Nice St-Paul Thorax

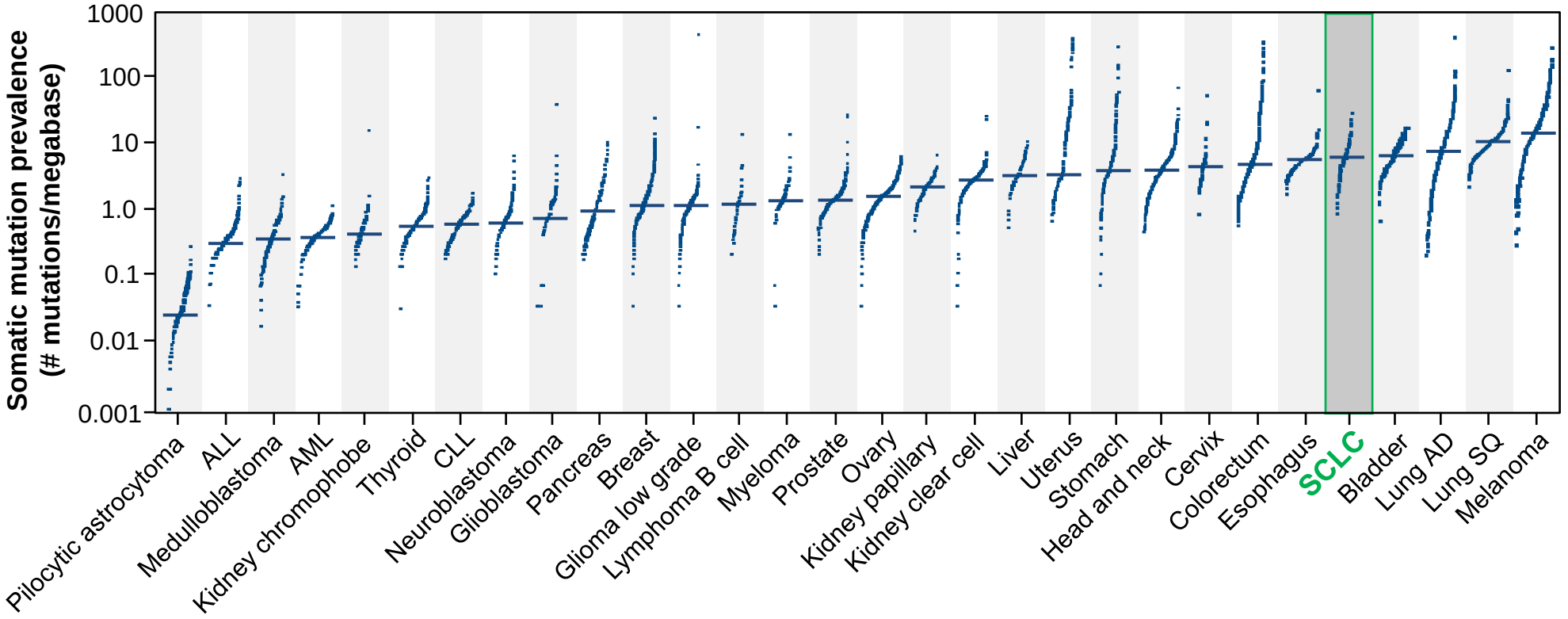
Quelles données suivre en 2019 pour l'édition 2020 ?

Jean Louis Pujol, Montpellier

CPC: Une charge mutationnelle élevée

- 8,6 mutations ponctuelles non synonymes par million de bases
- Transversions C:G>A:T
- *TP53* et *RB1*, *KIAA1211* et *COL22A1*, *RGS7* et *FPR1*.
- Inactivation de la voie *NOTCH*
- Mutations ponctuelles pour *P53*
- Réarrangements plus complexes pour *RB1*
- Surexpression de *CCND1* laquelle rend silencieux *RB1*
- Amplification des gènes de la famille *MYC* : *MYCL1, MYCN* et *MYC*
- *Chromothrypsie*

Rationale for Evaluating TMB in SCLC



- SCLC is almost exclusively found in patients with history of smoking and is characterized by high TMB[1,2]
- An association between TMB and efficacy has been seen with nivolumab in NSCLC and bladder cancer, and with ipilimumab in melanoma[3–5]
- **Hypothesis: high TMB may be associated with enhanced benefit from nivolumab ± ipilimumab in SCLC**

1. Adapted by permission from Macmillan Publishers Ltd: Alexandrov LB, et al. *Nature* 2013;500:415-421, copyright 2013. 2. Morabito A, et al. *Crit Rev Oncol Hematol* 2014;91:257–270. 3. Carbone DP et al. *N Engl J Med*. 2017;376:2415–2426. 4. Snyder A, et al. *N Engl J Med* 2014;371:2189–2199. 5 Galsky MD, et al. Poster Discussion at ESMO 2017. 848PD.

Peut on suivre les cancers à petites cellules sur l'ADN libre circulant

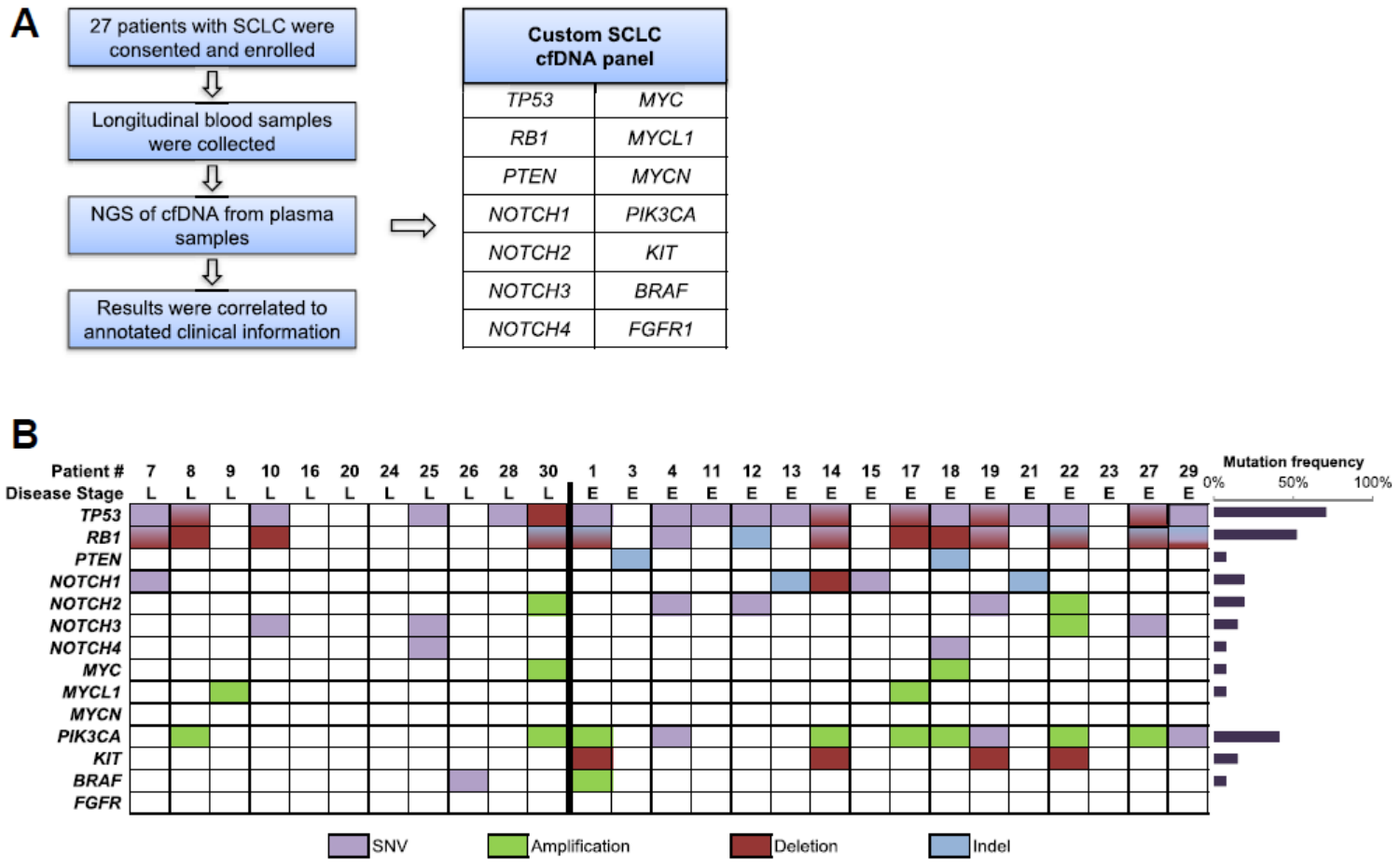


Figure 1. Mutational analysis in plasma cell-free DNA (cfDNA) from 27 patients using next-generation sequencing.

Journal of Thoracic Oncology *Vol. 13 No. 1: 112-123*

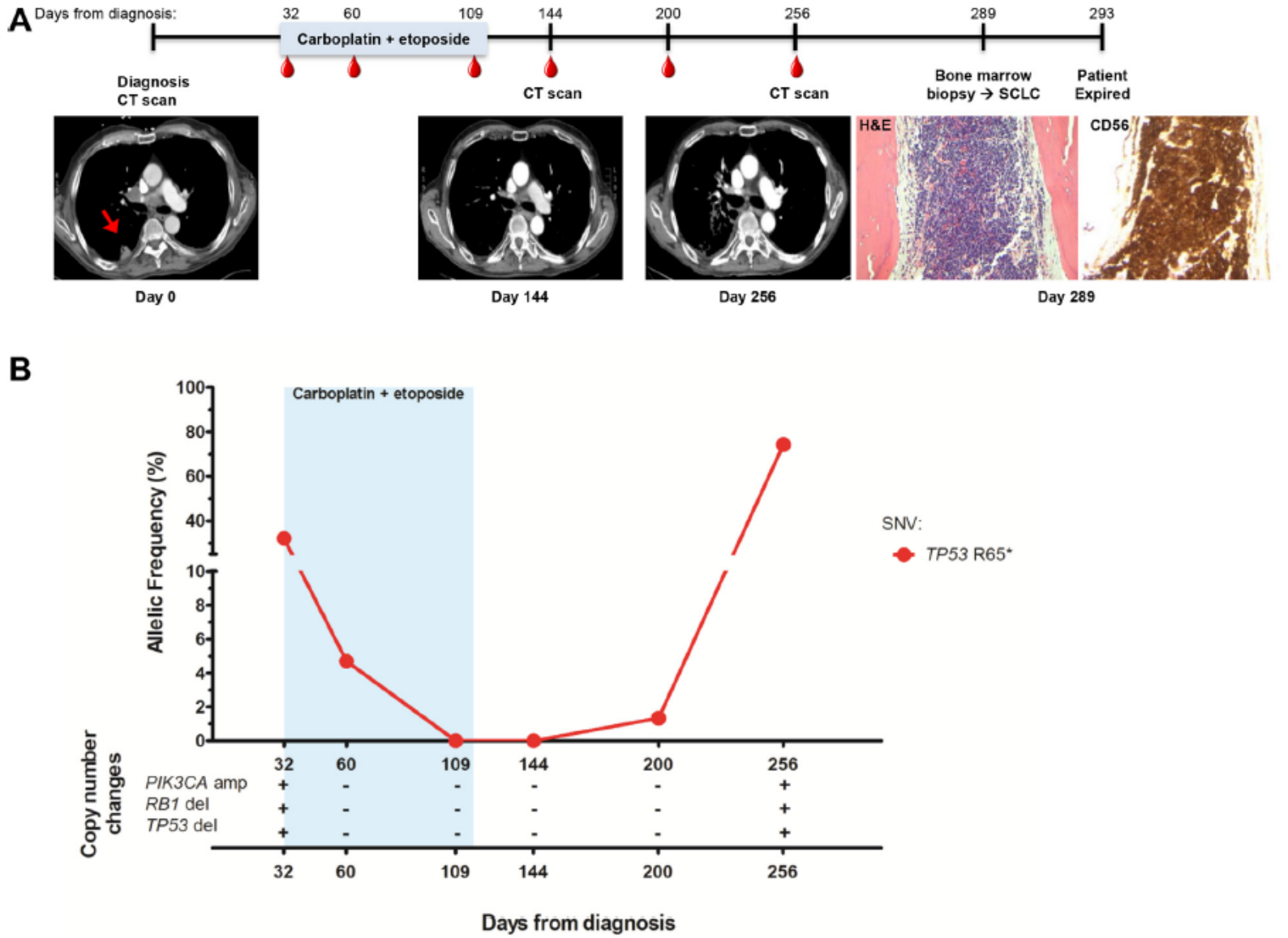
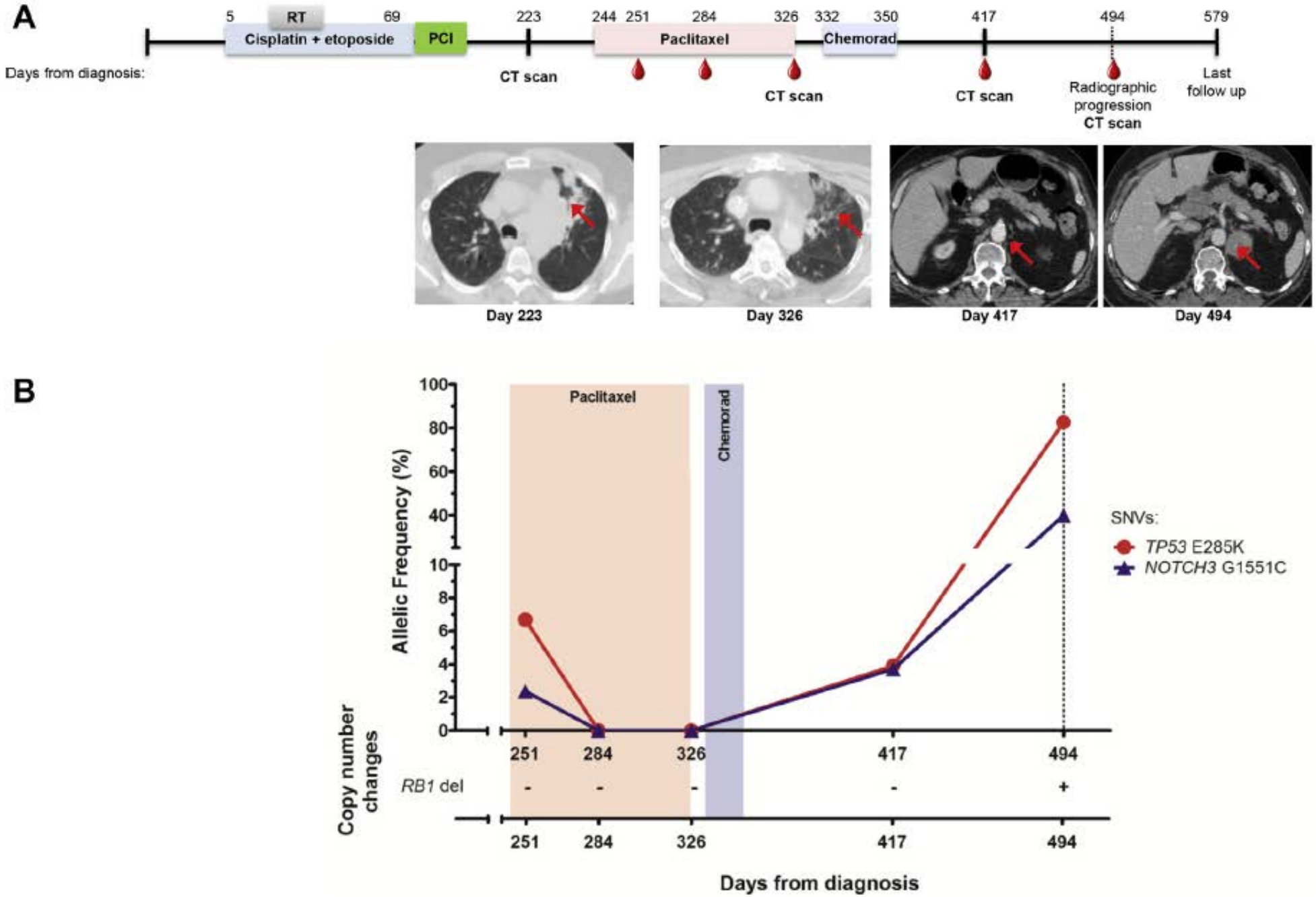
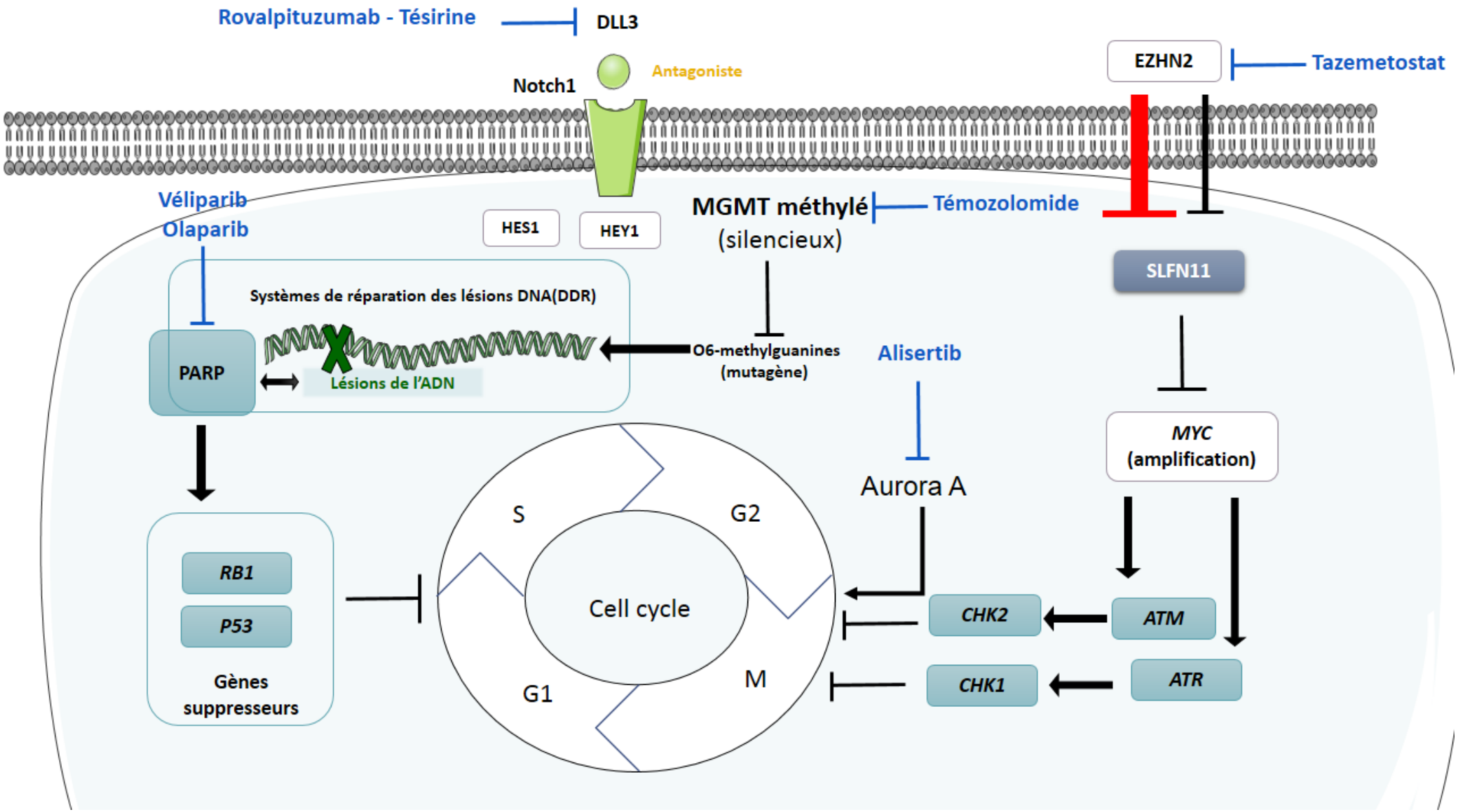


Figure 2. Cell-free DNA detection precedes clinical or radiographic disease progression. (*A*) The time line for the clinical

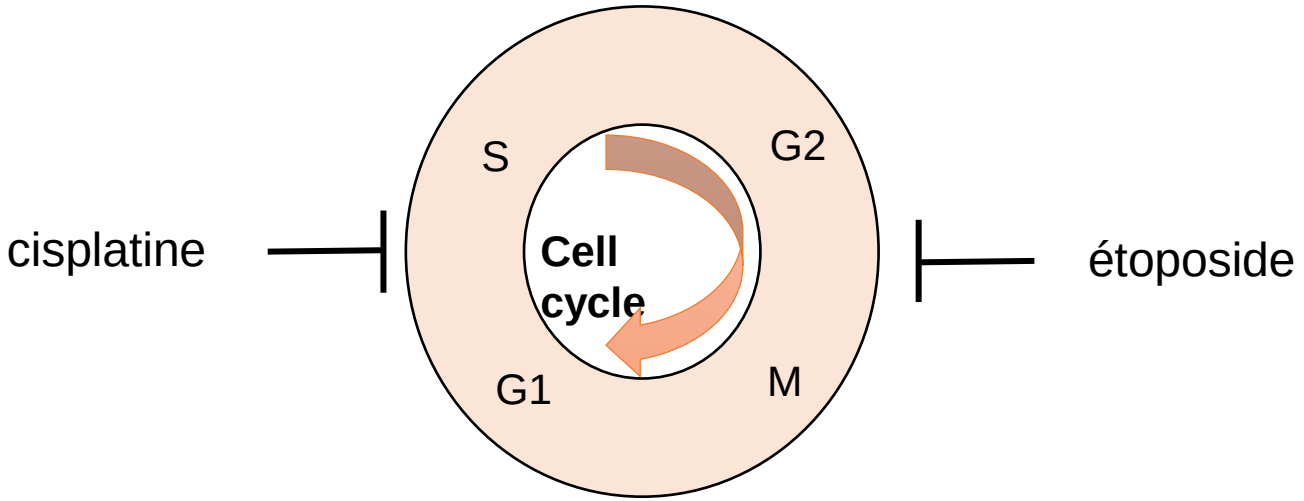

A
Days from diagnosis:
5
RT
69
Cisplatin + etoposide
PCI
223
CT scan
244
251
284
326
Paclitaxel
CT scan
332
350
Chemorad
417
CT scan
494
Radiographic progression CT scan
579
Last follow up
Day 223
Day 326
Day 417
Day 494
B
Paclitaxel
Chemorad
Allelic Frequency (%)
100
80
60
40
10
8
6
4
2
0
SNVs:
TP53 E285K
NOTCH3 G1551C
Copy number changes
RB1 del
251
284
326
417
494
- - - - +
Days from diagnosis

DDR*

*CIBLAGE DE LA REPARATION DES DOMMAGES DE L’ADN

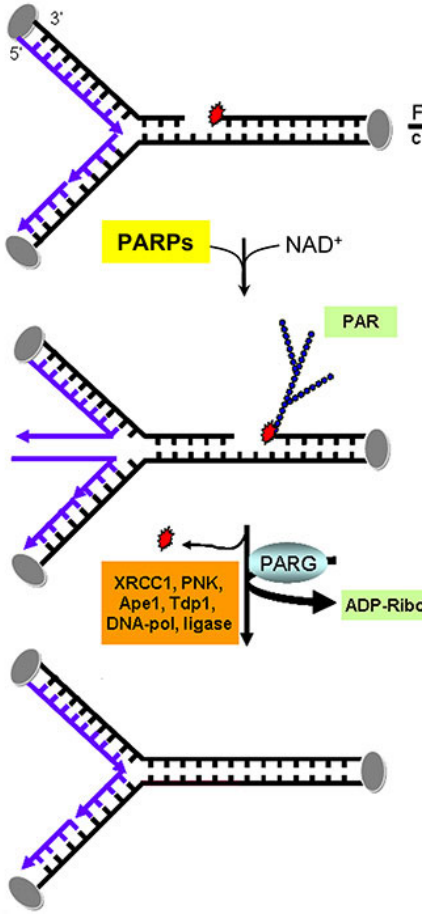


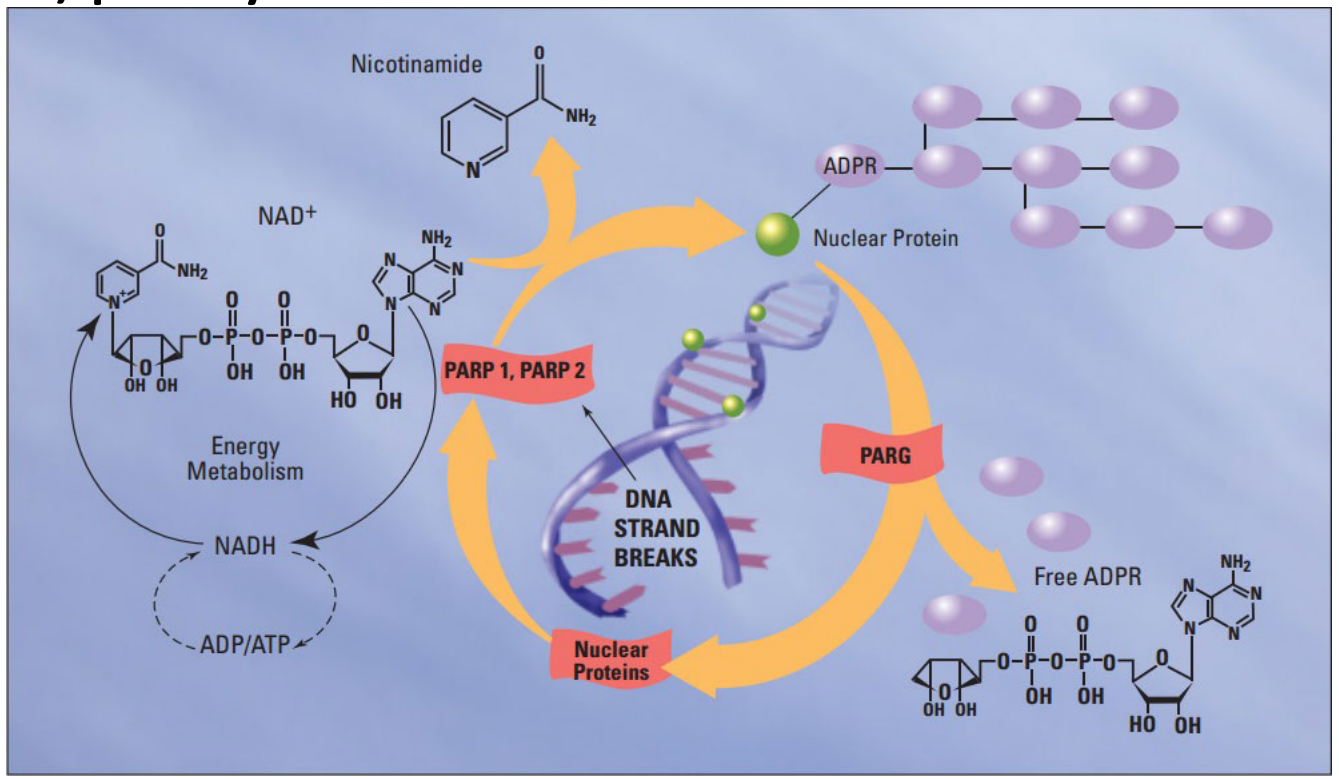
¨Pujol JL et al. Bulletin du cancer, 2018



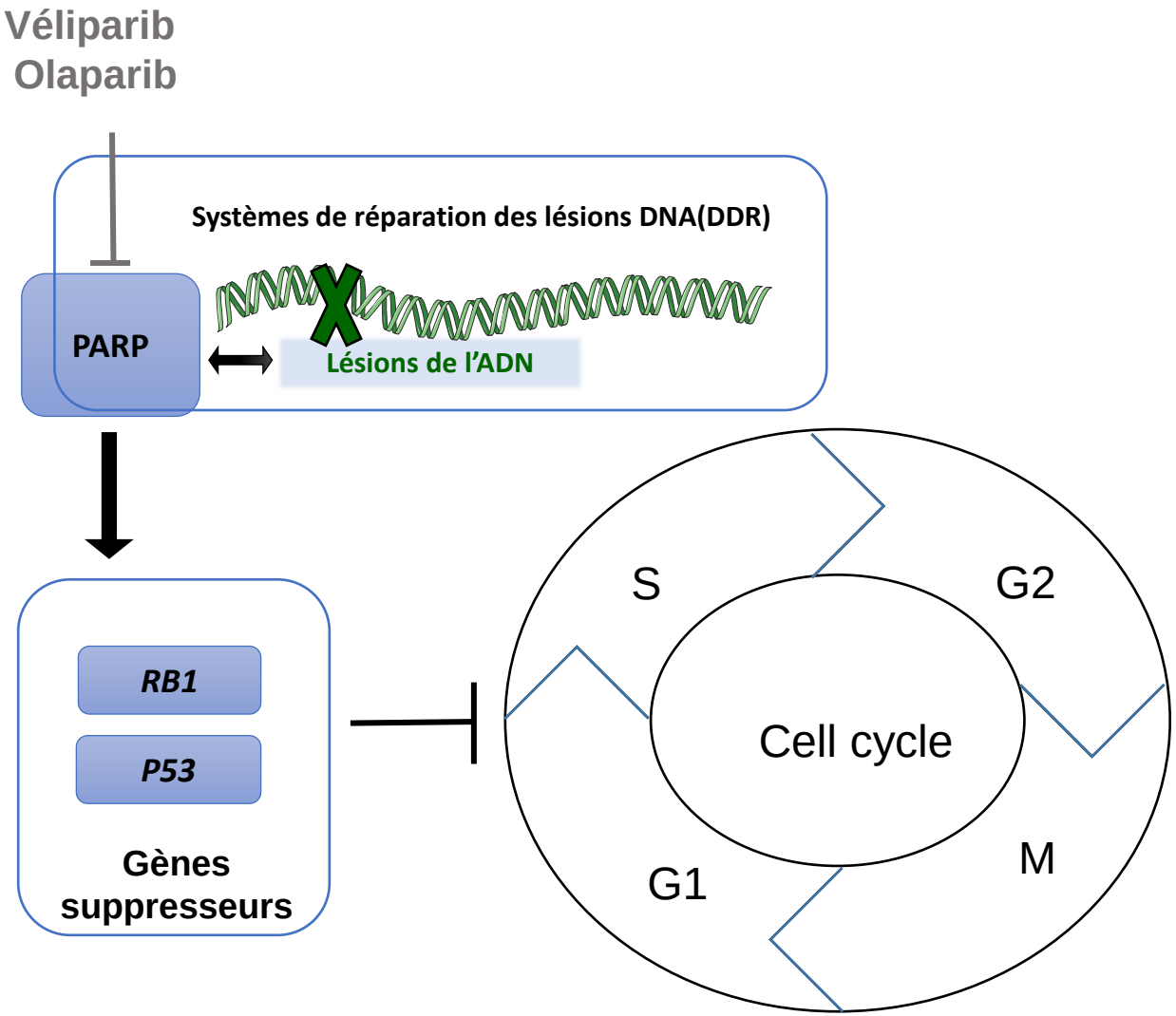
pourquoi la réinduction du protocole Cisplatine - Etoposide lors de la rechute se solde par des taux de réponses inférieures de moitié à ceux observés en induction?

poly(ADP-ribose)polymérases PARP





Poly-ADP-ribose polymerase (PARP) catalyzes the NAD dependent addition of poly-ADP-ribose (PAR) to adjacent nuclear proteins. PARP plays an important role in **DNA repair** but can also lead to **apoptosis** by depleting the cellular NAD pool. **PARP inhibition** has been shown to prevent tissue damage in animal models of myocardial & neuronal ischemia, diabetes, septic shock, & vascular stroke.


Véliparib
Olaparib
Systèmes de réparation des lésions DNA(DDR)
PARP
Lésions de l'ADN
RB1
P53
Gènes suppresseurs
S
G2
Cell cycle
M
G1

Les anti-PARP pour les CPC

- Activité inférieure à celle observée pour le cancer du sein:
  Talazoparib: 9% de taux de réponse
- Directions de recherche:
  - Utilisation de certains agents anti-PARP (Talazoparib) pour les patients en rechute,
  - Combinaison du Témozolomide et du Véliparib ou de l'Olaparib pour ces mêmes patients,
  - Adjonction du Véliparib à la chimiothérapie de type Cisplatine – Etoposide en première ligne.

Phase 1 talazoparib

Table 4. Clinical response rate (RECIST) by cancer type in patients treated with talazoparib 1.0 mg/day (recommended phase 2 dose)

Response	Breast[a] (*n* = 14)	Ovarian/ peritoneal[a] (*n* = 12)	SCLC (*n* = 23)	Pancreatic (*n* = 10)	Ewing's sarcoma (*n* = 13)
ORR,%	50.0	41.7	8.7	20.0	0
CR, *n*	1	1	0	0	0
PR, *n*	6	4	2	2	0
SD, *n*	5[b]	3[b]	4[c]	1[c]	3[c]
CBR,%[b,d]	85.7	66.7	26.1	30.0	23.1
Median PFS, weeks	34.6	36.4[§]	11.1	ND	ND

Abbreviations: CBR, clinical benefit rate; CR, complete response; ND, not determined; ORR, objective response rate; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors; SCLC, small cell lung cancer; SD, stable disease.

[a]Patients had *BRCA1/2* mutation.

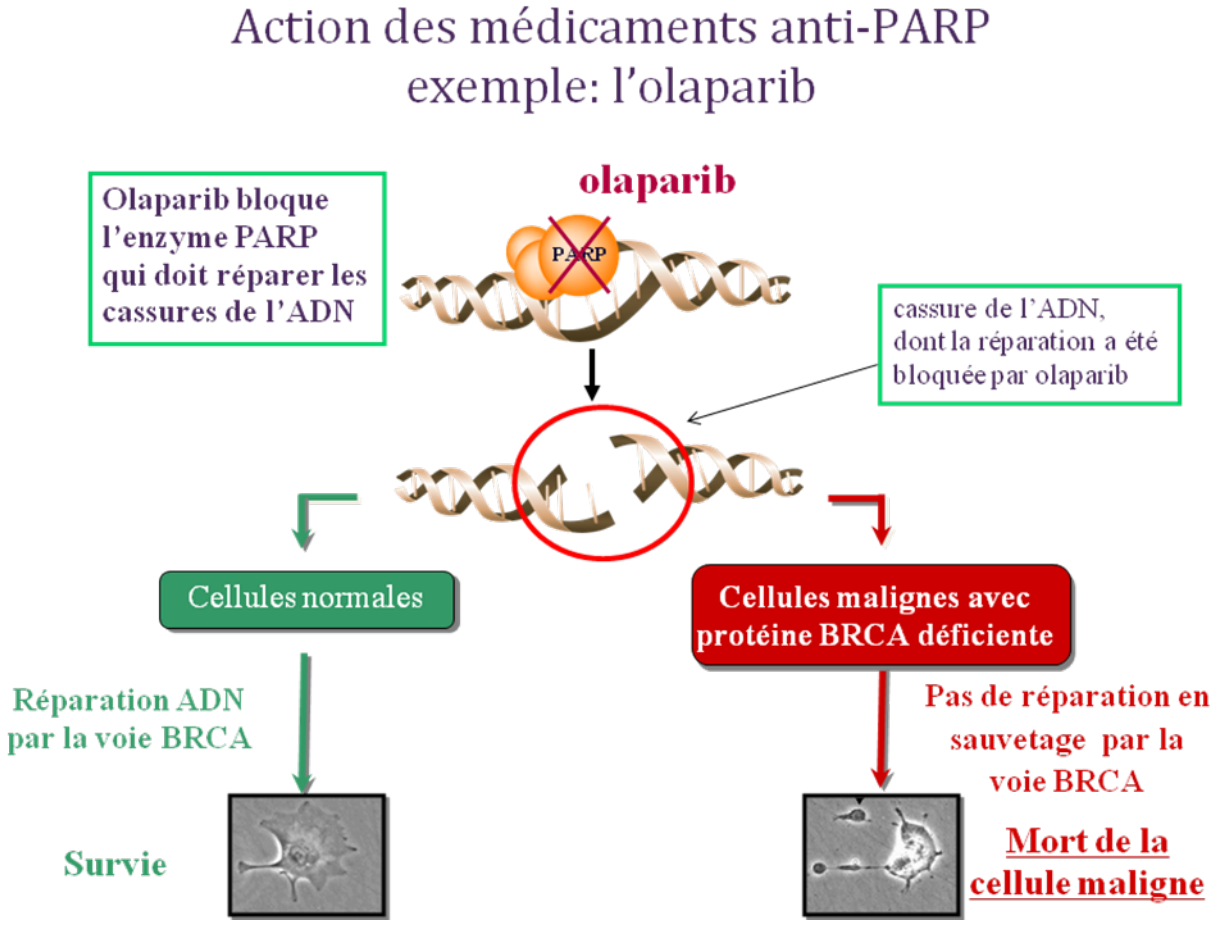
[b]Clinical benefit = CR + PR + SD ≥24 weeks for breast and ovarian cancers.

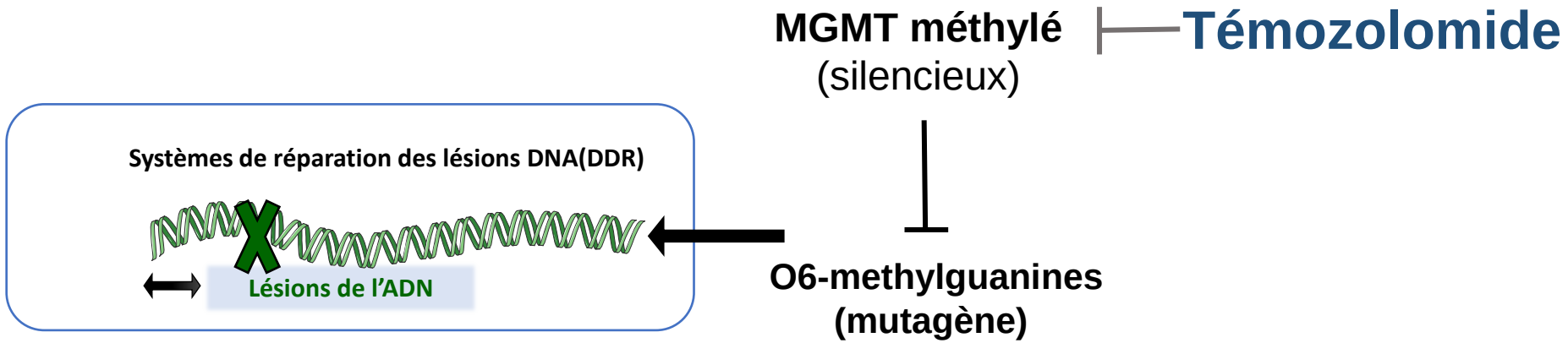
[c]Analysis on 14 patients, as two patients who did not have measurable disease at baseline were included in the PFS analysis but not in the response analysis.

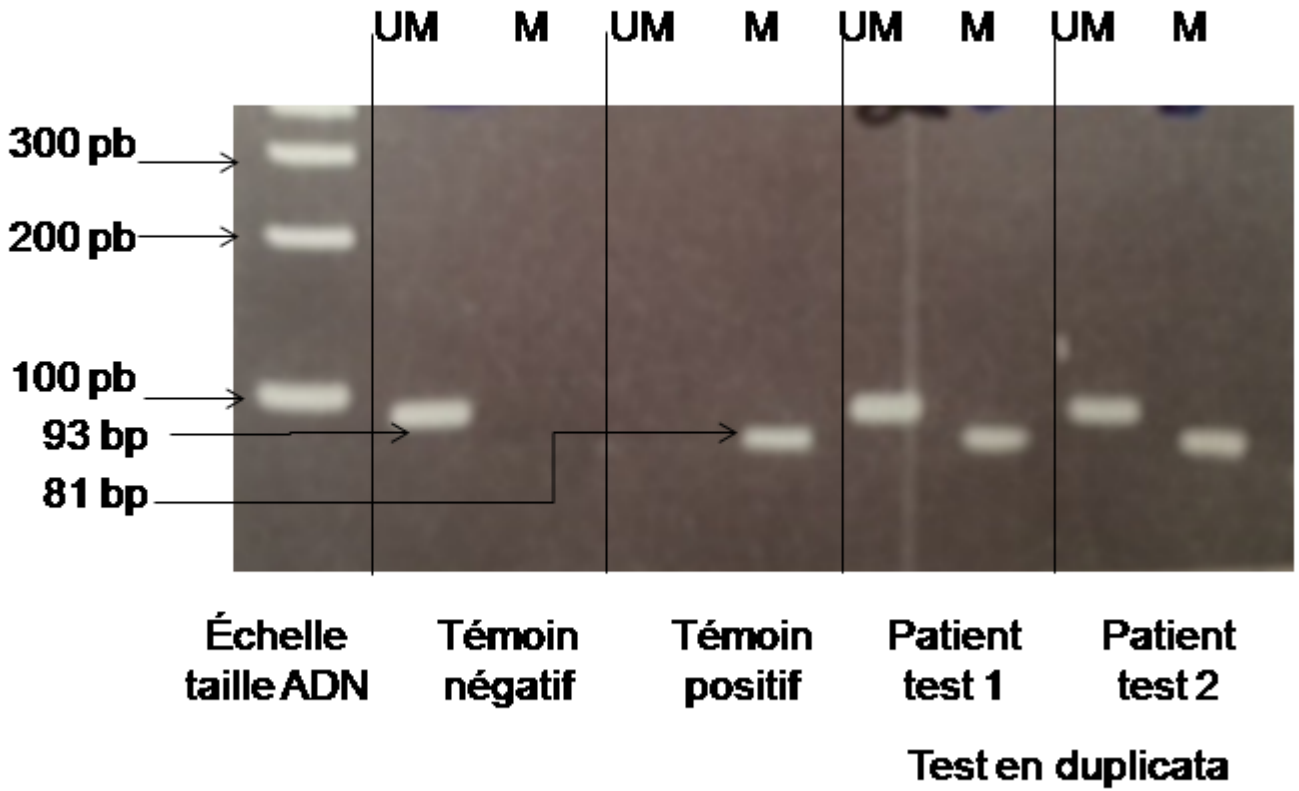
[d]Clinical benefit = CR + PR + SD ≥16 weeks for SCLC, pancreatic cancer, Ewing's sarcoma.

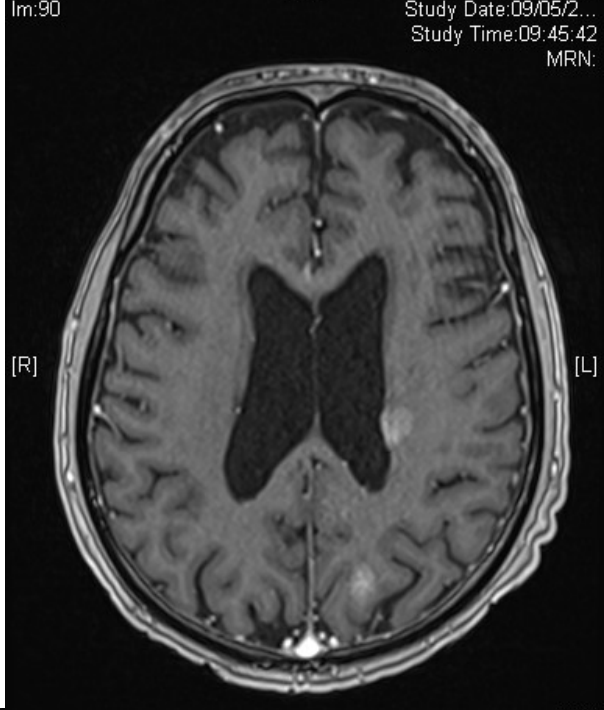
Johann de Bono, Drug discovery 2017

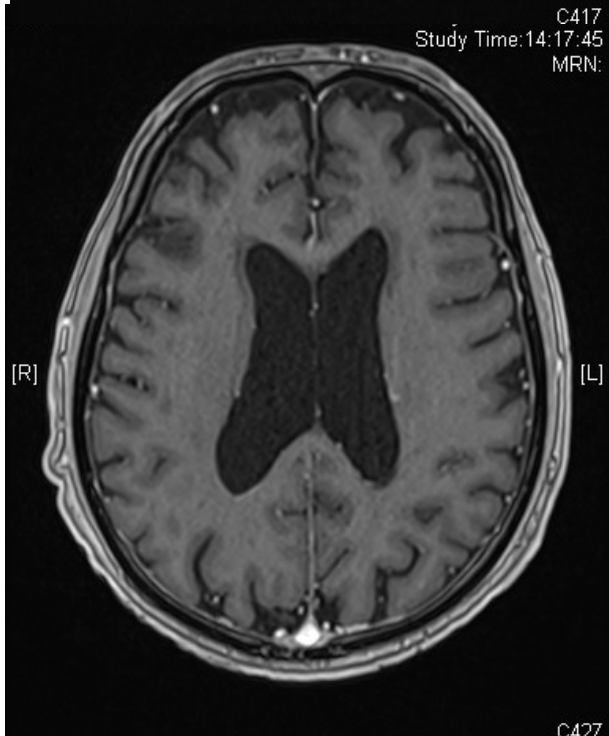
Pourquoi les anti-PARP sont-ils moins efficaces que dans le cancer du sein BRCA muté?

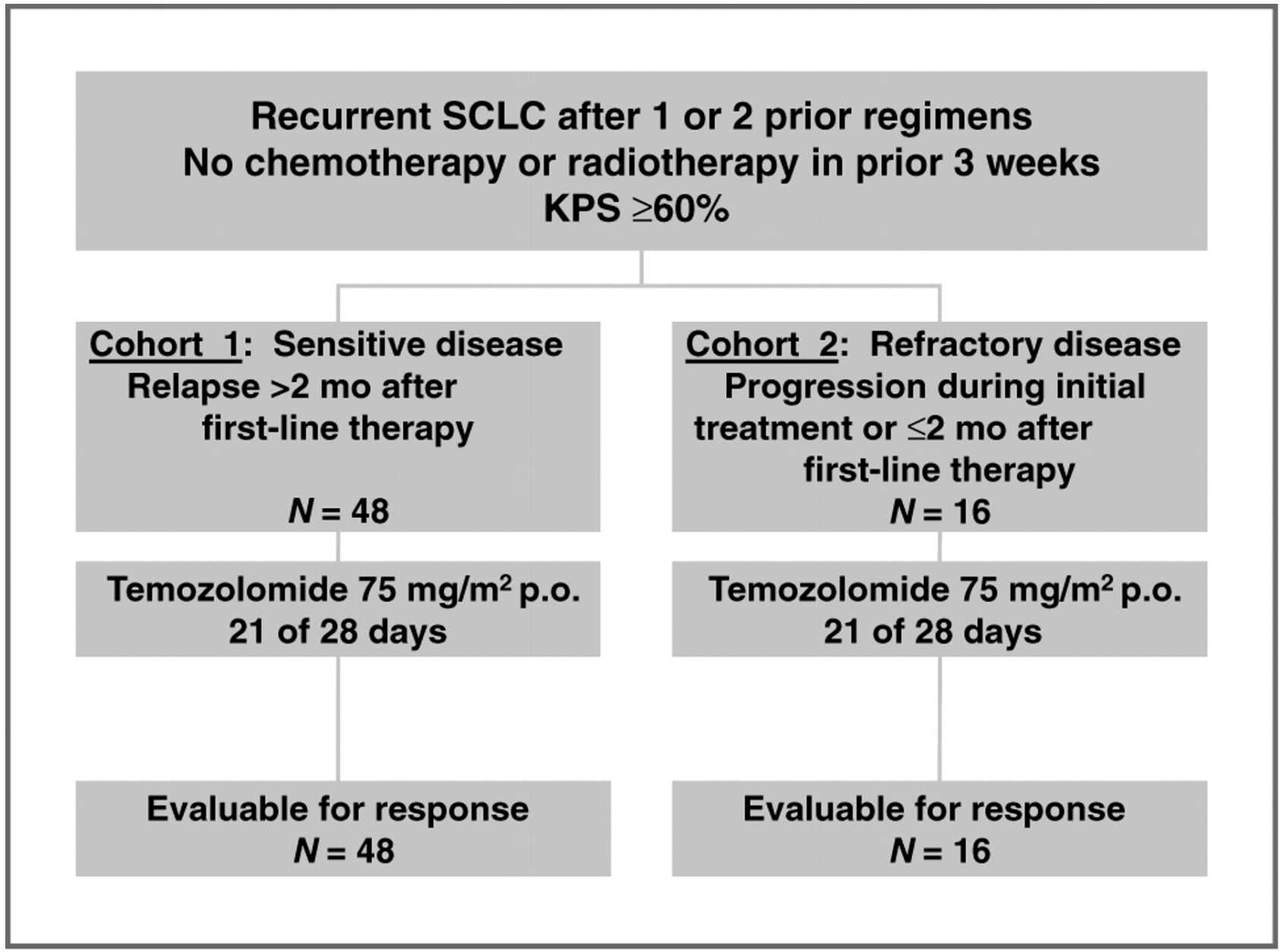



MGMT méthylé
(silencieux)
Témozolomide
Systèmes de réparation des lésions DNA(DDR)
Lésions de l'ADN
O6-methylguanines
(mutagène)

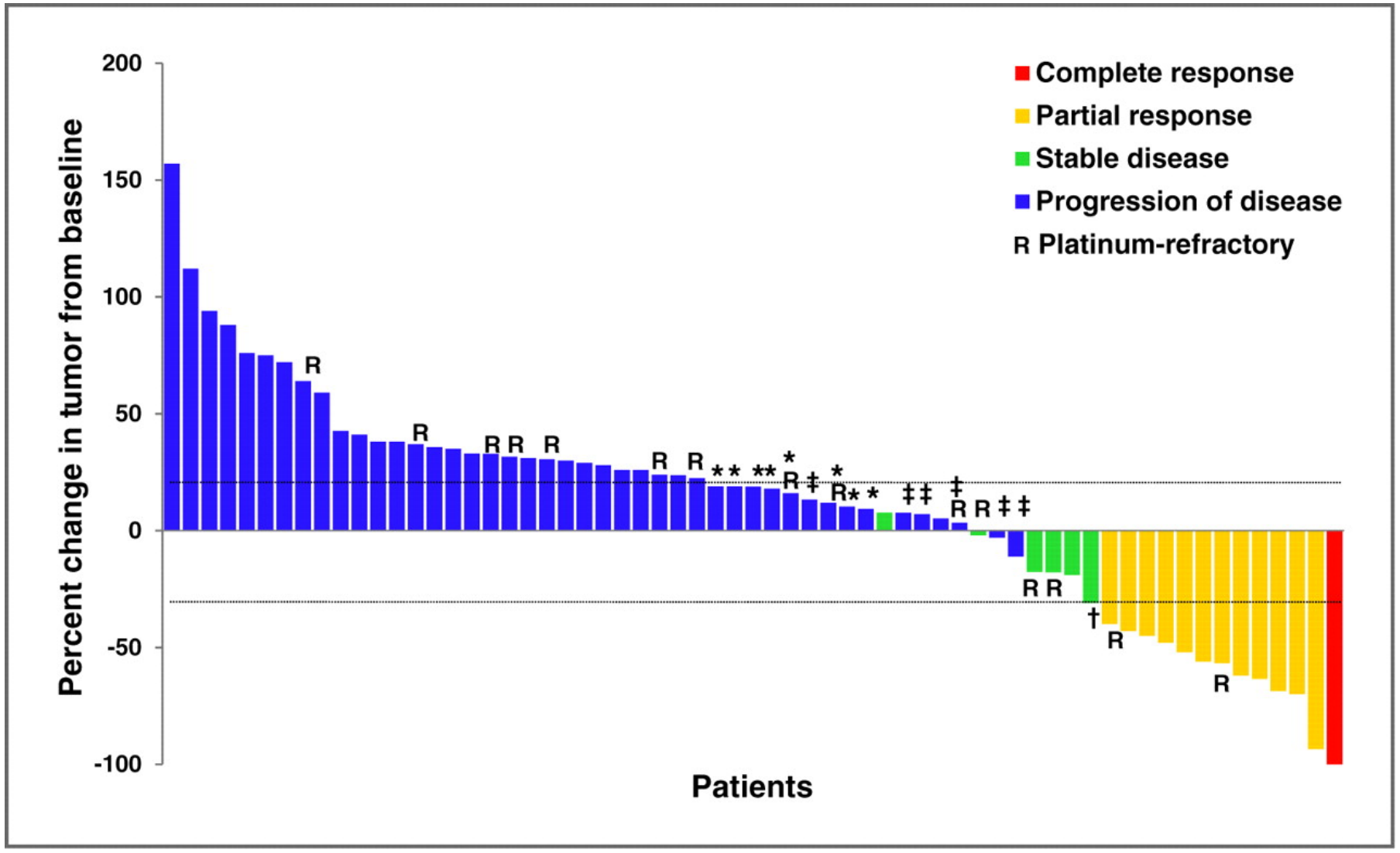

UM
M
UM
M
UM
M
UM
M
300 pb
200 pb
100 pb
93 bp
81 bp
Échelle taille ADN
Témoin négatif
Témoin positif
Patient test 1
Patient test 2
Test en duplicata


Im:90
Study Date:09/05/2...
Study Time:09:45:42
MRN:
[R]
[L]


C417
Study Time:14:17:45
MRN:
[R]
[L]



M. Catherine Pietanza; Clin Cancer Res 2012



M. Catherine Pietanza Clin Cancer Res 2012

Table 3. MGMT analyses

	Response		
	PR	**SD + POD**	***P***
MGMT methylation ($n = 27$)[a]			
Methylated ($n = 13$)	5 (38%)	8 (62%)	0.08[a]
Unmethylated ($n = 14$)	1 (7%)	13 (93%)	
MGMT expression ($n = 31$)			
Negative ($n = 13$)	5 (38%)	8 (62%)	0.23
Positive ($n = 18$)	3 (17%)	15 (83%)	

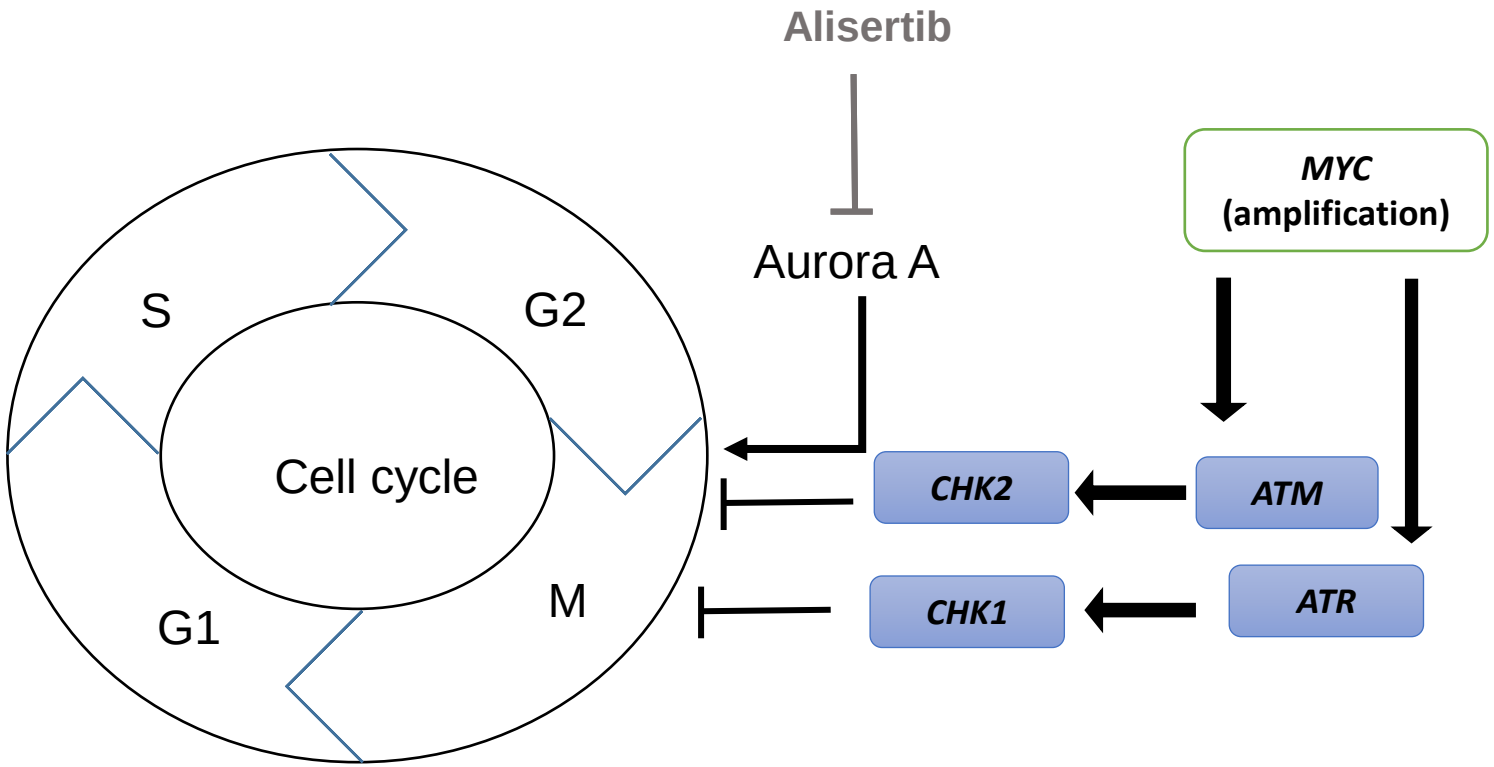
Abbreviations: NR, not reached; POD, progression of disease.

[a]The first 8 samples were carried out using methylation-specific PCR.

Pietanza M. Clin Cancer Res; 18, 2012

famille *MYC* et gènes effecteurs, notamment *ATM et ATR*

Normalement, les kinases ATR et ATM sont activées en réponse à la formation d'ADN monocaténaire et sont des enzymes permettant l'arrêt du cycle cellulaire par l'intermédiaire de Chk1 et Chk2.



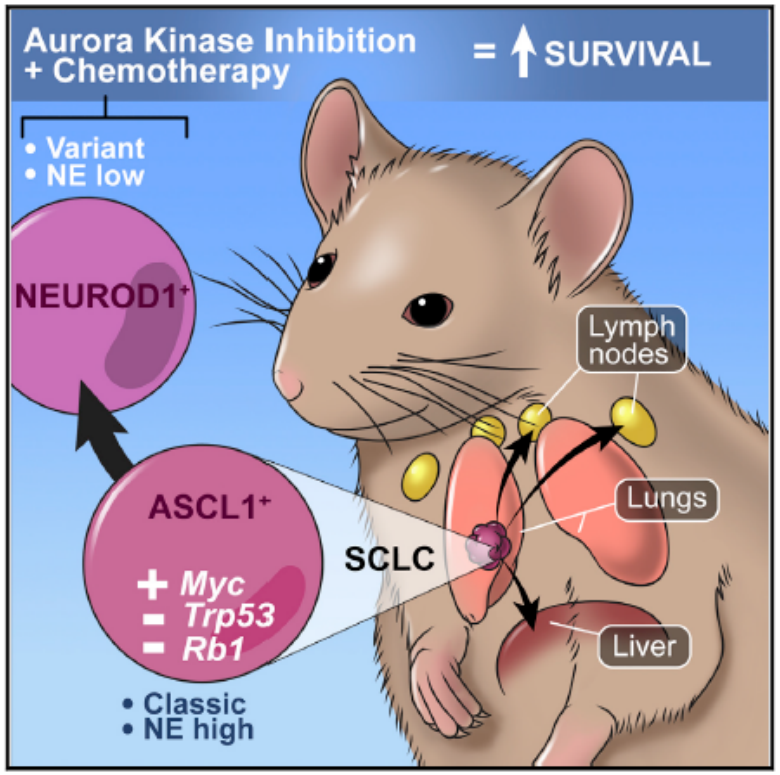
Le cancer à petites cellules P53- Rb1 – et Myc ++ est sensible aux inhibiteurs d'Aurora A

Article

Cancer Cell

MYC Drives Progression of Small Cell Lung Cancer to a Variant Neuroendocrine Subtype with Vulnerability to Aurora Kinase Inhibition

Graphical Abstract



Authors

Gurkan Mollaoglu, Matthew R. Guthrie, Stefanie Böhm, ..., Robert J. Wechsler-Reya, Martin L. Sos, Trudy G. Oliver

Correspondence

martin.sos@uni-koeln.de (M.L.S.), trudy.oliver@hci.utah.edu (T.G.O.)

In Brief

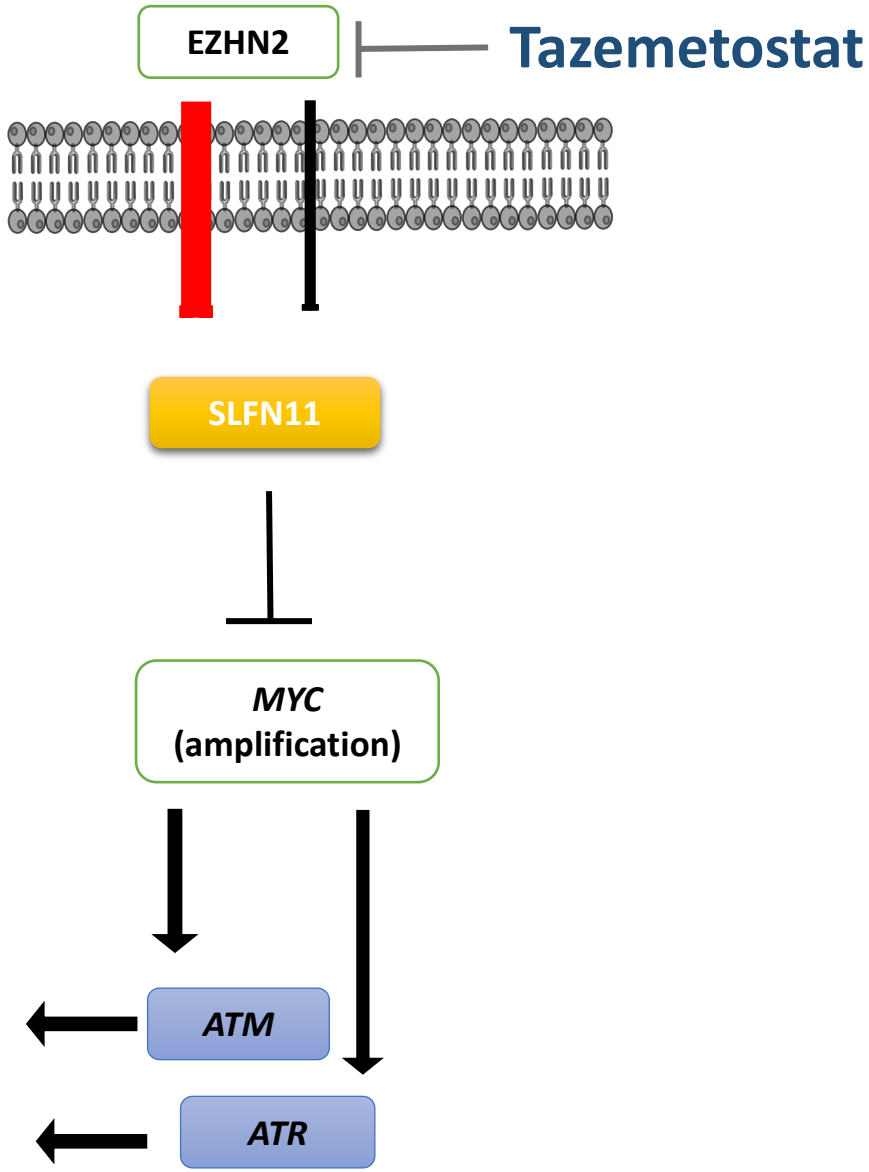
Mollaoglu et al. generate a mouse model of small cell lung cancer (SCLC) with elevated *Myc* expression and loss of *Rb1* and *Trp53*. MYC promotes a neuroendocrine-low variant subtype of SCLC, which is paralleled in patients. Mouse and human SCLC with high MYC levels display sensitivity to Aurora kinase inhibition.

Mollaoglu G. et al Cancer Cell. 2017

Alisertib + paclitaxel vs paclitaxel + pclb en 2ème ligne

	Alisertib + paclitaxel (n=89)	Placebo + paclitaxel (n=89)
Median PFS, days	101	66
IVRS stratification		
Corrected stratification		
Median overall survival (OS), days	186	165
IVRS stratification		
Corrected stratification		
Response, %		
Overall response rate (ORR)	22	18
Modified disease control rate (incl. stable disease confirmed for 8 weeks)	58	46
Stable disease	55	49
Progressive disease	15	26
Median time to symptom relief, months (n)		
Coughing	1.18 (25)	1.02 (21)
Dyspnea	1.18 (28)	0.99 (14)
Pain	0.99 (35)	0.99 (32)

Taofeek Owonikoko, et al. JTO 2017 (A)

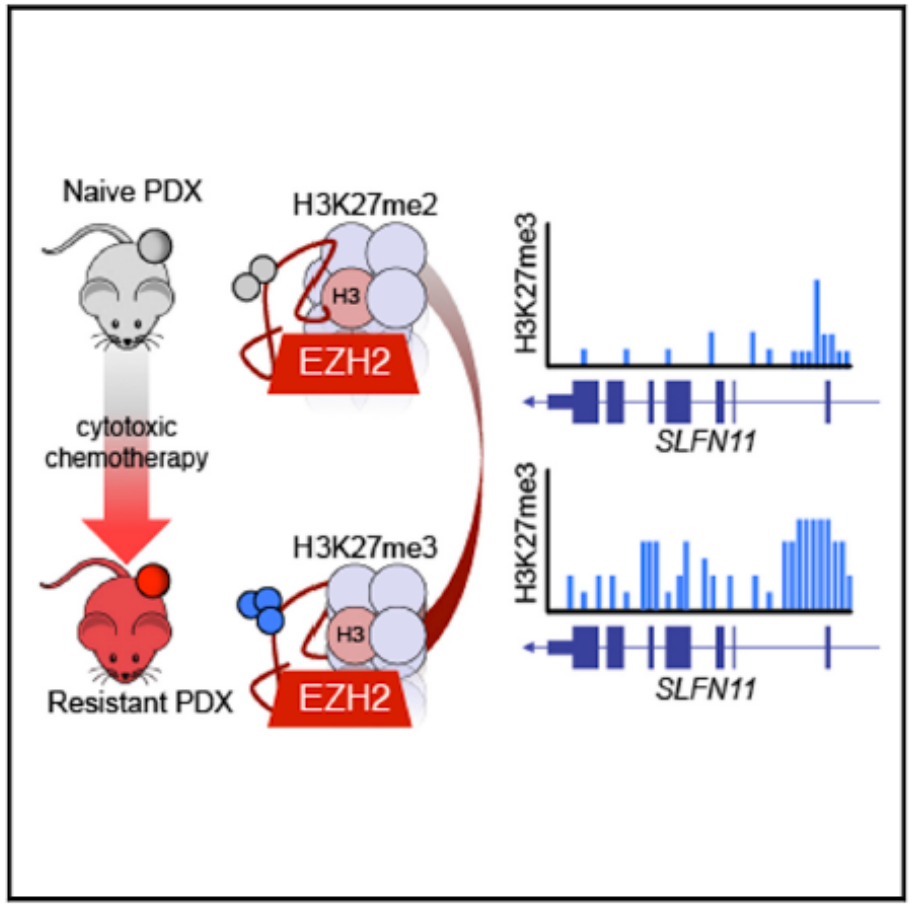

EZHN2
Tazemetostat
SLFN11
MYC
(amplification)
ATM
ATR

Article

Cancer Cell

Chemosensitive Relapse in Small Cell Lung Cancer Proceeds through an EZH2-SLFN11 Axis

Graphical Abstract



Authors

Eric E. Gardner, Benjamin H. Lok, Valentina E. Schneeberger, ..., Pierre P. Massion, Charles M. Rudin, John T. Poirier

Correspondence

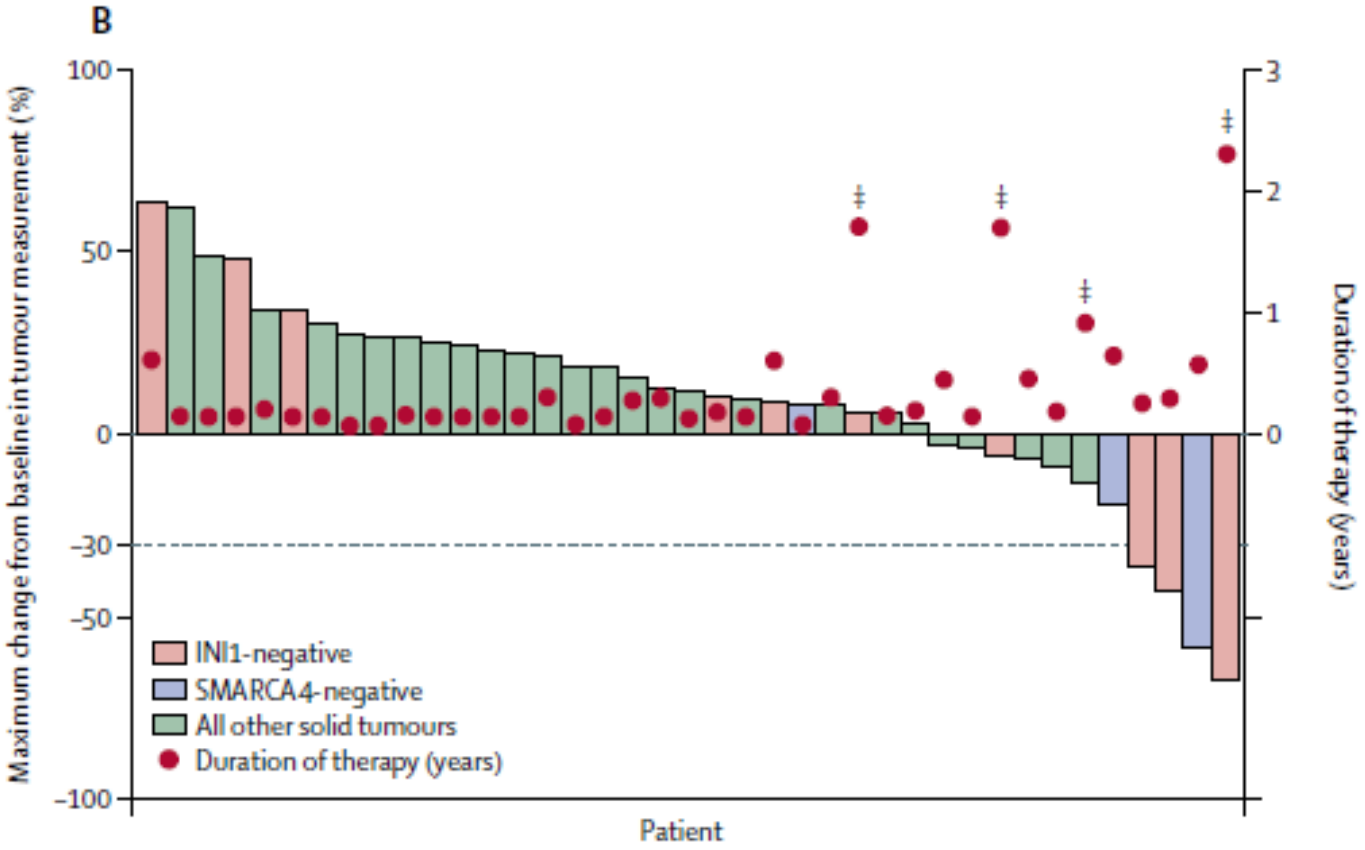
rudinc@mskcc.org (C.M.R.), poirierj@mskcc.org (J.T.P.)

In Brief

By generating paired chemonaive and chemoresistant small cell lung cancer (SCLC) patient-derived xenograft models, Gardner et al. find that EZH2 promotes chemoresistance by epigenetically silencing *SLFN11*. EZH2 inhibition prevents acquisition of chemoresistance and improves chemotherapeutic efficacy in SCLC.

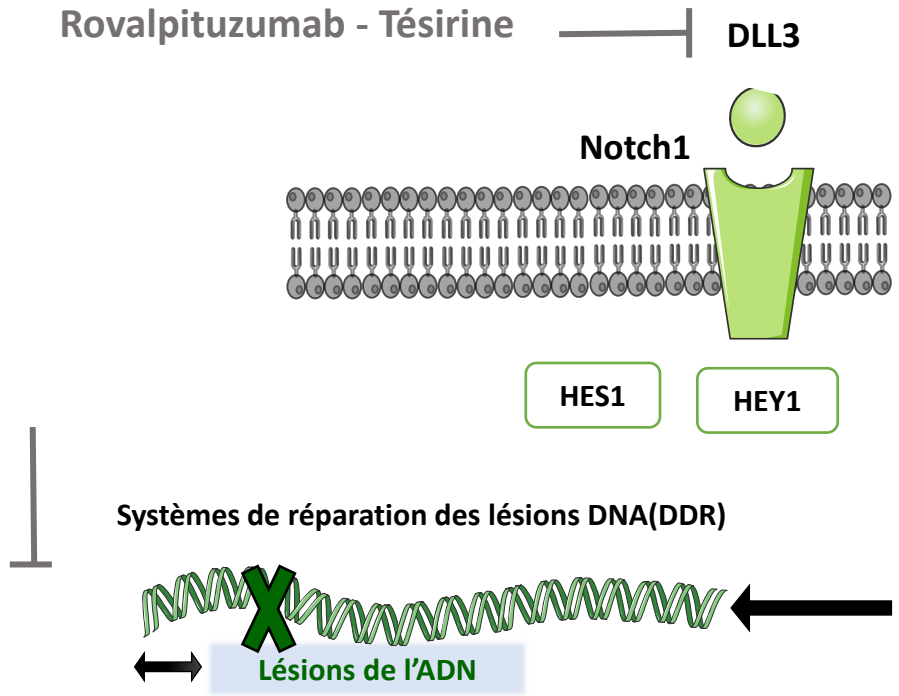
Gardner EE et al. Cancer cell 2017

Tazemostat, first in human, first in class phase 1



Antoine Italiano, Lancet Oncol 2018

Rovalpituzumab tesirine



Rudin M. Lancet Oncol 2017; 18:42–51

Tolérance

- Profil de tolérance acceptable aux doses de 0,4 mg/kg toutes les trois ou six semaines.
- Longue rémanence pharmacocinétique du médicament explique le caractère cumulatif des toxicités: thrombocytopénie, des atteintes cutanées, épanchements des séreuses (plèvre, péricarde).
- Arrêt de l’essai Rova T vs Topotécan

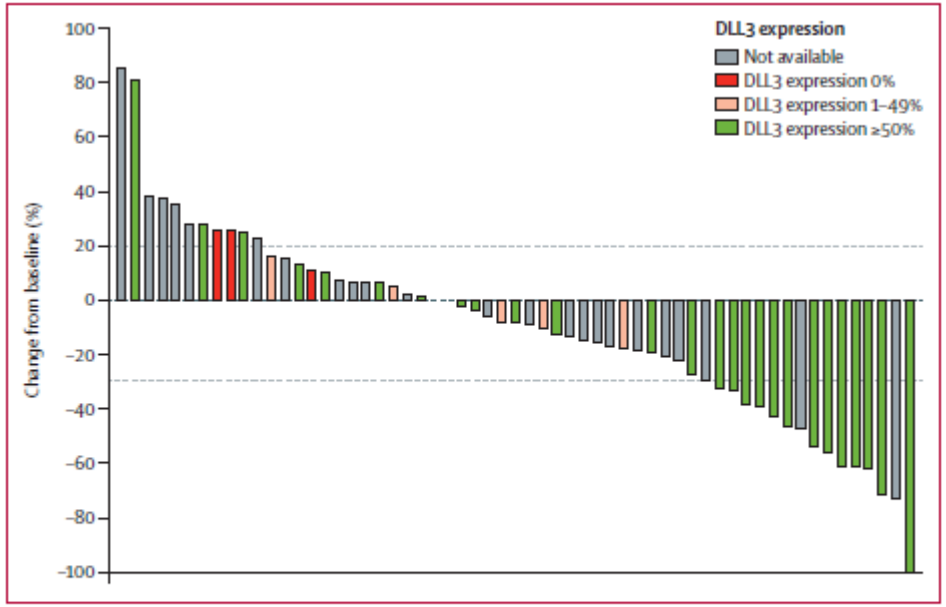


***Figure 1*: Waterfall plot showing best change in tumour burden from baseline at active treatment doses (n=60)**
Investigator-assessed best change from baseline was the change in the sum of longest diameters of target lesions for patients treated with rovalpituzumab tesirine 0·2 mg/kg or 0·4 mg/kg every 3 weeks or 0·3 mg/kg or 0·4 mg/kg every 6 weeks. Grey dotted line at 20% indicates the threshold for progressive disease and the line at –30% the threshold for partial response. One patient did not have a measurable target lesion.

Rudin M. Lancet Oncol 2017; 18: 42–51

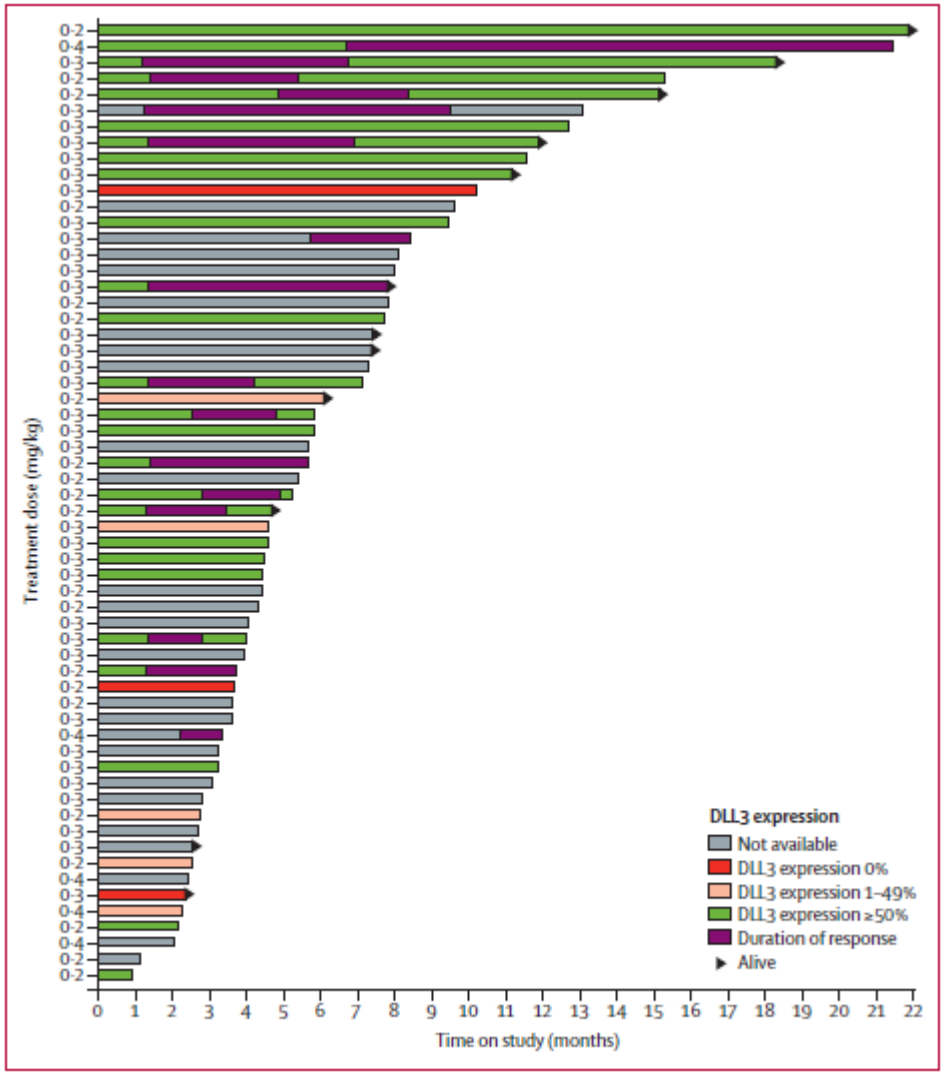


***Figure 2*: Swimmer's plot showing time on study and duration of response for patients treated with active treatment doses (n=60)**

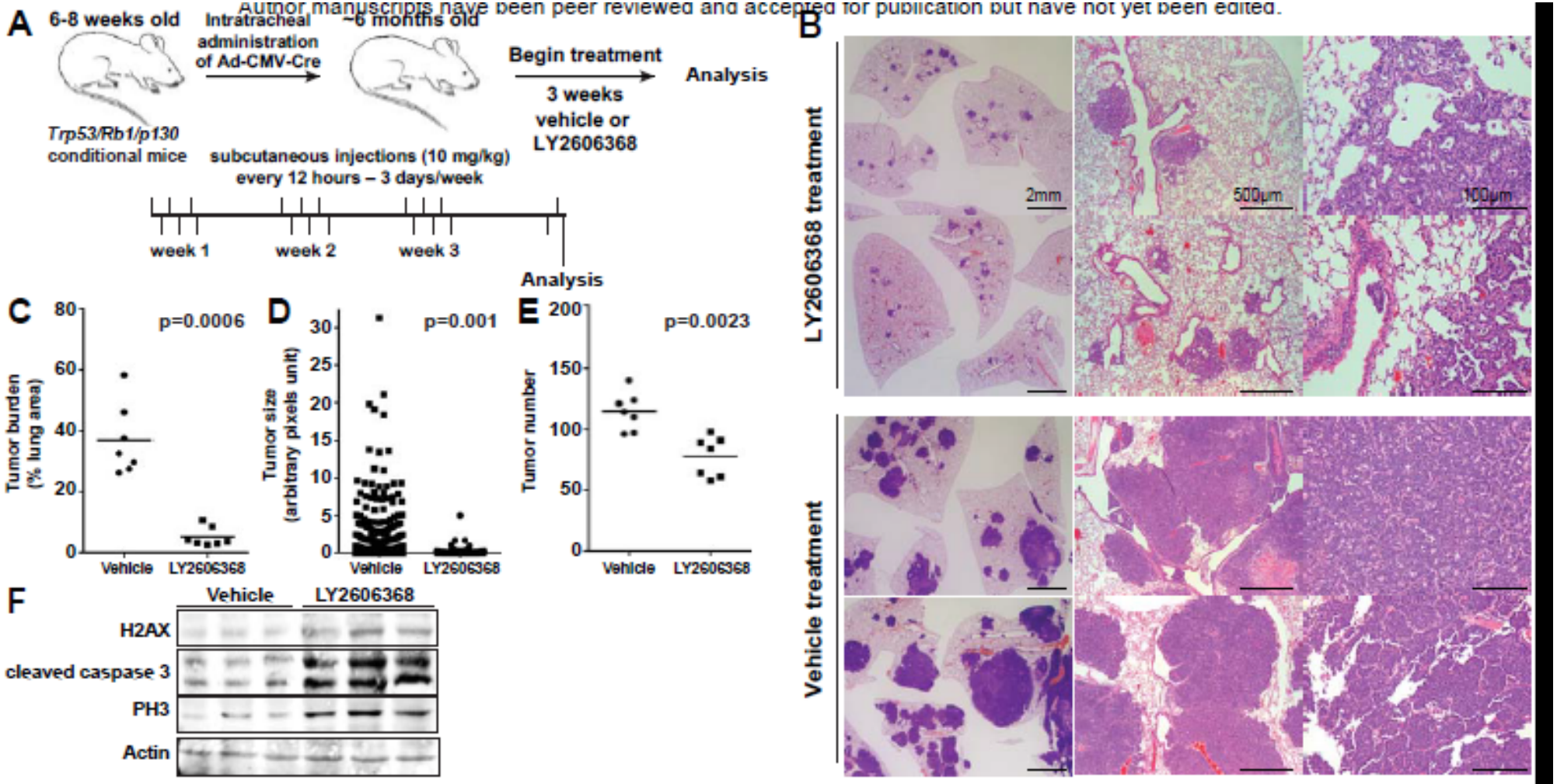
Table 4 Ongoing studies with rovalpituzumab tesirine (Rova-T)

Study	Phase	Patient's population	Study design	Primary endpoints
NCT0303511	III	After completion of first-line platinum-based chemotherapy	Rova-T versus dexamethasone versus placebo	PFS, OS
NCT03026166	I	Relapsed patients	Rova-T + nivolumab various doses; Rova-T + nivolumab + ipilimumab 1 mg/kg; Rova-T + nivolumab + ipilimumab 3 mg/kg	DLT
NCT02819999	I	Previously untreated DLL3+ patients	Rova-T or Rova-T followed by cisplatin–etoposide or Rova-T with cisplatin–etoposide; cisplatin–etoposide followed by Rova-T	DLT, toxicity evaluation, PFS for Phase IB
NCT03061812	III	Relapsed DLL3+ patients after first-line chemotherapy	Rova-T versus topotecan	ORR, OS

DLT dose-limiting toxicities, *DLL3* delta-like protein 3, *ORR* overall response rate, *OS* overall survival, *PFS* progression-free survival

Tartarone A et al. Med Oncol (2017) 34:110

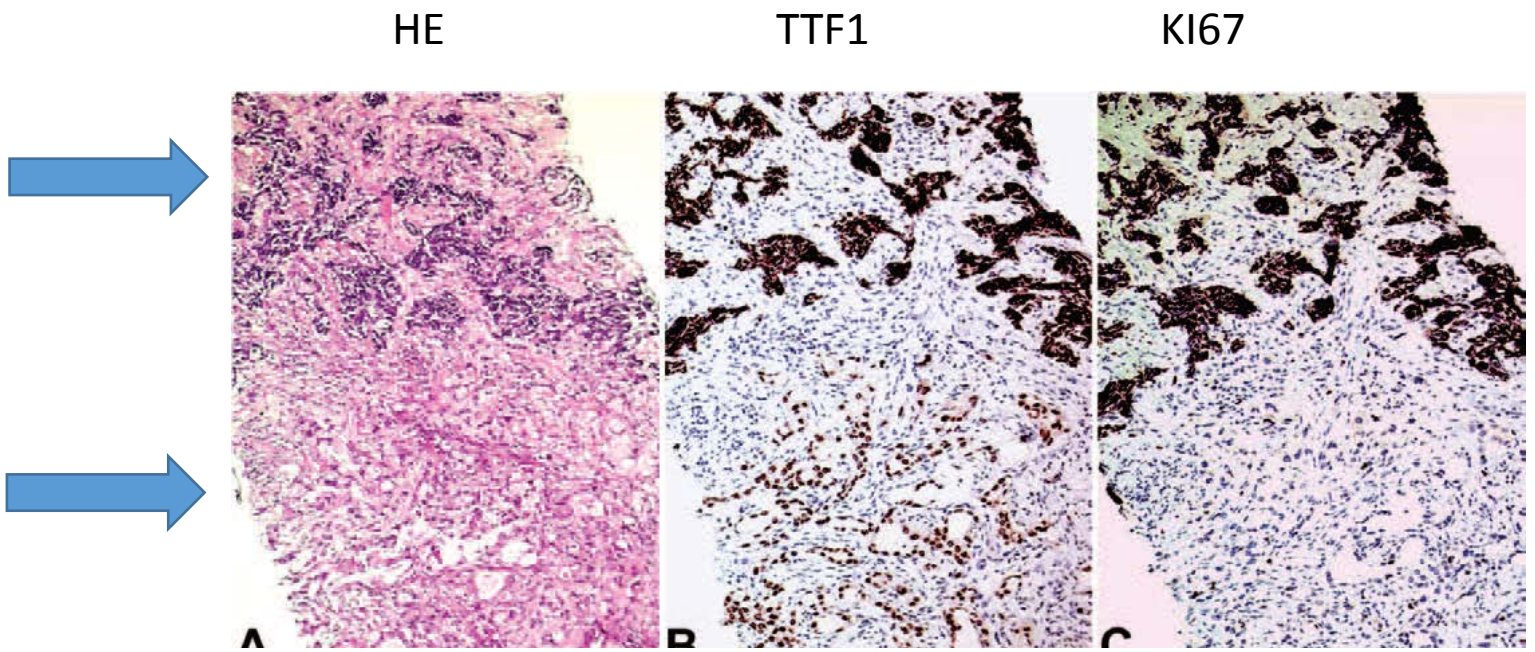
Prexasertib inhibiteur Chk1



Sen T et al Cancer Res 2017

ADC / CPC combinés et EGFR

- CPC
- ADE



E Norkowski et al. J Thorac Oncol. 2013;8: 1265–1271

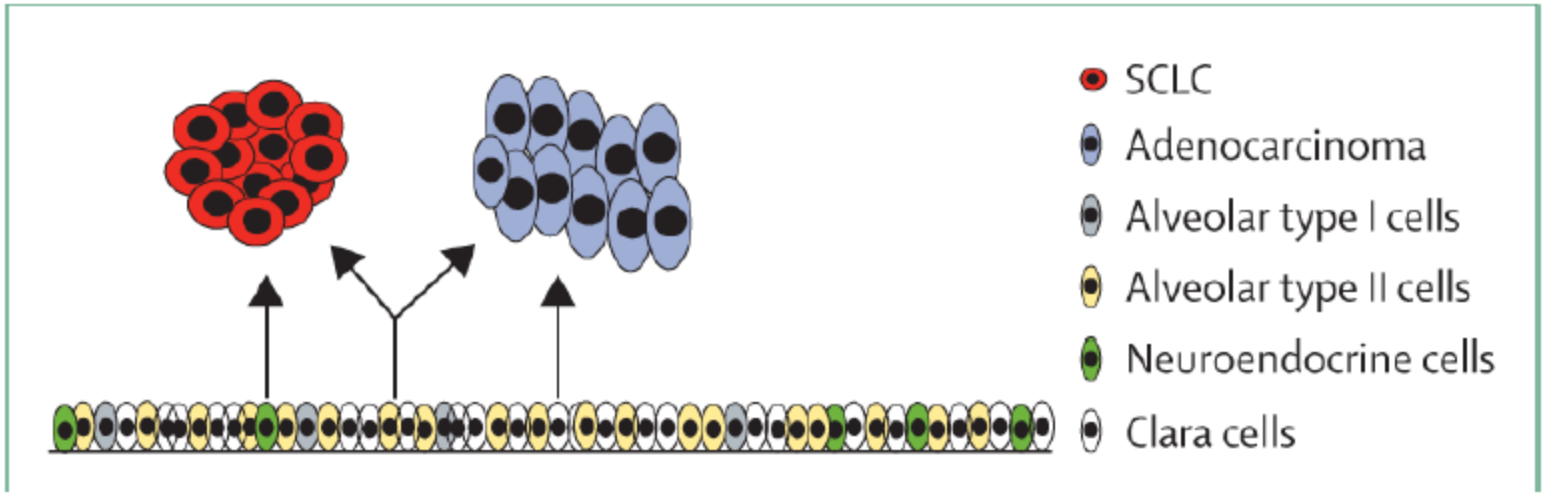


Figure 1. Alveolar type II cells could be a common precursor that can give rise to both adenocarcinoma and small-cell lung cancer (SCLC)

Diagram depicts the cells of origin of adenocarcinoma and SCLC. Neuroendocrine cells and possibly alveolar type II cells can give rise to SCLC (left and centre), whereas clara cells and alveolar type II cells can give rise to adenocarcinoma (right and centre).

Oser MG, et al. Lancet Oncol. 2015

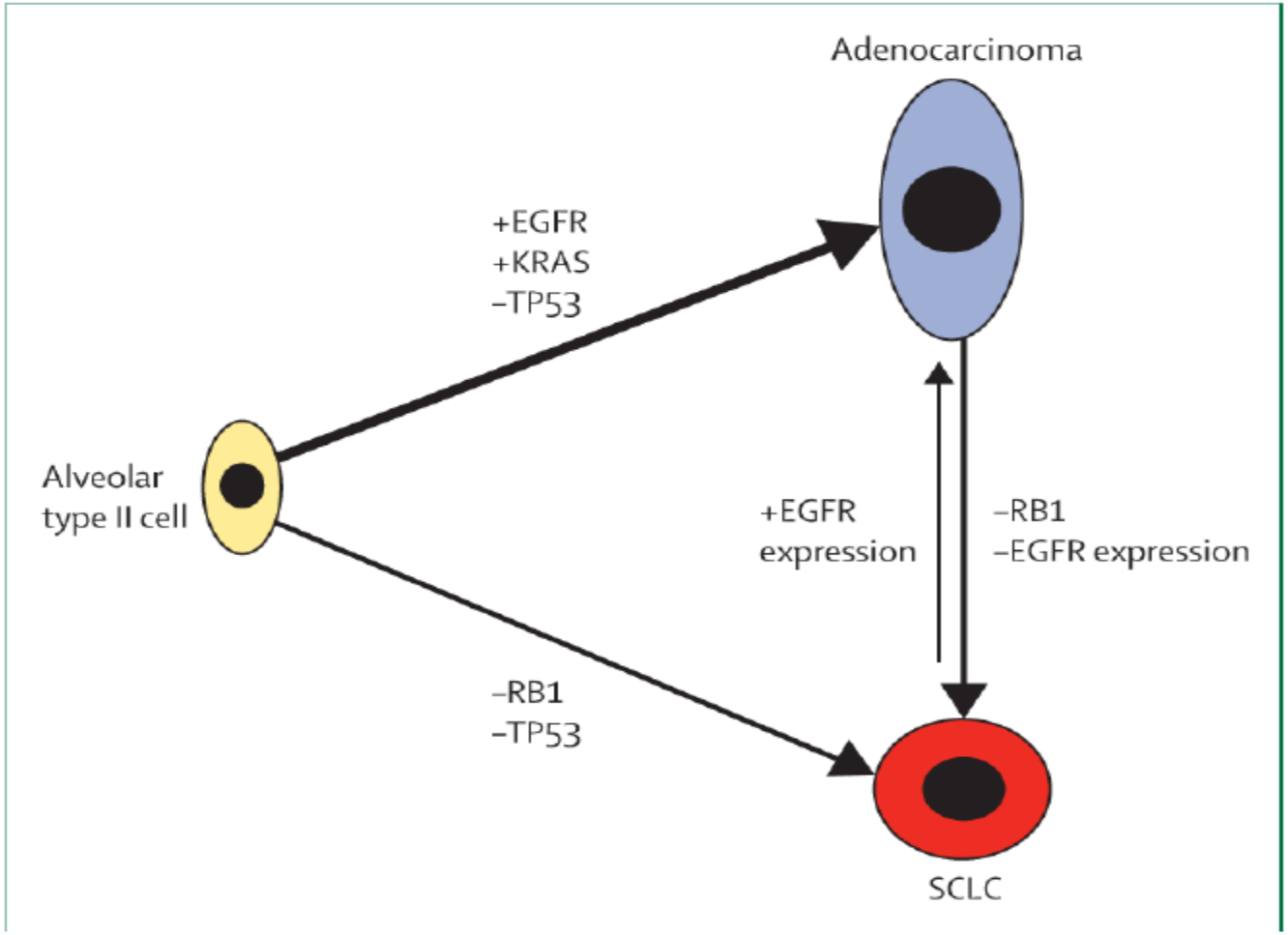
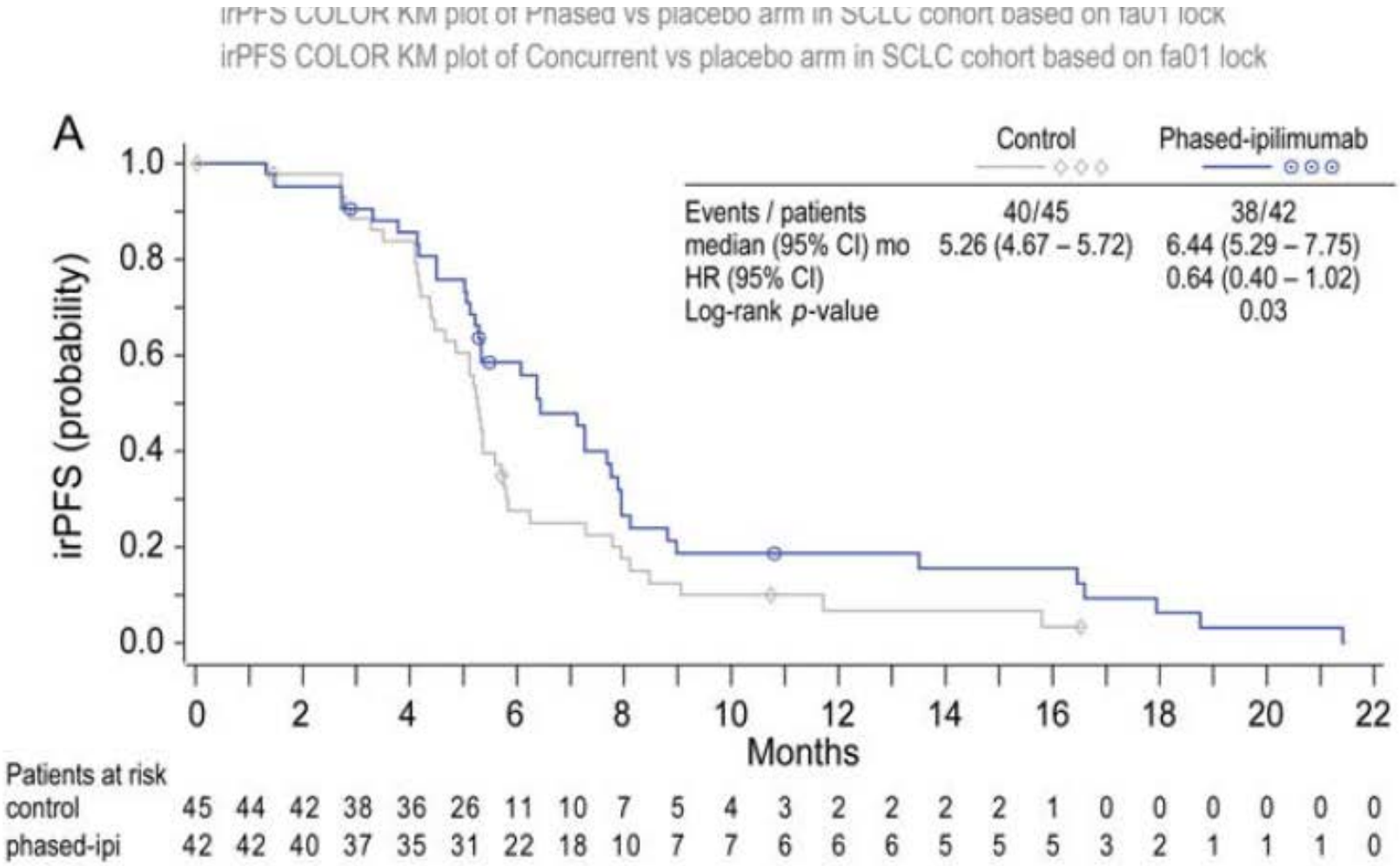


Figure 2. Hypothetical model depicting the molecular events that lead to transformation from adenocarcinoma to small-cell lung cancer (SCLC)

Oser MG, et al. Lancet Oncol. 2015

IPCI

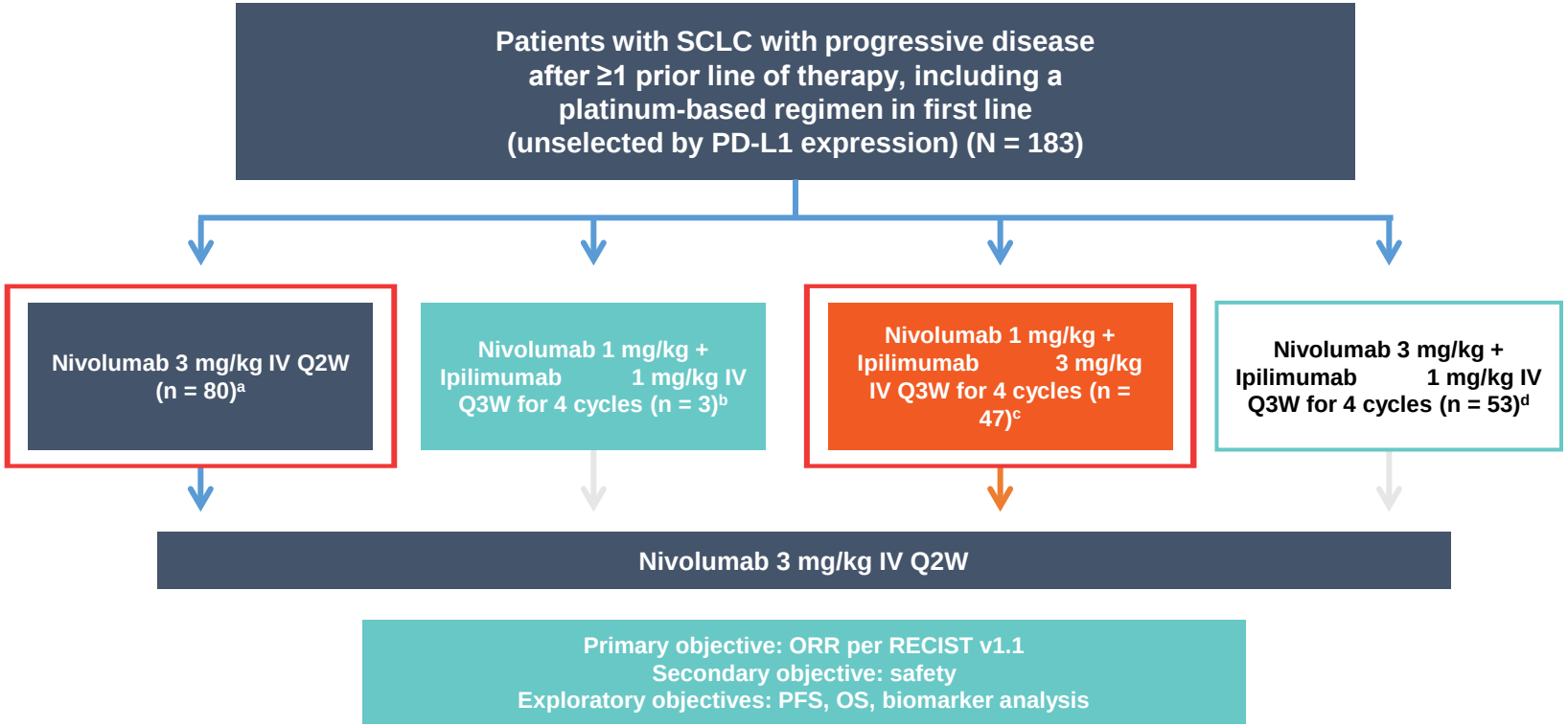
Ipilimumab in combination with paclitaxel and carboplatin as first-line therapy in extensive-



Reck M et al Annals of Oncology 2013

Methods (cont)

Figure 2. CheckMate 032 (NCT01928394) study design

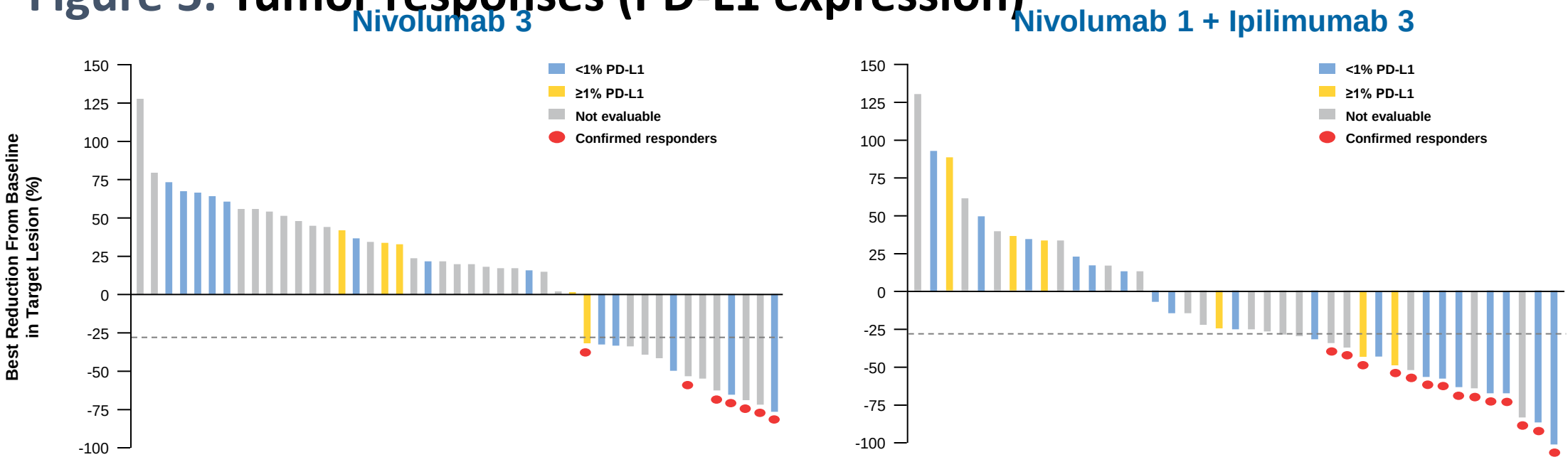


[a]Nivolumab 3: 15 patients in this arm had a follow-up of <6 weeks; follow-up defined as day of first dose to day of database lock; [b]Nivolumab 1 + ipilimumab 1: minimum follow-up of 546 days ; [c]Nivolumab 1 + ipilimumab 3: minimum follow-up of 120 days; [d]Nivolumab 3 + ipilimumab 1: minimum follow-up of 71 days.

ORR = objective response rate; OS = overall survival.

Results (cont)

Figure 5. Tumor responses (PD-L1 expression)



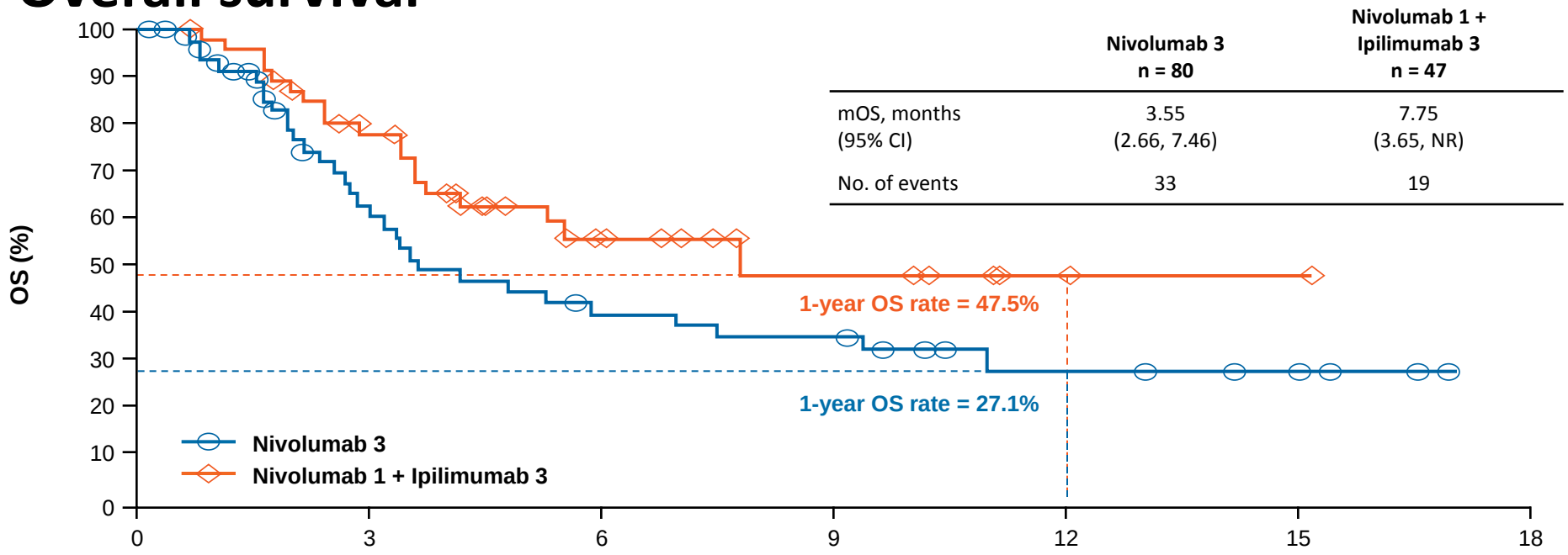
Evaluable samples (52 of 127)	PD-L1 expression level, n (%)	
	<1%	≥1%
Nivolumab 3 (n = 24)	17 (70.8)	7 (29.2)
Nivolumab 1 + Ipilimumab 3 (n = 28)	20 (71.4)	8 (28.6)

Only patients with target lesion at baseline and ≥1 on-treatment tumor assessment are included (nivolumab 3, n = 45; nivolumab 1 + ipilimumab 3, n = 41).

[a]Percentage based on the PD-L1 evaluable patients (n = 24 for nivolumab 3 and n = 28 for nivolumab 1 + ipilimumab 3). Percentages in Table 1 (baseline characteristics) differ because they are based on the total number of patients in each arm (n = 80 for nivolumab 3 and n = 47 for nivolumab 1 + ipilimumab 3).

Results (cont)

Figure 6. **Overall survival**



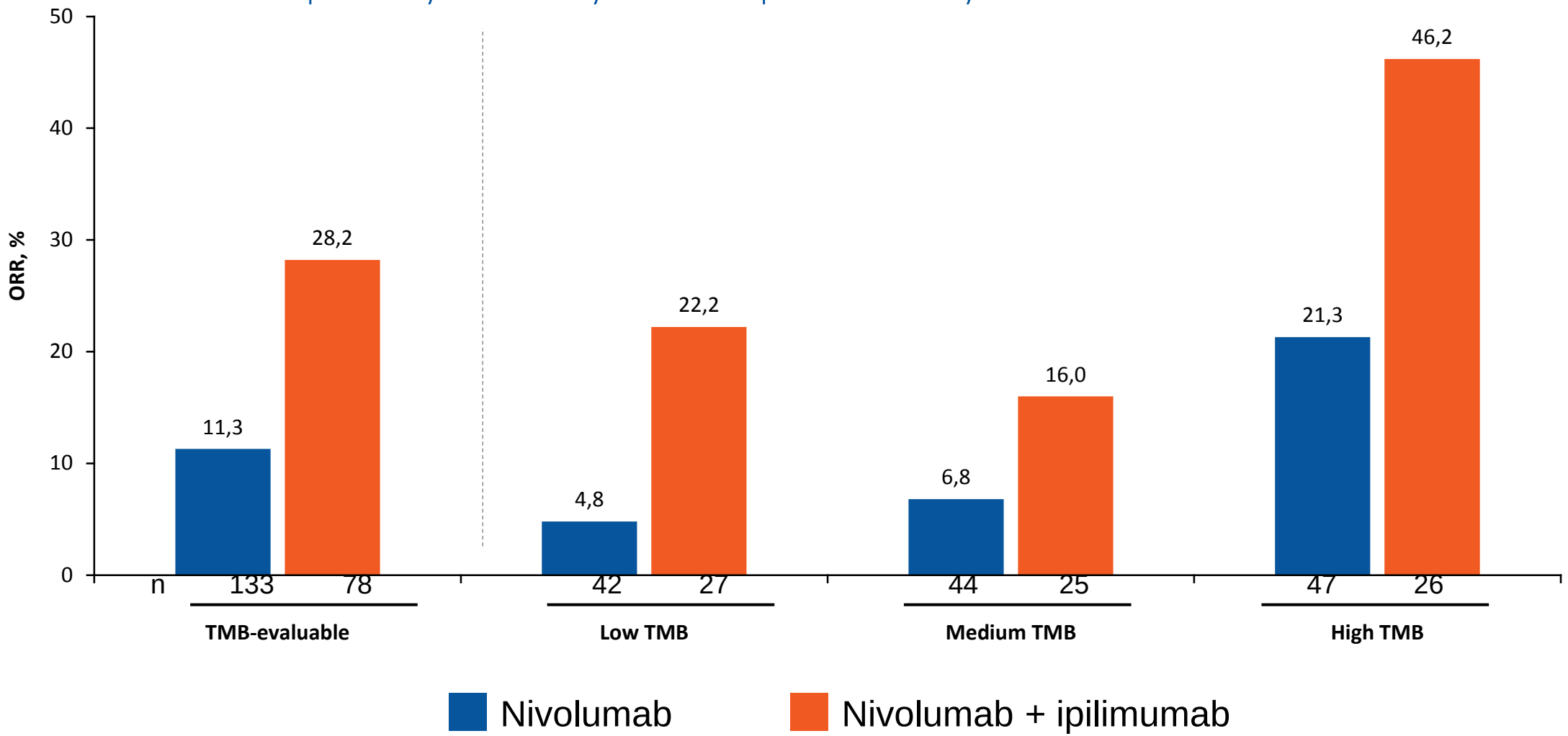
	Nivolumab 3 n = 80	Nivolumab 1 + Ipilimumab 3 n = 47
mOS, months (95% CI)	3.55 (2.66, 7.46)	7.75 (3.65, NR)
No. of events	33	19

Patients at risk							
Nivolumab 3 mg/kg	80	26	16	14	6	4	0
Nivolumab 1 mg/kg + Ipilimumab 3 mg/kg	47	32	13	6	2	1	0

mOS = median OS.

ORR by Tumor Mutation Burden Subgroup

CheckMate 032 Exploratory TMB Analysis Nivo ± Ipi in Previously Treated SCLC



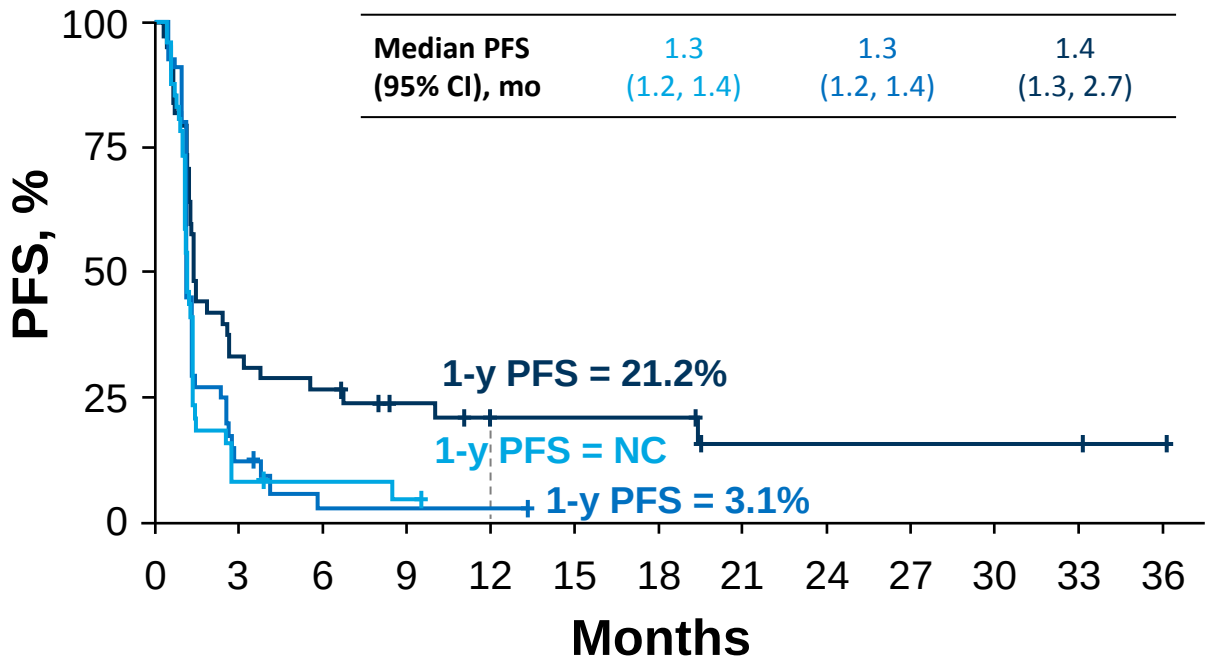
Scott J. Antonia, et al. WLCC 2017

PFS by Tumor Mutation Burden Subgroup

CheckMate 032 Exploratory TMB Analysis Nivo ± Ipi in Previously Treated SCLC

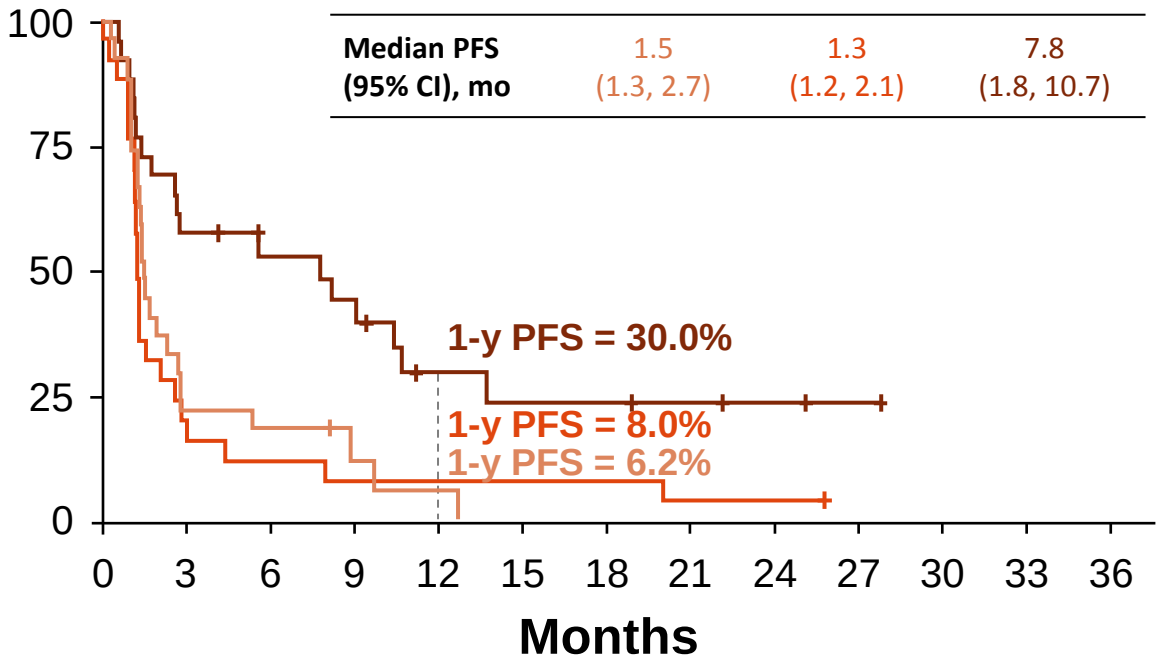
Nivolumab

	Low TMB	Med TMB	High TMB
Median PFS (95% CI), mo	1.3 (1.2, 1.4)	1.3 (1.2, 1.4)	1.4 (1.3, 2.7)



Nivolumab + ipilimumab

	Low TMB	Med TMB	High TMB
Median PFS (95% CI), mo	1.5 (1.3, 2.7)	1.3 (1.2, 2.1)	7.8 (1.8, 10.7)



No. at risk													
Low	42	3	2	1	0	0	0	0	0	0	0	0	0
Medium	44	5	1	1	1	0	0	0	0	0	0	0	0
High	47	15	12	8	5	5	5	2	2	2	2	2	1

Low	27	6	5	2	1	0	0	0	0	0	0	0	0
Medium	25	5	3	2	2	2	2	1	1	0	0	0	0
High	26	15	12	10	5	4	4	3	2	1	0	0	0

Median (95% CI) PFS, overall TMB-evaluable population: 1.4 (1.3, 1.4) months for nivolumab and 1.7 (1.4, 2.7) months for nivolumab + ipilimumab
NC = not calculable

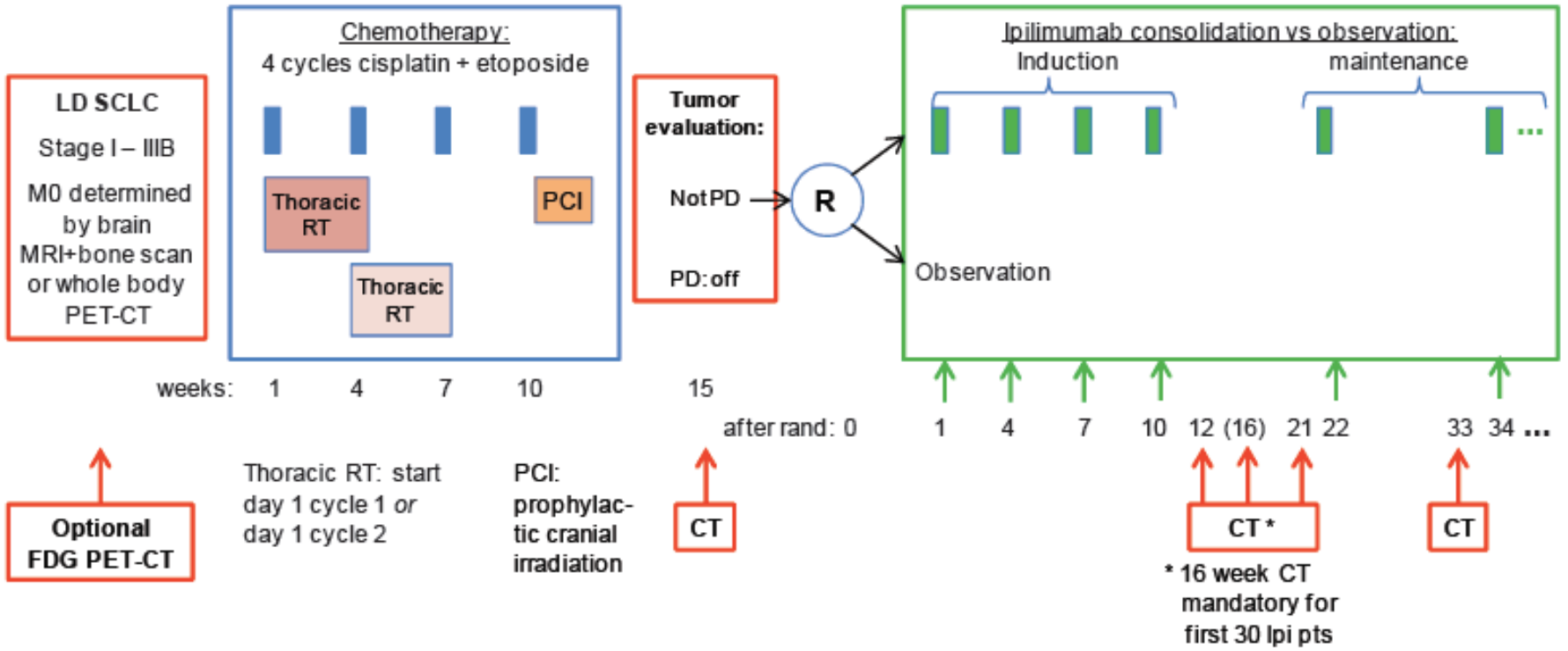
Table 3 Main ongoing studies with immune checkpoint inhibitors in SCLC

Study	Phase	Patient's population	Study design	Primary endpoints
CheckMate 331 (NCT02481830)	III	Relapsed disease	Nivolumab versus topotecan or amrubicin	OS
CheckMate 451 (NCT02538666)	III	After completion of platinum-based chemotherapy	Nivolumab versus nivolumab + ipilimumab versus placebo	OS, PFS
NCT02359019	II	After completion of platinum-based chemotherapy	Pembrolizumab	PFS
REACTION trial (NCT02580994)	II	Previously untreated patients	Pembrolizumab + chemotherapy versus chemotherapy	PFS
NCT02963090	II	Relapsed disease	Pembrolizumab versus topotecan	PFS
STIMULI (NCT02046733)	II	Limited stage after chemoradiotherapy	Nivolumab + ipilimumab versus observation	OS, PFS

OS overall survival, *PFS* progression-free survival

Tartarone A et al. Med Oncol (2017) 34:110

Stimuli (ipilimumab - nivolumab)



IFCT 16-03: Atezoluzumab versus chimiothérapie en deuxième ligne

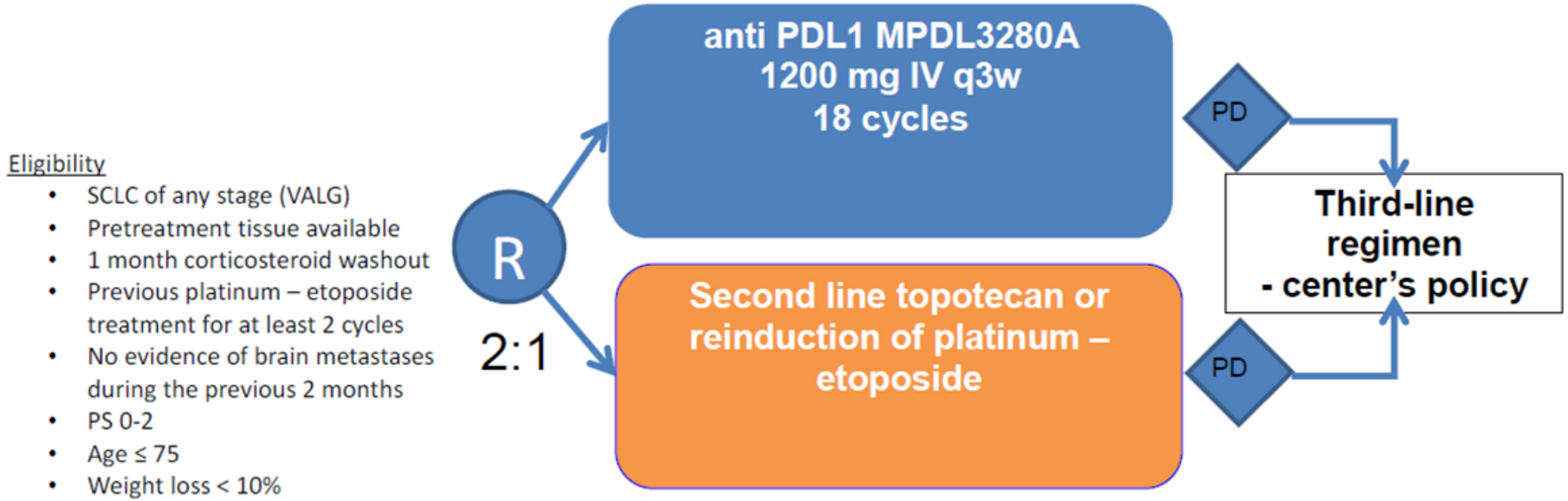


Fig. 2a

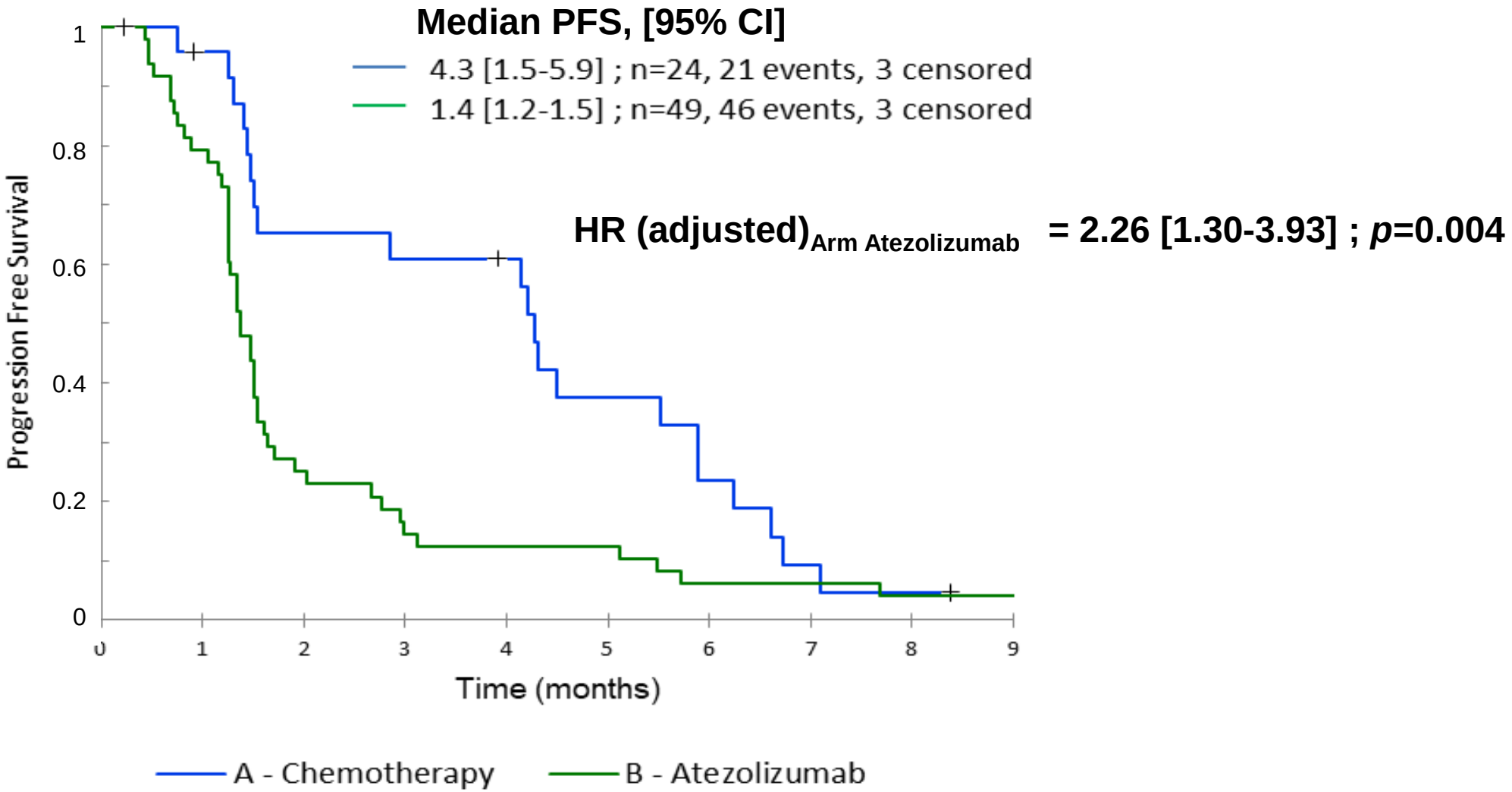

Median PFS, [95% CI]
4.3 [1.5-5.9] ; n=24, 21 events, 3 censored
1.4 [1.2-1.5] ; n=49, 46 events, 3 censored
HR (adjusted)Arm Atezolizumab = 2.26 [1.30-3.93] ; p=0.004
Progression Free Survival
1
0.8
0.6
0.4
0.2
0
0
1
2
3
4
5
6
7
8
9
Time (months)
A - Chemotherapy
B - Atezolizumab

Fig. 2b

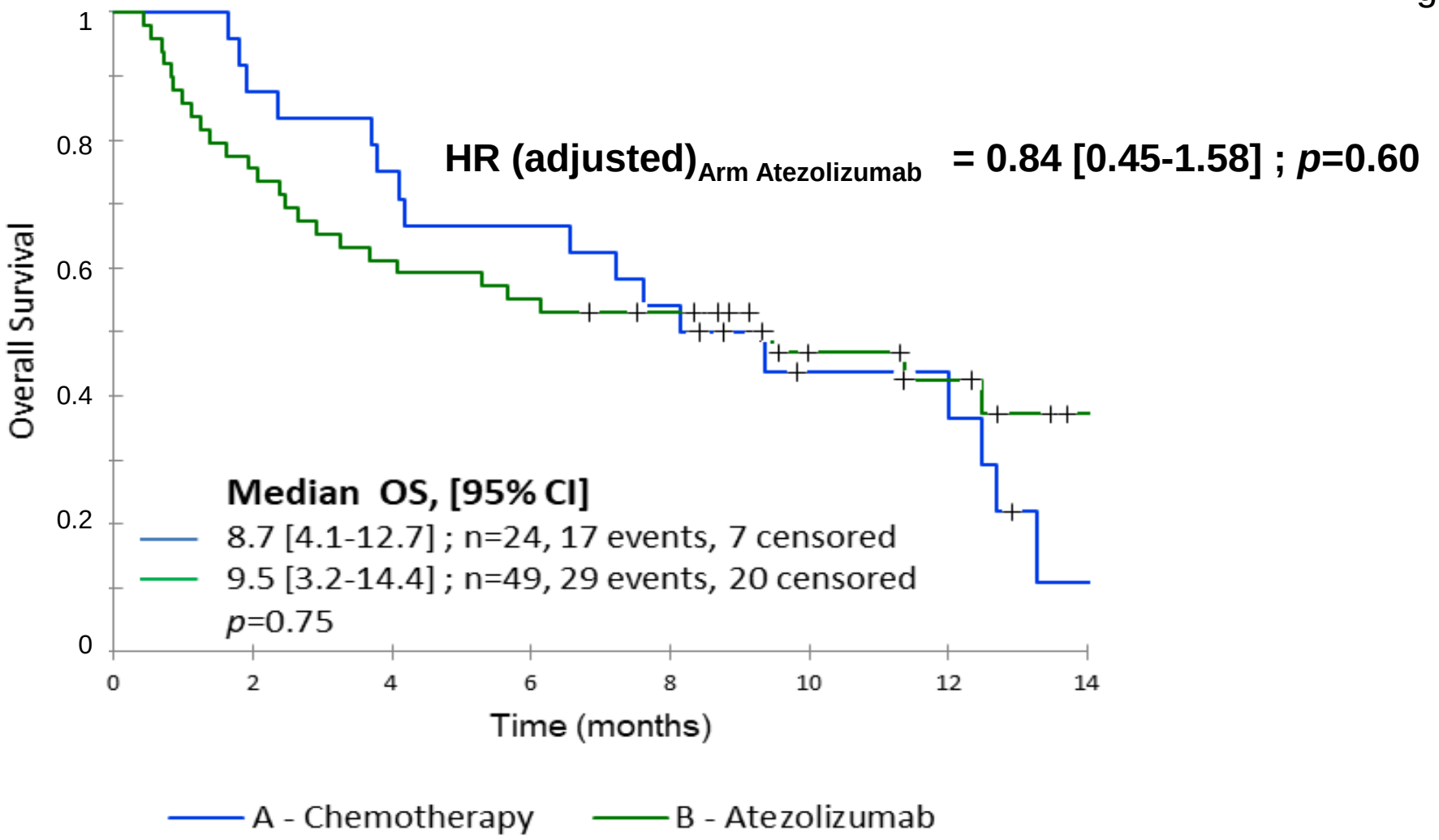
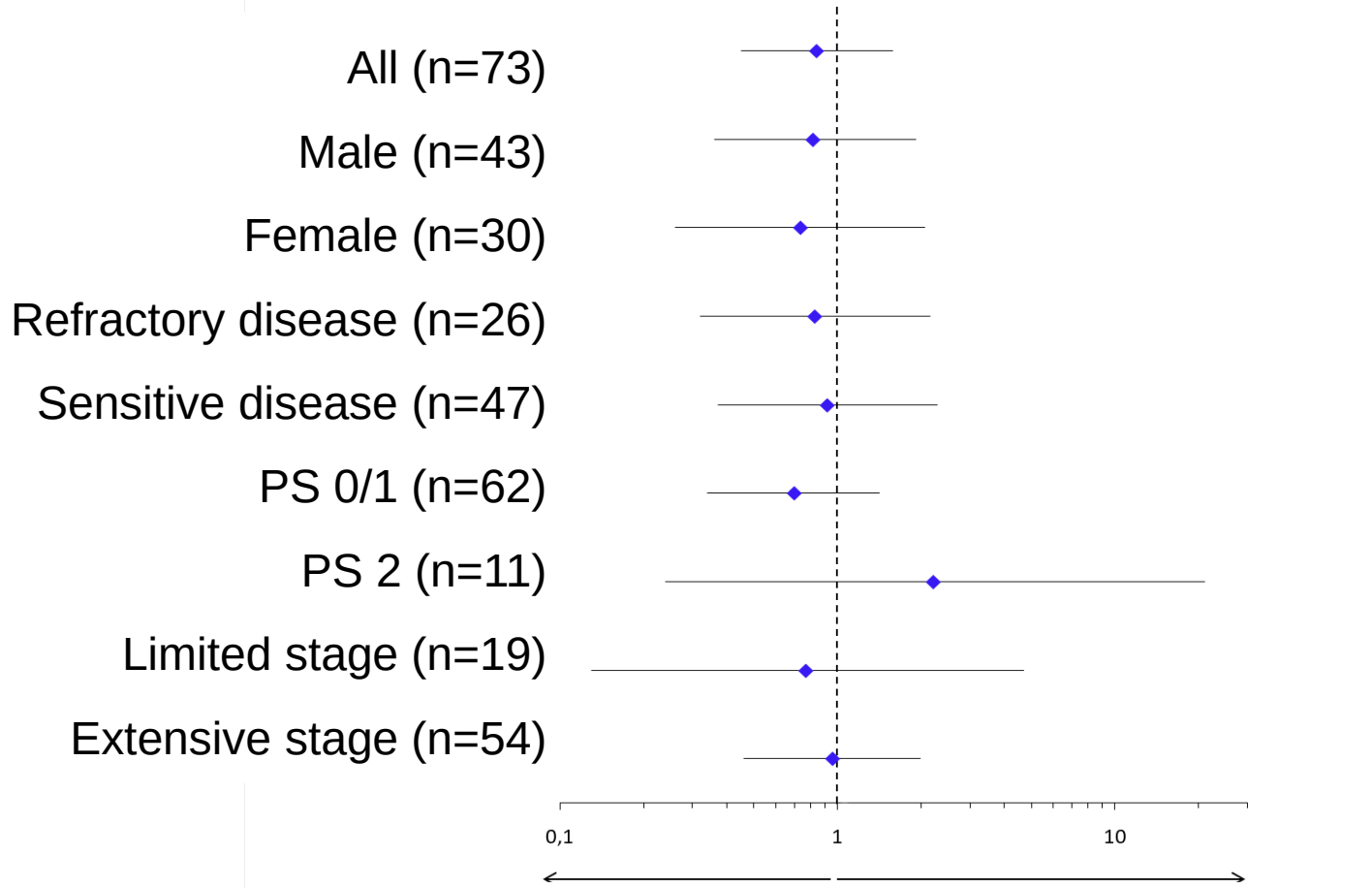

HR (adjusted)Arm Atezolizumab = 0.84 [0.45-1.58] ; p=0.60
Overall Survival
1
0.8
0.6
0.4
0.2
0
0
2
4
6
8
10
12
14
Time (months)
Median OS, [95% CI]
8.7 [4.1-12.7] ; n=24, 17 events, 7 censored
9.5 [3.2-14.4] ; n=49, 29 events, 20 censored
p=0.75
A - Chemotherapy
B - Atezolizumab

Fig. 2c



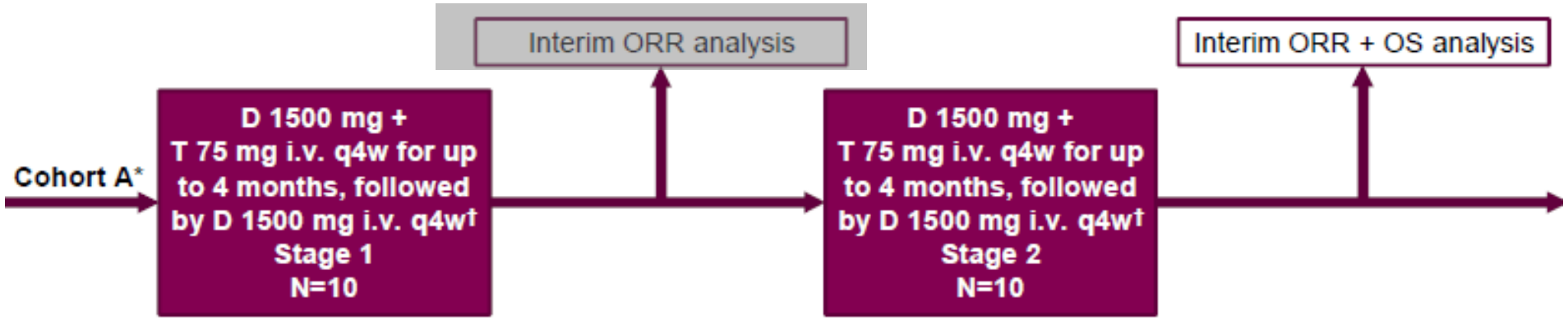
	HR (adjusted)$_{\text{Arm Atezolizumab}}$
All (n=73)	0.84 [0.45-1.58]
Male (n=43)	0.82 [0.36-1.91]
Female (n=30)	0.74 [0.26-2.07]
Refractory disease (n=26)	0.83 [0.32-2.15]
Sensitive disease (n=47)	0.92 [0.37-2.29]
PS 0/1 (n=62)	0.70 [0.34-1.42]
PS 2 (n=11)	2.23 [0.24-21.16]
Limited stage (n=19)	0.77 [0.13-4.69]
Extensive stage (n=54)	0.96 [0.46-1.99]

Study design

Endpoint: Response rate
Investigators' assessment

Eligibility

- ED SCLC (VALG)
- Platinum-refractory recurrent disease
- PS 0-1
- Measurable disease (RECIST 1,1)

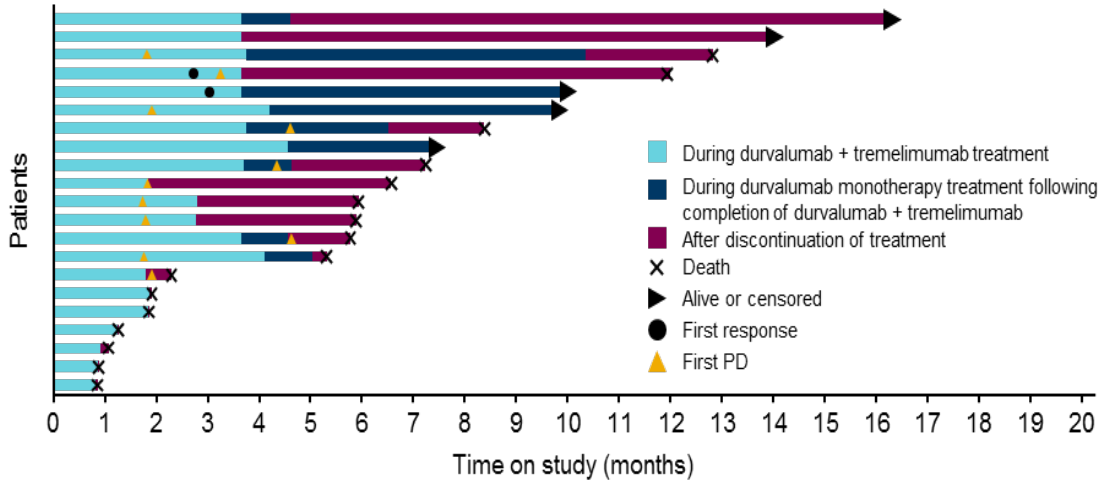


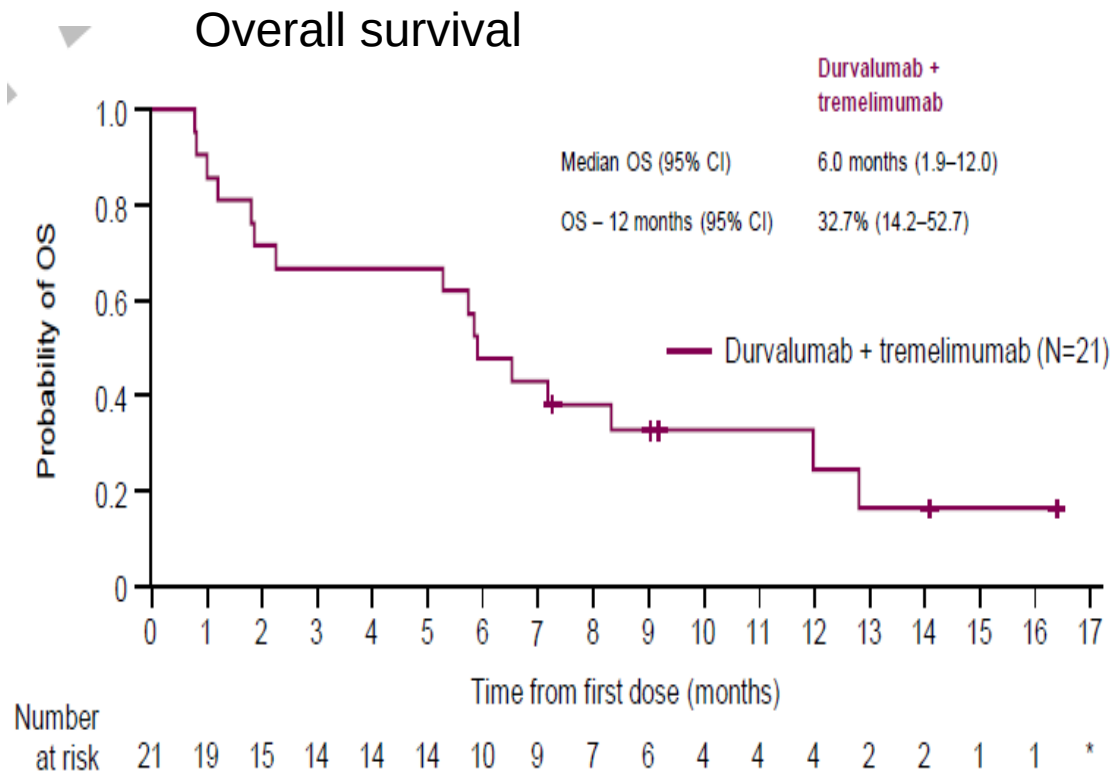
Outcome

Endpoints:

- 2 responders: ORR 9.5% (95% CI, 1.2–30.4)
- Median PFS : 1.9 months (95% CI, 1.8–4.3)
- Median OS : 6.0 months (95% CI, 1.9–12.0)

n = 21



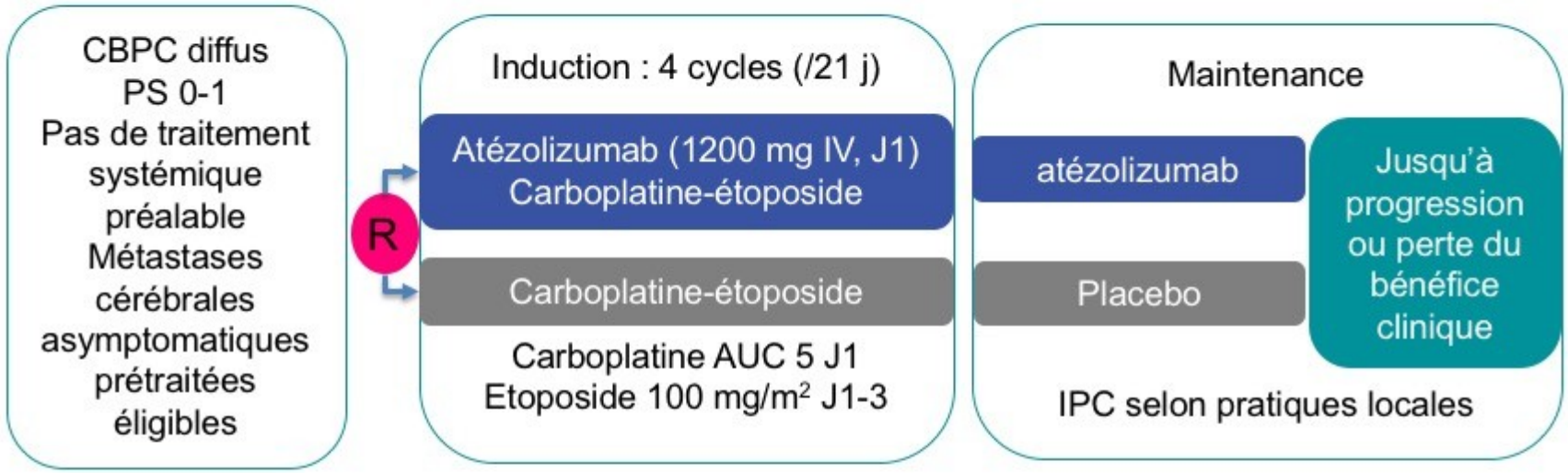


Study	Agent(s)	n	Median PFS (months)	Median OS (months)
Baltic cohort A	Tremelemumab durvalumab	21	1.9	6.0
CheckMate 032	nivolumab	98	1.4	4.4
CheckMate 032	Nivolumab-1 ipilimumab-3	61	2.6	7.7
Keynote 028*	Pemetrexed	24	1.9	9.7
IFCT 1603	Atezolizumab	49	1.4	11.4
Eckardt	Oral topotecan	153	2.7	7.7

* Selected on tumor cell 22C3 PD-L1 expression (> 1%)

IMpower 133

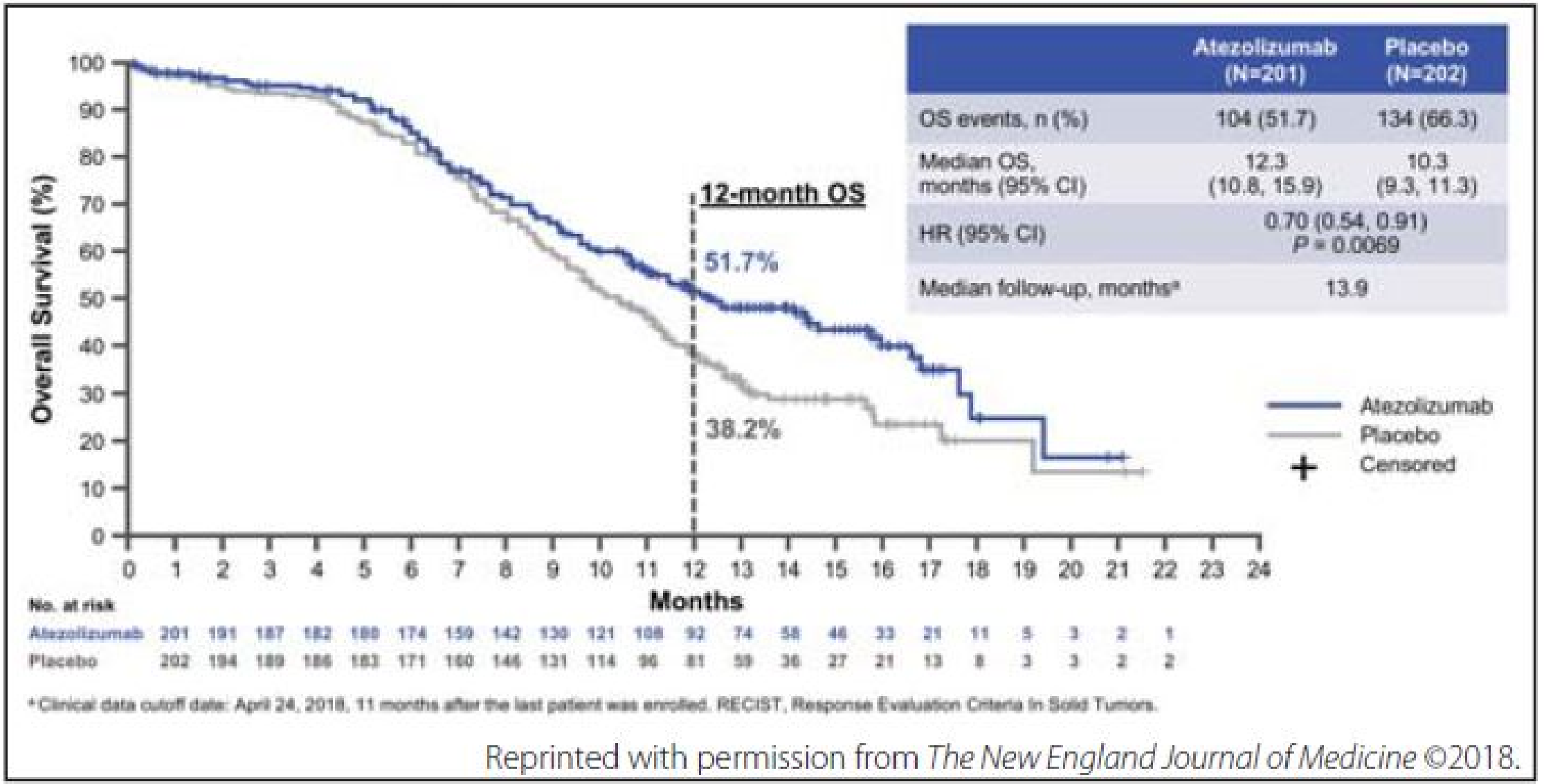
Phase 3 carboplatine-étoposide-atézolizumab



- **Objectifs principaux :**
  - **survie globale**
  - **survie sans progression (investigateur)**
- Stratification : sexe, PS, métastases cérébrales (O/N)

WCLC 2018 – D'après SV Liu et al., abstr. PL02.07, actualisé

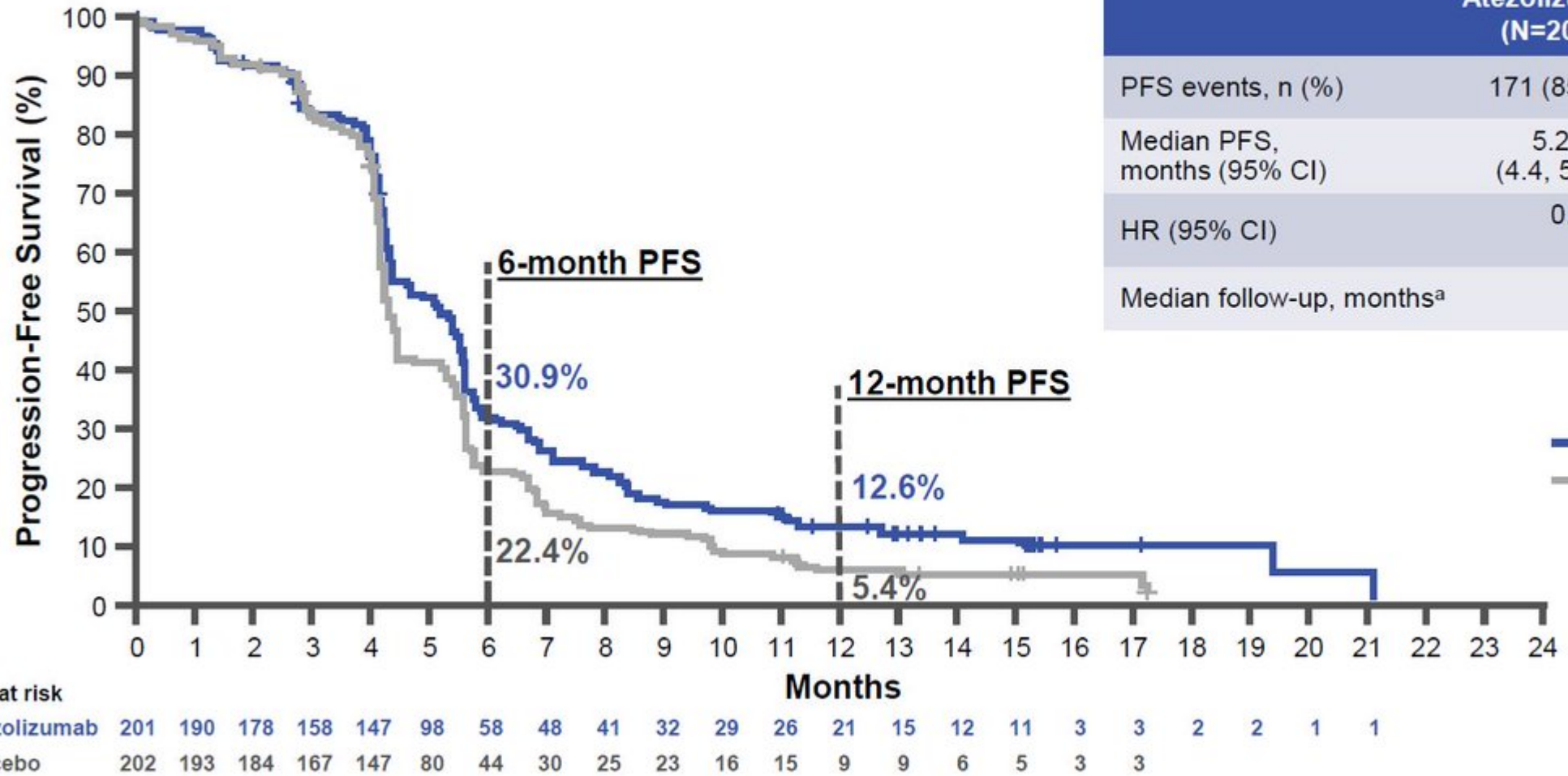
Fig. 3. Overall Survival in Key Subgroups of IMpower133



	Atezolizumab (N=201)	Placebo (N=202)
OS events, n (%)	104 (51.7)	134 (66.3)
Median OS, months (95% CI)	12.3 (10.8, 15.9)	10.3 (9.3, 11.3)
HR (95% CI)	0.70 (0.54, 0.91) *P* = 0.0069	
Median follow-up, months[a]	13.9	

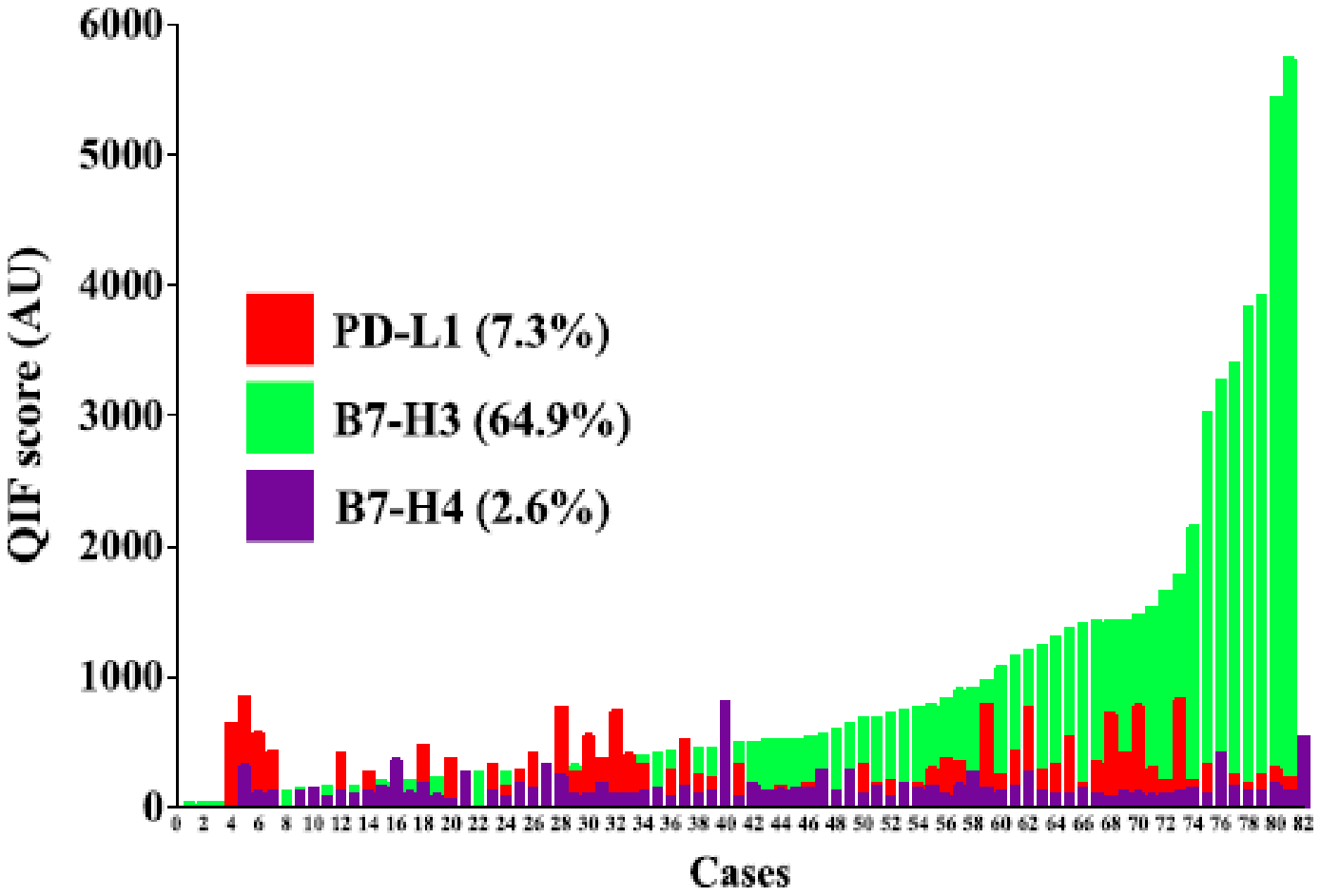
[a]Clinical data cutoff date: April 24, 2018, 11 months after the last patient was enrolled. RECIST, Response Evaluation Criteria in Solid Tumors.

Investigator-assessed progression-free survival



	Atezolizumab (N=201)	Placebo (N=202)
PFS events, n (%)	171 (85.1)	189 (93.6)
Median PFS, months (95% CI)	5.2 (4.4, 5.6)	4.3 (4.2, 4.5)
HR (95% CI)	0.77 (0.62, 0.96) *P* = 0.017	
Median follow-up, months[a]	13.9	

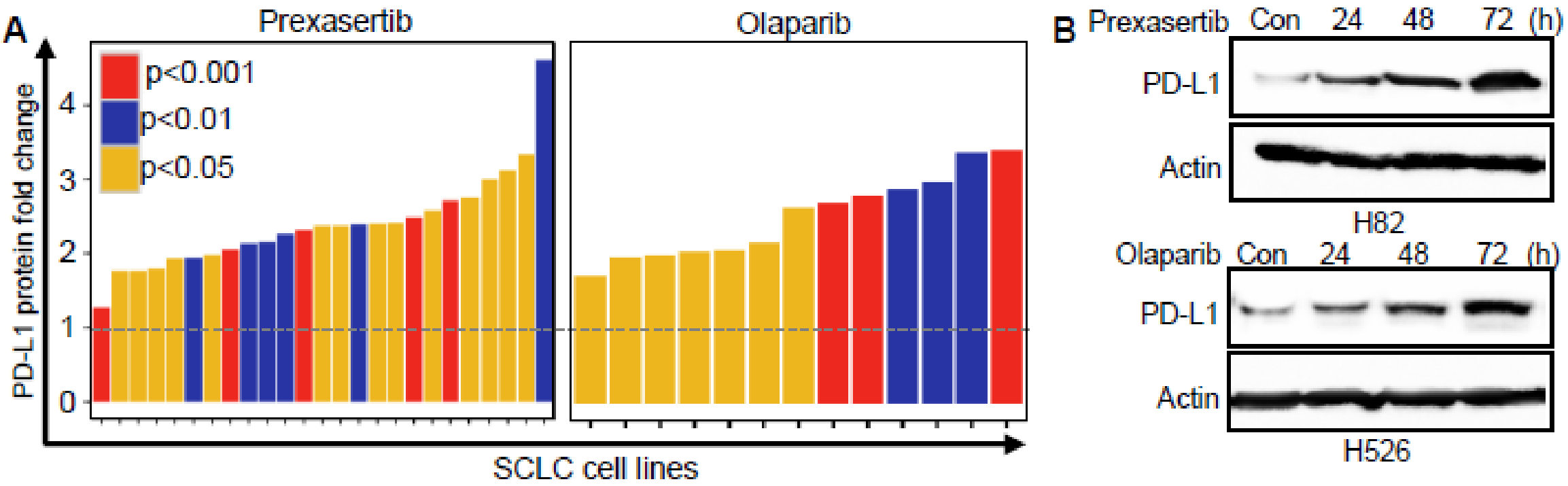
[a] Clinical data cutoff date: April 24, 2018, 11 months after the last patient was enrolled. CI, confidence interval; HR, hazard ratio.



Niveaux de différentes cibles immunitaires en CPPC. Distribution des scores QIF PD-L1 (rouge), B7-H3 (vert) et B7-H4 (magenta) dans les CPPC

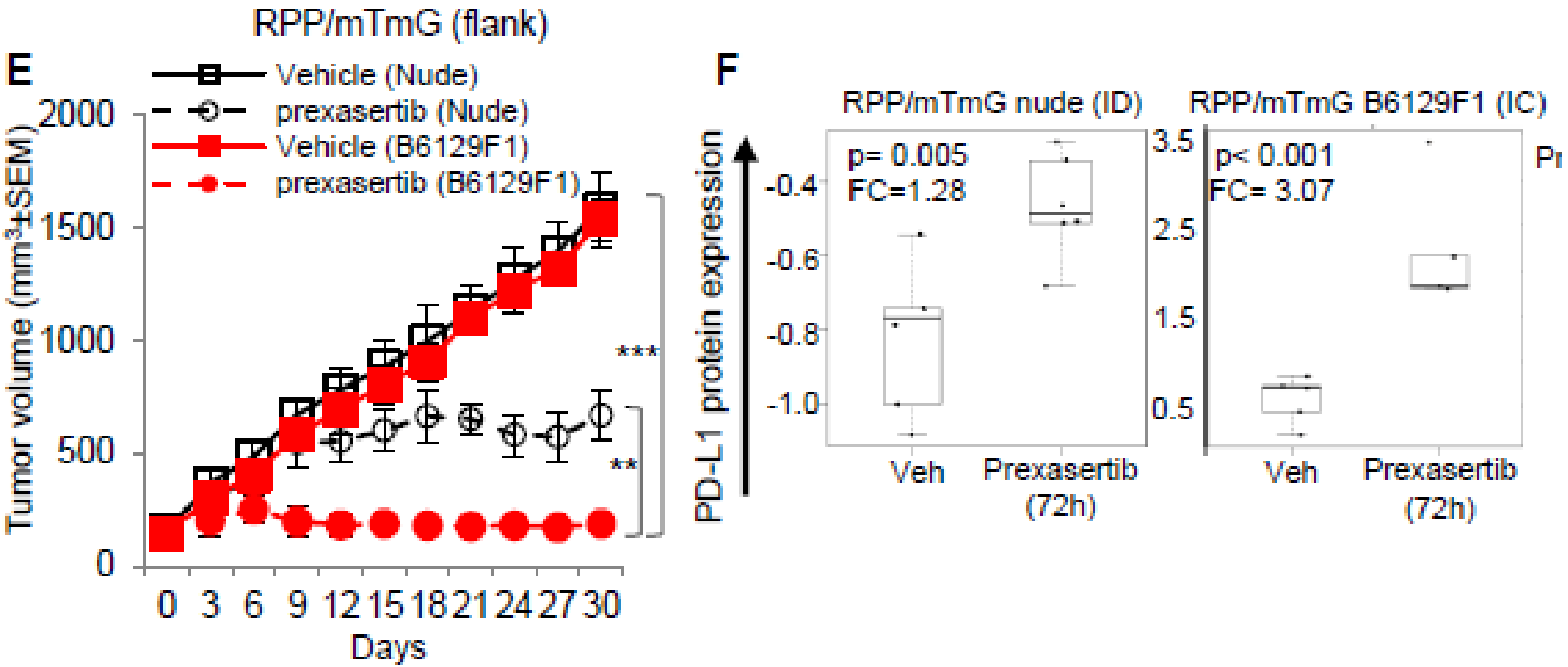
Carvajal-Hausdorf D, et al. J Immunother Cancer. 2019 ; 7(1):65.

Interactions DDR - IPCI



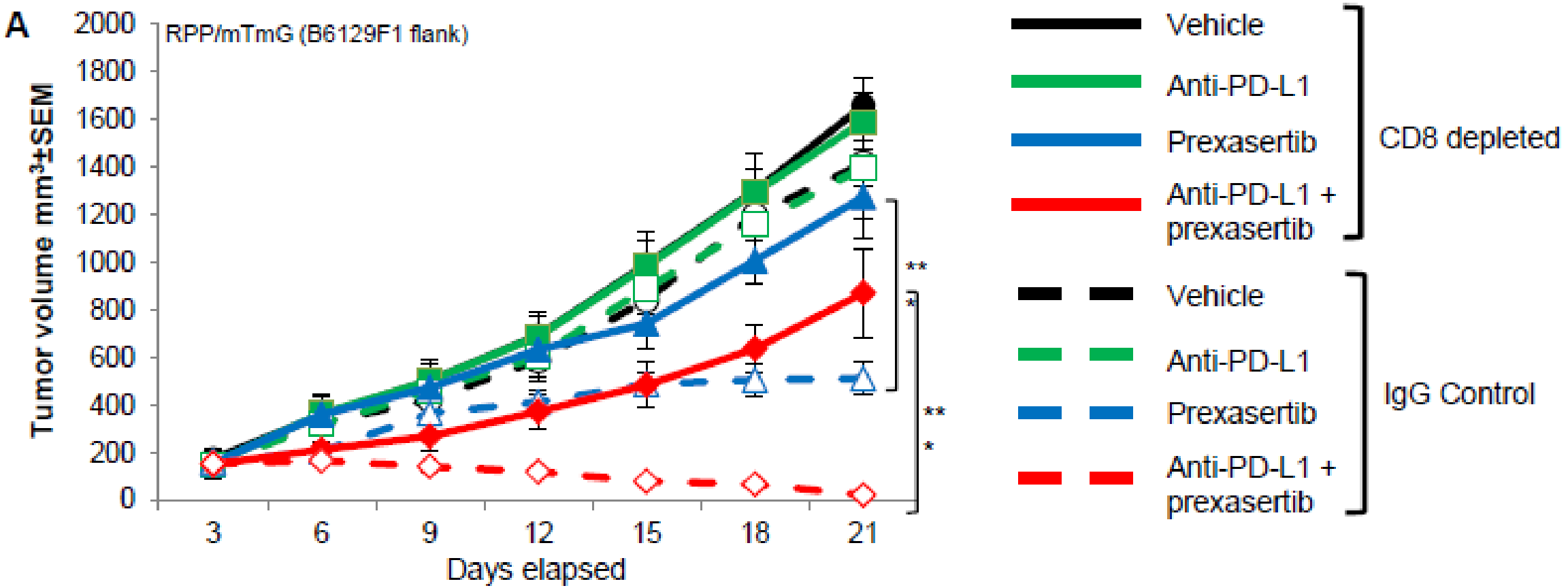
L'inhibition de la DDR par ciblage avec de petites molécules inhibitrices de CHK1 (prexasertib) et de PARP (olaparib) améliore l'expression de la protéine PD-L1

Triparna Sen et al. Cancer Discovery in press



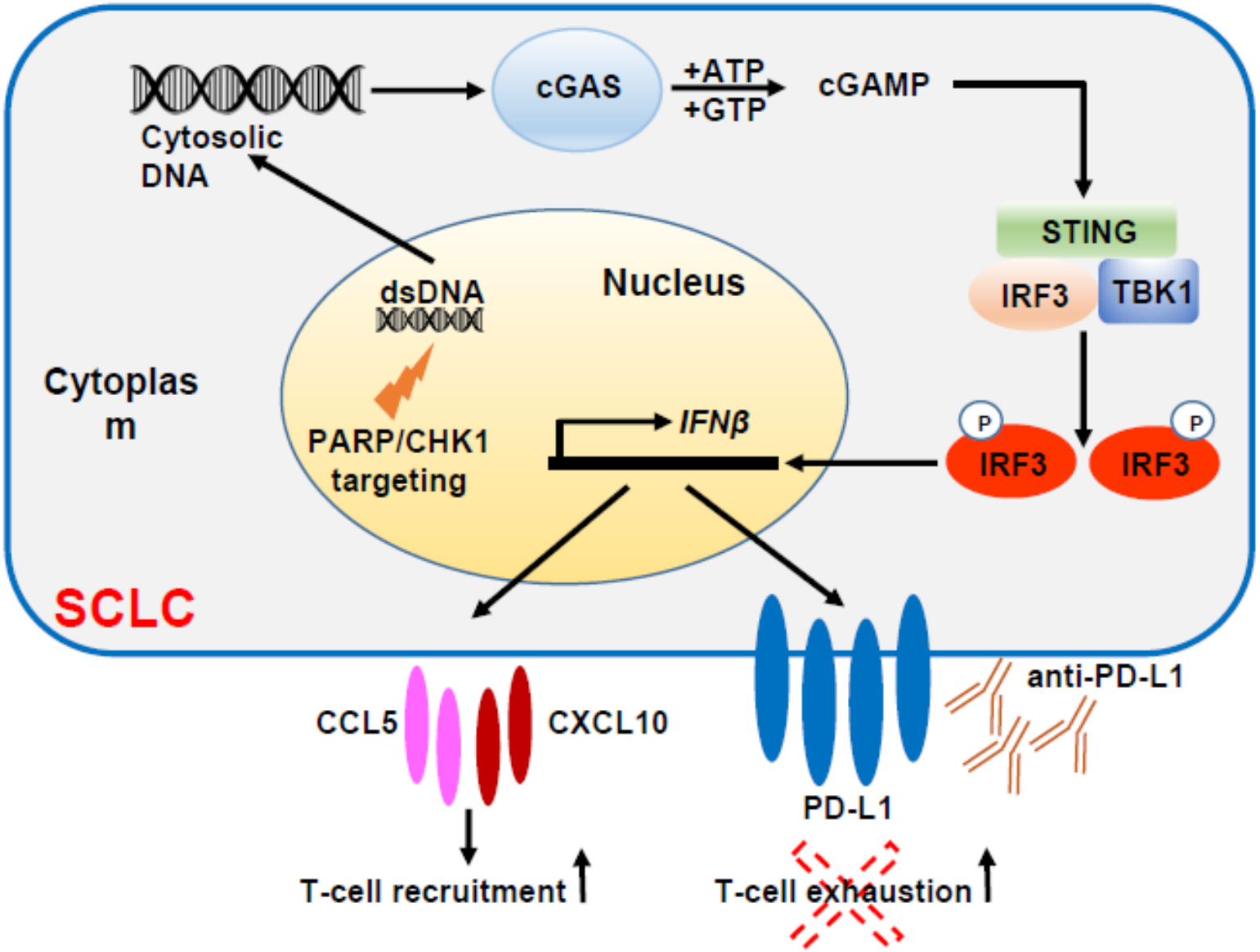
Les anti CHK1 ont une action dépendante d'un système immunitaire intact et augmente l'expression de PD-L1

Triparna Sen et al. Cancer Discovery in press



Les lymphocytes T CD8 + sont nécessaires pour l'immunité anti-tumorale induite par CHK1i avec ou sans blocage anti-PD-L1.

Triparna Sen et al. Cancer Discovery in press



Triparna Sen et al. Cancer Discovery in press