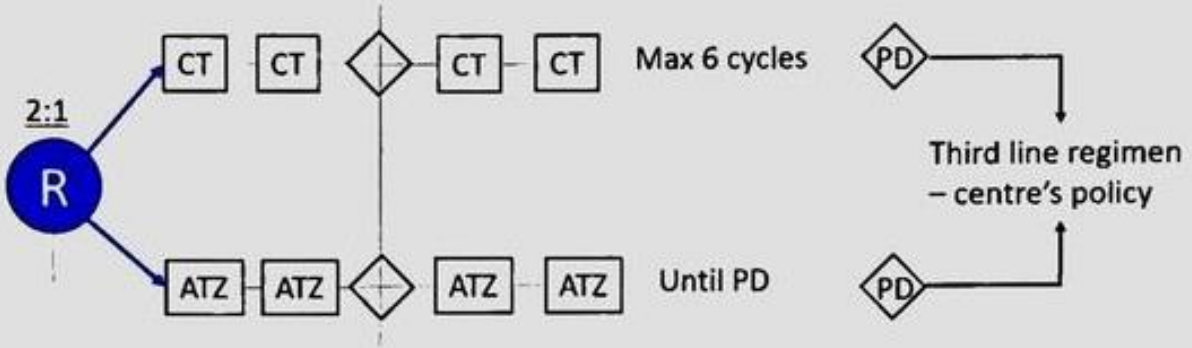
ClinicalTrials.gov Identifier: NCT03059667

IFCT

Phase II of atezolizumab in relapsed SCLC
IFCT 16-03

Eligibility

- ED or LD SCLC (VALG)
- Progressive disease
- PS 0-2
- Measurable disease (RECIST 1,1)
- No autoimmune disease
- No brain metastases
- No corticosteroids
- Informed consent



Stratification
Sensitive vs refractory disease
PS (0-1 versus 2)
Limited versus extensive disease
Gender

Endpoint: Response rate in the experimental arm at 6 weeks (confirmation needed at 12 weeks)

Post-hoc analyses
PD-L1 tumor staining (SP142)
NGS analysis of selected genes

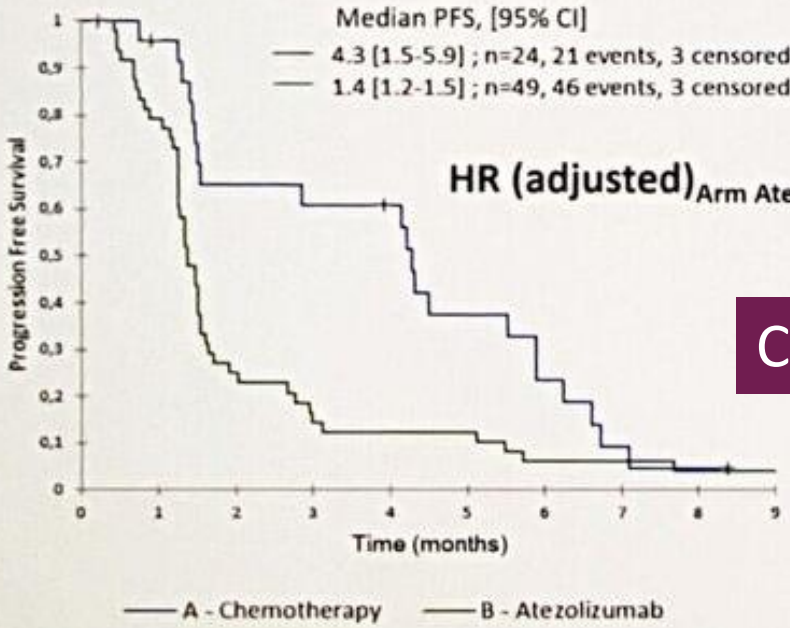
ATZ : Atezolizumab 1,200 mg q3w
CT: oral or IV topotecan q3w or [carboplatin – etoposide] q3w (investigators' choice).

Cáncer de célula pequeña de pulmón

Evaluación a las 6 semanas	Quimioterapia	Atezolizumab
ORR	10%	2.3%
DCR	65%	20.9%
PD	30%	69.8%

PFS in IFCT 1603: phase 2 comparing atezolizumab vs CT

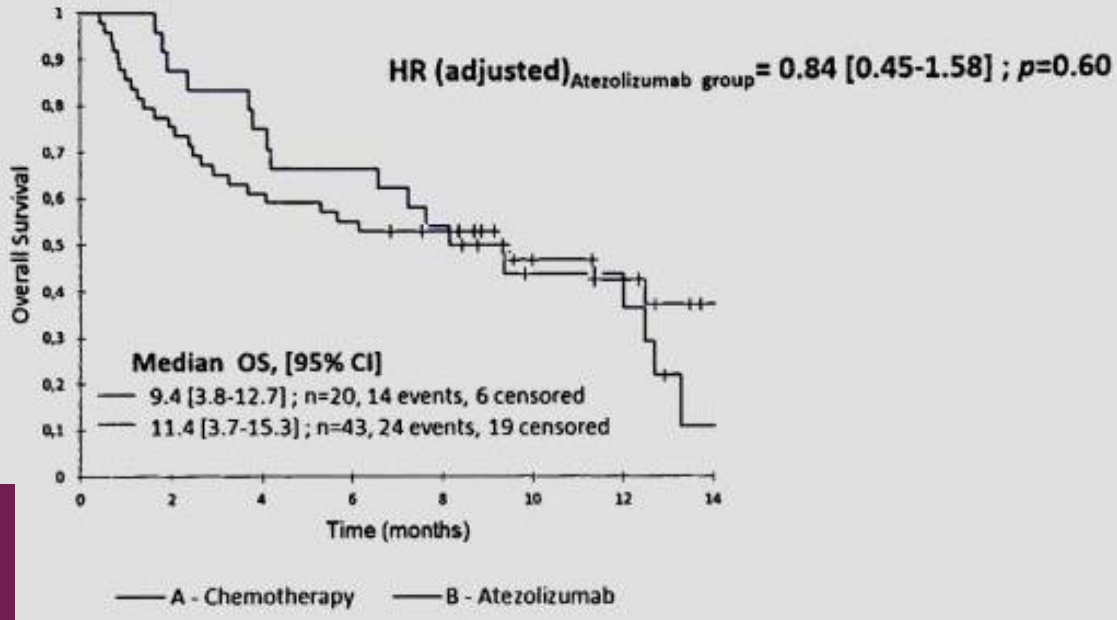
Median follow-up [95% CI]: 13.7 months [12.7-NR]



HR (adjusted)$_{\text{Arm Atezolizumab}}$ = 2.26 [1.30-3.93] ; *p*=0.004

CT: 4.3 m vs Atezo:1.4 m

Overall survival (intent-to-treat population)



1-year OS rate for Atezolizumab group : 42.5% [26.9% ;58.2%]

CT: 9.4 m vs
Atezo:11.4 m
P=0.6

Cáncer de célula pequeña de pulmón

IO in SCLC

> data in the relapse setting

	N	ORR (%)	mPFS	mOS	1-year OS
Topotecan [1]	107	24%	2.8 m (13w)	5.6 m (25w)	14%
CAV [1]	104	24%	2.7 m (12w)	5.6 m (25w)	14%
Amrubicin [2]	424	31%	4.1 m	7.5 m	27%
Topotecan [2]	213	17%	3.5 m	7.8 m	25%
Control (IFCT-1603)	24	10%	4.3 m	8.7 m	NR
Atezolizumab (IFCT-1603)	49	2%	1.4 m	9.5 m	NR
Nivolumab (CM-032) [3]	98	10%	1.4 m	4.1 m	33%
Pembrolizumab (KN-028) [4]	24	33% *(PDL1+)*	1.9 m	9.7 m	38%
Pembrolizumab (KN-158) [5]	107	19% *(36 v 6%)*	2.0 m	9.1 m	40%
Atezolizumab (PCD4989) [6]	17	6%	-	-	-
Durvalumab [7]	21	10%	1.5 m	4.8 m	28%

1 Von Pawel et al, J Clin Oncol 17:658-667, 1999
2 Von Pawel et al, J Clin Oncol 32:4012-4019, 2014
3 Hellmann et al, abstract 8503, ASCO 2017
4 Ott et al, J Clin Oncol 35:3823-3829, 2017
5 Chung et al, abstract 8506, ASCO 2018
6 Goldman et al, abstract 8518, ASCO 2018
7 Sequist et al, abstract 1425PD, ESMO 2017

Respiratory Oncology Unit
Univ. Hospital Leuven
Leuven Lung Cancer Group
http://www.LLCG.be

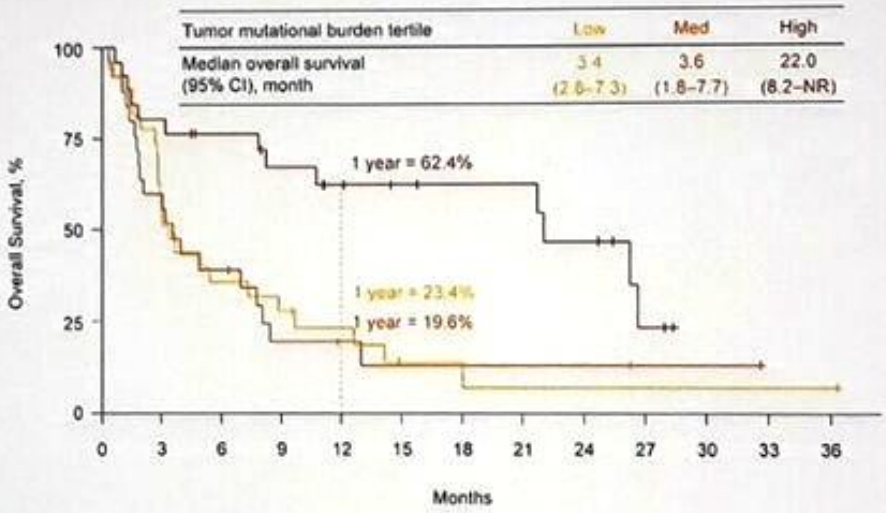
IO in SCLC

> we need smarter approaches

- **Combination IO**
  - **Checkmate-032: nivolumab ± ipilimumab**
  - **Use of biomarkers to predict the long-term result**

Supervivencia al año del 62.4% en los pacientes con alta carga mutacional tumoral

Nivolumab + Ipilimumab



Hellmann et al, abstract 8503, ASCO 2017
Hellmann et al, Cancer Cell 33: 853–861, 2018

Cáncer de célula pequeña de pulmón

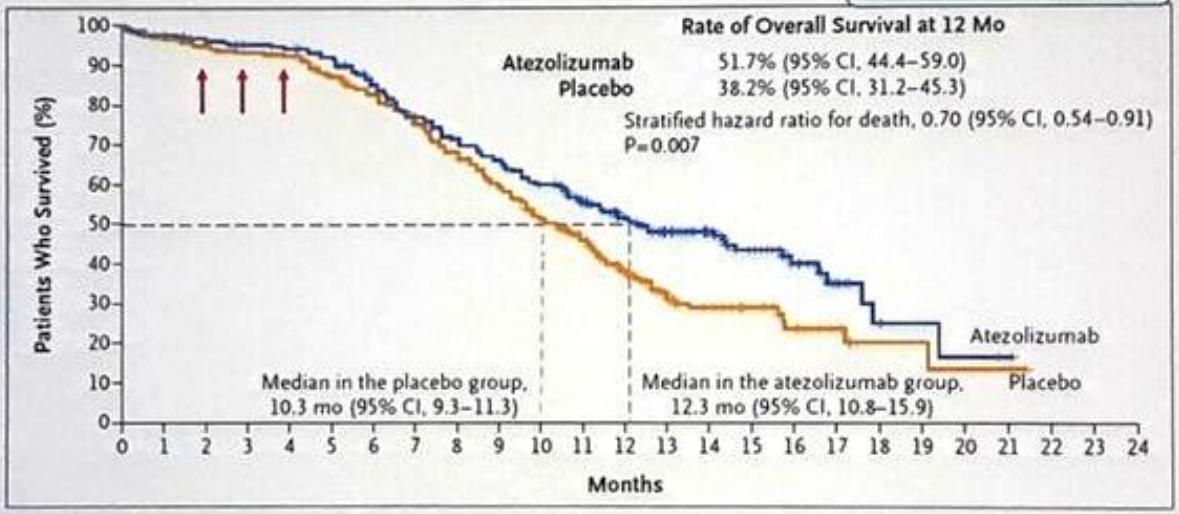
IO in SCLC

> we need smarter approaches

- Combination IO
- **Take advantage of IO & chemotherapy interaction**

Landmark trial

Beneficio en 1ª línea de añadir atezolizumab al platino-etoposido



Horn et al, N Engl J Med Sep 25, 2018

Cáncer de célula pequeña de pulmón

- Resultados pendientes de Rovalpituzumab en combinación con immunoterapia o en mantenimiento.

- Resultados con Lurbinectidina (PM1183) en el fase III en marcha