COURS DU GOLF
GROUPE D'ONCOLOGIE DE LA SOCIÉTÉ DE PNEUMOLOGIE DE LANGUE FRANÇAISE

cancer à petites cellules

traitements standards et progrès

jean louis pujol,
CHU34 et INSERM 1194 Montpellier

Standards…

Le CPC aujourd'hui

- Doublets sels de platine + étoposide comme socle de développement
- Radiothérapie thoracique concomittante dans les formes limitées
- Irradiation prophylactique encéphalique pour les malades en réponse
- Deuxième ligne: réinduction ou topotécan
- Déclin épidémiologique dans les pays industrialisés depuis deux décennies

Cis – étoposide

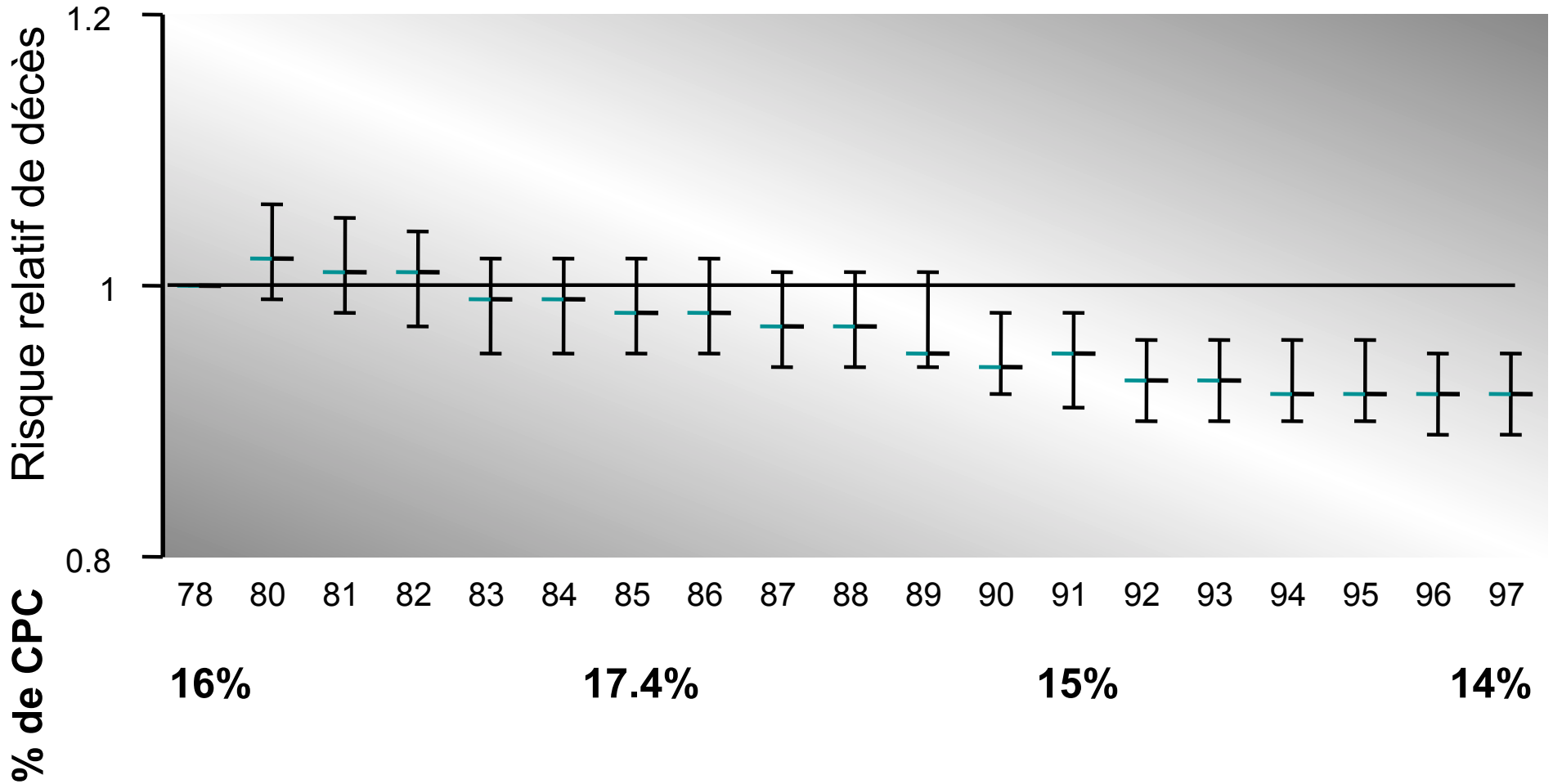
Clinical Applications of Therapeutic Advances

The median [ ] seven to 14 weeks, depending on whether the disease is "extensive" or "limited"
The median survival [ ] nine months with extensive disease and 12 to 18 months with limited disease.

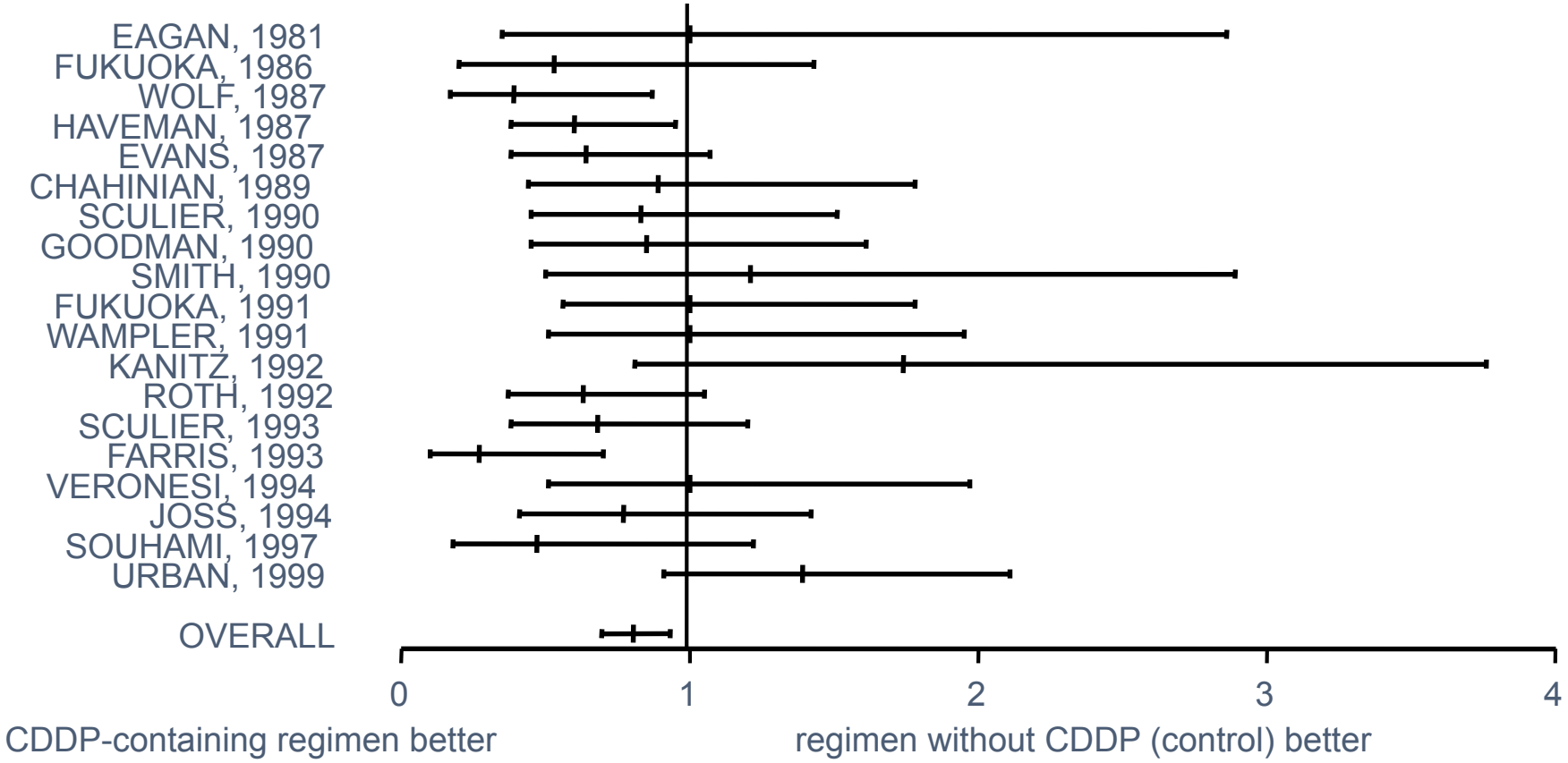
Treatment of Small Cell Lung Cancer—1981

Larry M. Weisenthal, MD, PhD

Epidémiologie du CPC - SEER



Odds ratio et IC 95% de la survie à 1 an



Pujol JL et al. Br J Cancer, 2000;83 :8-15

Platine - étoposide

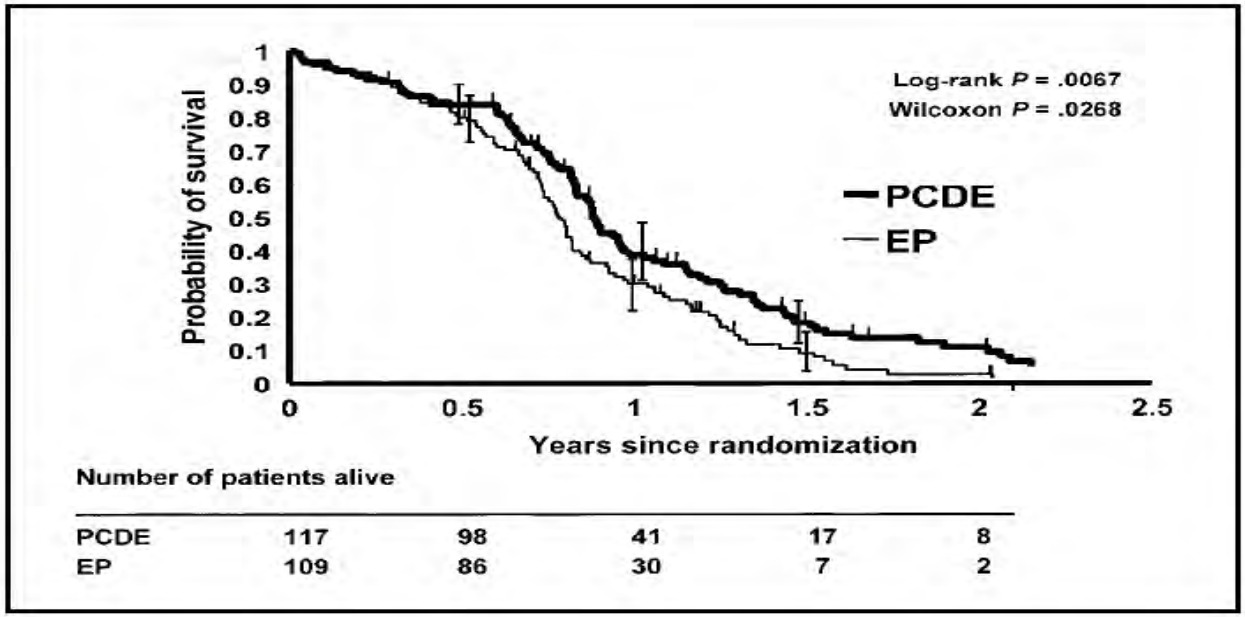
Standard:

- Amélioration de la survie au début des 90,
- Méta-analyses,
- Profil de tolérance favorable,
- Peut être associé concomitamment à la radiothérapie,
- Inscrit par 3 décennies de pratique.

Plus de chimiothérapie?

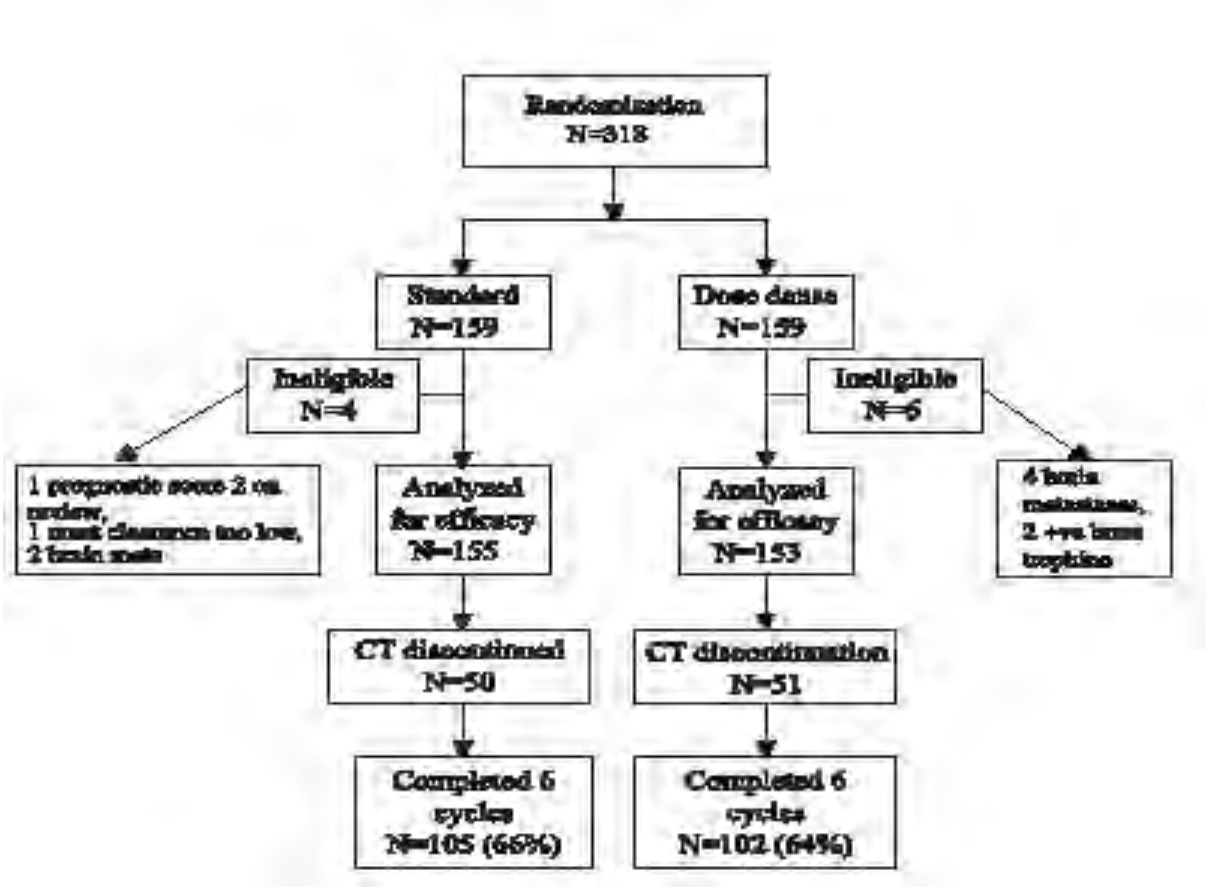
- Durée
- Intensité
- Addition de drogues
- Substitution de drogues
- Séquençage de drogues

Cis – étoposide *vs* PCDE



Pujol JL et al, J Natl Cancer Inst. 2001

Phase 3, dose dense + CD 34



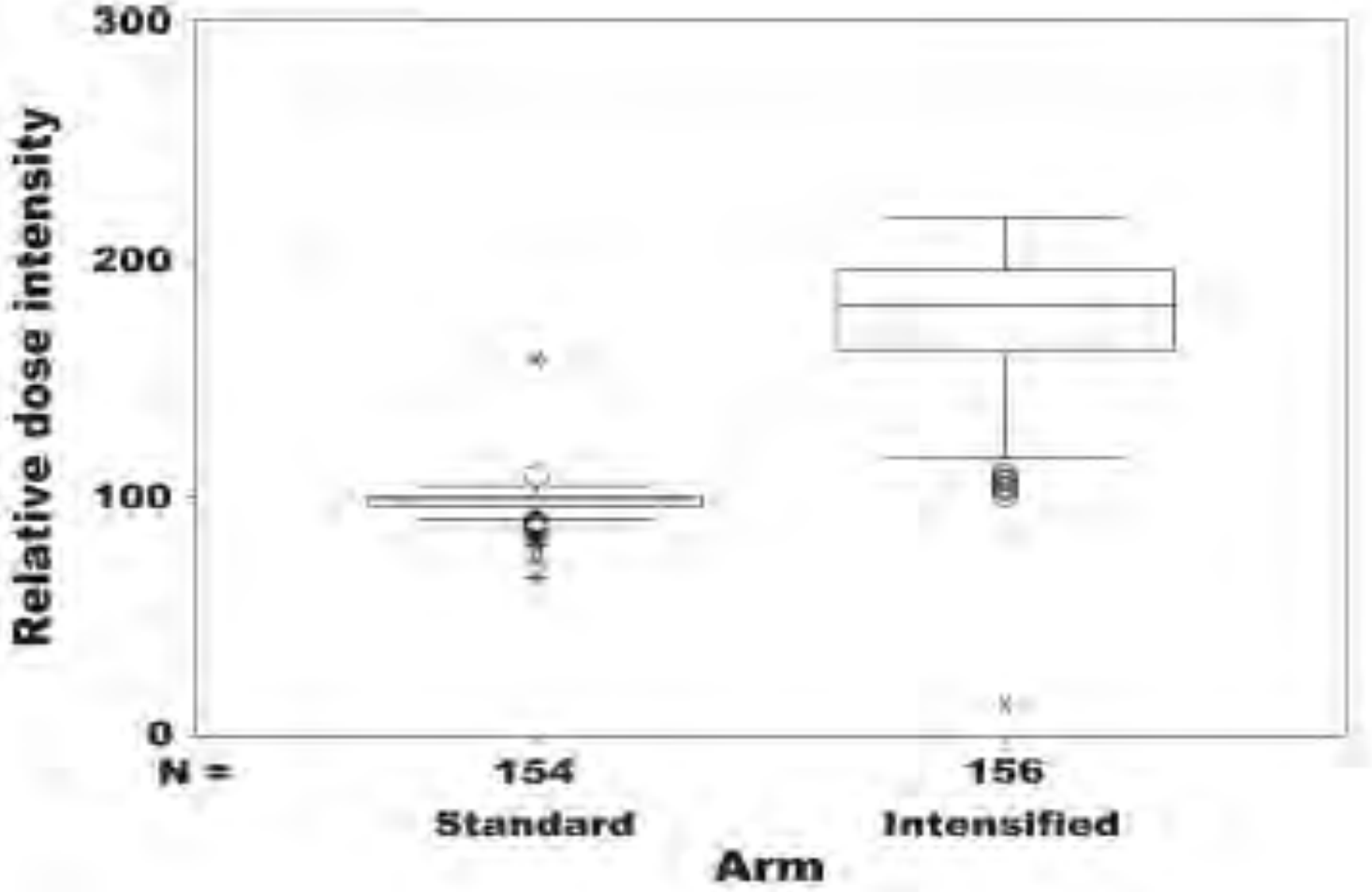
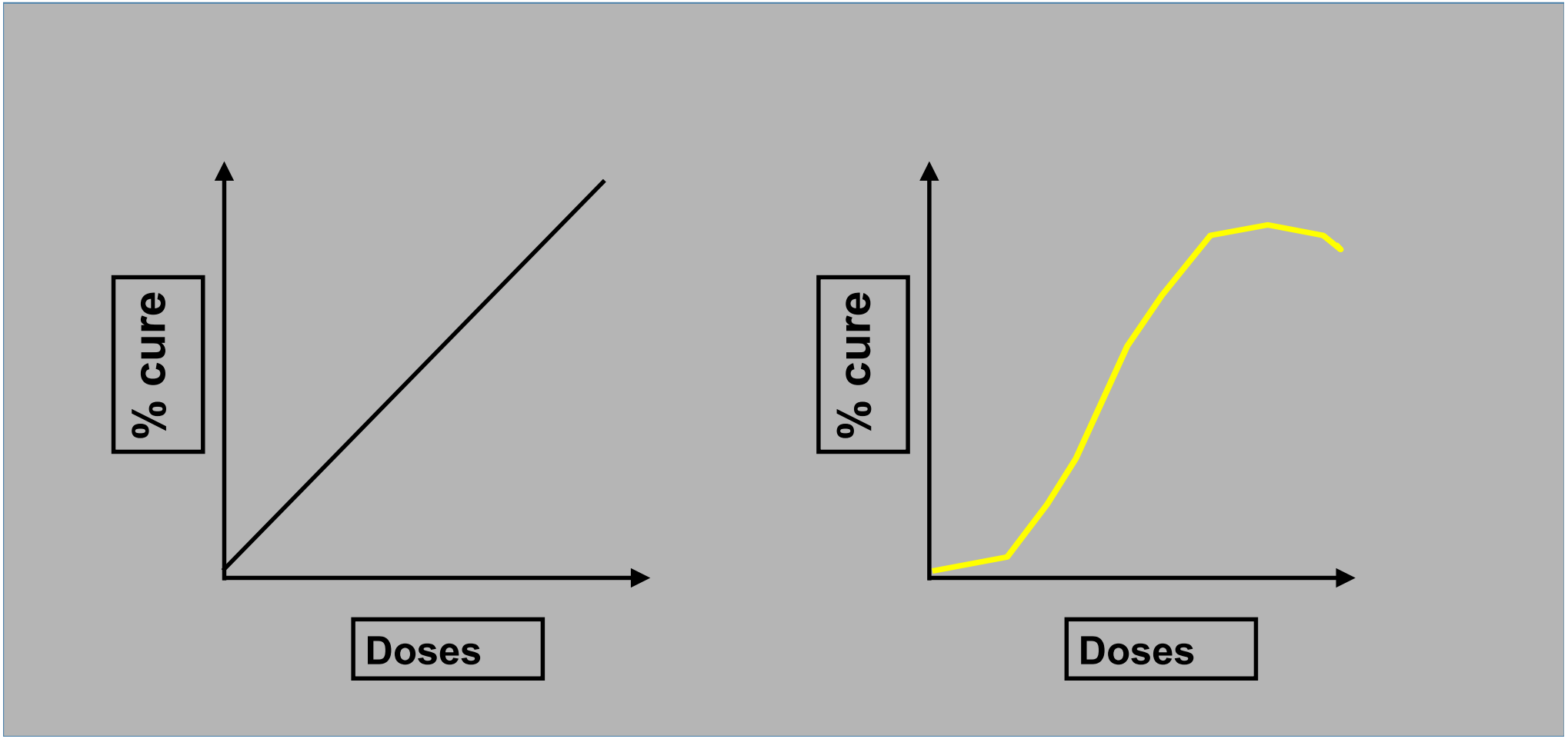

300
200
100
0
Relative dose intensity
N =
154
Standard
156
Intensified
Arm

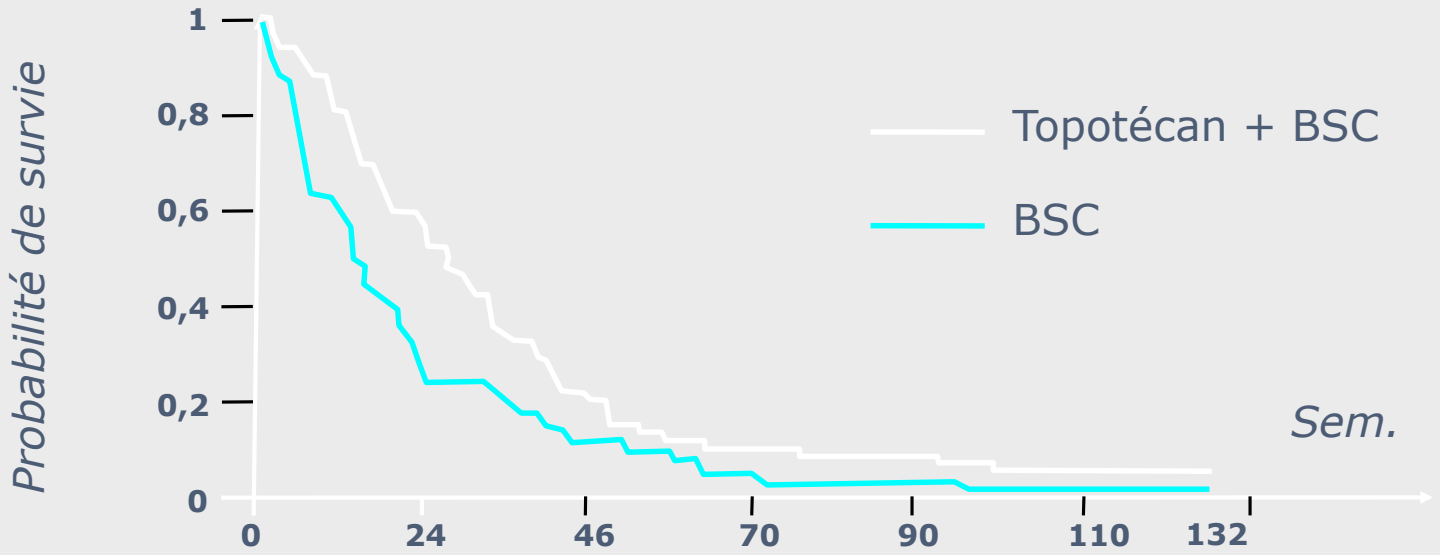
Table 4. Survival

	Standard arm	Dose-dense arm	*P*
Median survival, mo (95% CI)	13.9 (12.9 to 15.8)	14.4 (12.7 to 16.0)	.76
1-y survival, % (95% CI)	63 (55 to 70)	66 (58 to 73)	.67
2-y survival, % (95% CI)	22 (16 to 29)	19 (14 to 27)	.67
Time to progression, mo (95% CI)	10.8 (9.5 to 12.2)	10.7 (9.9 to 11.5)	.2

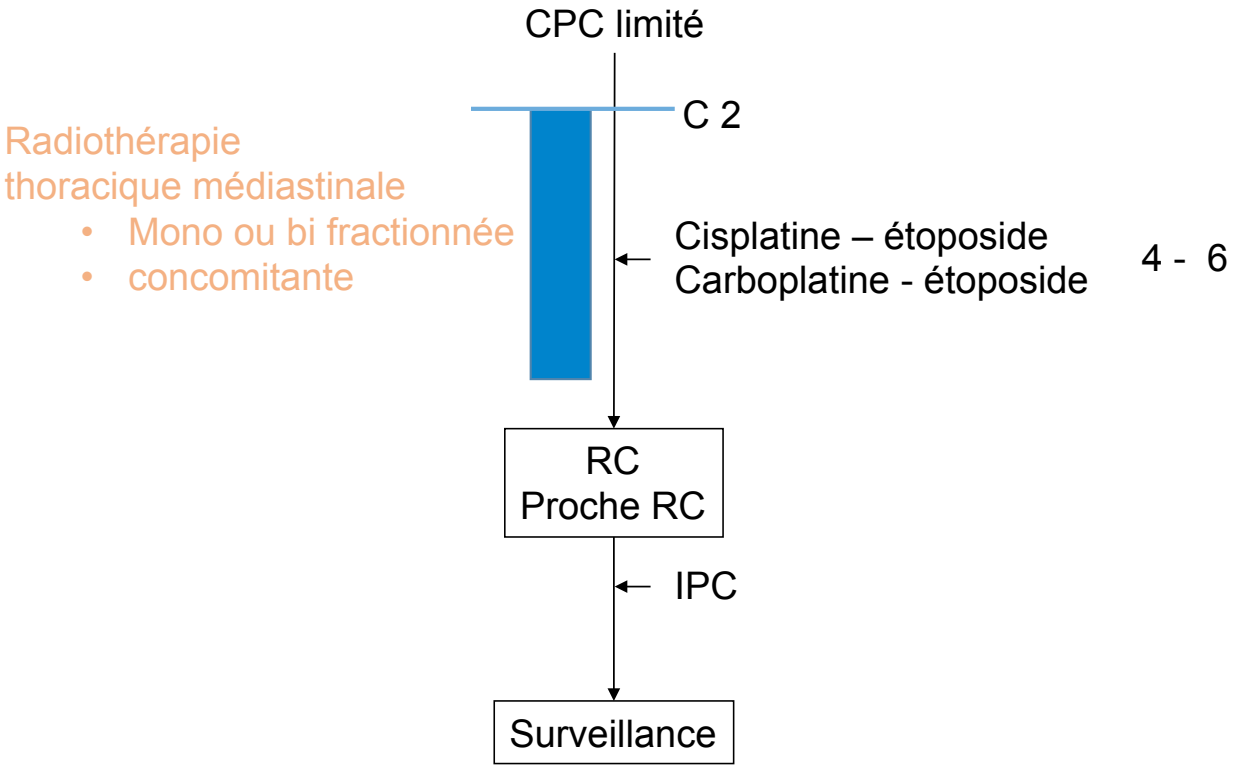
hypothèses

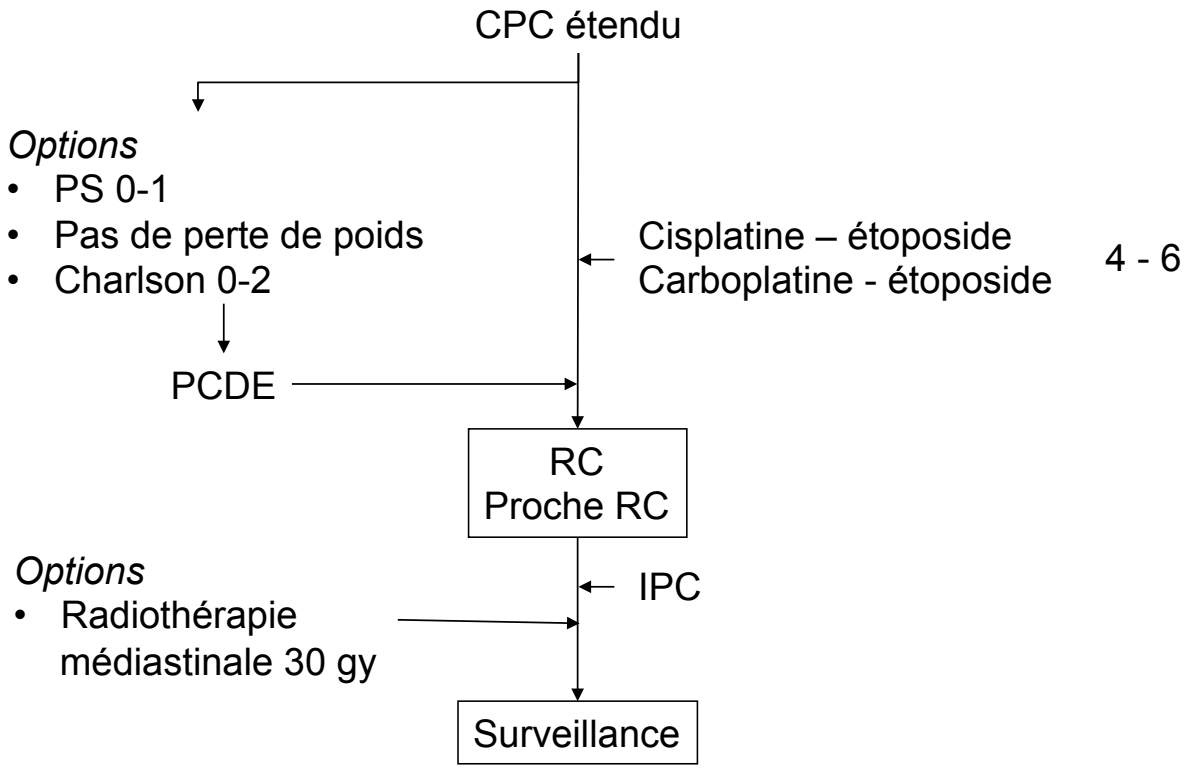


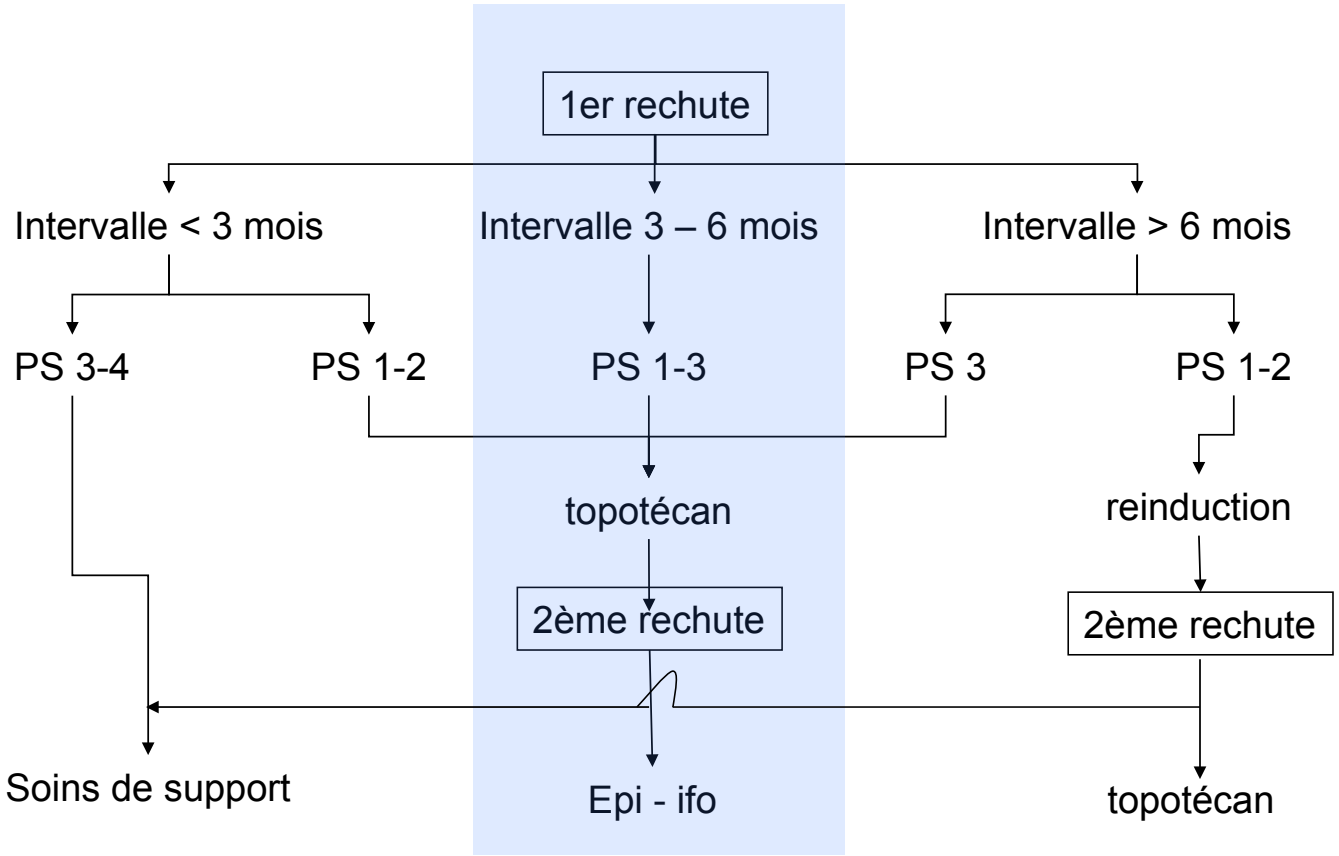
Topotécan



	Topotecan (n=71)	BSC (n=70)	Hazard Ratio (CI 95%) Log-rank P-value
Survie médiane (sem)	26	14	0.64 (0.45-0.90) p = 0.01
Survie à 6 mois	49%	26%	


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
Cisplatine – étoposide
Carboplatine - étoposide
4 - 6
PCDE
RC
Proche RC
Options
• Radiothérapie médiastinale 30 gy
IPC
Surveillance


1er rechute
Intervalle < 3 mois
Intervalle 3 – 6 mois
Intervalle > 6 mois
PS 3-4
PS 1-2
PS 1-3
PS 3
PS 1-2
topotécan
reinduction
2ème rechute
2ème rechute
Soins de support
Epi - ifo
topotécan

Biologie

Biologie - génétique

- Surexpression récepteur de type c-kit
- *l'insulin like growth factor* récepteur de type 1 (IGF-1R) ;
- Perte d'allèle 3p-, locus porteur du gène FHIT
- Importance de Rb 1 et Tp53
- Promotion: Mycl et Nfib

Chirurgie?

Surgery for Small Cell Lung Cancer

A Retrospective Analysis of 243 Patients from Japanese Lung Cancer Registry in 2004

Hidefumi Takei, MD, Haruhiko Kondo, MD,* Etsuo Miyaoka, PhD,† Hisao Asamura, MD,‡ Ichiro Yoshino, MD,§ Hiroshi Date, MD,‖ Meinoshin Okumura, MD,¶ Hirohito Tada, MD,# Yoshitaka Fujii, MD,** Yoichi Nakanishi, MD,†† Kenji Eguchi, MD,‡‡ Hirotoshi Dosaka-Akita, MD,§§ Hideo Kobayashi, MD,‖‖ Noriyoshi Sawabata, MD,¶ and Kohei Yokoi, MD;¶¶ for the Japanese Joint Committee of Lung Cancer Registry*

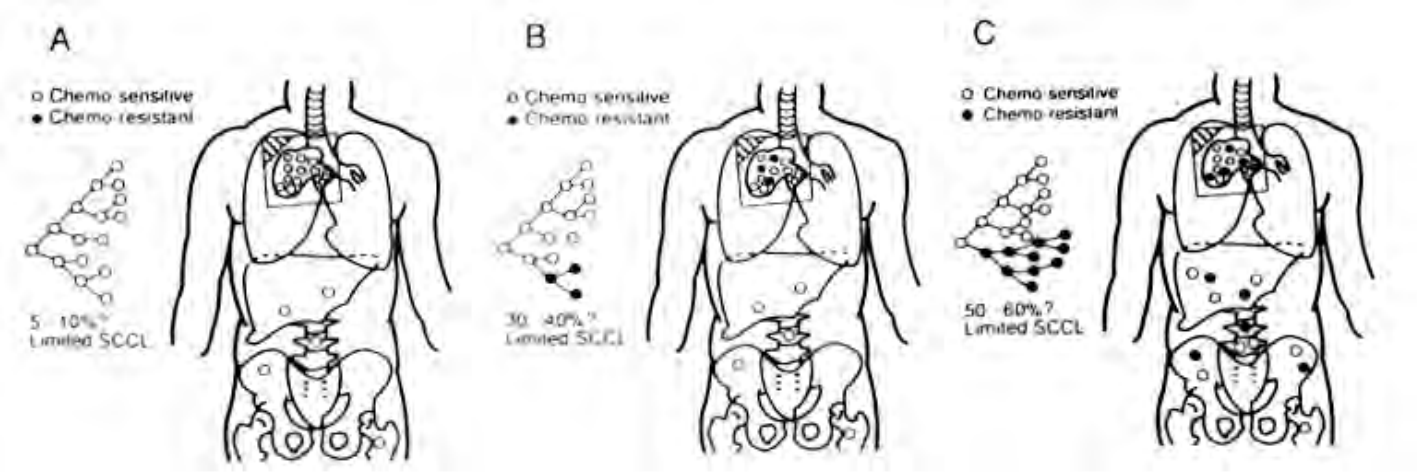
(J Thorac Oncol. 2014;9: 1140–1145)

Multimodalité NSCLC like?

- 243 patients opérés pour CPC
- Soit 2,1 % résections pulmonaires durant l'année 2004
- Discordance anatomo-clinique: cas en apparence de stade II, requalifiés au stade III et inversement
- Chimiothérapie adjuvante meilleur pronostic?

Homogénéité pronostique?

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



EGFR ?

Small-Cell Carcinoma in the Setting of Pulmonary Adenocarcinoma

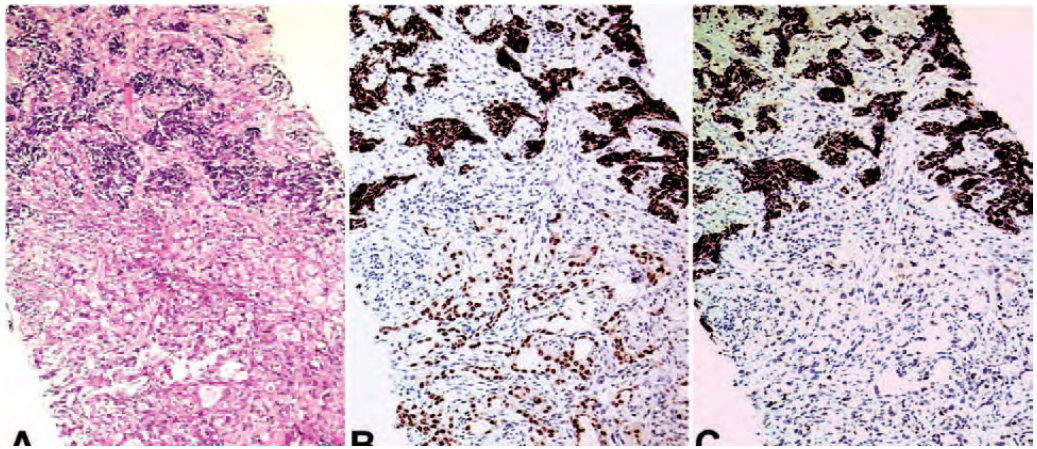
New Insights in the Era of Molecular Pathology

Emma Norkowski, MD, Maria-Rosa Ghigna, MD,* Ludovic Lacroix, PhD,† Thierry Le Chevalier, MD,‡ Élie Fadel, MD, PhD,§ Philippe Dartevelle, MD,§ Peter Dorfmuller, MD, PhD,* and Vincent Thomas de Montpréville, MD**

(*J Thorac Oncol.* 2013;8: 1265–1271)

HE TTF1 KI67

- CPC
- ADE



- génotype des CPC accompagnant un adénocarcinome
- CPC après TKI pour Ad EGFR+: Switch? Hétéroclonalité?
- Neuf observations
  - Ad associés au CPC ont une fréquence de mutation du gène de l'EGFR élevée
  - Le composant CPC est souvent porteur d'une mutation du gène de l'EGFR
  - Ces phénomènes coexistent en l'absence de traitement par TKI de EGFR

Non fumeurs…

BRIEF REPORT

Small-Cell Lung Cancers in Patients Who Never Smoked Cigarettes

Anna M. Varghese, MD,† Maureen F. Zakowski, MD,†‡ Helena A. Yu, MD,*† Helen H. Won, MS,‡§ Gregory J. Riely, MD, PhD,*† Lee M. Krug, MD,*† Mark G. Kris, MD,*† Natasha Rekhtman, MD, PhD,‡ Marc Ladanyi, MD,‡§ Lu Wang, MD, PhD,‡ Michael F. Berger, PhD,‡§ and M. Catherine Pietanza, MD*†*

Journal of Thoracic Oncology ® • Volume 9, Number 6, June 2014

- 2 % des 1040 cas de CPC pris en charge entre 2005 et 2012.
- Mutation L858R de l'exon 21 du gène de l'EGFR
- Hétérogénéité des anomalies identifiées
  - PHOX2B,
  - NOTCH 1,
  - TP53,
  - ….

TABLE 3. Pathologic Characteristics of Small-Cell Lung Cancers (SCLC) among Never-Smokers

Pathologic Confirmation of SCLC	SCLC as Acquired Resistance ($n = 4$)	de novo SCLC ($n = 19$)
Pure SCLC	2	15
Mixed Histology	2	4
EGFR mutations found/*EGFR* testing performed	4* of 4	2 of 8
KRAS mutations found/*KRAS* testing performed	0 of 2	0 of 8
ALK rearrangements found/*ALK* testing performed	0 of 0	0 of 5
RB loss found/RB testing performed	0 of 0	6 of 7

*All four patients with *EGFR* mutations had *EGFR* Exon 19 deletions present at biopsies taken at baseline and at the time of acquired resistance to EGFR TKIs.

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 Keijser, Corinne Faivre-Finn, Suresh Senan**

Lancet 2015; 385: 36–42

Summary

Background Most patients with extensive stage small-cell lung cance

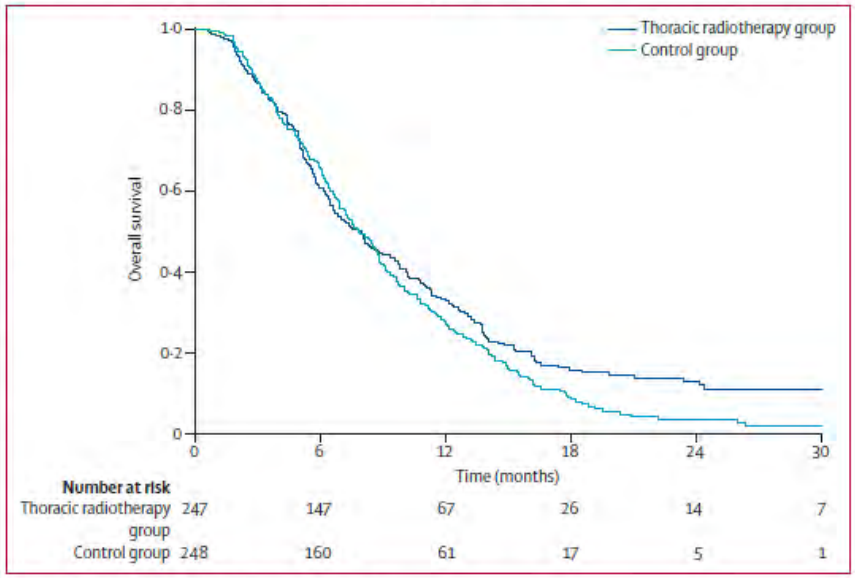


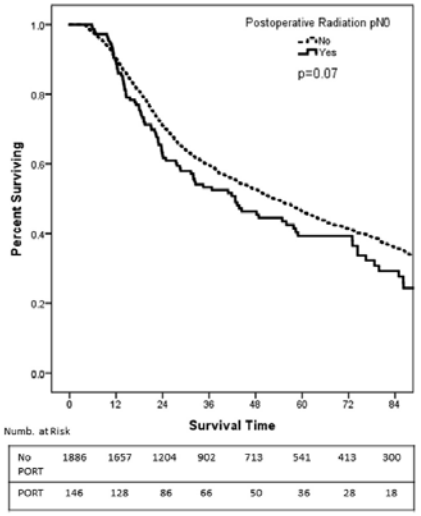
Figure 2: Kaplan-Meier curves for overall survival

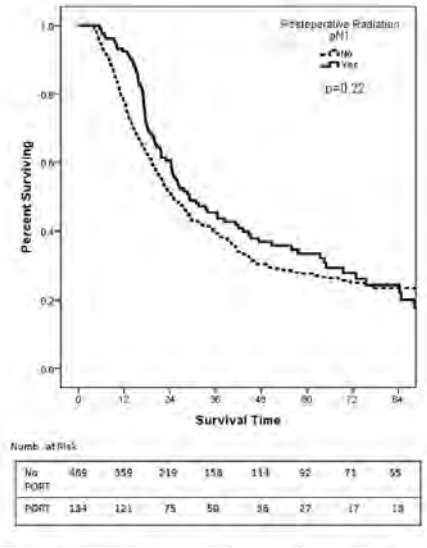
PORT?

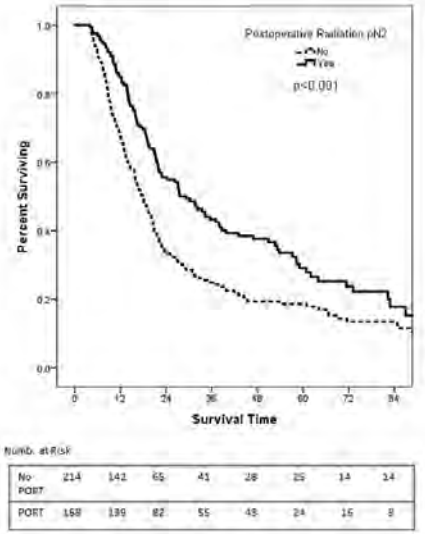
ORIGINAL ARTICLE

Assessing the Impact of Postoperative Radiation Therapy for Completely Resected Limited-Stage Small Cell Lung Cancer Using the National Cancer Database

Chemotherapy, n (%)			<0.001
Yes	1415 (55.1)	431 (96.2)	
No	1154 (44.9)	17 (3.8)	
Pathologic N stage, n (%)			<0.001
N0	1886 (73.4)	146 (32.6)	
N1	469 (18.3)	134 (29.9)	
N2	214 (8.3)	168 (37.5)	







Nouveaux traitements systémiques

Irinotecan

Etoposide and cisplatin versus irinotecan and cisplatin in patients with limited-stage small-cell lung cancer treated with etoposide and cisplatin plus concurrent accelerated hyperfractionated thoracic radiotherapy (JCOG0202): a randomised phase 3 study

Kaoru Kubota, Toyoaki Hida, Satoshi Ishikura, Junki Mizusawa, Makoto Nishio, Masaaki Kawahara, Akira Yokoyama, Fumio Imamura, Koji Takeda, Shunichi Negoro, Masao Harada, Hiroaki Okamoto, Nobuyuki Yamamoto, Tetsu Shinkai, Hiroshi Sakai, Kaoru Matsui, Kazuhiko Nakagawa, Taro Shibata, Nagahiro Saijo, Tomohide Tamura, on behalf of the Japan Clinical Oncology Group

Lancet Oncol 2014; 15: 106–13

Summary

Background Four cycles of etoposide plus cisplatin and accelerated hyperfractionated thoracic radiotherapy (AHTRT) is

- Induction cis – etoposide + HART
- Rando: cis – étoposide versus cis – irinotecan
- UDP-glucuronosyltransferase?

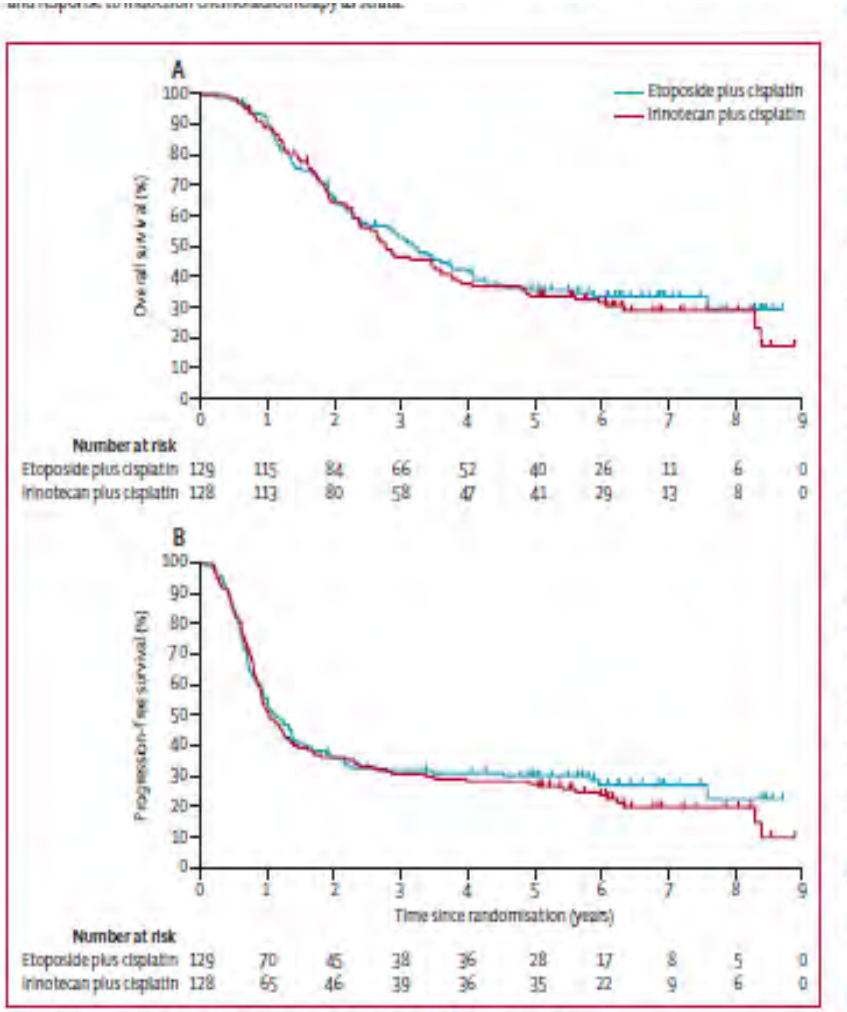


Figure 3: **Overall survival (A) and progression-free survival (B) after randomisation**
*p value from unstratified log-rank test.

Amrubicine

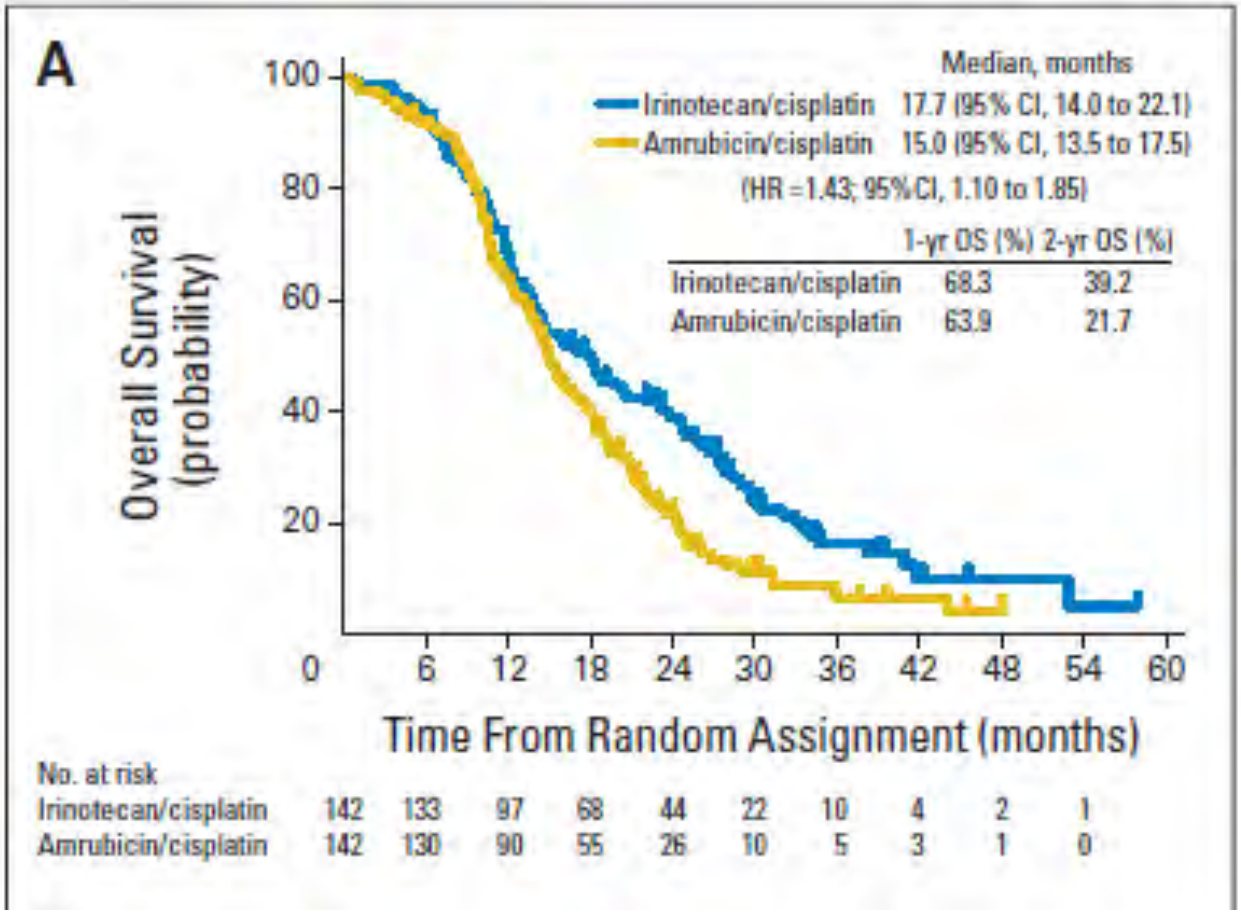
VOLUME 32 · NUMBER 12 · APRIL 20 2014

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Phase III Study Comparing Amrubicin Plus Cisplatin With Irinotecan Plus Cisplatin in the Treatment of Extensive-Disease Small-Cell Lung Cancer: JCOG 0509

Miyako Satouchi, Yoshikazu Kotani, Taro Shibata, Masahiko Ando, Kazuhiko Nakagawa, Nobuyuki Yamamoto, Yukito Ichinose, Yuichiro Ohe, Makoto Nishio, Toyoaki Hida, Koji Takeda, Tatsuo Kimura, Koichi Minato, Akira Yokoyama, Shinji Atagi, Haruhiko Fukuda, Tomohide Tamura, and Nagahiro Saijo


A
Median, months
Irinotecan/cisplatin 17.7 (95% CI, 14.0 to 22.1)
Amrubicin/cisplatin 15.0 (95% CI, 13.5 to 17.5)
(HR = 1.43; 95% CI, 1.10 to 1.85)
1-yr OS (%) 2-yr OS (%)
Irinotecan/cisplatin 68.3 39.2
Amrubicin/cisplatin 63.9 21.7
Overall Survival (probability)
100
80
60
40
20
0
6
12
18
24
30
36
42
48
54
60
Time From Random Assignment (months)
No. at risk
Irinotecan/cisplatin 142 133 97 68 44 22 10 4 2 1
Amrubicin/cisplatin 142 130 90 55 26 10 5 3 1 0

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)

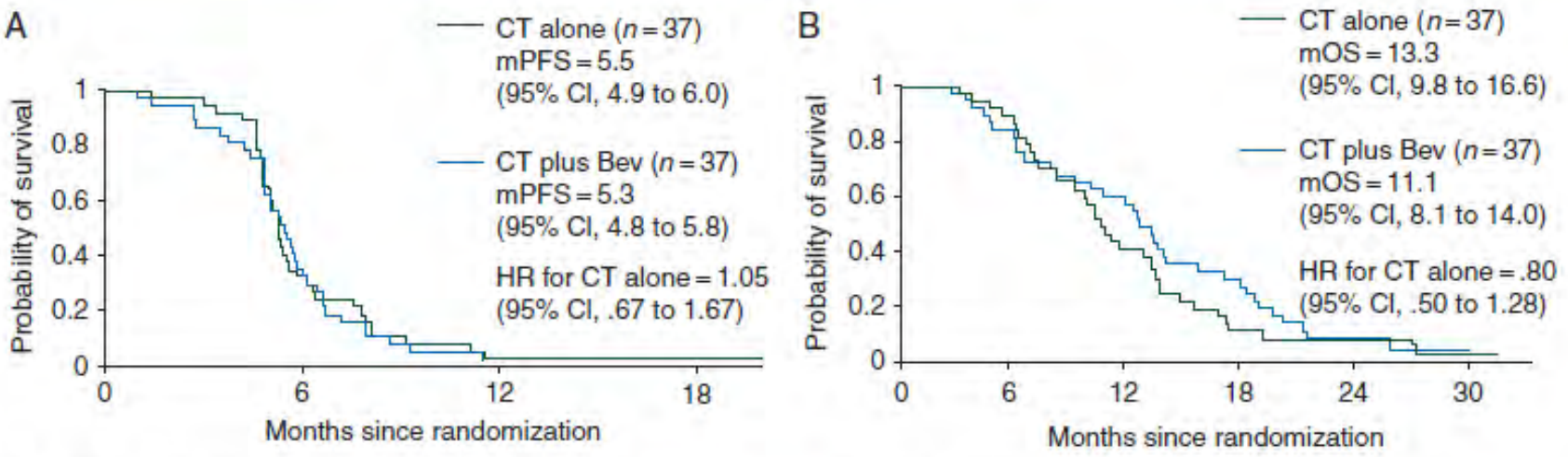


Figure 2. Survival from date of randomization: (a) progression-free survival (PFS); (b) overall survival (OS).

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)

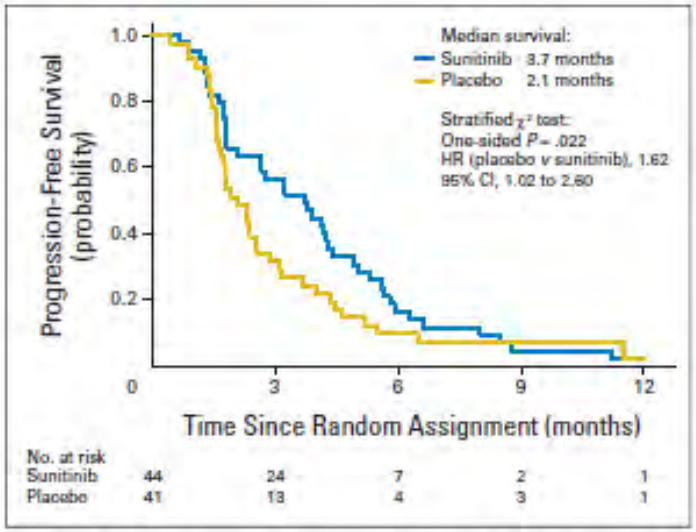


Fig 2. Kaplan-Meier curve for progression-free survival after random assignment to placebo (n = 41) or sunitinib (n = 44). HR, hazard ratio.

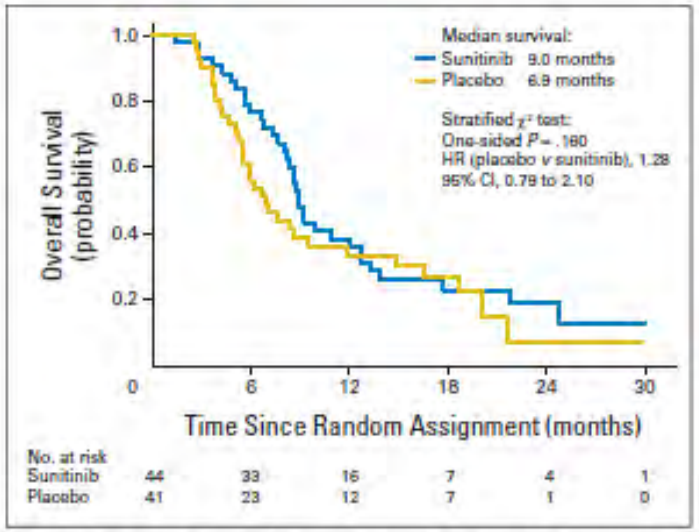


Fig 3. Kaplan-Meier curve for overall survival after random assignment to placebo (n = 41) or sunitinib (n = 44). HR, hazard ratio.

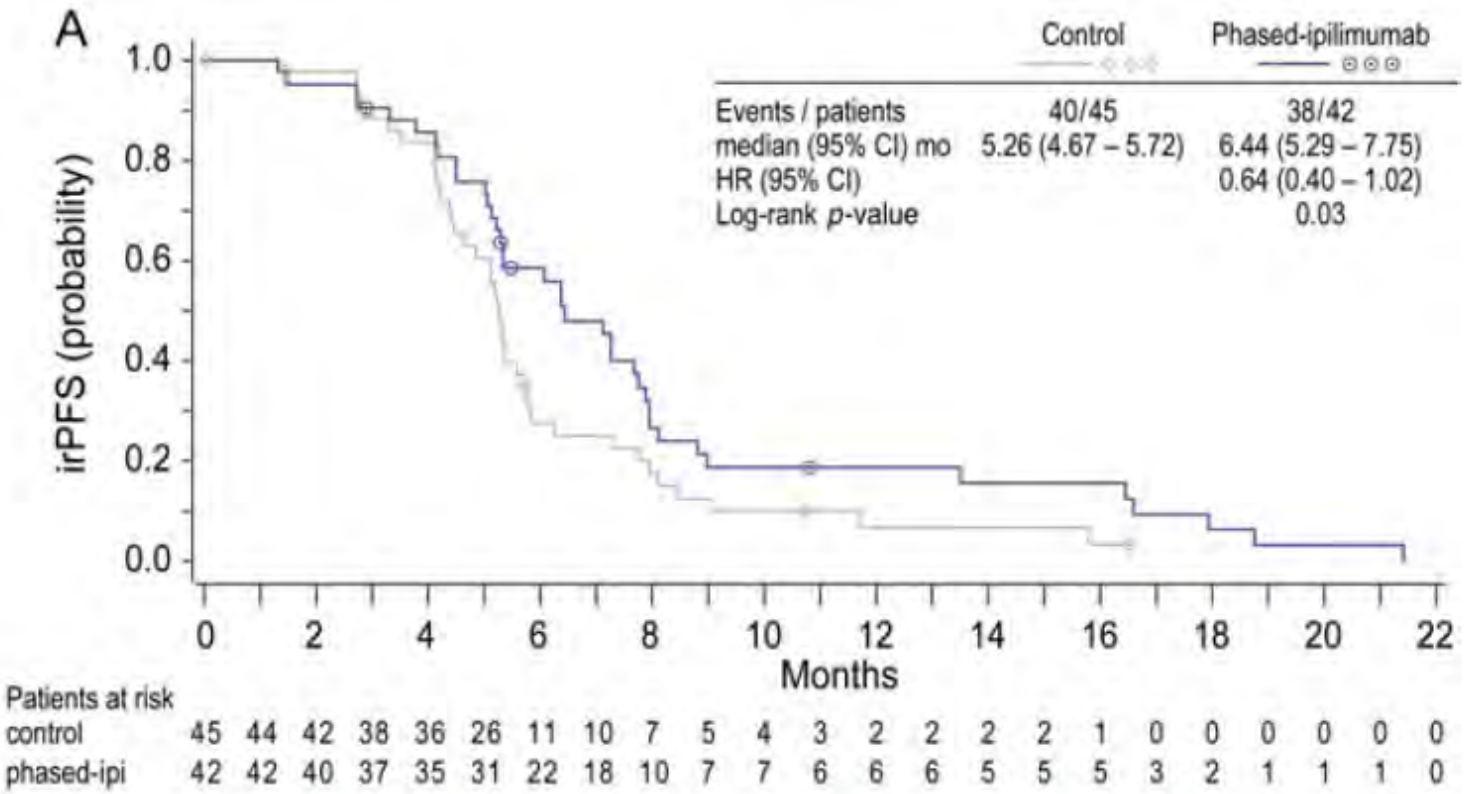
Annals of Oncology 24: 75–83, 2013
doi:10.1093/annonc/mds213
Published online 2 August 2012

Ipilimumab in combination with paclitaxel and carboplatin as first-line therapy in extensive-disease-small-cell lung cancer: results from a randomized, double-blind, multicenter phase 2 trial†

M. Reck[1*], I. Bondarenko[2], A. Luft[3], P. Serwatowski[4], F. Barlesi[5], R. Chacko[6], M. Sebastian[7], H. Lu[8], J. -M. Cuillerot[8] & T. J. Lynch[9]

[1]Department of Thoracic Oncology, Hospital Grosshansdorf, Grosshansdorf, Germany; [2]Clinical Facility, Dnepropetrovsk City Hospital, Dnepropetrovsk, Ukraine; [3]Leningrad Regional Clinical Hospital, St. Petersburg, Russia; [4]Department of Chemotherapy, Specjalistyczny Szpital im., Szczecin, Poland; [5]Faculty of Medicine, Service d'Oncologie Multidisciplinaire & Innovations Thérapeutiques, University of Mediterranée, Assistance Publique Hopitaux de Marseille, Marseille, France; [6]Department of Medical Oncology, Christian Medical College, Vellore, India; [7]Department of Medicine III, Medical Center of the Johannes Gutenberg Universitaetsmedizin, Mainz, Germany; [8]Research and Development, Bristol-Myers Squibb, Wallingford; [9]Yale Cancer Center and Smilow Cancer Hospital, New Haven, USA

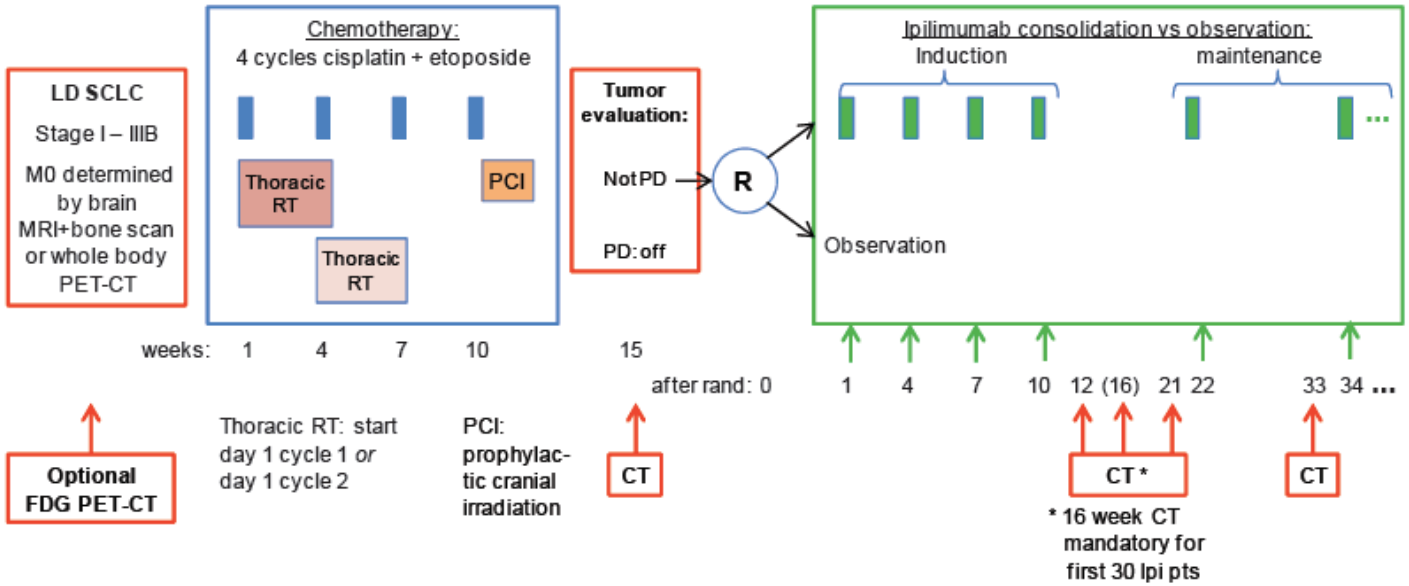
irPFS COLOR KM plot of Phased vs placebo arm in SCLC cohort based on fa01 lock
irPFS COLOR KM plot of Concurrent vs placebo arm in SCLC cohort based on fa01 lock



Ipilimumab

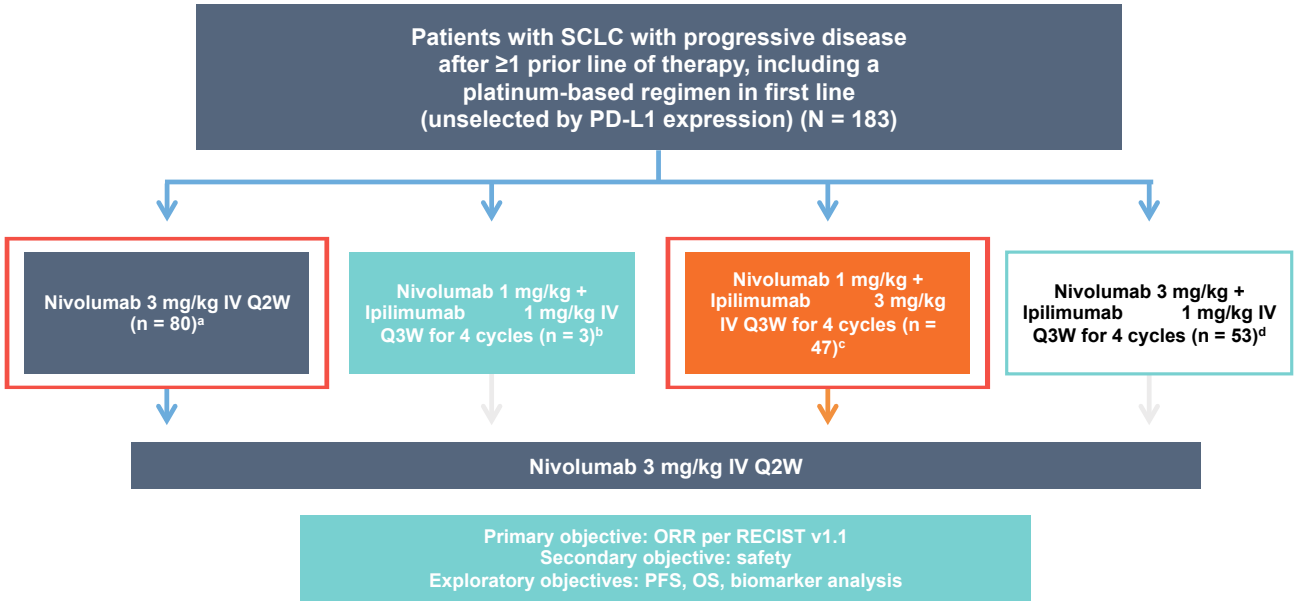
- Blocage du CTL-A4
- Intensification de la réponse à cellules T
- Action synergique possible avec la chimiothérapie (modèle pré-clinique)

Stimuli (ipilimumab - nivolumab)



Methods (cont)

Figure 2. CheckMate 032 (NCT01928394) study design

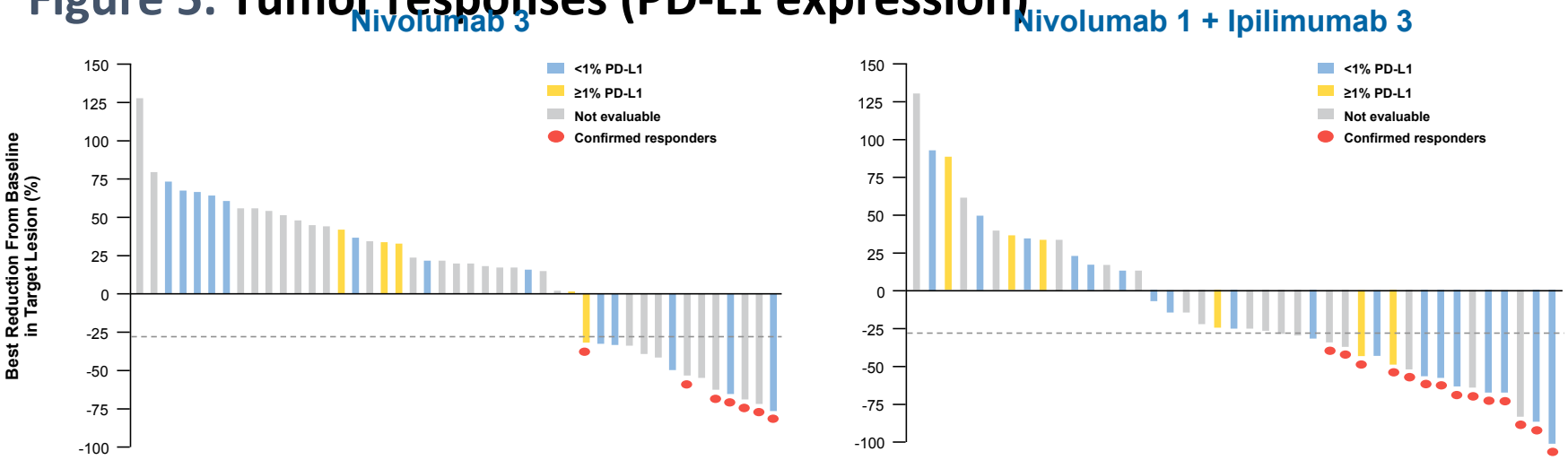


[a]Nivolumab 3: 15 patients in this arm had a follow-up of <6 weeks; follow-up defined as day of first dose to day of database lock; [b]Nivolumab 1 + ipilimumab 1: minimum follow-up of 546 days ; [c]Nivolumab 1 + ipilimumab 3: minimum follow-up of 120 days; [d]Nivolumab 3 + ipilimumab 1: minimum follow-up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

ORR = objective response rate; OS = overall survival.

Results (cont)

Figure 5. Tumor responses (PD-L1 expression)



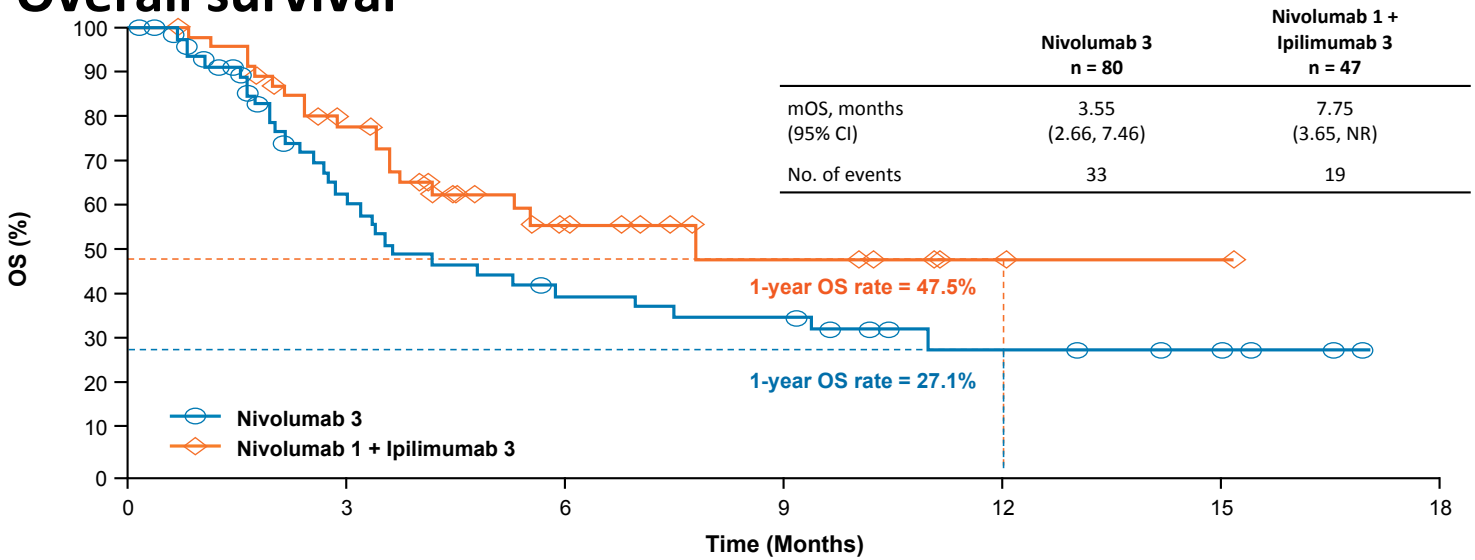
Evaluable samples (52 of 127)	PD-L1 expression level, n (%) <1%	≥1%
Nivolumab 3 (n = 24)	17 (70.8)	7 (29.2)
Nivolumab 1 + Ipilimumab 3 (n = 28)	20 (71.4)	8 (28.6)

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

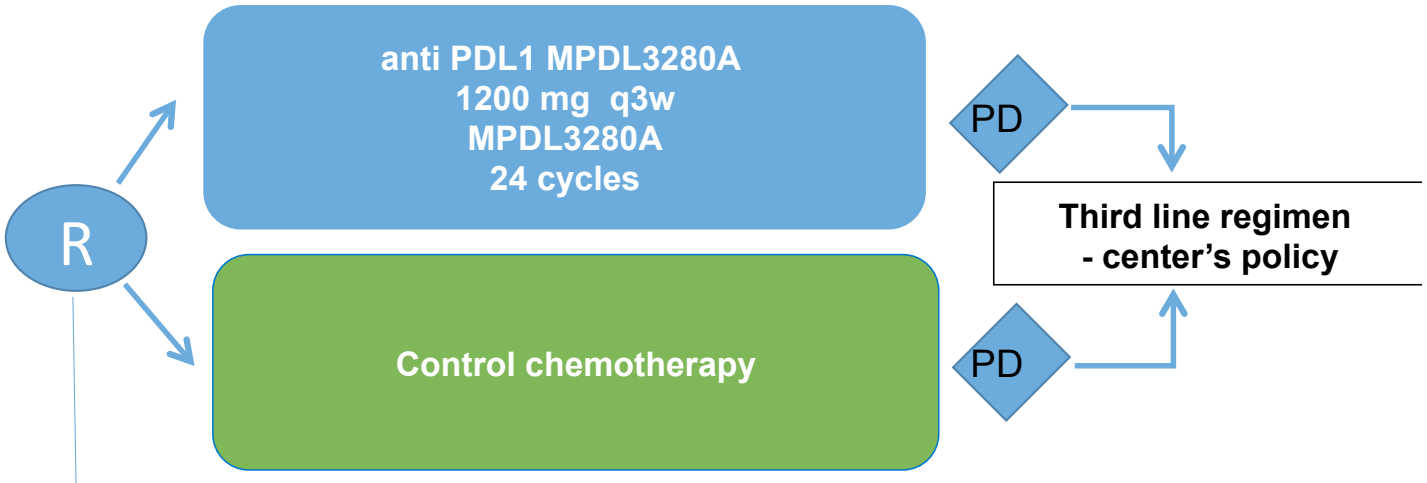
mOS = median OS.

Questions en cours

PDL1 Antibody as SCLC 2nd Therapy :
PAST phase II - IFCT 140X

<u>Eligibility</u>

- SCLC (VALG)
- Pretreatment tissue available
- 1 month corticosteroid washout
- Previous platinum – etoposide treatment for at least 2 cycles
- No evidence of brain metastases during the previous 2 months
- PS 0-2
- Age ≤ 75
- Weight loss < 10%
- Informed consent



<u>Stratification variables</u>

•> 90 days versus < 90 days PFS since end of first line

•Limited versus extensive at diagnosis

•PS

IFCT

Immunothérapie en première ligne?

SYNOPSIS PROTOCOLE IFCT-160Y SCLC
PD1 and CTLA4 ANTIBODIES as FIRST-LINE THERAPY
in Extensive–SCLC

CODE	IFCT-160Y
PRINCIPE INVESTIGATOR	Pr Jean-Louis PUJOL, CHU Arnaud de Villeneuve - Montpellier
SPONSOR	Intergroupe Francophone de Cancérologie Thoracique (IFCT) 10 rue de la Grange-Batelière, 75009 PARIS
TITLE	A single arm phase IIa study to evaluate immunotherapy (nivolumab + ipilimumab) in chemonaive patients with extensive small cell lung cancer.
TRIAL DESIGN	Multicenter, open label, single arm phase IIa study