Cancers à petites cellules: que faire en cas de rechute ?

Cours du G.O.L.F.

Limoges, 21 septembre 2017

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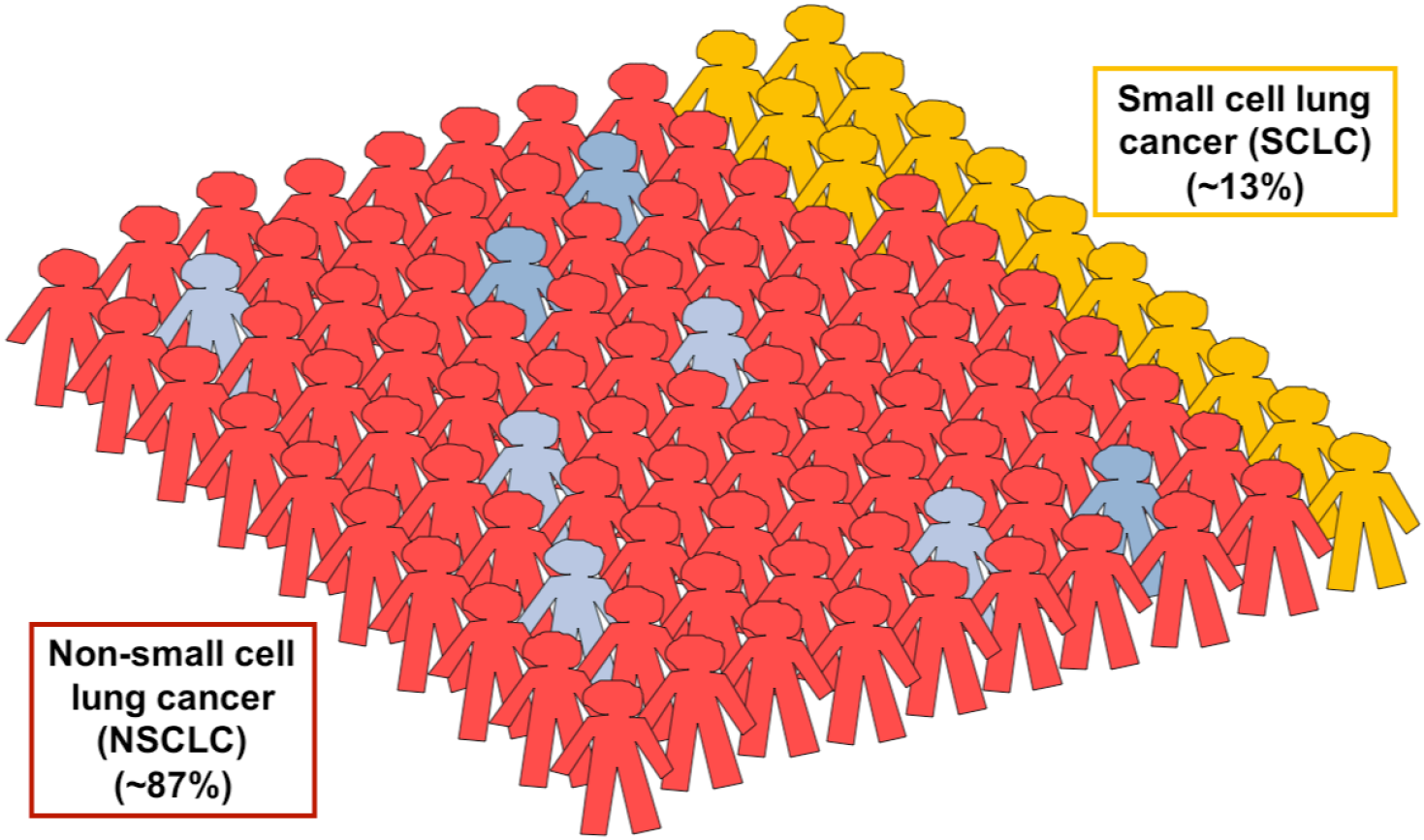
Liens d'intérêt

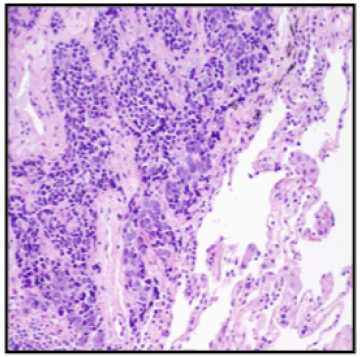
- Abbvie
- Bristol Myers Squibb
- Merck
- Stemcentrx

Une maladie de plus en plus rare…



Govindan R et al, J Clin Oncol 2006

…mais toujours aussi grave !



- Pathologie extrêmement agressive
- Faibles taux de survie

- Initialement chimio- et radio-sensible
- Mais émergence rapide de résistances

- **Quelles options thérapeutiques aujourd'hui ?**
- **Quels espoirs thérapeutiques demain?**

Agenda

- Chimiothérapie
- Thérapie ciblée
- Immunothérapie

Agenda

- Chimiothérapie
- Thérapie ciblée
- Immunothérapie

Probabilité de réponse en 2ème ligne

- Réponse au traitement de 1ère ligne
- Délai entre fin 1ère ligne et rechute

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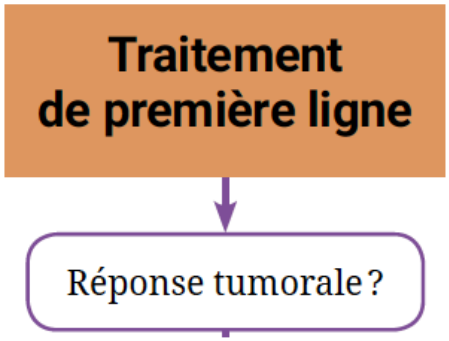

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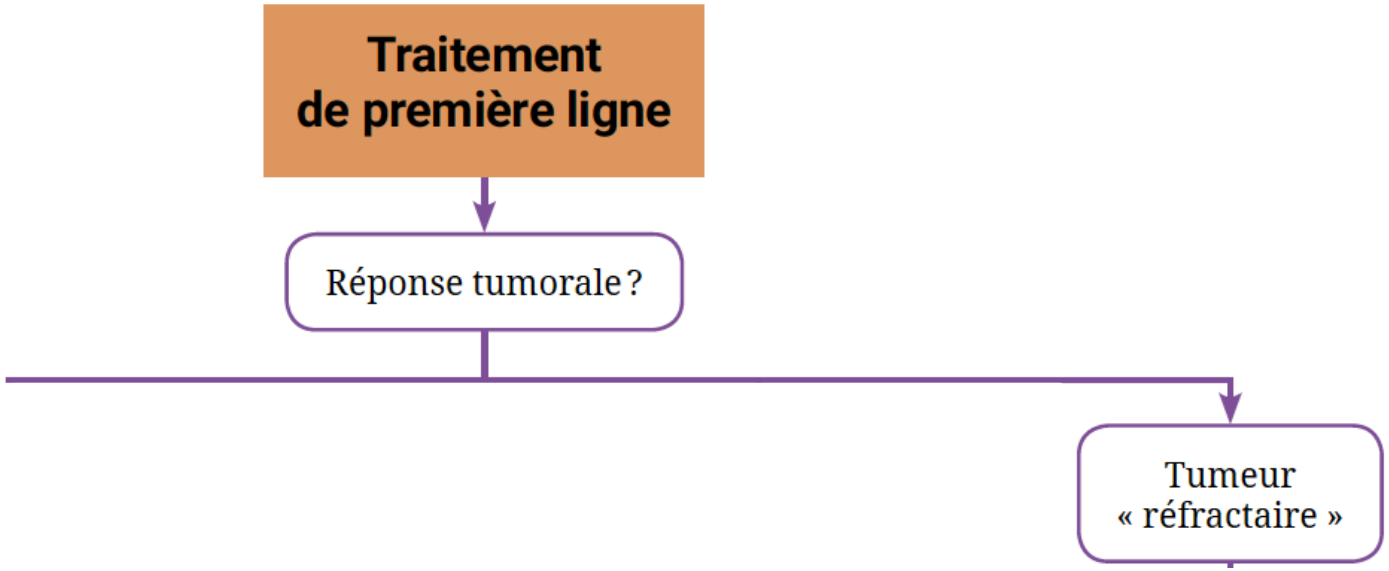

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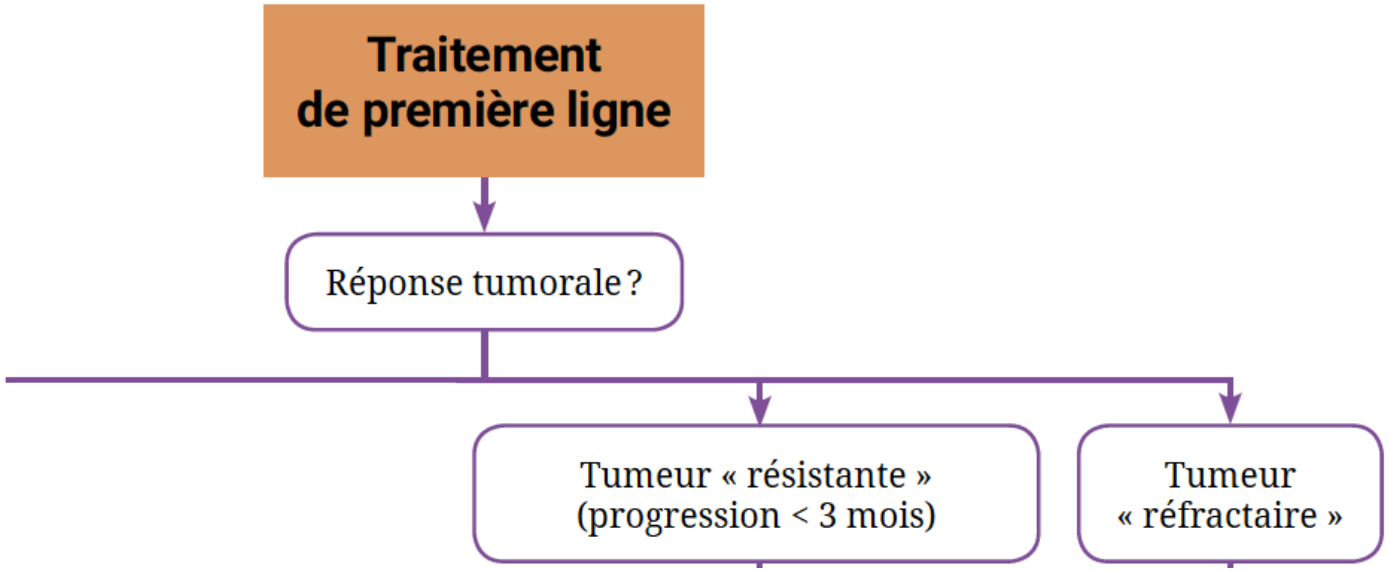

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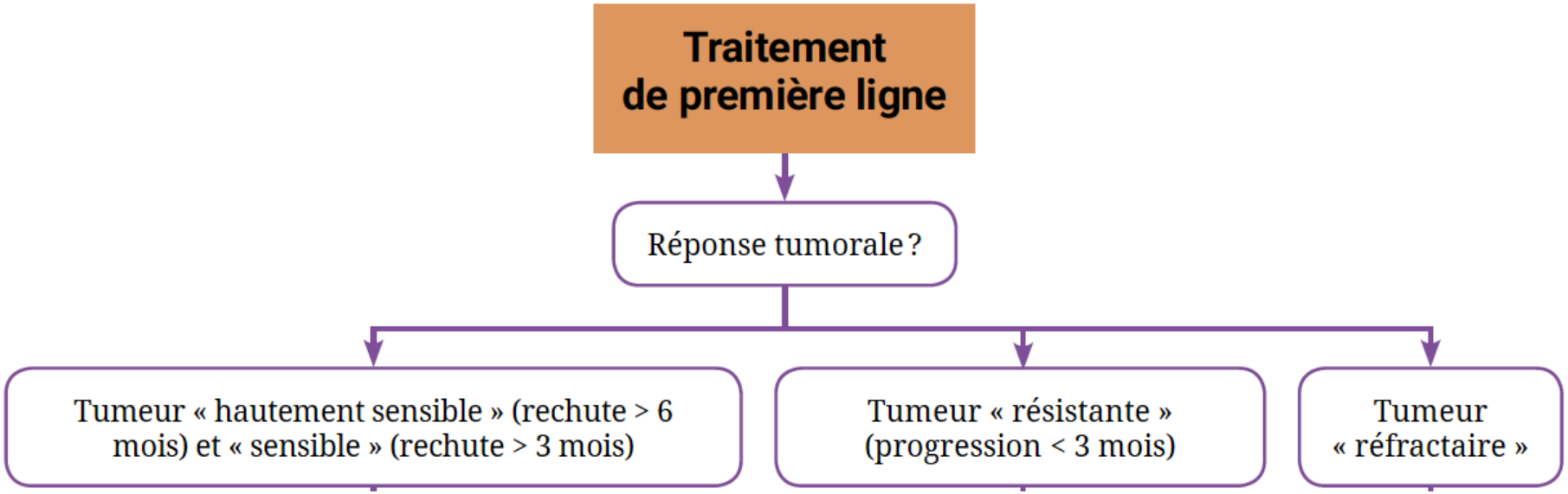


Topotecan PO

Critères d'inclusion:

- CBPC prouvé
- Rechute après Cx 1ère ligne
- Inéligibilité à Cx 2ème ligne
- Age ≥18 ans
- ECOG PS 0–2
- Fonctions hématologiques, rénales et hépatiques normales

(n=141)

R

Topotecan PO
2,3 mg/m² J1-J5, 21 j

PD

Stratification

- Sexe
- PS: 0-1 vs 2
- Rechute: ≦ 60 jours ou > 60 jours
- Métastases hépatiques

Soins de support exclusifs

PD

Objectif principal: Survie globale

Objectif secondaires

- Taux de réponse, temps jusqu'à progression
- Symptômes, qualité de vie
- Toxicité

O'Brien MER et al. J Clin Oncol 2006

Topotecan PO

Characteristic	BSC (n = 70)		Topotecan (n = 71)	
	No. of Patients	%	No. of Patients	%
Sex				
Male	51	73	52	73
Female	19	27	19	27
Age, years				
Mean	58.6		59.8	
SD	8.2		9.0	
Range	43-79		37-76	
Performance status				
0	6	9	8	11
1	41	59	44	62
2	23	33	19	27
Disease stage				
Limited	27	39	23	32
Extensive	43	61	48	68
Maximum lesion diameter, cm				
< 2	2	3	7	10
2- < 5	25	36	34	48
5-10	32	46	19	27
> 10	5	7	2	3
Not measurable	6	9	9	13

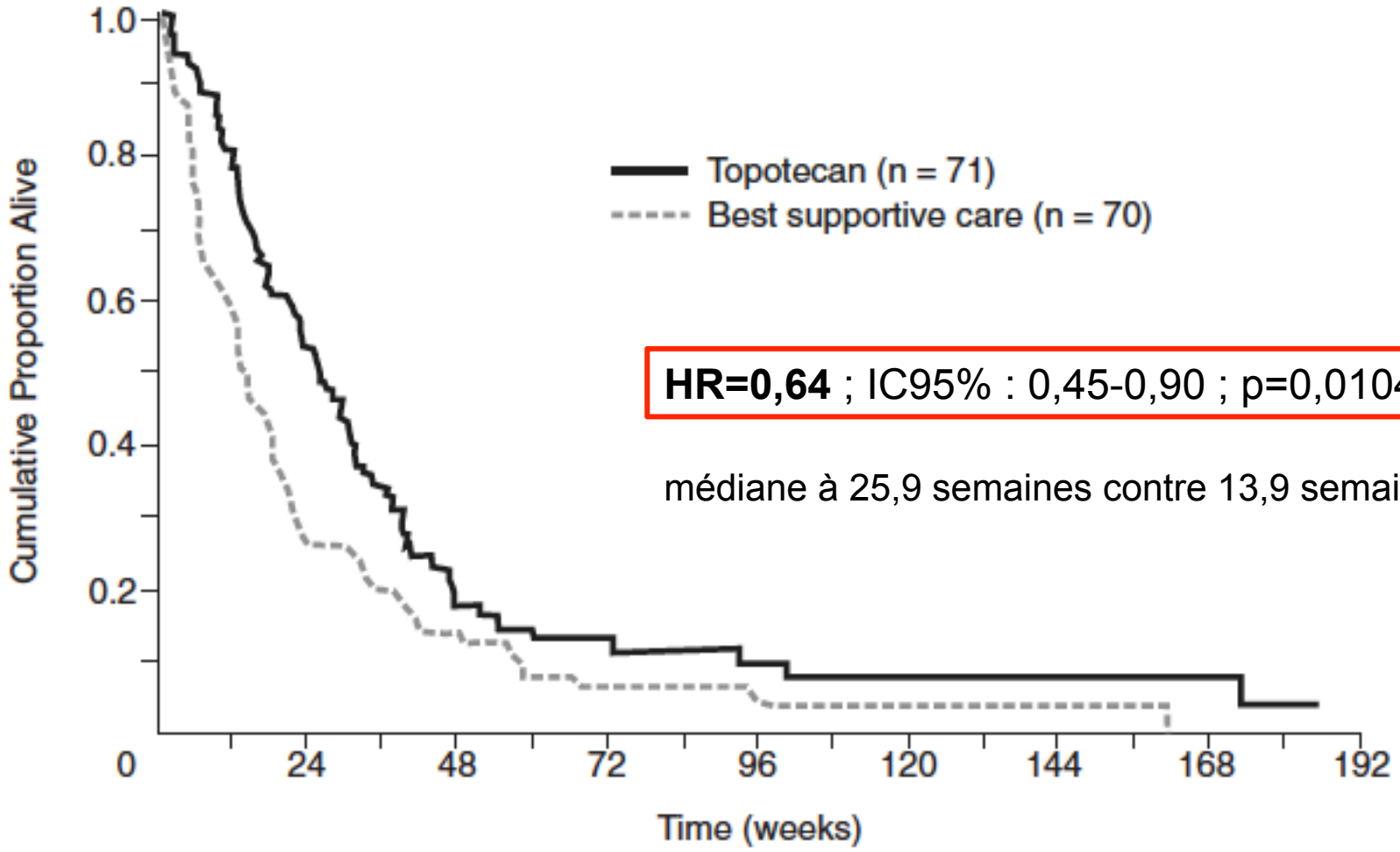
O'Brien MER et al. J Clin Oncol 2006

Topotecan PO

Characteristic	BSC (n = 70)		Topotecan (n = 71)	
	No. of Patients	%	No. of Patients	%
Prior cancer therapy*				
Any prior therapy	48	69	46	65
Radiotherapy	34	49	38	54
Surgery	20	29	18	25
Immunotherapy	4	6	0	
Liver metastases				
No	56	80	51	72
Yes	14	20	20	28
Treatment-free interval, days†				
≤ 60	20	29	22	31
> 60	50	71	49	69
≤ 90	35	50	41	58
> 90	35	50	30	42
Median	90		84	
Range	14 to 1,409		34-1,996	

O'Brien MER et al. J Clin Oncol 2006

Topotecan PO

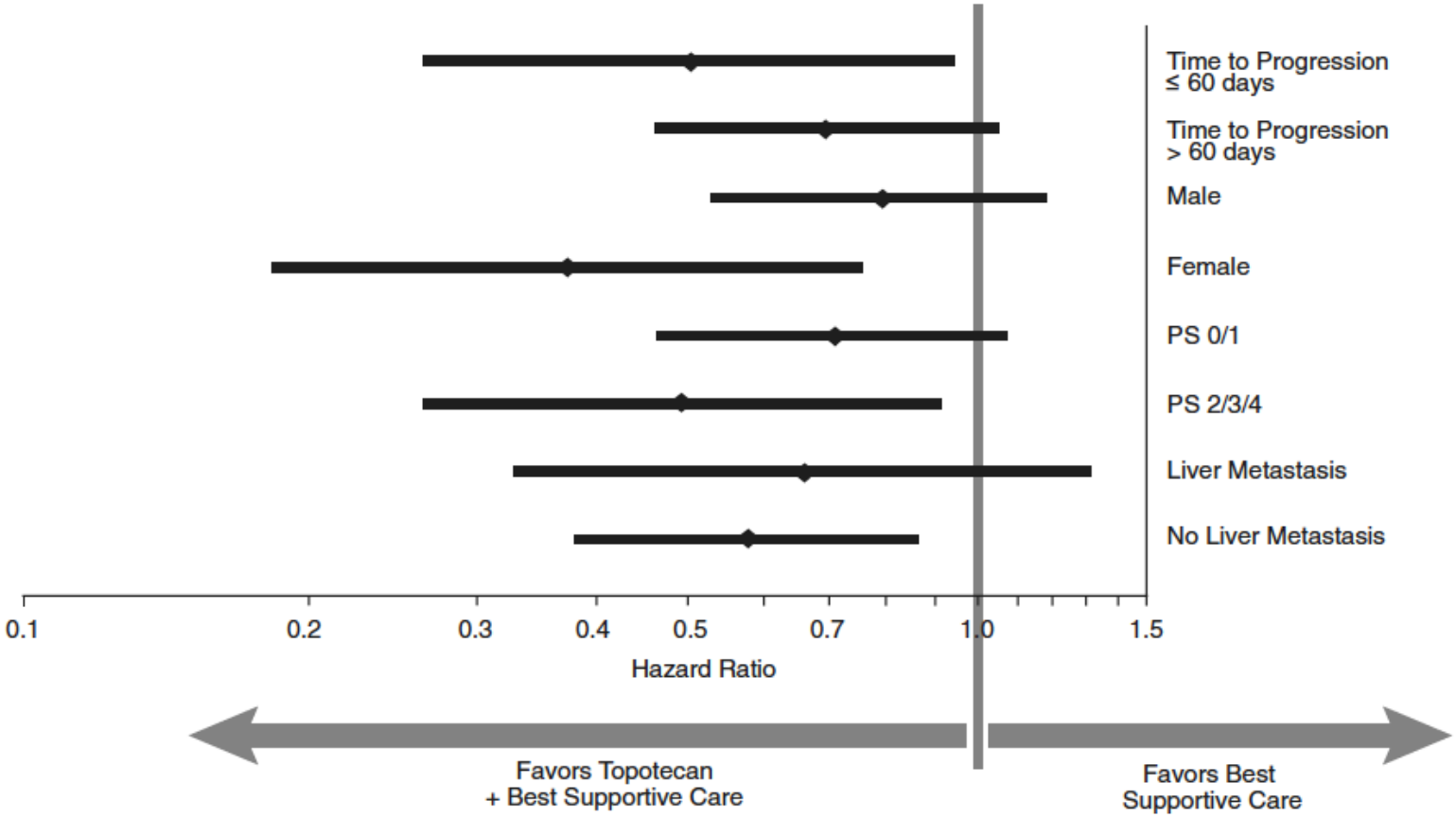


HR=0,64 ; IC95% : 0,45-0,90 ; p=0,0104

médiane à 25,9 semaines contre 13,9 semaines

O'Brien MER et al. J Clin Oncol 2006

Topotecan PO



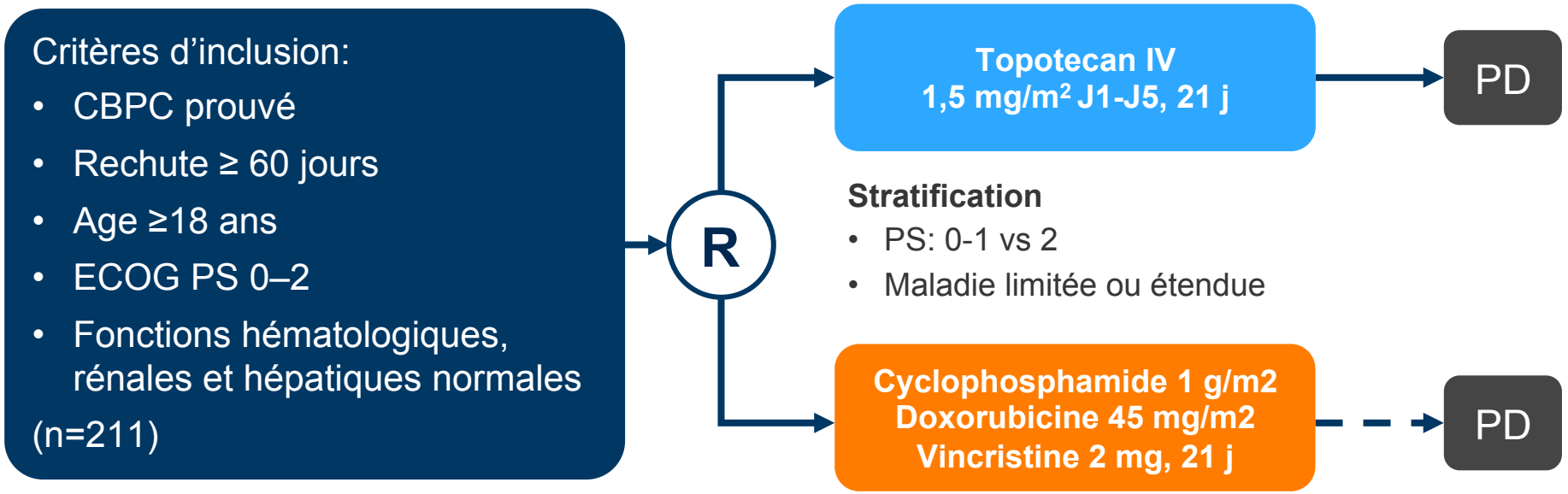
O'Brien MER et al. J Clin Oncol 2006

Topotecan PO

- Taux de réponse = 7%, taux de contrôle = 51%
- Dégradation plus lente de la qualité de vie
- Meilleur contrôle des symptômes
- Toxicité gérable

O'Brien MER et al. J Clin Oncol 2006

Topotecan IV



Objectif principal: **Taux de réponse (revue indépendante)**

Objectif secondaires

- Temps jusqu'à progression, durée de réponse
- Survie globale
- Contrôle des symptômes

Von Pawel J et al. J Clin Oncol 1999

Topotecan IV

Response to Treatment	Intent-to-Treat			
	Topotecan (n = 107)		CAV (n = 104)	
	No.	%	No.	%
Responders				
Complete response	0	0.0	1	1.0
Partial response	26	24.3	18	17.3
Total	26	24.3	19	18.3
95% CI	16.2-32.4		10.8-25.7	
Nonresponders				
Stable disease	21	19.6	12	11.5
Progressive disease	49	45.8	55	52.9
Not assessable	11	10.3	18	17.3
Total	81	75.7	85	81.7
Total patients	107	100.0	104	100.0

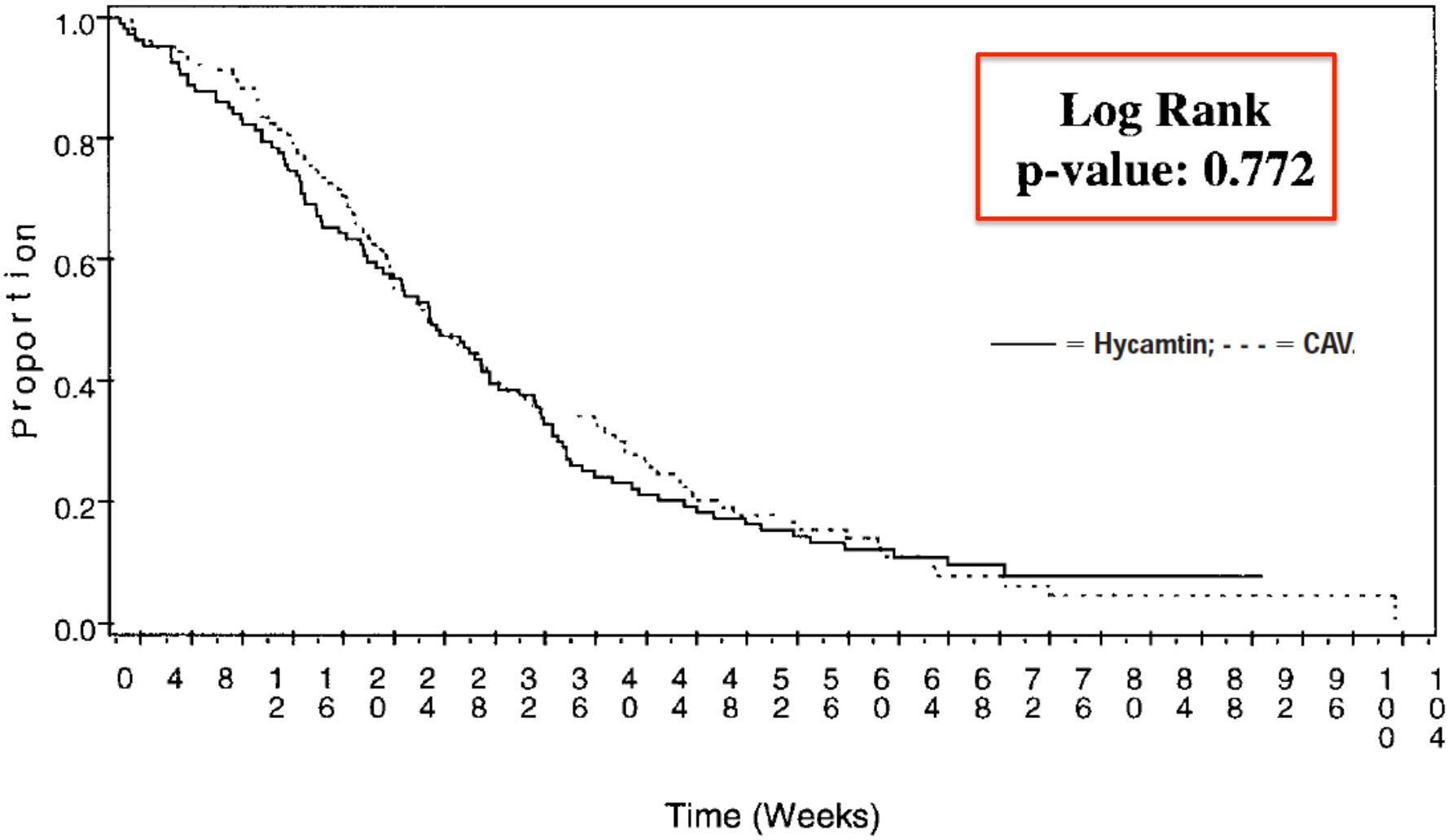
Von Pawel J et al. J Clin Oncol 1999

Topotecan IV

Time-to-Event Parameters, weeks	Topotecan	CAV	*P*
Response duration	n = 26	n = 19	
Median	14.4	15.3	.300
Range	9.4-50.1	8.6-69.9*	
Time to response	n = 26	n = 19	
Median	6.0	6.1	.953
Range	2.4-15.7	5.1-18.1	
Time to progression	n = 107	n = 104	
Median	13.3	12.3	.552
Range	0.4-55.1	0.1-75.3*	
Survival	n = 107	n = 104	
Median	25.0	24.7	.795
Range	0.4-90.7*	1.3-101.3	

Von Pawel J et al. J Clin Oncol 1999

Topotecan IV



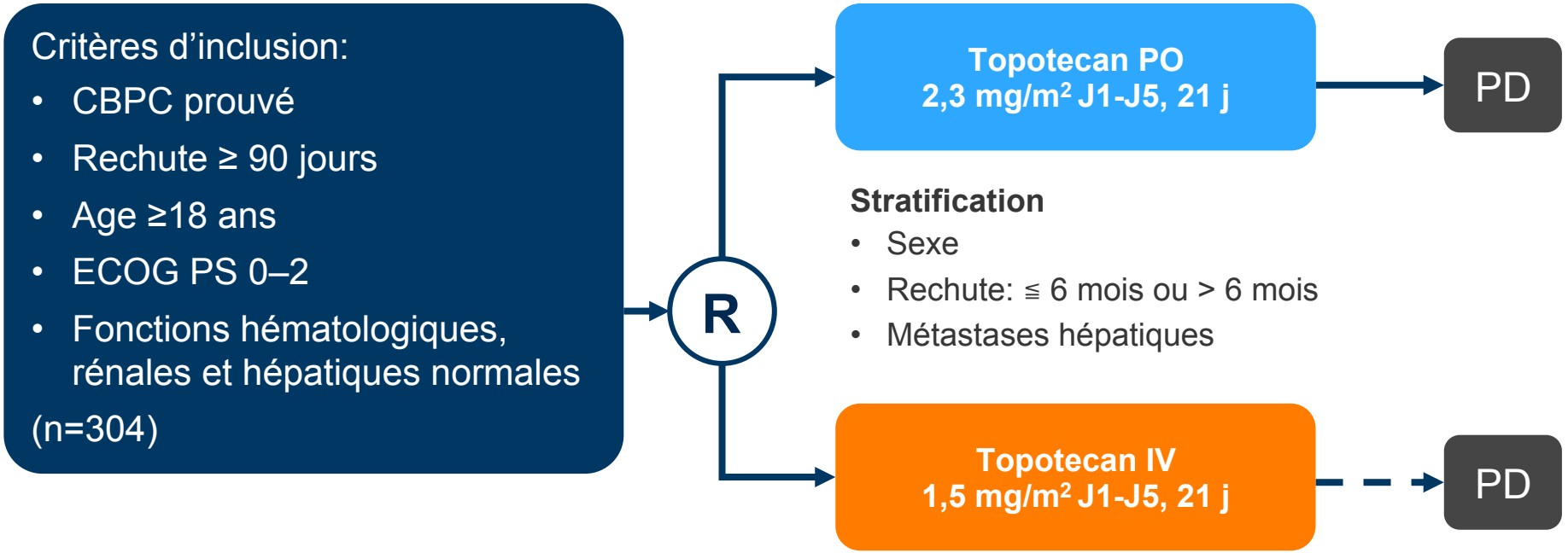
Von Pawel J et al. J Clin Oncol 1999

Topotecan IV

Symptom†	Topotecan (n = 107) n‡	Topotecan (n = 107) n	Topotecan (n = 107) %	CAV (n = 104) n‡	CAV (n = 104) n	CAV (n = 104) %	$\chi^2 P$*
Dyspnea	68	19	27.9	61	4	6.6	.002§
Cough	69	17	24.6	61	9	14.8	.160
Chest pain	44	11	25.0	41	7	17.1	.371
Hemoptysis	15	4	26.7	12	4	33.3	.706
Anorexia	56	18	32.1	57	9	15.8	.042§
Insomnia	57	19	33.3	53	10	18.9	.085
Hoarseness	40	13	32.5	38	5	13.2	.043§
Fatigue	70	16	22.9	65	6	9.2	.032§
Interference with daily activity	67	18	26.9	63	7	11.1	.023§

Von Pawel J et al. J Clin Oncol 1999

Topotecan PO vs IV



Objectif principal: **Taux de réponse (revue indépendante)**

Objectif secondaires

- Temps jusqu'à progression, durée de réponse
- Survie globale
- Qualité de vie et toxicité

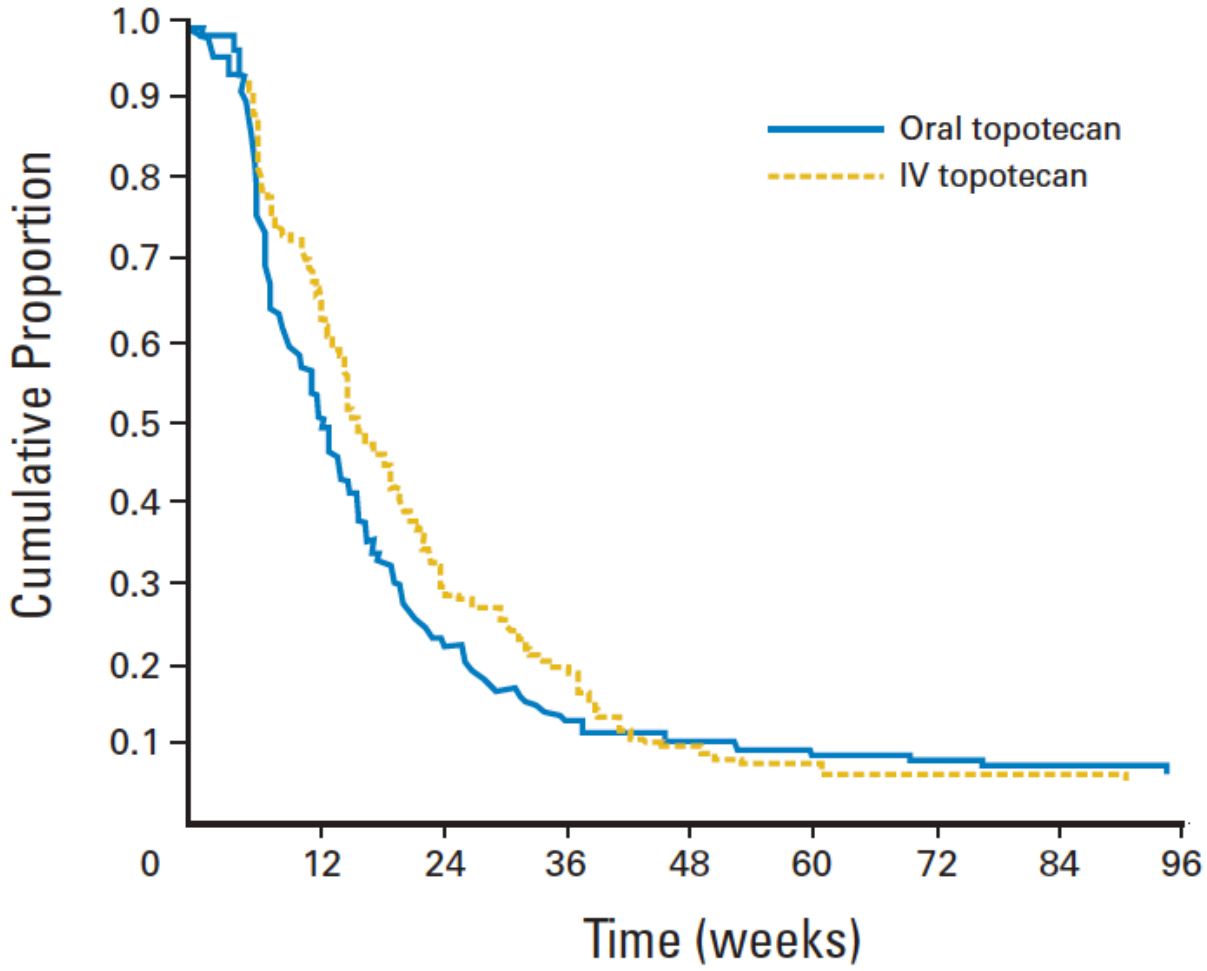
Eckardt JR et al. J Clin Oncol 2007

Topotecan PO vs IV

Response	Oral Topotecan (n = 153) No. of Patients	Oral Topotecan (n = 153) %	IV Topotecan (n = 151) No. of Patients	IV Topotecan (n = 151) %
Responders				
Complete response	2	1.3	0	
Partial response	26	17.0	33	21.9
Overall response*	28	18.3	33	21.9
95% CI, %	12.2 to 24.4		15.3 to 28.5	
Nonresponders				
Stable disease	27	17.6	35	23.2
Progressive disease	78	51.0	65	43.0
Not assessable†	20	13.1	18	11.9

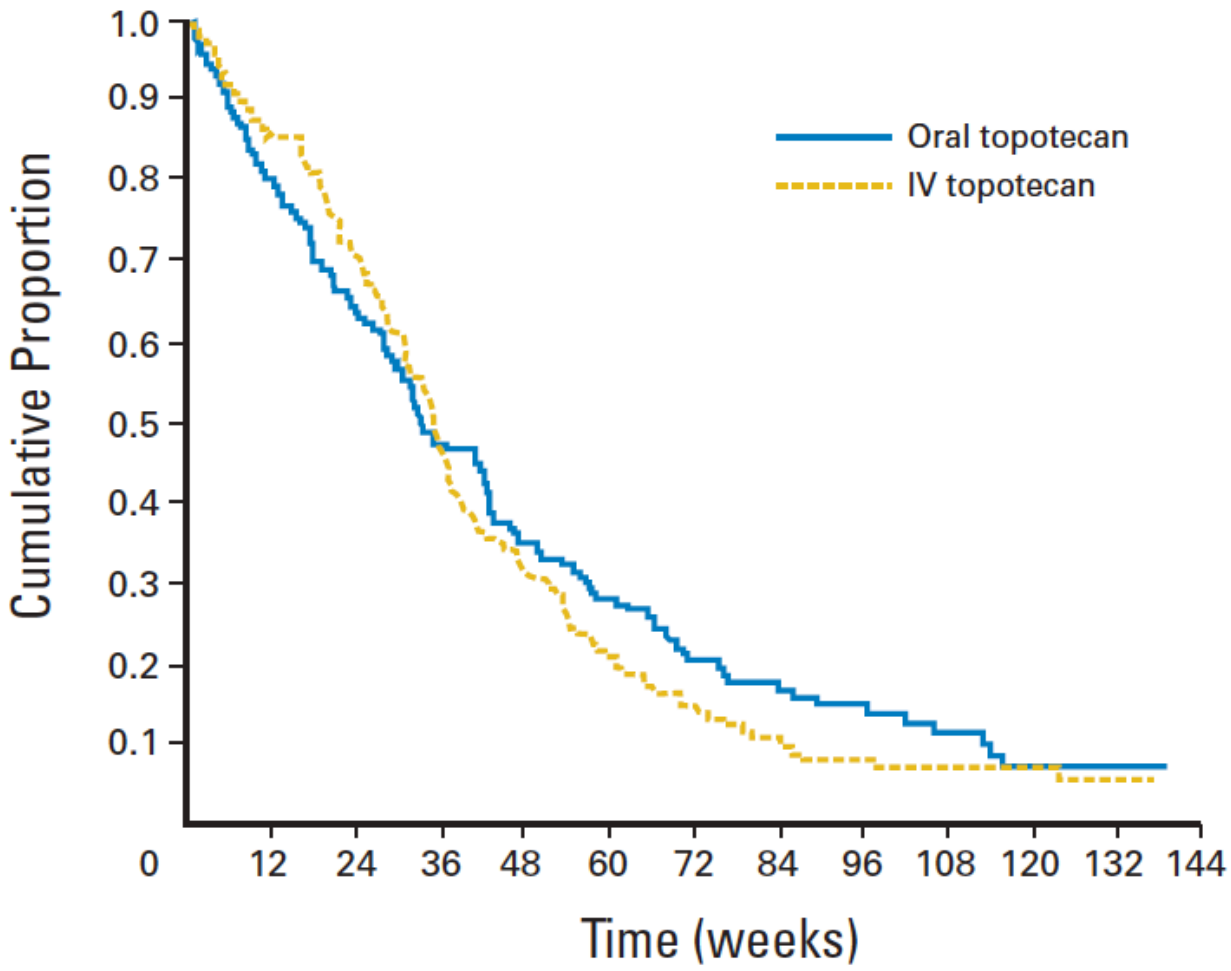
Eckardt JR et al. J Clin Oncol 2007

Topotecan PO vs IV



Eckardt JR et al. J Clin Oncol 2007

Topotecan PO vs IV



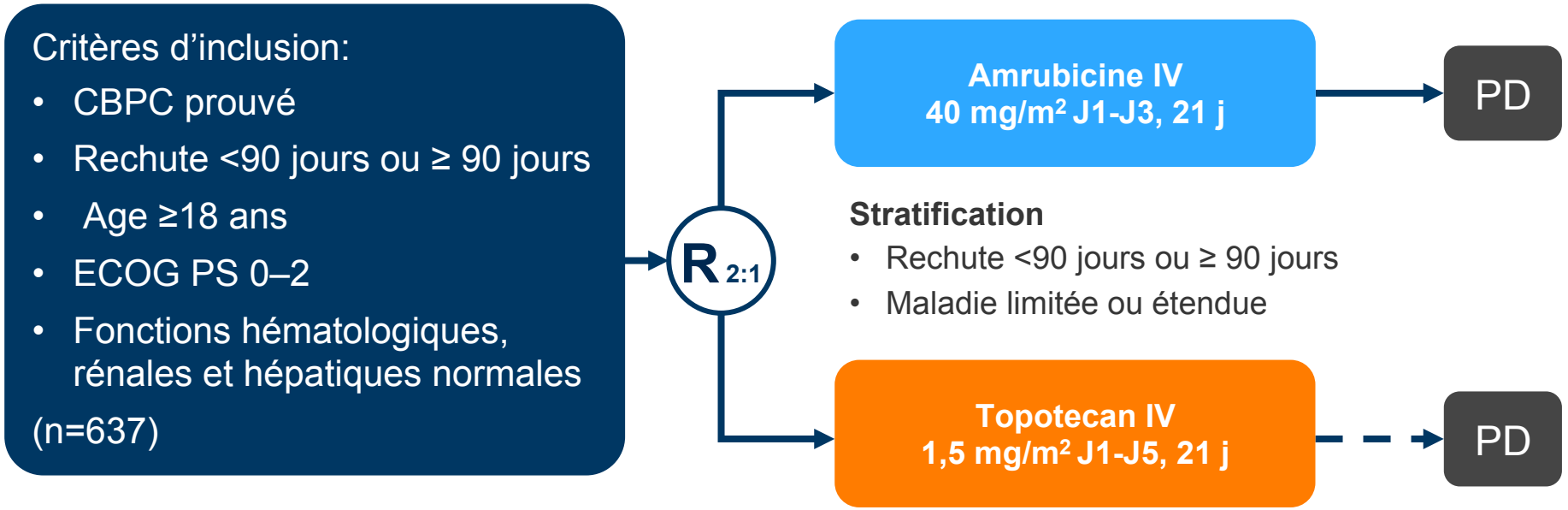
Eckardt JR et al. J Clin Oncol 2007

Topotecan PO vs IV

Toxicity	Oral Topotecan (n = 153)		IV Topotecan (n = 151)	
	No. of Patients	%	No. of Patients	%
Hematologic				
Leukopenia				
Grade 3	64	42.7	74	49.3
Grade 4	34	22.7	39	26.0
Neutropenia				
Grade 3	39	26.2	35	23.6
Grade 4	70	47.0	95	64.2
Thrombocytopenia				
Grade 3	30	20.0	38	25.3
Grade 4	43	28.7	27	18.0
Anemia				
Grade 3	26	17.3	42	28.0
Grade 4	8	5.3	4	2.7

Eckardt JR et al. J Clin Oncol 2007

Amrubicine



Objectif principal: Survie globale

Objectif secondaires

- Survie sans progression
- Taux de réponse, durée de réponse
- Tolérance

Von Pawel J et al. J Clin Oncol 2014

Amrubicine

Characteristic	Amrubicin (n = 424) No.	%	Topotecan (n = 213) No.	%
Age, years				
Median	62		61	
Range	22-81		30-81	
≥ 65	169	39.9	74	34.7
≥ 75	32	7.5	12	5.6
Male sex	244	57.5	127	59.6
ECOG PS				
0	126	29.7	72	33.8
1	289	68.2	137	64.3
2	9	2.1	4	1.9
Actual disease stage				
Limited	53	12.5	26	12.2
Extensive	371	87.5	187	87.8
Time from SCLC diagnosis, months				
Median	8.4		8.4	
Range	1.2-108		1.6-49.6	
Smoking status				
Current	126	29.7	49	23.0
Former	253	59.7	140	65.7
Never	45	10.6	24	11.3

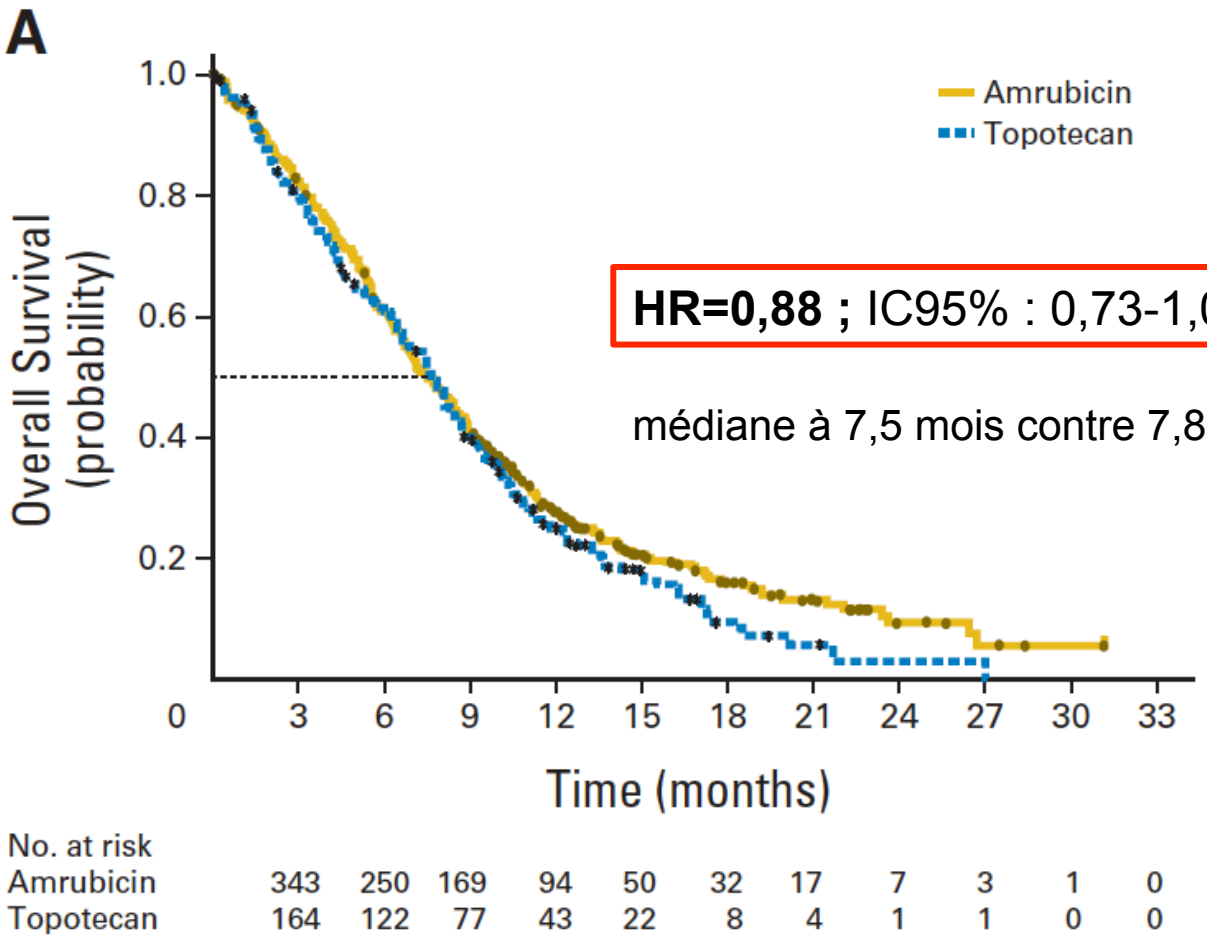
Von Pawel J et al. J Clin Oncol 2014

Amrubicine

Characteristic	Amrubicin (n = 424) No.	%	Topotecan (n = 213) No.	%
First-line chemotherapy				
Median No. of cycles	6		5	
Response				
CR	54	12.7	33	15.5
PR	239	56.4	105	49.3
SD	84	19.8	49	23.0
PD	47	11.1	25	11.7
Missing	0	0.0	1	0.5
Prior radiotherapy	200	47.2	106	49.8
Response to prior first-line therapy				
Sensitive	225	53.1	117	54.9
Refractory	199	46.9	96	45.1
Time from end of first-line treatment to PD, days				
Median	96.0		107.0	
< 90	197	46.5	93	43.7
≥ 90	227	53.5	120	56.3

Von Pawel J et al. J Clin Oncol 2014

Amrubicine



HR=0,88 ; IC95% : 0,73-1,06 ; p=0,17

médiane à 7,5 mois contre 7,8 mois

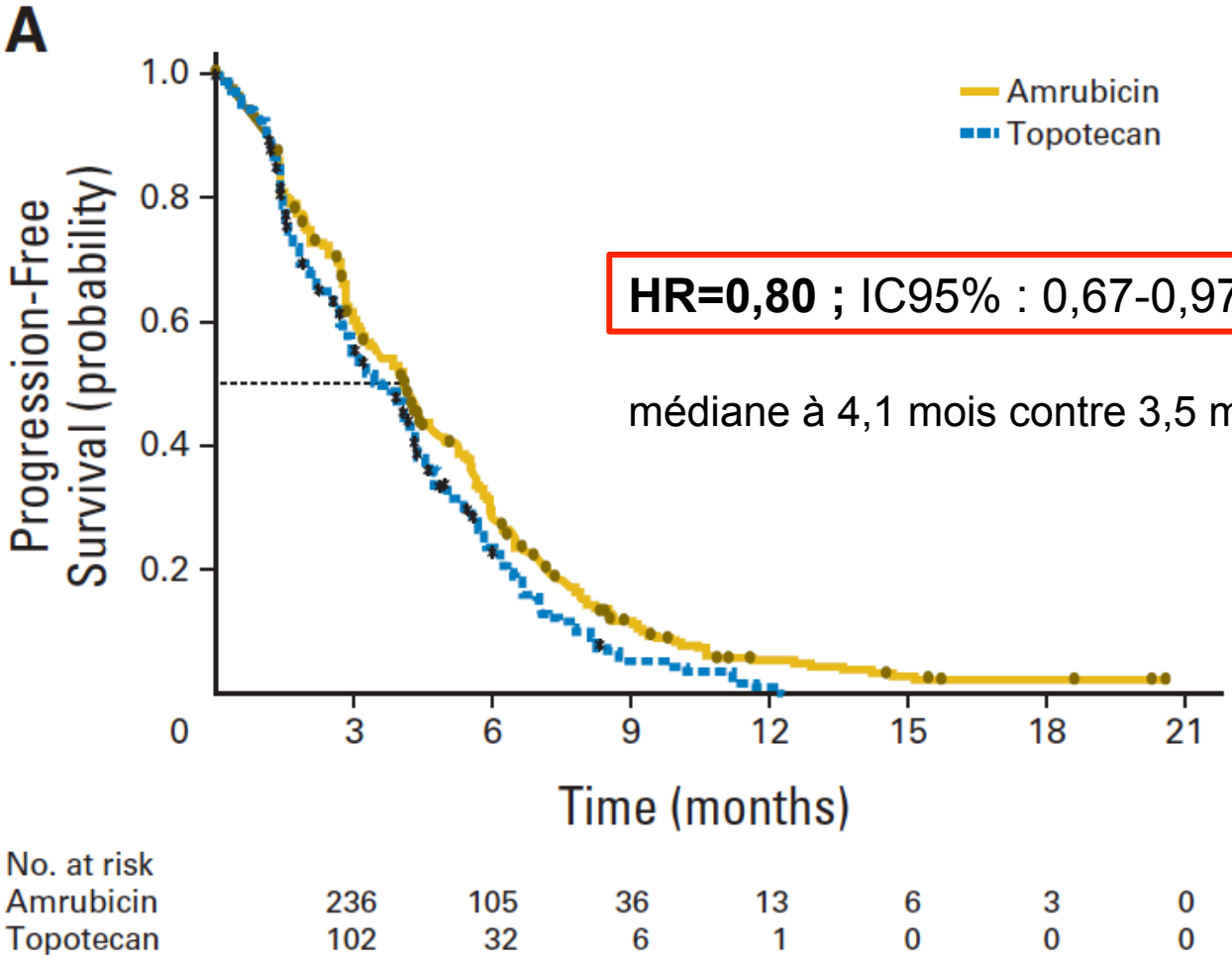
Von Pawel J et al. J Clin Oncol 2014

Amrubicine

Efficacy Parameter	Amrubicin (n = 424)		Topotecan (n = 213)	
	No.	%	No.	%
ORR (CR or PR)	132	31.1	36	16.9
CR	7	1.7	1	0.5
PR	125	29.5	35	16.4
Response duration, months	4.8		4.2	
SD	165	38.9	95	44.6
PD	70	16.5	44	20.7

Von Pawel J et al. J Clin Oncol 2014

Amrubicine

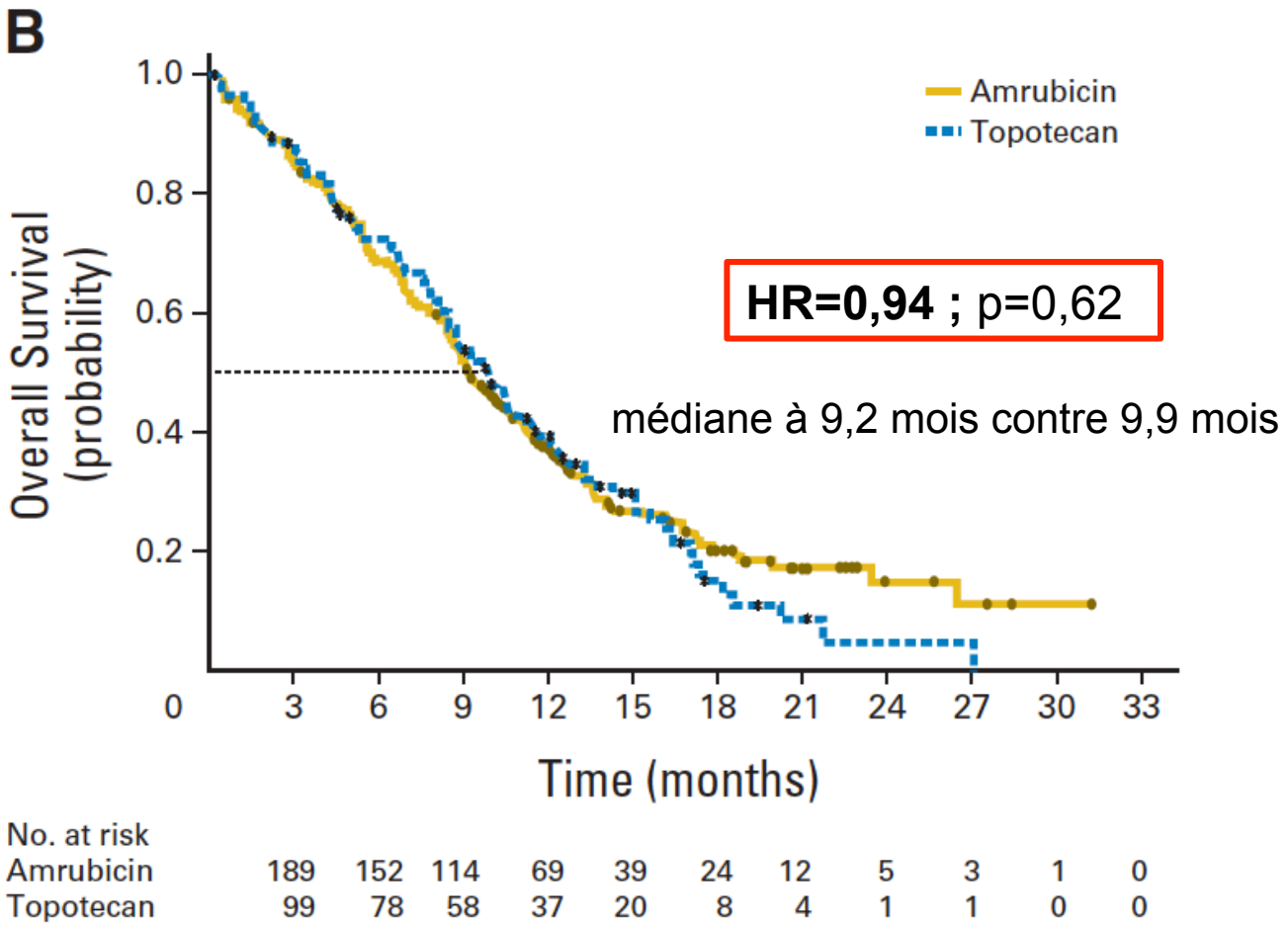


HR=0,80 ; IC95% : 0,67-0,97 ; p=0,018

médiane à 4,1 mois contre 3,5 mois

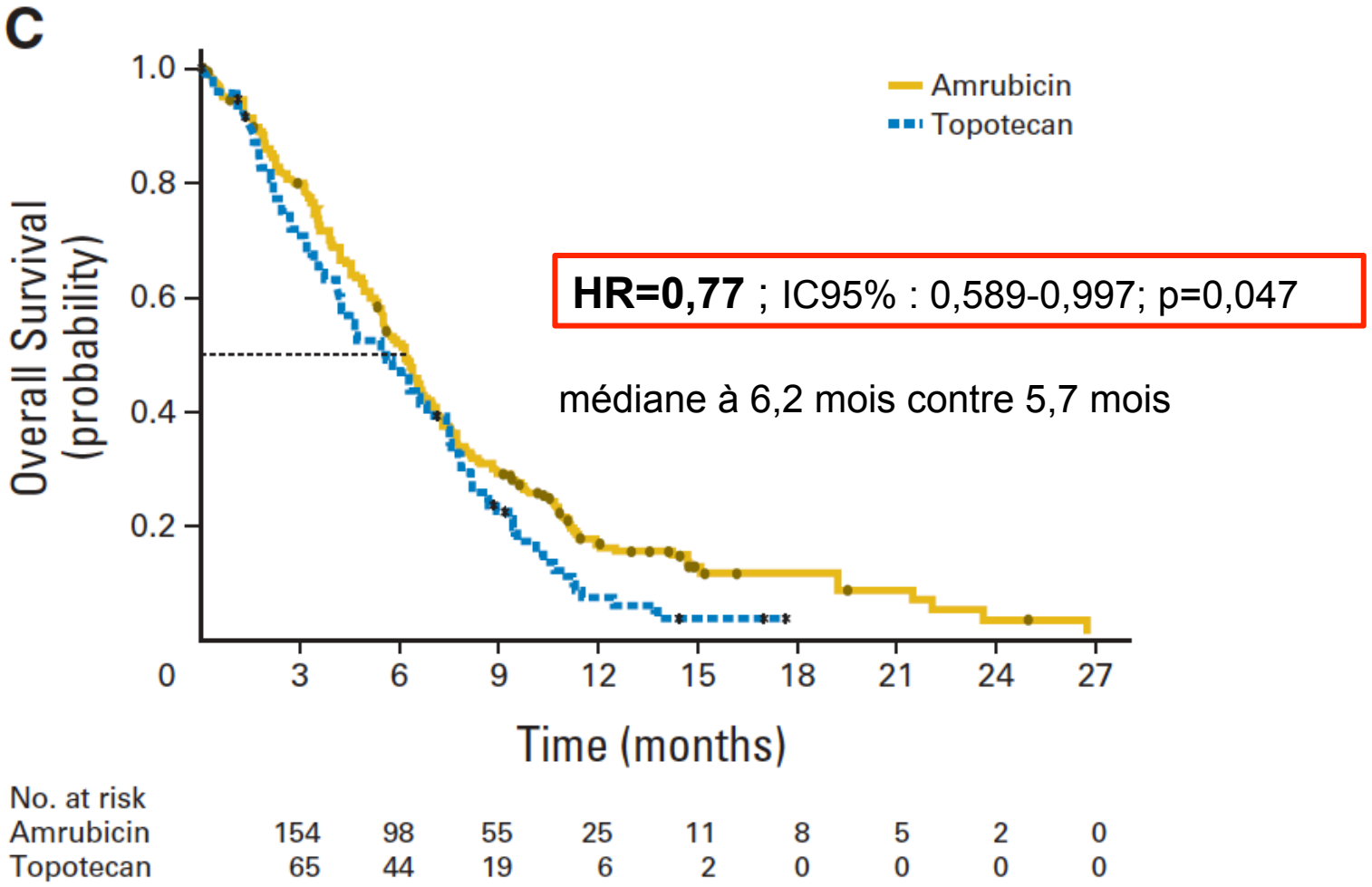
Von Pawel J et al. J Clin Oncol 2014

Amrubicine: CPC sensible



Von Pawel J et al. J Clin Oncol 2014

Amrubicine: CPC résistant/réfractaire



HR=0,77 ; IC95% : 0,589-0,997; p=0,047

médiane à 6,2 mois contre 5,7 mois

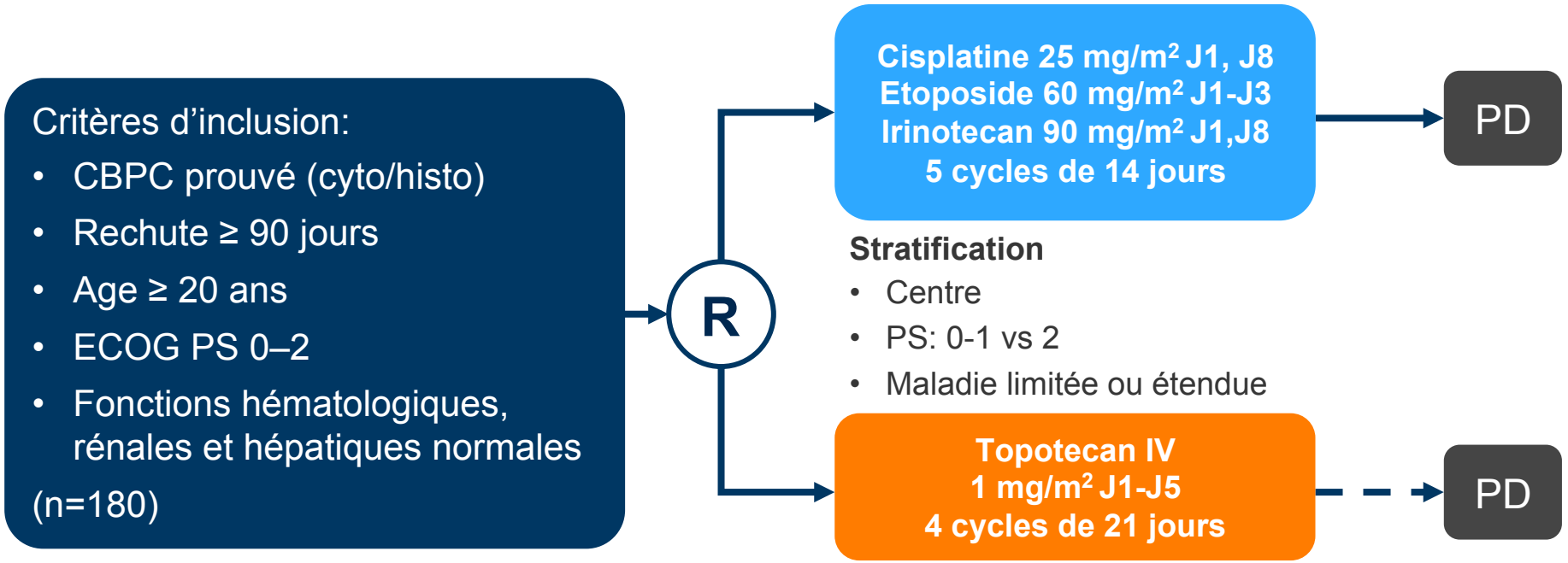
Von Pawel J et al. J Clin Oncol 2014

Amrubicine

AE	Amrubicin (n = 408) No.	%	Topotecan (n = 197) No.	%	*P*
Hematologic					
Anemia	65	15.9	60	30.5	< .001
Febrile neutropenia	41	10.0	6	3.0	.003
Leukopenia	62	15.2	43	21.8	.044
Neutropenia	169	41.4	106	53.8	.004
Thrombocytopenia	86	21.1	107	54.3	< .001
Nonhematologic					
Dyspnea	18	4.4	13	6.6	.253
Fatigue	43	10.5	24	12.2	.546
Hyponatremia	21	5.1	11	5.6	.822
Infections	64	15.7	19	9.6	.430
Pneumonia	27	6.6	6	3.0	.070

Von Pawel J et al. J Clin Oncol 2014

Triplet de chimiothérapie



Objectif principal: Survie globale

Objectif secondaires

- Survie sans progression
- Taux de réponse
- Tolérance

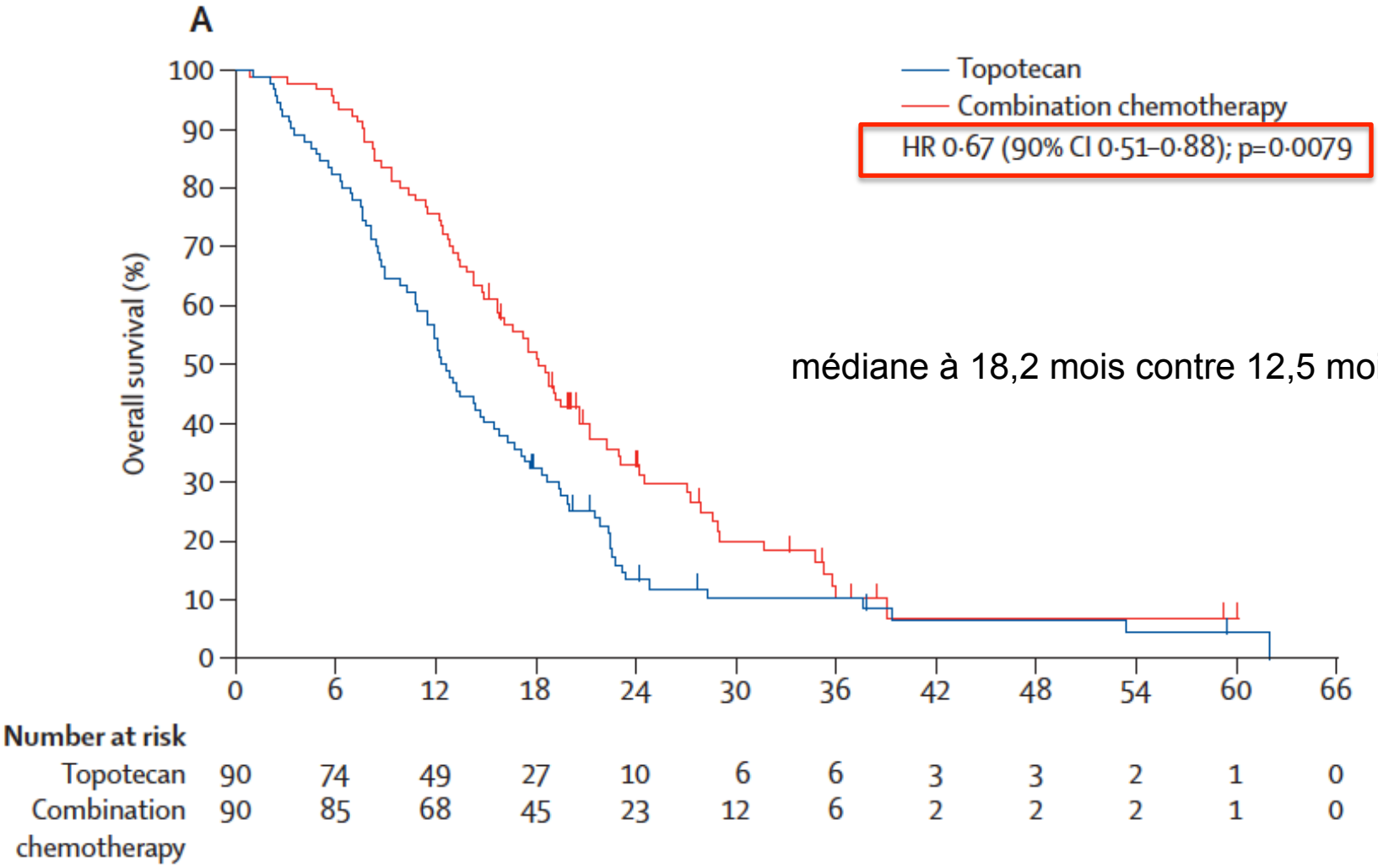
Goto K et al. Lancet Oncol 2016

Triplet de chimiothérapie

	Topotecan (n=90)	Combination chemotherapy (n=90)
Age (years)	64 (60–70; 44–75)	64 (61–68; 44–75)
Sex		
Male	78 (87%)	77 (86%)
Female	12 (13%)	13 (14%)
Disease stage at entry		
Limited	25 (28%)	20 (22%)
Extensive	65 (72%)	70 (78%)
ECOG performance status		
0	40 (44%)	52 (58%)
1	47 (52%)	36 (40%)
2	3 (3%)	2 (2%)
Time from first-line chemotherapy to relapse or progression (days)	148 (113–228; 92–2318)	181 (120–285; 91–1746)
First line chemotherapy (including patient in more than one category)		
Cisplatin or carboplatin plus etoposide	49 (54%)	50 (56%)
Cisplatin or carboplatin plus irinotecan	31 (34%)	32 (36%)
Cisplatin or carboplatin plus amrubicin	15 (17%)	17 (19%)
First-line thoracic radiotherapy		
Yes	38 (42%)	42 (47%)
No	52 (58%)	48 (53%)
Response to first-line treatment		
Complete response	20 (22%)	23 (26%)
Partial response	70 (78%)	67 (74%)

Goto K et al. Lancet Oncol 2016

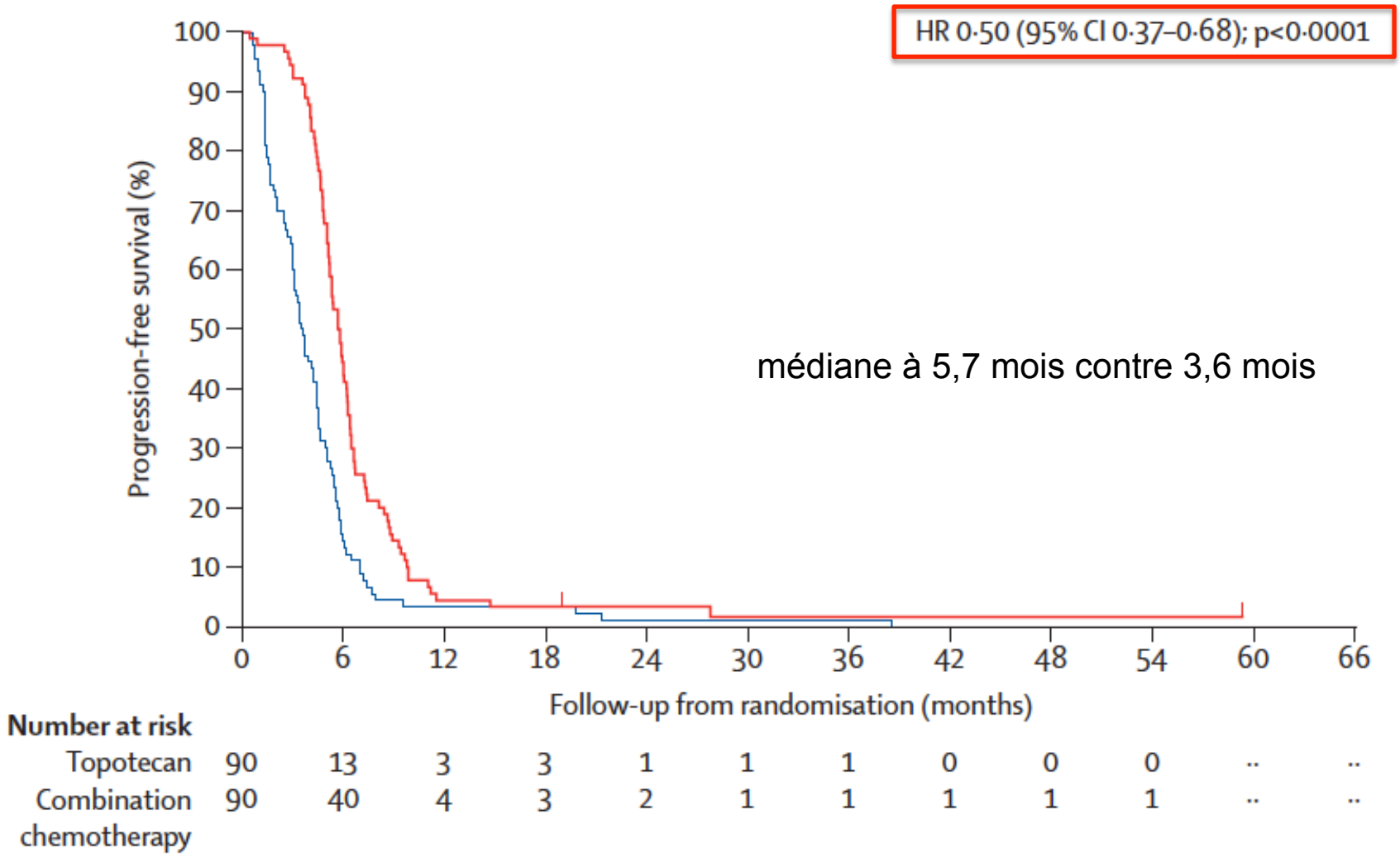
Triplet de chimiothérapie



médiane à 18,2 mois contre 12,5 mois

Goto K et al. Lancet Oncol 2016

Triplet de chimiothérapie



médiane à 5,7 mois contre 3,6 mois

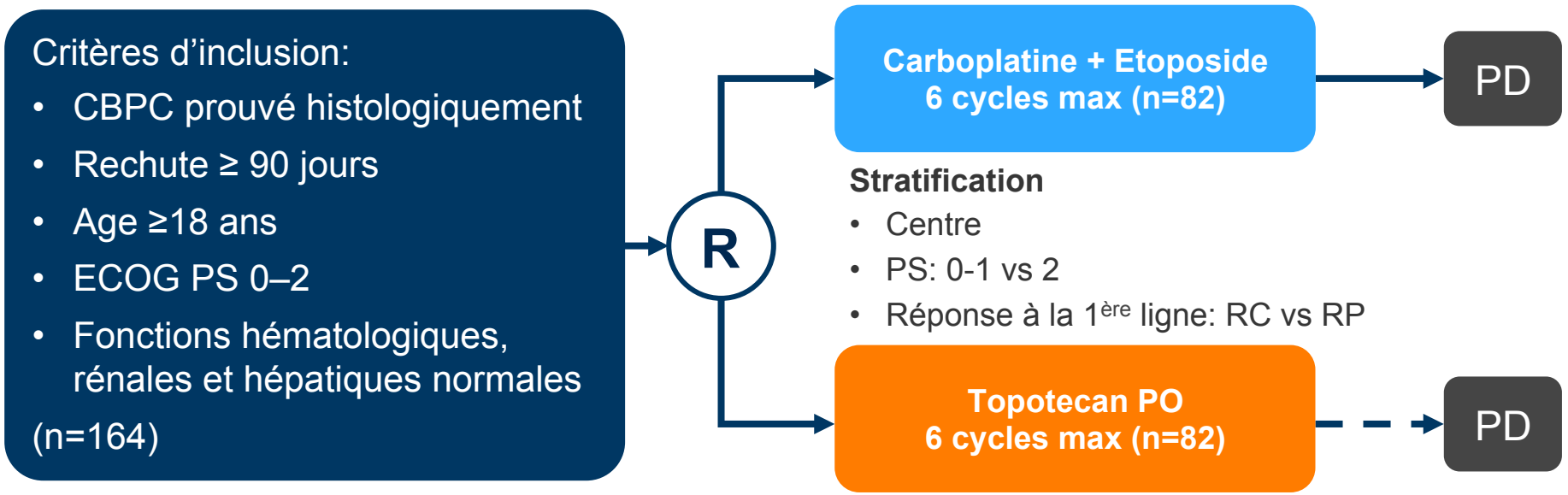
Goto K et al. Lancet Oncol 2016

Triplet de chimiothérapie

	Topotecan (n=90)			Combination chemotherapy (n=90)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Leucopenia	43 (48%)	42 (47%)	4 (4%)	15 (17%)	41 (46%)	31 (34%)
Neutropenia	13 (14%)	47 (52%)	30 (33%)	10 (11%)	23 (26%)	52 (58%)
Anaemia	55 (61%)	22 (24%)	3 (3%)	12 (13%)	50 (56%)	26 (29%)
Thrombocytopenia	45 (50%)	19 (21%)	6 (7%)	33 (37%)	27 (30%)	10 (11%)
Febrile neutropenia	..	6 (7%)	0	..	26 (29%)	2 (2%)

Goto K et al. Lancet Oncol 2016

GFPC 01-2013



Objectif principal: Survie sans progression

Objectif secondaires

- Taux de réponse
- Survie globale
- Toxicité, qualité de vie

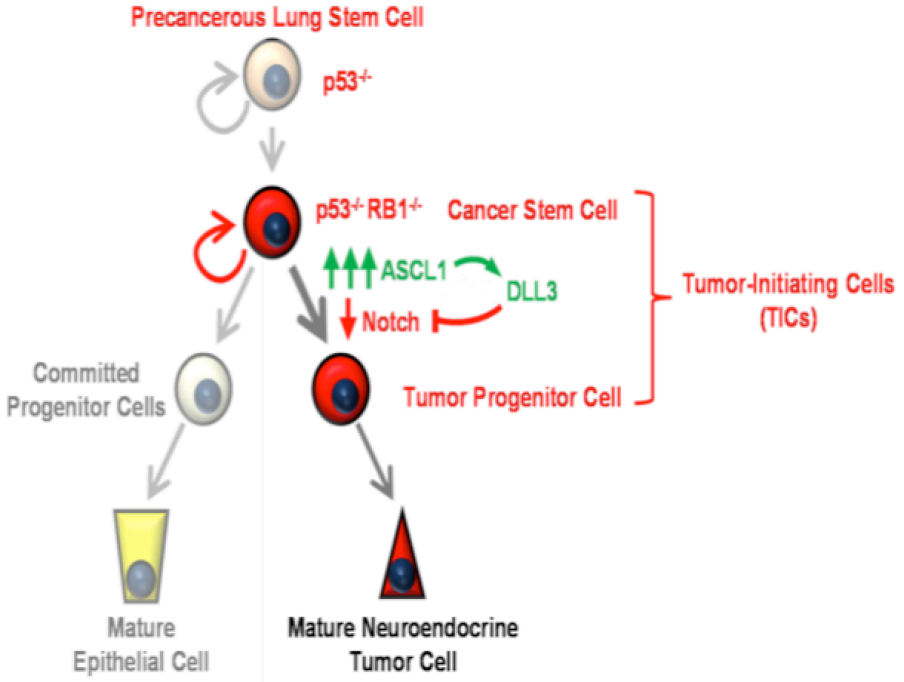
PI: Baize N, CHU Angers

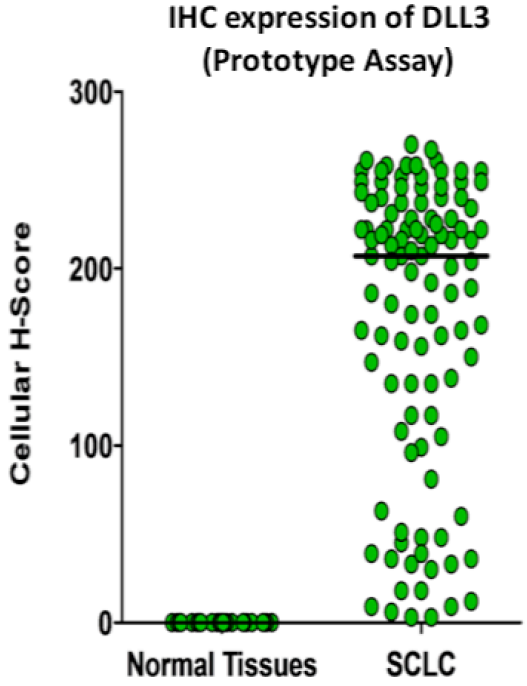
Agenda

- Chimiothérapie
- Thérapie ciblée
- Immunothérapie

Delta-like Protein 3 (DLL3)

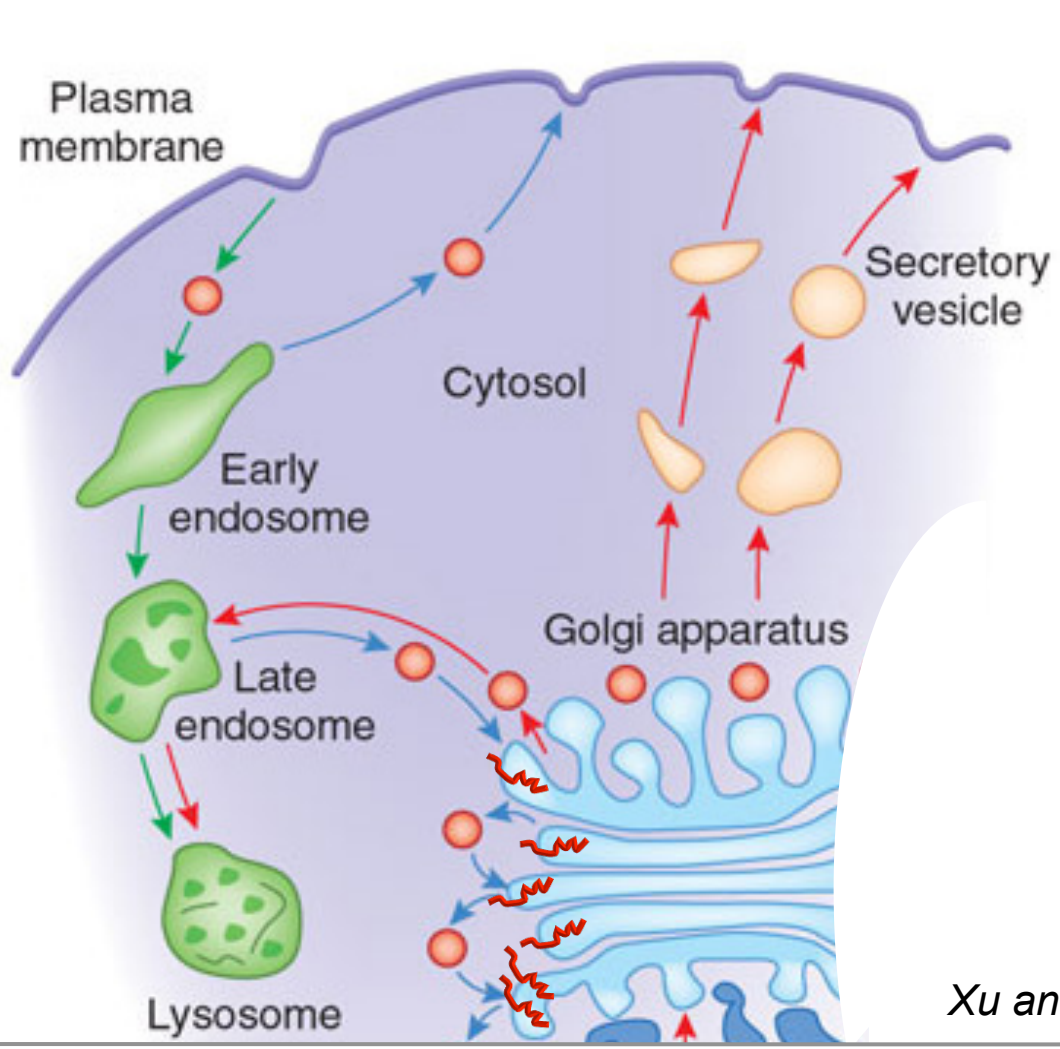
- An inhibitory Notch ligand identified on SCLC cancer stem cells (CSCs)
- Downstream of ASCL1, a marker of neuroendocrine cell differentiation
- Expressed highly in ~70-80% of SCLC, but not normal adult tissues





Rudin et al. ASCO 2016

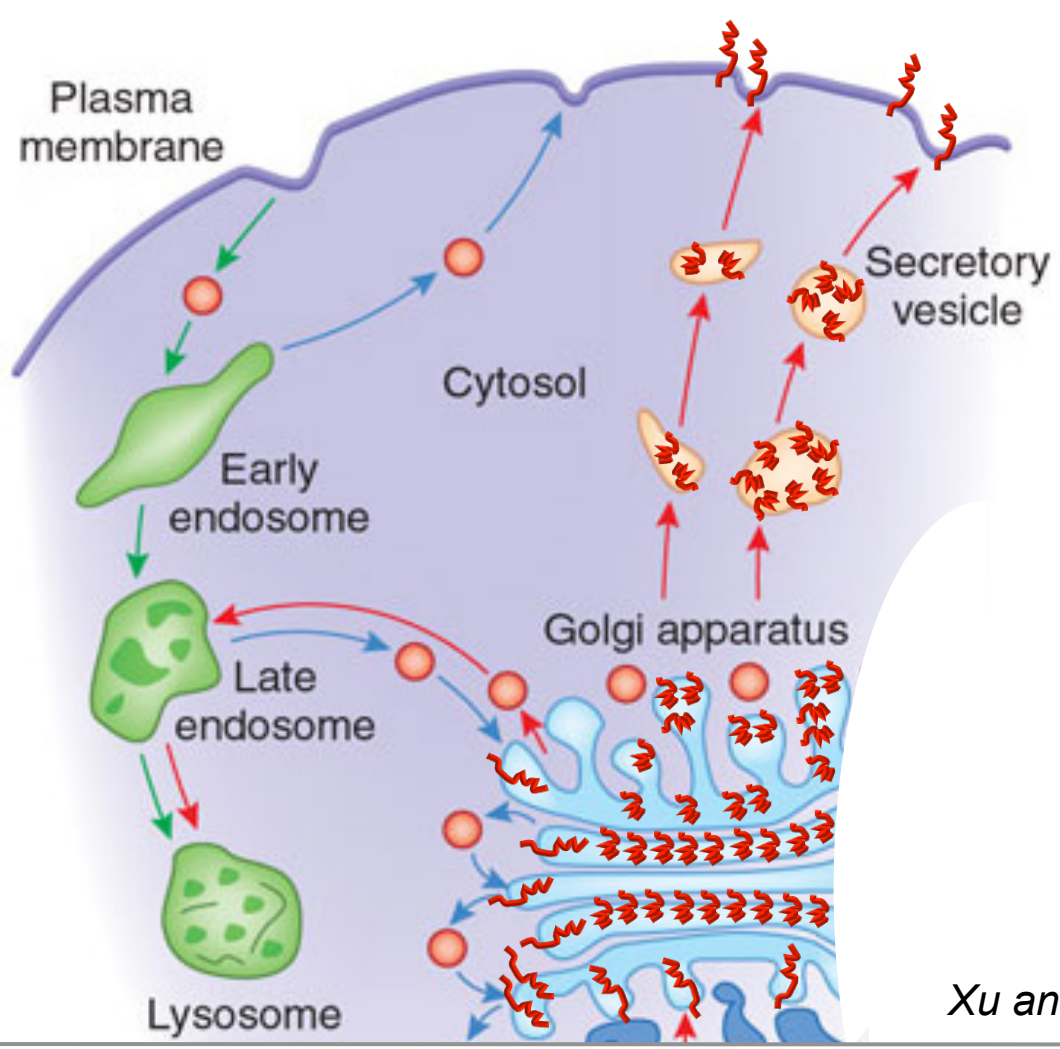
DLL3: cellule normale



= DLL3

Xu and Esko, Nat Chem Biol 2009

DLL3: cellule CPC

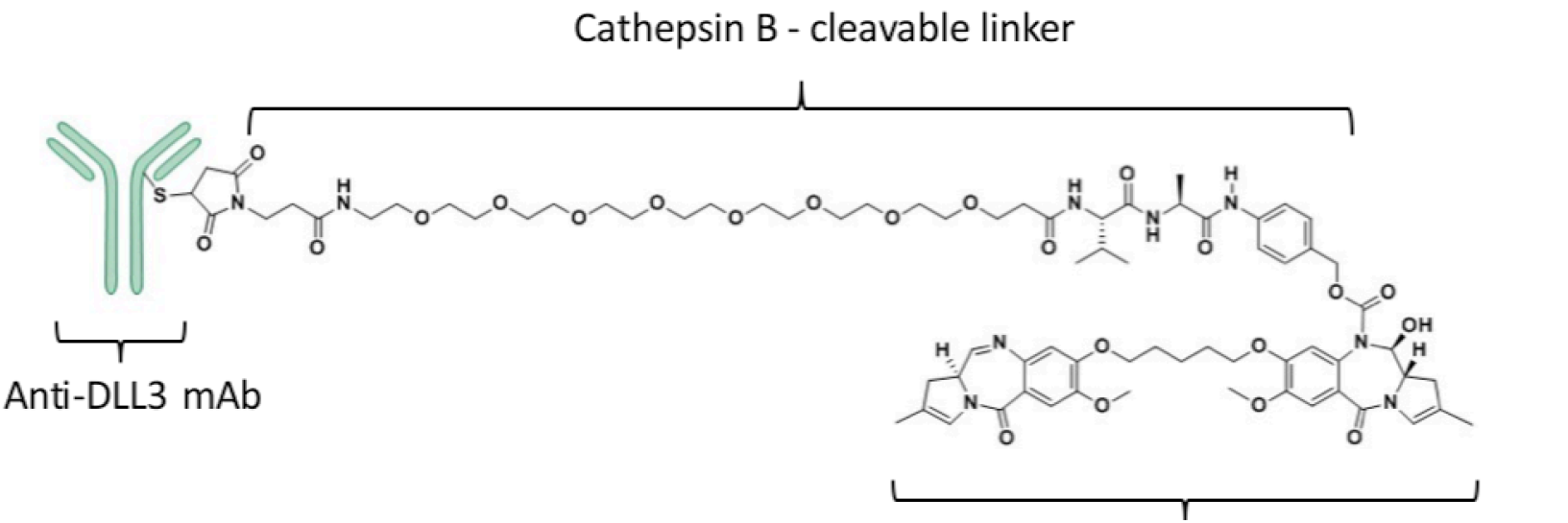


= DLL3

Xu and Esko, Nat Chem Biol 2009

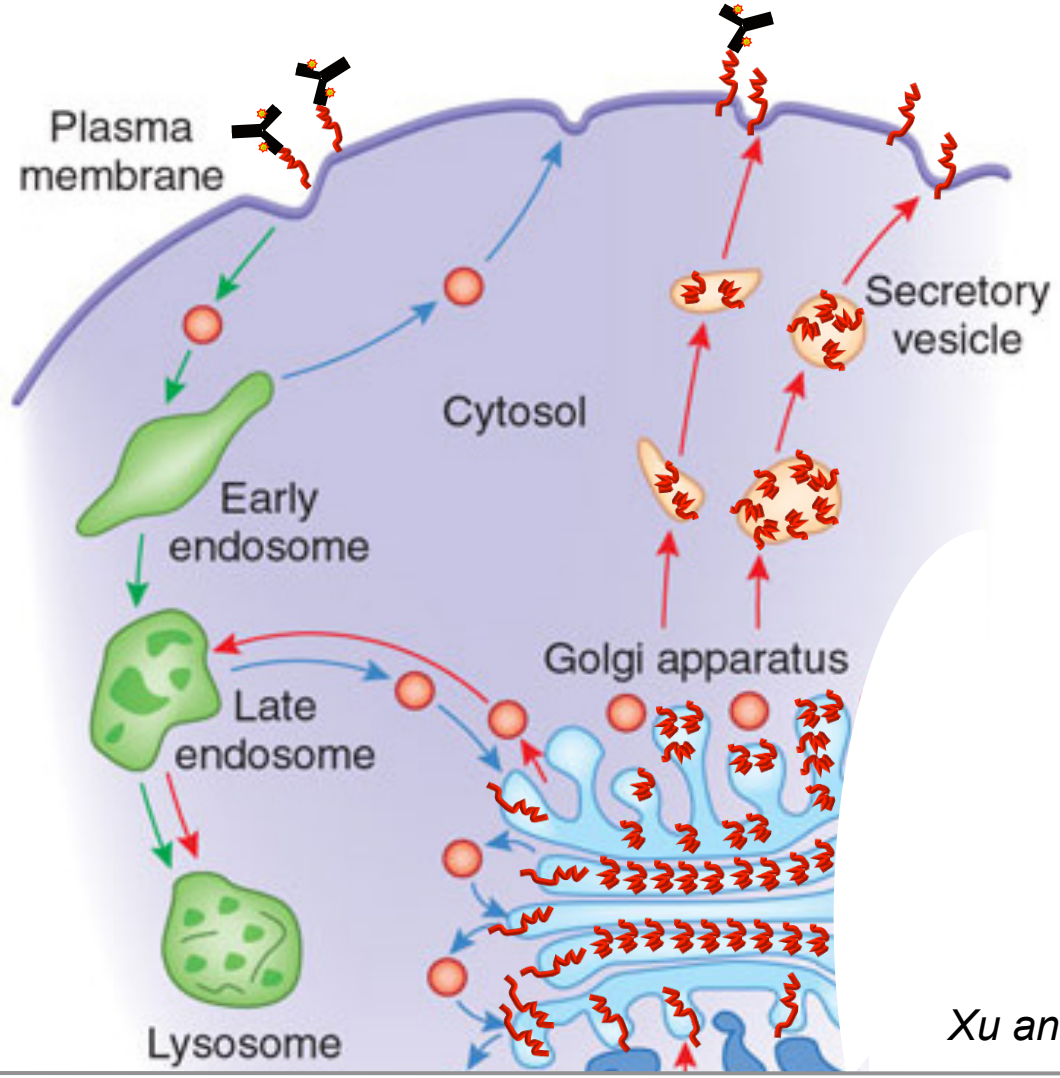
Rovalpituzumab tesirine (Rova-T)

A DLL3-Targeted Antibody-Drug Conjugate (ADC)



Rudin et al. ASCO 2016

Rova-T



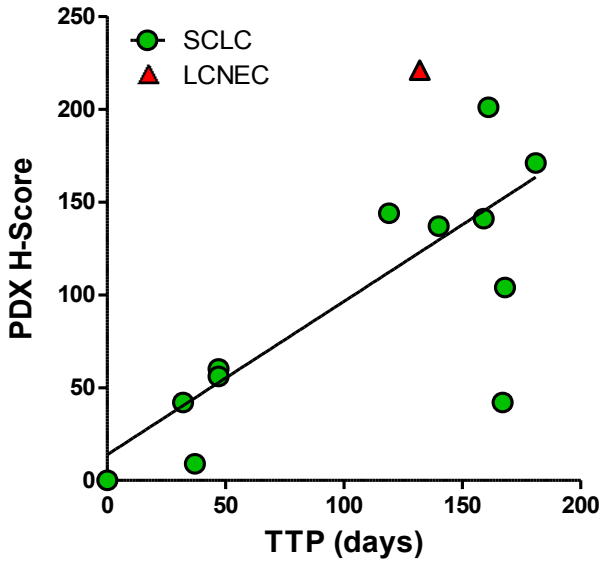
= DLL3

Rova-T

Xu and Esko, Nat Chem Biol 2009

Rova-T: préclinique

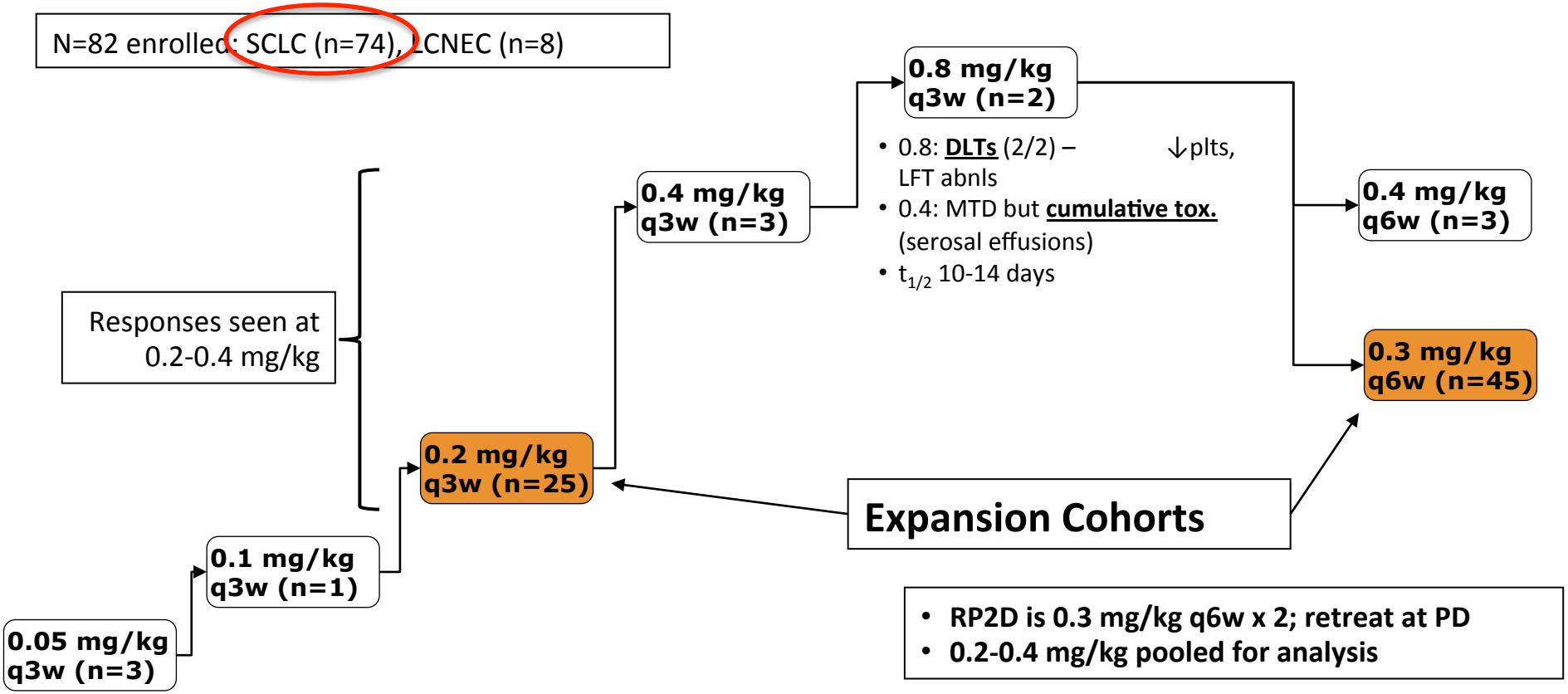
	Cisplatin/Etoposide (5 mpk x 1, 8 mpk qdx3)		Single Agent Rova-T (1 mpk q4d x 3)	
	%TGI	TTP (days)	%TGI	TTP (days)
LU102	97%	28	100%	> 181
LU95	56%	2	100%	> 168
LU117	98%	21	100%	> 167
LU149	90%	18	100%	> 161
LU129	87%	52	100%	> 159
LU111	84%	22	100%	> 140
LU37	60%	4	100%	> 132
LU64	78%	12	100%	> 119
LU124	83%	19	88%	47
LU73	85%	28	75%	47
LU80	75%	15	75%	37
LU86	26%	0	95%	32
LU100	100%	63	0%	0
Avg	**78%**	**22**	**87%**	**> 107**



Number of XY Pairs	13
Pearson r	0.7296
95% confidence interval	0.2985 to 0.9134
P value (two-tailed)	0.0046
P value summary	**
Is the correlation significant? (alpha=0.05)	Yes
R square	0.5323

Saunders al, Sci Transl Med 2015

Rova-T: phase I



Rudin et al. Lancet Oncol 2017

Rova-T: phase I

Characteristic	Number (%)
Median age, years (range)	61 (38-81)
Female	32 (43%)
Baseline ECOG: 0 / 1 / 2	21 (28%) / 50 (68%) / 3 (4%)
Extensive Disease at Presentation	56 (76%)
Response to 1st line therapy	
Sensitive[1]	39 (53%)
Resistant[2]	23 (31%)
Refractory[3]	7 (9%)
Not evaluable	5 (7%)
Treatment-free interval (before 2nd line)	4.1 months (0.2-89.1)
Hx CNS mets (Per investigator)	21 (28%)

Characteristic	Number (%)
Prior Lines of Therapy: 1 / 2	39 (53%) / 35 (47%)
Prior treatments	
Platinum/Etoposide	71 (96%)
Platinum/Other	5 (7%)
Platinum/Etoposide/Other	7 (9%)
Topotecan	8 (11%)
Temozolomide	10 (14%)
ABT-888	8 (11%)
Radiation	61 (82%)
Other	16 (22%)
Tumor DLL3 Expression (any intensity):	
≥ 1% of tumor cells	42/48 (88%)
≥ 50% of tumor cells	32/48 (67%)

[1,2] Best response of SD or better to 1st line therapy, and 1st-2nd line TFI [1]≥ 90 days or [2] < 90 days.
[3] Best response of PD to 1st line therapy.

Rudin et al. Lancet Oncol 2017

Rova-T: phase I

Highest Related AE Terms ≥ 15% for All Grades

Adverse Event PT	Grade 3+	All Grades
All	**28 (38%)**	**65 (88%)**
Fatigue	3 (4%)	26 (35%)
Pleural effusion	6 (8%)	23 (31%)
Oedema peripheral	2 (3%)	20 (27%)
Nausea	0 (0%)	14 (19%)
Hypoalbuminemia	0 (0%)	13 (18%)
Thrombocytopenia	9 (12%)	12 (16%)
Rash Maculo-Papular	2 (3%)	12 (16%)
Decreased Appetite	0 (0%)	12 (16%)

Highest Related AE Groups Grade 3+

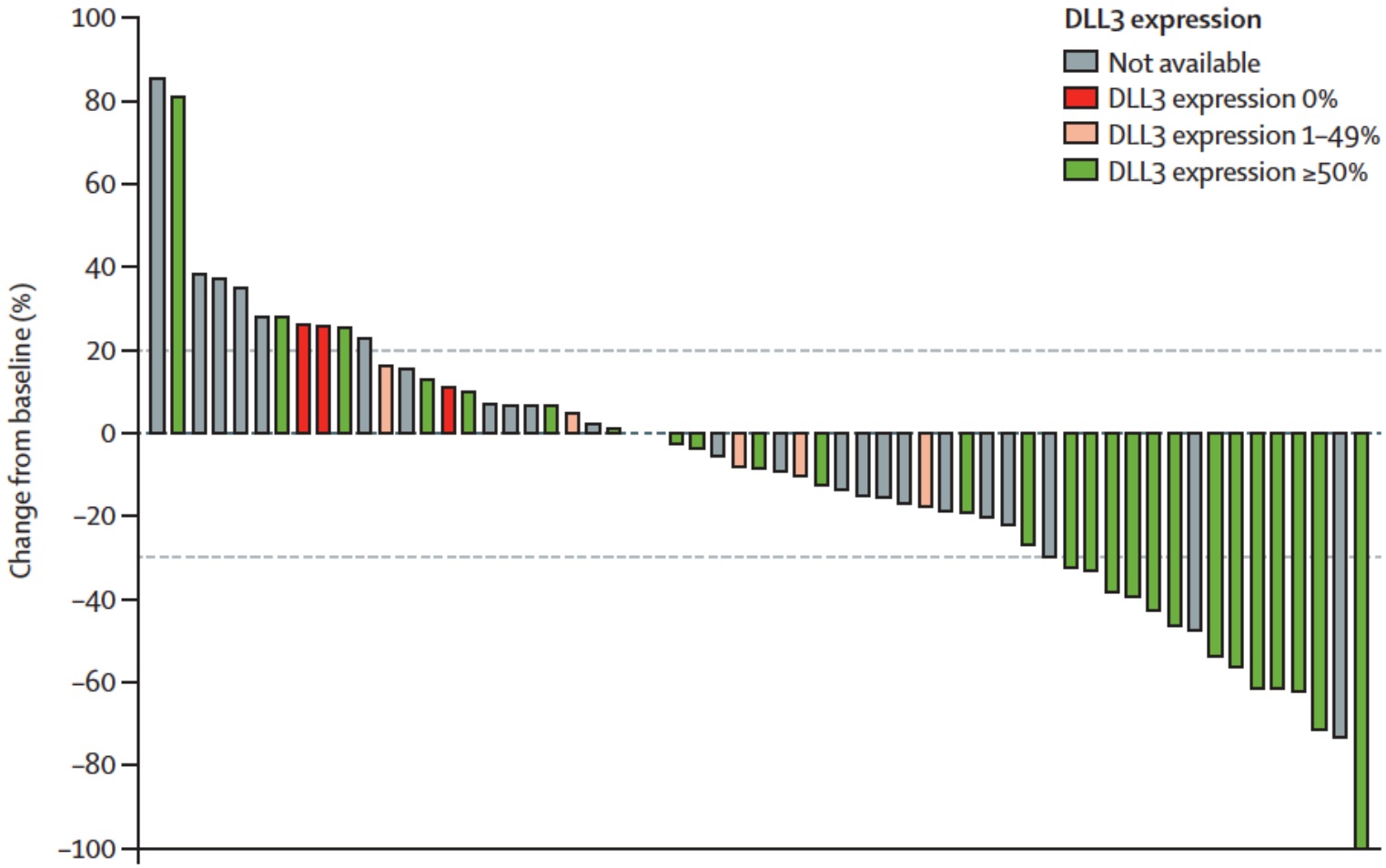
Adverse Event Group	Grade 3+	All Grades
Thrombocytopenia	9 (12%)	15 (20%)
Serosal Effusions[1]	8 (11%)	26 (35%)
Skin Reaction[2]	6 (8%)	36 (49%)

[1] Pleural or pericardial effusion, ascites, or "Capillary Leak Syndrome" (serosal effusions, peripheral edema, and/or hypoalbuminemia; recoding performed after cases were not adjudicated as CLS by a Data Monitoring Committee of CLS experts)

[2] Blister, Dermatitis Acneiform, Dry Skin, Erythema, Erythema Multiforme, Palmar-Plantar Erythrodysaesthesia Syndrome, Photosensitivity Reaction, Pruritus, Pruritus Generalised, Rash, Rash Erythematous, Rash Maculo-Papular, Skin Exfoliation, Skin Irritation

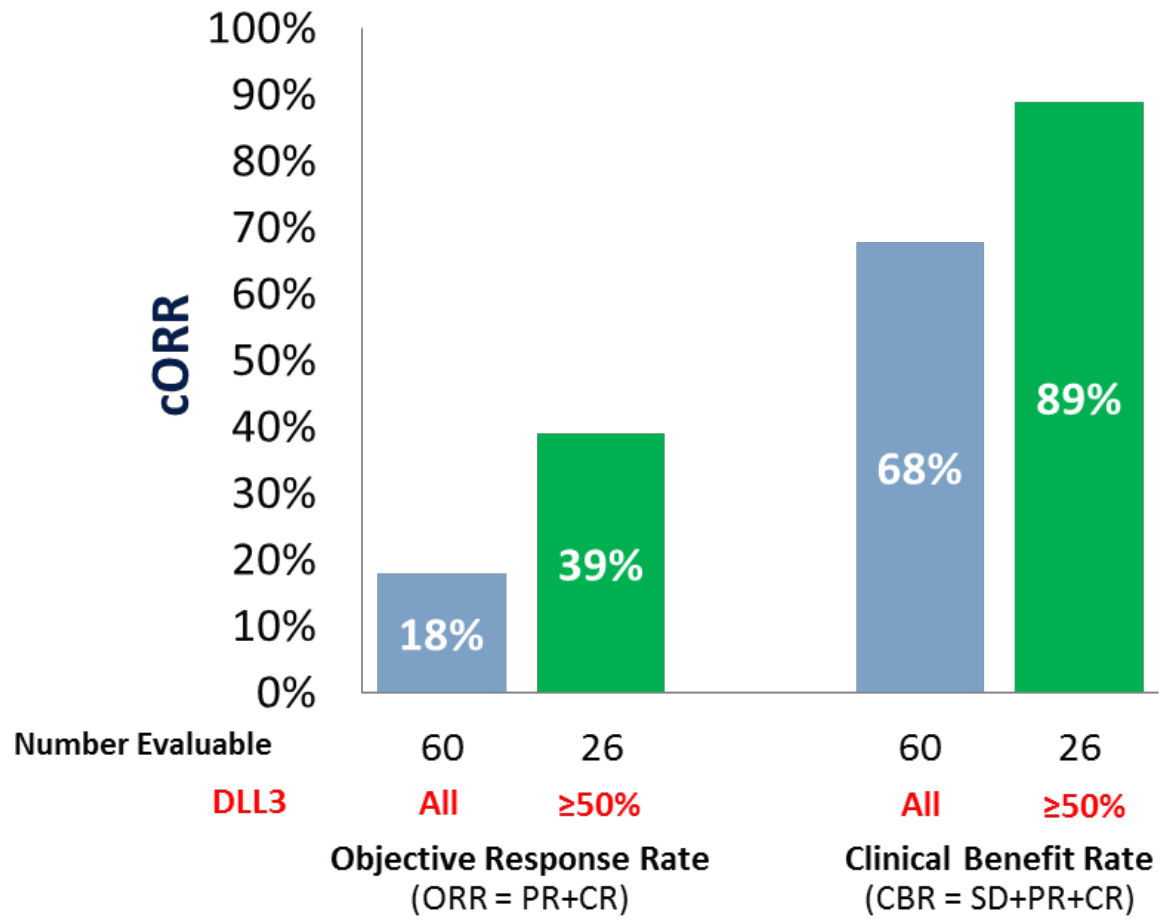
Rudin et al. Lancet Oncol 2017

Rova-T: phase I



Rudin et al. Lancet Oncol 2017

Rova-T: phase I

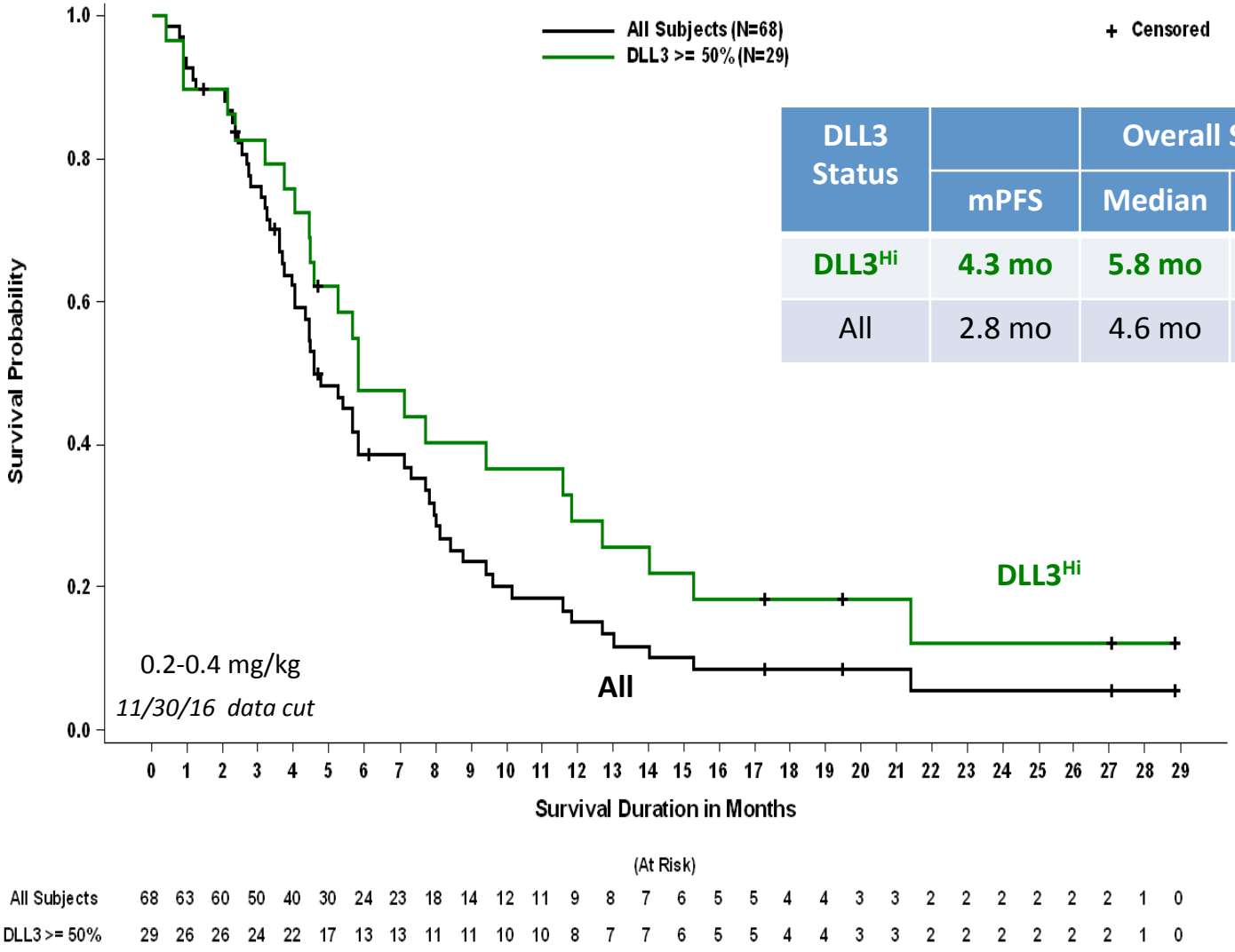


- 2ème / 3ème ligne
- Sensible / résistant

Response-Evaluable Subjects
Active Doses (0.2-0.4 mg/kg)

Rudin et al. Lancet Oncol 2017

Rova-T: phase I



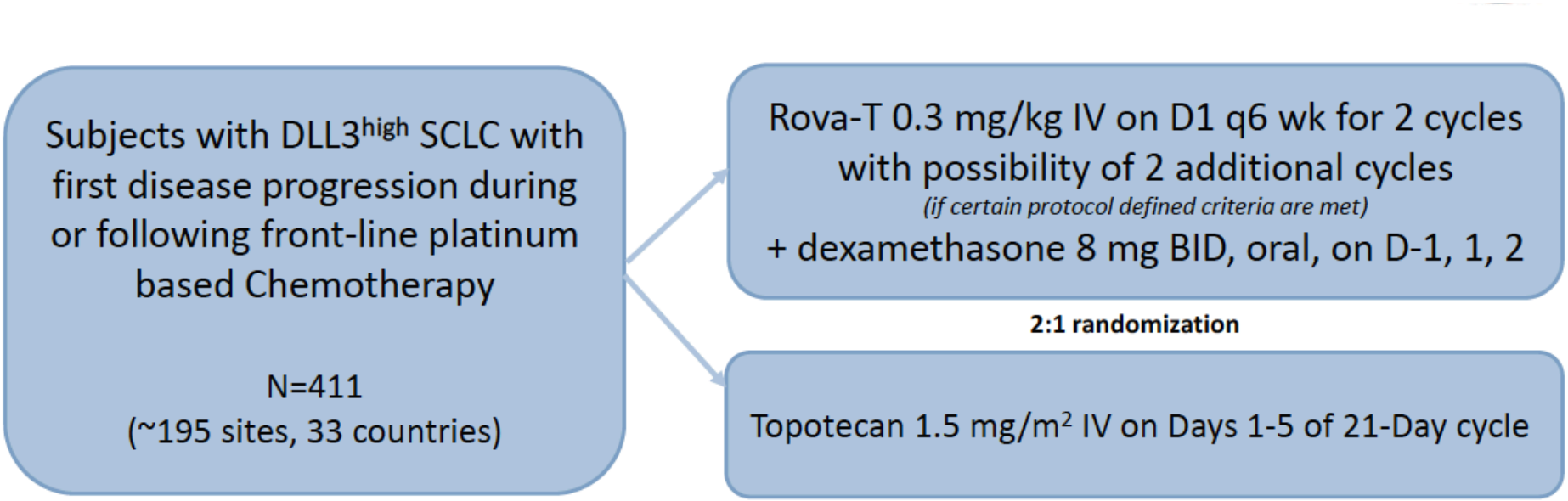
DLL3 Status		Overall Survival	
	mPFS	Median	1-Year
DLL3^{Hi}	4.3 mo	5.8 mo	29%
All	2.8 mo	4.6 mo	15%

Rova-T: phase II

CLINICAL PROTOCOL

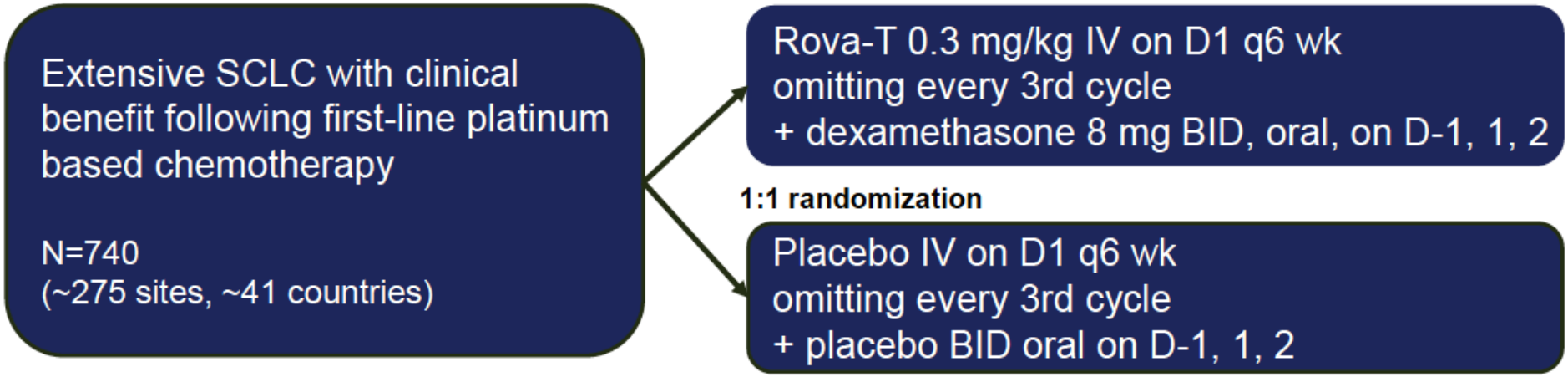
Protocol Number	SCRX001-002
Version and Date	Version 2.0, 12-Nov-2015
Protocol Title	An Open-label, Single-Arm, Phase 2 Study Evaluating the Efficacy, Safety and Pharmacokinetics of Rovalpituzumab Tesirine (SC16LD6.5) for Third-line and Later Treatment of Subjects with Relapsed or Refractory Delta-Like Protein 3-Expressing Small Cell Lung Cancer (TRINITY)
Investigational Drug	Rovalpituzumab tesirine
Phase	2
IND Number	117510
EUDRACT Number	2015 - 004506 - 42

Rova-T: phase III



Recrutement en cours

Rova-T: phase III

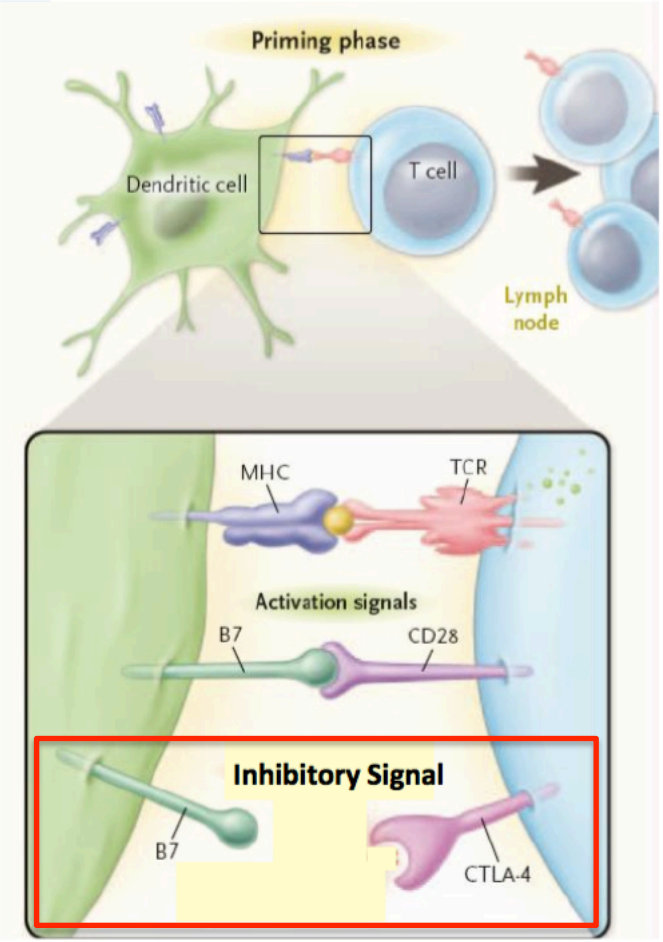


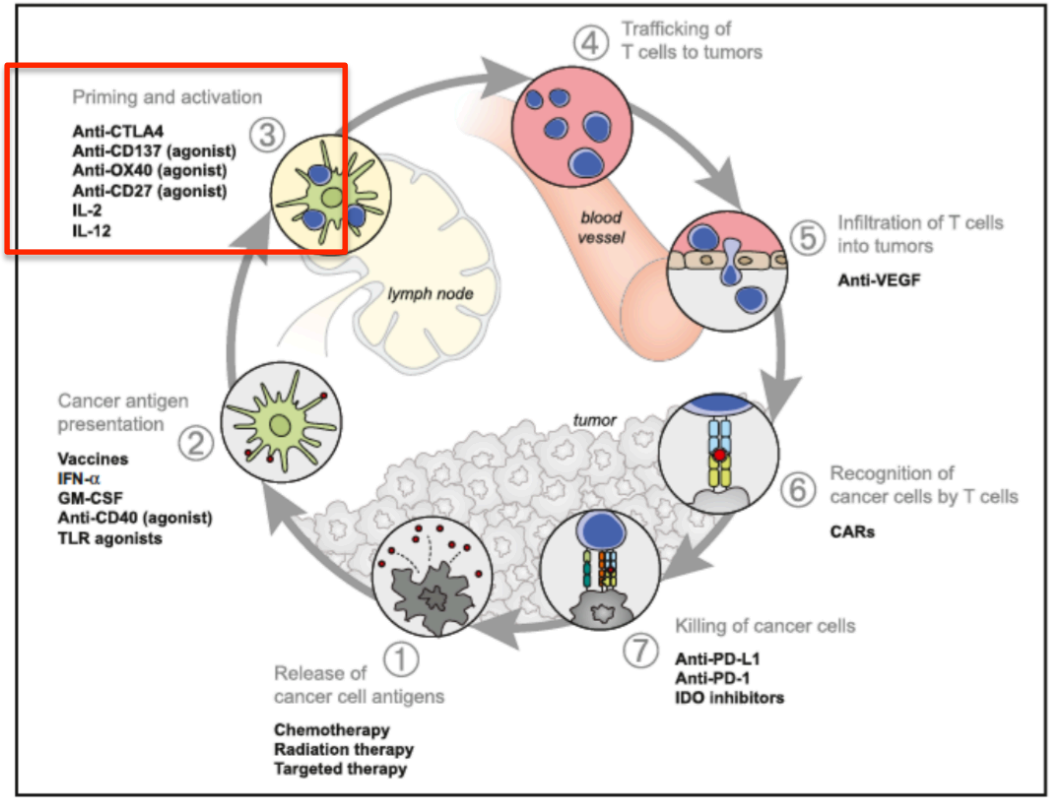
Recrutement en cours

Agenda

- Chimiothérapie
- Thérapie ciblée
- Immunothérapie

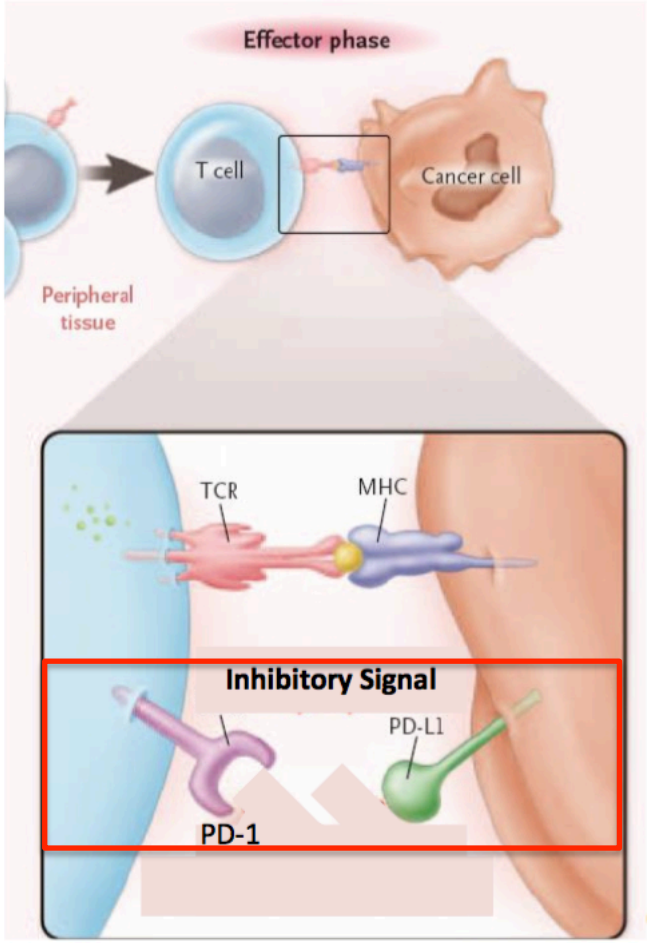
Immunothérapie

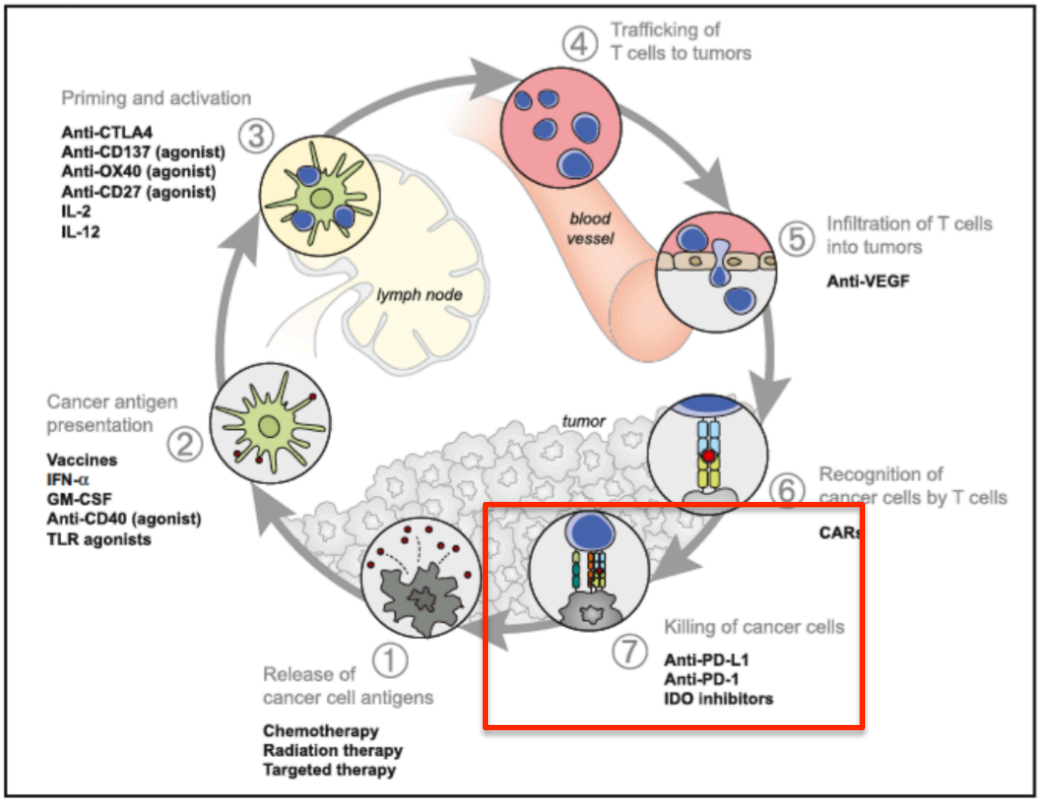




Chen et al. Autoimmunity 2012;12:252;Ribas. N Engl J Med 2012; 366:2517

Immunothérapie

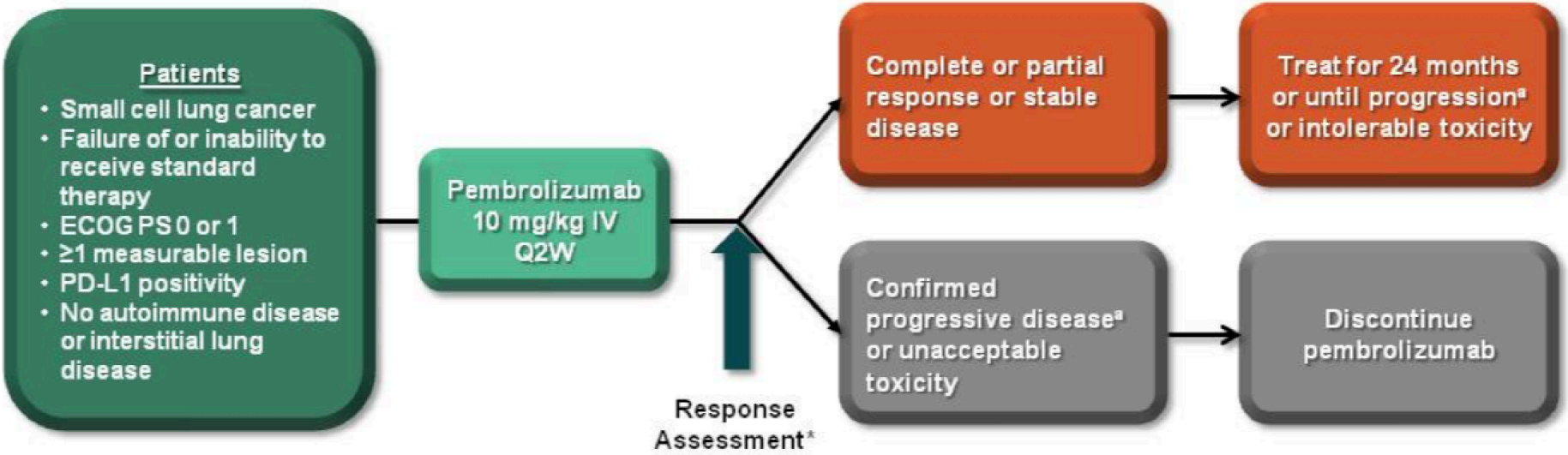




Chen et al. Autoimmunity 2012;12:252;Ribas. N Engl J Med 2012; 366:2517

Pembrolizumab

KEYNOTE-028 (NCT02054806): Phase 1b Multicohort Study of Pembrolizumab for PD-L1+ Advanced Solid Tumors



***Response assessment**: Every 8 weeks for the first 6 months; every 12 weeks thereafter

Primary end points: ORR per RECIST v1.1 and safety

Secondary end points: PFS, OS, duration of response

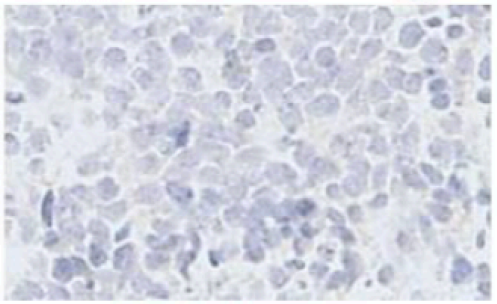
Ott P et al. ASCO 2015

Pembrolizumab

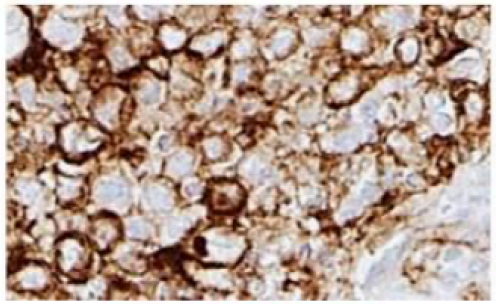
Analysis of PD-L1 Expression

- Tumor samples: archival or newly obtained core or excisional biopsy of a nonirradiated lesion
- Immunohistochemistry: assessed at a central laboratory using a prototype assay and the 22C3 antibody clone (Merck)
- Positivity: membranous PD-L1 expression in ≥1% of cells in tumor nests or positive bands in stroma

Examples of PD-L1 Staining in SCLC Specimens from KEYNOTE-028



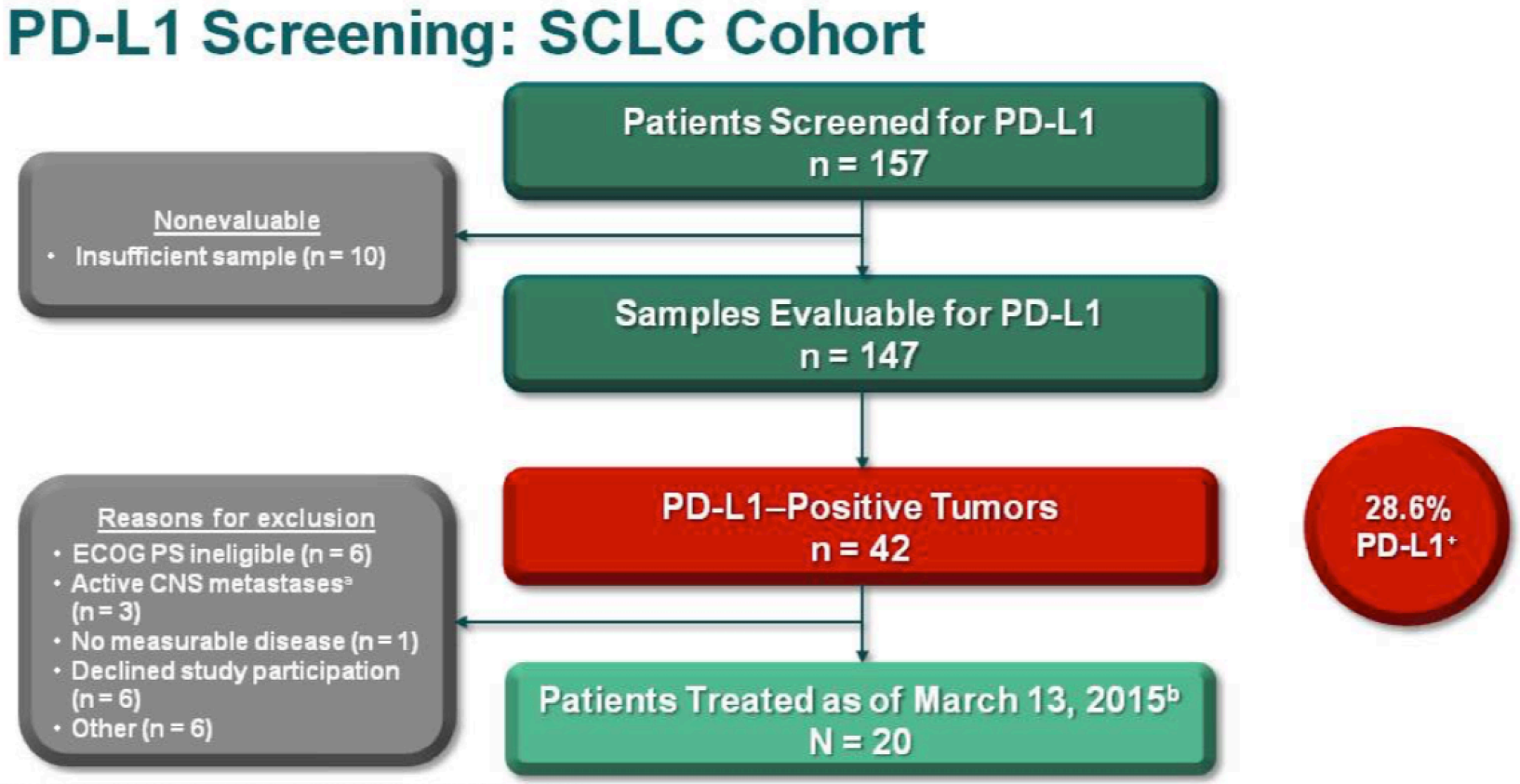
PD-L1 Negative



PD-L1 Positive

Ott P et al. ASCO 2015

Pembrolizumab



[a]Patients with CNS metastases that were stable for ≥4 weeks could enroll.
[b]1 additional patient was misenrolled and never treated. An additional 4 patients were enrolled and treated after the March 13, 2015, data cutoff date of this analysis.

Ott P et al. ASCO 2015

Pembrolizumab

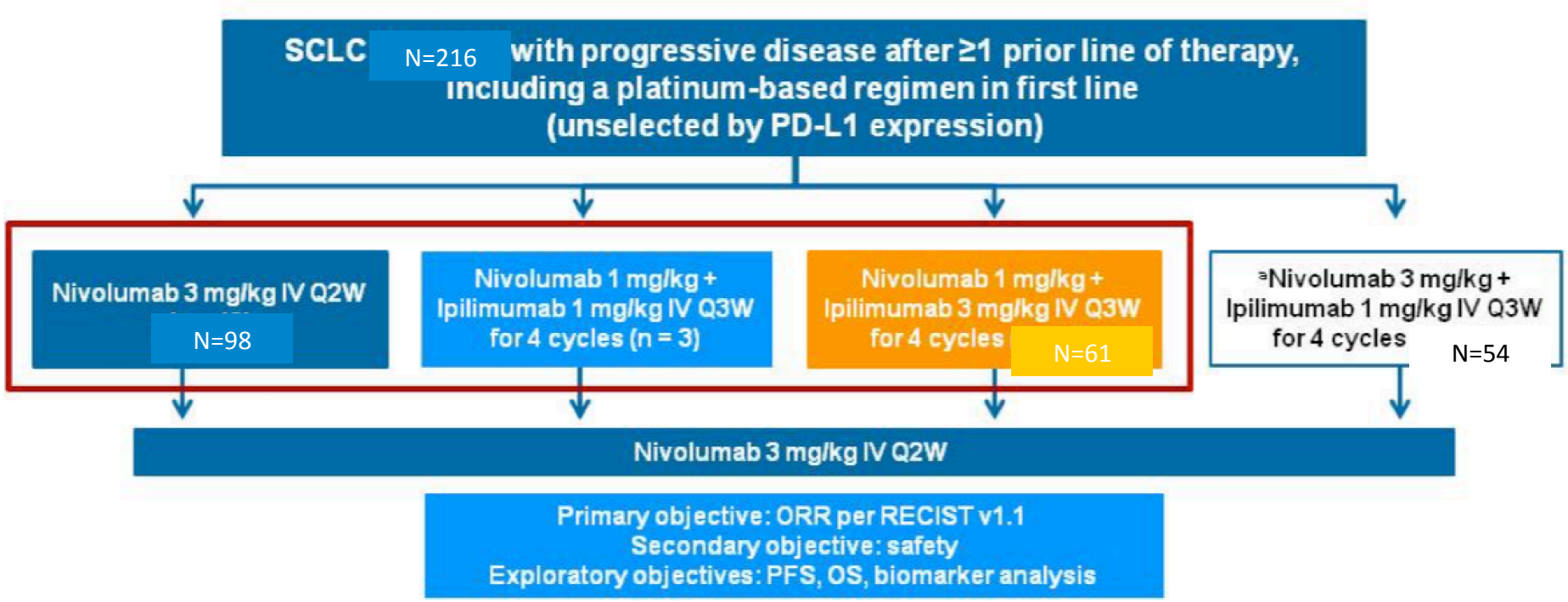
Antitumor Activity (RECIST v1.1, Investigator Review)

Best Overall Response	n	%	95% CI
ORR[a]	7	35	15-59
Complete response	0	0	0-17
Partial response	7	35	15-59
Stable disease	1	5	0-25
Progressive disease	9	45	23-69
No assessment[b]	3	15	3-38

Ott P et al. ASCO 2015

Nivolumab +/- Ipilimumab

Checkmate 032



Antonia SJ et al. Lancet Oncol 2016

Nivolumab +/- Ipilimumab

	Nivolumab 3 mg/kg (n=98)	Nivolumab 1 mg/kg plus ipilimumab 3 mg/kg (n=61)	Nivolumab 3 mg/kg plus ipilimumab 1 mg/kg (n=54)
Median age (years)	63 (57–68)	66 (58–71)	61 (56–65)
Age ≥75 years	9 (9%)	7 (11%)	0
Sex			
Male	61 (62%)	35 (57%)	32 (59%)
Female	37 (38%)	26 (43%)	22 (41%)
Race			
White	91 (93%)	60 (98%)	52 (96%)
Black or African American	3 (3%)	1 (2%)	0
Other	4 (4%)	0	1 (2%)
Not reported	0	0	1 (2%)
Previous treatment regimens			
1	40 (41%)	32 (52%)	23 (43%)
2–3	55 (56%)	23 (38%)	28 (52%)
>3	3 (3%)	6 (10%)	3 (6%)
First-line platinum-treated patients*			
Platinum-sensitive	55 (56%)	25 (41%)	21 (39%)
Platinum-resistant†	30 (31%)	23 (38%)	21 (39%)
Unknown	10 (10%)	11 (18%)	8 (15%)
Smoking status			
Current or former smoker	95 (97%)	57 (93%)	48 (89%)
Never smoked	3 (3%)	4 (7%)	5 (9%)
Unknown	0	0	1 (2%)
PD-L1 expression level‡			
≥1%	10 (14%)	9 (24%)	5 (13%)
<1%	59 (86%)	28 (76%)	35 (88%)
≥5%	4 (6%)	2 (5%)	1 (3%)
<5%	65 (94%)	35 (95%)	39 (98%)
Indeterminate, not evaluable, or missing	29 (30%)	24 (39%)	14 (26%)

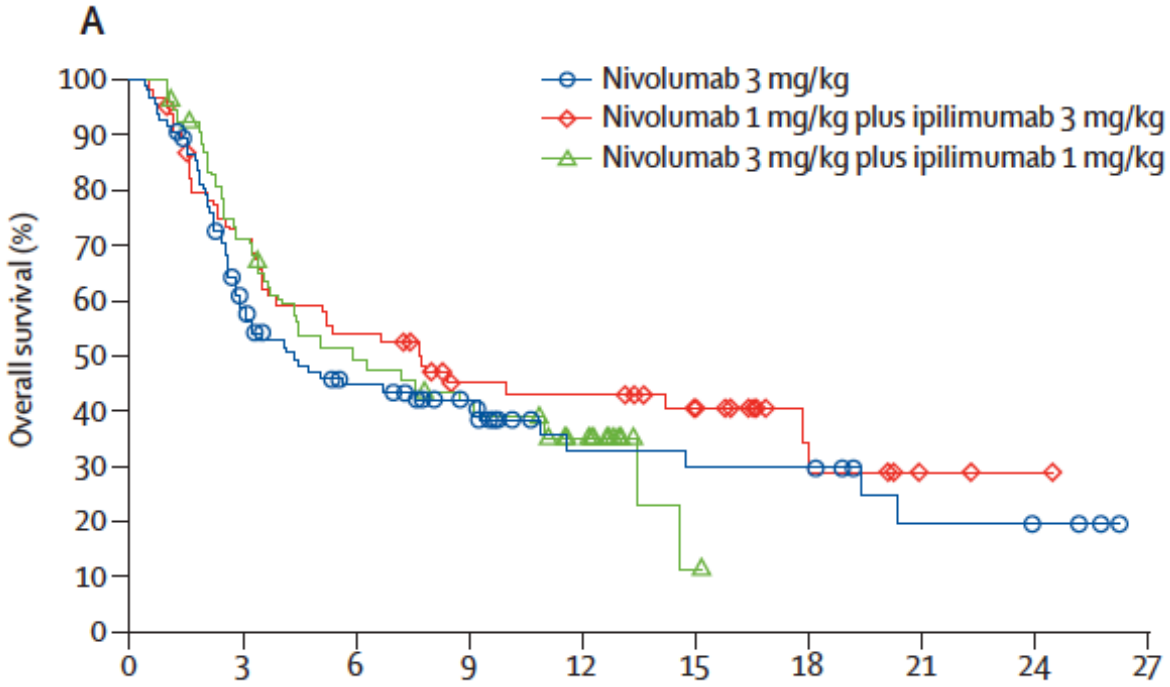
Antonia SJ et al. Lancet Oncol 2016

Nivolumab +/- Ipilimumab

	Nivolumab 3 mg/kg (n=98)	Nivolumab 1 mg/kg plus ipilimumab 3 mg/kg (n=61)	Nivolumab 3 mg/kg plus ipilimumab 1 mg/kg (n=54)
Objective response; 95% CI	10 (10%; 5–18)	14 (23%; 13–36)	10 (19%; 9–31)
Best overall response			
Complete response	0	1 (2%)	0
Partial response	10 (10%)	13 (21%)	10 (19%)
Stable disease	22 (22%)	13 (21%)	9 (17%)
Progressive disease	52 (53%)	23 (38%)	29 (54%)
Unable to determine	12 (12%)	8 (13%)	6 (11%)
Not reported	2 (2%)	3 (5%)	0
Time to objective response (IQR), months	2·0 (1·3–2·8)	2·1 (1·4–2·8)	1·4 (1·3–2·7)

Antonia SJ et al. Lancet Oncol 2016

Nivolumab +/- Ipilimumab

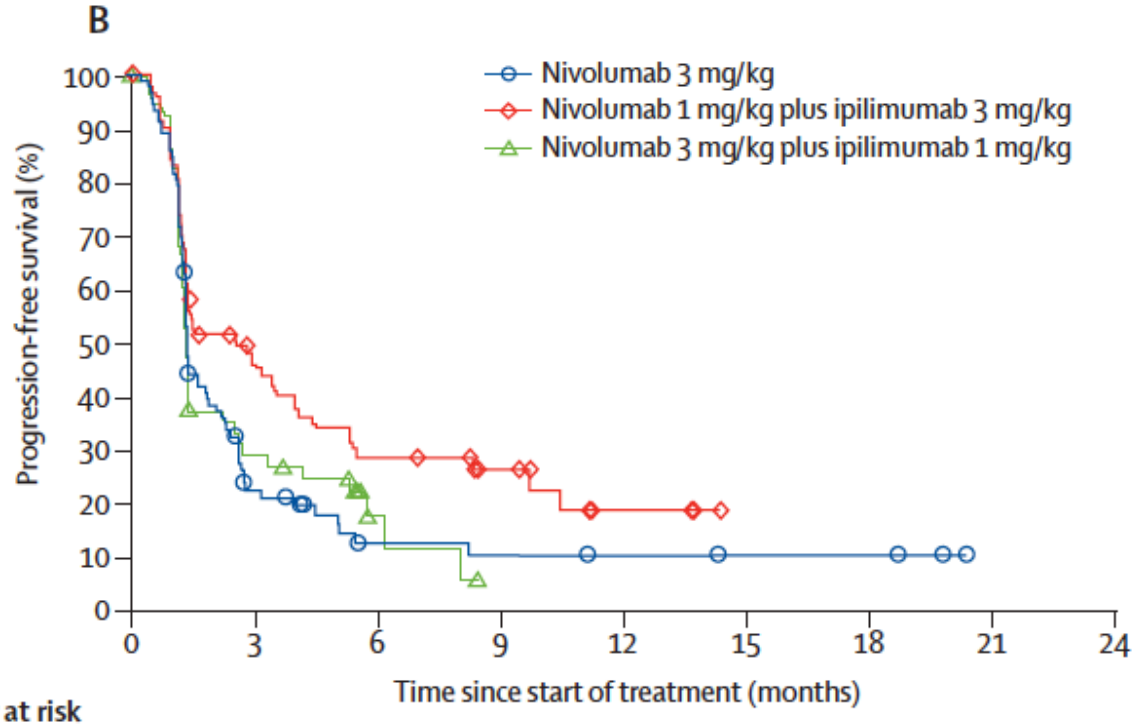


Number at risk										
Nivolumab 3 mg/kg	98	53	36	25	11	10	10	4	3	0
Nivolumab 1 mg/kg plus ipilimumab 3 mg/kg	61	42	32	22	21	15	6	2	1	0
Nivolumab 3 mg/kg plus ipilimumab 1 mg/kg	55	37	25	20	12	1	0	0	0	0

	Median OS (months)	1-year OS
Nivolumab 3 mg/kg	4.4	33%
Nivolumab 1 mg/kg plus ipilimumab 3 mg/kg	7.7	43%
Nivolumab 3 mg/kg plus ipilimumab 1 mg/kg	6.0	35%

Antonia SJ et al. Lancet Oncol 2016

Nivolumab +/- Ipilimumab

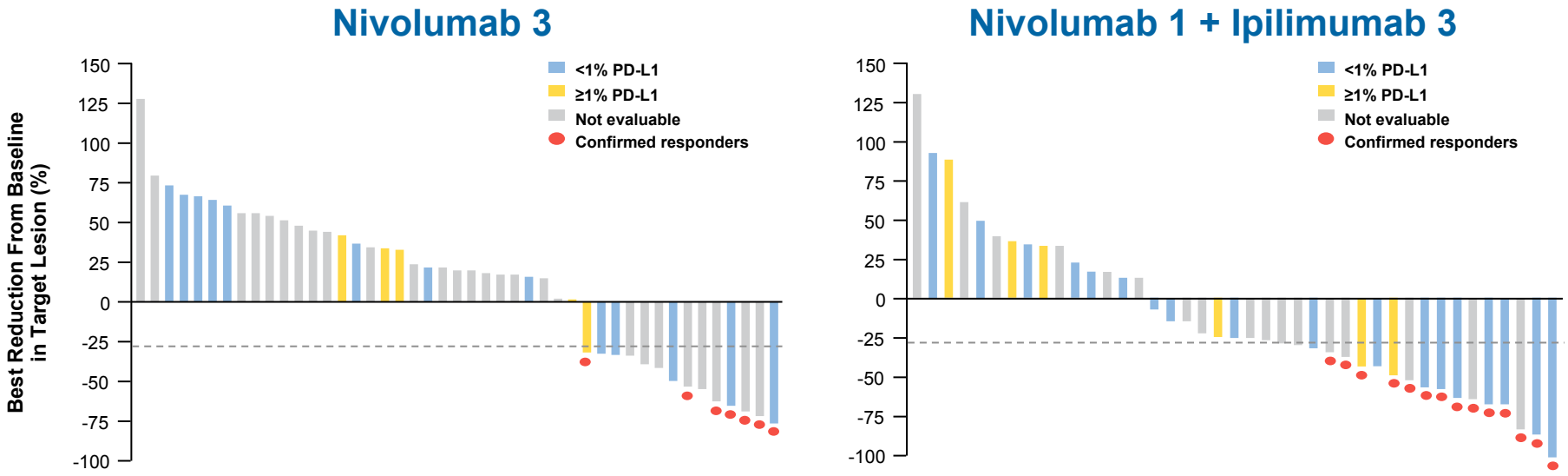


Number at risk									
Nivolumab 3 mg/kg	98	17	6	5	4	3	3	0	0
Nivolumab 1 mg/kg plus ipilimumab 3 mg/kg	61	24	15	9	3	0	0	0	0
Nivolumab 3 mg/kg plus ipilimumab 1 mg/kg	54	14	3	0	0	0	0	0	0

	Median PFS (months)	1-year PFS
Nivolumab 3 mg/kg	1.4	11%
Nivolumab 1 mg/kg plus ipilimumab 3 mg/kg	2.6	19%
Nivolumab 3 mg/kg plus ipilimumab 1 mg/kg	1.4	NR

Antonia SJ et al. Lancet Oncol 2016

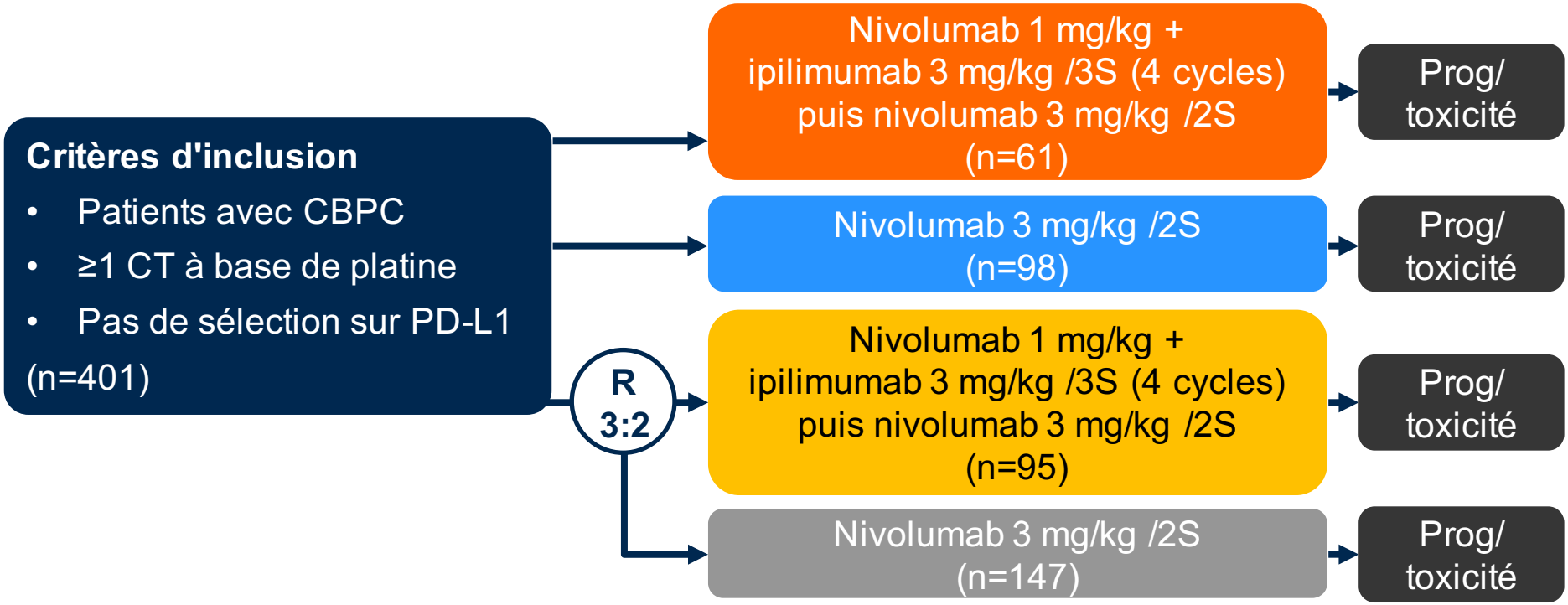
Nivolumab +/- Ipilimumab



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)

Antonia SJ et al. Lancet Oncol 2016

Nivolumab



Critère principal

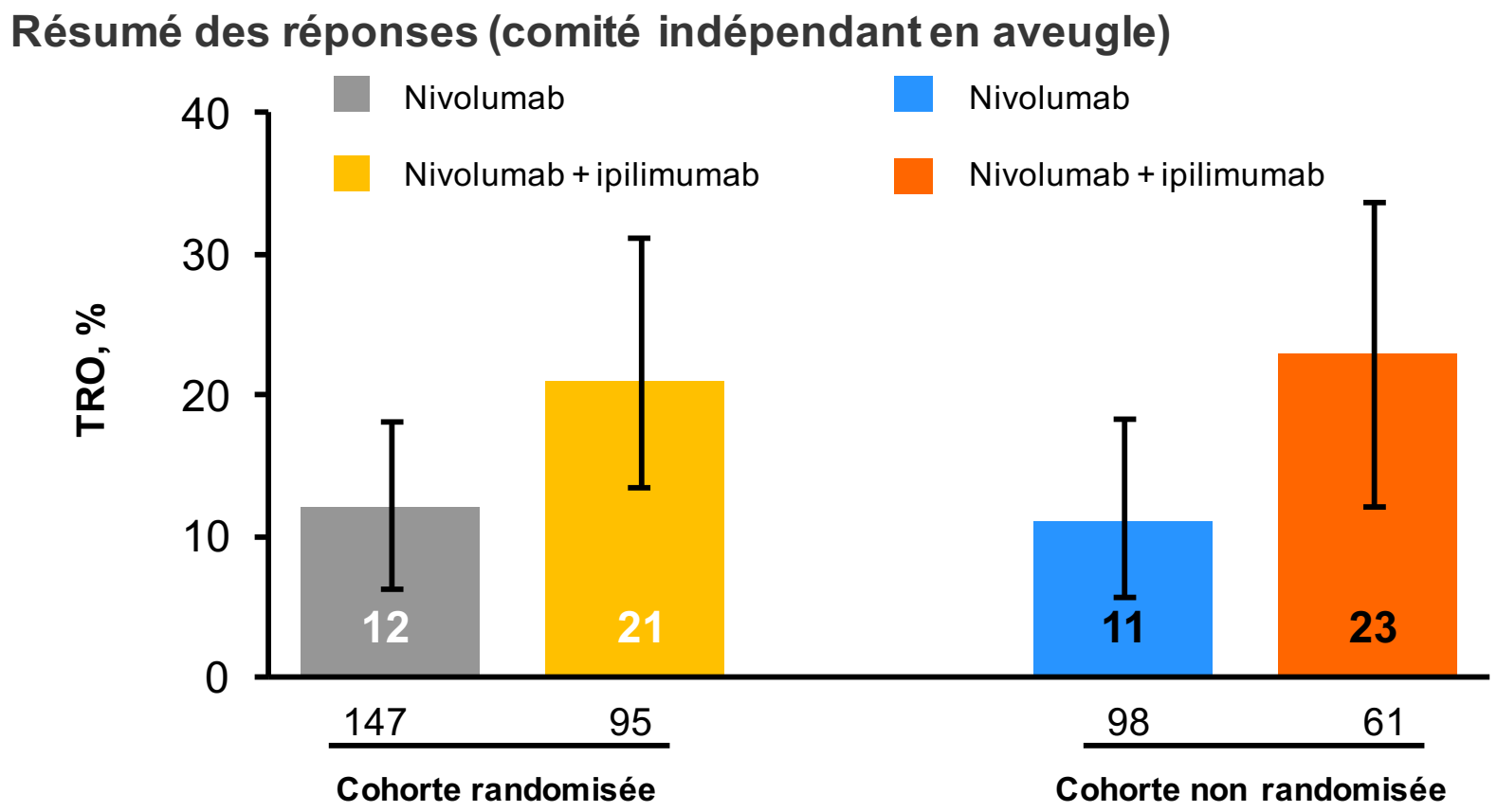
- TRO (RECIST v1.1)

Critères secondaires

- TCM, durée de réponse, SG, tolérance

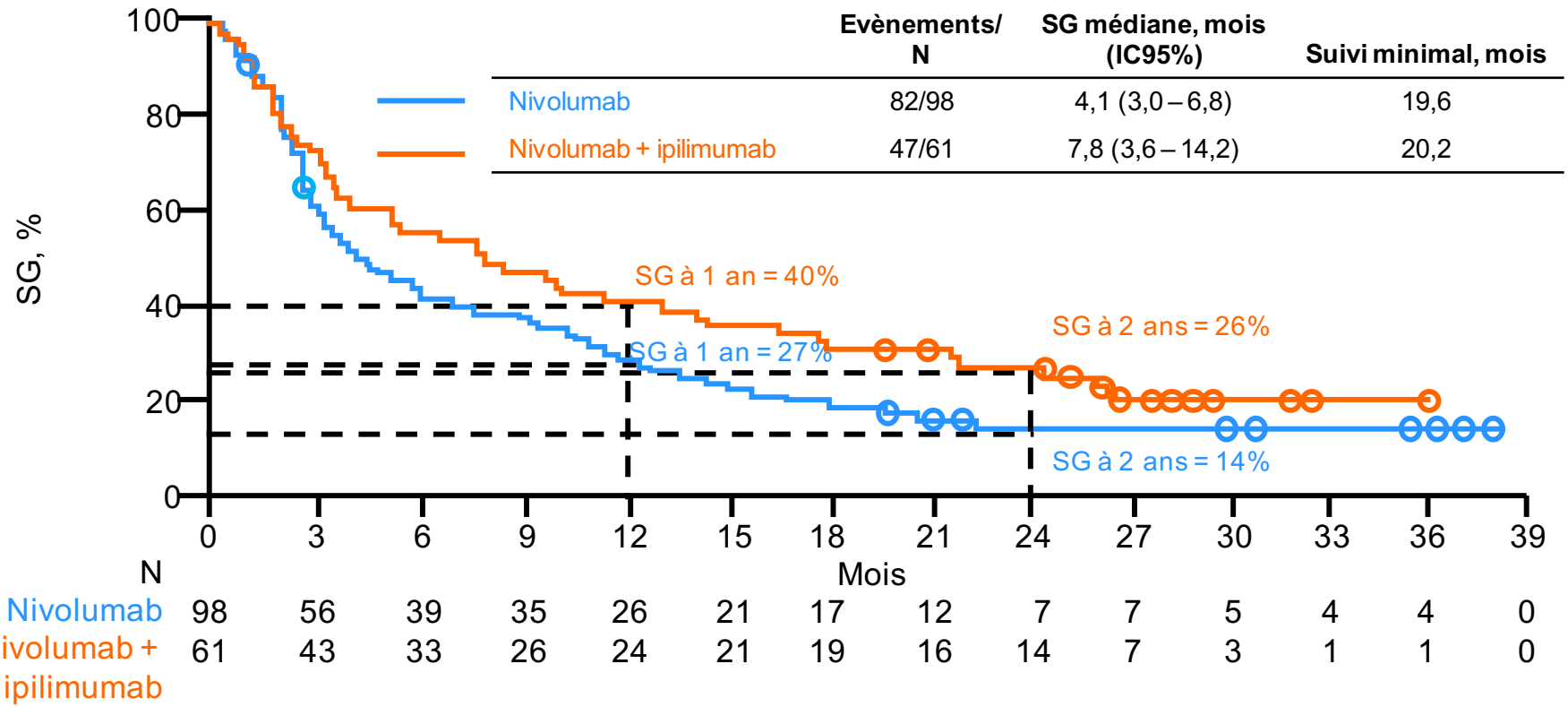
Hellmann MD et al. ASCO 2017

Nivolumab



Hellmann MD et al. ASCO 2017

Nivolumab



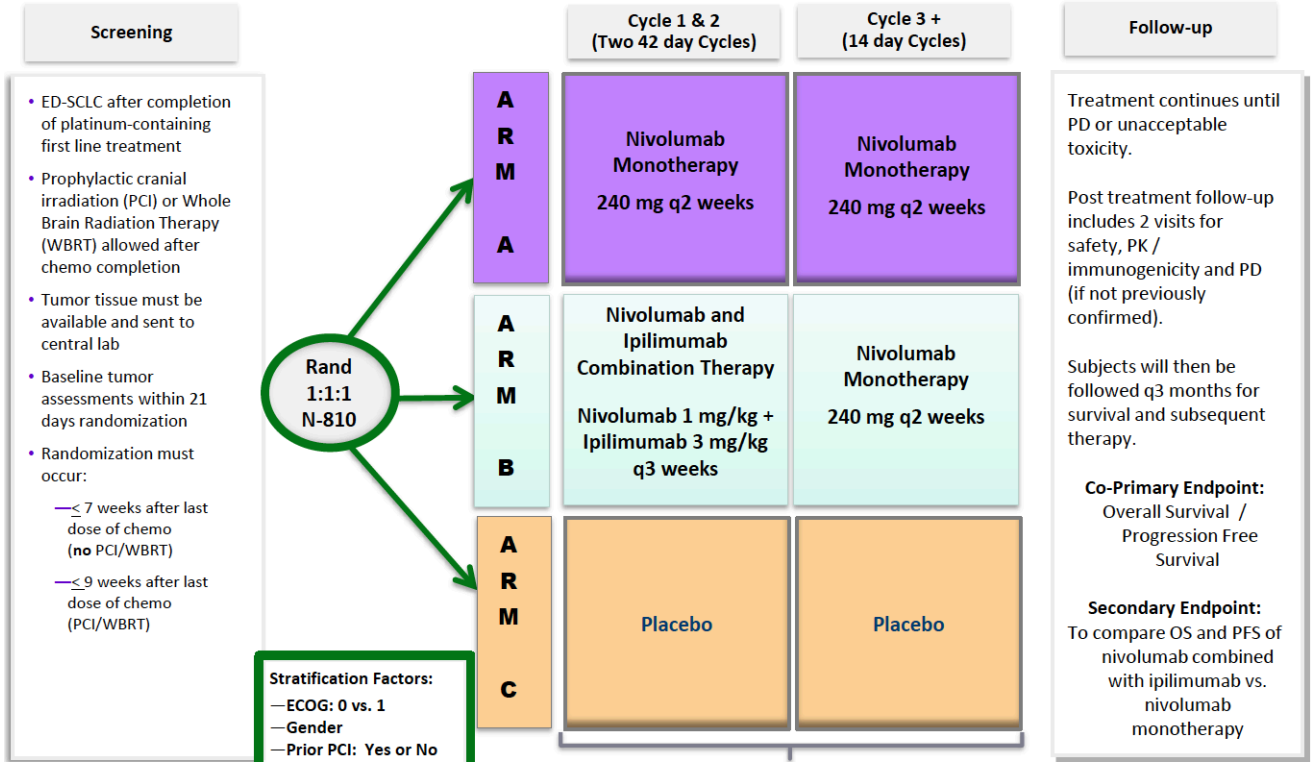
	Evènements/ N	SG médiane, mois (IC95%)	Suivi minimal, mois
Nivolumab	82/98	4,1 (3,0 – 6,8)	19,6
Nivolumab + ipilimumab	47/61	7,8 (3,6 – 14,2)	20,2

N													
Nivolumab	98	56	39	35	26	21	17	12	7	7	5	4	4	0
Nivolumab + ipilimumab	61	43	33	26	24	21	19	16	14	7	3	1	1	0

Hellmann MD et al. ASCO 2017

Phase III en cours

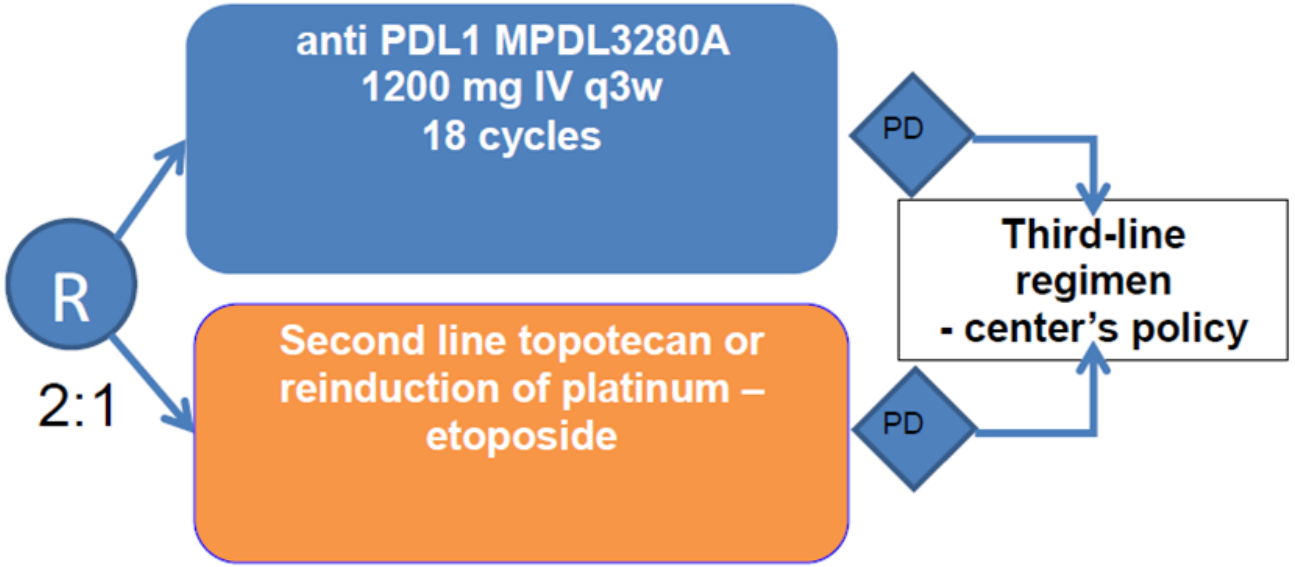
- **Checkmate 331** (NCT02481830): nivolumab vs chimiothérapie en 2ème ligne
- **Checkmate 451** (NCT02538666): maintenance ED-SCLC



IFCT 1603

Eligibility

- SCLC of any stage (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



Stratification variables

- > 90 days versus < 90 days PFS since end of first line
- Limited versus extensive at diagnosis
- PS
- Gender
- Center

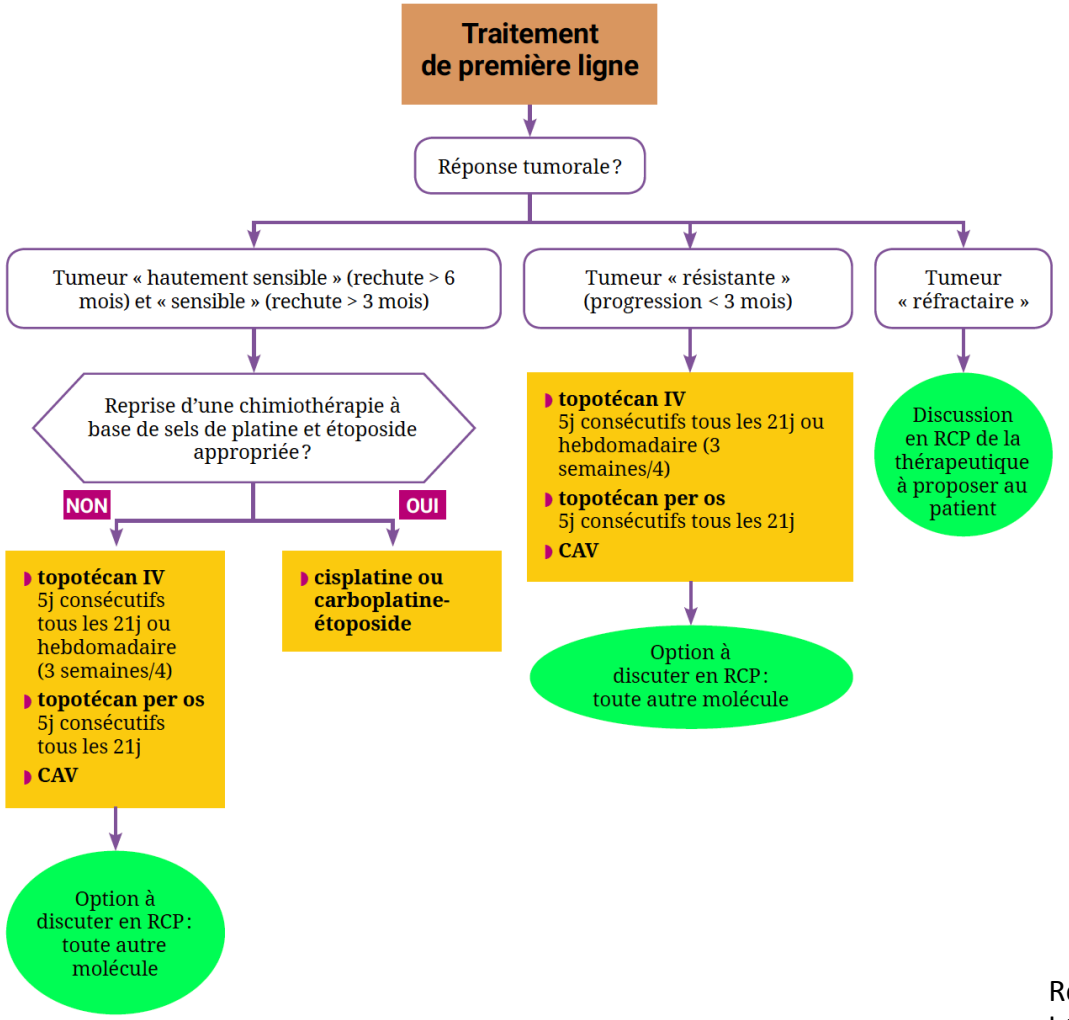
PI: Pujol JL, CHU Montpellier

Rova-T + Immunothérapie

Protocol Number	M16-300
Version and Date	Version 2, 16 December 2016, ***Final Protocol***
Protocol Title	A Phase 1/2 Study on the Safety of Rovalpituzumab Tesirine Administered in Combination with Nivolumab or Nivolumab and Ipilimumab for Adults with Extensive-Stage Small Cell Lung Cancer
Investigational Drugs	Rovalpituzumab tesirine (SC16LD6.5) Nivolumab (BMS-936558, MDX1106, ONO-4538, Opdivo®) Ipilimumab (MDX-010, Yervoy®)
Phase	1/2
EUDRA CT Number	2016-003686-26

Recrutement en cours

Conclusions



Référentiel national de RCP, 2015
http://www.e-cancer.fr/

Conclusions

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Les cancers à petites cellules : que faire en cas de rechute ?

Small cell lung cancer: What to do in case of relapse?

L. Greiller[1,*], N. Baize[2], C. Chouaïd[3]

Conclusions

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Second-line treatments of small-cell lung cancers

Nathalie Baize, Isabelle Monnet, Laurent Greillier, Gilles Quere, Mallorie Kerjouan, Henri Janicot, Alain Vergnenegre, Jean Bernard Auliac & Christos Chouaid