Quoi de neuf en radiothérapie thoracique en 2019 ?

Christophe Debelleix

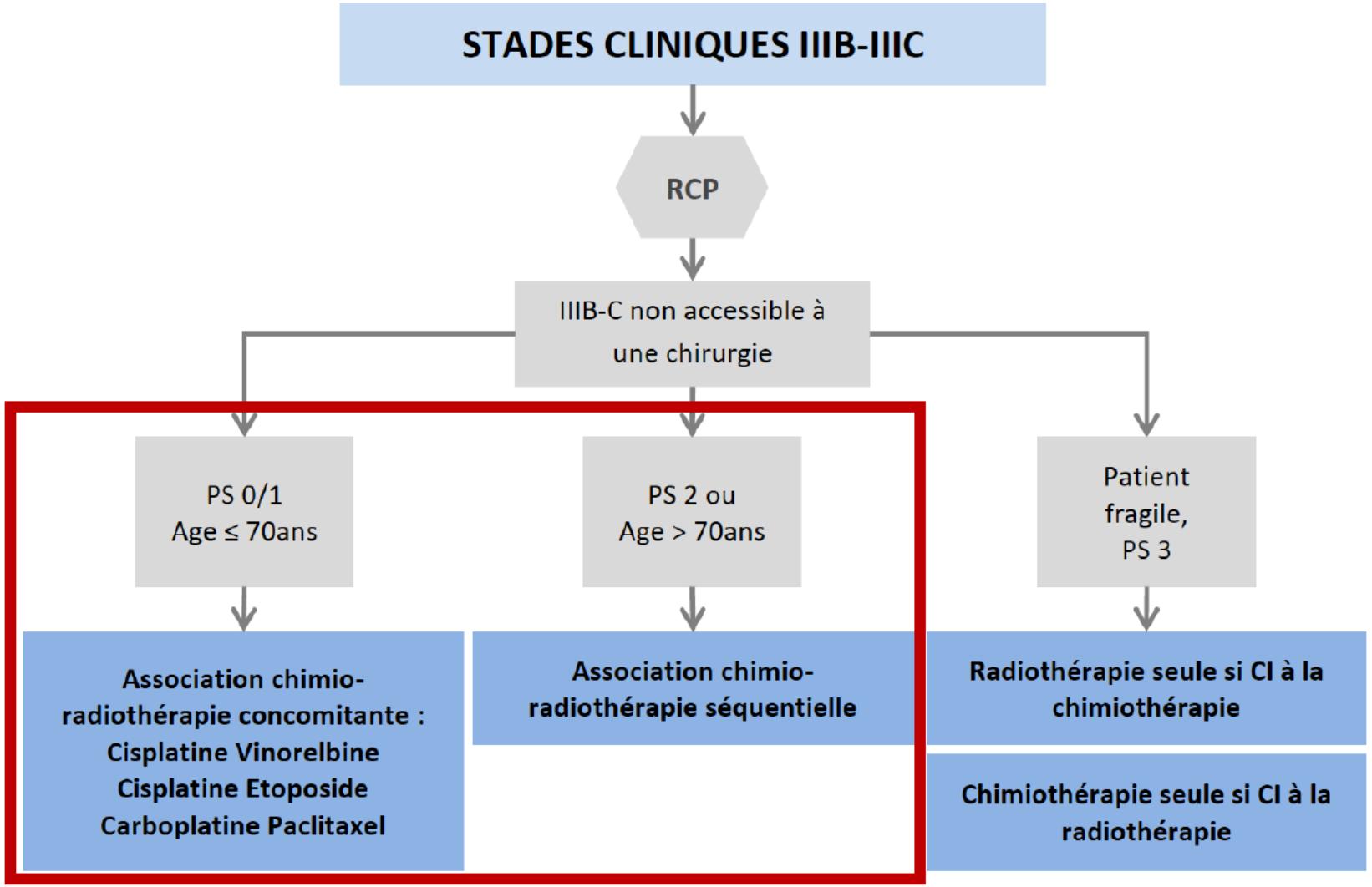
Clinique Tivoli Bordeaux

RADIOTHÉRAPIE - QUOI DE NEUF ?

POST-CONGRÈS 2019

Avant 2018…

La chimio-radiothérapie, traitement standard des CBNPC localement avancés non résécables



En pratique, jusqu'en 2018…

CT CT CT CT

RT 60 - 66 Gy

ou

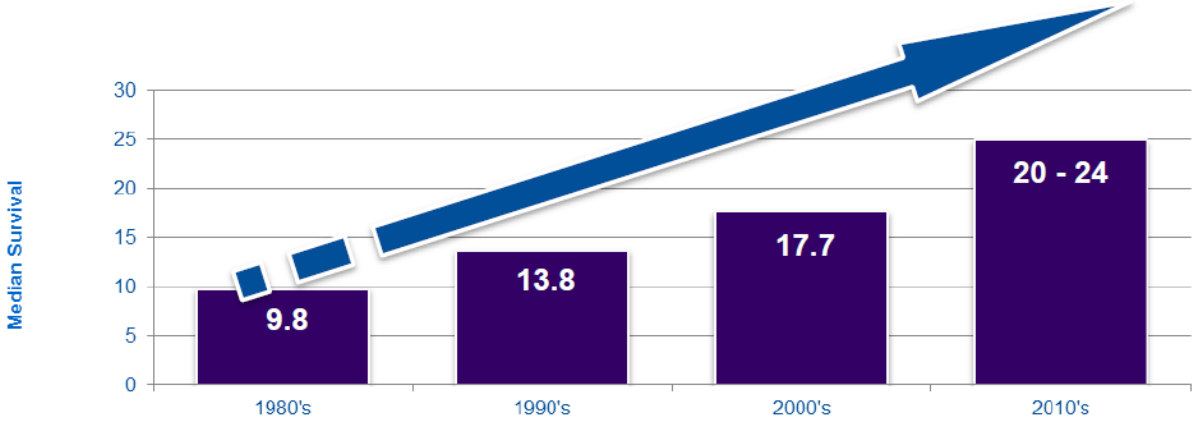
CT CT CT CT

RT 60 - 66 Gy

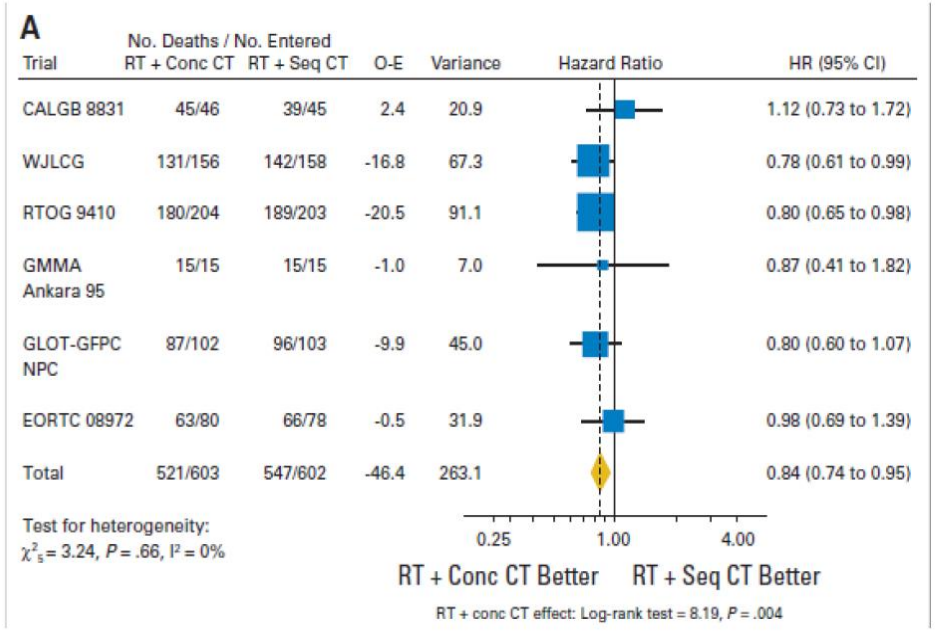
ou

CT CT CT

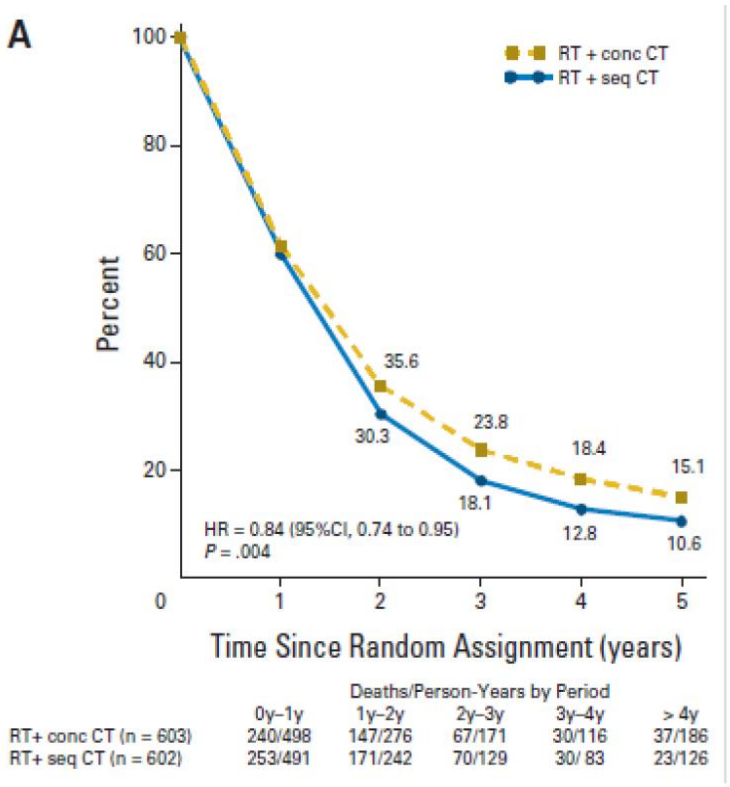
RT 60 - 66 Gy



Le standard est la chimio-radiothérapie



Bénéfice absolu en survie globale		
2 ans	3 ans	5 ans
5,3%	5,7%	4,5%



Aupérin A et al. JCO 2010; 28: 2181-90

1458PD

BARCELONA 2019 ESMO congress

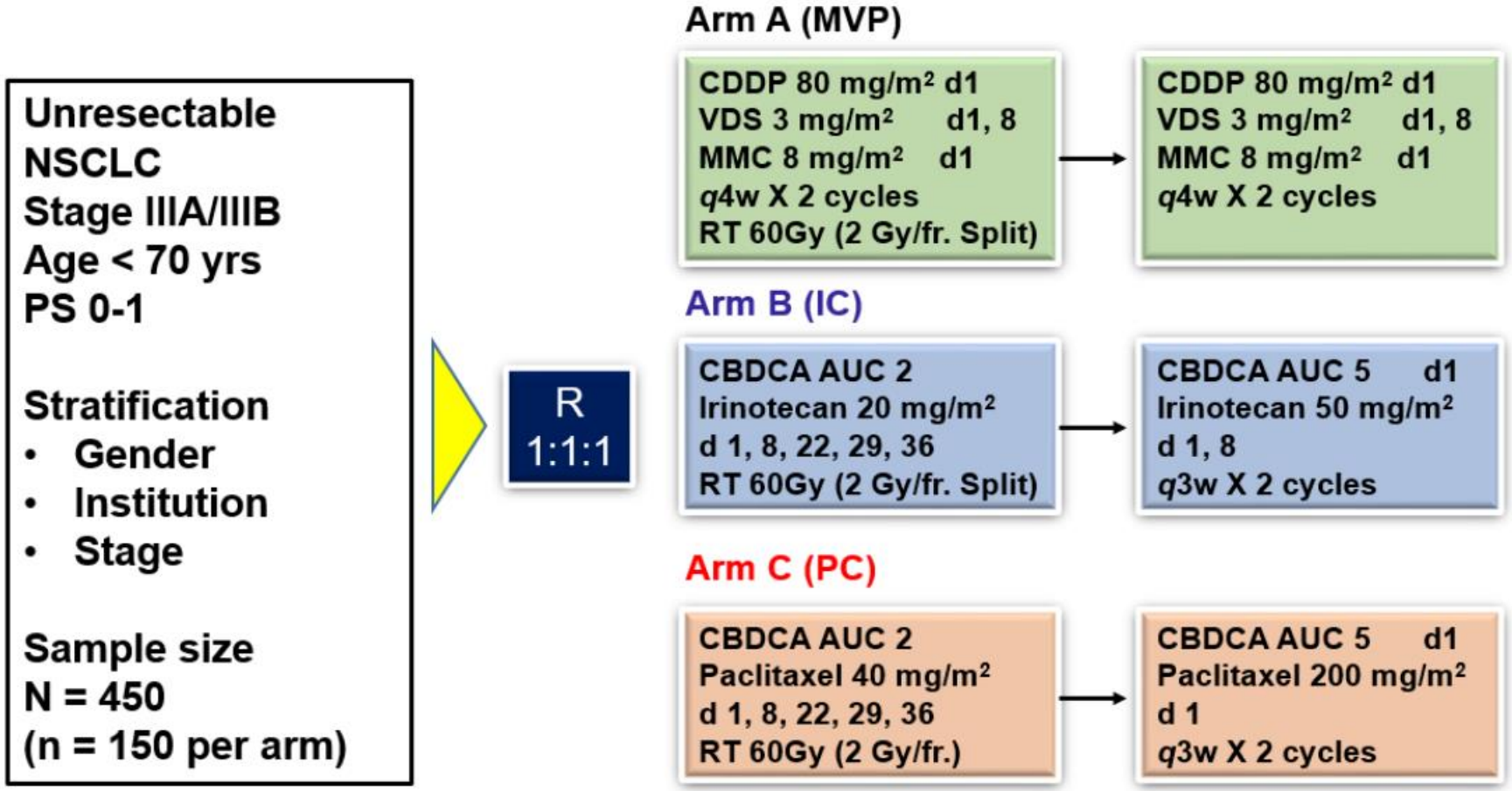
PHASE III STUDY COMPARING SECOND- AND THIRD GENERATION REGIMENS WITH CONCURRENT THORACIC RADIOTHERAPY IN PATIENTS WITH UNRESECTABLE STAGE III NON–SMALL-CELL LUNG CANCER:

10-year follow-up of West Japan Thoracic Oncology Group WJTOG0105

Yoshitaka Zenke [1], Masahiro Tsuboi [2], Yasutaka Chiba [3], Miyako Satouchi [4], Shigeki Mitsuoka [5], Junichi Shimizu [6], Haruko Daga [7], Daichi Fujimoto [8], Masahide Mori [9], Takuya Aoki [10], Toshiyuki Sawa [11], Shota Omori [12], Hideo Saka [13], Yasuo Iwamoto [14], Motoyasu Okuno [15], Tomonori Hirashima [16], Kosuke Kashiwabara [17], Motoko Tachihara [18], Nobuyuki Yamamoto [19], Kazuhiko Nakagawa [20]

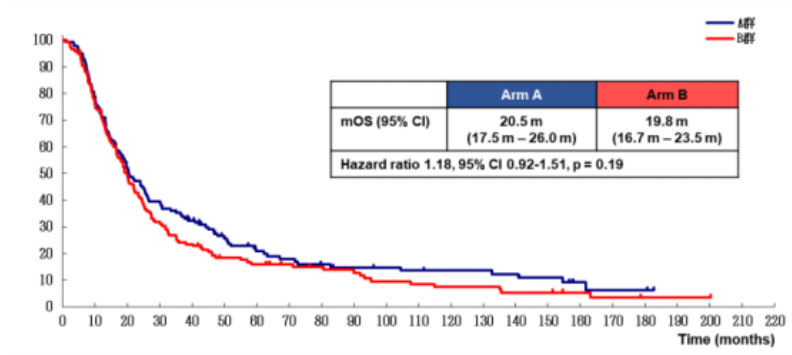
[1]Department of Thoracic Oncology, National Cancer Center Hospital East, [2]Department of Thoracic Surgery, National Cancer Center Hospital East, [3]Clinical Research Center, Kindai University Hospital, [4]Department of Thoracic Oncology, Hyogo Cancer Center, [5]Department of Clinical Oncology, Graduate School of Medicine, Osaka City University, [6]Department of Thoracic Oncology, Aichi Cancer Center Hospital, [7]Department of Medical Oncology, Osaka City General Hospital, [8]Department of Respiratory Medicine, Kobe City Medical Center General Hospital, [9]Department of Thoracic Oncology, National Hospital Organization Osaka Toneyama Medical Center, [10]Division of Pulmonary Medicine, Department of Medicine, Tokai University School of Medicine, [11]Division of Respiratory Medicine and Oncology, Gifu Municipal Hospital, [12]Division of Thoracic Oncology, Shizuoka Cancer Center, [13]Department of Respiratory Medicine and Medical Oncology, National Hospital Organization Nagoya Medical Center, [14]Department of Respiratory Medicine, Hiroshima City Hospital, [15]Department of Respiratory Medicine, Okazaki City Aichi Hospital, [16]Department of Thoracic Oncology, Osaka Prefectural Hospital Organization Osaka Habikino Medical Center, [17]Department of Respiratory Medicine, Kumamoto Regional Medical Center, [18]Division of Respiratory Medicine, Department of Internal Medicine, Kobe University Graduate School of Medicine, [19]Third Department of Internal Medicine, Wakayama Medical University, [20]Department of Medical Oncology, Kindai University Faculty of Medicine

STUDY DESIGN

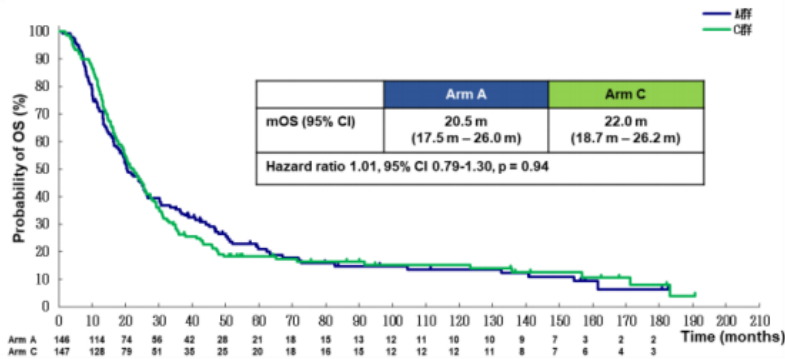


COMPARISON OF OVERALL SURVIVAL (OS) AND PROGRESSION-FREE SURVIVAL (PFS)

OS

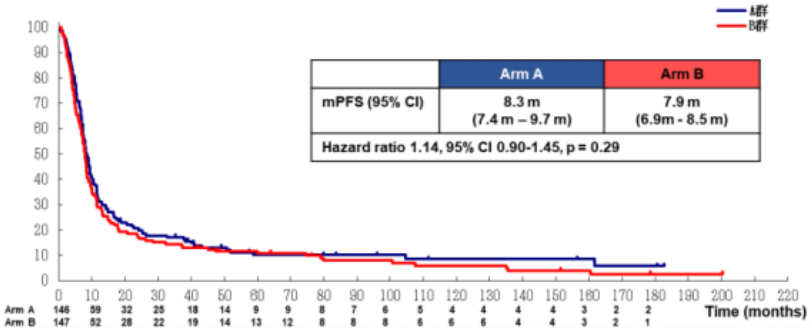


	5-yr (%) (95% CI)	7-yr (%) (95% CI)	10-yr (%) (95% CI)
Arm A	20.8 (14.3-28.3)	14.8 (9.1-21.9)	13.6 (8.0-20.7)
Arm B	16.0 (10.5-22.5)	13.9 (8.7-20.4)	7.5 (3.5-13.4)

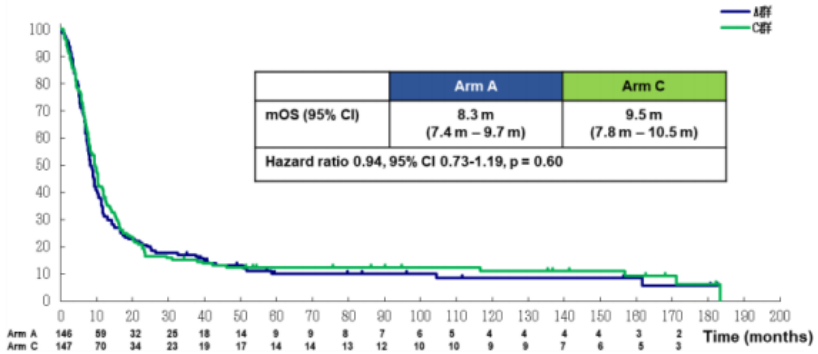


	5-yr (%) (95% CI)	7-yr (%) (95% CI)	10-yr (%) (95% CI)
Arm A	20.8 (14.3-28.3)	14.8 (9.1-21.9)	13.6 (8.0-20.7)
Arm C	18.3 (12.4-25.0)	16.3 (10.7-23.0)	15.2 (9.6-21.9)

PFS



	2-yr (%) (95% CI)	5-yr (%) (95% CI)	7-yr (%) (95% CI)	10-yr (%) (95% CI)
Arm A	20.7 (14.5-27.6)	10.2 (5.7-16.2)	10.2 (5.7-16.2)	8.5 (4.1-14.8)
Arm B	17.2 (11.6-23.7)	10.8 (6.4-16.5)	7.9 (4.1-13.4)	5.9 (2.6-11.1)

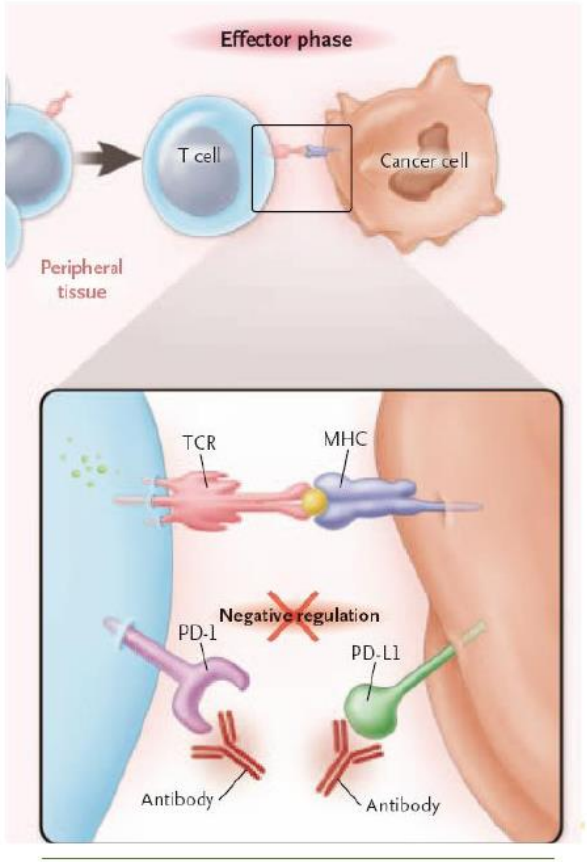


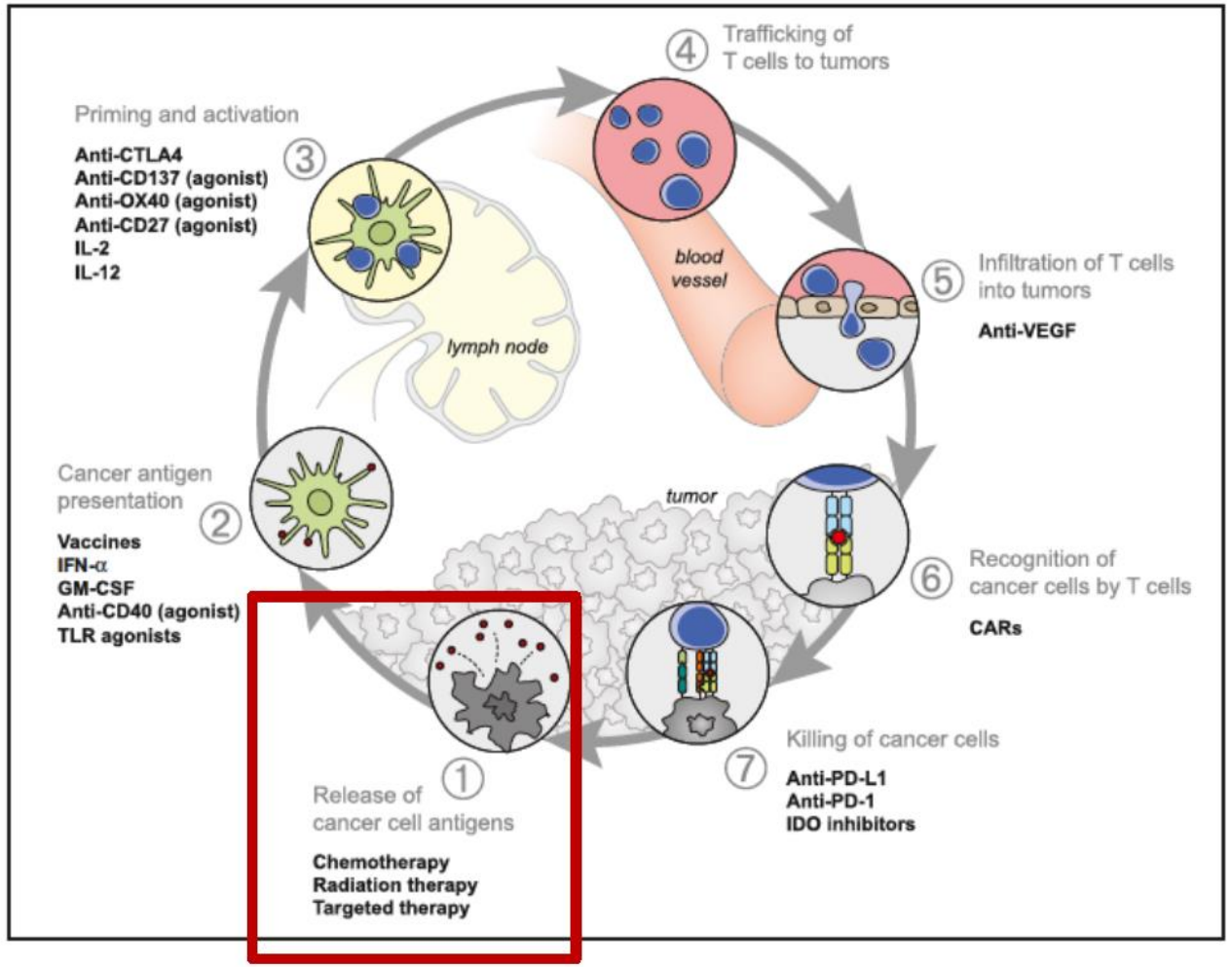
	2-yr (%) (95% CI)	5-yr (%) (95% CI)	7-yr (%) (95% CI)	10-yr (%) (95% CI)
Arm A	20.7 (14.5-27.6)	10.2 (5.7-16.2)	10.2 (5.7-16.2)	8.5 (4.1-14.8)
Arm C	16.6 (11.1-23.1)	12.3 (7.6-18.3)	12.3 (7.6-18.3)	11.1 (6.5-17.1)

BARCELONA 2019 ESMO congress


Immunothérapie

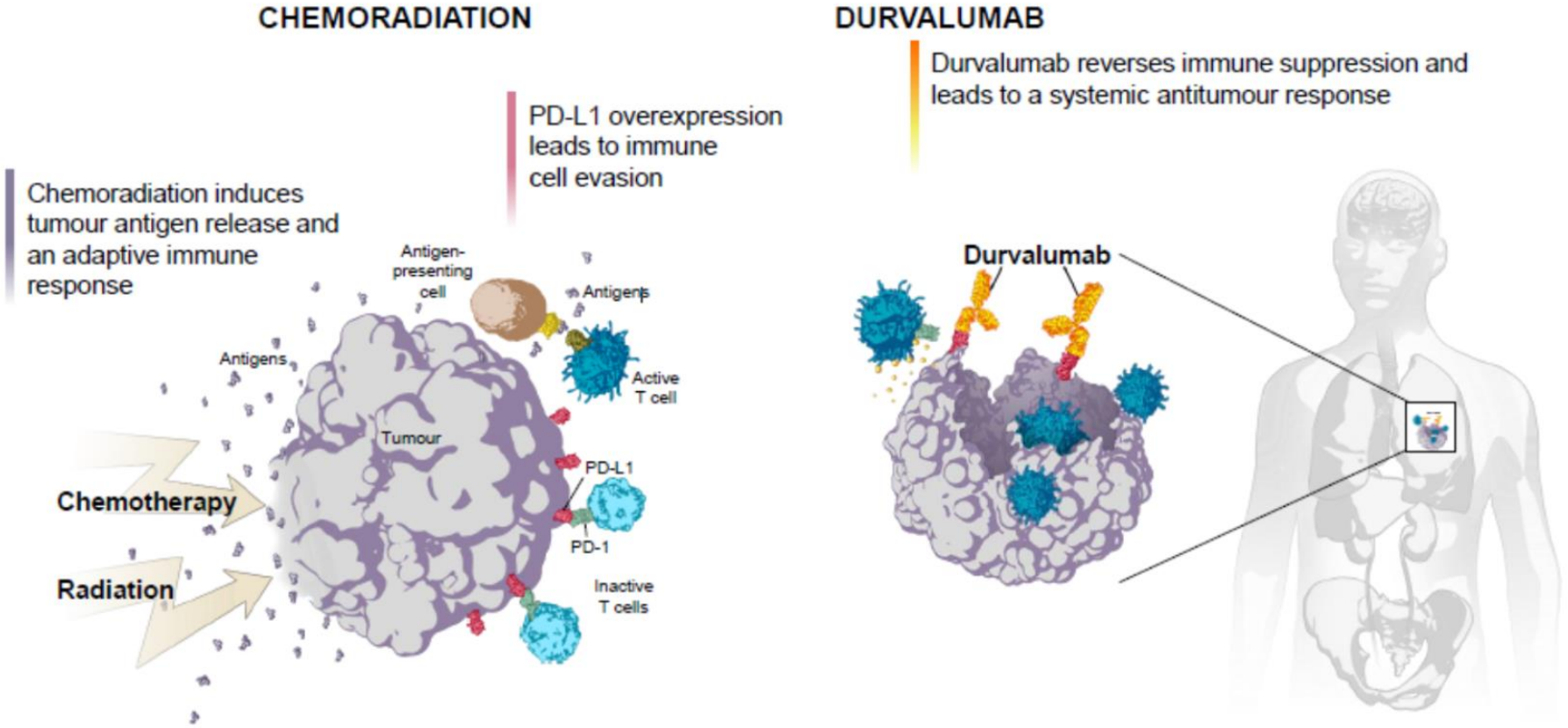
Inhibition de points de contrôle: PD-1 et PD-L1





Chen et al. Immunity 2013;39:1
Ribas. N Engl J Med 2012; 366:2517

Associer Immunothérapie et radiothérapie?



Deng et al. J Clin Invest 2014;124:687
Dovedi SJ et al. Cancer Res 2014;74:5458

ORIGINAL ARTICLE FREE PREVIEW

Overall Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC

Scott J. Antonia, M.D., Ph.D., Augusto Villegas, M.D., Davey Daniel, M.D., David Vicente, M.D., Shuji Murakami, M.D., Rina Hui, Ph.D., Takayasu Kurata, M.D., Ph.D., Alberto Chiappori, M.D., Ki H. Lee, M.D., Ph.D., Maike de Wit, M.D., Ph.D., Byoung C. Cho, M.D., Ph.D., Maryam Bourhaba, M.D., et al., for the PACIFIC Investigators*

December 13, 2018
N Engl J Med 2018; 379:2342-2350

Abstract

Immunothérapie en consolidation après chimio-radiothérapie

PACIFIC: Study Design

Phase 3, Randomized, Double-blind, Placebo-controlled, Multicenter, International Study[1]

- Unresectable, Stage III NSCLC without progression after definitive platinum-based cCRT (≥2 cycles)
- 18 years or older
- WHO PS score 0 or 1
- If available, archived pre-cCRT tumor tissue for PD-L1 testing*

All-comers population (i.e. irrespective of PD-L1 status)

N=713 randomized

1–42 days post-cCRT

R

2:1 randomization, stratified by age, sex, and smoking history

Durvalumab 10 mg/kg q2w for up to 12 months N=476

Placebo 10 mg/kg q2w for up to 12 months N=237

Primary endpoints

- PFS by BICR using RECIST v1.1†
- OS

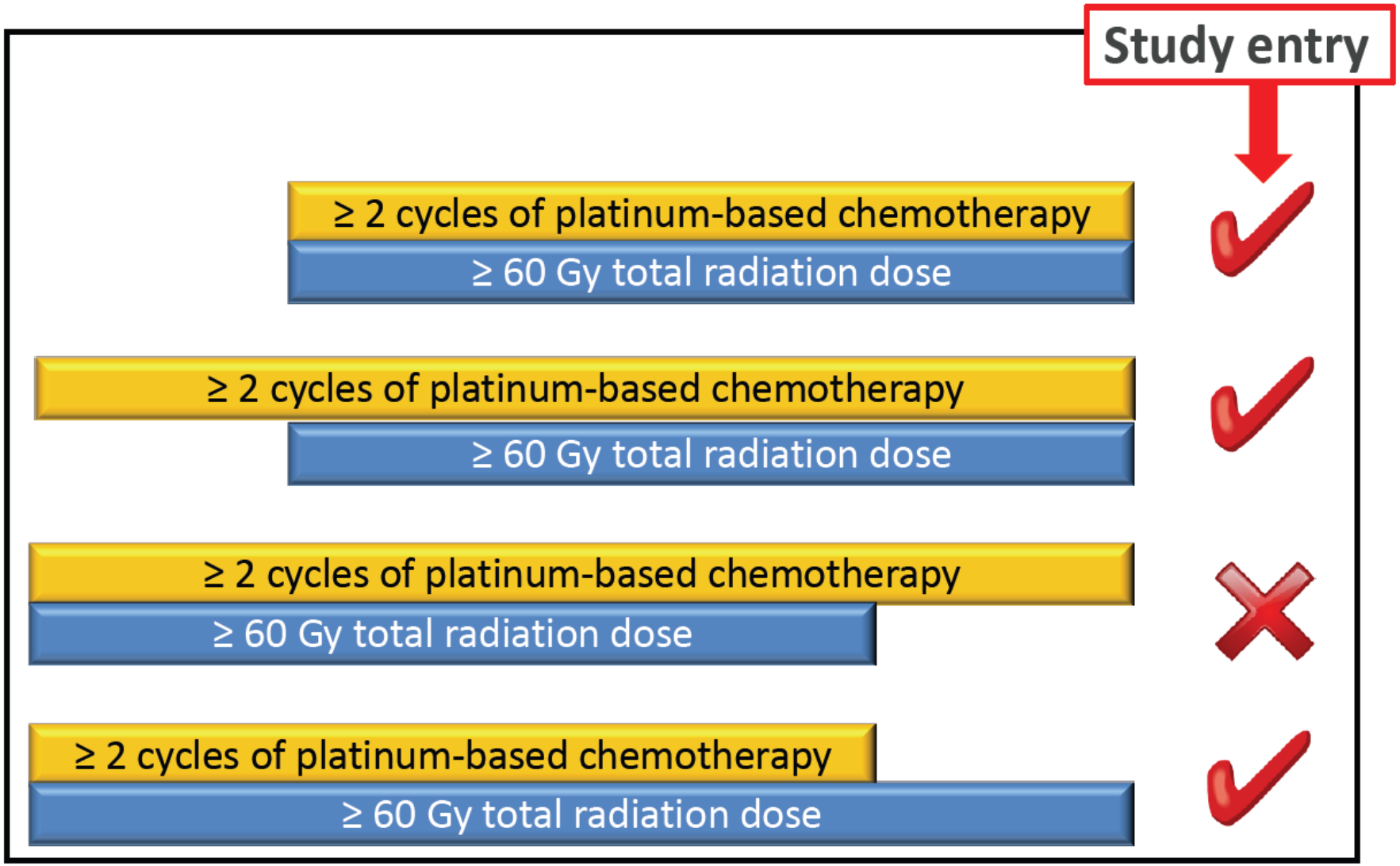
Key secondary endpoints

- ORR, DoR and TTDM by BICR
- PFS2 by investigator
- Safety
- PROs

*Using the Ventana SP263 immunohistochemistry assay

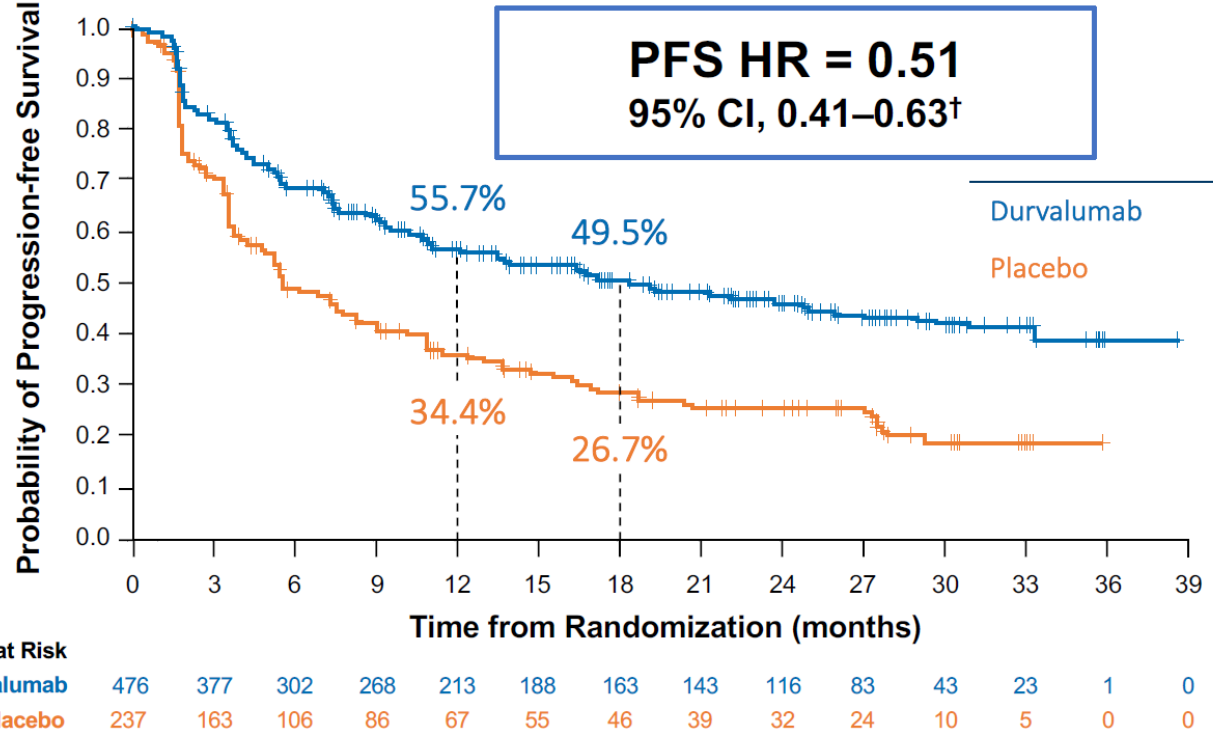
†Defined as the time from randomization until the date of objective disease progression or death by any cause in the absence of progression. BICR, blinded independent central review; cCRT, concurrent CRT; PFS2, time to second progression; RECIST, Response Evaluation Criteria in Solid Tumors; TTDM, time to death or distant metastasis. ClinicalTrials.gov number: NCT02125461

PACIFIC: Quelle séquence de chimio-radiothérapie?



Immunothérapie en consolidation après chimio-radiothérapie

Updated Progression-free Survival by BICR* (ITT)

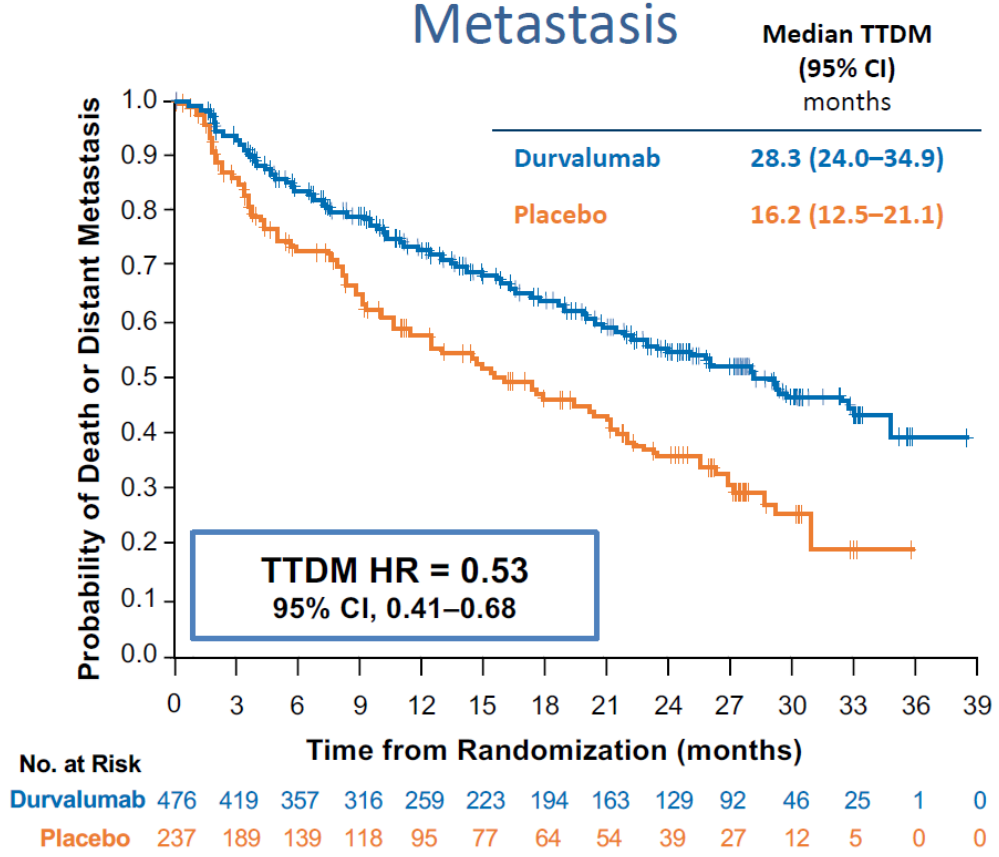


	No. of events / No. of patients (%)	Median PFS (95% CI) months
Durvalumab	243/476 (51.1)	17.2 (13.1–23.9)
Placebo	173/237 (73.0)	5.6 (4.6–7.7)

Antonia NEJM 2018

PACIFIC: survie sans métastases

Updated Time to Death or Distant Metastasis

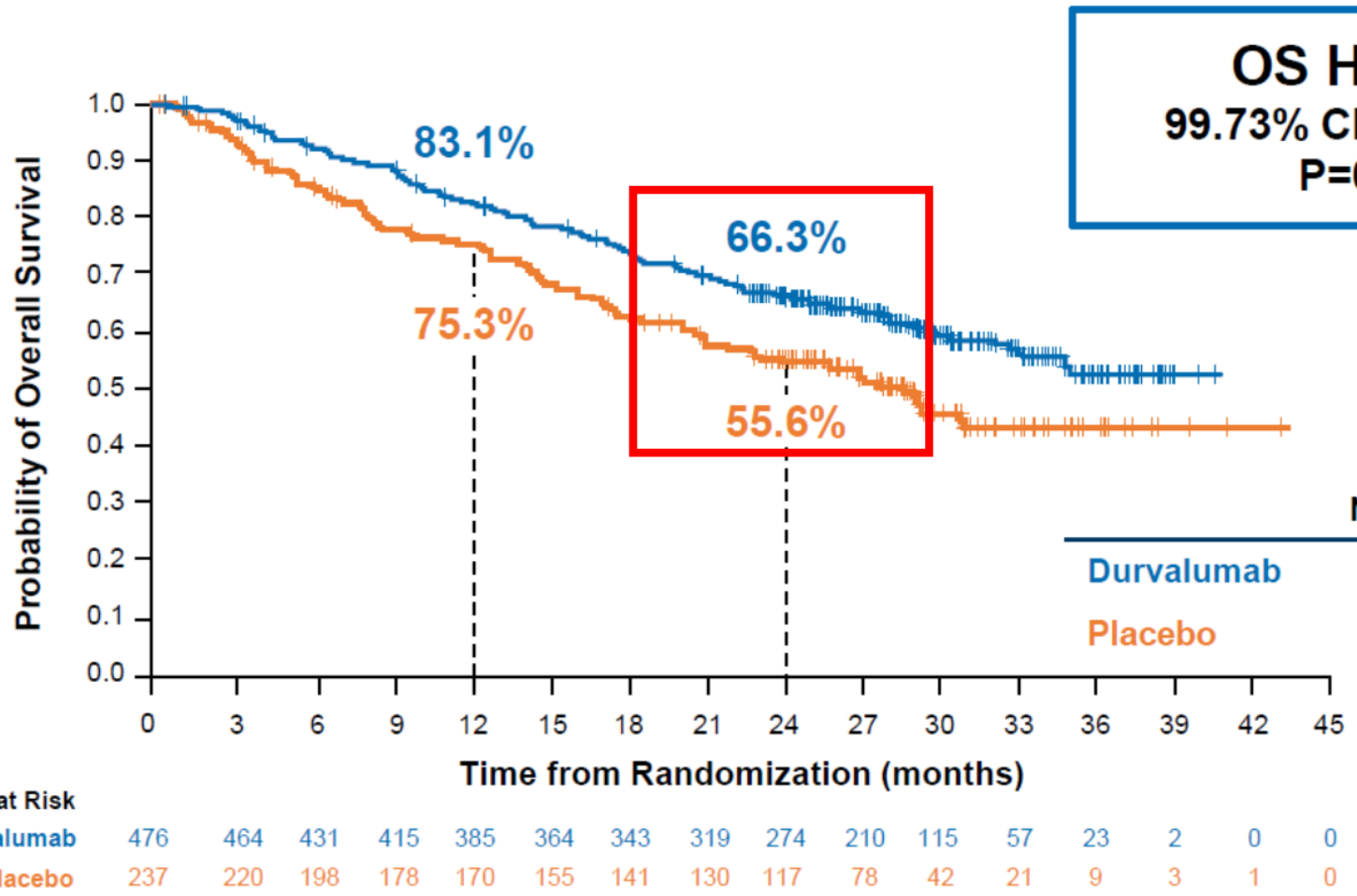


Updated Incidence of New Lesions by BICR* (ITT)

New Lesion Site†	Durvalumab (N=476)	Placebo (N=237)
Patients with any new lesion, n (%)	107 (22.5)	80 (33.8)
Lung	60 (12.6)	44 (18.6)
Lymph nodes	31 (6.5)	27 (11.4)
Brain	30 (6.3)	28 (11.8)
Liver	9 (1.9)	8 (3.4)
Bone	8 (1.7)	7 (3.0)
Adrenal	3 (0.6)	5 (2.1)
Other	10 (2.1)	5 (2.1)

Antonia et al. NEJM 2018

PACIFIC: survie globale

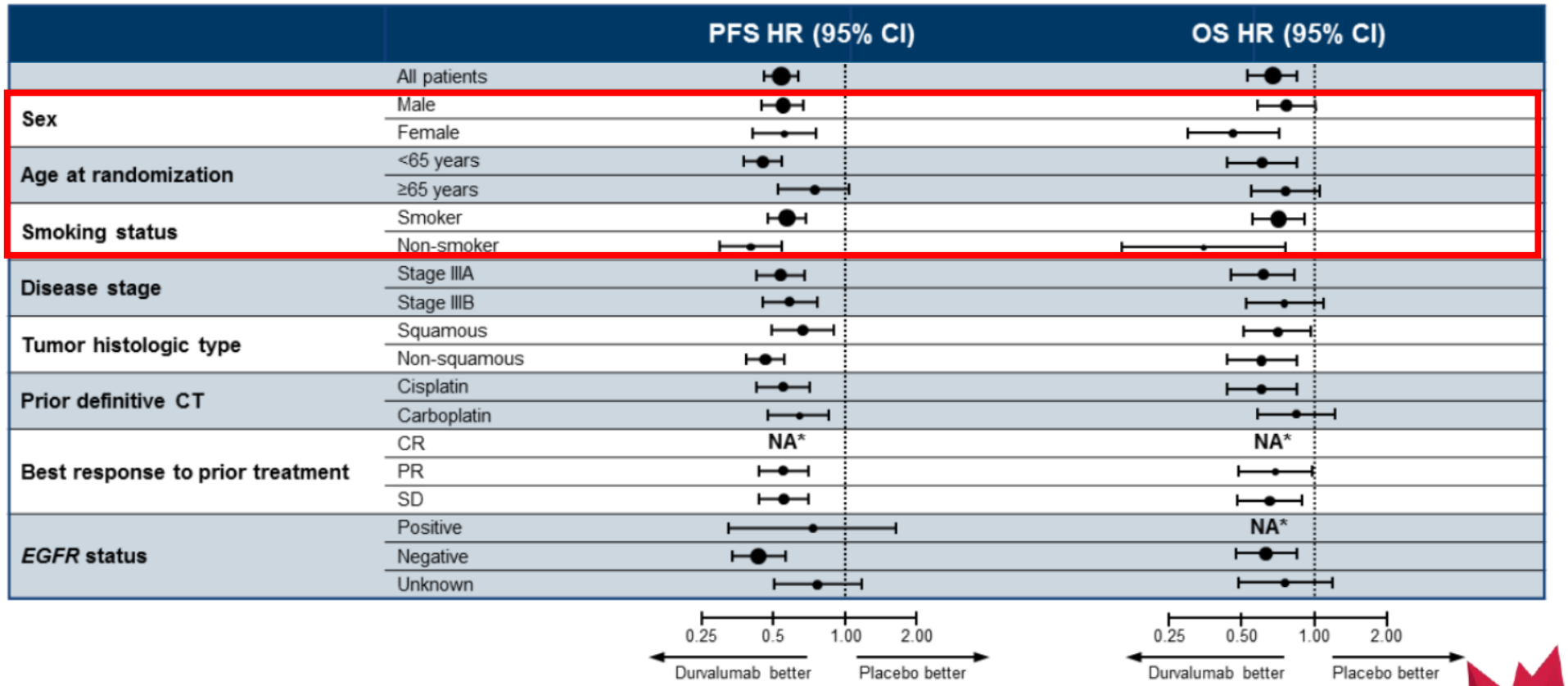


	No. of events / No. of patients (%)	Median OS (95% CI) months
Durvalumab	183/476 (38.4)	NR (34.7–NR)
Placebo	116/237 (48.9)	28.7 (22.9–NR)

Antonia NEJM 2018

PACIFIC

Analyse des sous groupes



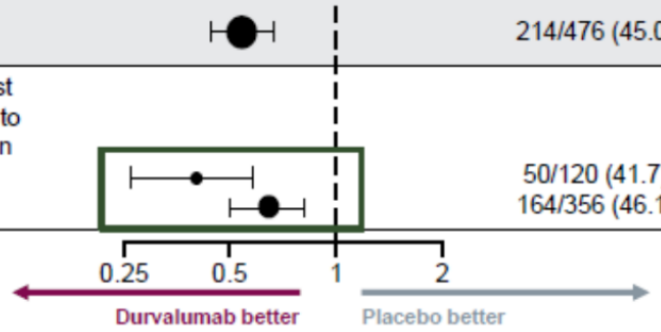
*Not calculated if subgroup has <20 events

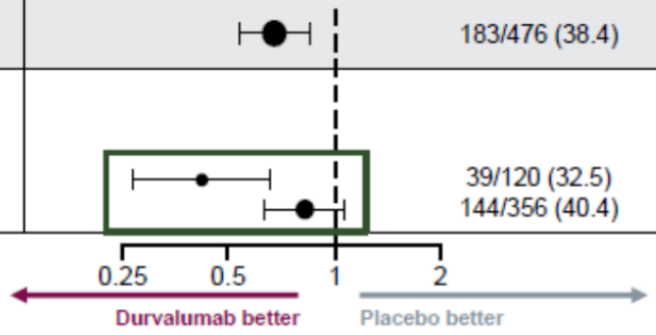
Antonia et al. NEJM 2018

Données exploratoires

Délai après radio-chimio

	PFS (BICR)			OS		
	HR	No. of events / No. of patients (%)		HR	No. of events / No. of patients (%)	
	(95% CI)	Durvalumab	Placebo	(95% CI)	Durvalumab	Placebo
ITT[1,2]		214/476 (45.0)	157/237 (66.2)		183/476 (38.4)	116/237 (48.9)
Time from last radiotherapy to randomisation						
<14 days		50/120 (41.7)	46/62 (74.2)		39/120 (32.5)	35/62 (56.5)
≥14 days		164/356 (46.1)	111/175 (63.4)		144/356 (40.4)	81/175 (46.3)

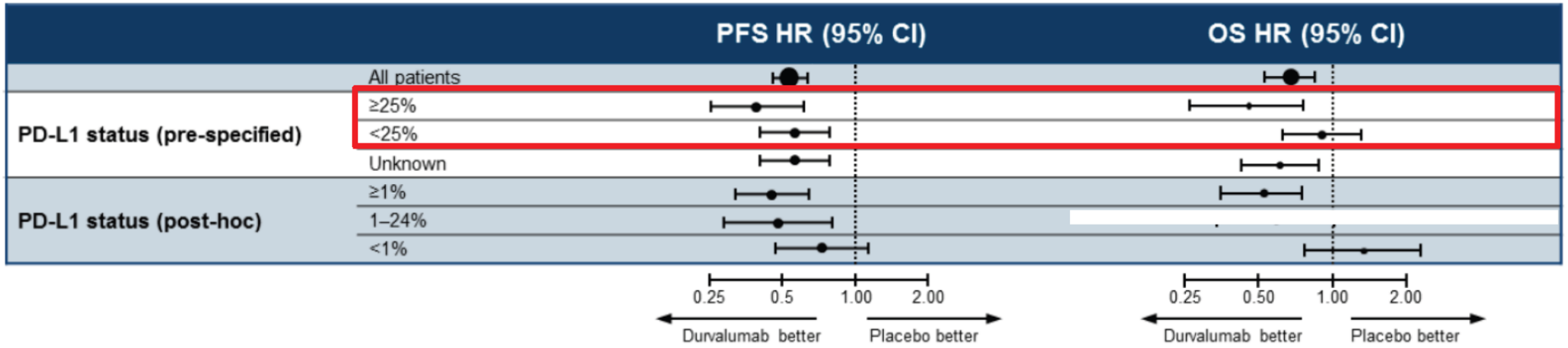




	TTDM (BICR)			ORR (BICR)	
	HR	No. of events / No. of patients (%)		%	
	(95% CI)	Durvalumab	Placebo	Durvalumab	Placebo
ITT[1]	0.52 (0.39, 0.69)	131/476 (27.5)	98/237 (41.4)	28.4	16.0
Time from last radiotherapy to randomisation					
<14 days	0.33 (0.20, 0.55)	30/120 (25.0)	34/62 (54.8)	34.2	16.4
≥14 days	0.70 (0.51, 0.95)	101/356 (28.4)	64/175 (36.6)	26.5	15.8

Faivre-Finn et al. ESMO 2018

PACIFIC: biomarqueur PD-L1

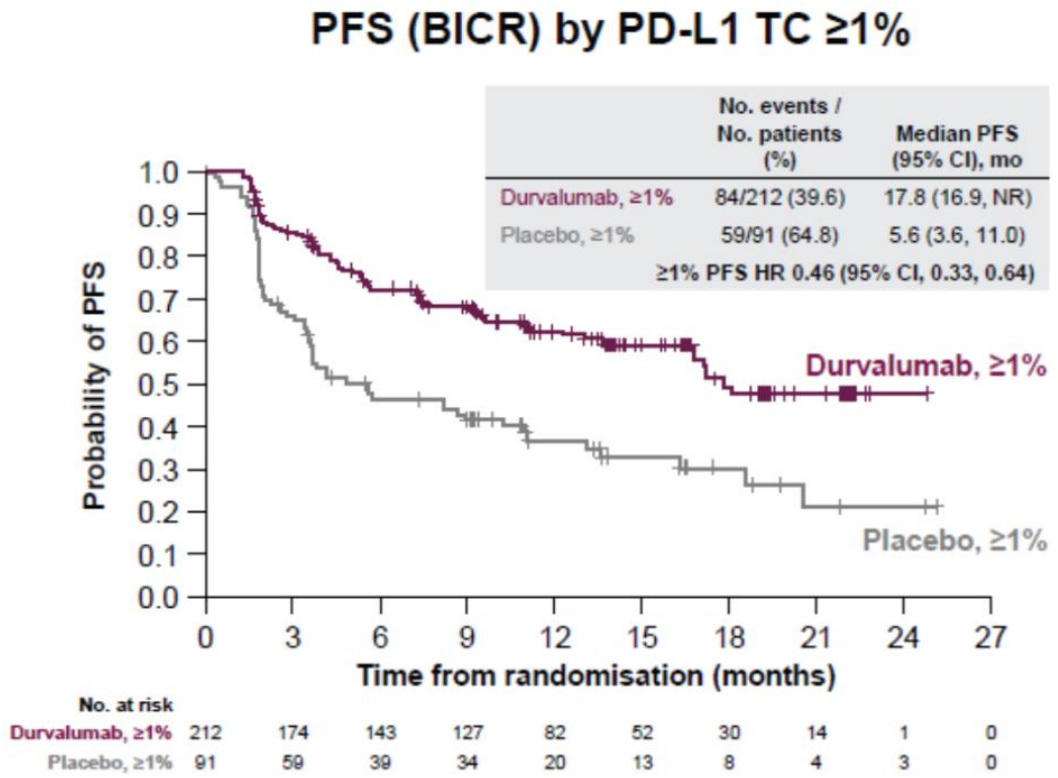


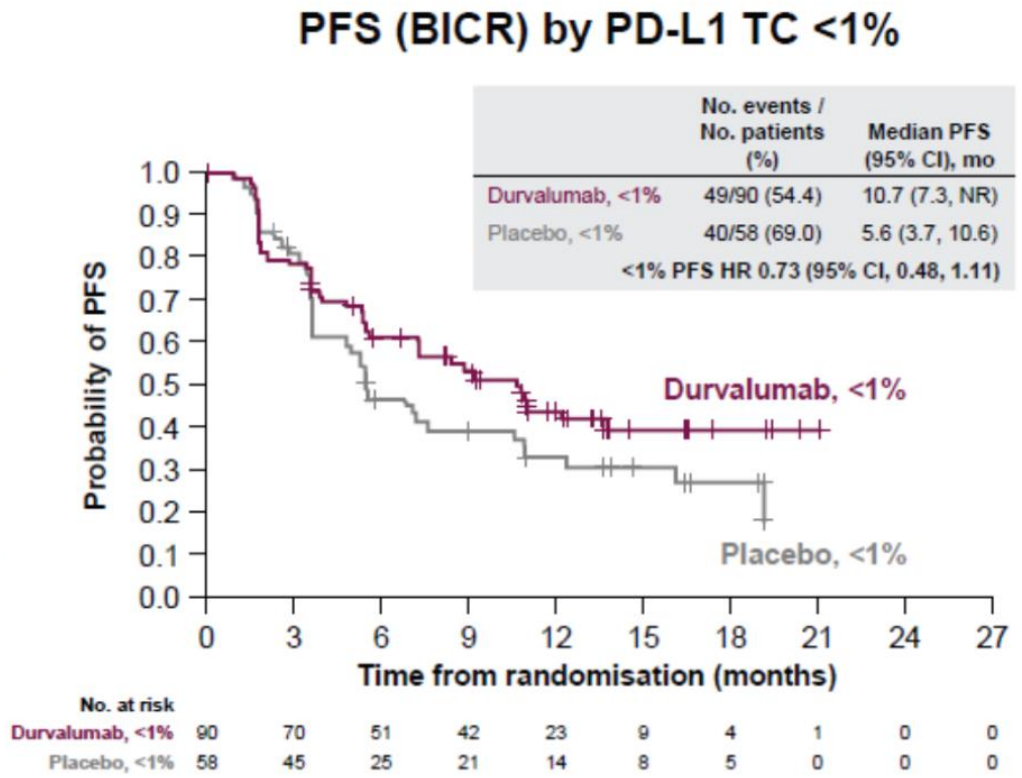
- Important facts regarding PD-L1 status:
  - PD-L1 testing was not required
  - 37% of patients with unknown PD-L1 status
  - PD-L1 status was obtained pre-CRT (getting a sample post-CRT medically not feasible)
  - PD-L1 expression-level cutoff of 1% was part of an unplanned post-hoc analysis requested by a health authority

Note : PFS data based on data cutoff of Feb 13, 2017, and OS data based cutoff of March 22, 2018

Faivre-Finn et al. ESMO 2018

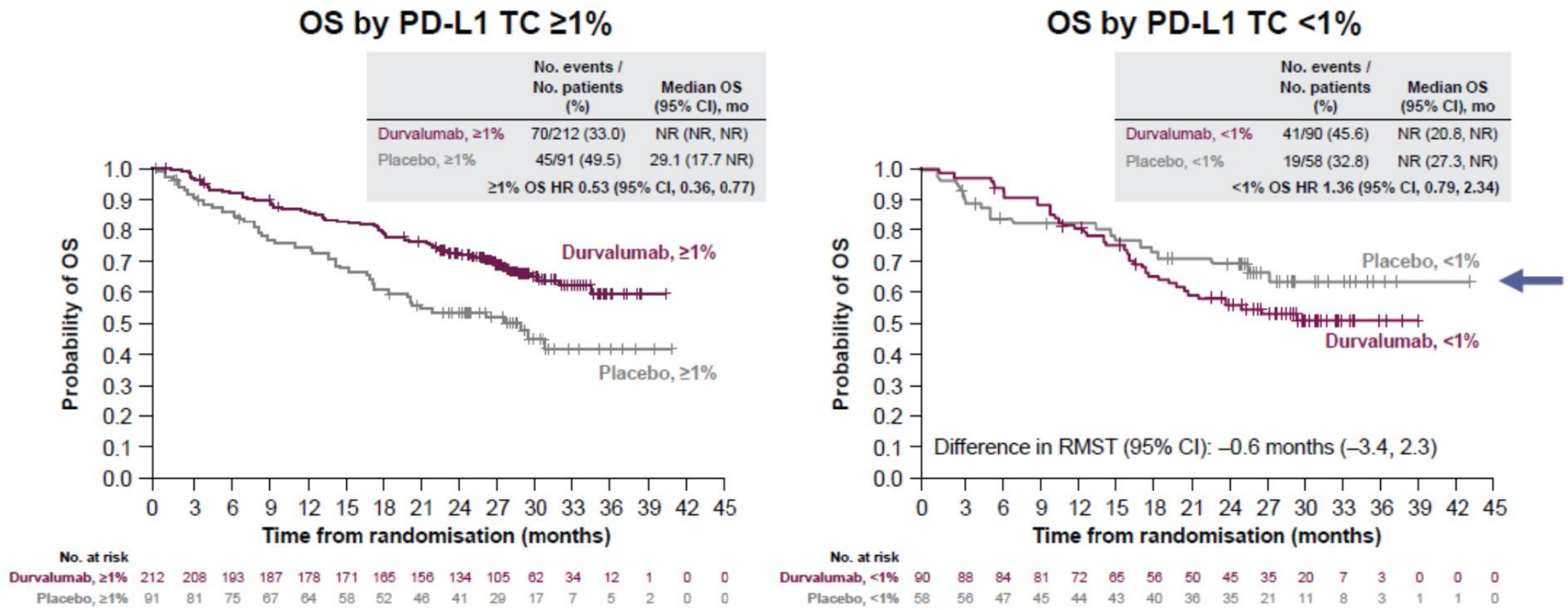
Analyse post-hoc: expression de PD-L1





Faivre-Finn et al. ESMO 2018

Analyse post-hoc: expression de PD-L1



- In the PD-L1 TC <1% subgroup, the number of events are low and overall the subgroup is small
- Imbalances in baseline characteristics

Faivre-Finn et al. ESMO 2018

AMM INFINZI® (DURVALUMAB)

L'indication validée par la décision de la Commission Européenne dans le cadre de l'AMM de IMFINZI (durvalumab) le 24 septembre 2018:

IMFINZI est indiqué en monothérapie dans le traitement des patients adultes atteints d'un cancer bronchique non à petites cellules (CBNPC) localement avancé, non opérable, dont les tumeurs expriment PD-L1 ≥ 1% des cellules tumorales et dont la maladie n'a pas progressé après une chimioradiothérapie à base de platine.

AMM INFINZI® (DURVALUMAB)

Profil de tolérance

MADRID 2017 ESMO congress

13 février 2017

Safety Summary*

	Durvalumab (N=475)	Placebo (N=234)
Any-grade all-causality AEs, n (%)	460 (96.8)	222 (94.9)
Grade 3/4	142 (29.9)	61 (26.1)
Grade 5	21 (4.4)	13 (5.6)
Leading to discontinuation	73 (15.4)	23 (9.8)
Any-grade treatment-related AEs, n (%)	322 (67.8)	125 (53.4)
SAEs, n (%)	136 (28.6)	53 (22.6)
Any-grade immune-mediated AEs, n (%)	115 (24.2)	
Grade 3/4	16 (3.4)	

*Two patients randomized to placebo received at least one dose of durvalu

22 mars 2018

	Durvalumab (N=475)	Placebo (N=234)
Any-grade all-causality AEs, n (%)	460 (96.8)	222 (94.9)
Grade 3/4	145 (30.5)	61 (26.1)
Outcome of death	21 (4.4)	15 (6.4)
Leading to discontinuation	73 (15.4)	23 (9.8)
Serious AEs, n (%)	138 (29.1)	54 (23.1)
Any-grade pneumonitis/radiation pneumonitis, n (%)	161 (33.9)	58 (24.8)
Grade 3/4	17 (3.6)	7 (3.0)
Outcome of death	5 (1.1)	5 (2.1)
Leading to discontinuation	30 (6.3)	10 (4.3)

ESMO 2019

Efficacy evaluation of concurrent nivolumab addition to a first-line, concurrent chemo-radiotherapy regimen in unresectable locally advanced NSCLC – Results from the European Thoracic Oncology Platform (ETOP 6-14) NICOLAS phase II trial.

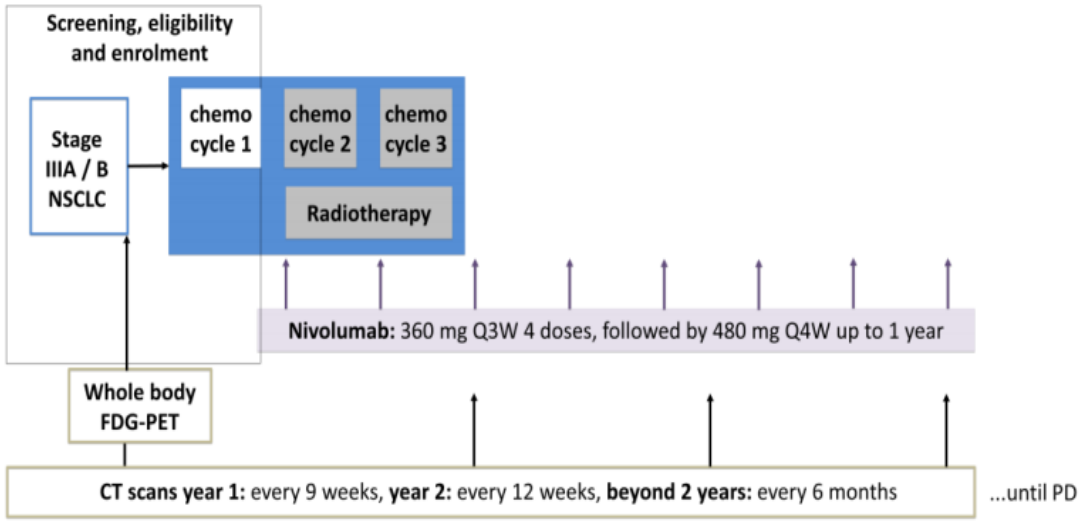
Solange Peters et al.

ESMO 2019 poster discussion

ESSAI NICOLAS

Essai de phase II non randomisé CBNPC stade III

- The safety analysis has earlier provided evidence that nivolumab administration concurrently to chemo-radiotherapy (CRT) is safe and tolerable, with respect to the occurrence of clinically relevant (grade≥3) pneumonitis.



Primary endpoints:

- Pneumonitis-free rate of grade ≥ 3 (CTCAE V4.0) any time during 6 months post radiotherapy.
- Hierarchically tested: 1-year progression-free survival (PFS) (from chemotherapy start)

Hierarchical design: IF safety proven → Efficacy evaluation:

- **1-year PFS, sample size n=74**
- H_0: $PFS_0 \leq 45\%$ vs H_1: $PFS_1 > 60\%$ (1-sided alpha=5%, power=83%)
- *Success rule: at least 41 patients reach 1-year without PFS event (i.e., maximum 33 PFS events)*

Results: Main Efficacy Analysis

Main Efficacy Analysis (21 August 2019): 1-year PFS

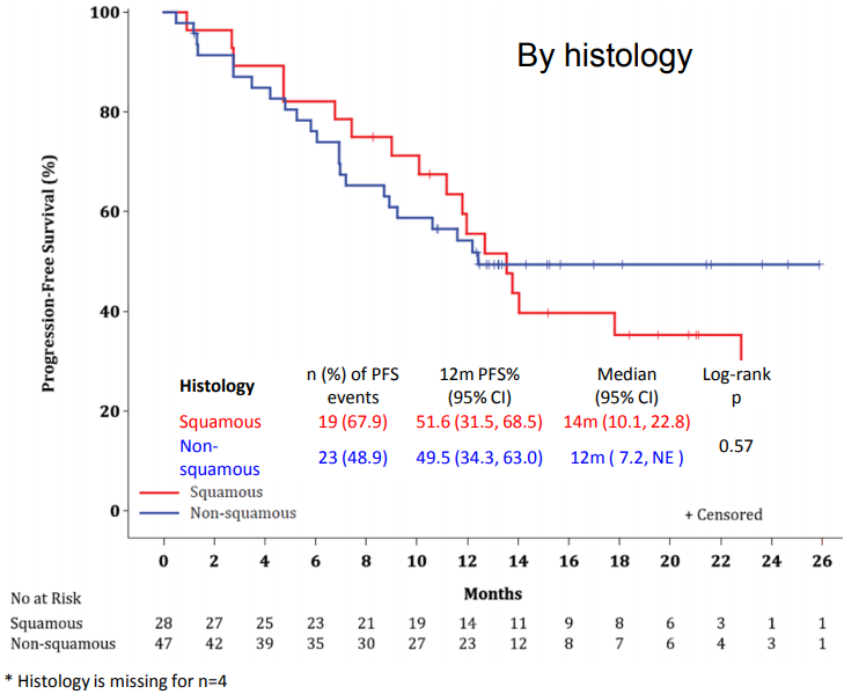
Among 74 evaluable patients:

- 37 PFS events have occurred
- 37 patients are progression-free
- 1-year PFS rate 50.0% (90% Exact binomial CI: 39.9%, 60.1%)

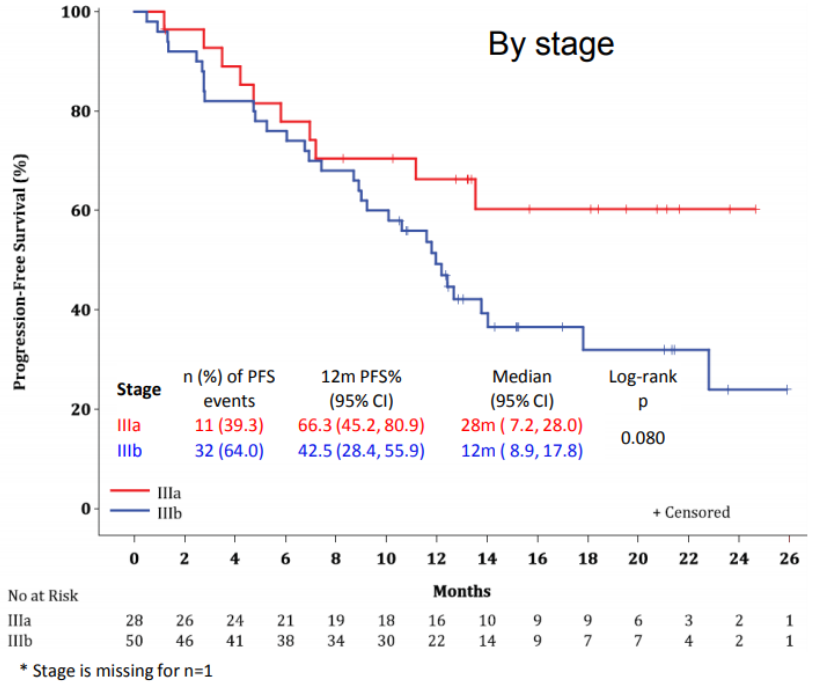
- The required number of 41 patients without progression at 1-year has not been reached.
- **Thus, we cannot reject the null hypothesis of 1-year PFS rate ≤45% versus 60% (p-value=0.23).**

Note: 1-year (12-month) PFS time is rounded to scheduled evaluation month.

7 | Results: Progression-free survival (for all N=79 enrolled patients, by 23 May 2019)



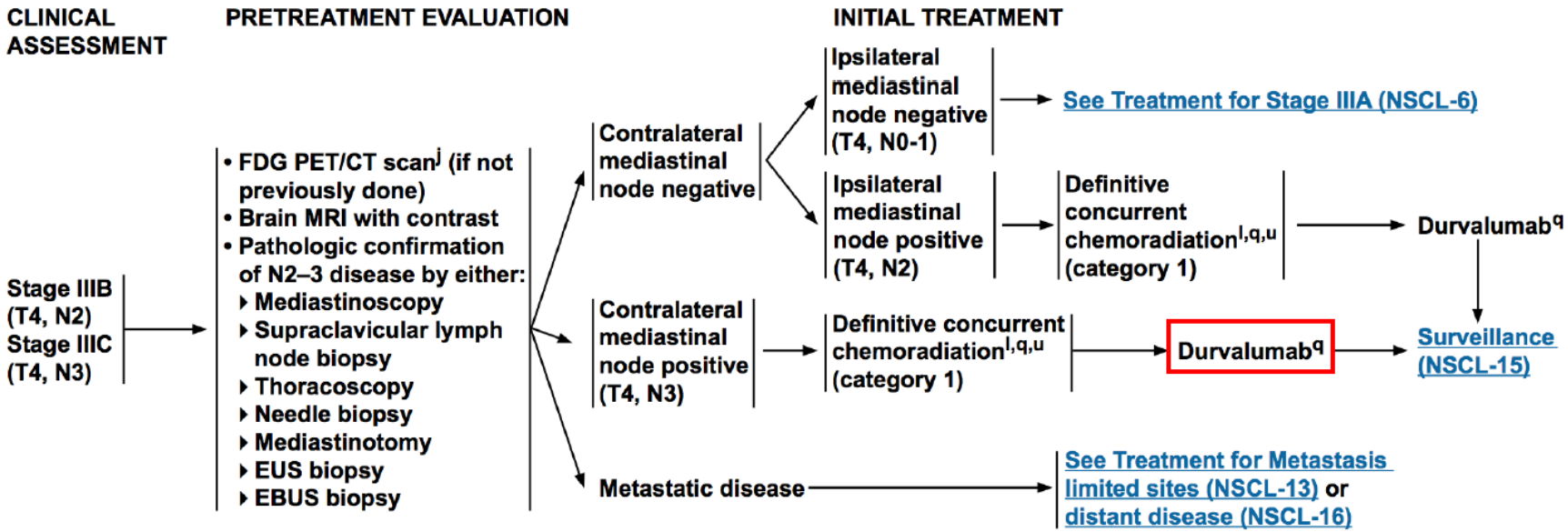
* Histology is missing for n=4



* Stage is missing for n=1

- SG à 1 an de 79 %
- Médiane de SG estimée à 25 mois (données non matures)
- Profil de toxicité acceptable de l'association RT/CT + nivolumab
- Résultats d'efficacité décevants

NCCN Guidelines 2018



CHEMOTHERAPY REGIMENS USED WITH RADIATION THERAPY

Concurrent Chemotherapy/RT Regimens

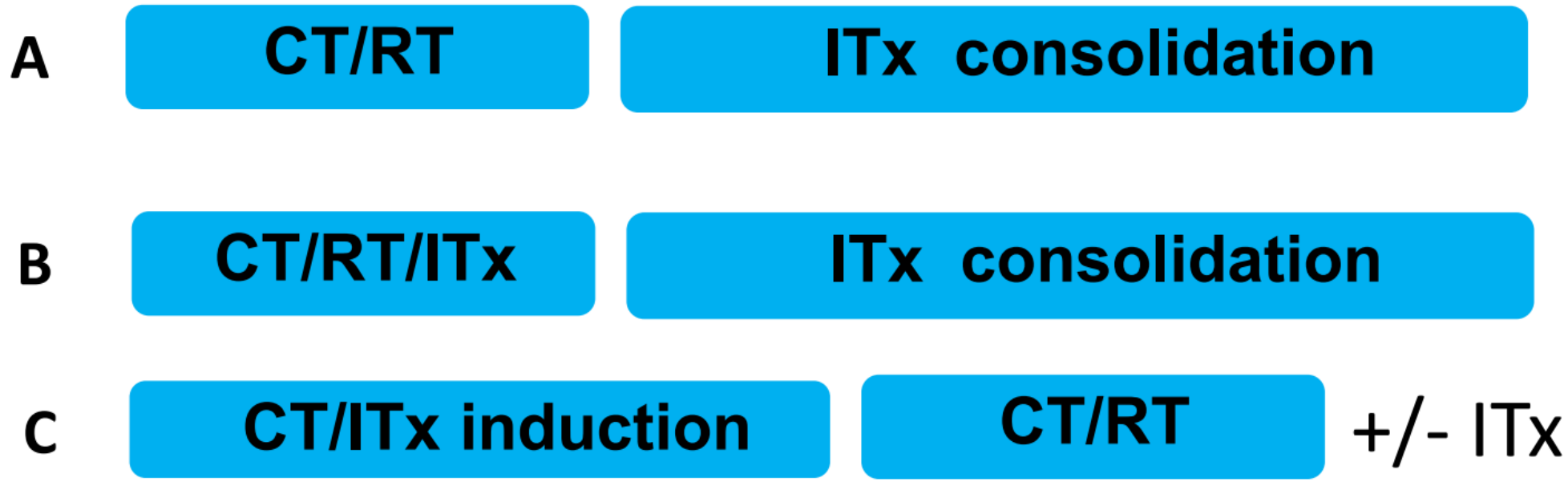
- Cisplatin 50 mg/m² on days 1, 8, 29, and 36; etoposide 50 mg/m² days 1–5, 29–33; concurrent thoracic RT[a,b,*,†]
- Cisplatin 100 mg/m² days 1 and 29; vinblastine 5 mg/m²/weekly x 5; concurrent thoracic RT[b,*,†]
- Carboplatin AUC 5 on day 1, pemetrexed 500 mg/m² on day 1 every 21 days for 4 cycles; concurrent thoracic RT[c] (nonsquamous)[*,†]
- Cisplatin 75 mg/m² on day 1, pemetrexed 500 mg/m² on day 1 every 21 days for 3 cycles; concurrent thoracic RT[d,e] (nonsquamous)[*,†] ± additional 4 cycles of pemetrexed 500 mg/m²[†]
- Paclitaxel 45–50 mg/m² weekly; carboplatin AUC 2, concurrent thoracic RT[f,*,†] ± additional 2 cycles of paclitaxel 200 mg/m² and carboplatin AUC 6[†]

Consolidation Therapy for Patients with Unresectable Stage III NSCLC, PS 0-1, and No Disease Progression After 2 or More Cycles of Definitive Chemoradiation

Durvalumab 10 mg/kg IV every 2 weeks for up to 12 months[h]

*Regimens can be used as preoperative/adjuvant chemotherapy/RT.
†Regimens can be used as definitive concurrent chemotherapy/RT.

Quelle stratégie optimale?



W.E.E.Eberhardt, ESMO 2019 Poster discussion 1457, 1458, 1459

Merci pour votre attention