Radiothérapie et immunothérapie : Situation actuelle

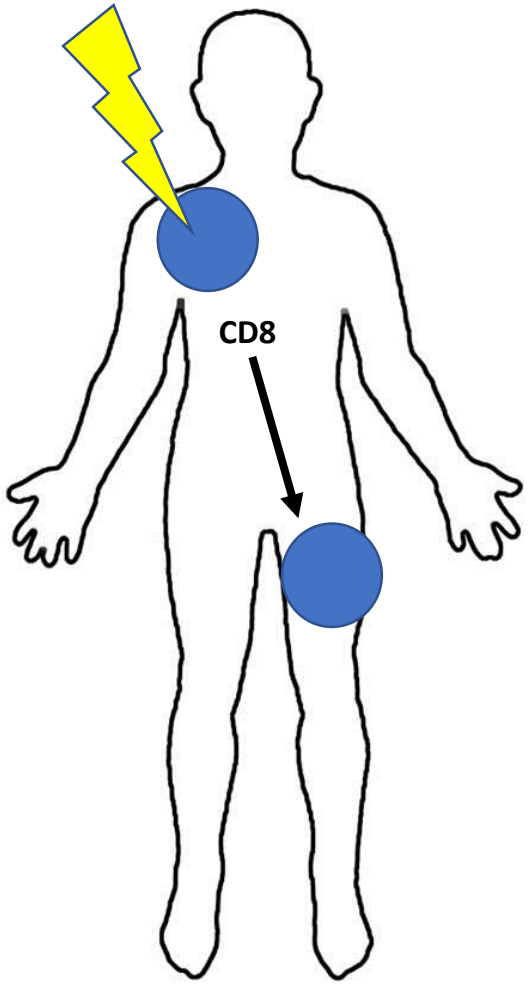
Vincent Atallah

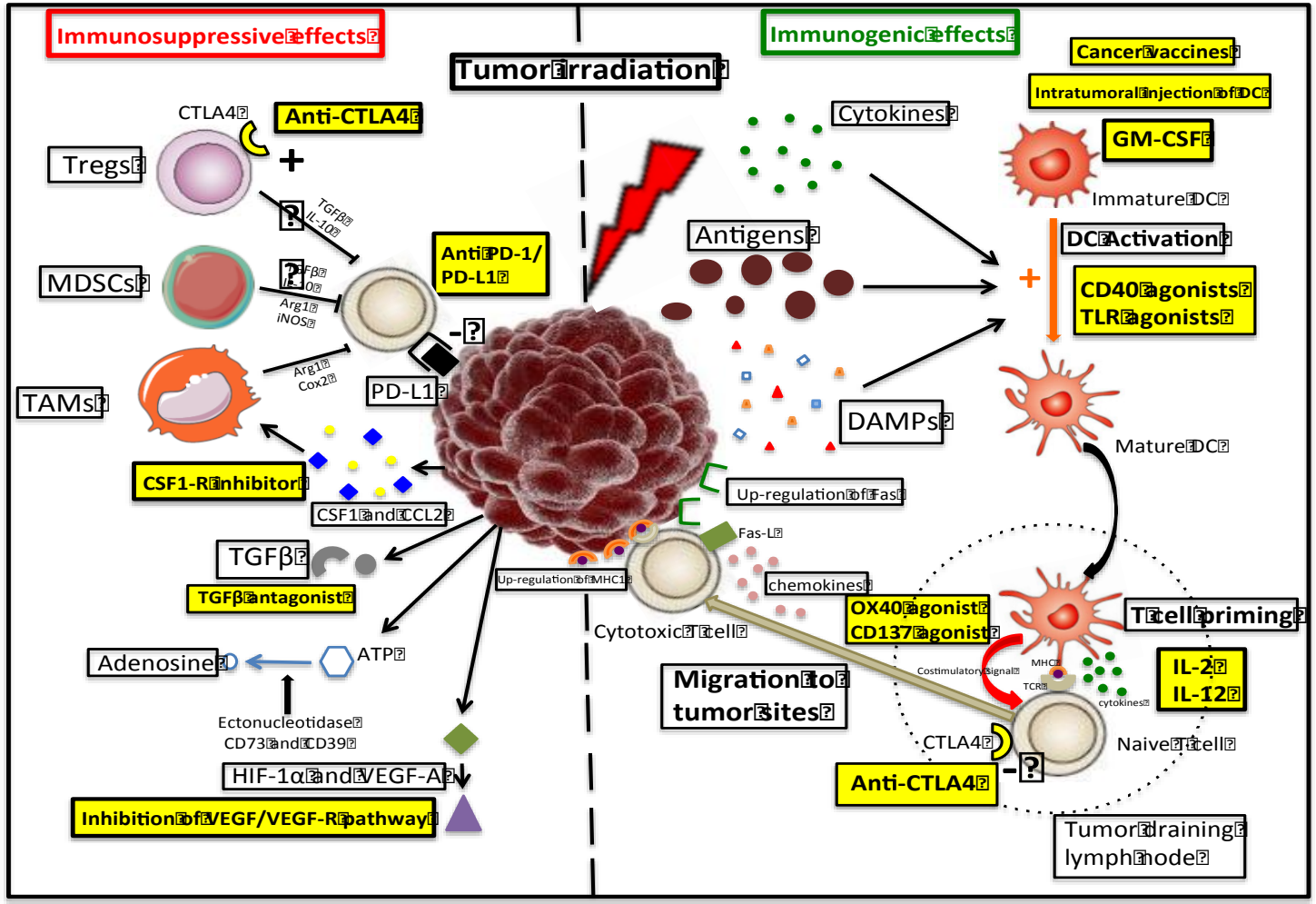
ONCOLIB Charente

RADIOTHÉRAPIE - QUOI DE NEUF ?

POST-CONGRÈS 2019

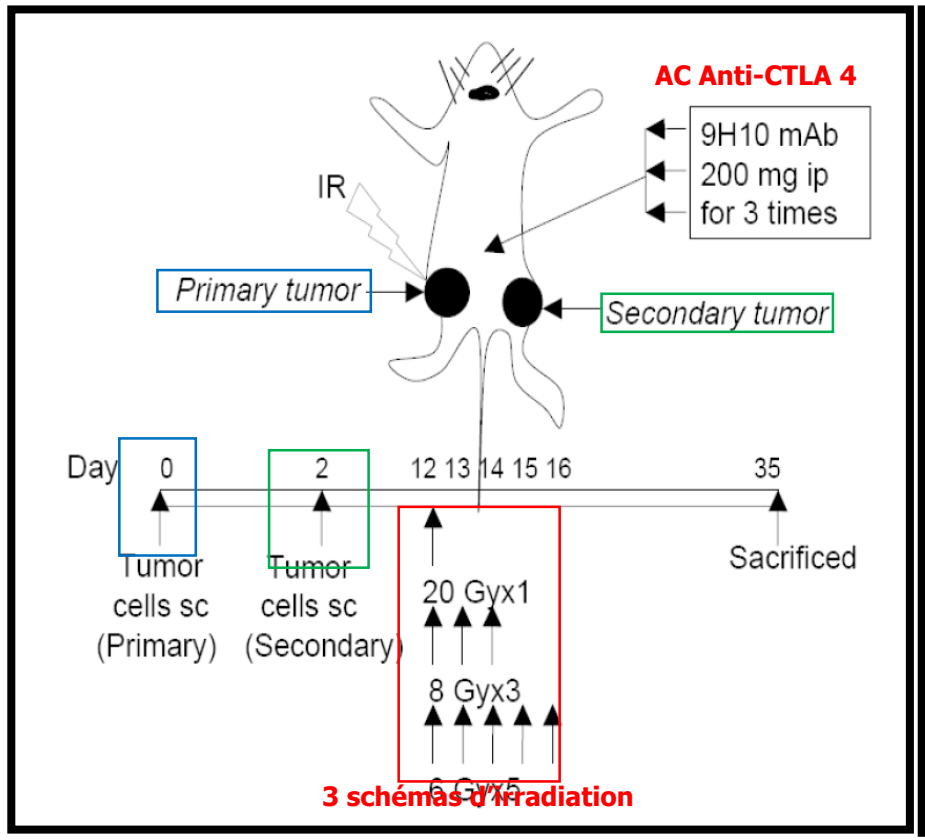
Abscopal effect: Principes de l'association radiothérapie et immunothérapie

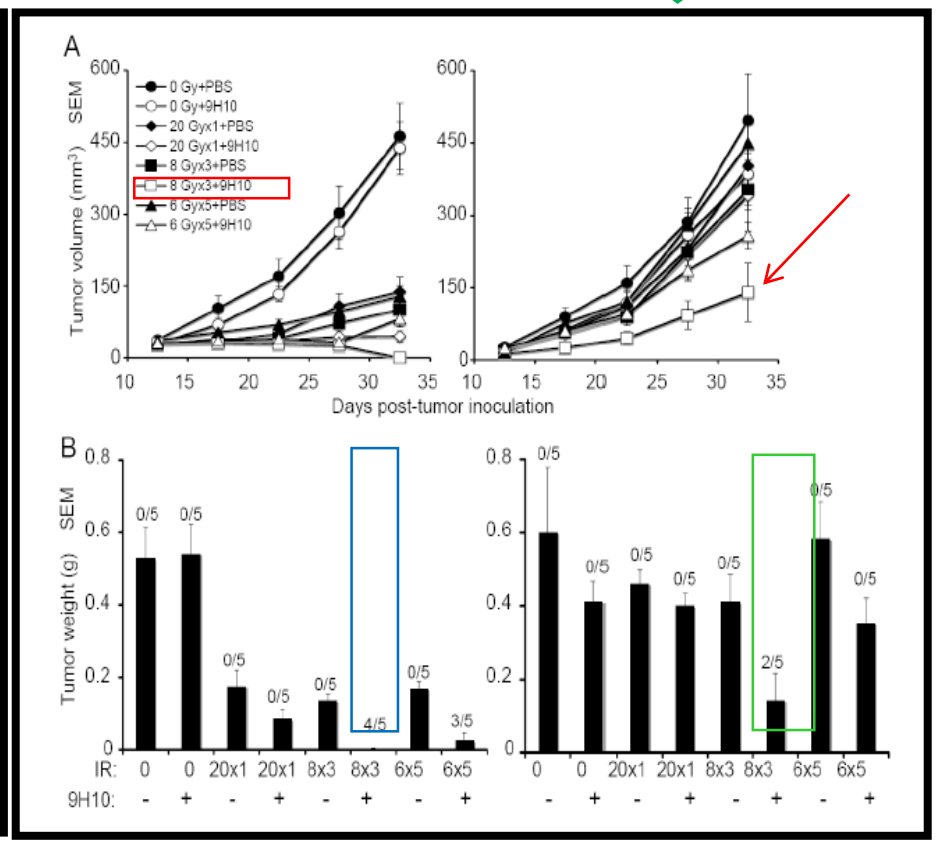


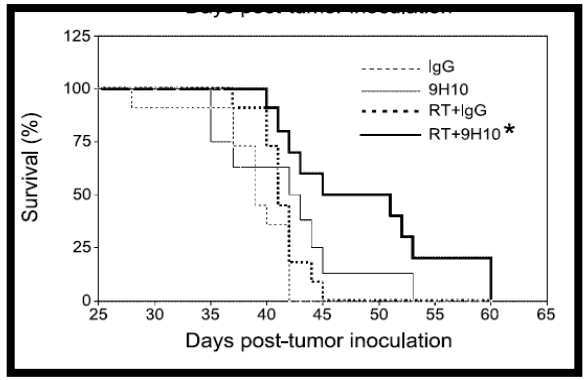


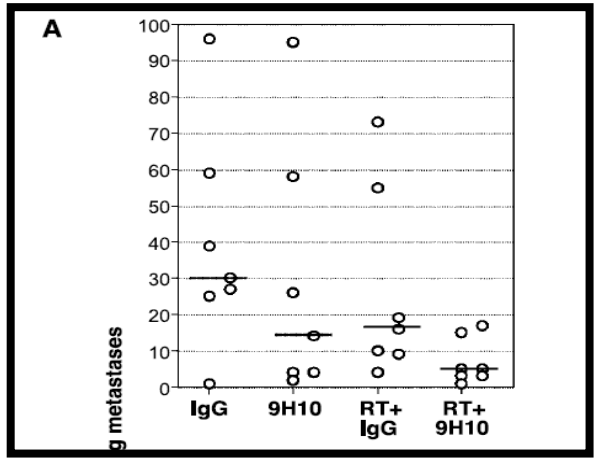
Abscopal effect :Bases pré-cliniques

Site irradié **Site « abscopal »**





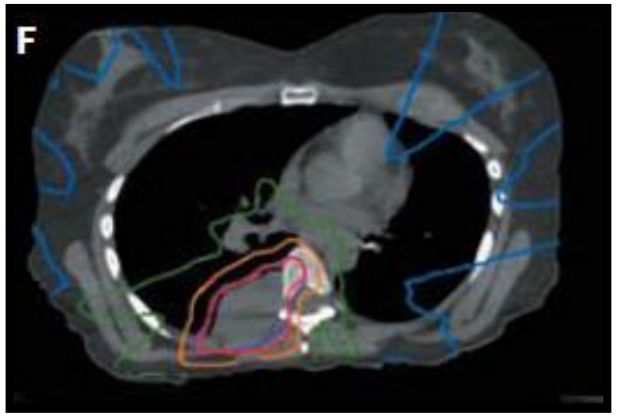


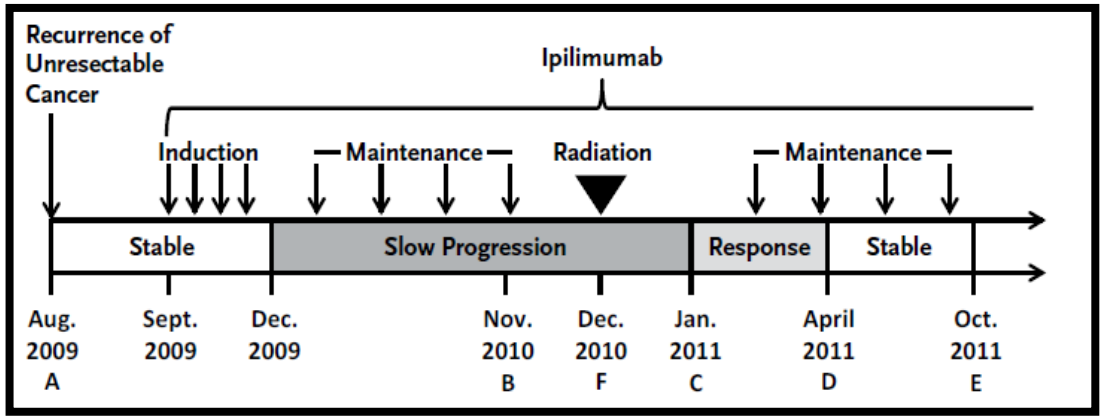


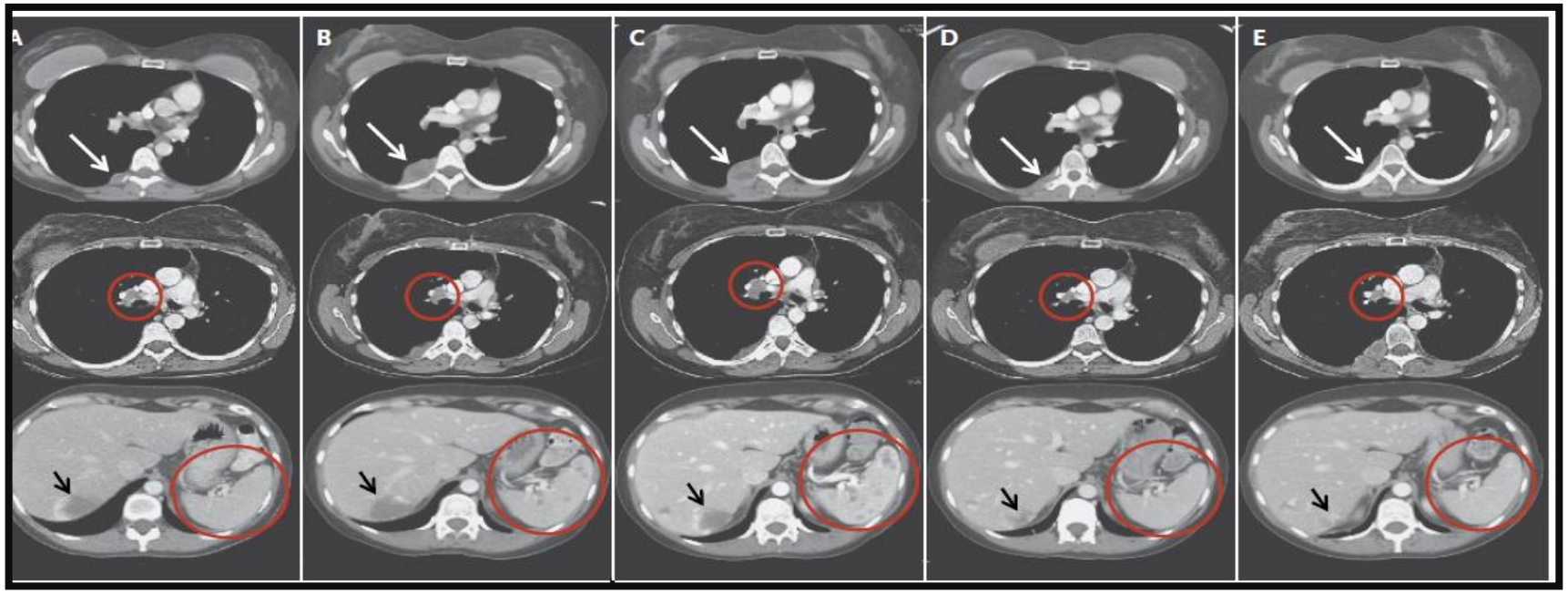
Demaria et al. *Clin Cancer Res* 2005

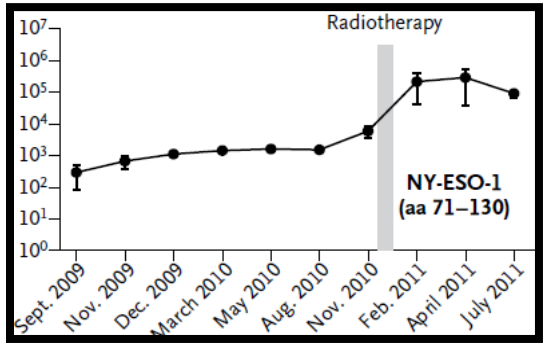
Dewan et al., *Int Journal Rad Oncol Biol Phy* 2009

Abscopal effect: Premiers éléments cliniques

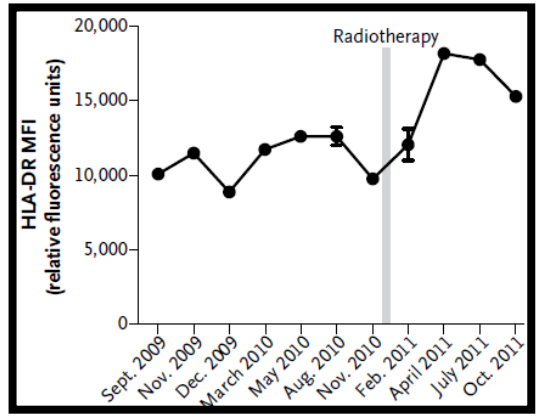








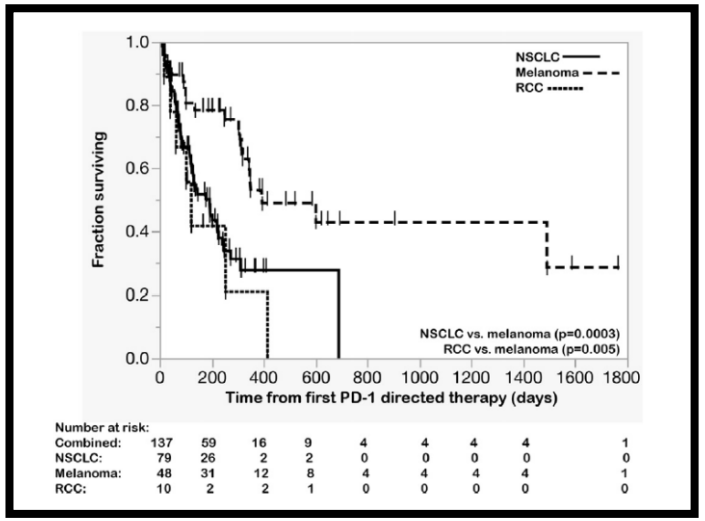
Augmentation des antigènes circulants

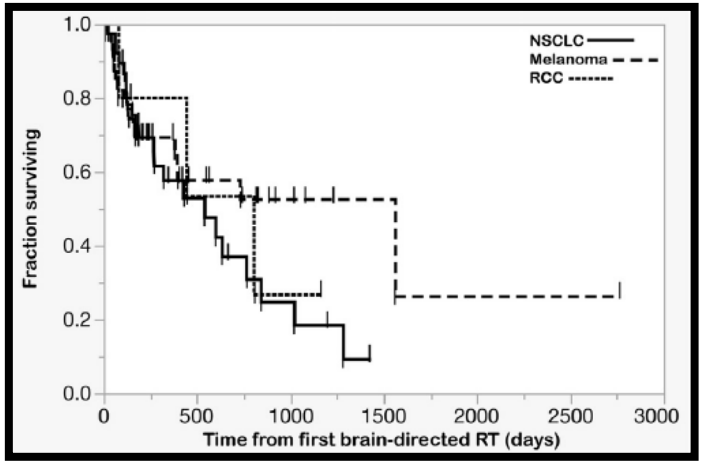


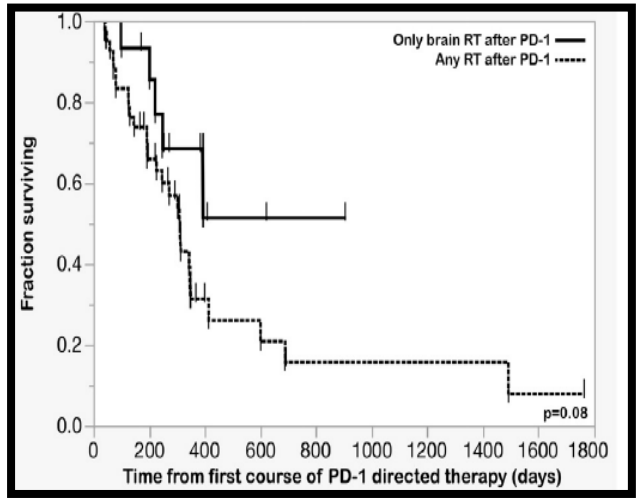
Augmentation des monocytes HLA DR = augmentation de la présentation antigénique

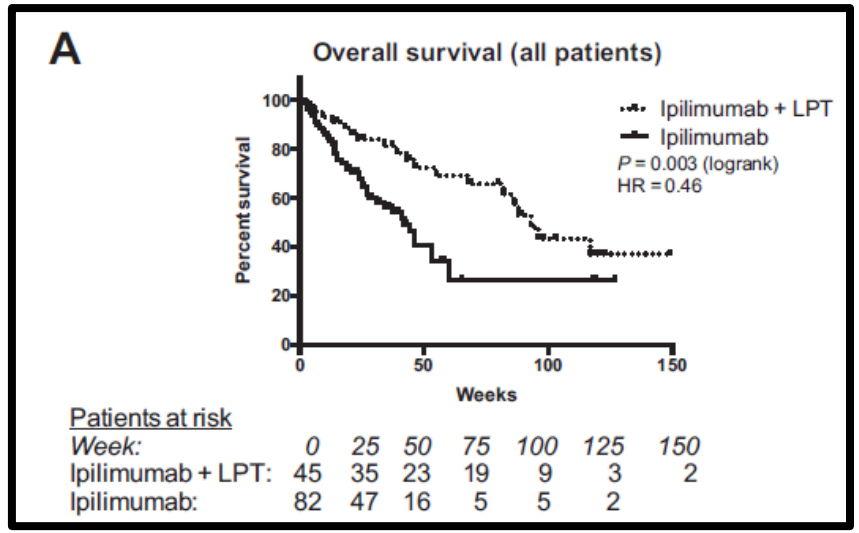
Postow et al. *N Engl J Med* 2012

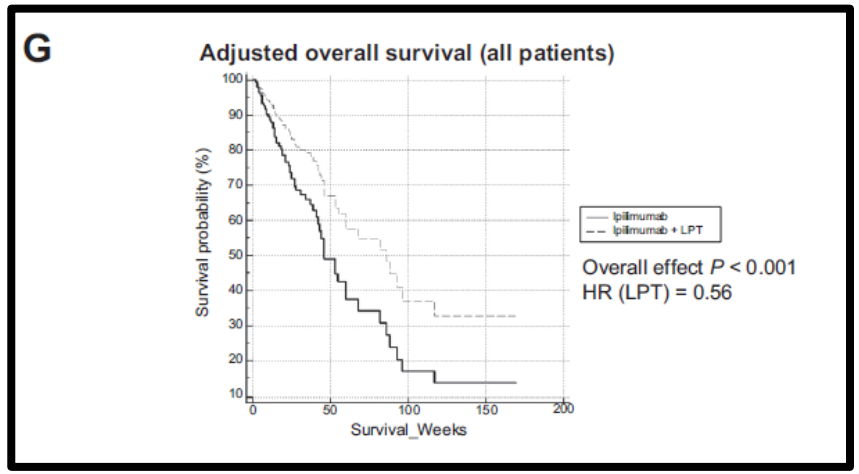
Abscopal effect: Premiers éléments cliniques









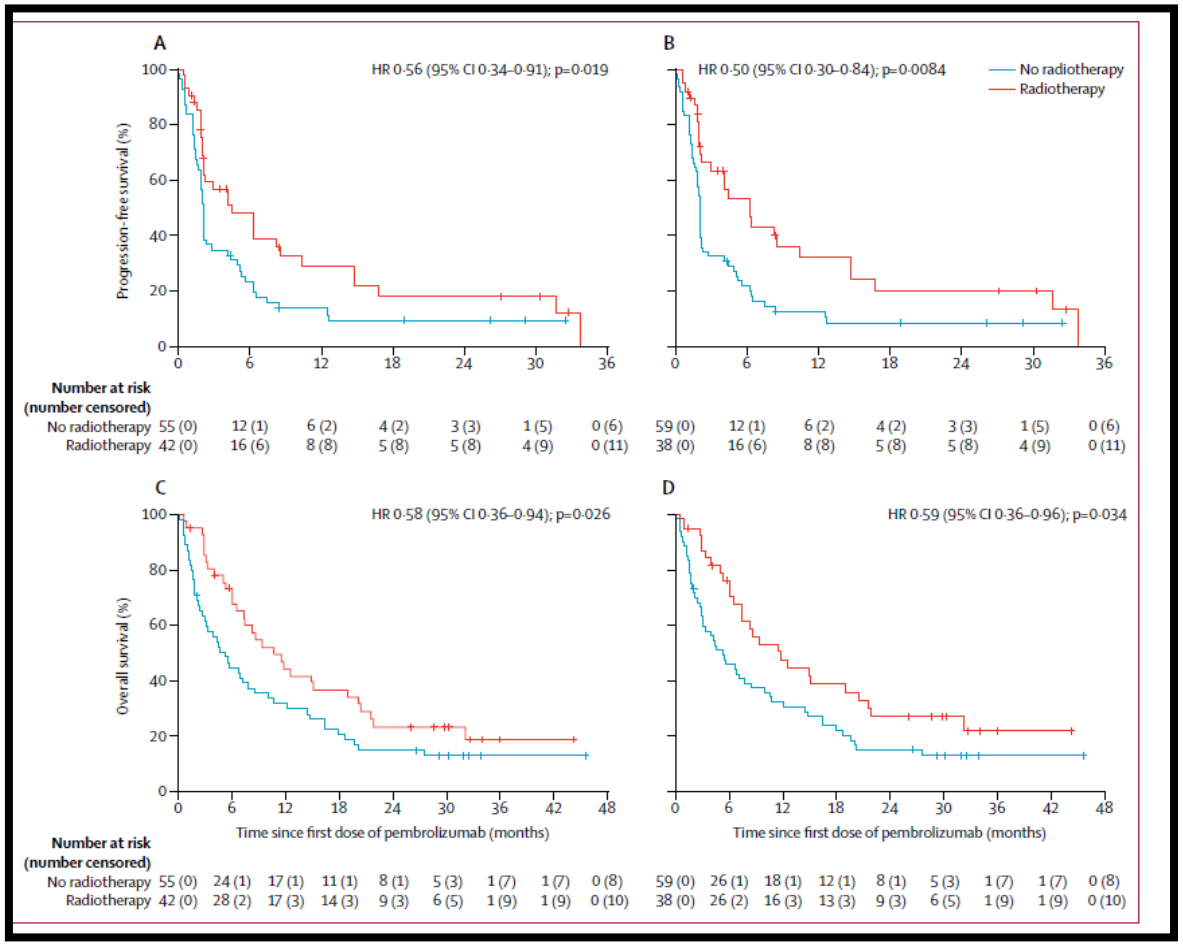


Comparaison avec séries historiques en faveur de l'association avec radiothérapie et Ac anti-PDL1 surtout si RT cérébrale

Pike et al. *Radiother Oncol* 2017

Theurich et al. *Cancer Immunology research 2016*

Abscopal effect: Premiers éléments cliniques



Shaverdian et al, *Lancet Oncol* 2017

Estimation 2016 : plus de 5000 patients en cours d'inclusion dans les essais d'association immuno+RT

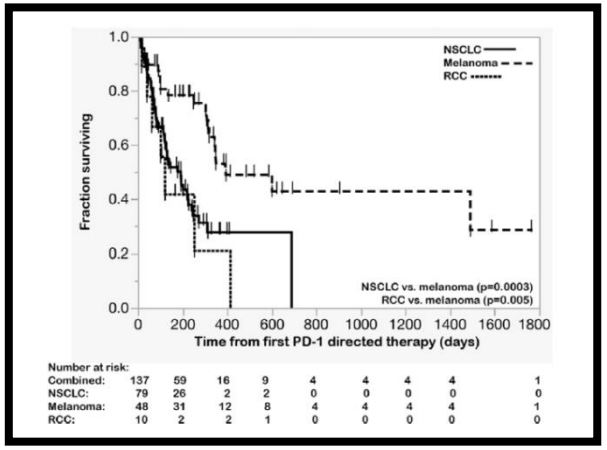
Table 1 Overview of ongoing clinical trials combining RT with IT

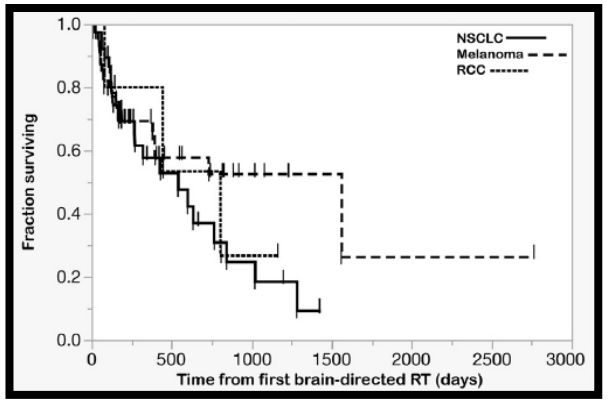
	Vaccination	CTLA-4	PD-1	Others*	Total
Estimated enrollment	3310	692	692	667	5252†
No. of trials	30	20	15	18	81†
No. primarily sponsored by industry†	15	0	2	1	18
Phase					
0	0	1	1	2	4
1	9	9	7	3	26†
1/2	1	3	2	8	14
2	16	7	5	5	32†
3	4	0	0	0	4
Cancer type					
Breast	1	0	1	6	8
GBM	5	0	1	0	6
Melanoma	1	14	2	1	17†
NSCLC	2	1	4	1	7
Pancreatic	9	1	2	1	12†
Prostate	6	0	0	1	7
Others	6	4	6	9	25

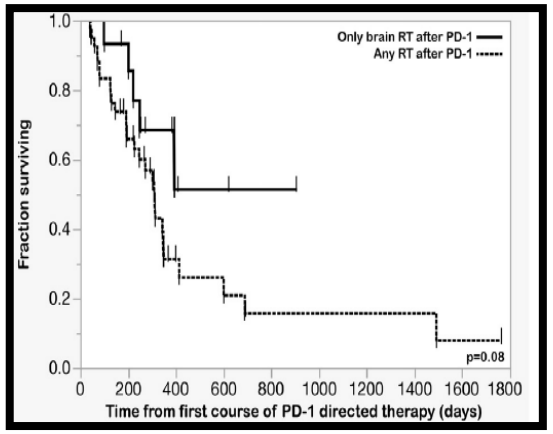
Johnson et al. *Int J Rad Oncol Biol Phys* 2016

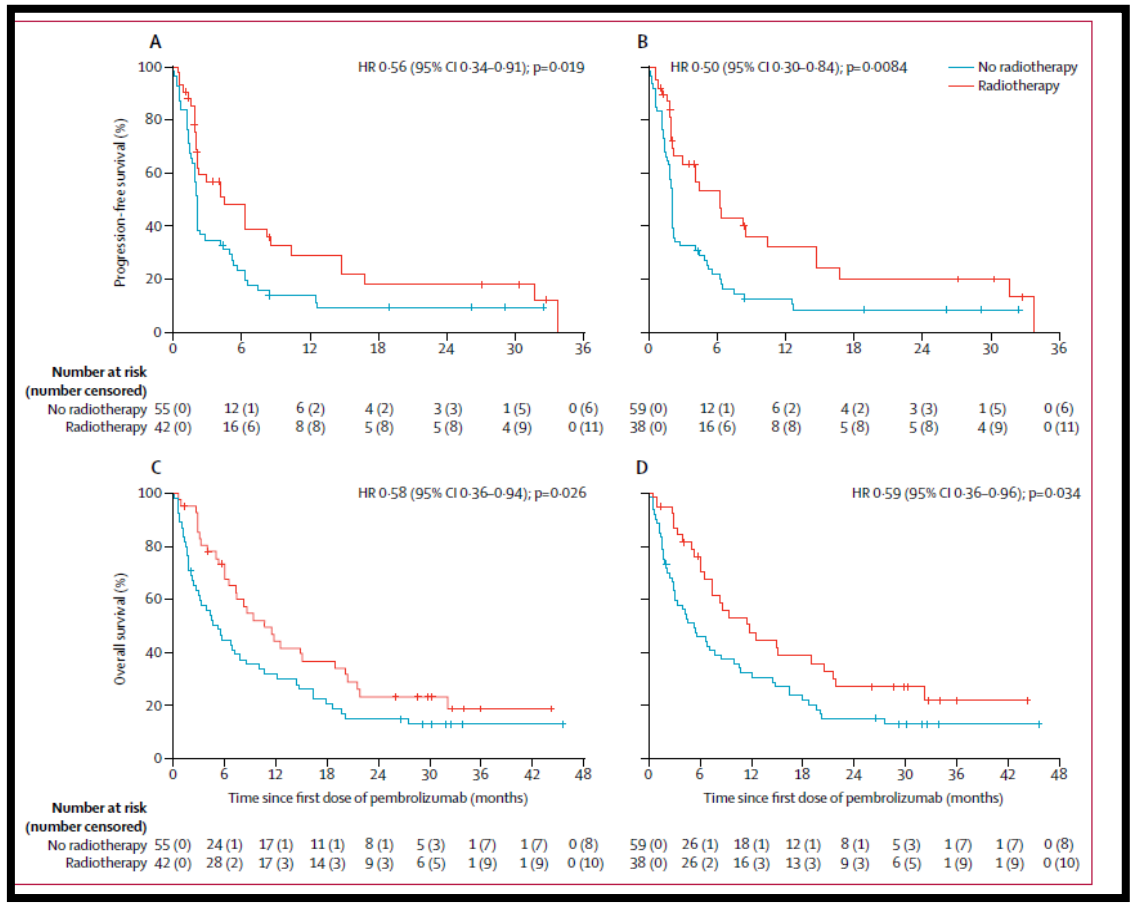
Abscopal effect: Premiers éléments cliniques

De nombreux biais









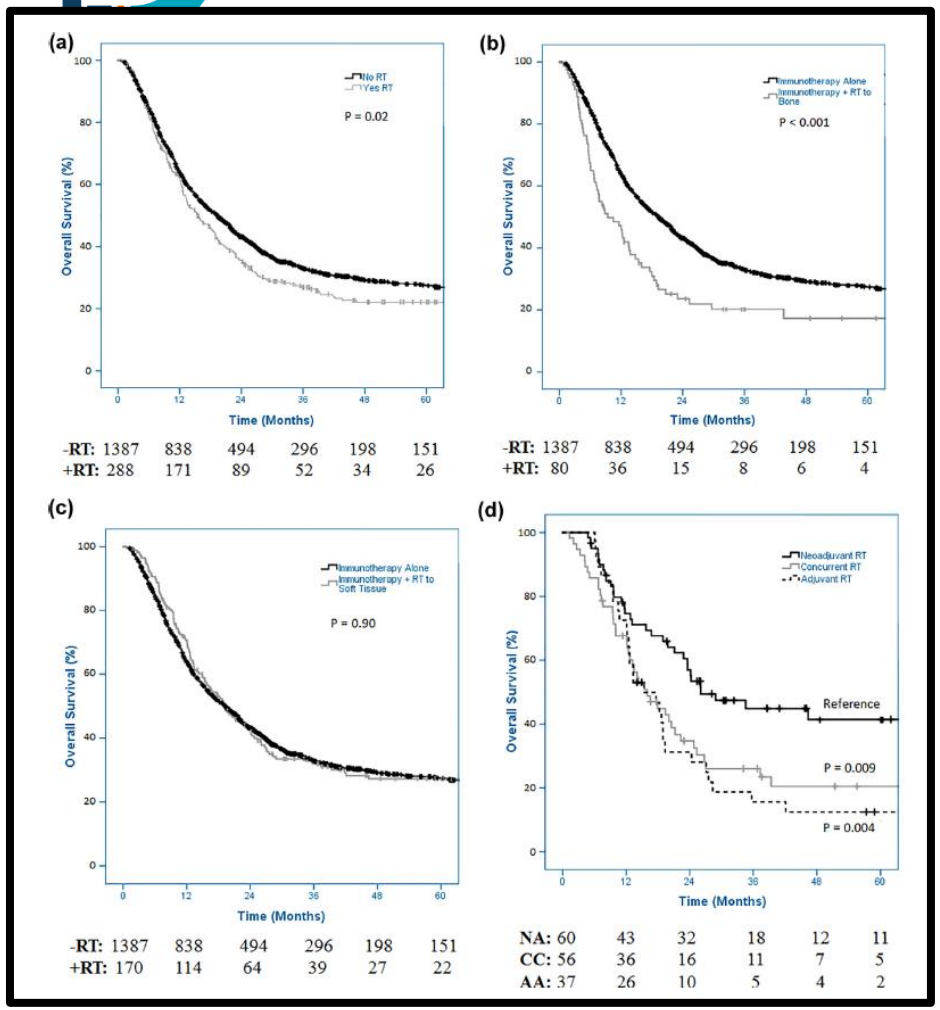
Hétérogénéité majeure: pooling de molécules différentes, lignes différentes ou histologies différentes

Pike et al. *Radiother Oncol* 2017

Non vérifié par d'autres séries, aucune information sur la RT

Shaverdian et al, *Lancet Oncol* 2017

Abscopal effect: Premiers éléments cliniques discordants



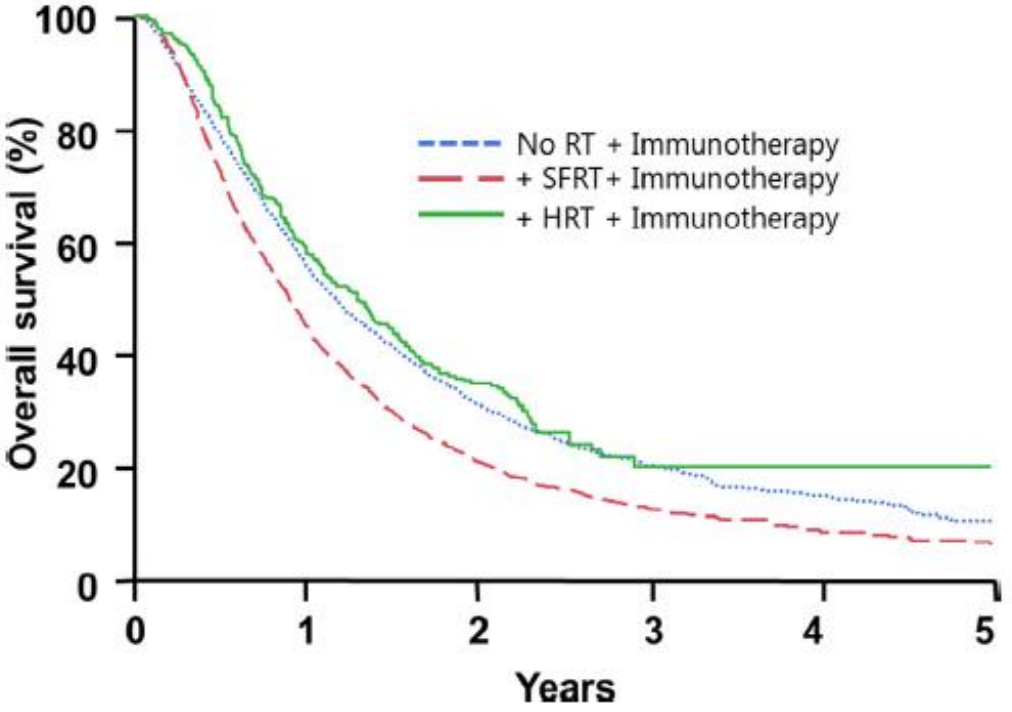


Fig. 1. Overall survival for patients with metastatic NSCLC at diagnosis treated with immunotherapy. RT = radiotherapy; HRT = hypofractionated radiotherapy (defined as ≥5 Gy/treatment day); SFRT = standard fractionation RT (RT not meeting the definition of SABR).

Même biais que les articles en faveur Abscopal effect voire plus car pas de contrôle de la ligne de traitement et inclusion de tout type d'immuno (IL2 , vaccination)

Gabani et al. *Radiother Oncol* 2018

Bates et al. *Radiother Oncol* 2019

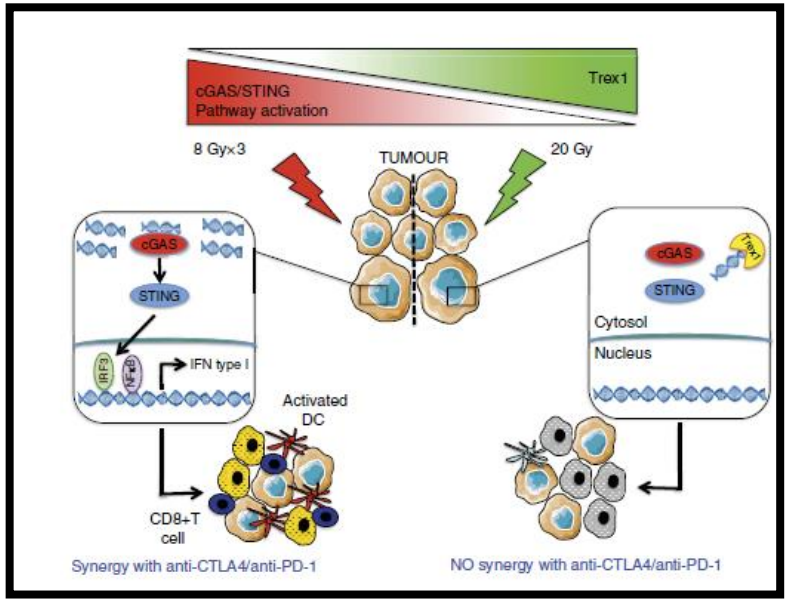
Abscopal effect : premiers doutes

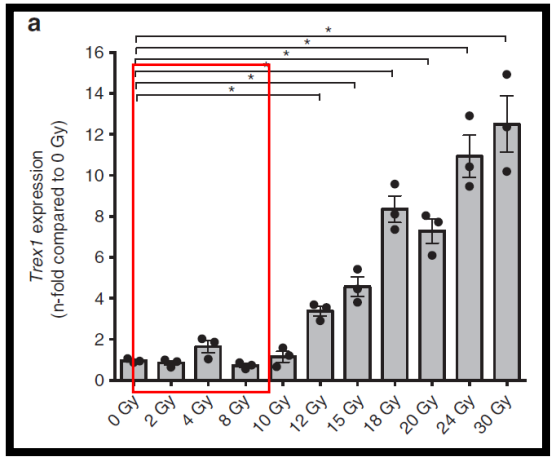
Le théorème de la licorne

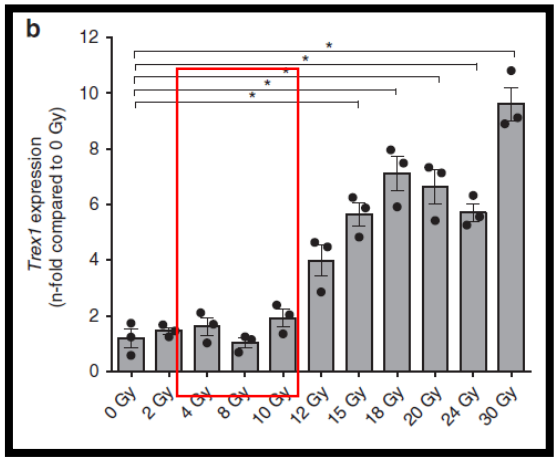
Abscopal effect is like unicorns. We do not know if it exists, and if it exists it must be very rare

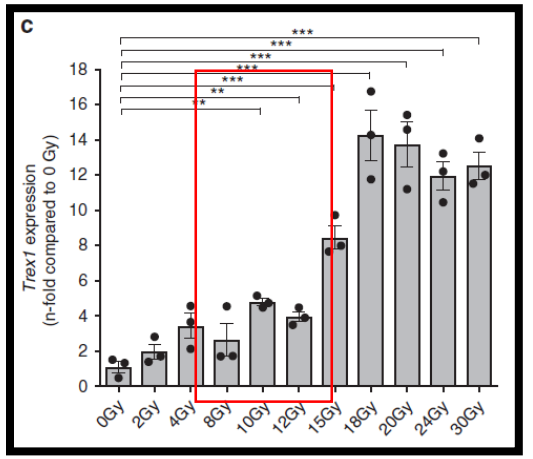
ASTRO congress 2019

Si association RT + Immuno : quelle dose ?









⇒ Dose d'irradiation pas trop élevée (< 10 Gy),
NI trop faible (≥ 4 Gy)
(… mais cas rapporté d'effet abscopal avec 2 Gy par séance
= la dose totale doit jouer également)

Vanpouille-Box et al. *Nat commun* 2017

Si association RT + Immuno : quelle séquence ?

- **Débuter par irradiation** = augmenter l'expression tumorale de PD-L1 (Dovedi *et al*, Cancer Research 2014), évite la destruction des lymphocytes qui ont infiltré

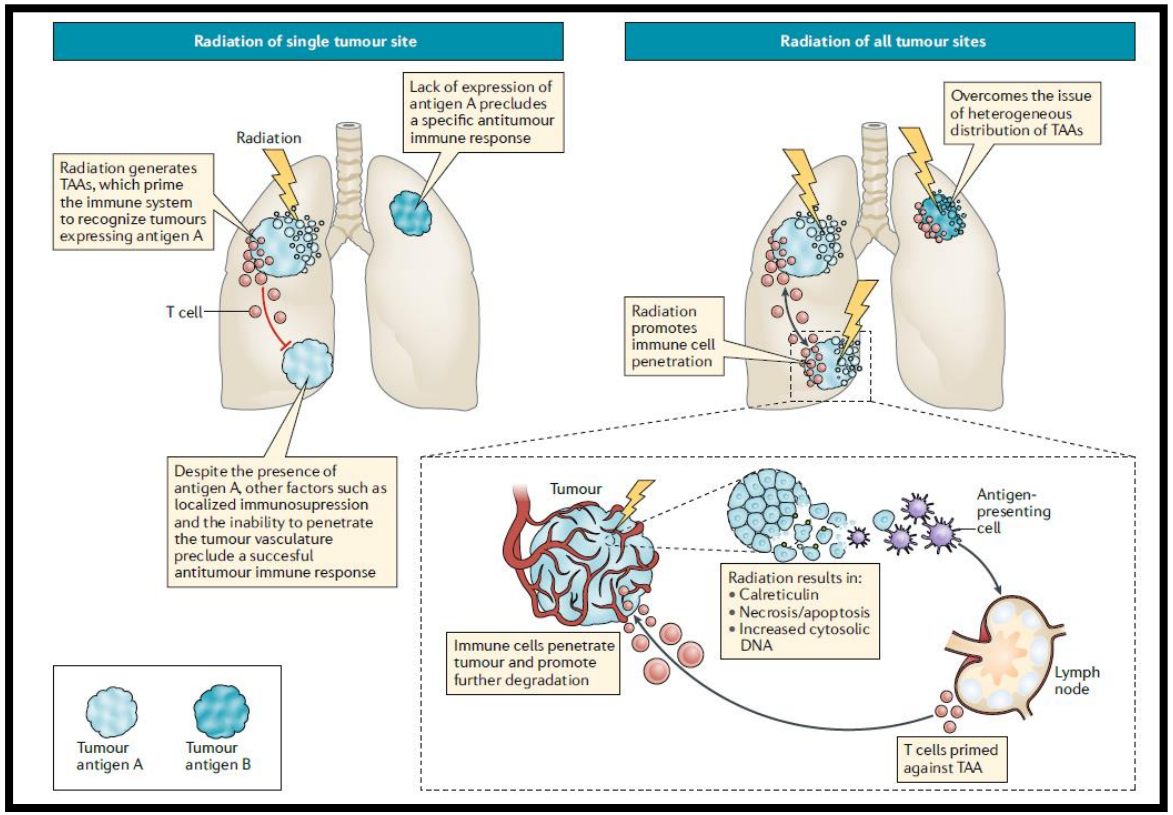
- **Irradier pendant immunothérapie** = augmentation le relargage antigénique = augmenter l'exposition antigénique (Postow et al NEJM 2012)

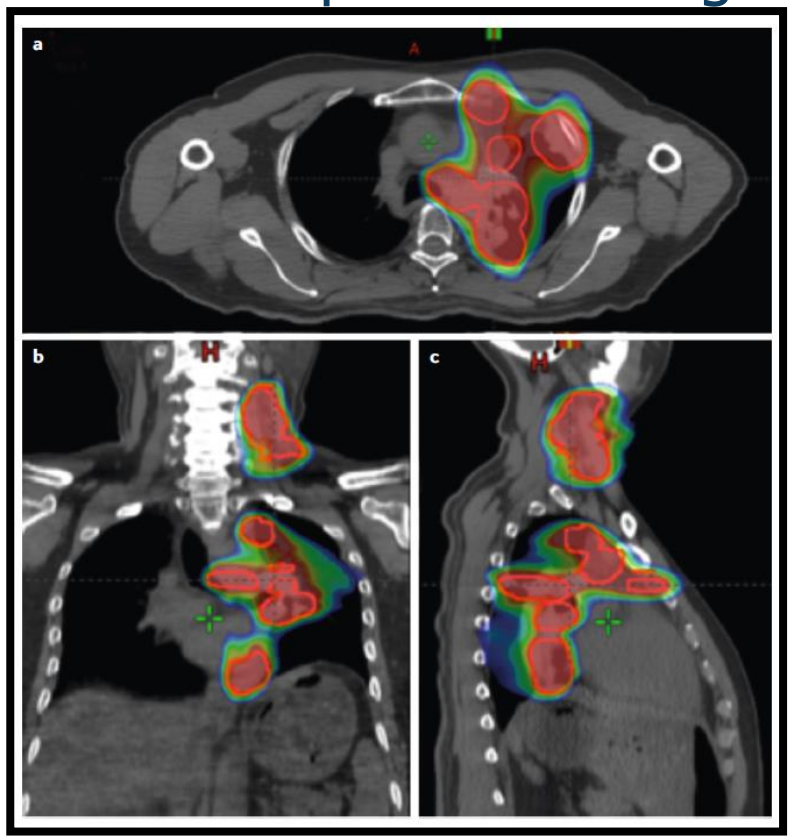
- Les case reports d'effet abscopaux le sont avec une **association concomitante** (Postow et al NEJM 2012)

- **ASCO 2019 (Wegner et al, abstract 9024):** étude de registre, rétrospective, 371 patients traités par irradiation + immunothérapie: plus tôt est effectuée l'irradiation (cut-off de 21 jours) plus longue est la survie globale (19 vs 15 mois, p=0,03, analyse multivariée + score de propension)

Si association RT + Immuno : quelles cibles ?

- Irradiation un seul site ou plusieurs sites ?
- Irradiation multisite favoriserait la diversité de l'exposition antigénique





Brooks et al. *Nat Reviews* 2018

Si association RT + Immuno : quelle technique d'irradiation ?

- Problème des irradiations modernes VMAT = faibles doses d'irradiation corps entier (lymphocyte très radiosensible): privilégier RC3D, RCMI avec peu de faisceaux, protons (?)

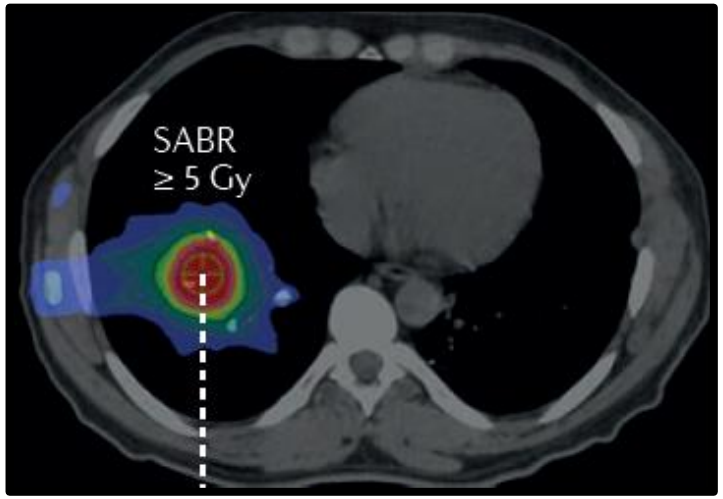
- Ladbury CJ et al (IJROBP 2019): impact de l' « estimated dose of radiation to immune cells » (EDRIC), n=117 patients,
  EDRIC est corrélée avec lymphopénie et indépendamment corrélée avec SG (HR=1,17, p=0,03; **cut-off 5,1 Gy 14 vs 28 mois**)

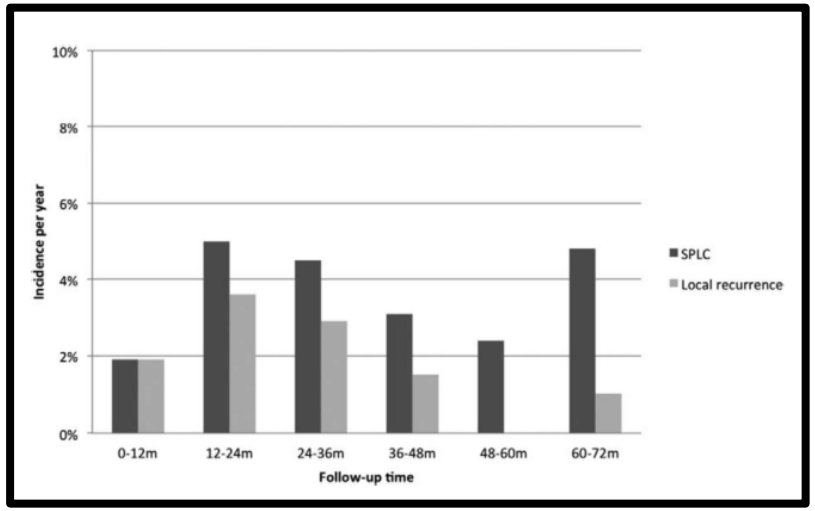
- Tang C *et al* (IJROBP 2014): 711 pts RT-CT CBNPC, impact pronostique ++++ V5 poumons et lymphopénie

Table 3 Multivariate Cox regression association baseline variables with outcomes during radiation treatment

	Overall survival			Event-free survival			Locoregional failure			Distant metastatic failure		
Characteristic	HR	95% CI	*P*	HR	95% CI	*P*	HR	95%CI	*P*	HR	95% CI	*P*
Lymphocyte nadir (10^3 cells/μL)†	0.59	0.37-0.95	.03	0.54	0.35-0.83	.005	0.51	0.26-1.0	.05	NI		

Si association RT + Immuno : A quel stade de la maladie ?





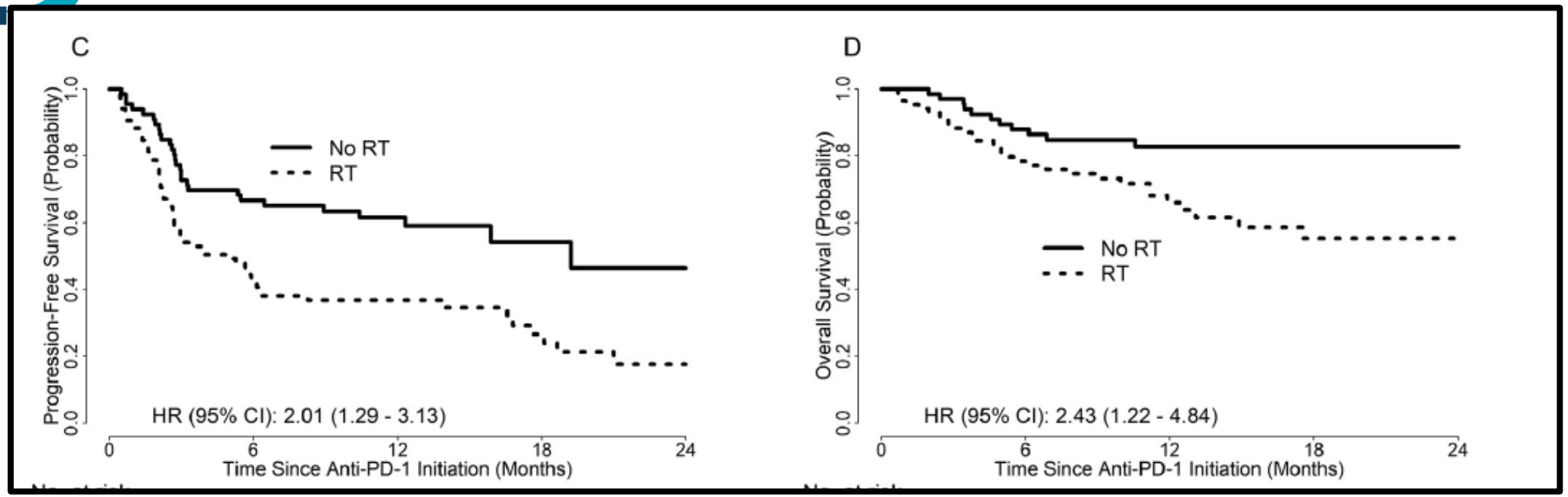
Verstegen et al. *J Thorac Oncol* 2012

Table 3
Trials of stereotactic ablative radiotherapy (SABR) in combination with anti-PD therapy in early stage non-small cell lung cancer in set-up or recruiting

Study name [reference]/NCT number	Trial status	Phase	Estimated enrolment (*n*)	Immunotherapy agents	Dose fractionation	Time of immunotherapy	Study arms	Primary end point
I-SABR [94]/NCT03110978	Recruiting	II	140	Nivolumab	50 Gy/4 fractions or 70 Gy/10 fractions	Before and after first SABR; every 2 weeks for a total of 7 doses	SABR + immunotherapy versus SABR alone	Event-free survival
ASTEROID [95]/NCT03446547	Recruiting	II	216	Durvalumab	NA	After radiotherapy	SABR + immunotherapy versus SABR alone	Time to progression
NCT03050554 [96]	Active, not recruiting	I/II	56	Avelumab	48 Gy/4 fractions or 50 Gy/5 fractions	After radiotherapy	Single	Safety and tolerability; relapse-free survival
STILE [97]/NCT03383302	Not open	I/II	31	Nivolumab	54 Gy/4 fractions or 55 Gy/5 fractions	After final radiotherapy within 24 h	Single	Assessment of lung toxicity
NCT03574220 [98]	Not open	I	15	Pembrolizumab	50 Gy/5 fractions or 60 Gy/3 fractions	After radiotherapy	Single	Tolerability

Xing et al. *Clin Oncol* 2019

Données récentes: mélanome



Cox Multivariable Analysis of RT Timing Including No RT Group, Model 1.

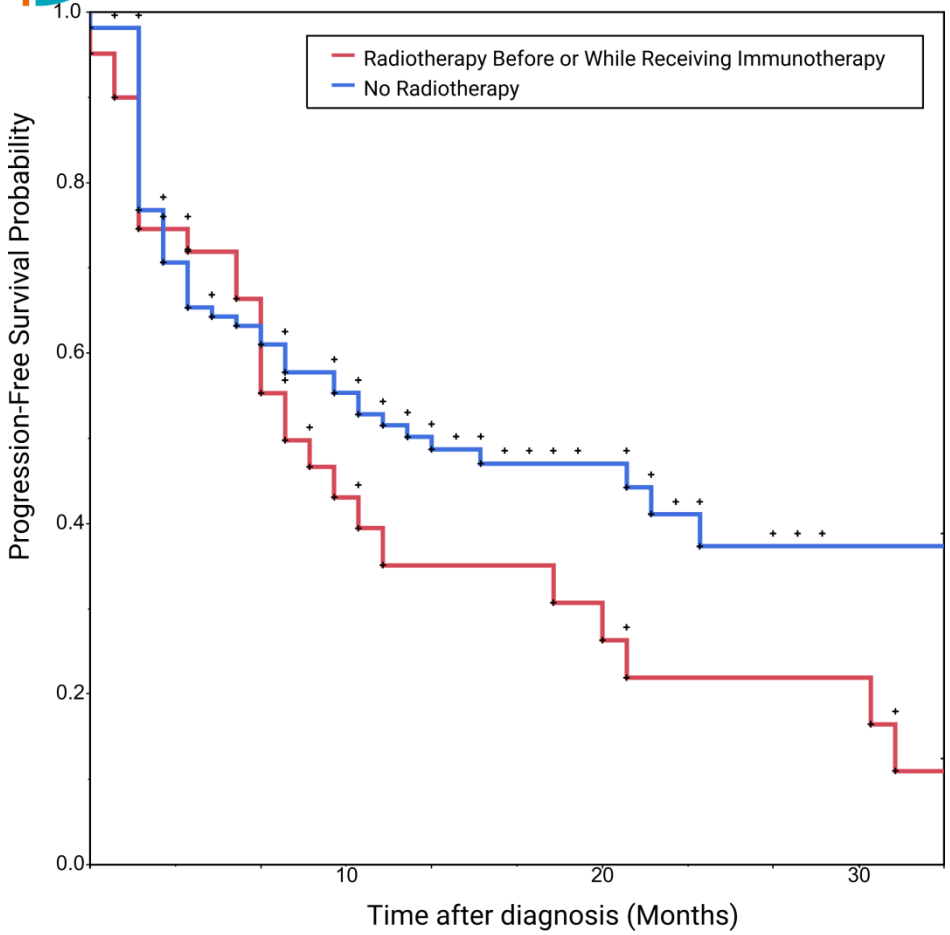
	PFS		OS	
	HR (95% CI)	Adj. *p*	HR (95% CI)	Adj. *p*
No RT vs. RT during anti-PD-1	0.455 (0.254–0.815)	0.05	1.072 (0.406–2.835)	1.00
No RT vs. RT after anti-PD-1	0.249 (0.131–0.474)	0.0001	0.399 (0.154–1.034)	0.35
No RT vs. RT before anti-PD-1	0.996 (0.510–1.947)	1.00	0.556 (0.213–1.455)	1.00
# Mets, continuous	1.068 (0.996–1.144)	0.06	1.340 (1.189–1.509)	<0.0001
CNS mets vs. no CNS mets	1.351 (0.741–2.464)	0.33	1.387 (0.573–3.354)	0.47

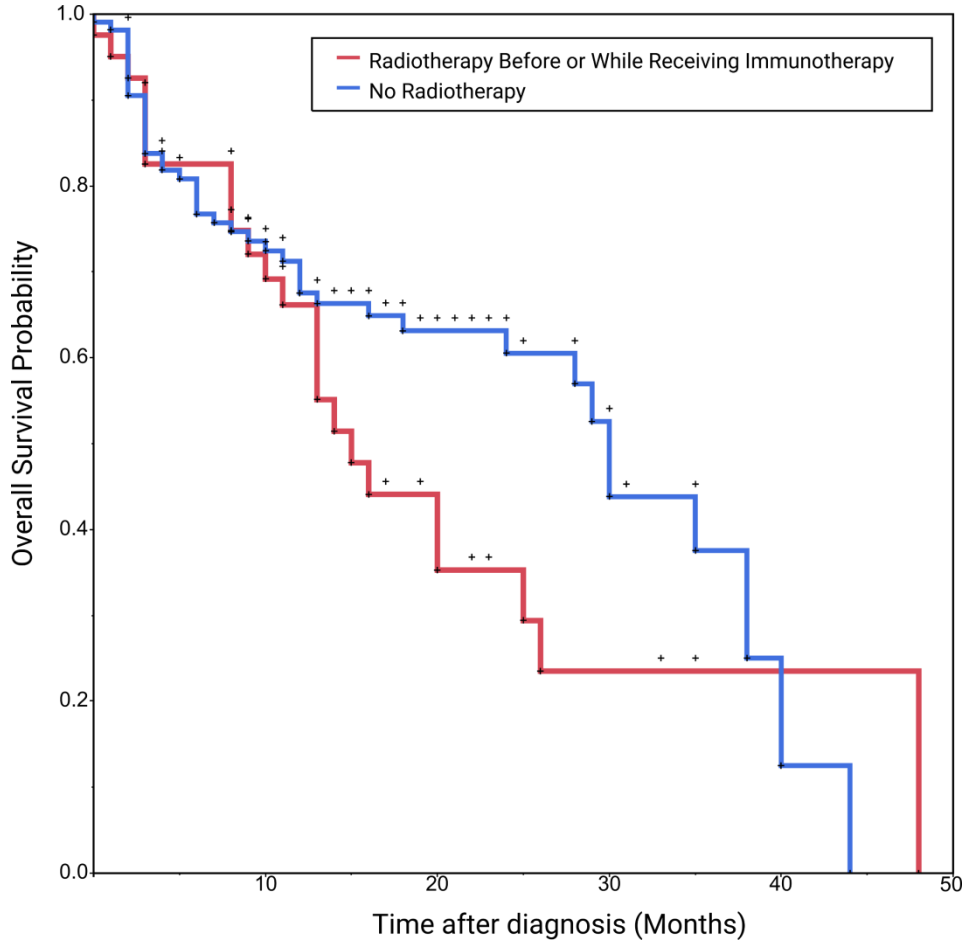
151 patients sous immuno dont 88 irradiés . Analyse de Cox complémentaire montre absence de différences en SSP et SG alors que patients IR de moins bon pronostic initial.

Mais hypothèse initiale α en non β : impossible de conclure à une équivalence

Mowery et al. *Radiother Oncol* 2019

Données récentes: mélanome (travail bordelais)



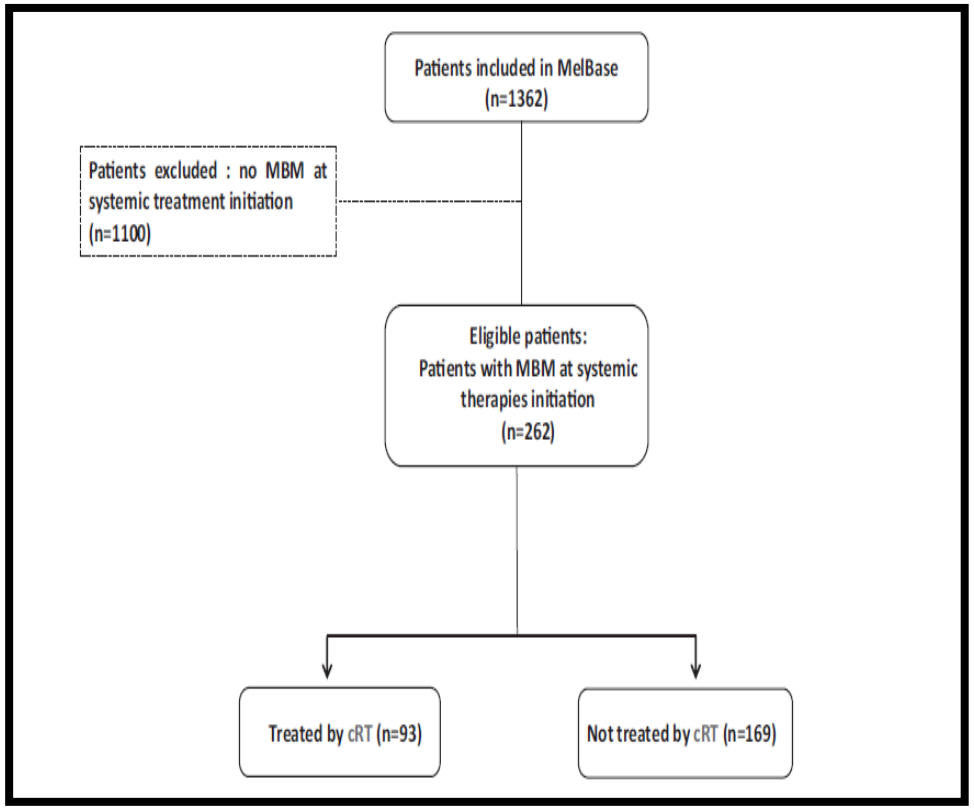


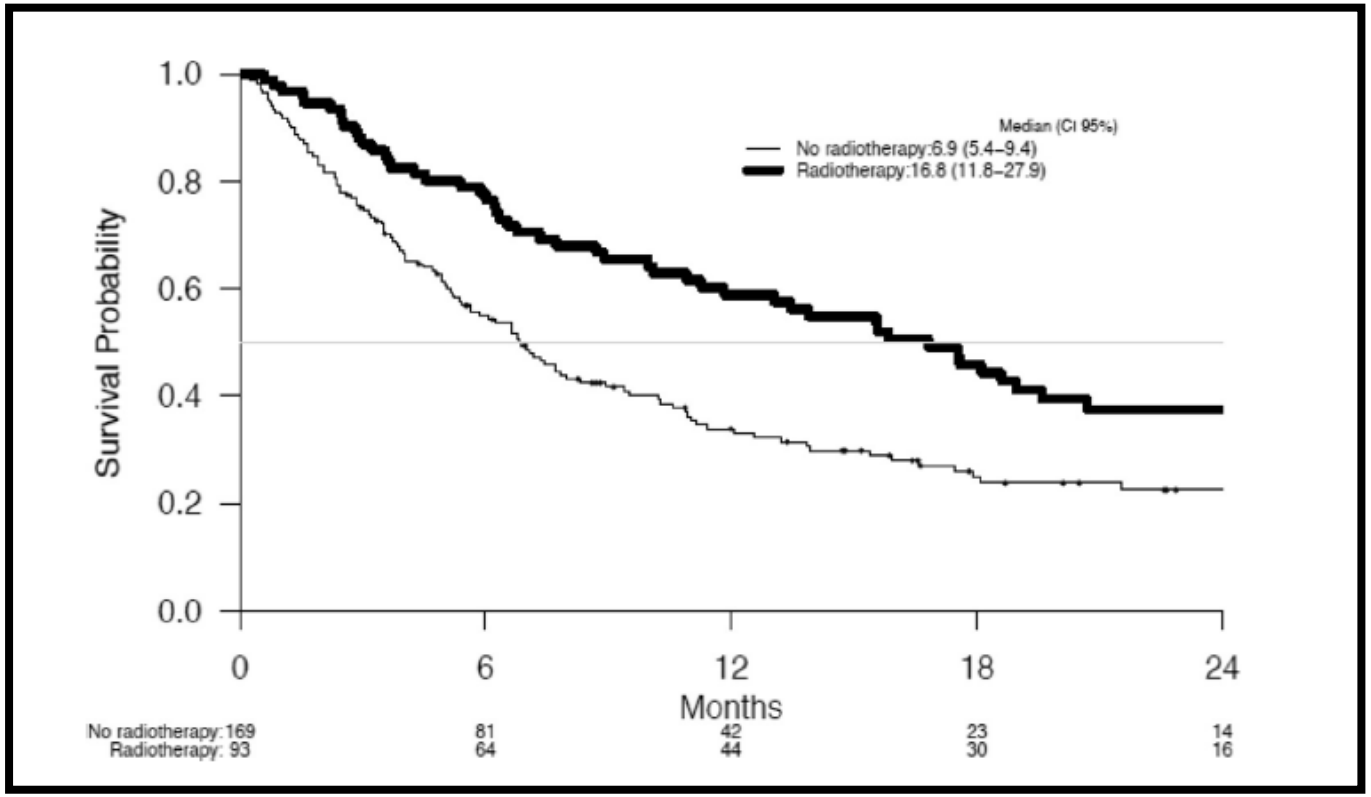
149 patients traités au CHU de Bordeaux par anti-PDL1 en 1ère ligne
Exclusion des patients traités en 2ème ou 3ème ligne

ASTR0 2018 communication orale

Données récentes: mélanome

Base française MELBASE





Score de propension (multiples facteurs): avantage ajout RT
que ce soit avec thérapie ciblée (36%) ou immunothérapie (p=0,007)
80 % de SRS / 61% de 1ère ligne

Tetu et al. *Eur J Cancer* 2019

Données récentes: poumon

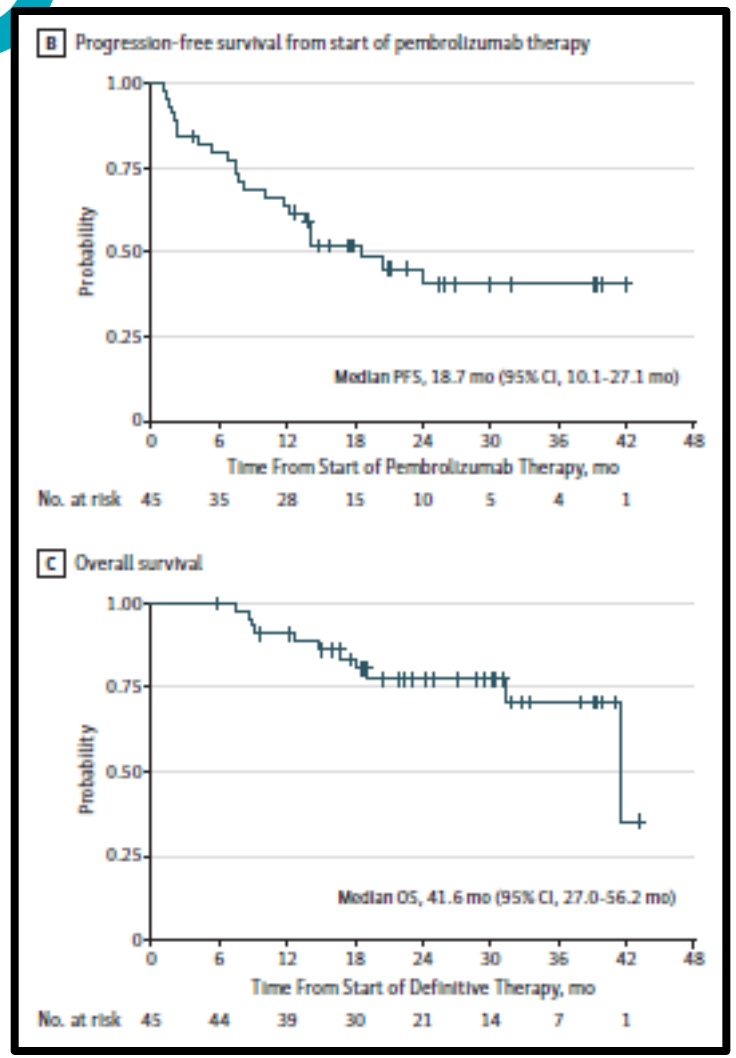
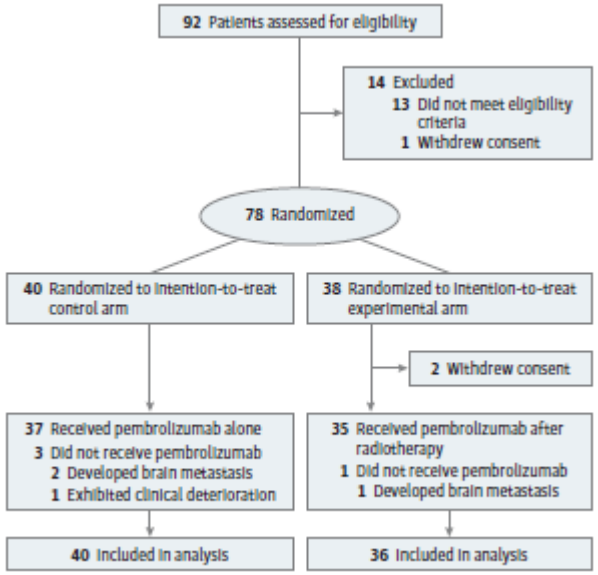


Table 3. Treatment-Related Adverse Events With at Least 10% Incidence in Study Population per Common Terminology Criteria for Adverse Events

	No. (%) of Patients (n = 45)				
	Grades 1-4	Grade 1	Grade 2	Grade 3	Grade 4
Pain	19 (42)	13 (29)	5 (11)	1 (2)	0
Fatigue	16 (36)	11 (24)	5 (11)	0	0
Rash	10 (22)	10 (22)	0	0	0
Dyspnea	8 (18)	3 (7)	4 (9)	1 (2.2)	0
Cough	7 (16)	4 (9)	3 (7)	0	0
Pruritus	7 (16)	7 (16)	0	0	0
Dizziness	6 (13)	6 (13)	0	0	0
Edema	6 (13)	4 (8.9)	2 (4)	0	0
Nausea	6 (13)	5 (11)	0	1 (2)	0
Pneumonitis	5 (11)	0	2 (4)	2 (4)	1 (2)
Dry eyes	5 (11)	4 (9)	1 (2)	0	0
Headache	5 (11)	5 (11)	0	0	0
Insomnia	5 (11)	4 (9)	1 (2)	0	0

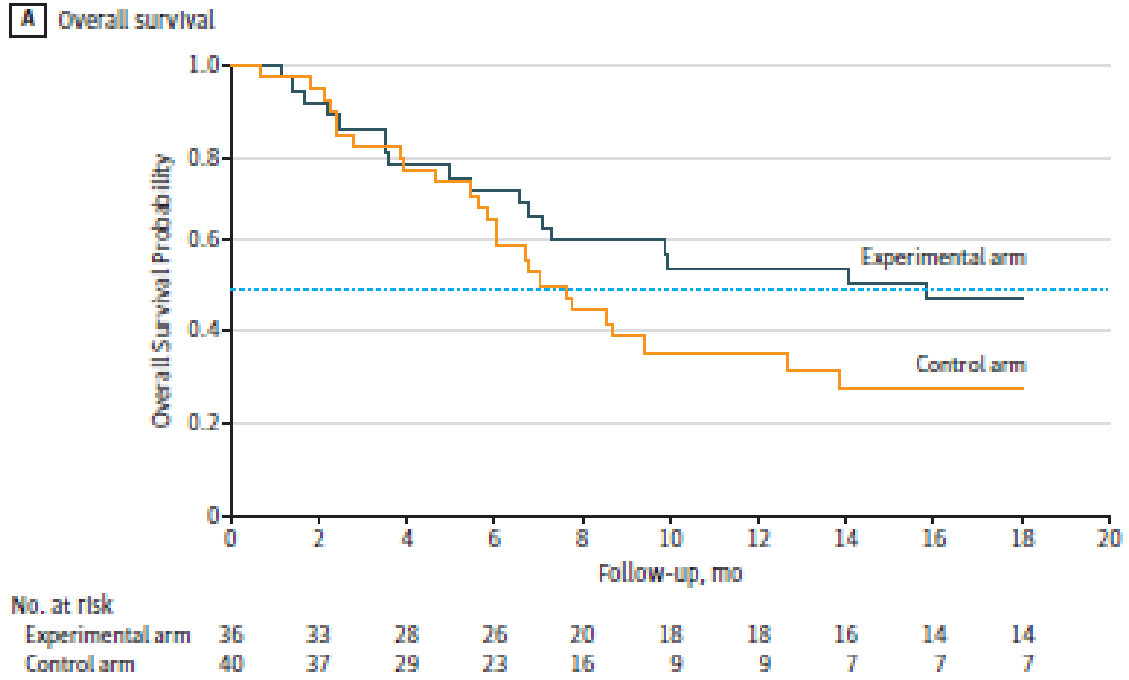
19.1 mois de médiane SG comparé aux 6,6 mois des séries historiques
Association Pembro à un traitement local de l'ensemble des lésions patients oligo-métas *Baumi et al. JAMA Oncol 2019*

Données récentes: poumon



Response	Experimental Arm, No./Total No. (%) (n = 36)[a]	Control Arm, No./Total No. (%) (n = 40)[b]
Best overall response, No.		
Complete response	3	1
Partial response	14	8
Stable disease	9	10
Progressive disease	10	21
Objective response rate at 12 wk		
Overall[c]	13/36 (36)	7/40 (18)
PD-L1 TPS, %		
0	4/18 (22)	1/25 (4)
1-49	3/8 (38)	3/8 (38)
≥50	6/10 (60)	3/5 (60)
Disease control rate at 12 wk[d]	23/36 (64)	16/40 (40)

Figure 3. Overall Survival in the Intent-to-Treat Population



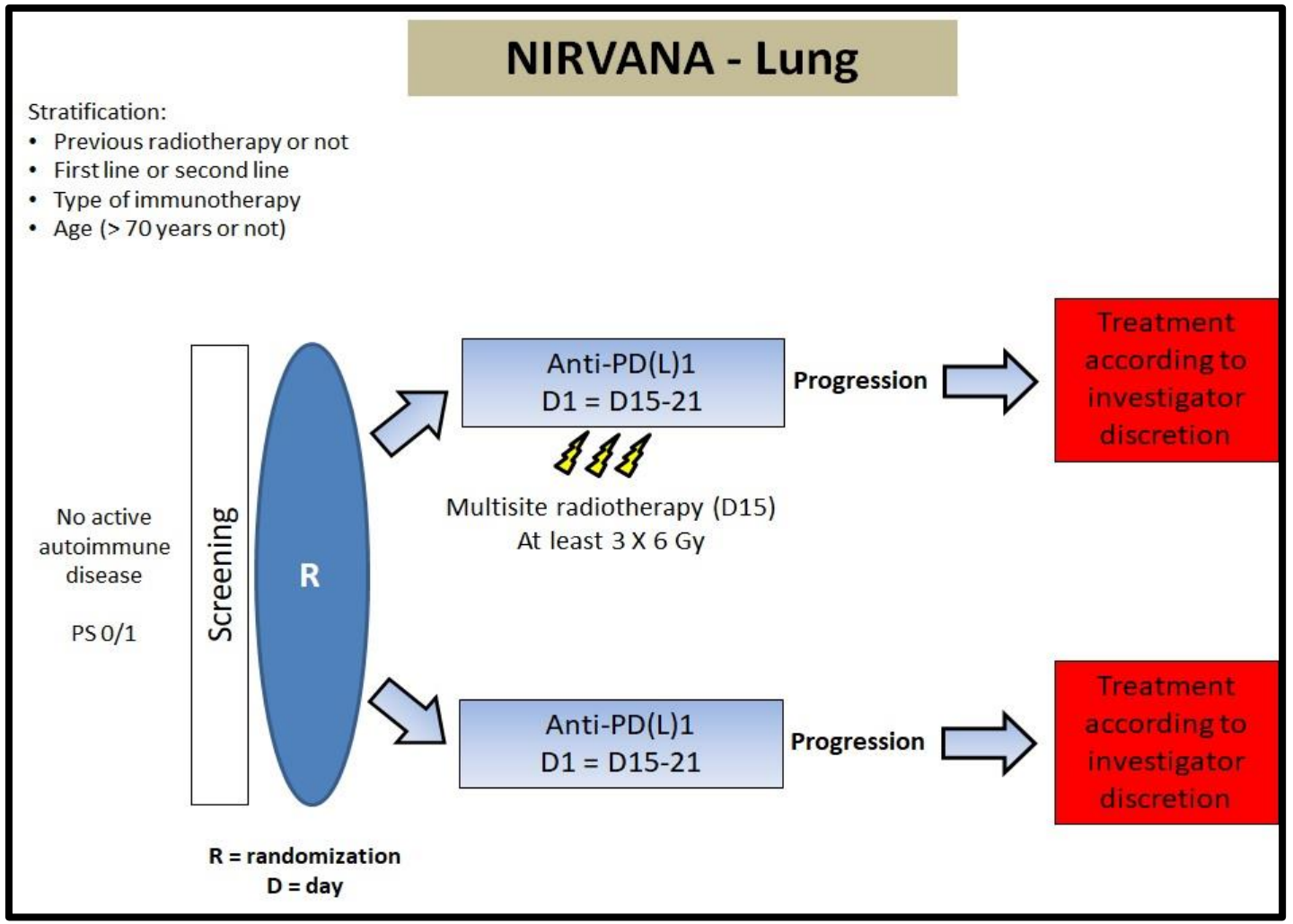
Toute la population :p=0,16
PD-L1 négatif : p=0,04

Non significatif mais tendance
En attente des résultats complémentaires

Theelen et al., JAMA Oncol 2019

A retenir

- **Sujet très clivant car données cliniques disponibles présentant de nombreux biais (mais base préclinique réelle)**
- **Nécessité de pragmatisme dans l'analyse des résultats**
- **Raisonnement comme pour les molécules : inclusion dans les essais et utilisation des protocoles de RT efficaces**
- **Potentiellement un traitement associé à l'immunothérapie avec effet bénéfique majeur pour les patients (comparaison avec double immunothérapie)**



Essai académique français de phase III design le plus prometteur

Merci pour votre attention