Le cancer à petites cellules : quoi de neuf?

Jean Louis Pujol, Montpellier

Groupe d'Oncologie de Langue Française

COURS DU GOLF 2019

BASES

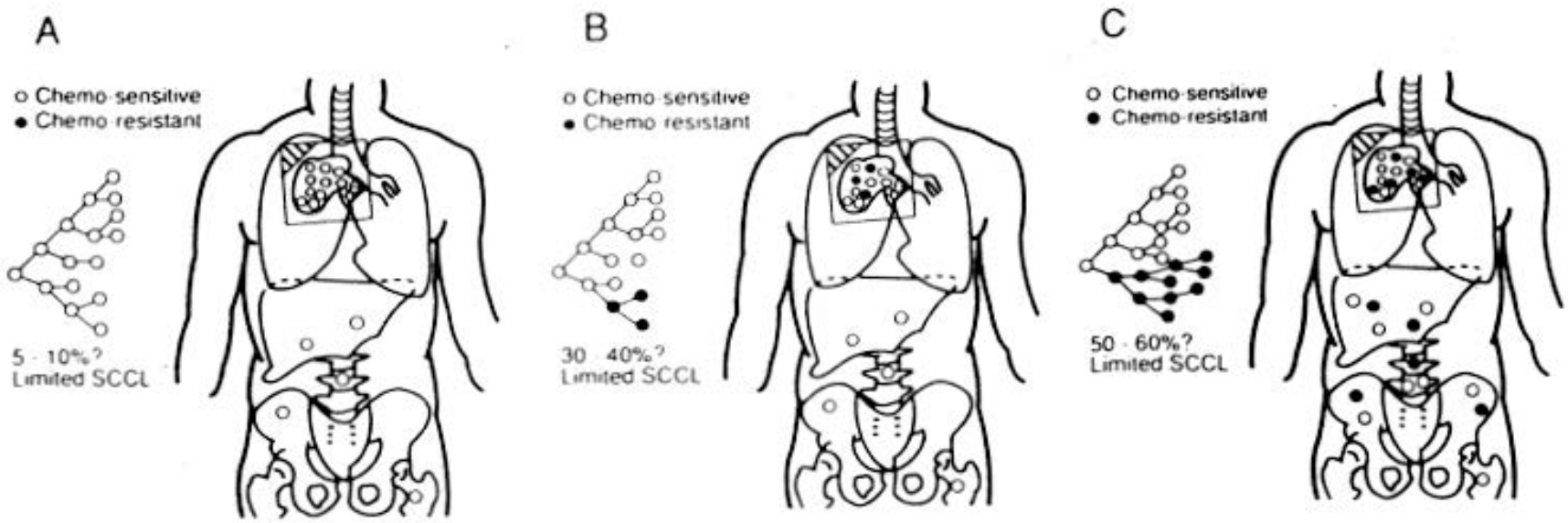
- Pujol JL. Cancer bronchique à petites cellules: la pneumologie fondée sur les preuves. Sous l'égide de la SPLF. Coordinatation Sylain Marchand; Edition Margaux Orange, Paris. 5ème édition pp 443-457.

- Pujol JL, Roch B, Pujol CN, Goze C. [Medical treatment of small cell lung cancer: Can we leave the area of cisplatin-etoposide?]. Bull Cancer. 2018 Oct;105(10):955-966. doi: 10.1016/j.bulcan.2018.05.014. Epub 2018 Aug 9. Review.

Nouveauté en radiothérapie

Homogénéité pronostique?

- la frontière entre limité et étendu n’est pas nette



Radiothérapie de consolidation

Use of thoracic radiotherapy for extensive stage small-cell lung cancer: a phase 3 randomised controlled trial

Ben J Slotman, Harm van Tinteren, John O Praag, Joost L Knegjens, Sherif Y El Sharouni, Matthew Hatton, Astrid Keiiser, Corinne Faivre-Finn*, Suresh Senan*

Lancet 2015; 385: 36–42

Summary

Background Most patients with extensive stage small-cell lung cance

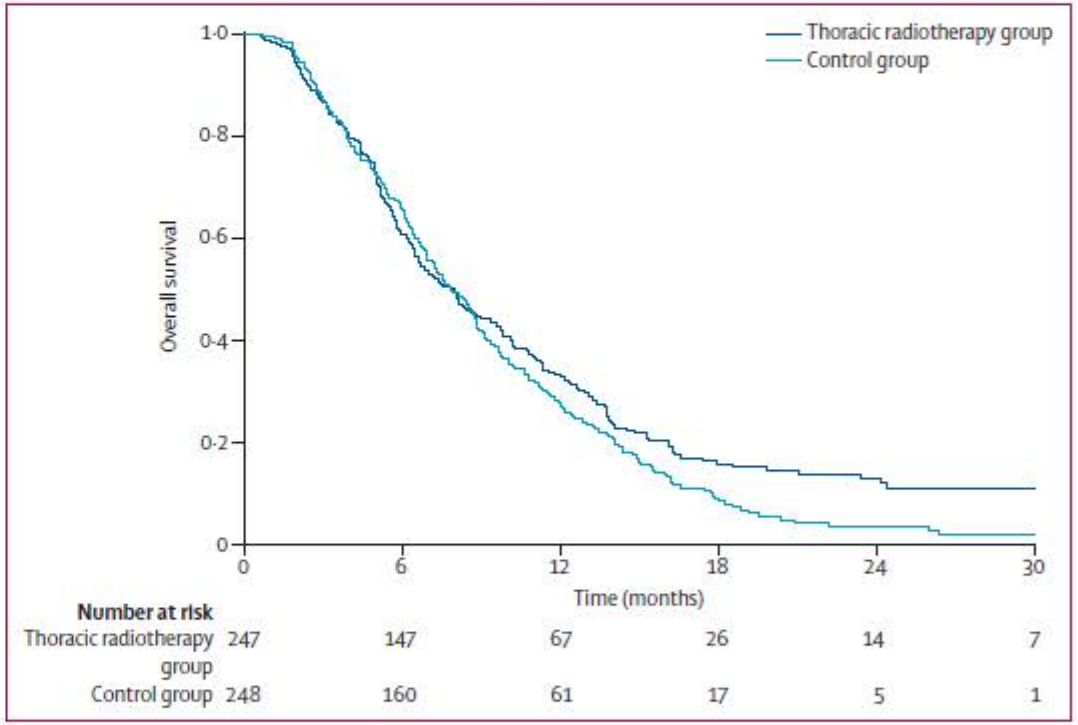
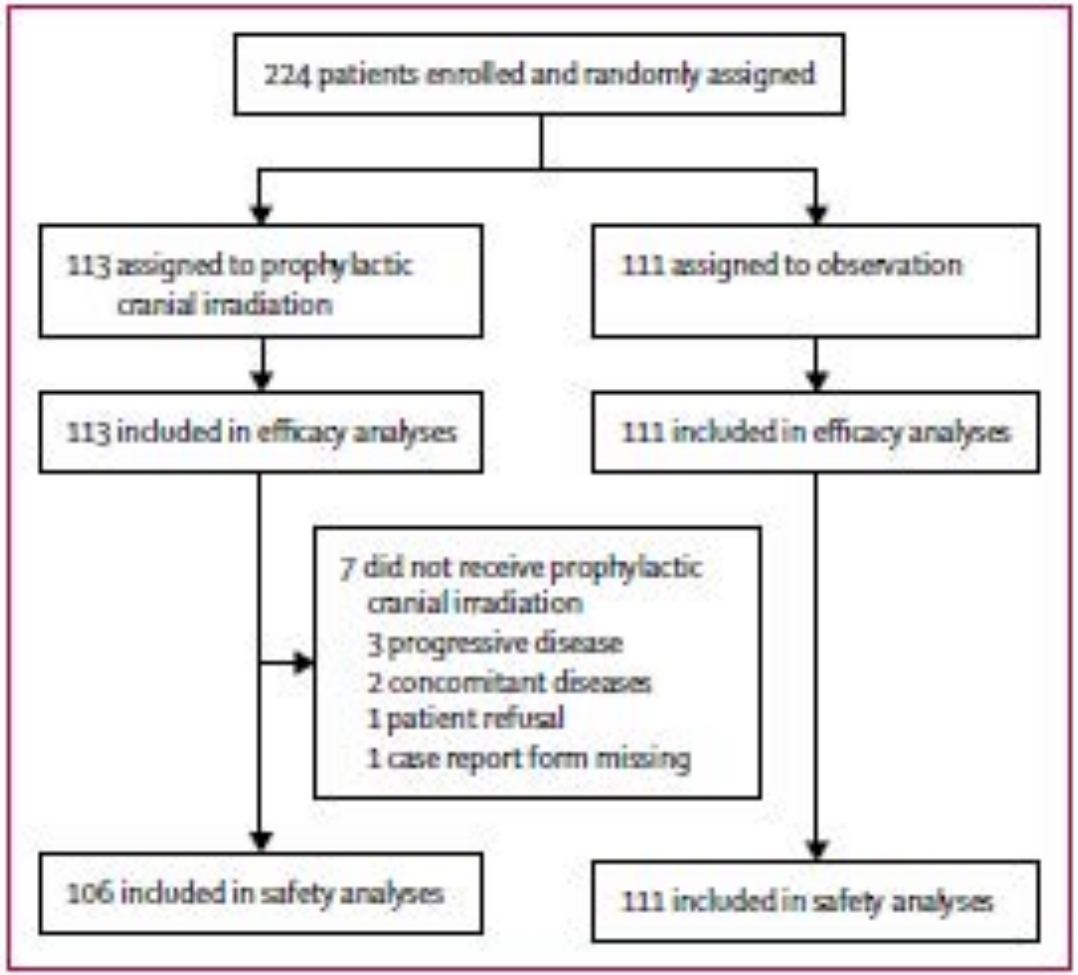
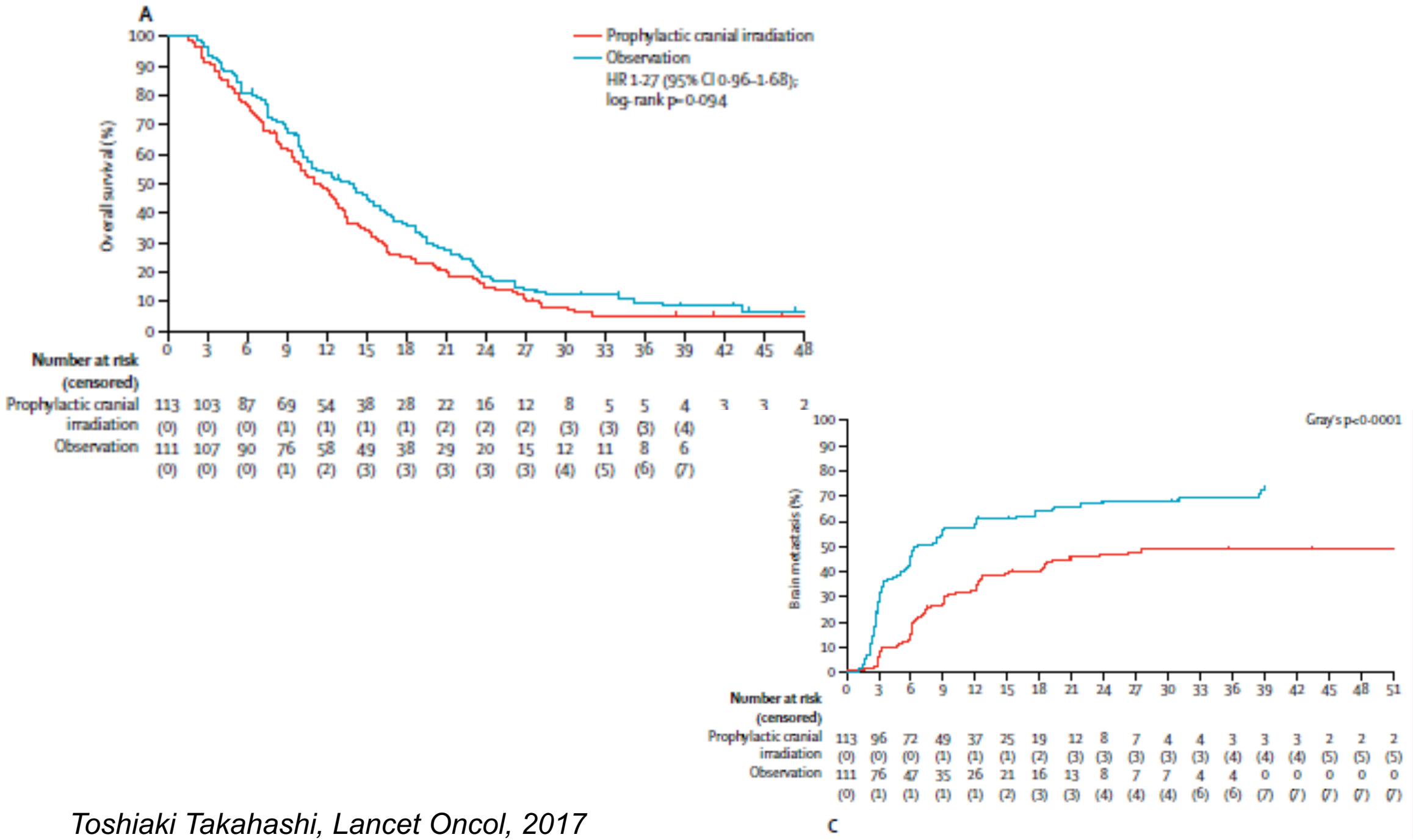


Figure 2: Kaplan-Meier curves for overall survival

CPC étendu: IPC utile?

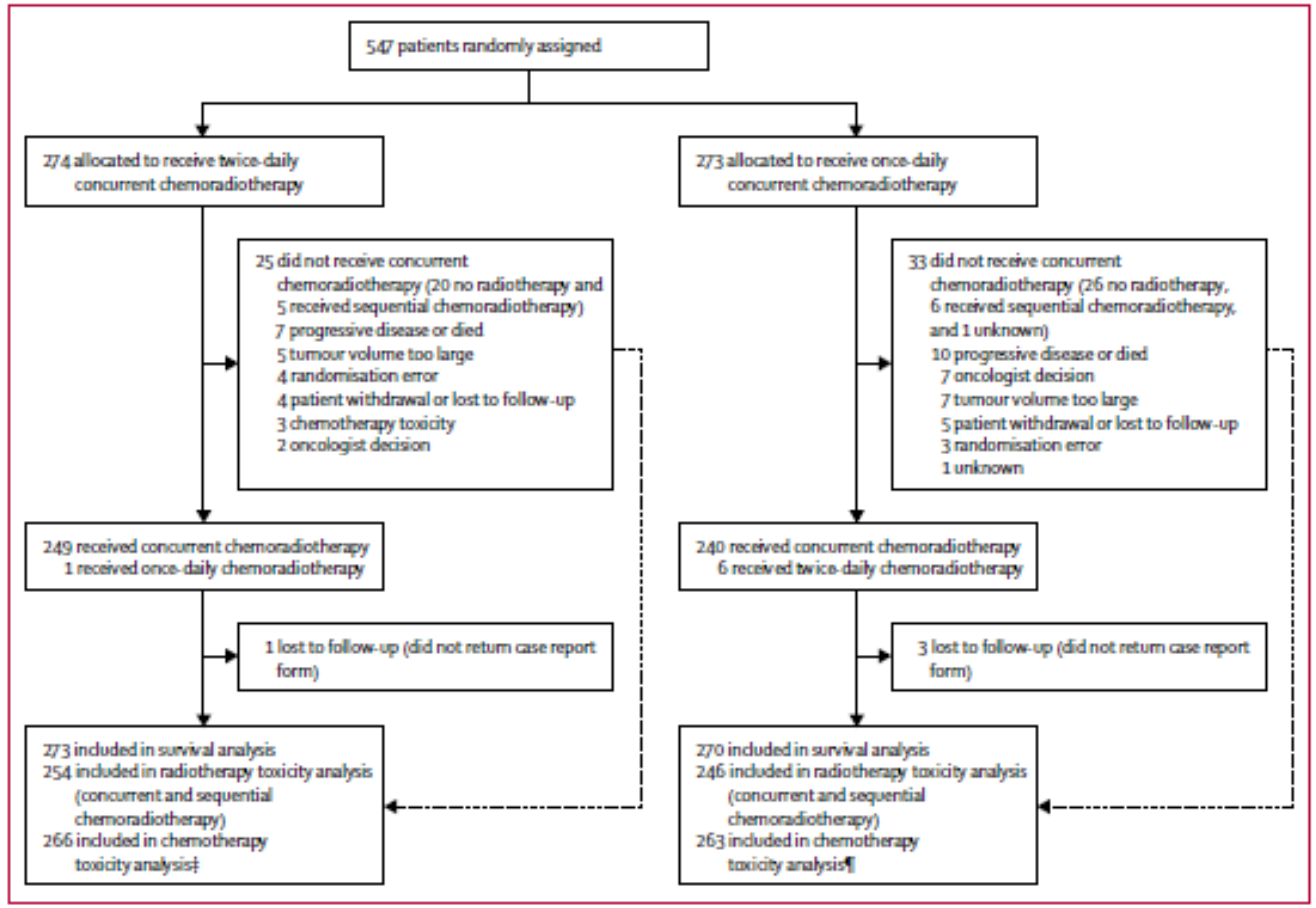


Toshiaki Takahashi, Lancet Oncol, 2017



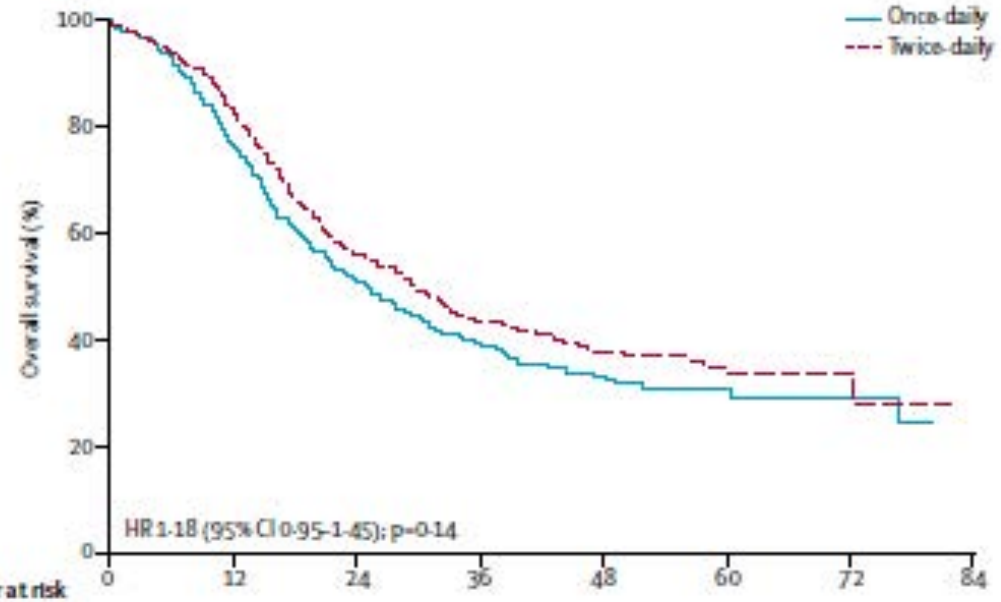
Toshiaki Takahashi, Lancet Oncol, 2017

Concurrent once-daily versus twice-daily chemoradiotherapy in patients with limited-stage small-cell lung cancer (CONVERT): an open-label, phase 3, randomised, superiority trial



Corinne Faivre-Finn, lancet Oncol Juin 2017

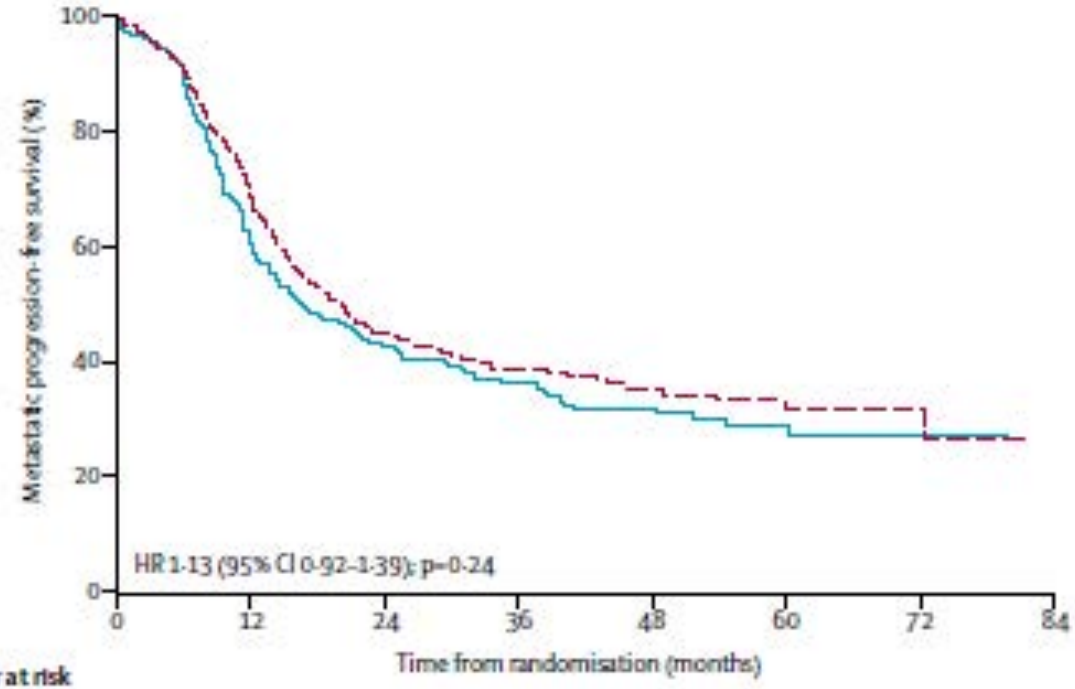
A



Number at risk (number censored)								
Once-daily	270	202 (5)	134 (6)	88 (23)	46 (53)	21 (75)	7 (88)	3 (91)
Twice-daily	273	224 (3)	151 (4)	92 (31)	54 (60)	25 (85)	6 (104)	2 (107)

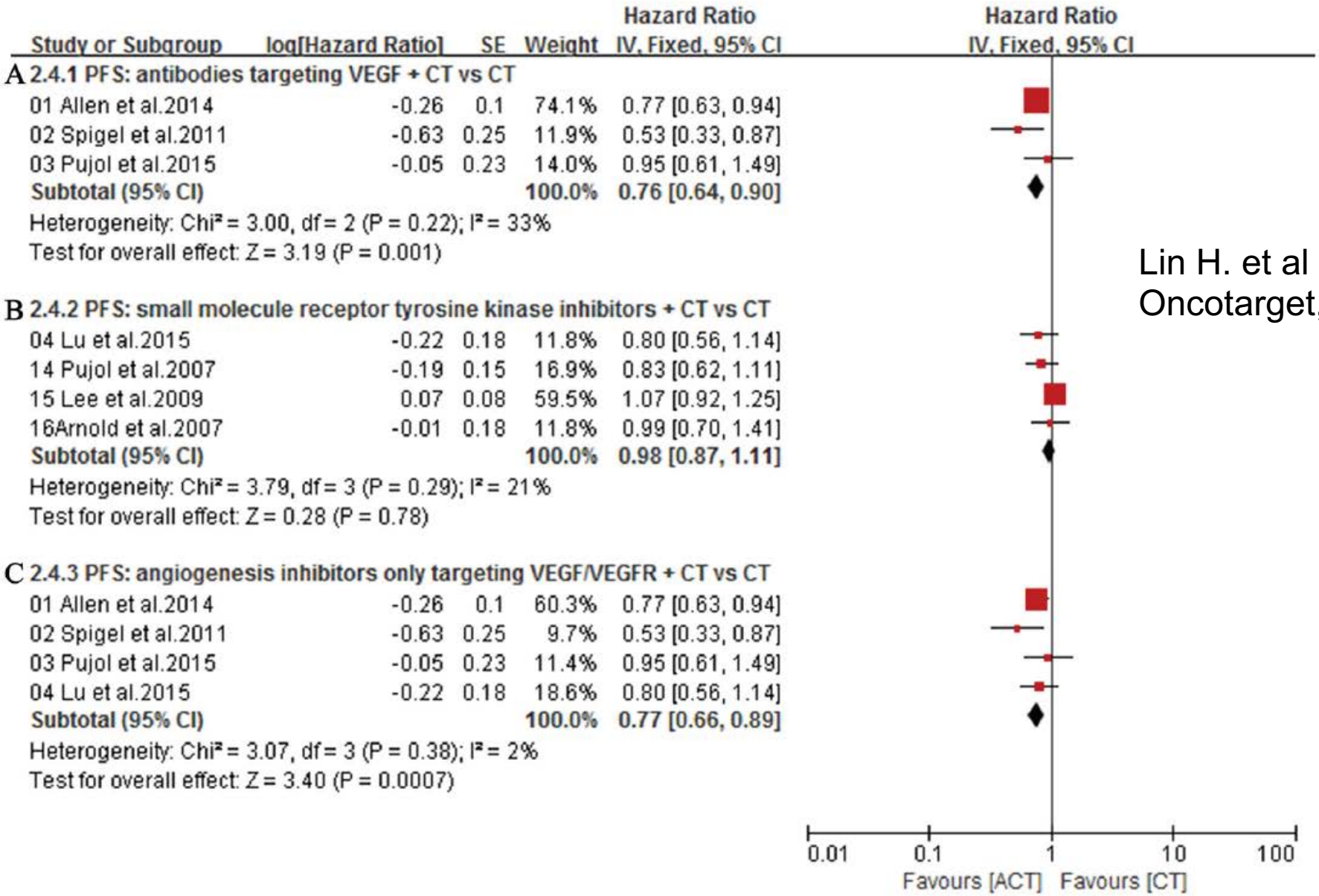
B

C



Number at risk (number censored)								
Once-daily	270	159 (5)	113 (5)	82 (20)	43 (49)	19 (70)	6 (82)	3 (85)
Twice-daily	273	186 (2)	122 (2)	85 (23)	53 (49)	24 (74)	6 (92)	2 (95)

Focus sur les traitements anti-angiogéniques



Lin H. et al
Oncotarget, 2017, 8, 1141-1155

Figure 7: A. Subgroup analysis of PFS for antibodies targeting VEGF plus CT versus CT; **B.** Subgroup analysis of PFS for small molecule angiogenesis inhibitors plus CT versus CT; **C.** Subgroup analysis of PFS for angiogenesis inhibitors only targeting VEGF/VEGFR plus CT versus CT.

bevacizumab

Annals of Oncology

Annals of Oncology 26: 908–914, 2015
doi:10.1093/annonc/mdv065
Published online 16 February 2015

Randomized phase II–III study of bevacizumab in combination with chemotherapy in previously untreated extensive small-cell lung cancer: results from the IFCT-0802 trial†

J.-L. Pujol[1*], A. Lavole[2], E. Quoix[3], O. Molinier[4], P.-J. Souquet[5], F. Barlesi[6], H. Le Caer[7], D. Moro-Sibilot[8], P. Fournel[9], J. P. Oster[10], P. Chatellain[11], P. Barre[12], G. Jeannin[13], P. Mourlanette[14], M. Derollez[15], D. Herman[16], A. Renault[17], C. Dayen[18], P. J. Lamy[19], A. Langlais[20], F. Morin[20] & G. Zalcman[21] on behalf of the French Cooperative Thoracic Intergroup (IFCT)

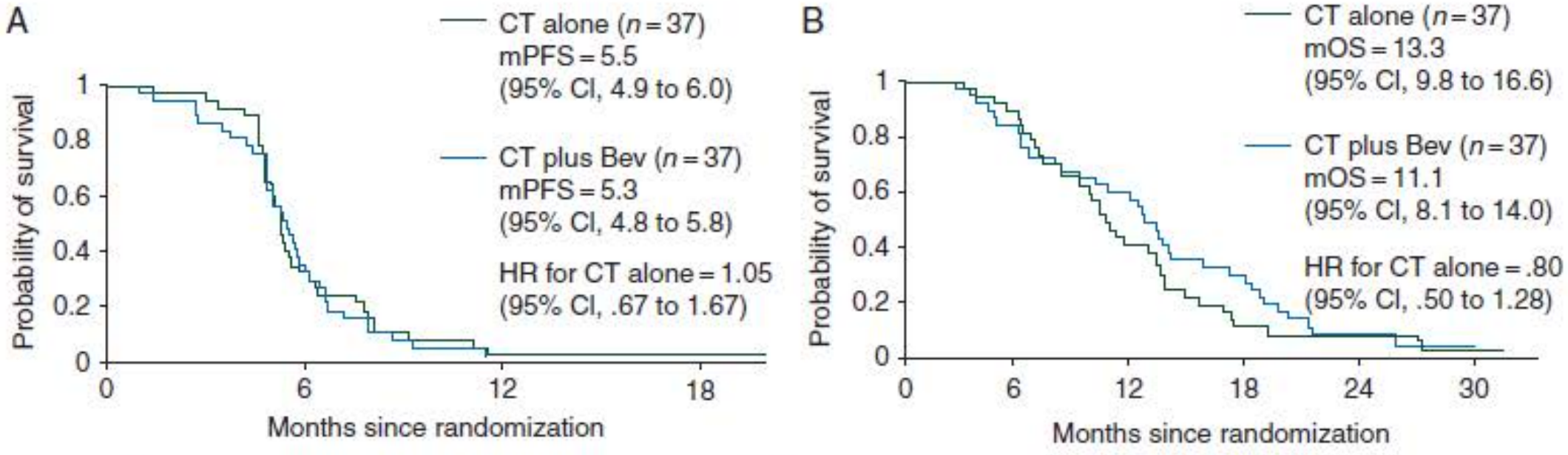


Figure 2. Survival from date of randomization: (a) progression-free survival (PFS); (b) overall survival (OS).

Sunitinib?

Chemotherapy With or Without Maintenance Sunitinib for Untreated Extensive-Stage Small-Cell Lung Cancer: A Randomized, Double-Blind, Placebo-Controlled Phase II Study—CALGB 30504 (Alliance)

Chemotherapy Followed by Sunitinib in Small-Cell Lung Cancer

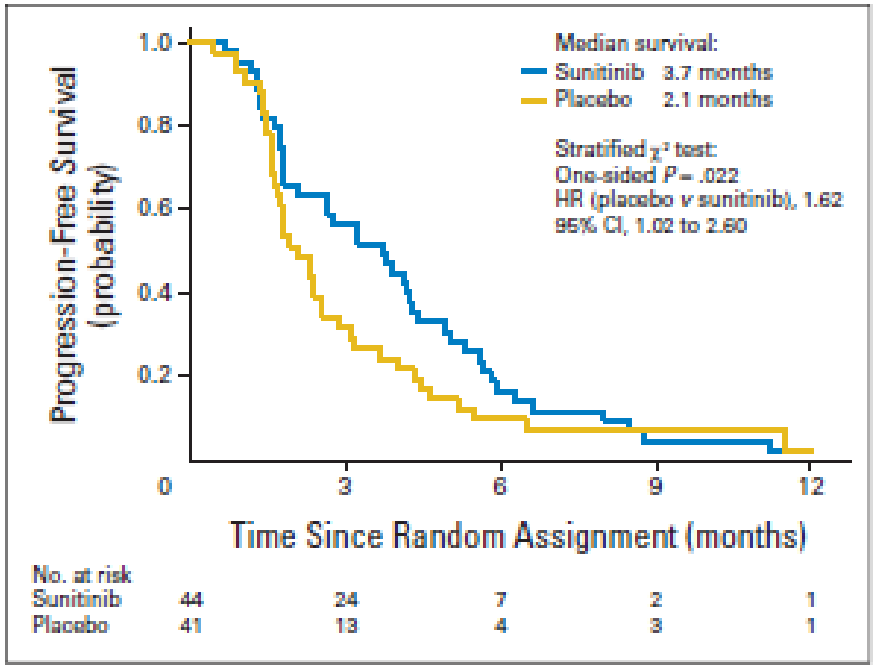


Fig 2. Kaplan-Meier curve for progression-free survival after random assignment to placebo (n = 41) or sunitinib (n = 44). HR, hazard ratio.

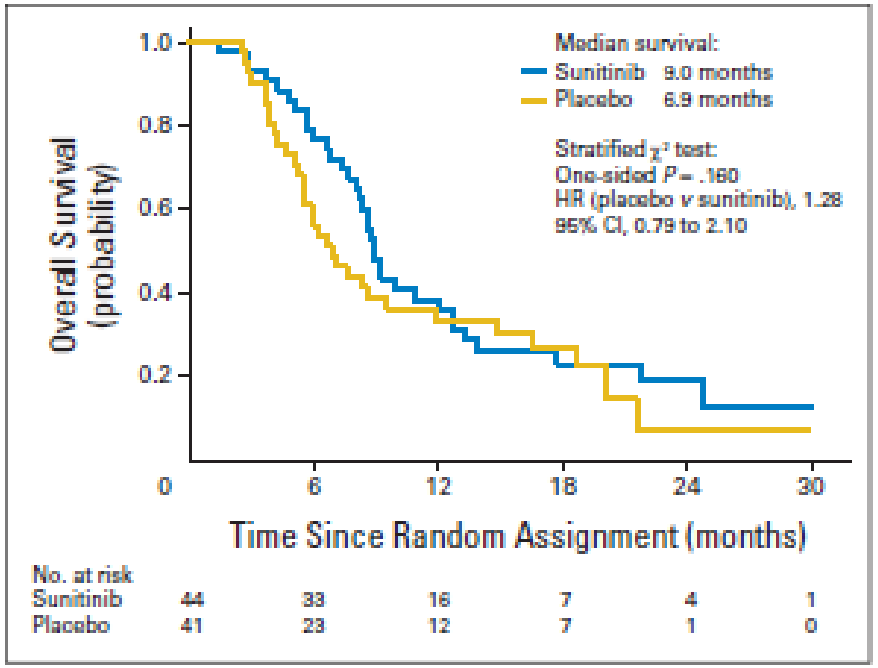


Fig 3. Kaplan-Meier curve for overall survival after random assignment to placebo (n = 41) or sunitinib (n = 44). HR, hazard ratio.

ME 33 · NUMBER 15 · MAY 20 2015

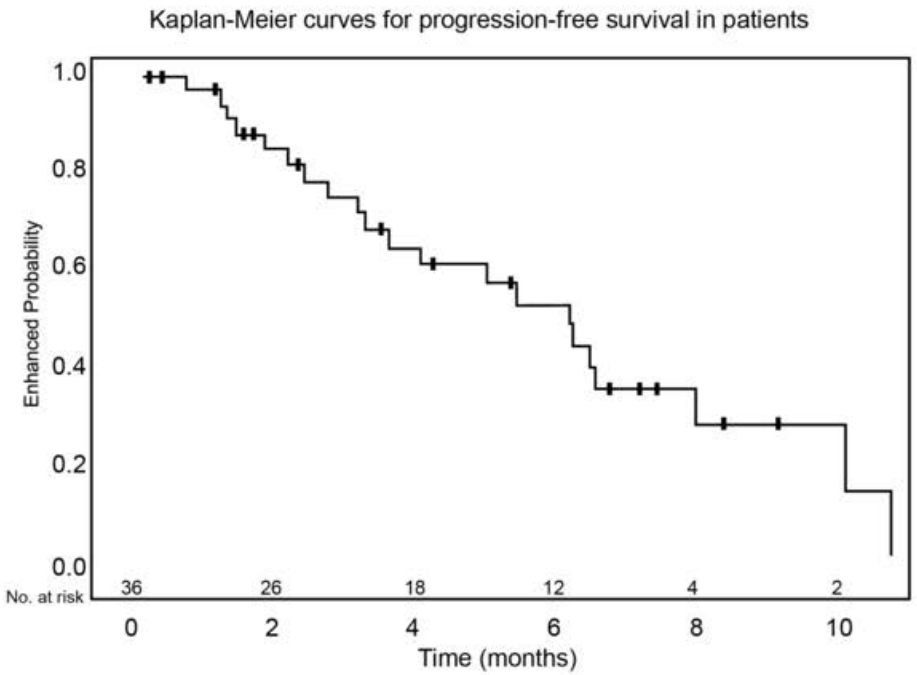
URNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

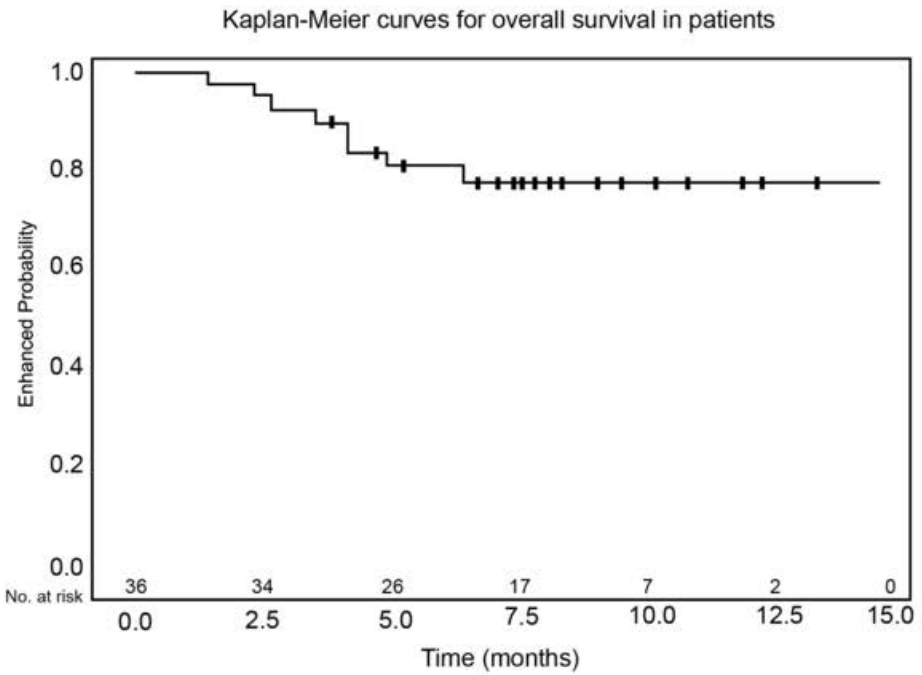
Apatinib : TKI anti-VEGFR2 (phase 2)

Baseline characteristics	N = 36	Percentage
Age (< 60 / ≥ 60)	13/ 23	36.11%/ 63.89%
Gender (male/ Female)	30/ 6	83.33%/ 16.67%
ECOG (0/ 1/ 2)	3/ 18/ 15	8.33% / 50.00%/ 41.67%
Primary lesion (Right lung/ Left lung)	25/ 11	69.44%/ 30.56%
Radiotherapy (Yes /No)	30/ 6	83.33%/ 16.67%
First line-PFS (< 6 m / ≥ 6 m)	19/ 17	52.78%/ 47.22%
The number of treatment lines for apatinib		
Second line treatment	18	50.00%
Three-line treatment	15	41.67%
Four-line treatment	3	8.33%

taux de réponses 19.35%
taux de contrôles 83.87%

The median PFS was **6.18 months** (95%CI: 3.26-7.99)





The median OS was not achieved. The mPFS of patients received apatinib as second-line treatment was 6.48 months.

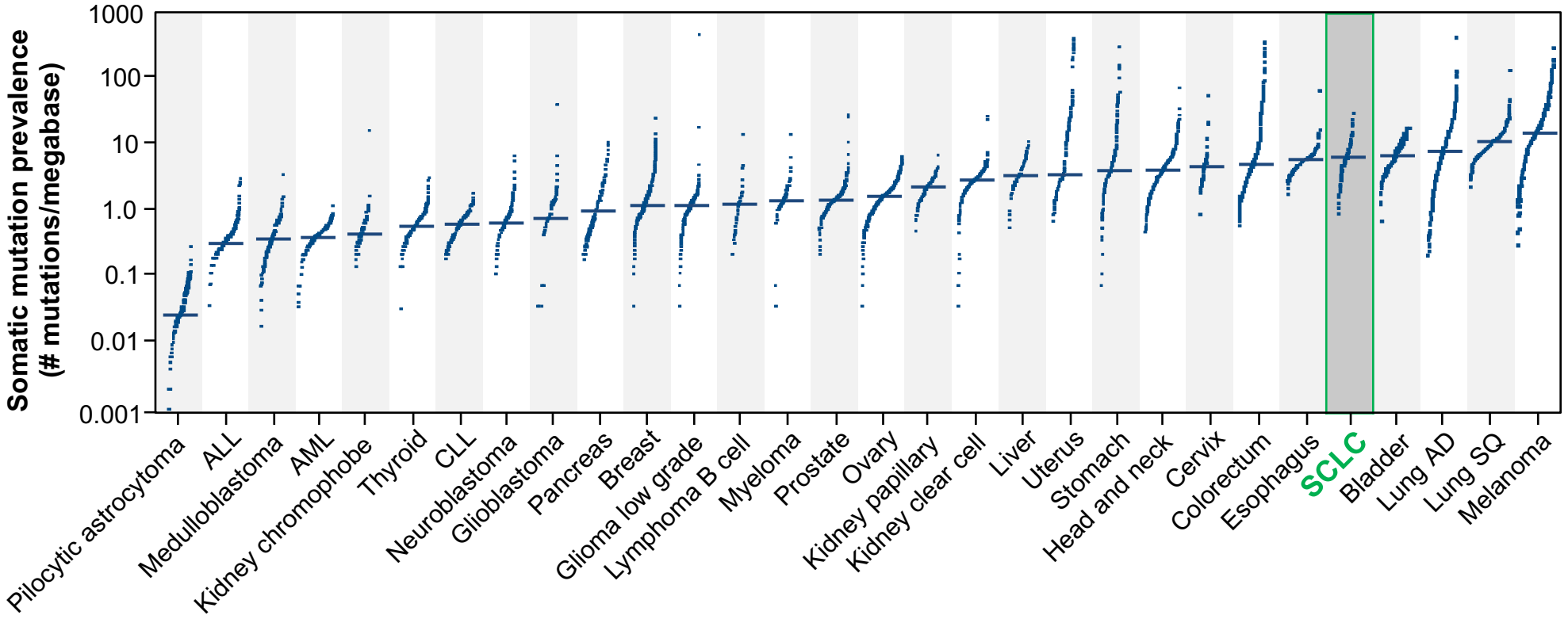
Focus sur l’immunothérapie

ICPI en monothérapie
IPCI et chimiothérapie combinés

Premières tentatives d'immunothérapie des cancers à petites cellules utilisant les interférons

	Type d'interféron	Résumé des résultats
Mattson (1)	IFN naturel	Positif à 2 ans pour les malades avec stade limité
Van Zandwijk (2)	IFN-α	Pas d'amélioration de la survie
Kelly (3)	rIFN-gamma	Pas d'amélioration de la survie
Jett (4)	rIFN-gamma	Différence numérique favorisant le bras observation

Rationnel pour évaluer l'immuno-thérapie



- 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.

Rationnel: Certains syndromes paranéoplasiques ont l'effet d'une immunothérapie endogène

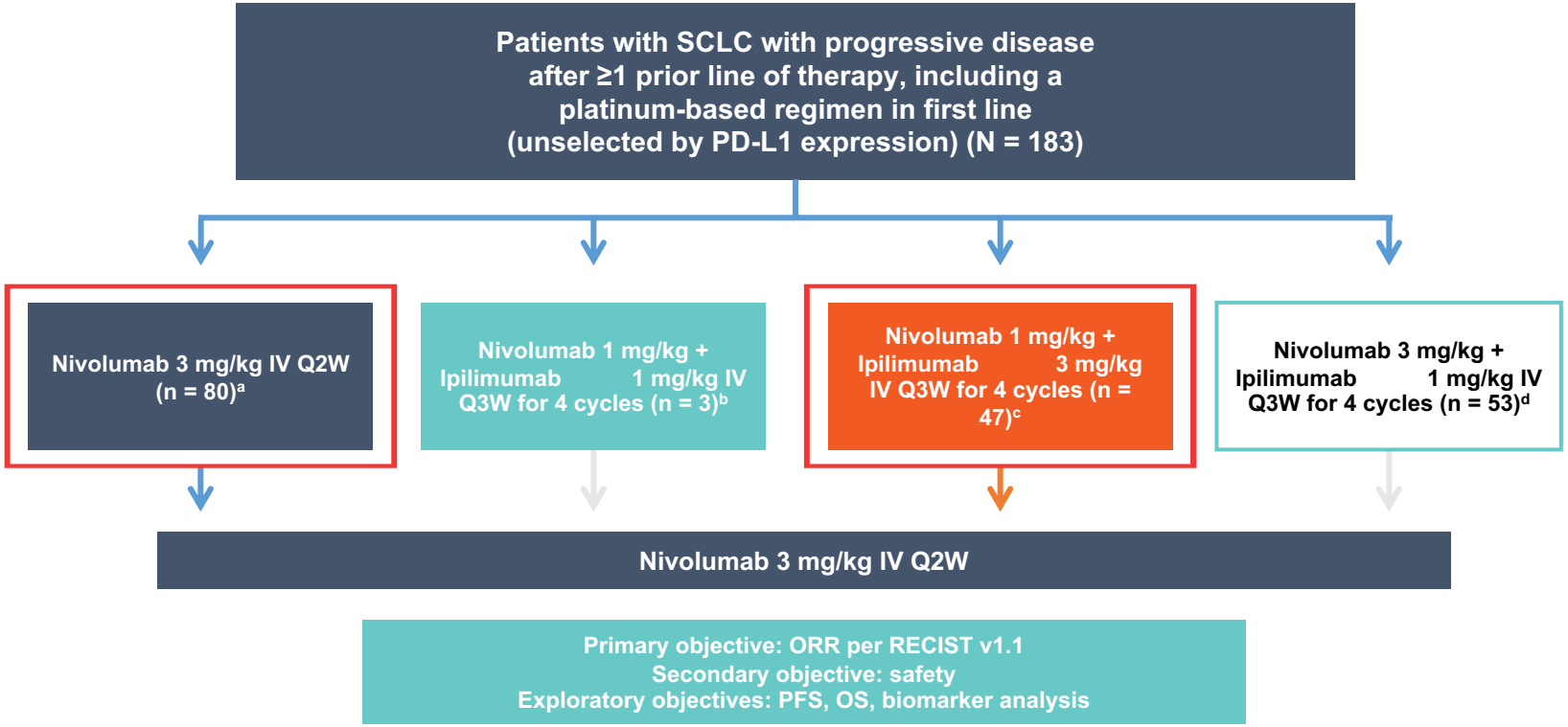
Spontaneous Complete Remission of a Non-small Cell Lung Cancer Associated with Anti-Hu Antibody Syndrome

Jean-Louis Pujol, MD, Anne-Laure Godard, MD,† William Jacot, MD,* and Pierre Labauge, MD, PhD†*

Abstract: Anti-Hu antibodies are directed against lung cancer cell antigens. The anti-tumor effect of anti-Hu antibodies has been suggested by several studies demonstrating that patients presenting with anti-Hu antibodies have a longer survival. In this case report, we suggest that the immunology of HuAb paraneplastic syndrome by itself could induce tumor response.

magnetic resonance imaging were normal; particularly, neither metastasis nor cerebellum atrophy was found. The patient was denied surgery because her poor physiological condition was thought to be incompatible with pulmonary resection. Neither radiotherapy nor chemotherapy was initiated because of the patient's poor performance status of 3 and a 12% body mass weight loss. A joint follow-up by neurology

CheckMate 032 (NCT01928394) study design

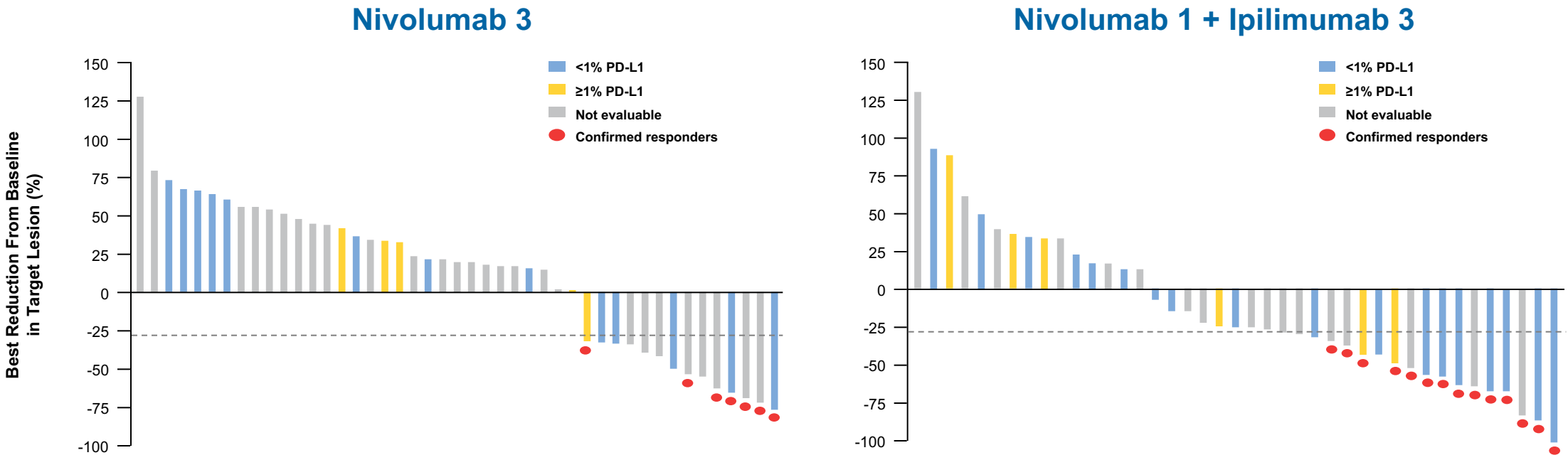


[a]Nivolumab 3: 15 patients in this arm had a follow-up of <6 weeks; follow-up defined as day of first dose to day of database lock; [b]Nivolumab 1 + ipilimumab 1: minimum follow-up of 546 days ; [c]Nivolumab 1 + ipilimumab 3: minimum follow-up of 120 days; [d]Nivolumab 3 + ipilimumab 1: minimum follow-up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

ORR = objective response rate; OS = overall survival.

Results

Figure 5. Tumor responses (PD-L1 expression)



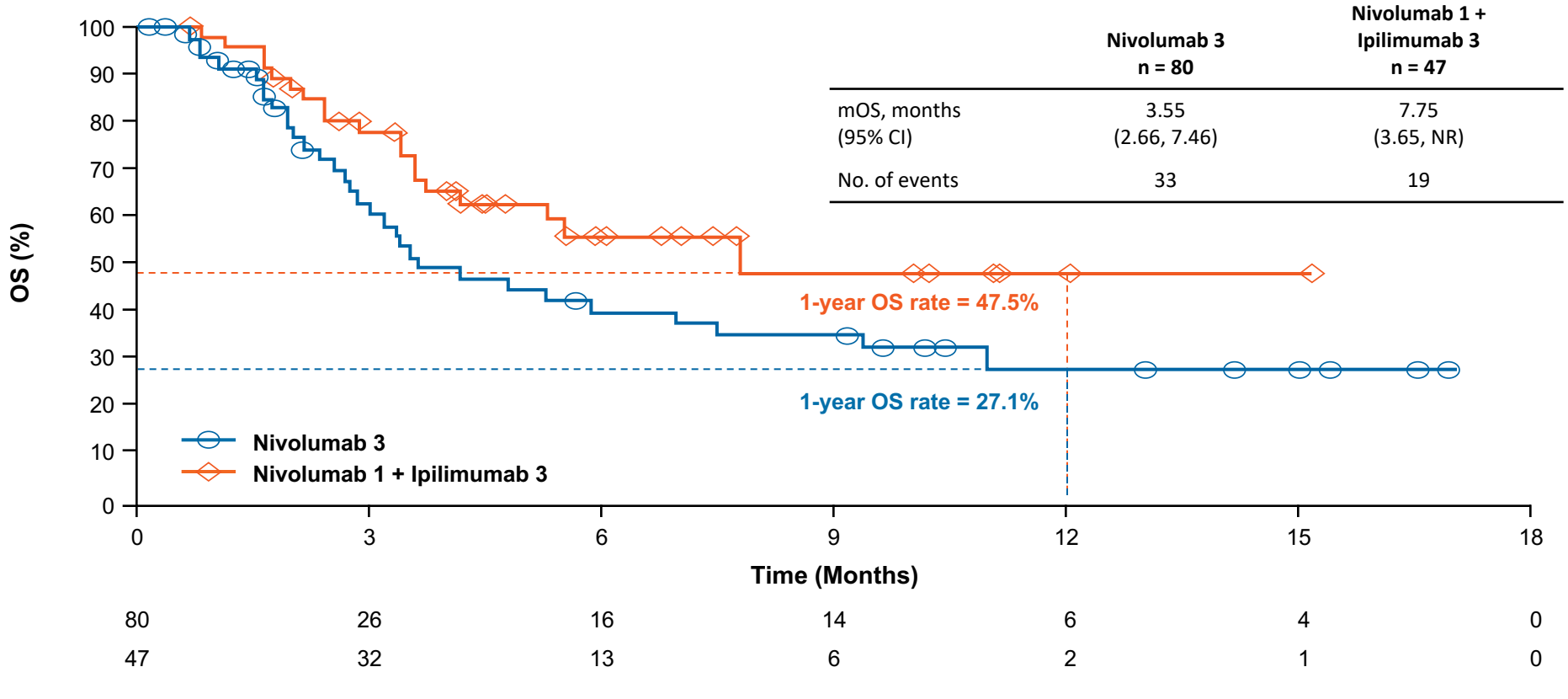
Evaluable samples (52 of 127)	PD-L1 expression level, n (%)	
	<1%	≥1%
Nivolumab 3 (n = 24)	17 (70.8)	7 (29.2)
Nivolumab 1 + Ipilimumab 3 (n = 28)	20 (71.4)	8 (28.6)

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**



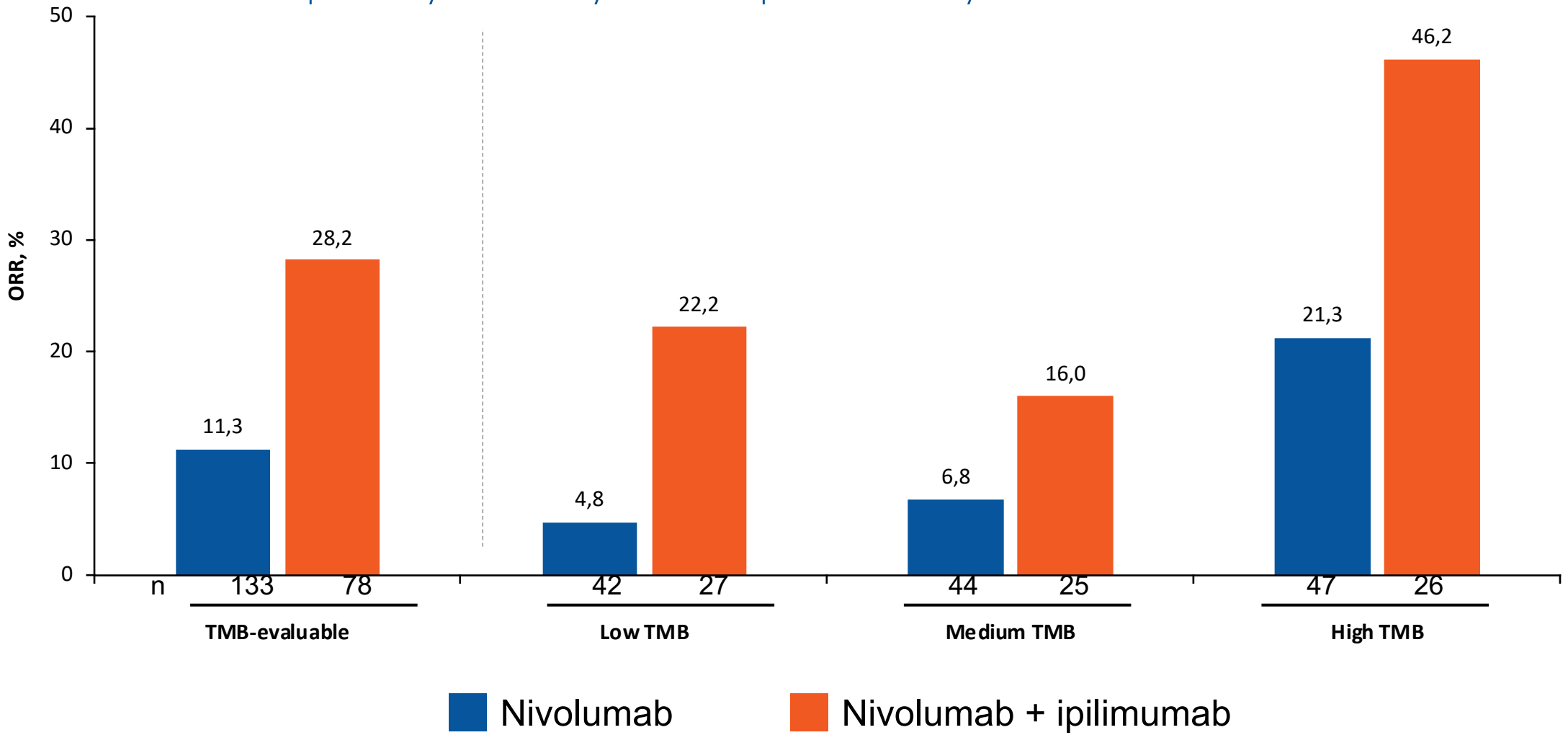
	Nivolumab 3 n = 80	Nivolumab 1 + Ipilimumab 3 n = 47
mOS, months (95% CI)	3.55 (2.66, 7.46)	7.75 (3.65, NR)
No. of events	33	19

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



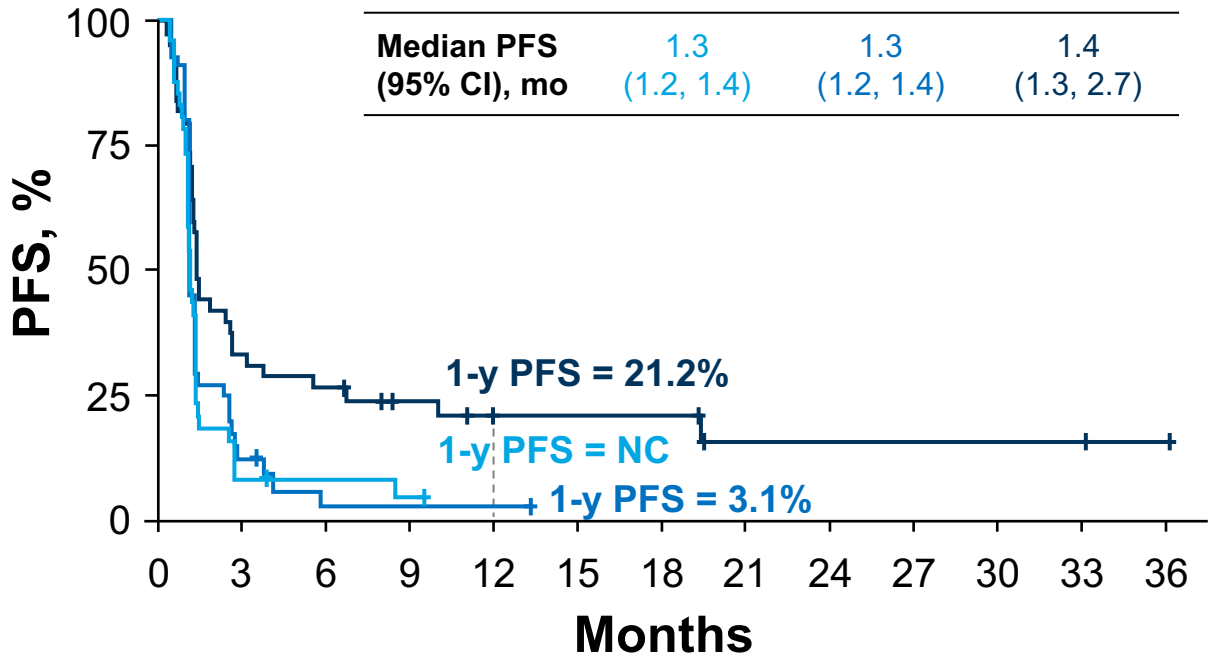
Scott J. Antonia, et al. WLCC 2017

PFS by Tumor Mutation Burden Subgroup

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

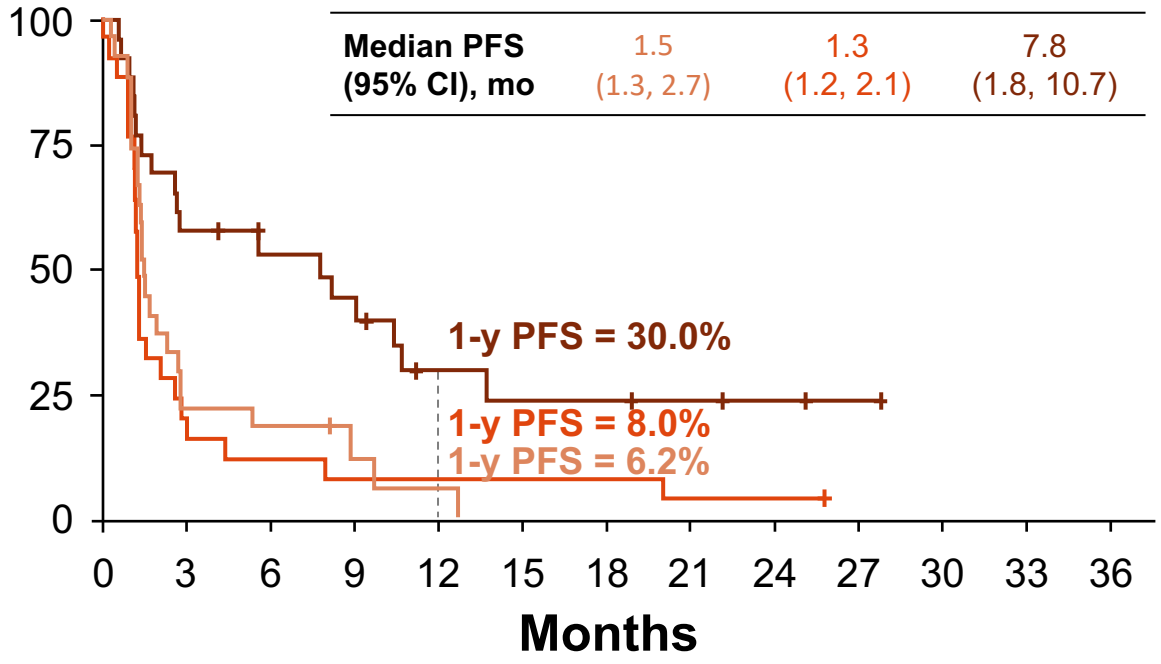
Nivolumab

	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)

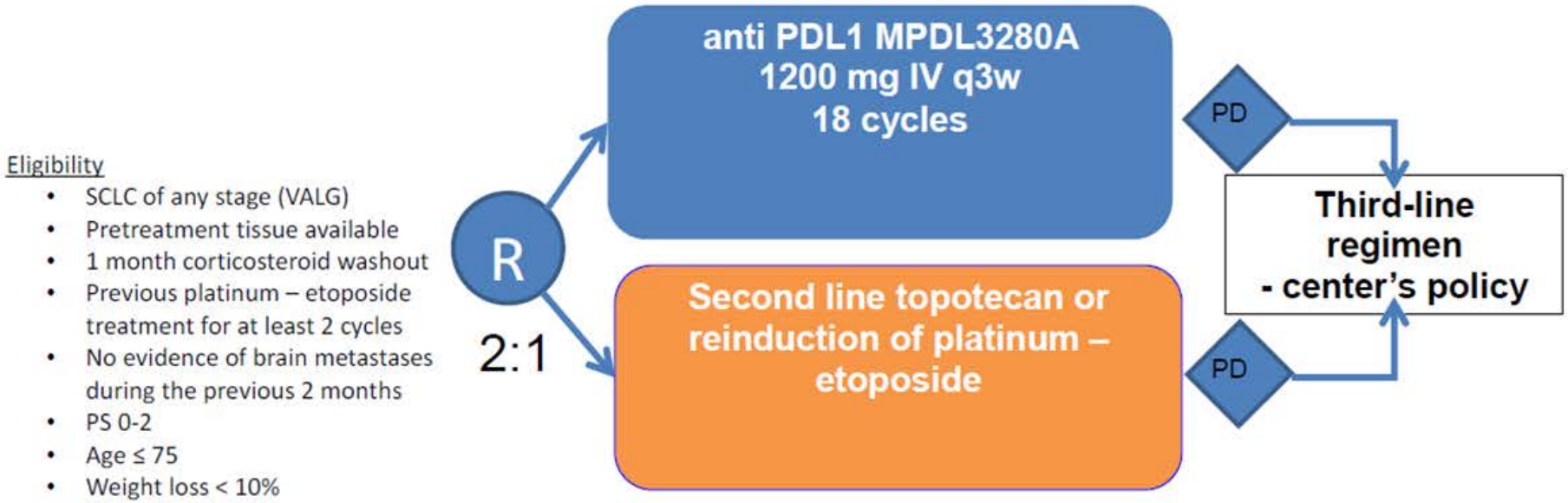


No. at risk													
Low	42	3	2	1	0	0	0	0	0	0	0	0	0
Medium	44	5	1	1	1	0	0	0	0	0	0	0	0
High	47	15	12	8	5	5	5	2	2	2	2	2	1

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

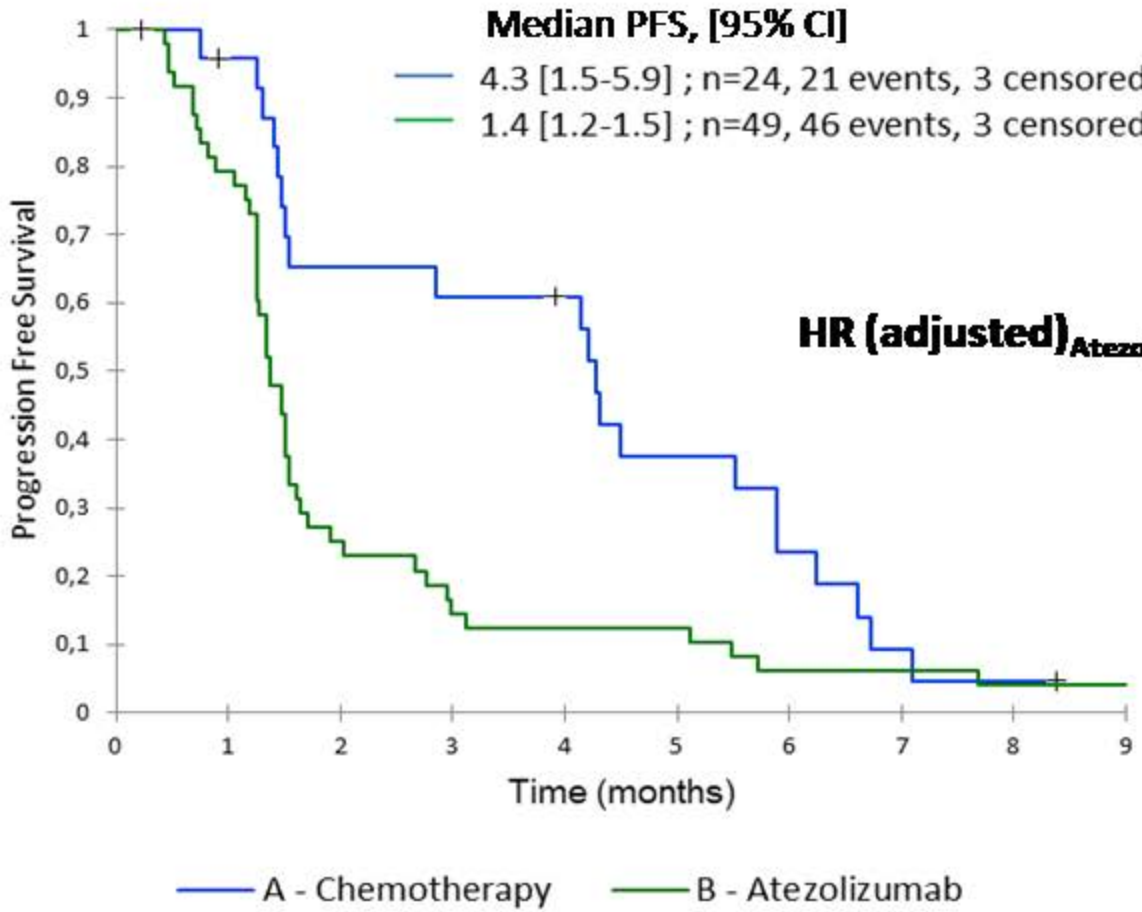
Median (95% CI) PFS, overall TMB-evaluable population: 1.4 (1.3, 1.4) months for nivolumab and 1.7 (1.4, 2.7) months for nivolumab + ipilimumab
NC = not calculable

IFCT 16-03: Atezoluzumab versus chimiothérapie en deuxième ligne



Survie sans progression (intention de traiter)

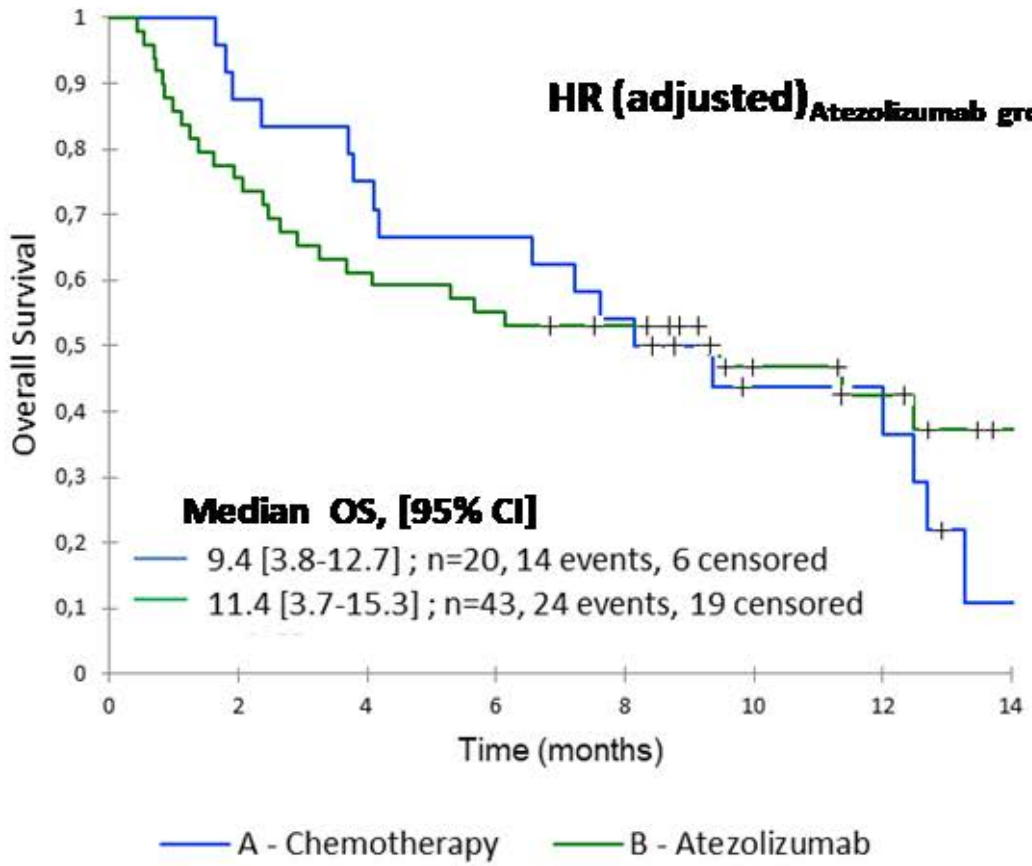
Median follow-up [95% CI]: 13.7 months [12.7-NR]



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

6-months PFS rate for Atezolizumab group : 6.3% [0.0% ; 13.1%]

Survie globale (intention de traiter)

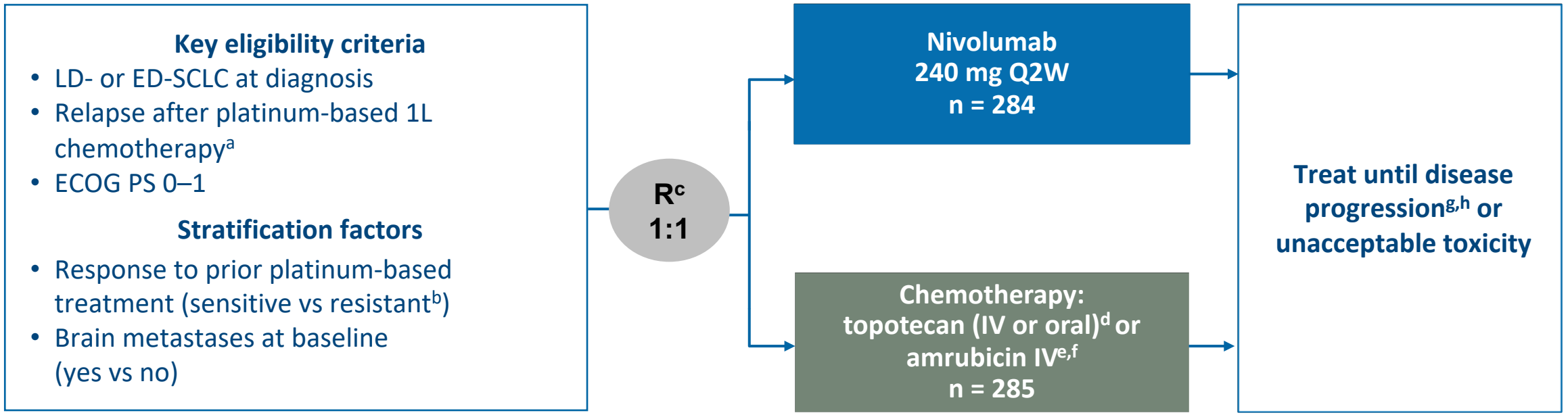


1-year OS rate for Atezolizumab group : 42.5% [26.9% ;58.2%]

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%)

CheckMate 331 Study Design



Primary endpoint: OS

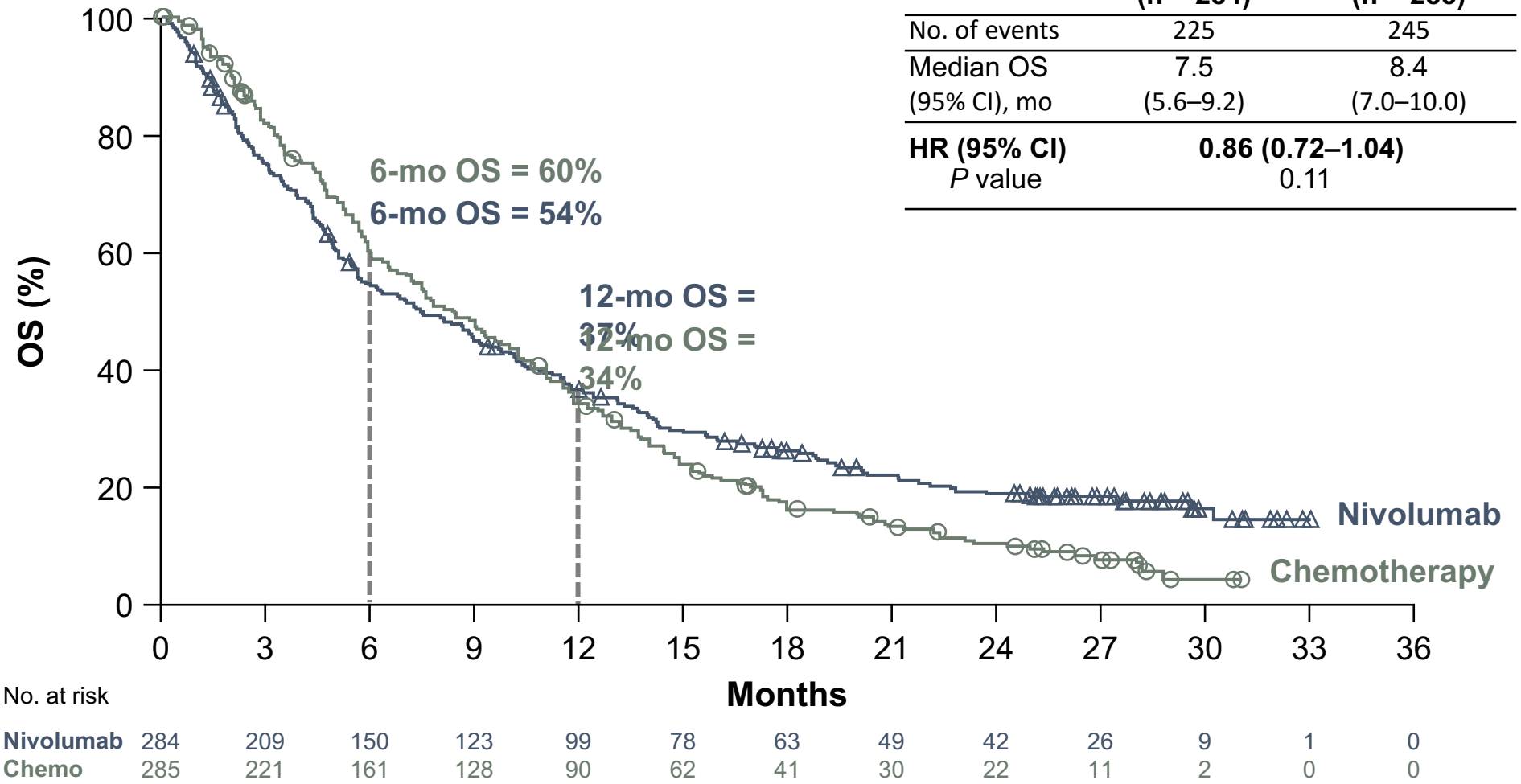
Secondary endpoints: PFS[g] and ORR[g] (investigator assessed)

- Database lock: 28 September 2018; minimum follow-up for OS: 15.8 months
- Median follow-up[i]: 7.0 months (nivolumab), 7.6 months (chemotherapy)

[a]Patients must have had ≥4 cycles of platinum-based, 1L chemotherapy or if <4 cycles, must have had a BOR of at least partial or complete response. [b]Platinum resistance defined as progression-free interval <90 days after completion of platinum therapy. [c]Crossover between treatment groups was not allowed. [d]Administered at 1.5 mg/m^2 IV or 2.3 mg/m^2 oral capsule once daily on days 1–5 of a 21-day cycle. [e]40 mg/m^2 IV once daily on days 1–3 of a 21-day cycle. [f]Where locally approved. [g]Defined by RECIST 1.1. [h]Patients assigned to nivolumab may be treated beyond progression under protocol-defined circumstances. [i]Time between randomization date and last known date alive (for patients who are alive) or death

Primary Endpoint: OS With Nivolumab vs Chemotherapy

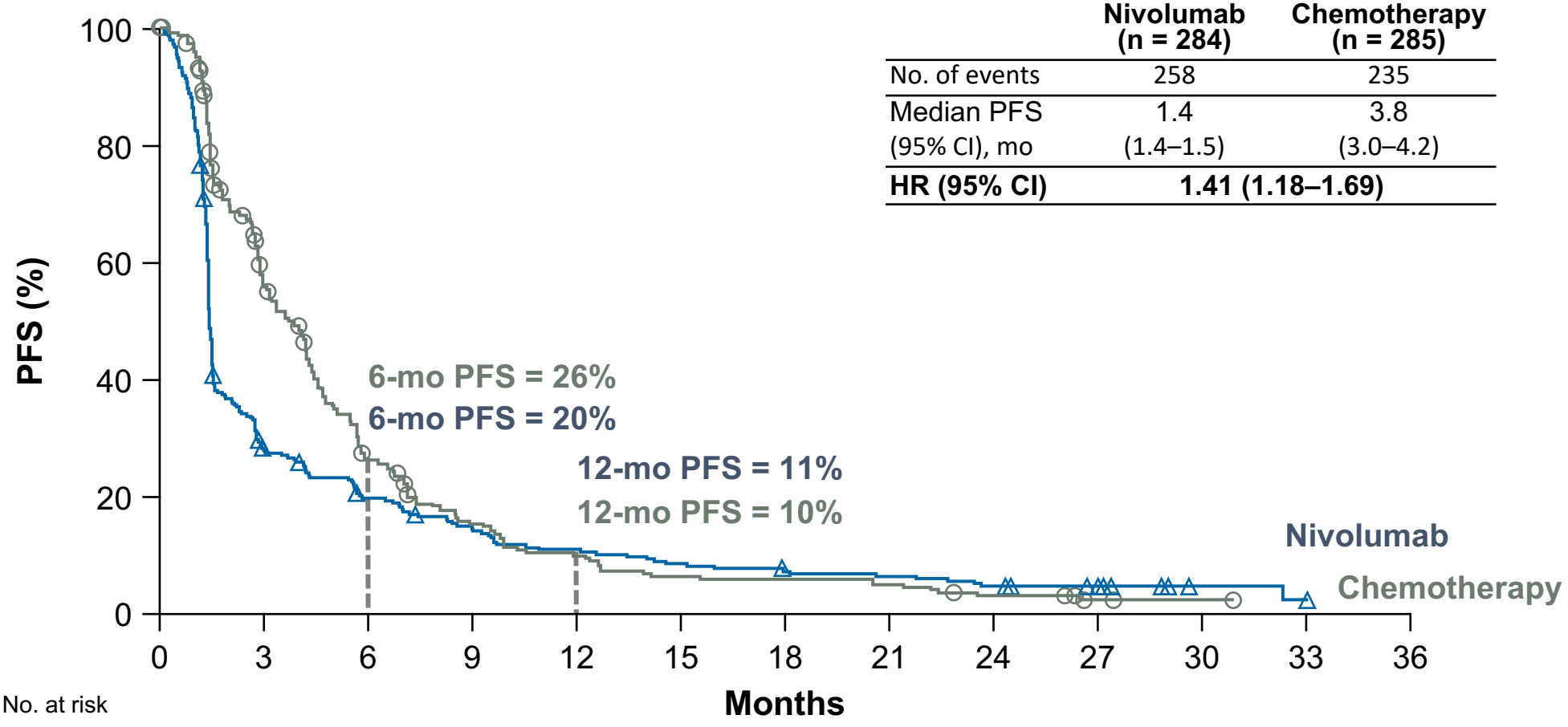
	Nivolumab (n = 284)	Chemotherapy (n = 285)
No. of events	225	245
Median OS (95% CI), mo	7.5 (5.6–9.2)	8.4 (7.0–10.0)
HR (95% CI)	**0.86 (0.72–1.04)**	
P value	0.11	



Minimum follow-up: 15.8 months; 59 patients (21%) in the nivolumab arm and 40 patients (14%) in the chemotherapy arm were censored

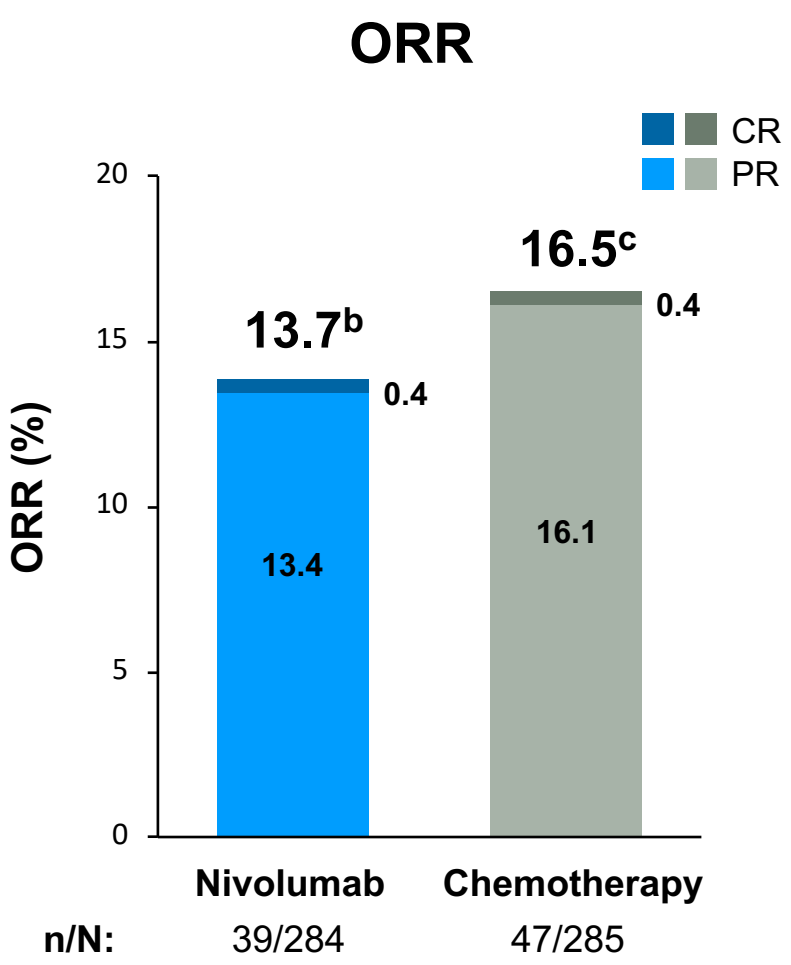
PFS With Nivolumab vs Chemotherapy[a]

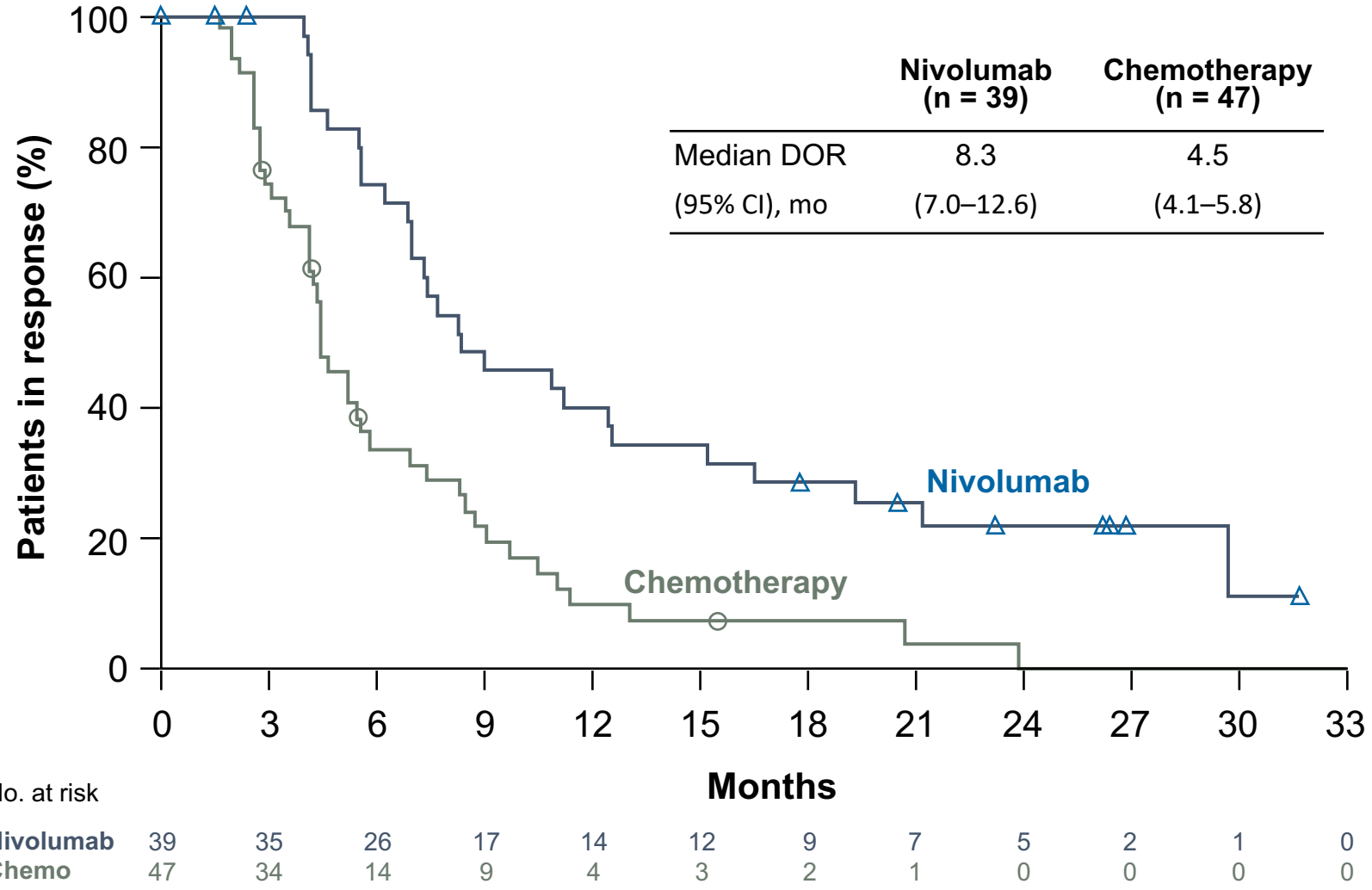
	Nivolumab (n = 284)	Chemotherapy (n = 285)
No. of events	258	235
Median PFS (95% CI), mo	1.4 (1.4–1.5)	3.8 (3.0–4.2)
HR (95% CI)	**1.41 (1.18–1.69)**	



[a]Per local investigator

ORR and DOR With Nivolumab vs Chemotherapy[a]

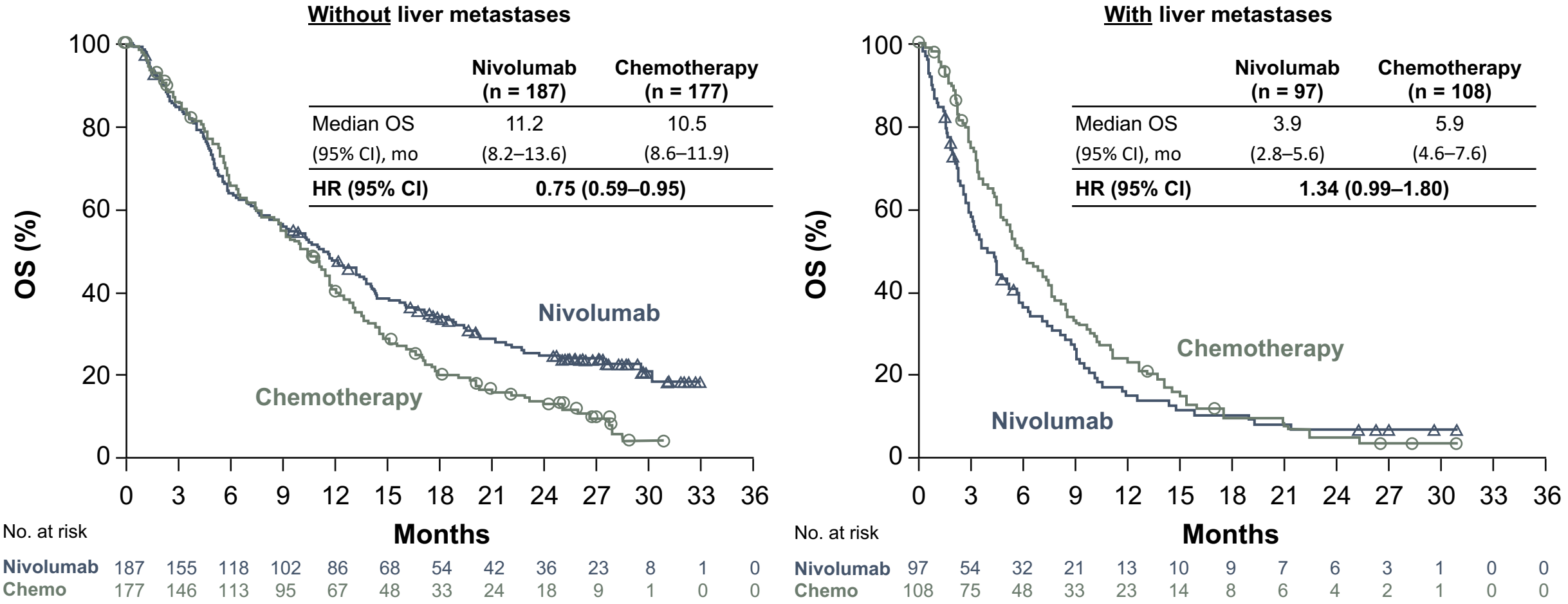




	Nivolumab (n = 39)	Chemotherapy (n = 47)
Median DOR (95% CI), mo	8.3 (7.0–12.6)	4.5 (4.1–5.8)

[a]Per local investigator. [b]95% CI, 10.0–18.3%. [c]12.4–21.3%

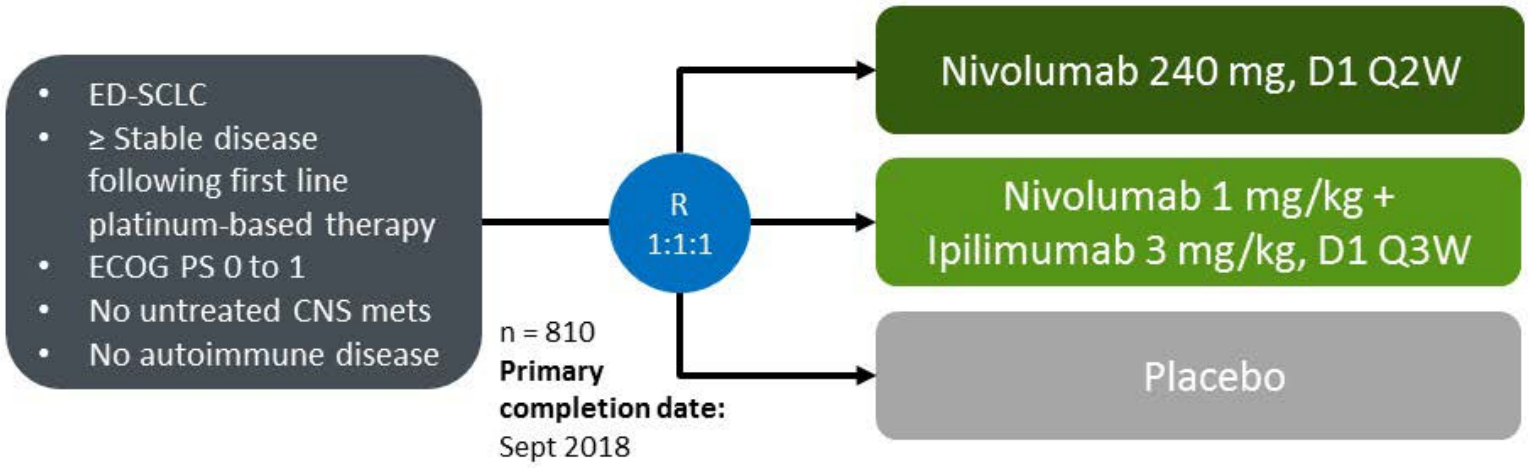
OS in Patients Without and With Baseline Liver Metastases



Minimum follow-up: 15.8 months; 59 patients (21%) in the nivolumab arm and 40 patients (14%) in the chemotherapy arm were censored

Nivolumab +/- ipilimumab en maintenance

CheckMate-451: Phase 3 Study of Nivolumab, Nivolumab in Combination With Ipilimumab, or Placebo as Maintenance Therapy in Patients With ED-SCLC After Completion of Platinum-Based First-Line Chemotherapy

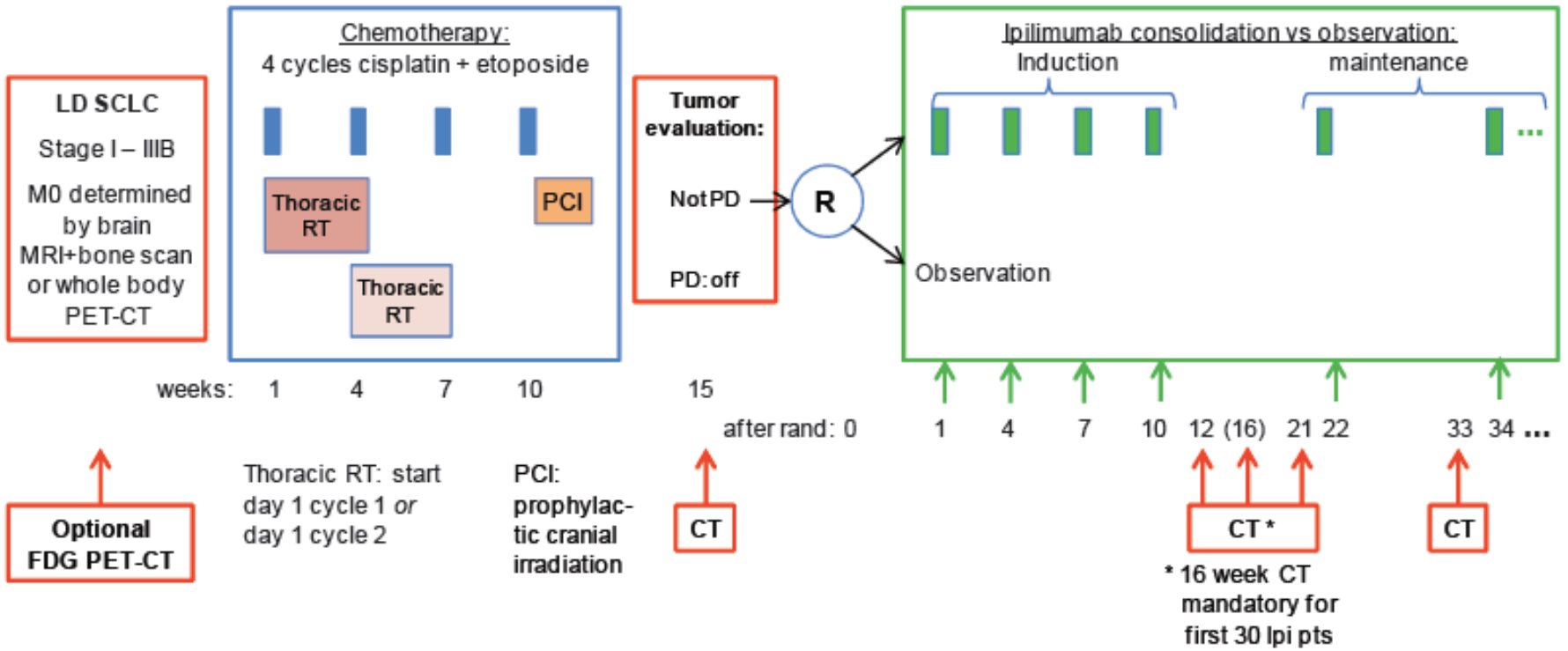


- Coprimary endpoints: OS, PFS
- Secondary endpoints: ORR, PFS

Clinicaltrials.gov. NCT02538666.

- 810 patients et comparait Ipilimumab 3 mg/kg – Nivolumab 1 mg/kg au placebo
- Critère d'évaluation principal : survie globale
- Médiane de 9,2 pour Ipi – Nivo versus 9,6 mois pour le placebo
- rapport de risque non significatif de 0,92.
- Les taux de survie à un an : de 41% et 40%.

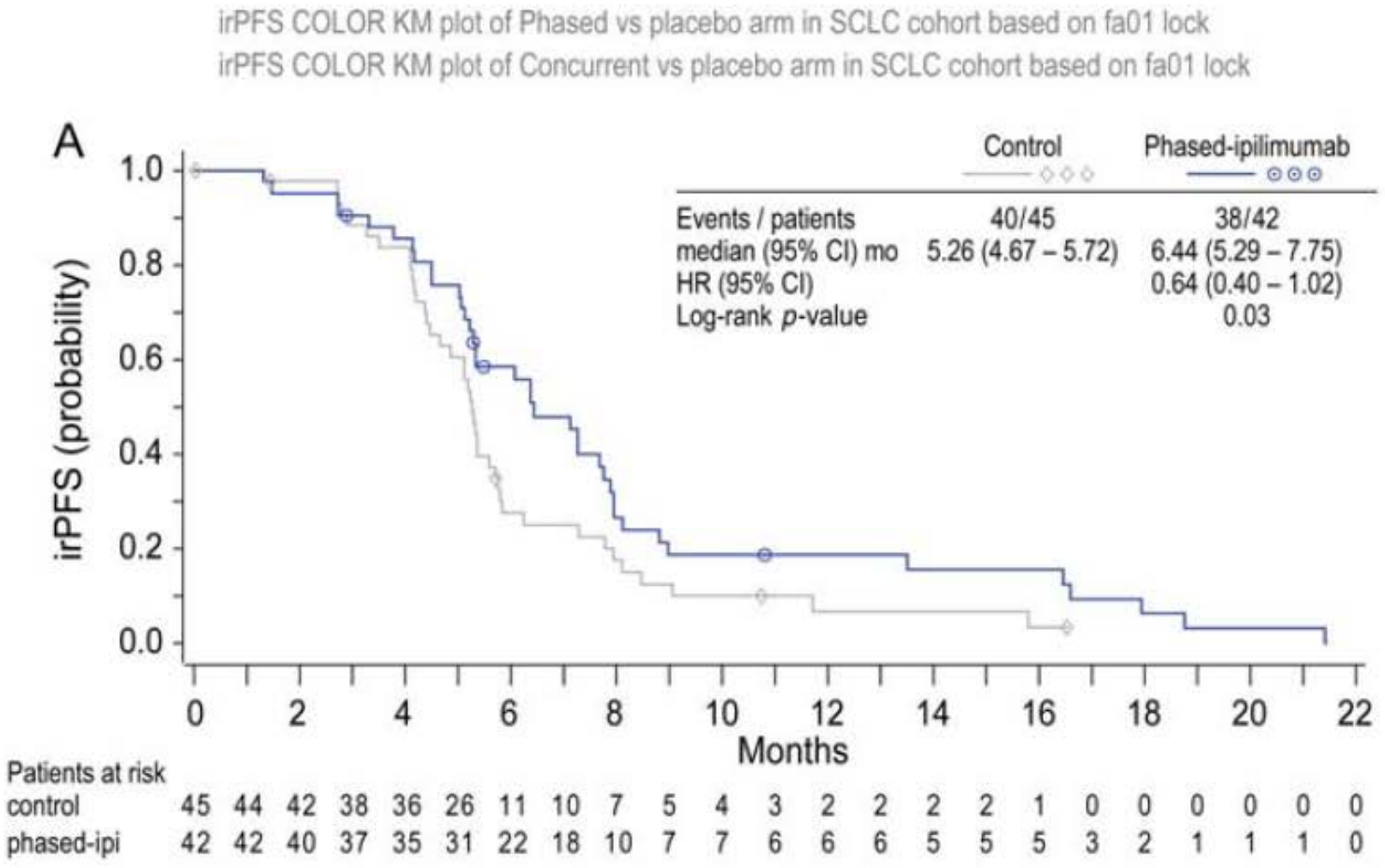
Stimuli (ipilimumab - nivolumab)



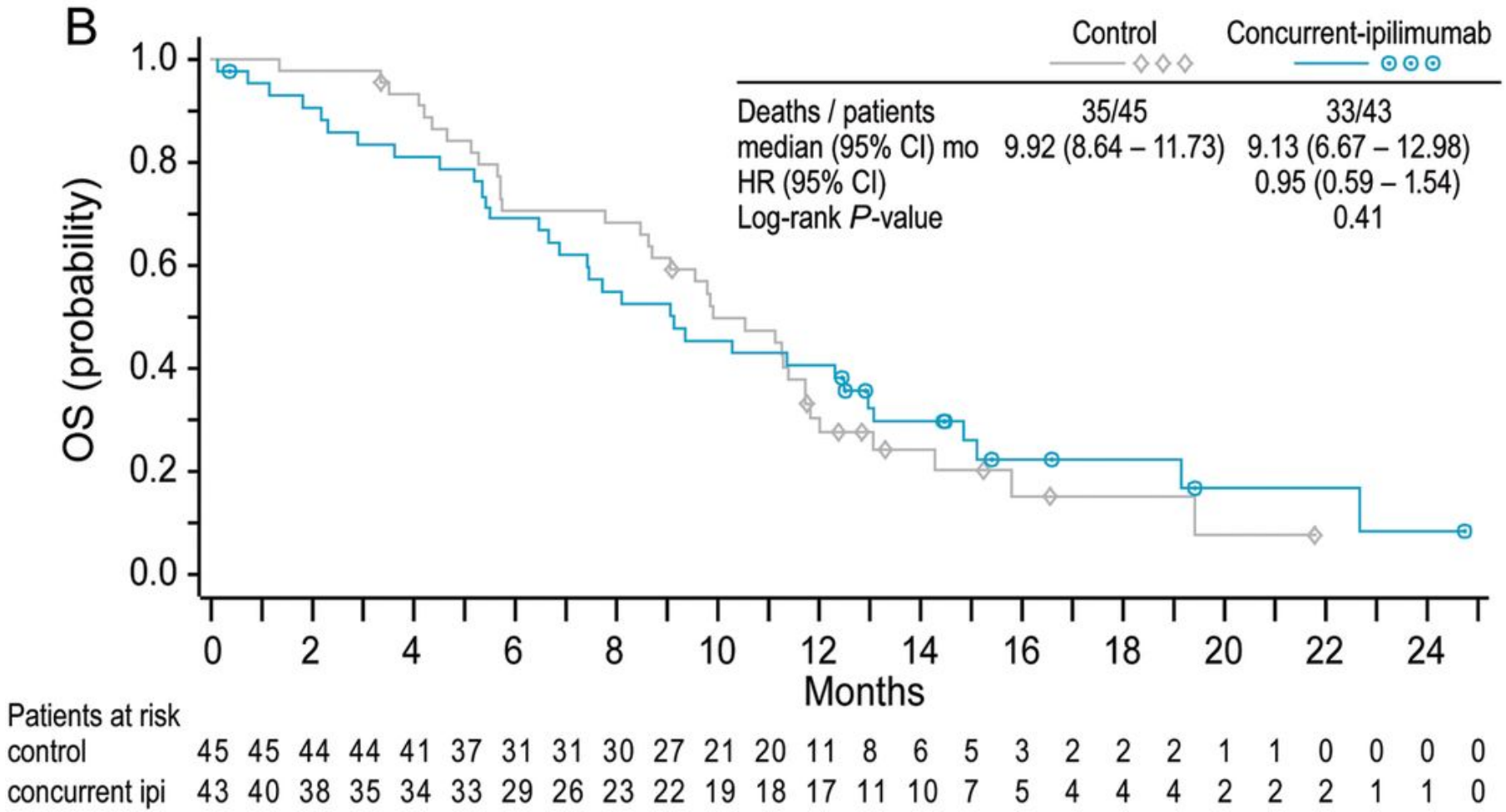
Ipilimumab

- Blocage du CTL-A4
- Intensification de la réponse à cellules T
- Action synergique possible avec la chimiothérapie

Carboplatine paclitaxel +/- ipilimumab pour les les CPC étendus



Reck M et al Annals of Oncology 2013


B
OS (probability)
1.0
0.8
0.6
0.4
0.2
0.0
0
2
4
6
8
10
12
14
16
18
20
22
24
Months
Control
Concurrent-ipilimumab
Deaths / patients 35/45 33/43
median (95% CI) mo 9.92 (8.64 – 11.73) 9.13 (6.67 – 12.98)
HR (95% CI) 0.95 (0.59 – 1.54)
Log-rank P-value 0.41
Patients at risk
control 45 45 44 44 41 37 31 31 30 27 21 20 11 8 6 5 3 2 2 2 1 1 0 0 0 0
concurrent ipi 43 40 38 35 34 33 29 26 23 22 19 18 17 11 10 7 5 4 4 4 2 2 2 1 1 0

IMpower 133

Phase 3 carboplatine-étoposide-atézolizumab

CBPC diffus
PS 0-1
Pas de traitement systémique préalable
Métastases cérébrales asymptomatiques prétraitées éligibles

R

Induction : 4 cycles (/21 j)

- Atézolizumab (1200 mg IV, J1) Carboplatine-étoposide
- Carboplatine-étoposide

Carboplatine AUC 5 J1
Etoposide 100 mg/m^2 J1-3

Maintenance

- atézolizumab
- Placebo

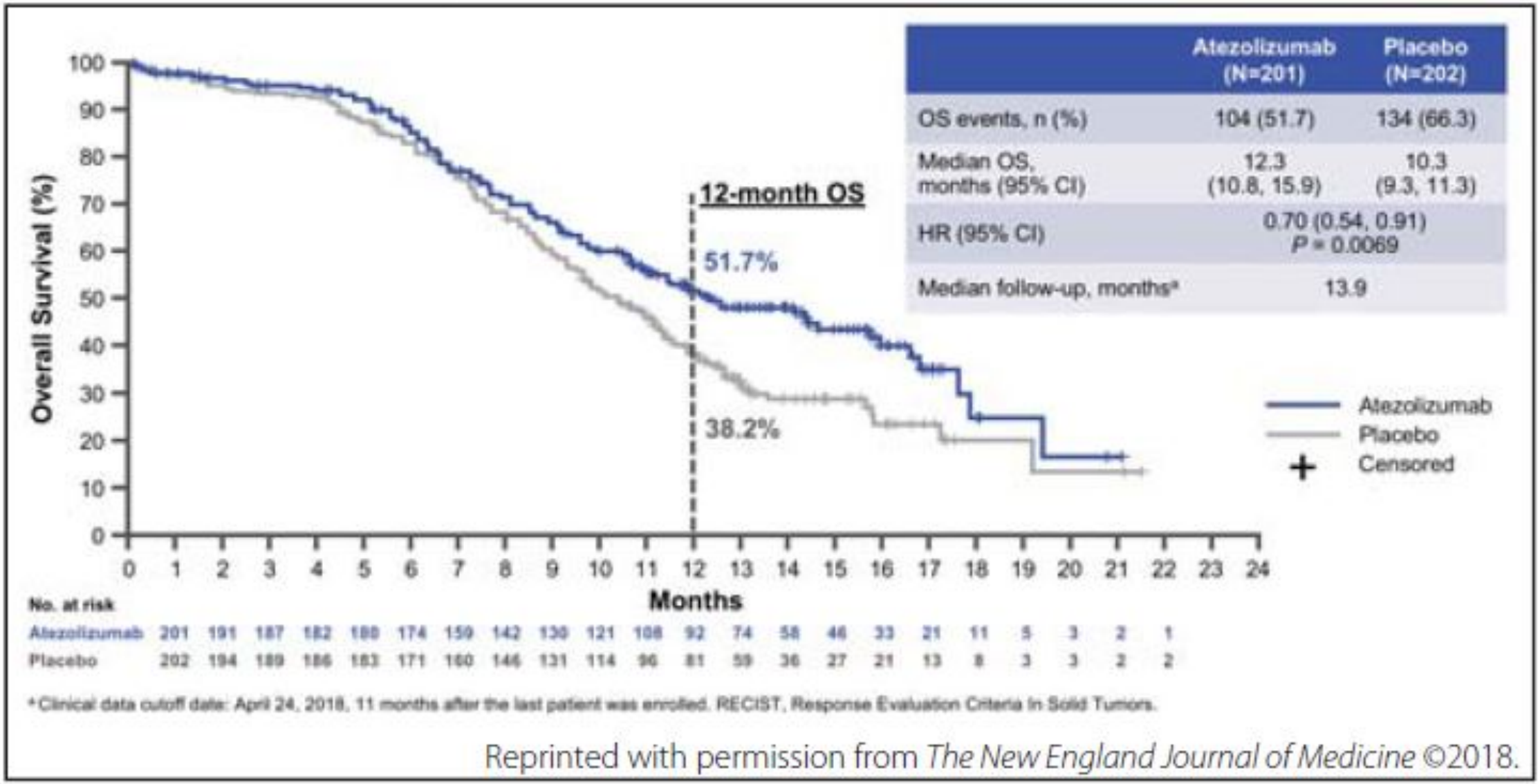
Jusqu'à progression ou perte du bénéfice clinique

IPC selon pratiques locales

- **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

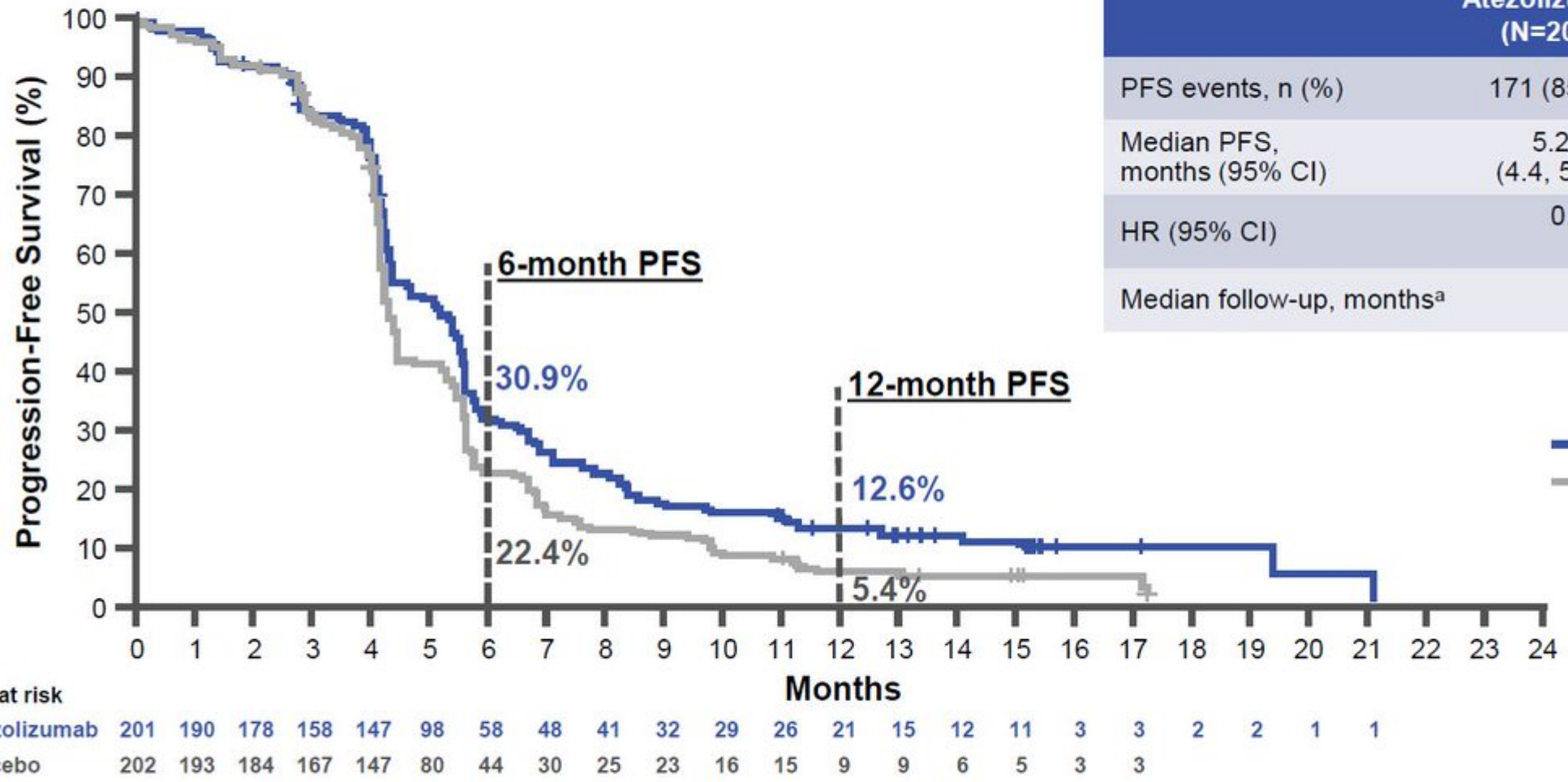
Fig. 3. Overall Survival in Key Subgroups of IMpower133



	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.

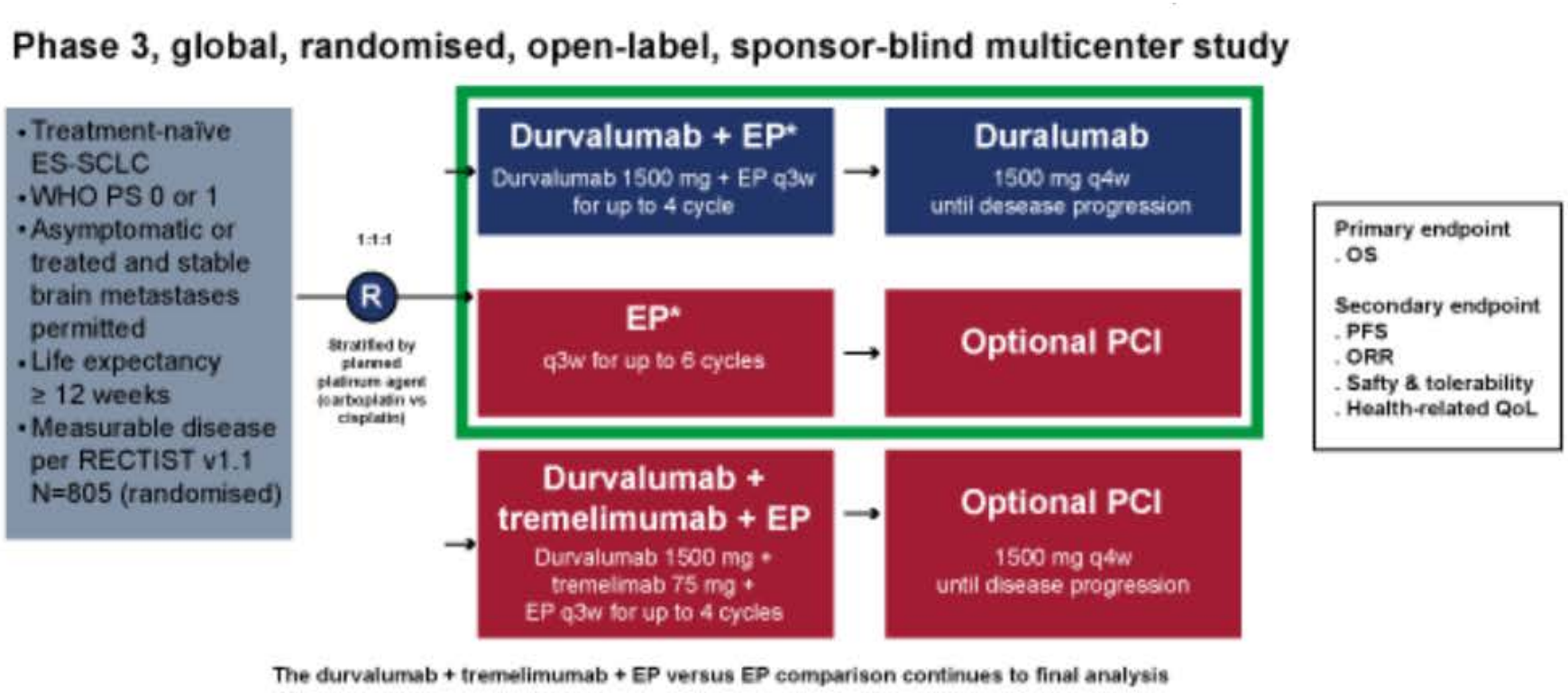
Investigator-assessed progression-free survival



	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	

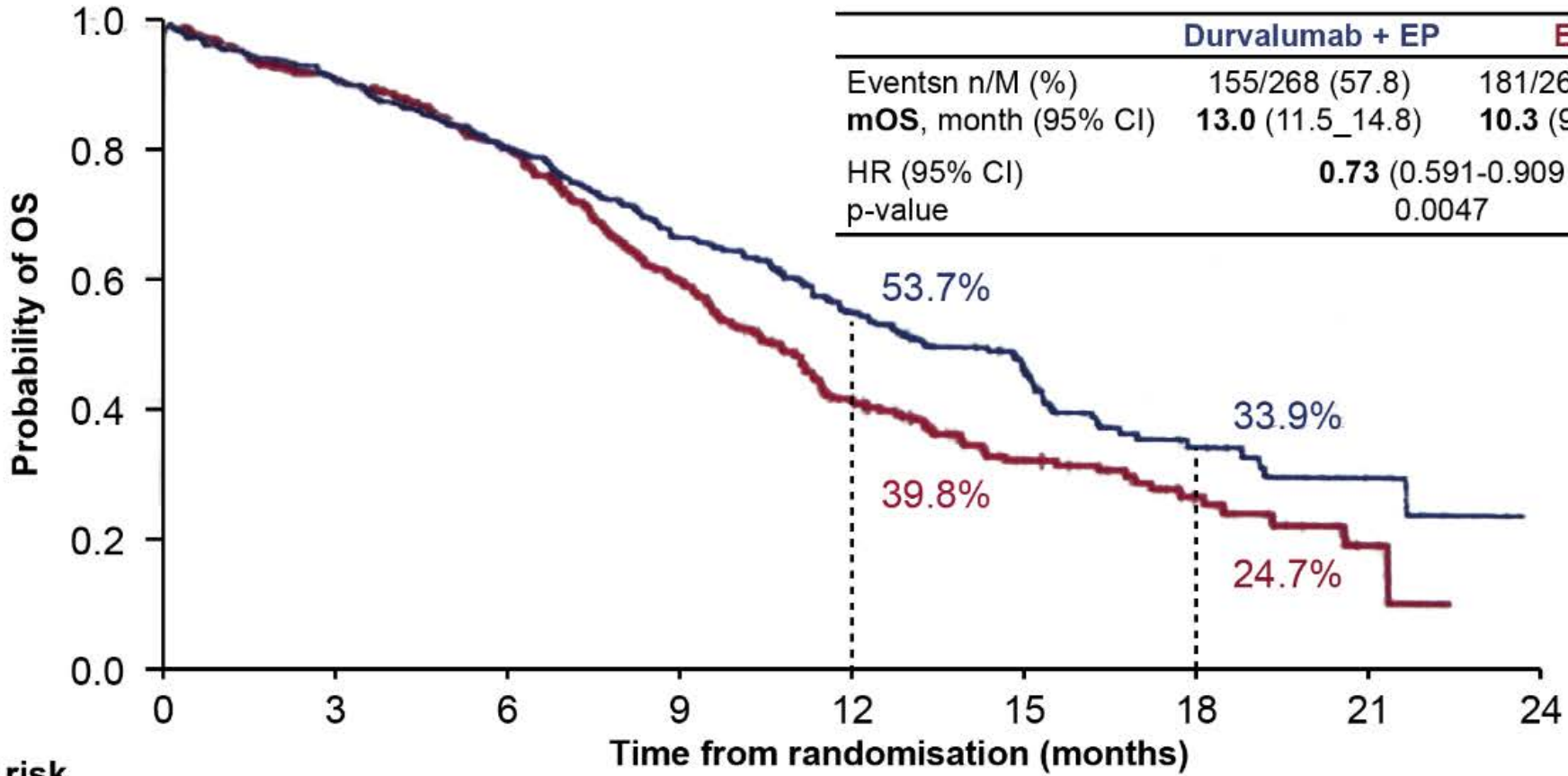
[a] Clinical data cutoff date: April 24, 2018, 11 months after the last patient was enrolled. CI, confidence interval; HR, hazard ratio.

Caspian: etoposide – platine +/- durvalumab



Luis Paz Ares *et al.*
WCLC 2019, Barcelone

Overall Survival (Primary Endpoint)

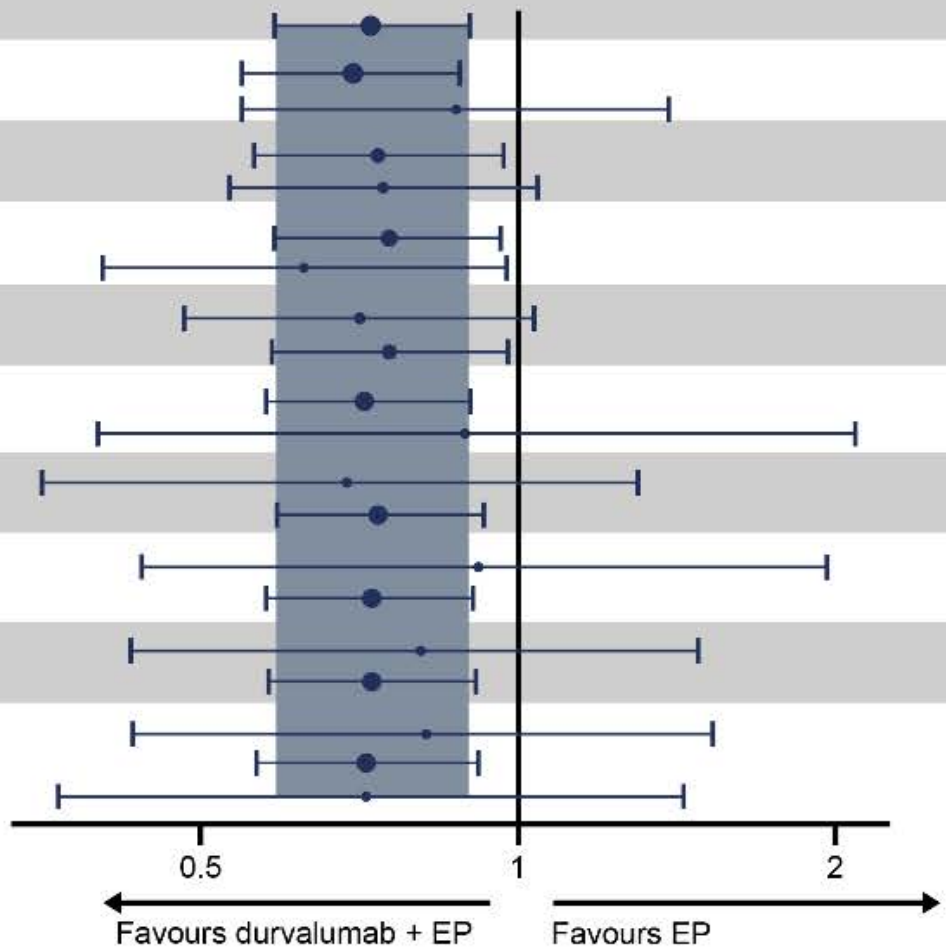


	Durvalumab + EP	EP
Eventsn n/M (%)	155/268 (57.8)	181/269 (67.3)
mOS, month (95% CI)	**13.0** (11.5_14.8)	**10.3** (9.3-11.2)
HR (95% CI)	**0.73** (0.591-0.909	
p-value	0.0047	

No. at risk									
Durvalumab + EP	268	244	177	177	116	57	25	5	0
EP	269	242	153	153	82	44	17	1	0

Overall survival Subgroup Analysis

Pre-specified subgroup		HR (95% CI)
All patients (n=537)		0.73 (0.591-0.909)
Planned platinum agent	Carboplatin (n=402)	0.70 (0.548-0.890)
	Cisplatin (n=135)	0.88 (0.549-1.408
Age	<65 years (n=24)	0.74 (0.562-0.982)
	≤65 years (n=24)	0.75 (0.536-1.058)
Sex	Male (n=374)	0.76 (0.590-0.968)
	Female (n=163)	0.63 (0.402-0.984)
Performance status	0 (n=189)	0.71 (0.483-1.043)
	1 (n=348)	0.76 (0.586-0.986)
Smoking status	Smoker (n=500)	0.72 (0.579-0.905)
	Non smoker (n=37)	0.90 (0.399-2.107)
Brain/CNS metastases	Yes (n=55)	0.69 (0.351-1.312)
	No (n=482)	0.74 (0.591-0.933)
AJCC disease stage at diagnosis	Stage III (n=52)	0.92 (0.439 -1.977)
	Stage IV (n=485)	0.73 (0.579-0.908)
Race	Asian (n=78)	0.81 (0.429-1.486)
	Non-Asian (n=458)	0.73 (0.580-0.919)
Region	Asia (n=76)	0.82 (0.430-1.536)
	Europe (n=405)	0.72 (0.564-0.919)
	Americas (n=56)	0.72 (0.366-1.438)

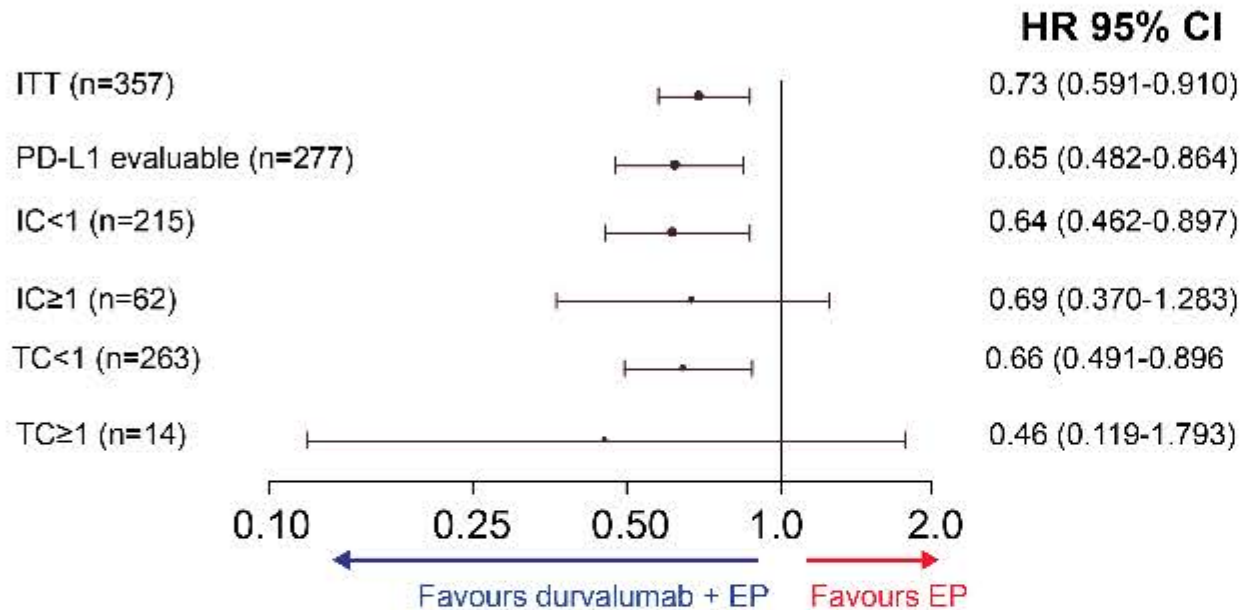


Marquage PD-L1

SP 263

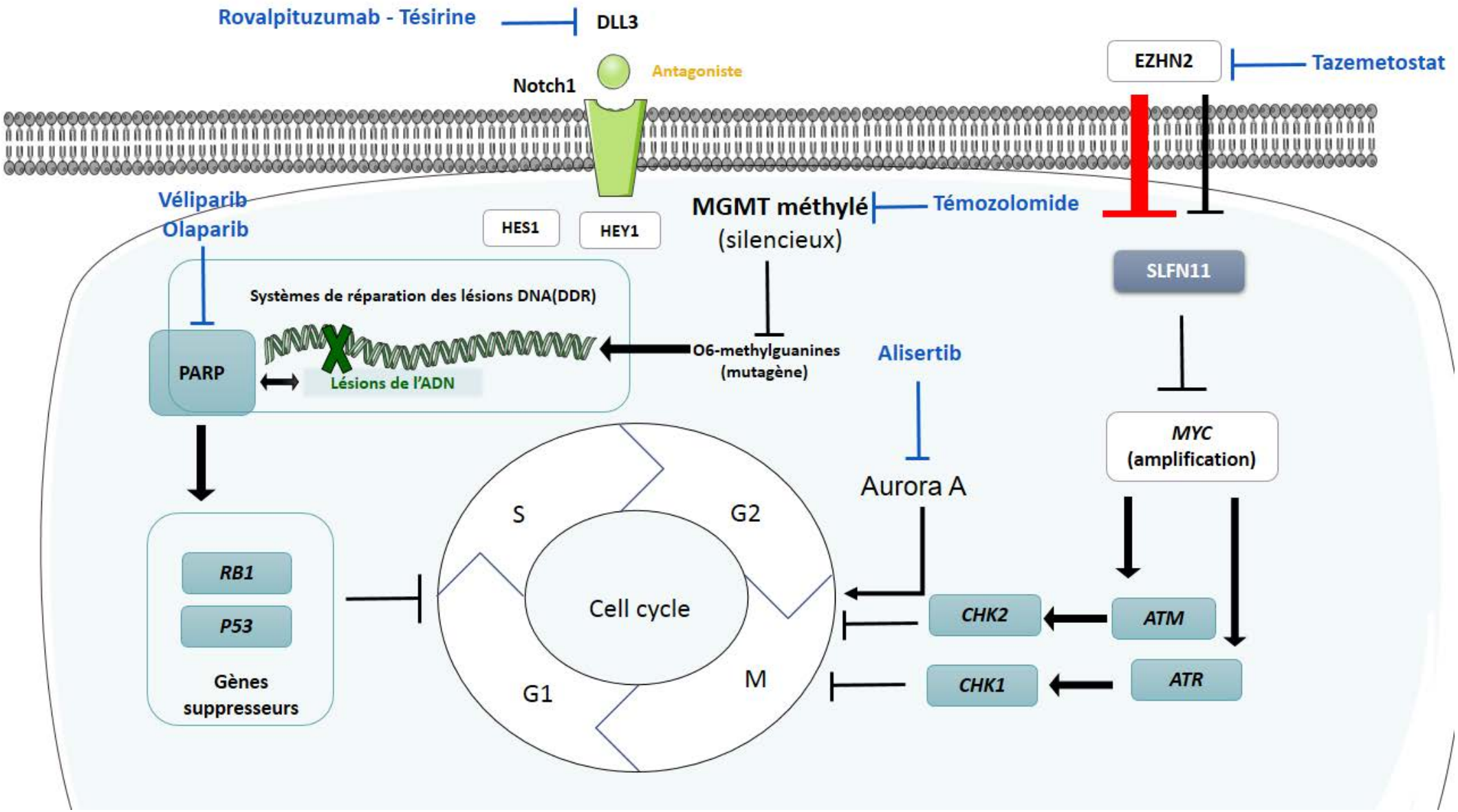
- 95% négatif sur CT
- 77% négatif sur CI

OVERALL SURVIVAL BASED ON PD-L1 EXPRESSION

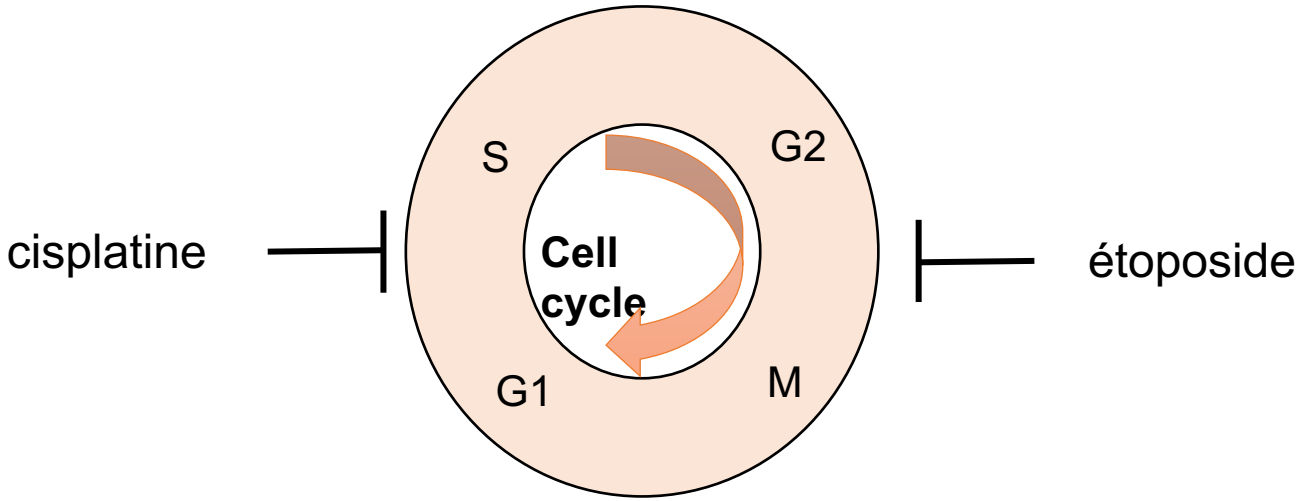


Durvalumab+EP was associated with improved OS vs EP, regardless of PD-L1 expression with a 1% cut-off. No significant interactionwas observed with OS based on PD-L1 expression as a continuous variable (TC, p=0.54; IC, p=0.23); similar results were observed with PFS and ORR

Focus sur la chimiothérapie et autres agents ciblés

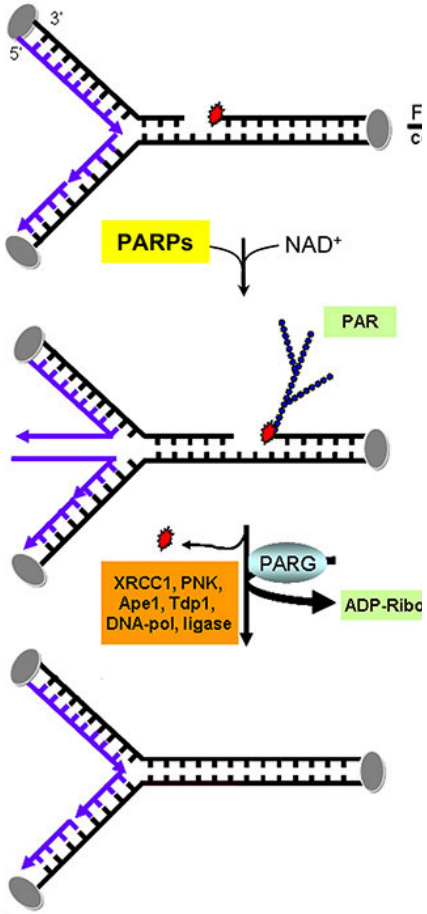


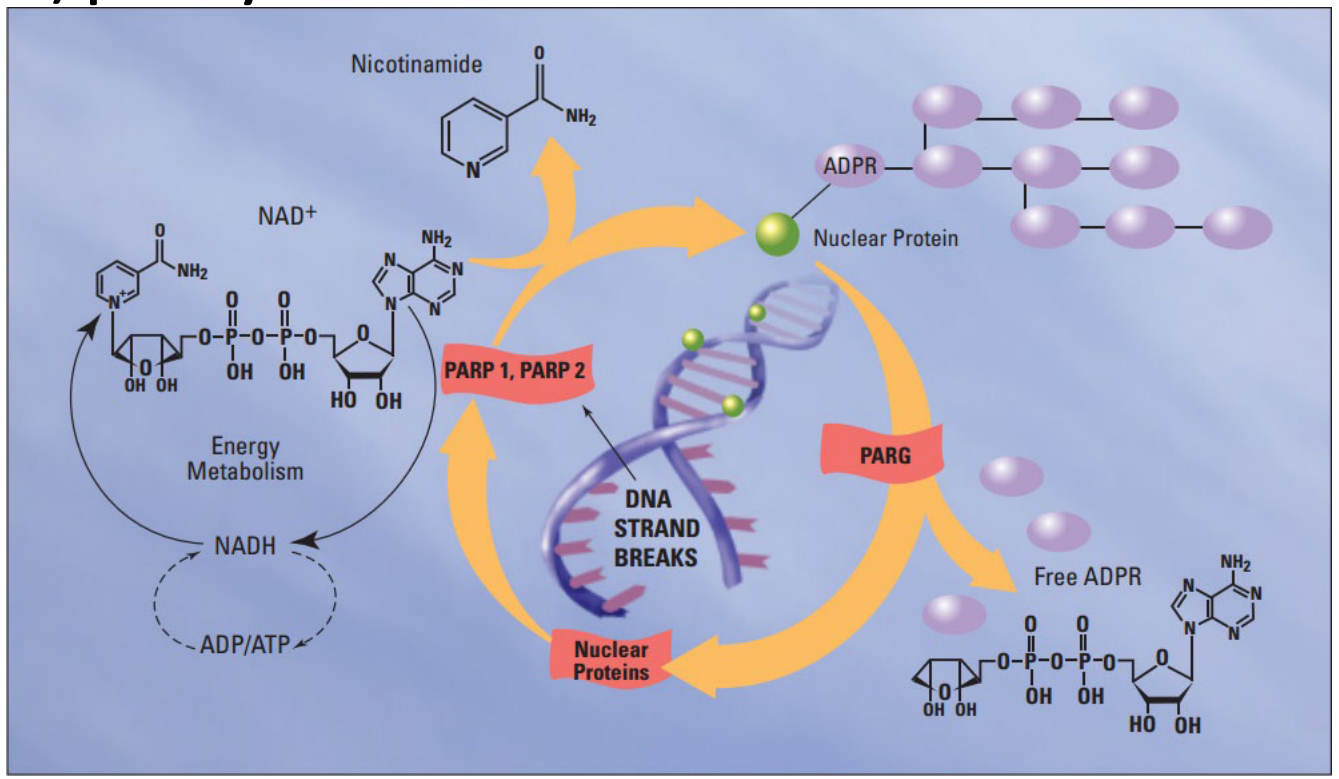
¨Pujol JL et al. Bulletin du cancer, 2018



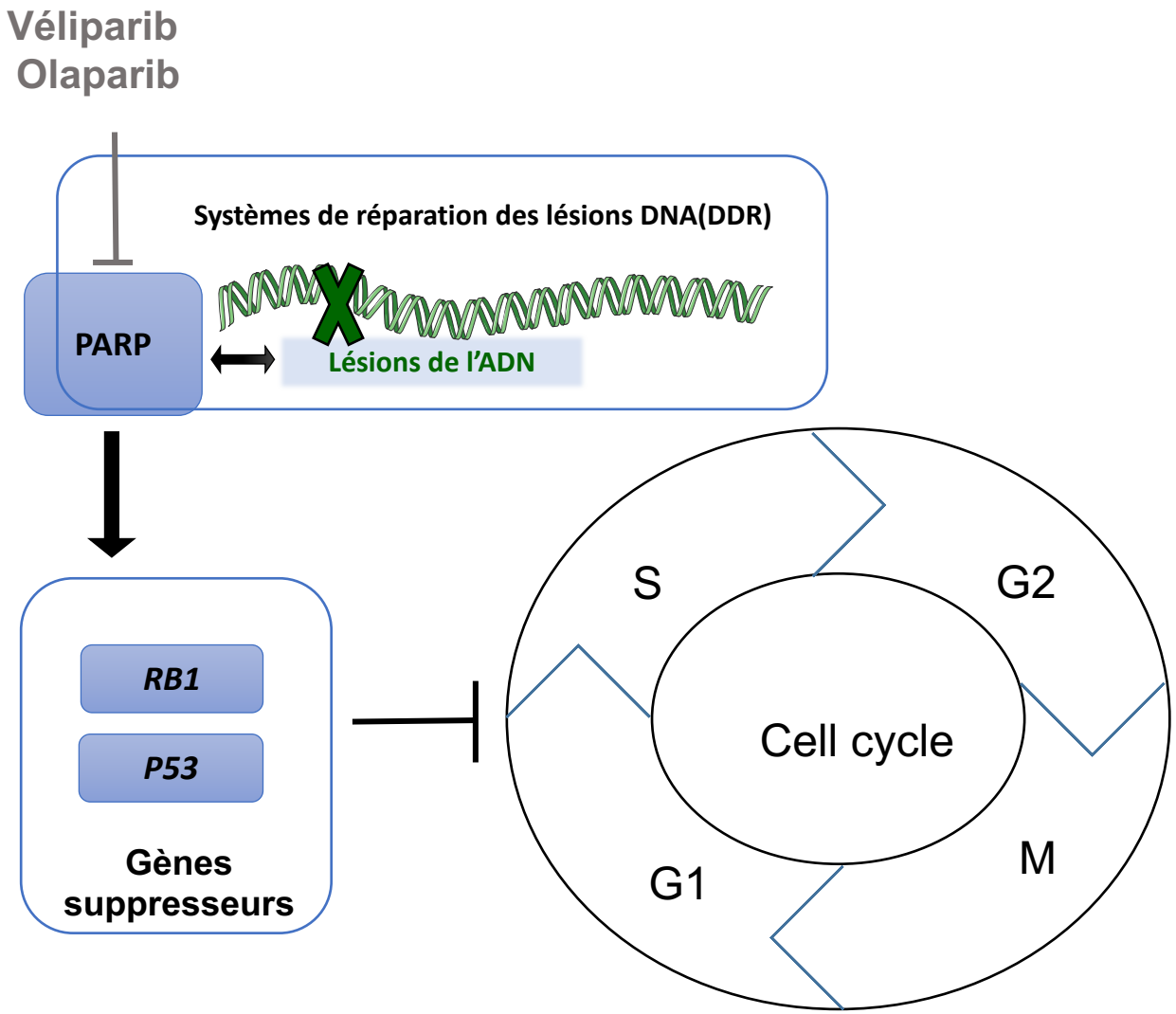
pourquoi la réinduction du protocole Cisplatine - Etoposide lors de la rechute se solde par des taux de réponses inférieures de moitié à ceux observés en induction?

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
G1
M

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.

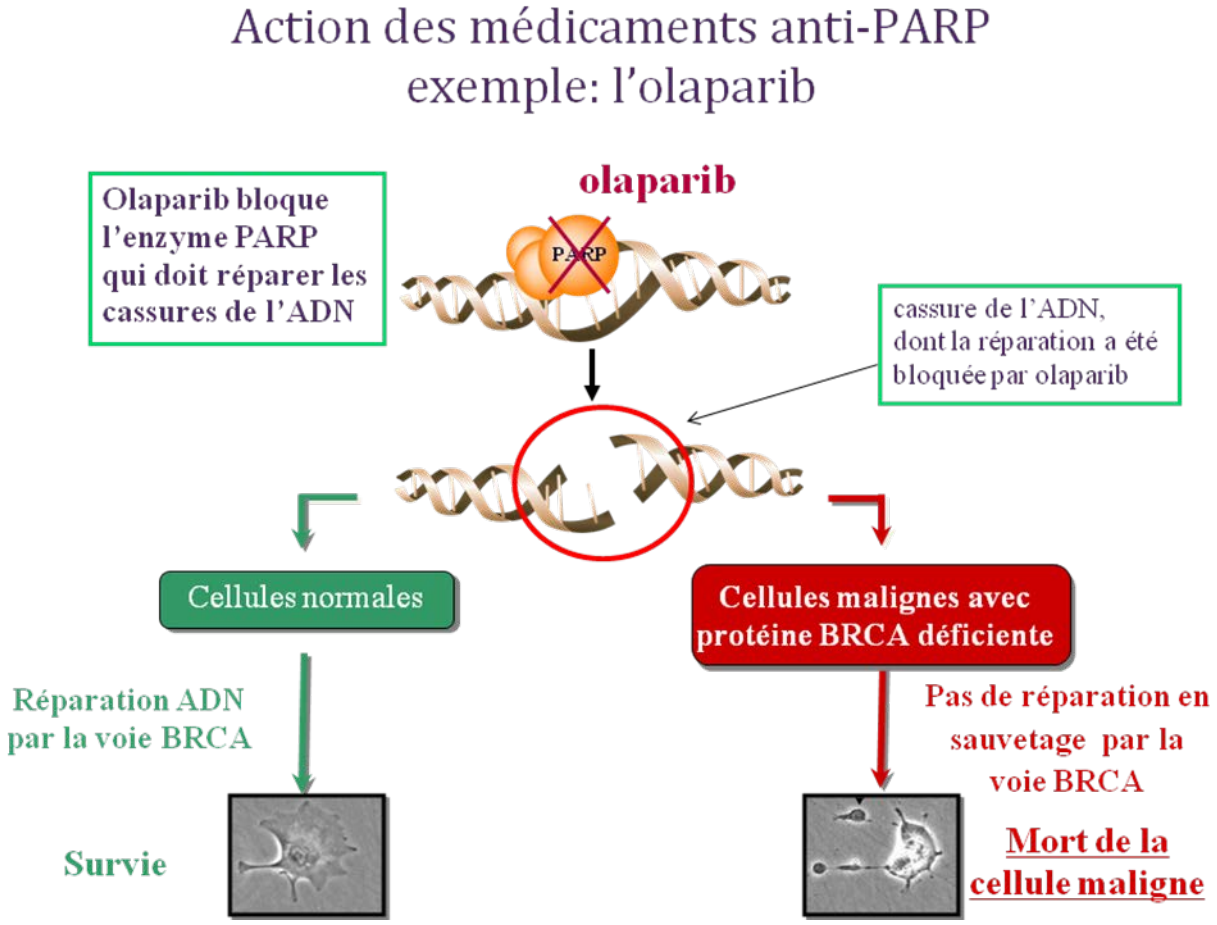
[b]Clinical benefit = CR + PR + SD ≥24 weeks for breast and ovarian cancers.

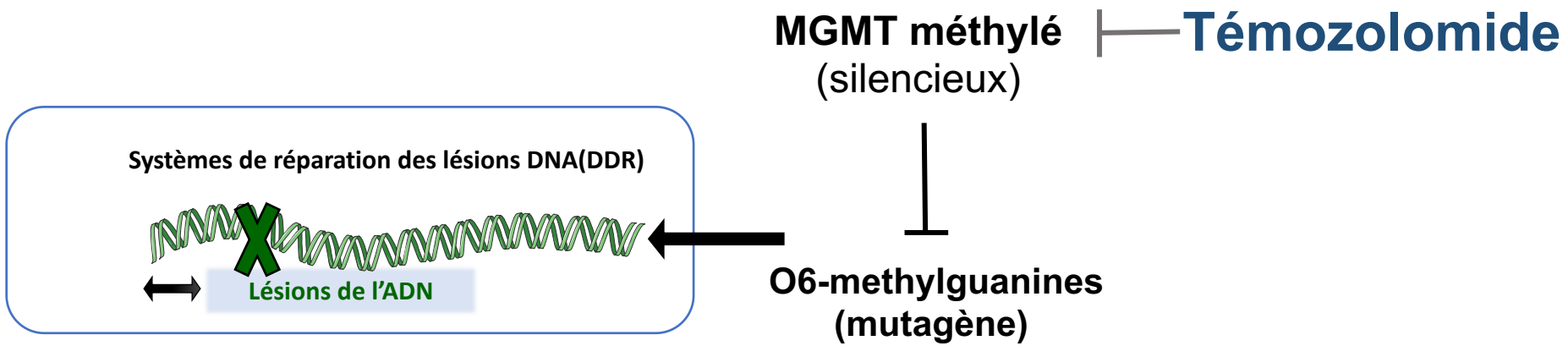
[c]Analysis on 14 patients, as two patients who did not have measurable disease at baseline were included in the PFS analysis but not in the response analysis.

[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?

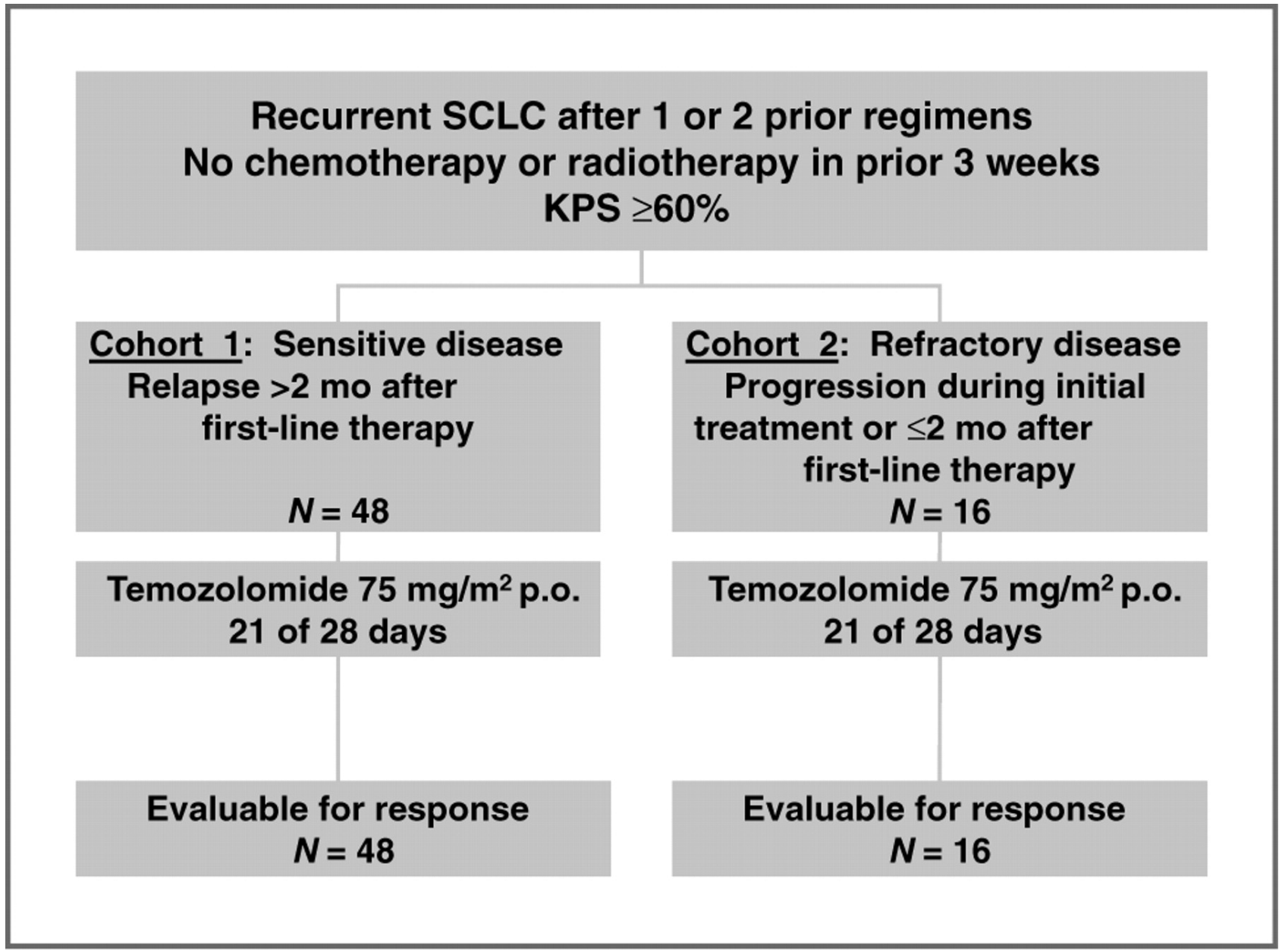



MGMT méthylé
(silencieux)
Témozolomide
Systèmes de réparation des lésions DNA(DDR)
Lésions de l'ADN
O6-methylguanines
(mutagène)

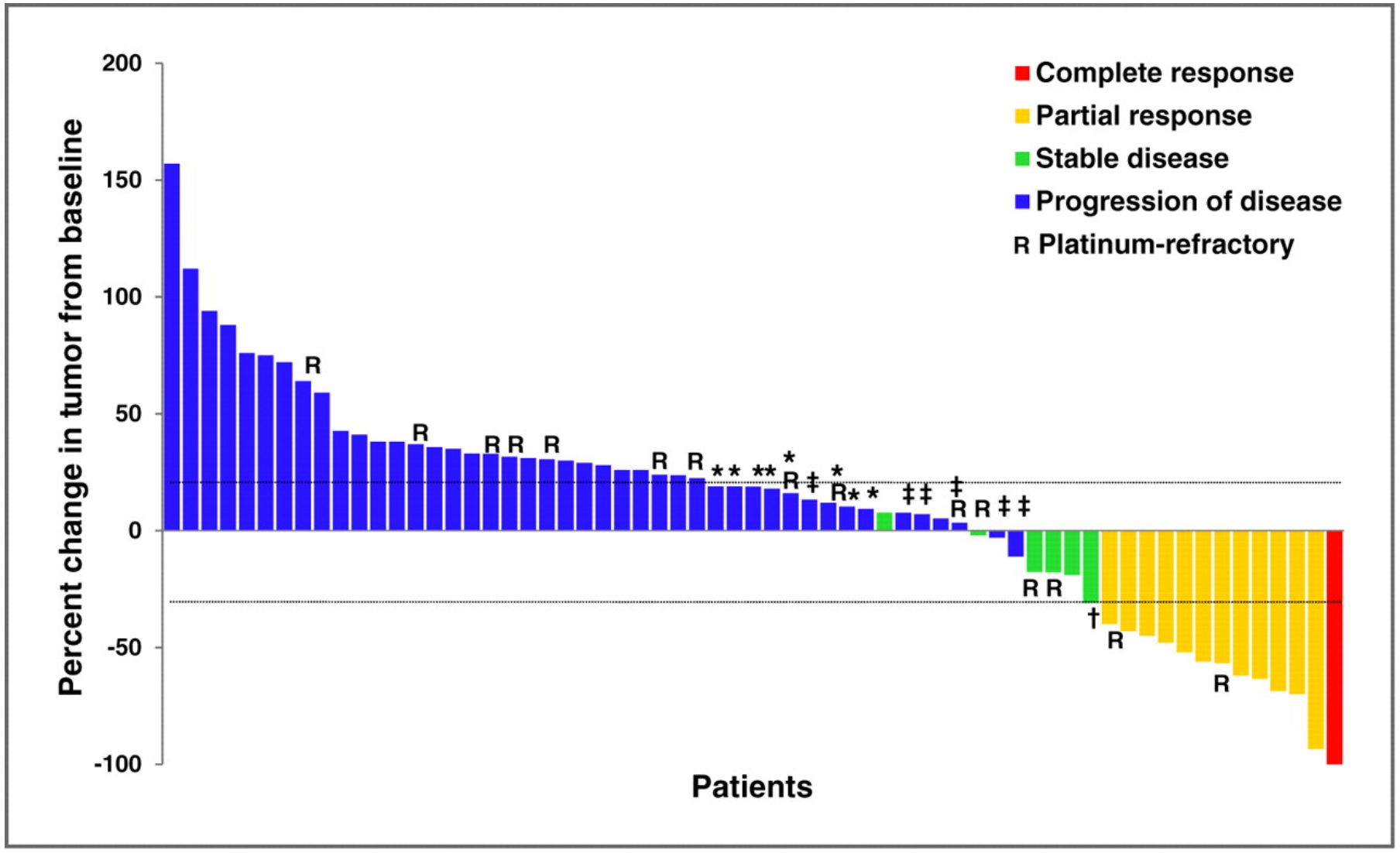
Témozolomide

- Témozolomide est un agent alkylant oral non classique, qui produit des lésions O6-alkylguanine (O6-AG) sur l'ADN
- Des niveaux élevés d'activité de MGMT dans des cellules cancéreuses perturbent les effets thérapeutiques de cet agent alkylant.

Pietanza M. Clin Cancer Res; 18, 2012



M. Catherine Pietanza; Clin Cancer Res 2012



M. Catherine Pietanza Clin Cancer Res 2012

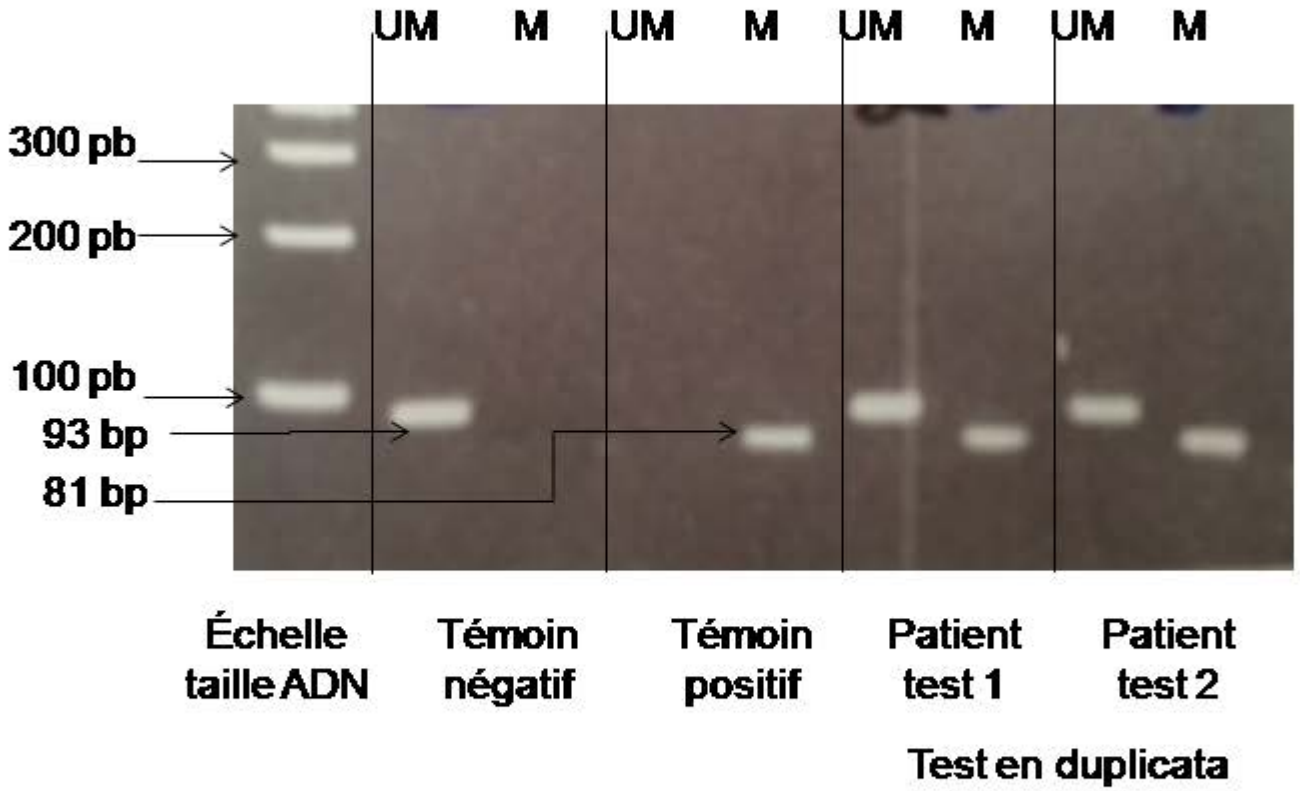
Table 3. MGMT analyses

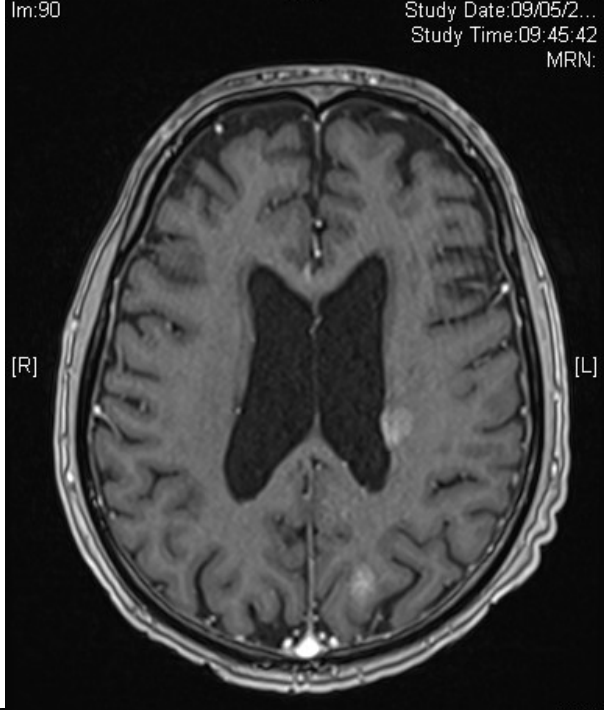
	Response		
	PR	**SD + POD**	***P***
MGMT methylation ($n = 27$)[a]			
Methylated ($n = 13$)	5 (38%)	8 (62%)	0.08[a]
Unmethylated ($n = 14$)	1 (7%)	13 (93%)	
MGMT expression ($n = 31$)			
Negative ($n = 13$)	5 (38%)	8 (62%)	0.23
Positive ($n = 18$)	3 (17%)	15 (83%)	

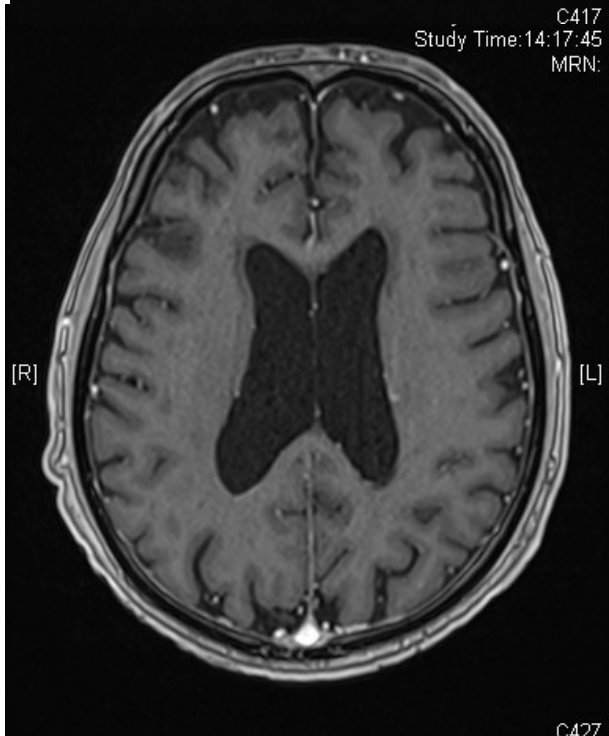
Abbreviations: NR, not reached; POD, progression of disease.

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

Pietanza M. Clin Cancer Res; 18, 2012

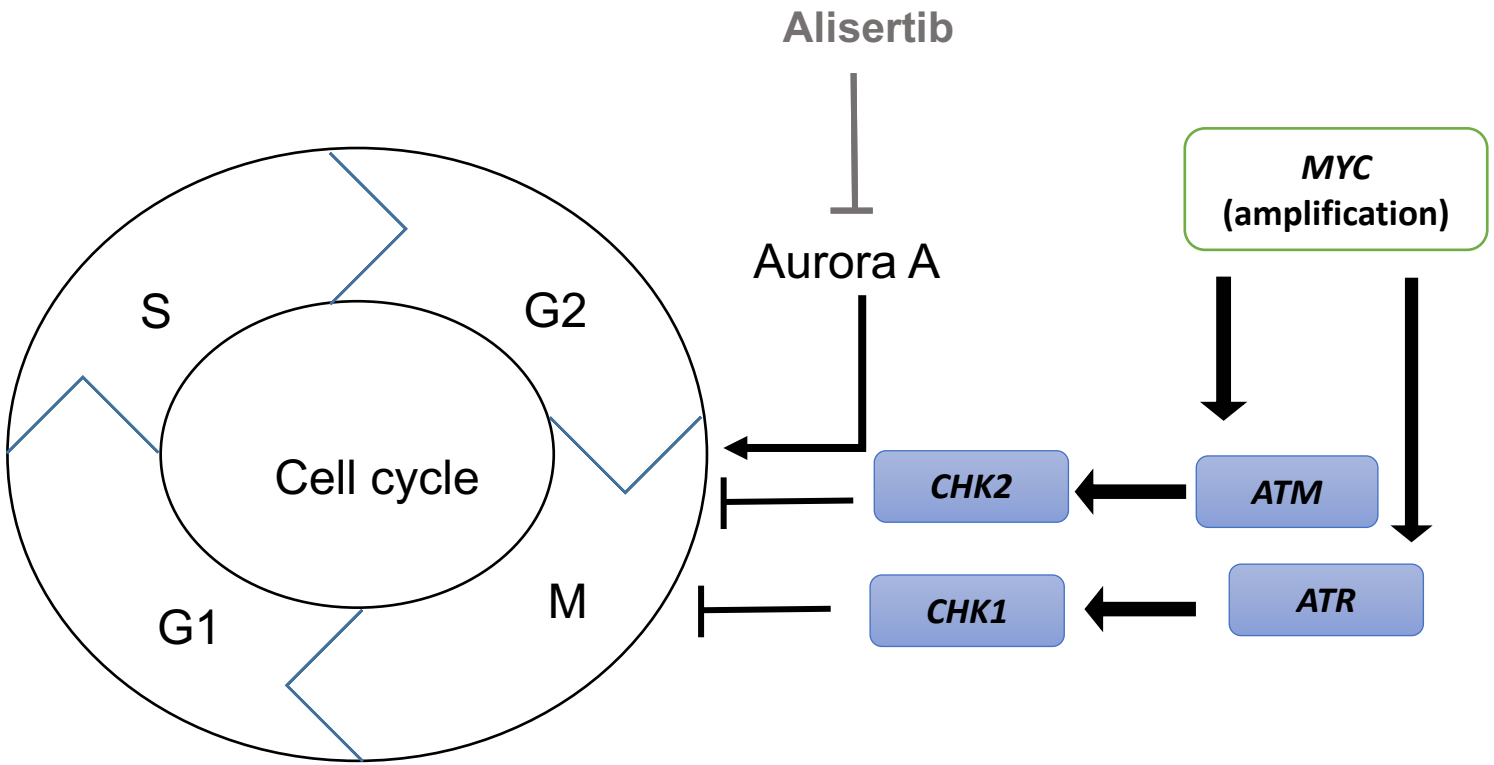

UM
M
UM
M
UM
M
UM
M
300 pb
200 pb
100 pb
93 bp
81 bp
Échelle taille ADN
Témoin négatif
Témoin positif
Patient test 1
Patient test 2
Test en duplicata


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


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

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.



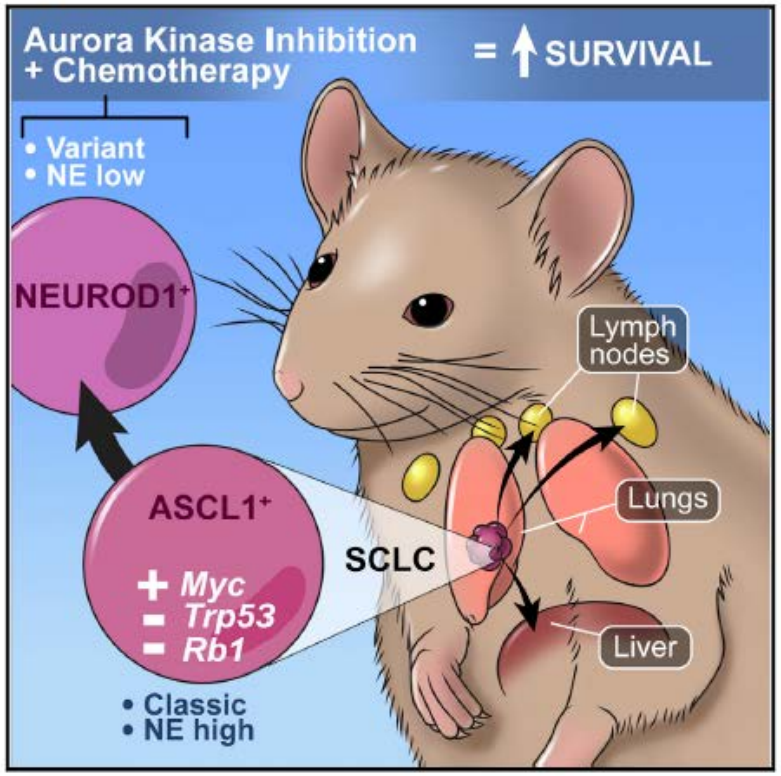
Le cancer à petites cellules P53- Rb1 – et Myc ++ est sensible aux inhibiteurs d'Aurora A

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

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Correspondence

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

In Brief

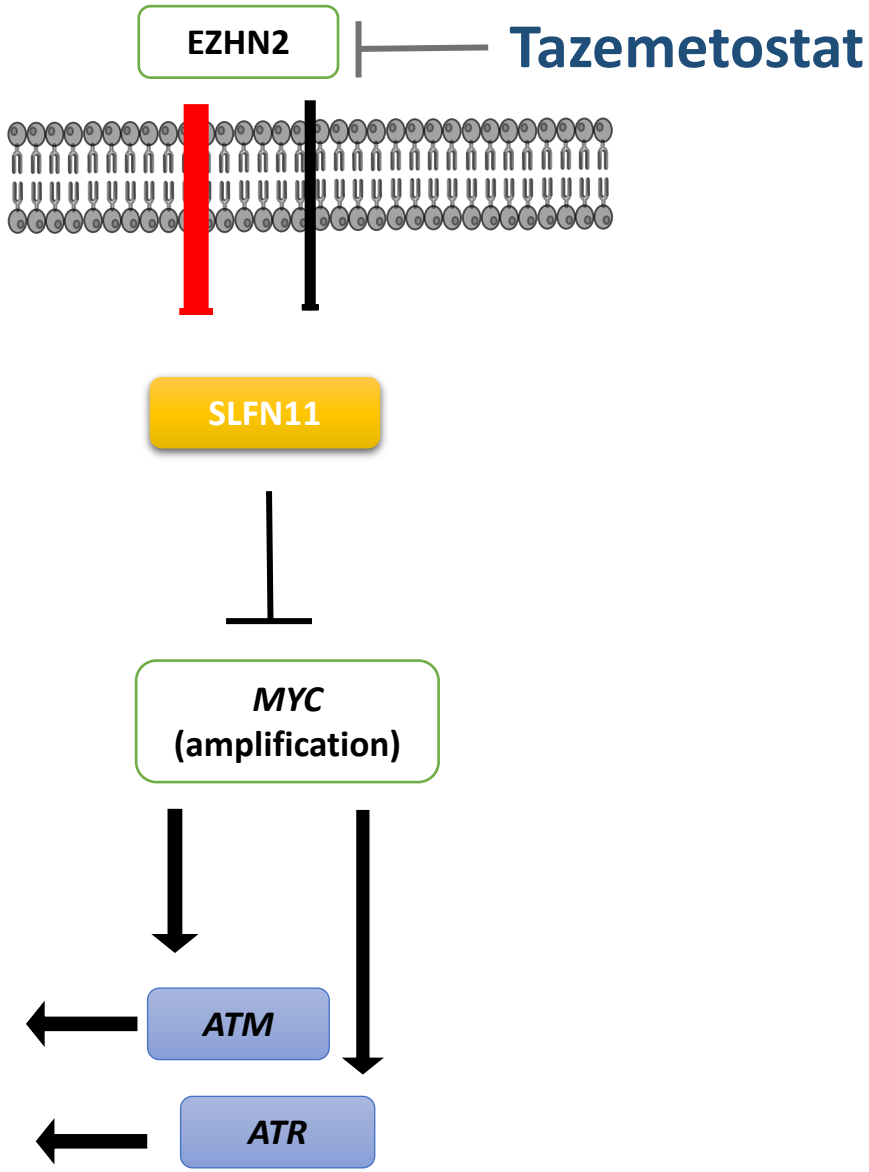
Mollaoglu et al. generate a mouse model of small cell lung cancer (SCLC) with elevated *Myc* expression and loss of *Rb1* and *Trp53*. MYC promotes a neuroendocrine-low variant subtype of SCLC, which is paralleled in patients. Mouse and human SCLC with high MYC levels display sensitivity to Aurora kinase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

Mollaoglu G. et al Cancer Cell. 2017

Alisertib + paclitaxel vs placébo + paclitaxel 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)

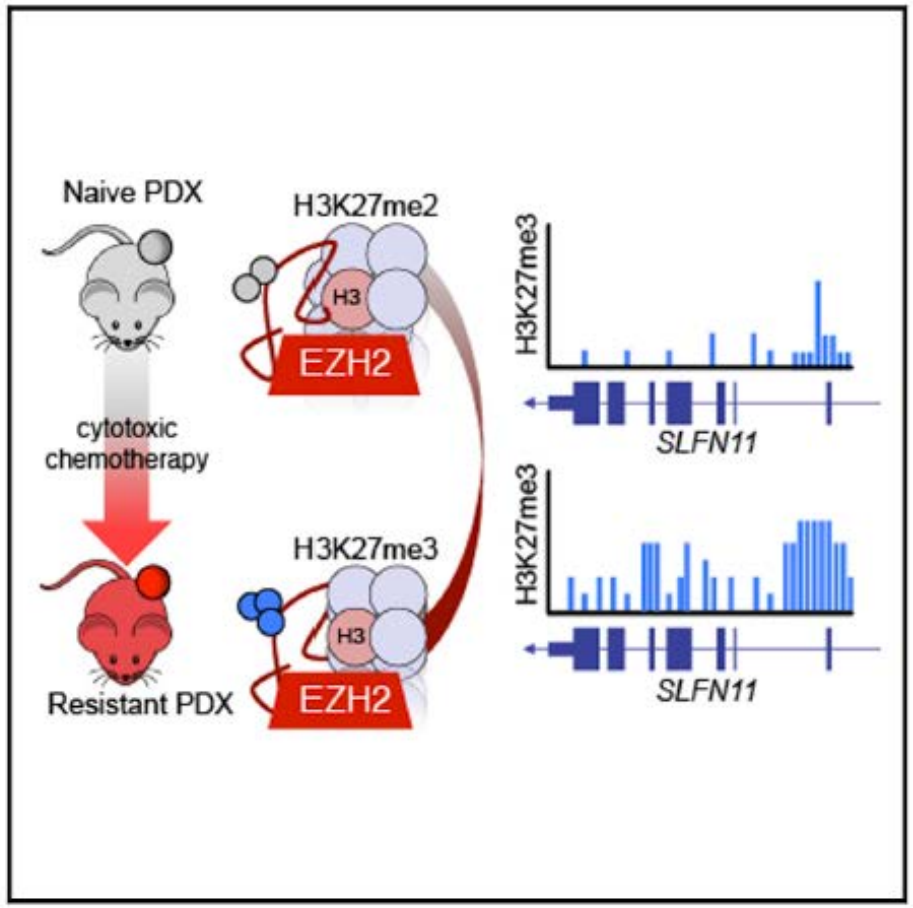

EZHN2
Tazemetostat
SLFN11
MYC
(amplification)
ATM
ATR

Article

Cancer Cell

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

Graphical Abstract



Authors

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Correspondence

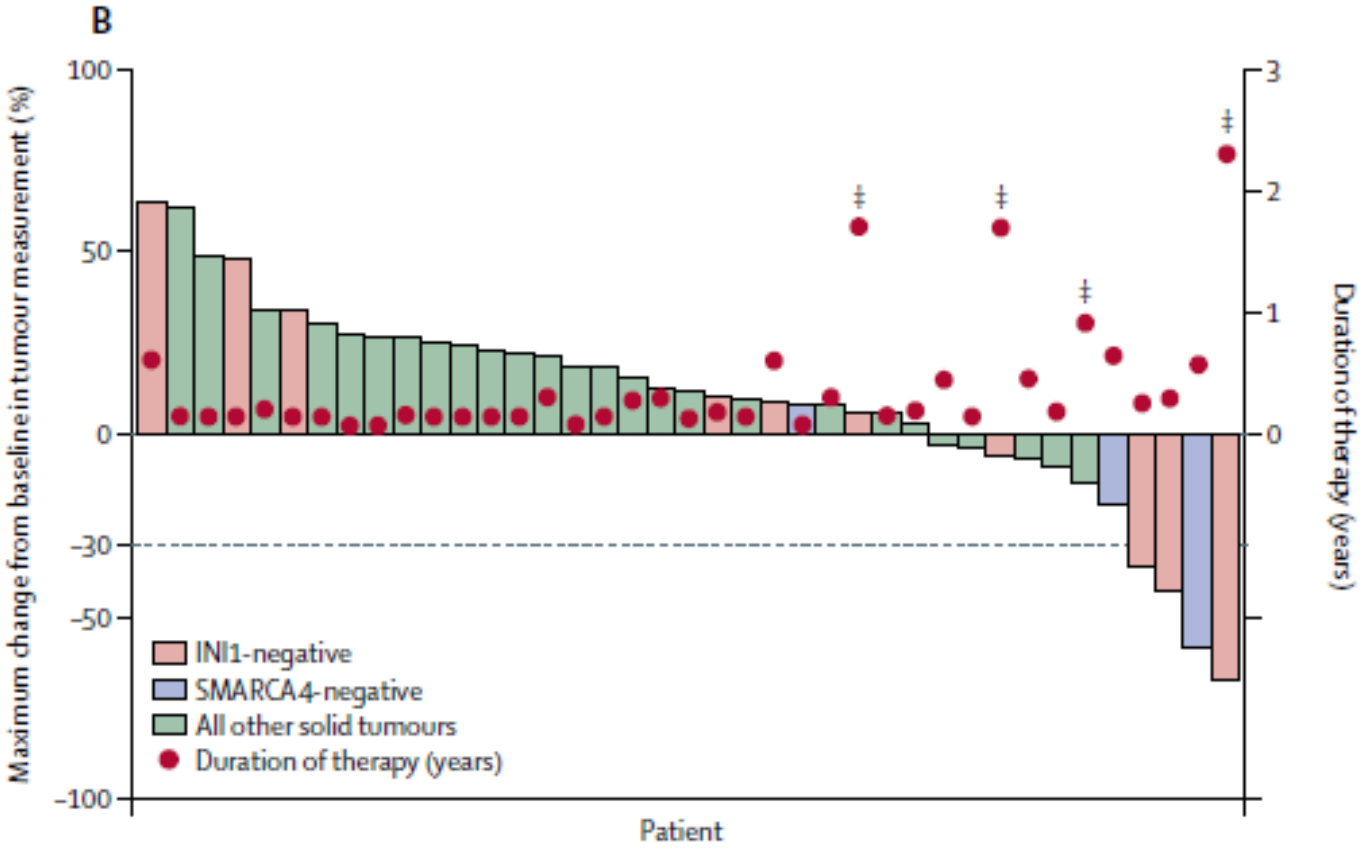
rudinc@mskcc.org (C.M.R.), poirierj@mskcc.org (J.T.P.)

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.

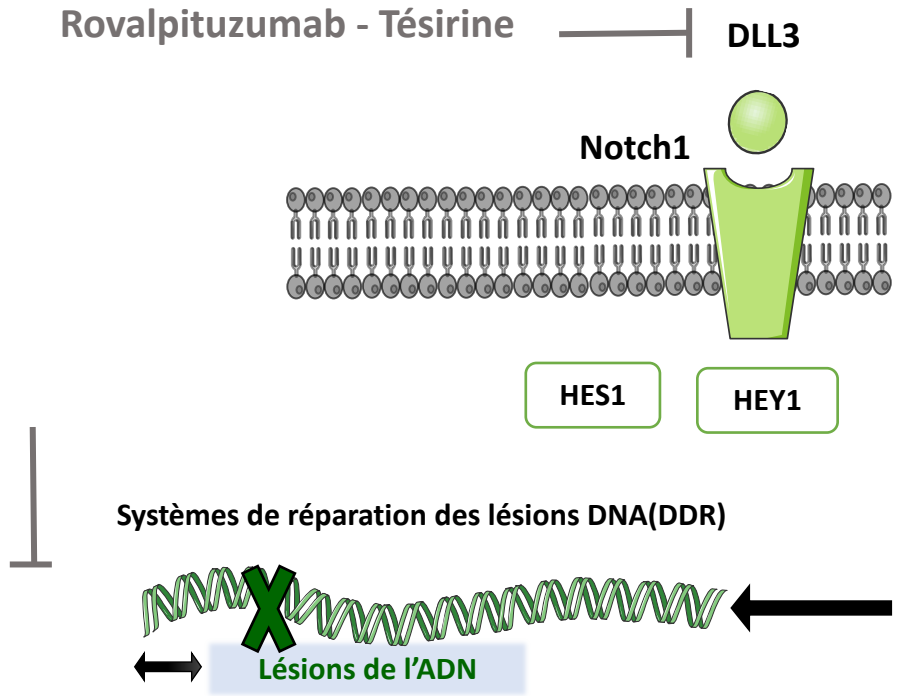
Gardner EE et al. Cancer cell 2017

Tazemetostat, first in human, first in class phase 1



Antoine Italiano, Lancet Oncol 2018

Rovalpituzumab tesirine



Rudin M. Lancet Oncol 2017; 18:42–51

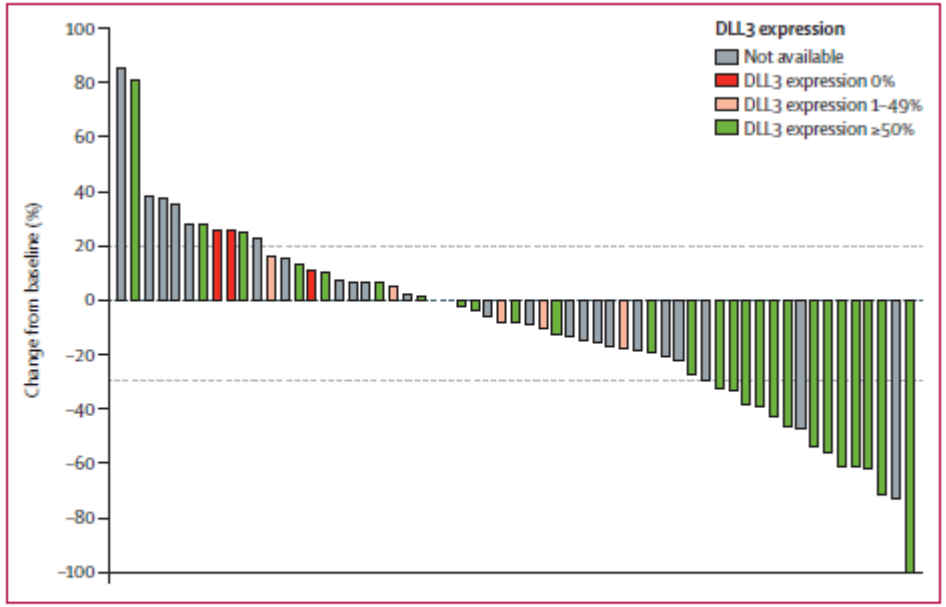


***Figure 1*: Waterfall plot showing best change in tumour burden from baseline at active treatment doses (n=60)**
Investigator-assessed best change from baseline was the change in the sum of longest diameters of target lesions for patients treated with rovalpituzumab tesirine 0·2 mg/kg or 0·4 mg/kg 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

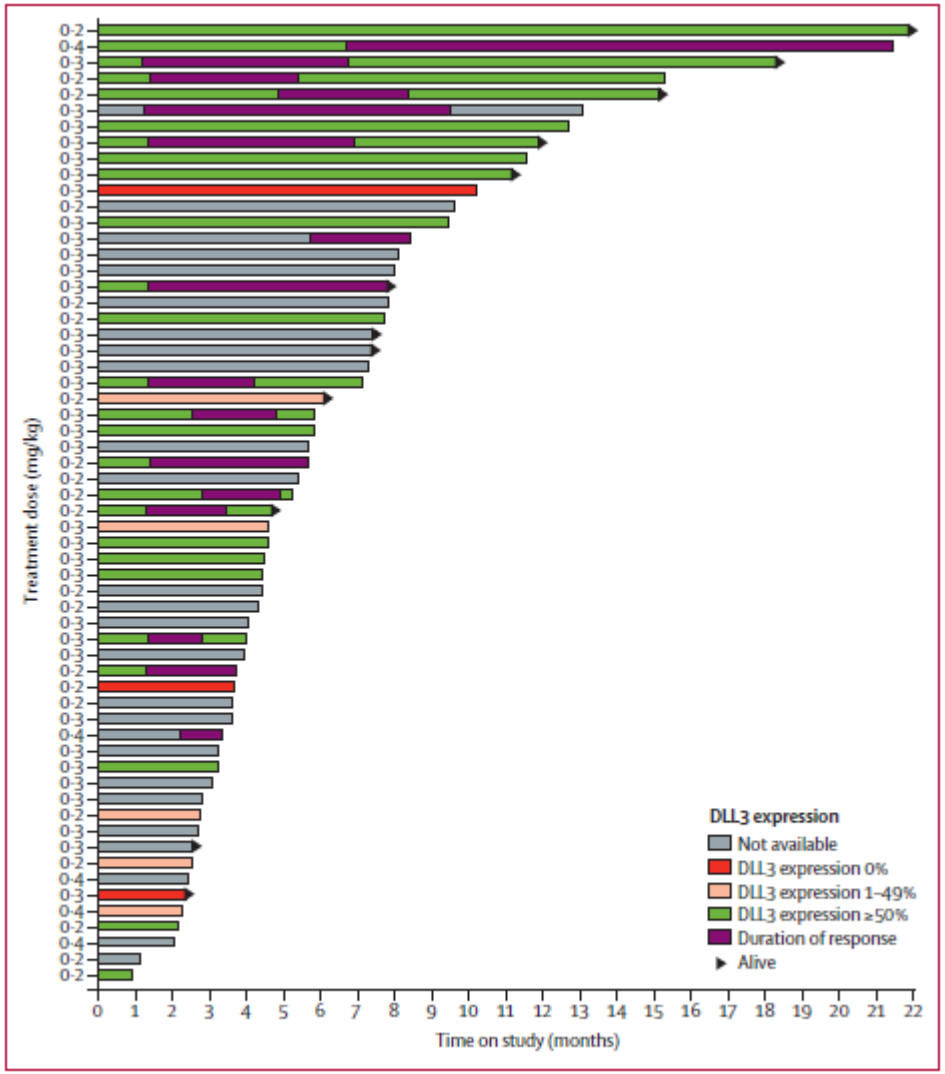


***Figure 2*: Swimmer's plot showing time on study and duration of response for patients treated with active treatment doses (n=60)**

August 29, 2019

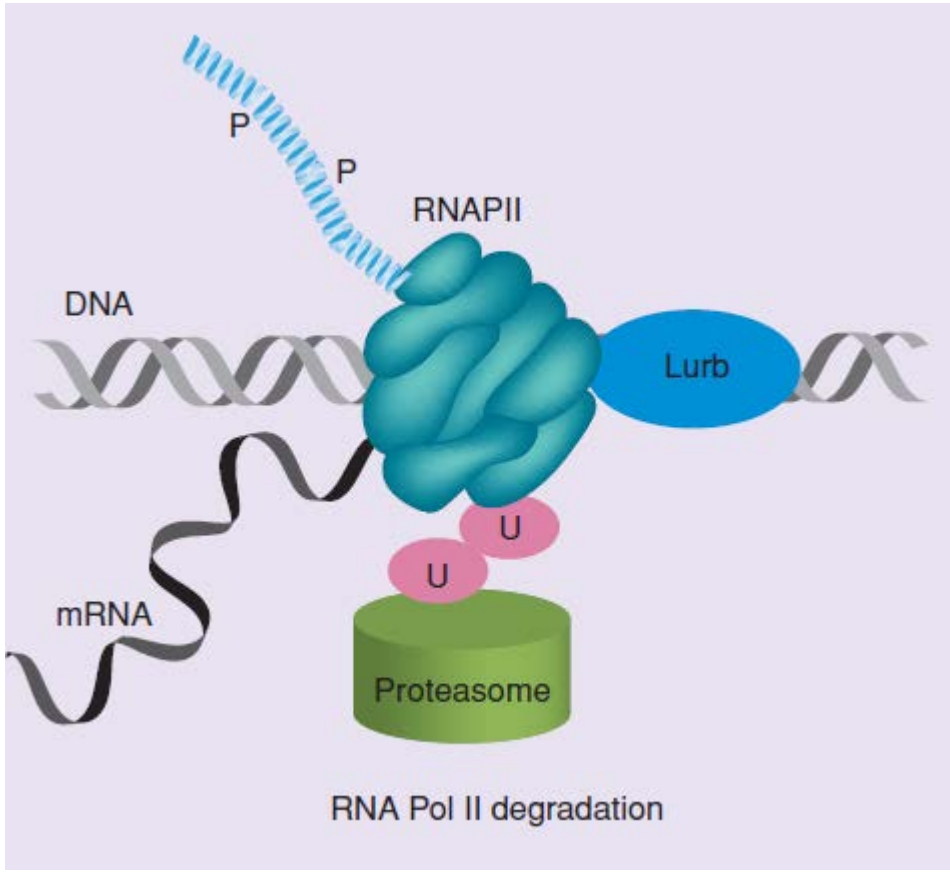
AbbVie Discontinues Rovalpituzumab Tesirine (Rova-T) Research and Development Program

- MERU, a Phase 3 placebo-controlled trial evaluating Rova-T as a first-line maintenance therapy for advanced small-cell lung cancer (SCLC), demonstrated no survival benefit for patients receiving Rova-T at the interim analysis
- Independent Data Monitoring Committee recommended terminating the study due to lack of survival benefit

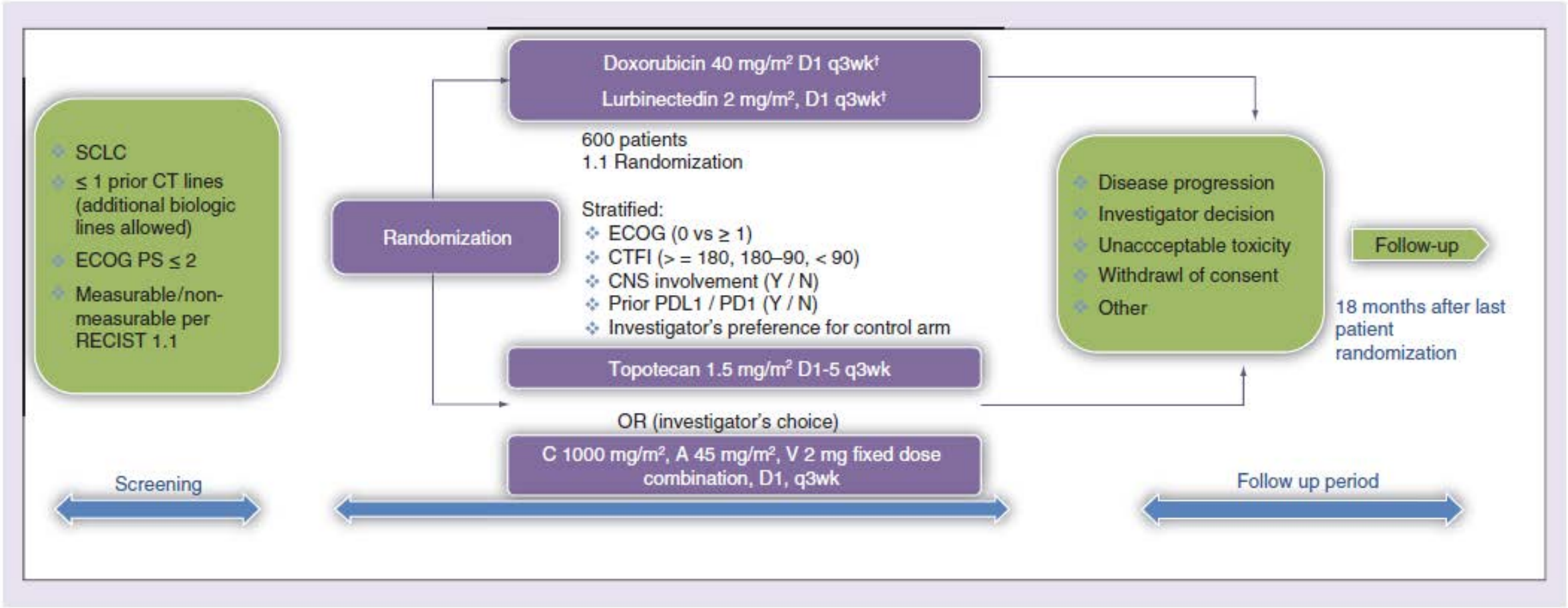
NORTH CHICAGO, Ill., Aug. 29, 2019 /PRNewswire/ -- AbbVie (NYSE: ABBV), a research based global biopharmaceutical company, today announced that MERU, a Phase 3 trial evaluating Rova-T as a first-line maintenance therapy for advanced small-cell lung cancer (SCLC), demonstrated no survival benefit at a pre-planned interim analysis for patients receiving Rova-T as compared with placebo. The overall safety profile was generally consistent with that observed in previous studies. The MERU trial is being closed, and the Rova-T research and development program has been terminated. AbbVie will move forward prioritizing other development programs within its oncology pipeline.

Lurbinectédine

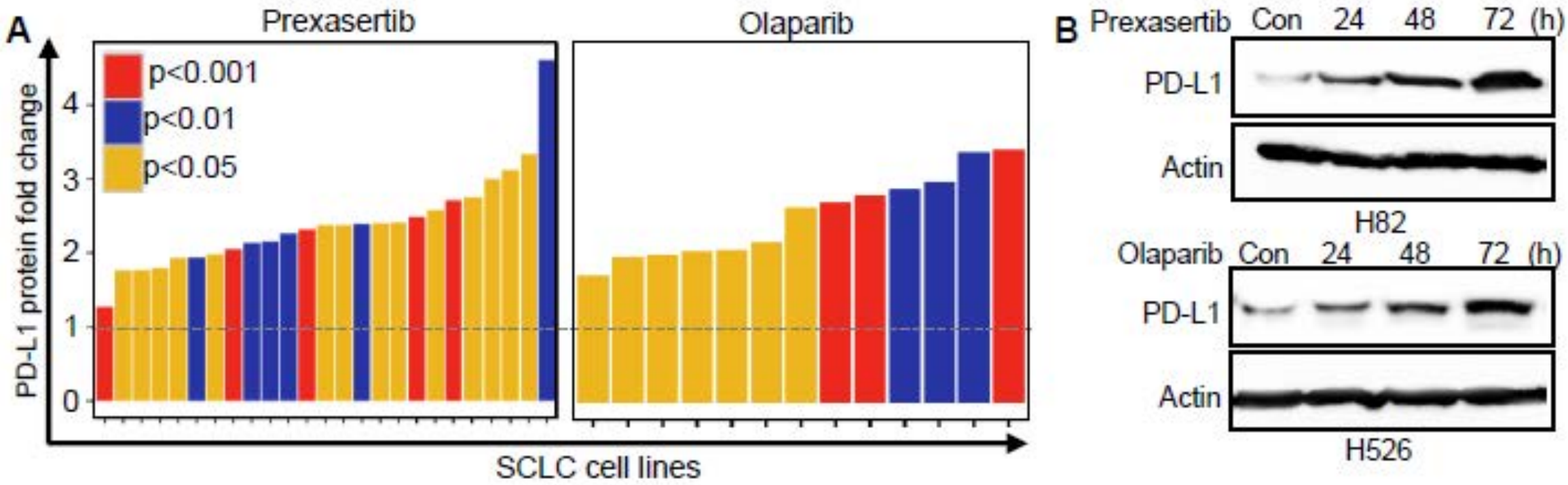
- est un analogue synthétique de la tétrahydroisoquinoléine d'origine marine
- La lurbinectédine induit une dégradation spécifique de l'ARN transcripteur Pol II et l'accumulation ultérieure de cassures de l'ADN
- Une étude de phase lurbinectédine + doxorubicine: RR 37% - 67%



Atlantis: doxo Lurbinectédine vs standard CT

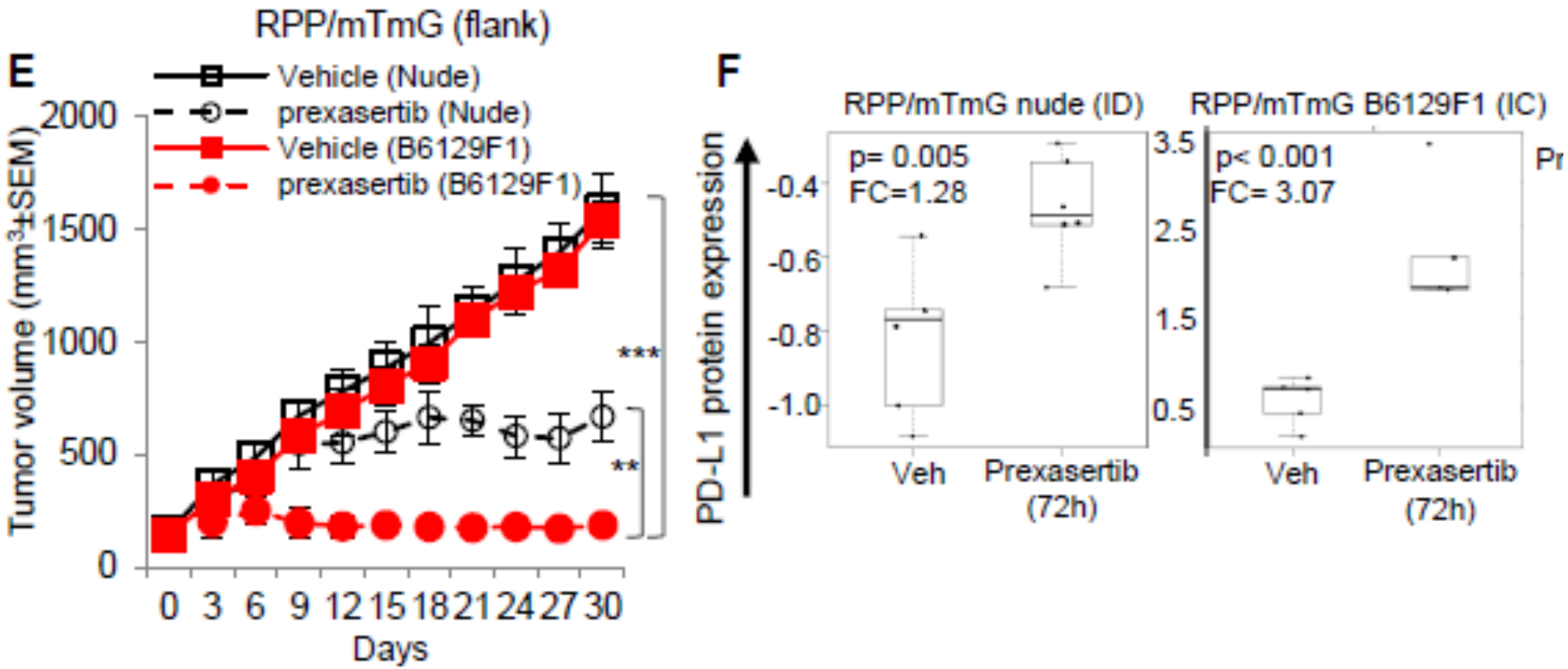


Interactions DDR - IPCI



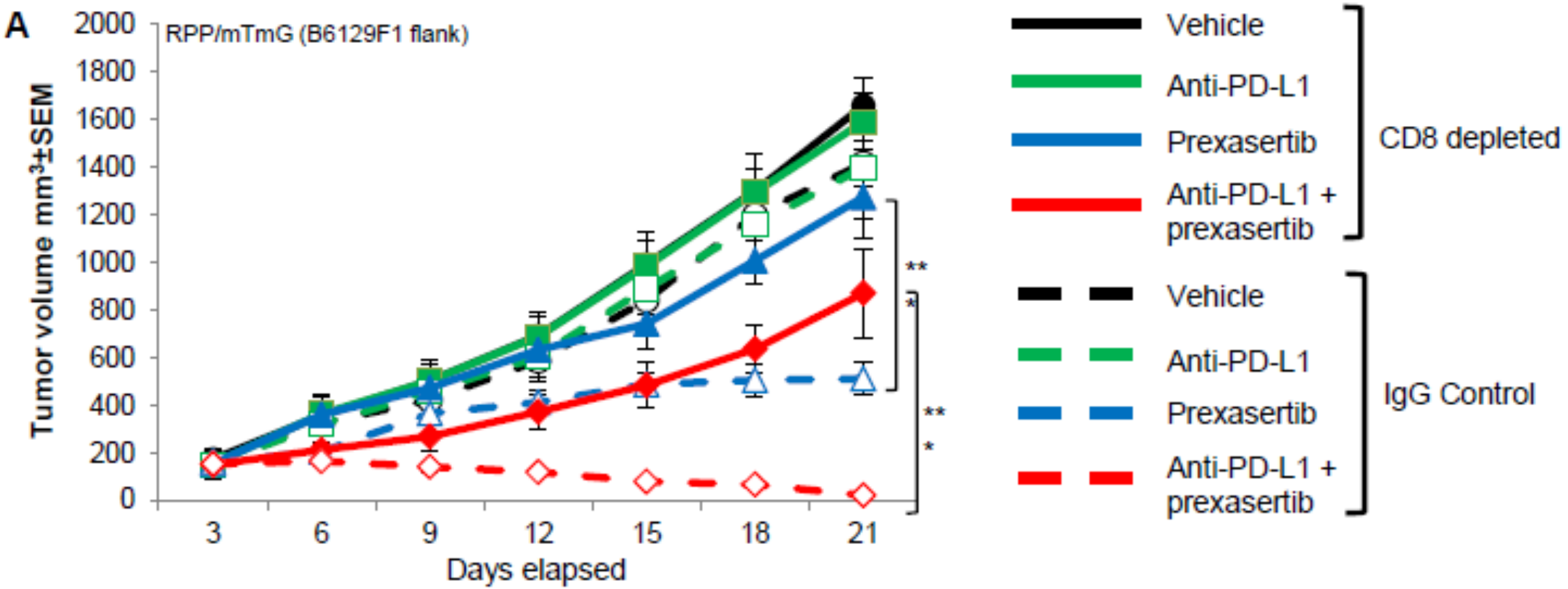
L'inhibition de la DDR par ciblage avec de petites molécules inhibitrices de CHK1 (prexasertib) et de PARP (olaparib) améliore l'expression de la protéine PD-L1

T. Sen et al. Cancer Discovery. Mai 2019



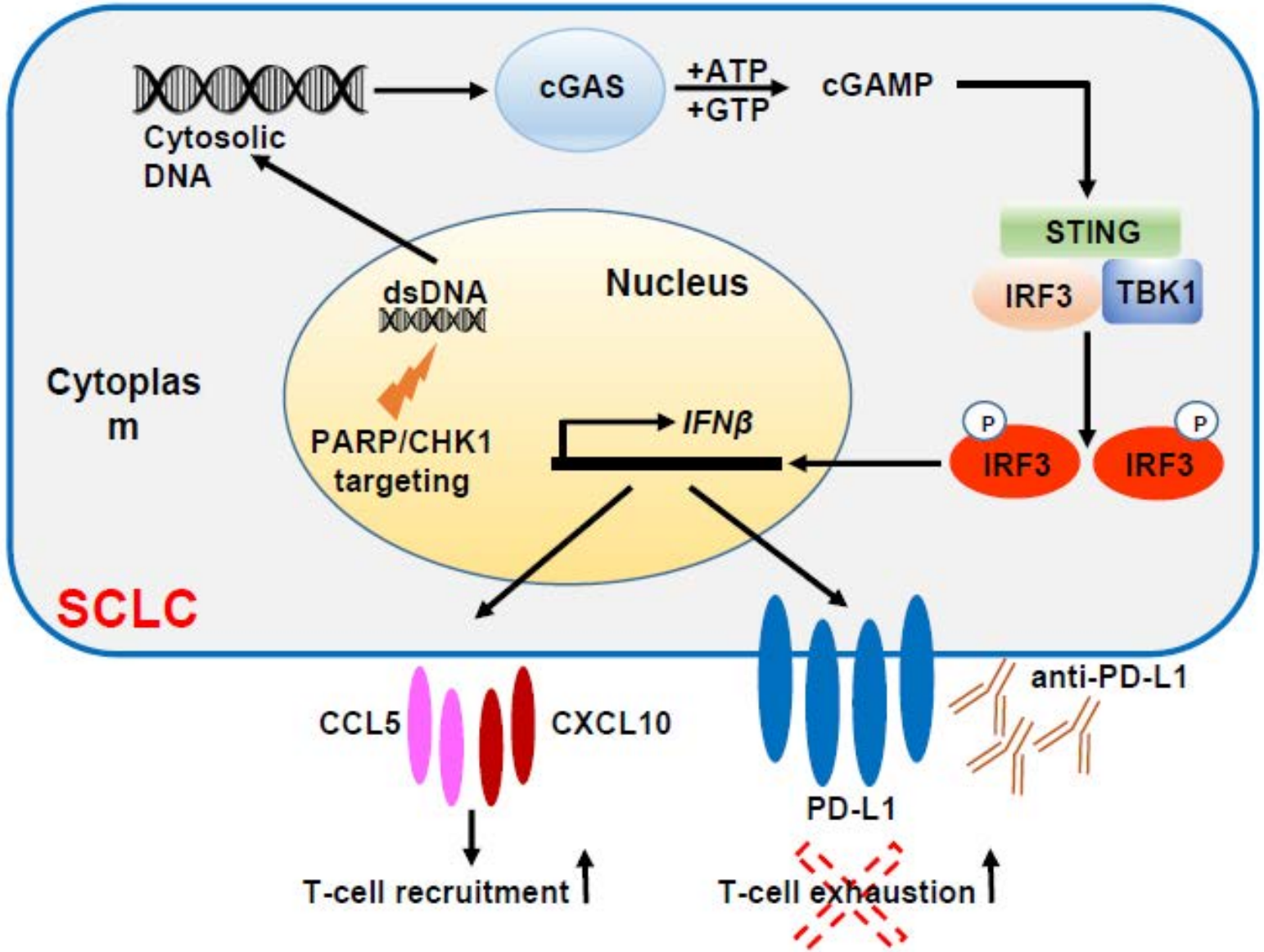
Les anti CHK1 ont une action dépendante d'un système immunitaire intact et augmente l'expression de PD-L1

T; Sen et al. Cancer Discovery. Mai 2019

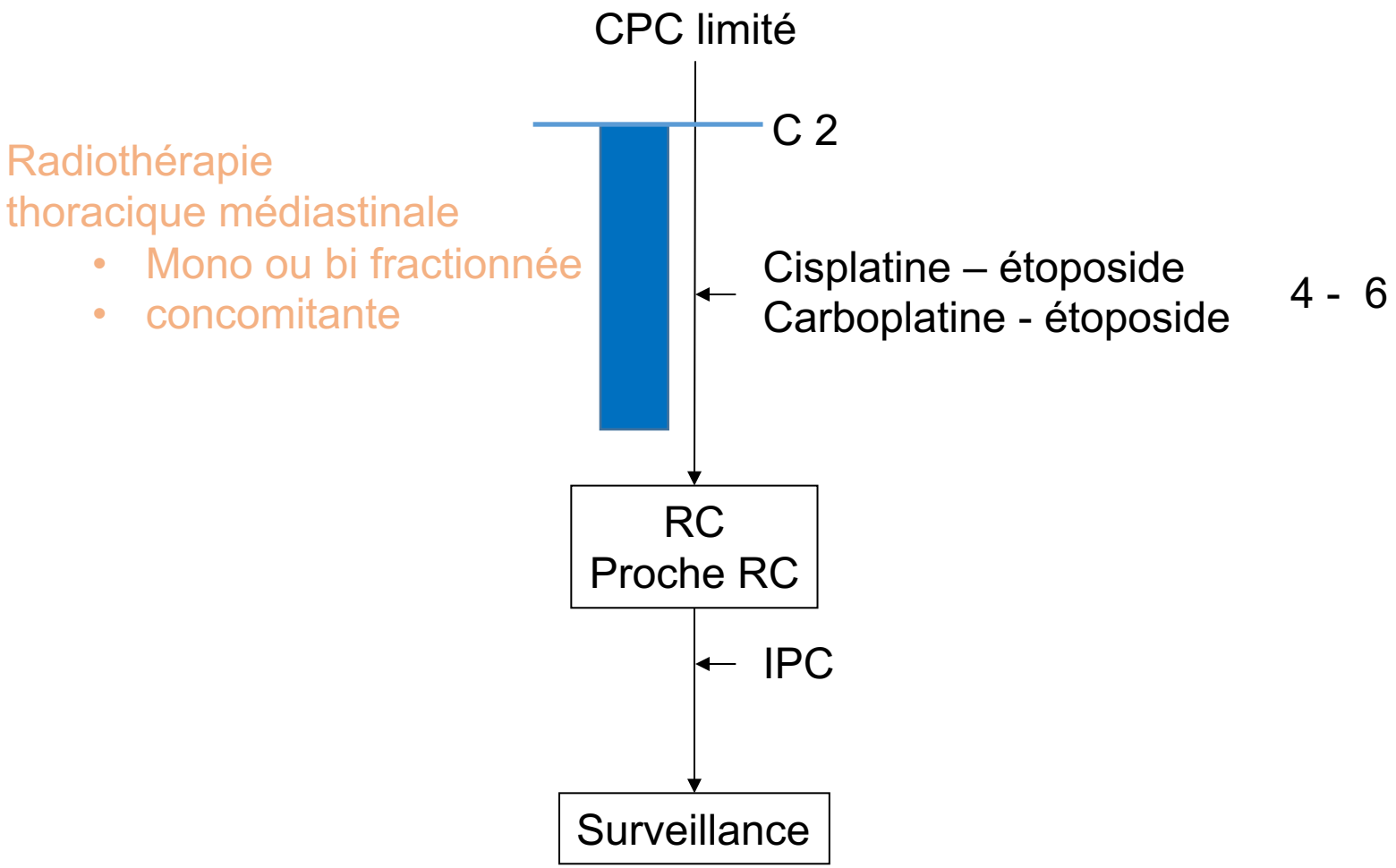


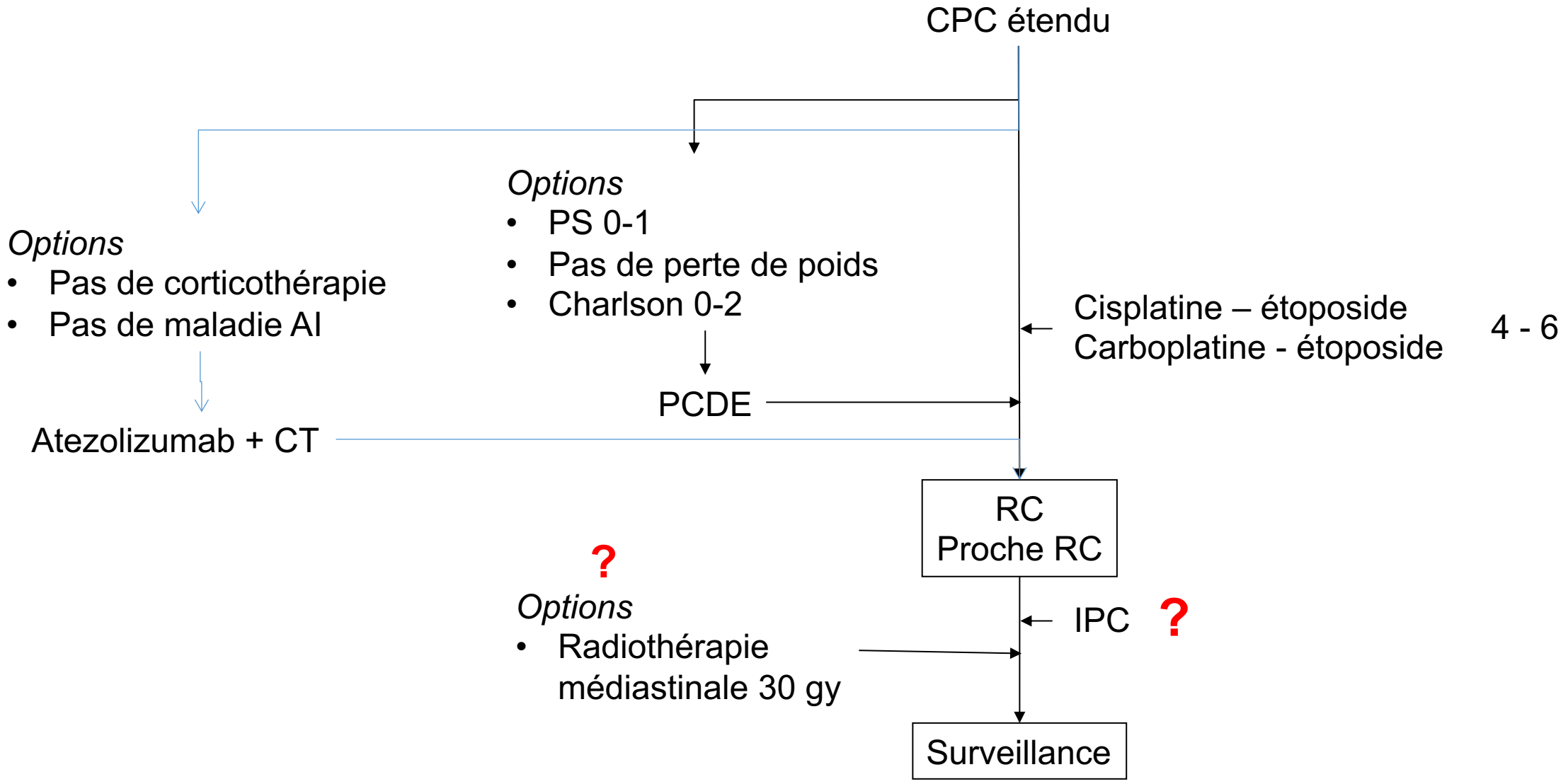
Les lymphocytes T CD8 + sont nécessaires pour l'immunité anti-tumorale induite par CHK1i avec ou sans blocage anti-PD-L1.

T; Sen et al. Cancer Discovery. Mai 2019



T; Sen et al. Cancer Discovery. Mai 2019


CPC limité
C 2
Radiothérapie
thoracique médiastinale
• Mono ou bi fractionnée
• concomitante
Cisplatine – étoposide
Carboplatine - étoposide
4 - 6
RC
Proche RC
IPC
Surveillance


CPC étendu
Options
• PS 0-1
• Pas de perte de poids
• Charlson 0-2
Options
• Pas de corticothérapie
• Pas de maladie AI
Cisplatine – étoposide
Carboplatine - étoposide
4 - 6
PCDE
Atezolizumab + CT
RC
Proche RC
?
Options
• Radiothérapie médiastinale 30 gy
IPC
?
Surveillance

Messages

- Faible impact des traitements anti-angiogéniques
- Immunothérapie : un premier pas ATZ ou DURVA en première ligne
- Nouvelles drogues: lurbinectédine? apatinib?
- Altérations génotypiques à suivre: CG MGMT, EZH2, SLFN11, NOTCH