Immunotherapie dans les lymphomes, modèle du Hodgkin

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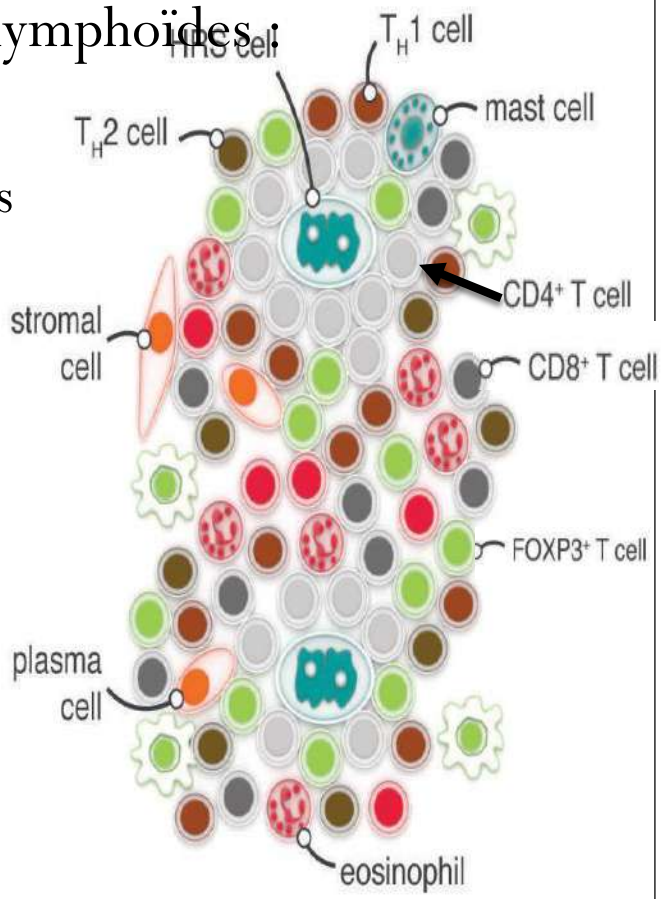
Préambule

- Le LH se différencie des autres hémopathies lymphoïdes :
  - Présence de cellules de Reed-Sternberg
  - Présentation clinique localisée dans 2/3 des cas
  - Survie à 5 ans ≈ 85%

- LH classique ≈ 1500 cas/ans en France
  1ère ligne: ABVD +/- radiothérapie, BEACOPP
  Rechute: Chimiothérapie + autogreffe
- AMM du brentuximab en 2012



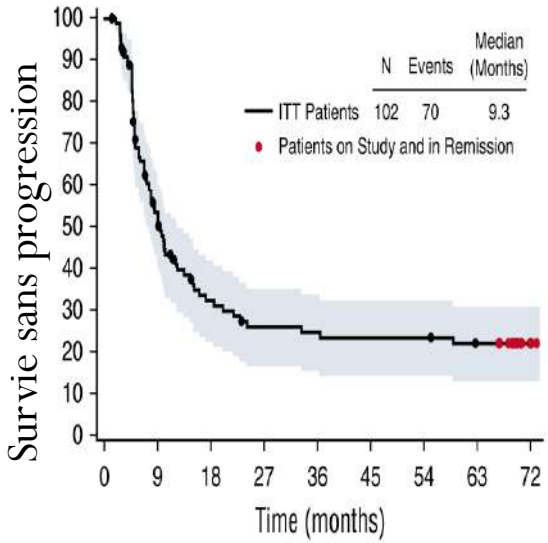
D'après *Scott et al. Nat Rev Can. 2014*

Préambule

- **Rechute post-intensification**:
  Objectif = rémission +/- consolidation par allogreffe

→ Place du brentuximab-vedotin
ORR = 75% ; CR = 34%

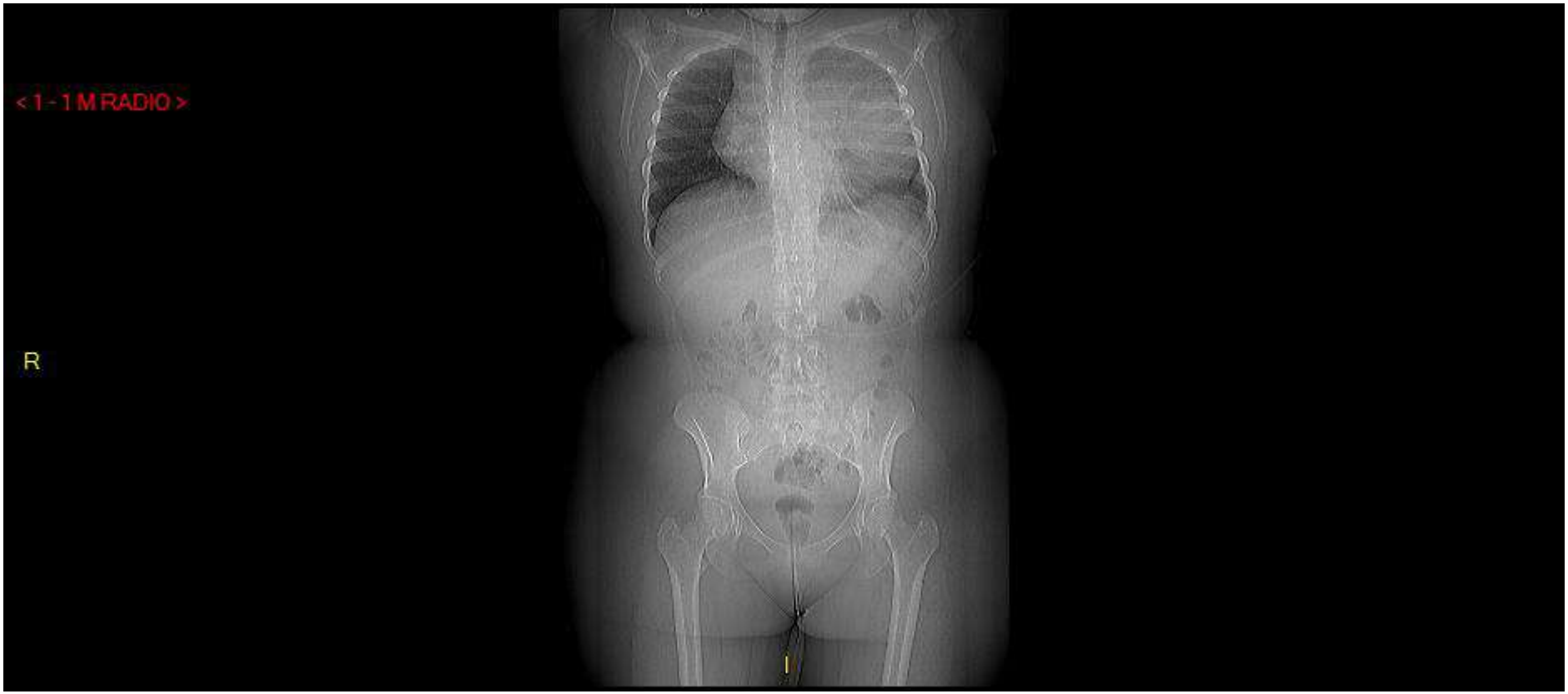
Ac anti-CD30
+
Auristatine



22%

Chen et al. Blood 2016

CAS CLINIQUE F née en 1988 diagnostic mai 2007



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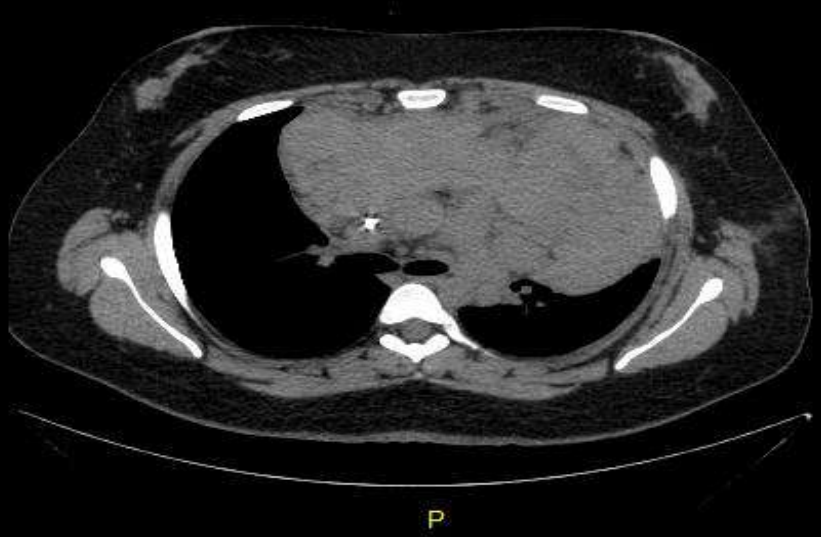

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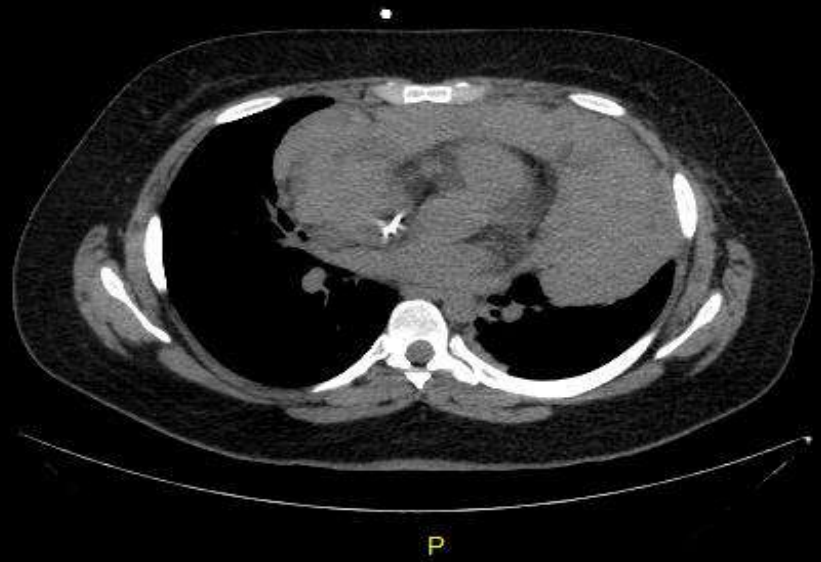


Résumé clinique

- 05/07 STADE IVA sus diaphr mediastin bulky + plevre
- Pas de syndrome inflammatoire PS à 0
- Première ligne
- ABVD x 4 non RC
- Prise en charge à saint louis car refractaire primaire

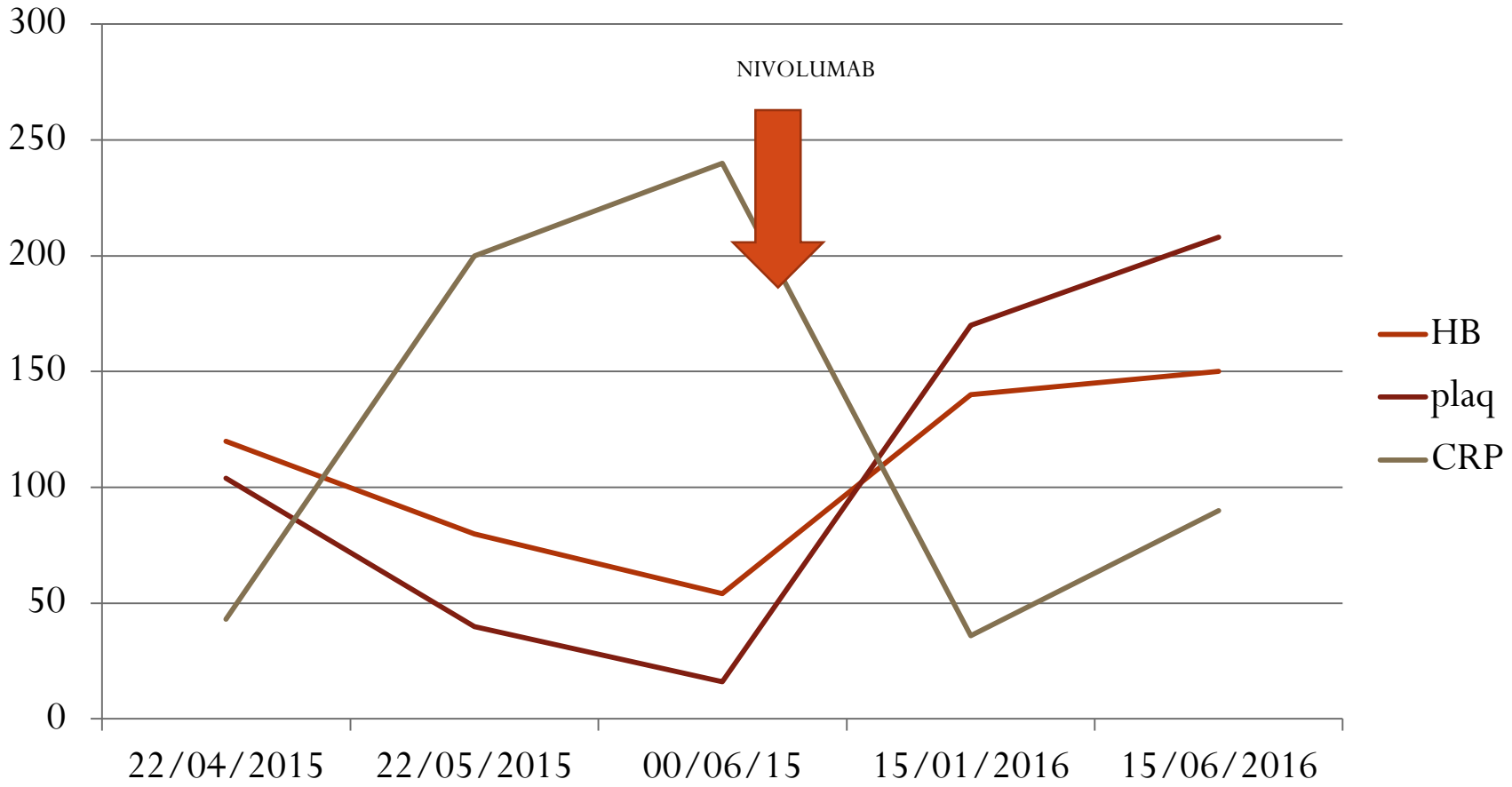
Traitement reçu en échec

- ICE x 3 RP puis ASHAP x 4 et intensification par BEAM et autogreffe en RP le 01/07/2008 (recueil de CSH insufisant pour 2 autogreffes) puis entretien VELBE
- Progression sous velbe le 28/03/2009
  - 10 cures eto/ifosfamide
  - 6 cures GEMZ NVB
  - Brentuximab en ATU le 22/02/2011 6 cures
  - CAELYX du 24/06/11 au 22/04/15: 46 injections

Progression en mai 2015

- Pancytopenie avec Hb 5,4 g necessitant des transfusions et plaq à 40 G/L puis 16G/L
- Syndrome inflammatoire avec CRP à 200
- Myelogramme normal pas de MDS
- Progression osteomedullaire et splenique sur la TEP
- Mise sous NIVOLUMAB en ATU le 22/06 dernière transfusion le 09/07/15. RP sur TEP

EVOLUTION HEMATOLOGIQUE

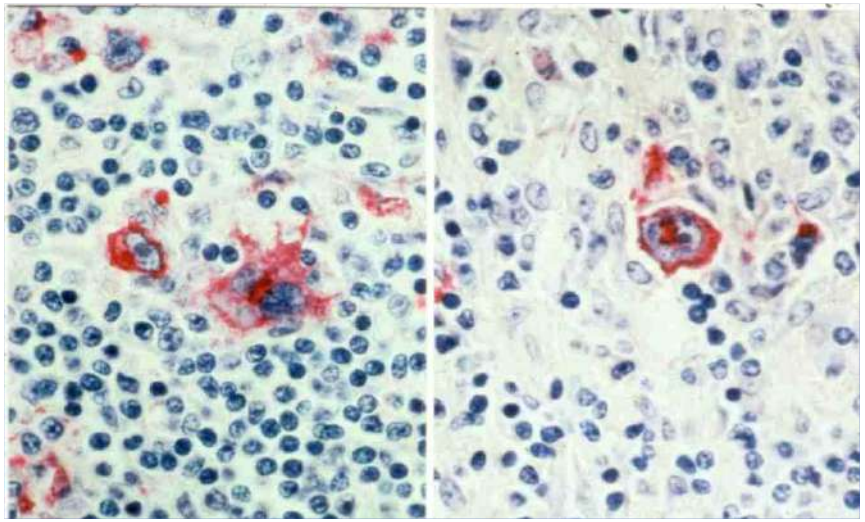


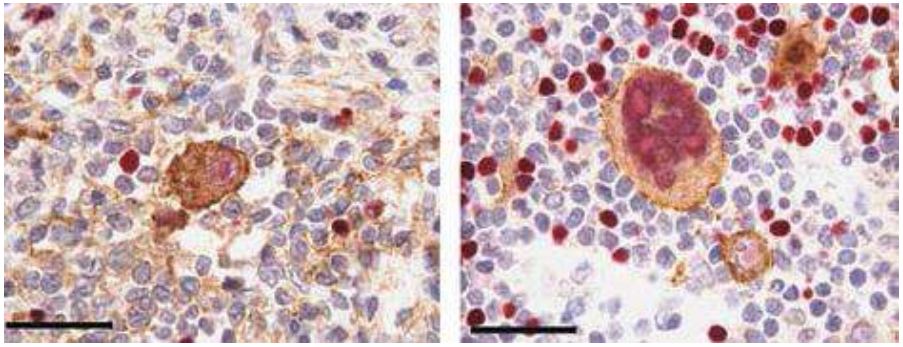
Suivi

- perte de la réponse sur TEP mais asymptomatique en oct 2016 (cycle 42) poursuite NIVO
- Progression en juin 2017 asymptomatique mais risque épidurite
- Rajout velbe
- Modification par caelyx en 2019
- Actuellement NIVO N°104
- PS à 0 NFS (Globules blancs 5300, hémoglobine 12, PNN 3200, lymphocytes 1600, plaquettes 178000)
- Aucun effet secondaire

Hodgkin Lymphoma (HL) Biology

- Classic HL include small numbers of malignant Reed–Sternberg cells (CD30+) within an extensive but ineffective inflammatory and immune-cell infiltrate
- Preclinical studies suggest that Reed–Sternberg cells exploit the programmed death 1 (PD-1) pathway to evade immune detection
- PD-L1/PD-L2 alterations are a defining feature of cHL
  - Amplification of 9p24.1 is more common in patients with advanced stage disease and associated with shorter PFS



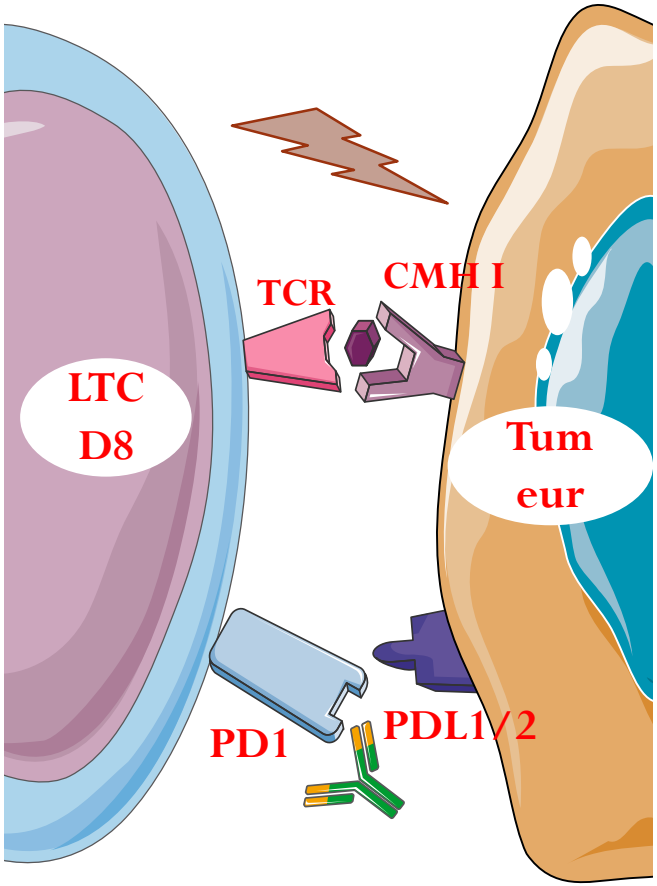


Figures from Ansell SM, et al.[1]

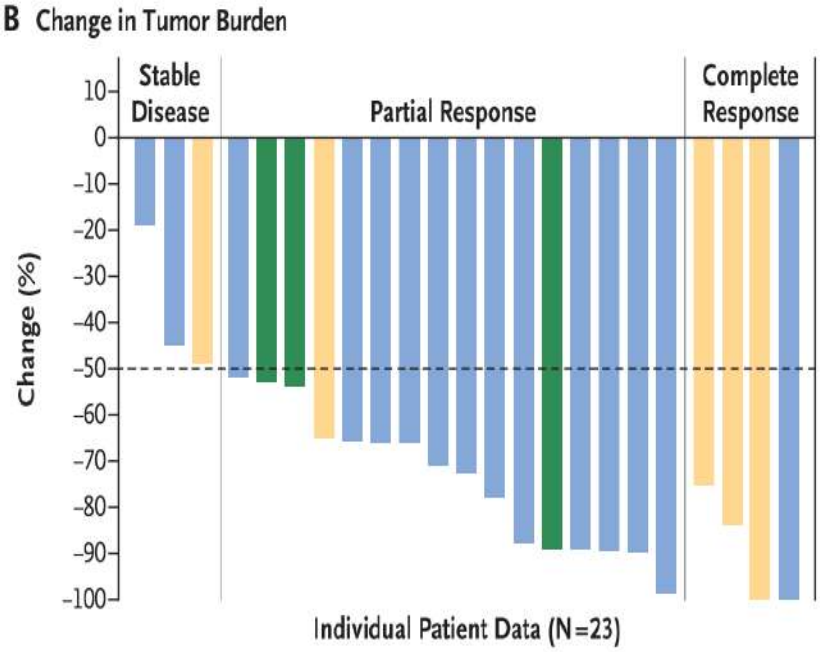
PD-1, programmed death 1; PD-L1, programmed death ligand 1; PD-L2, programmed death ligand 2; PFS, progression free survival.

1. Ansell SM, et al. *N Engl J Med*. 2015;372:311-319. 2. Roemer MG, et al. *J Clin Oncol*. 2016;34:2690-7.

L'immunothérapie du LH

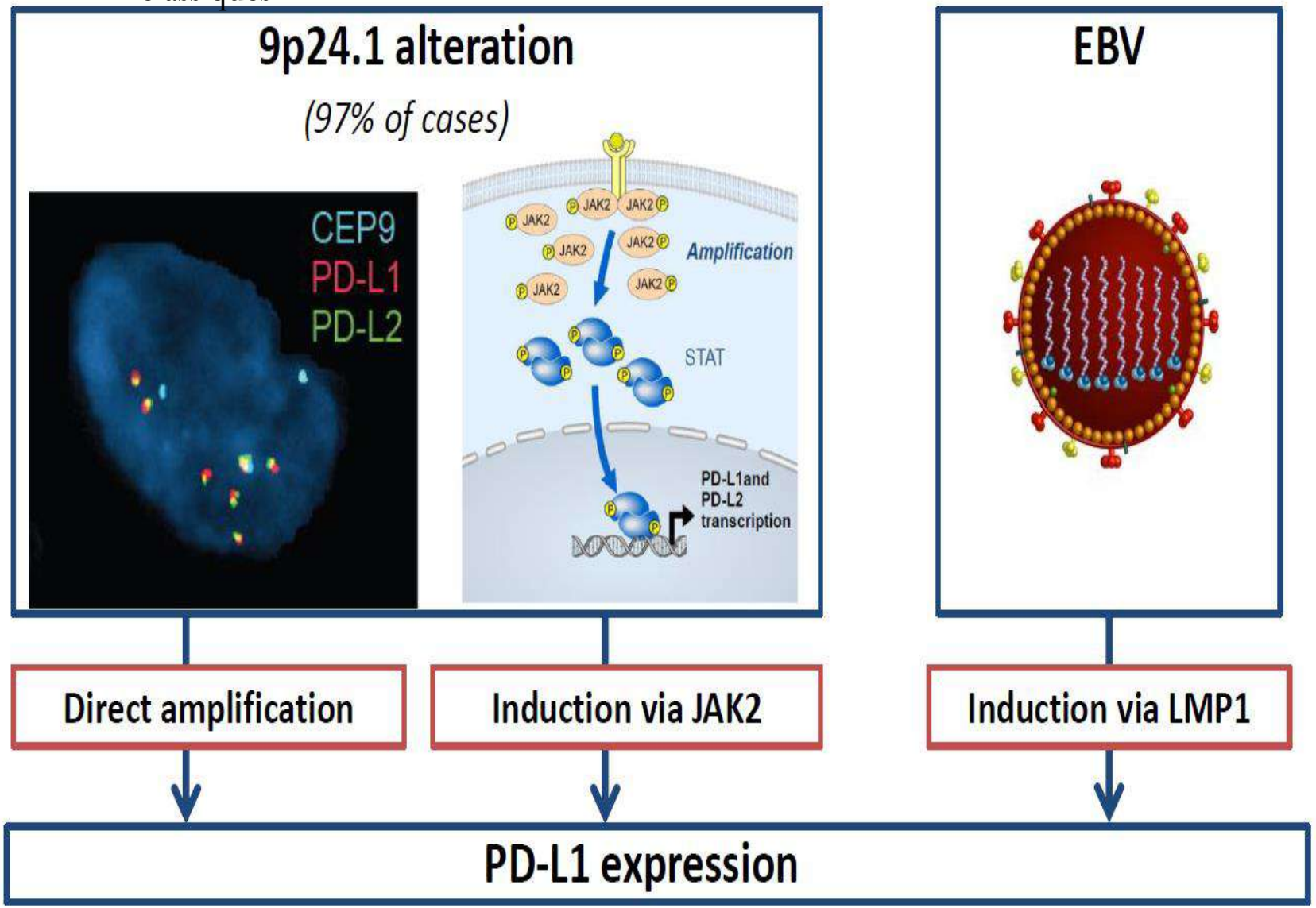


- Nivolumab = Ig4 monoclonale humanisée anti-PD1



Ansell et al. NEJM 2015

Mécanismes expliquant l'expression de PD1/PDL1 dans les LH classiques



Check point inhibitors in relapsed/refractory HL Phases II

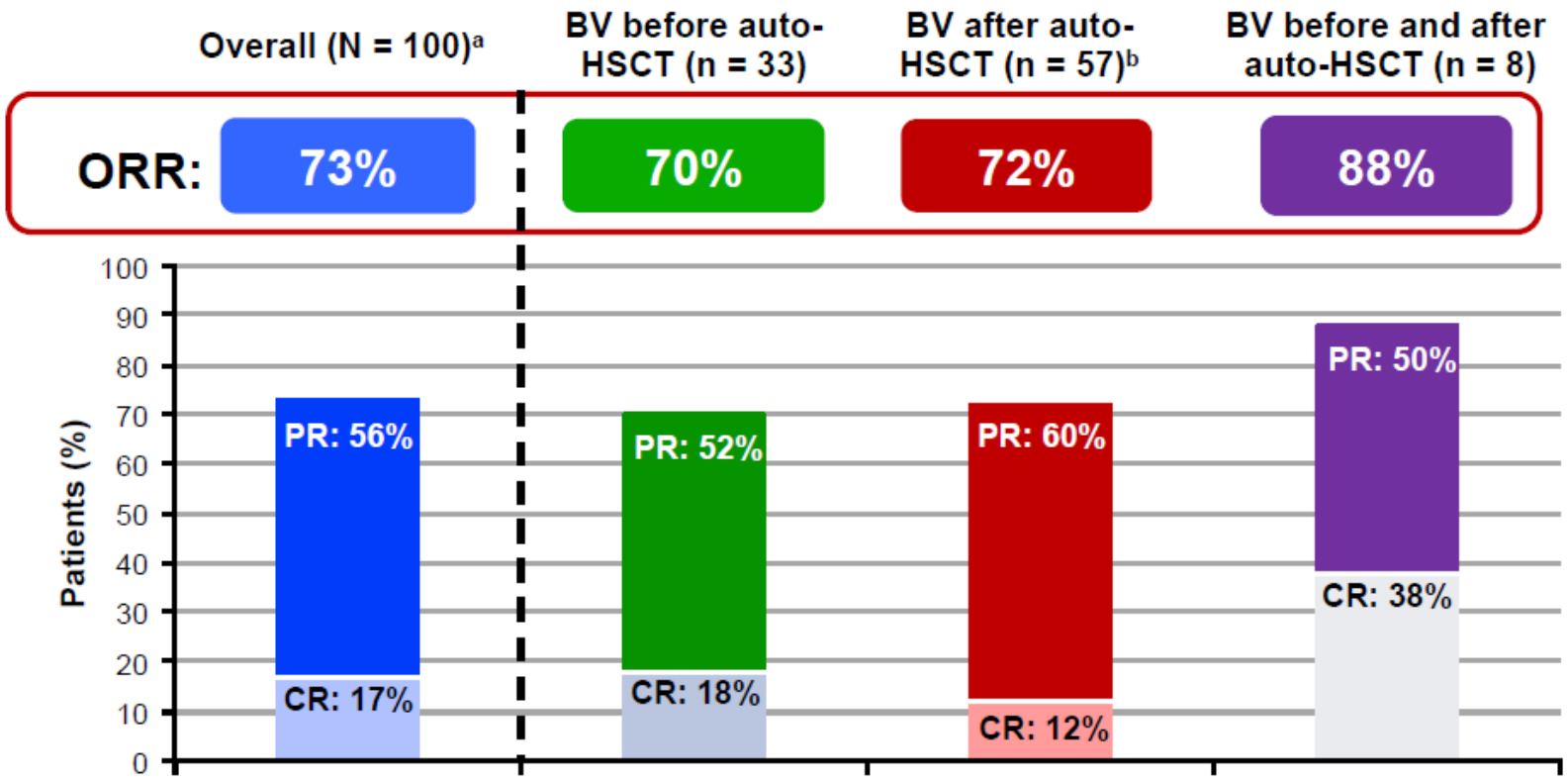
	NIVOLUMAB	PEMBROLIZUMAB
PATIENTS	80	80
ORR CR	67,5 % 8 %	55 % 18 %
MEDIAN RESPONSE	13 mo	NR
FOLLOW UP	12 MO	7 mo

Younes Lancet oncol 2016

Moskowitz JCO 2017

Réponse aux antiPD1 identique en rechute post autogreffe et/ou post BV

Essai Phase II Nivolumab Checkmate 205



SD	17 (17)	7 (21)	9 (16)	1 (13)
PD	6 (6)	3 (9)	3 (5)	0

Chen, JCO 2017
Armand, JCO 2018

ANTI-PD1/PDL1 toxicities

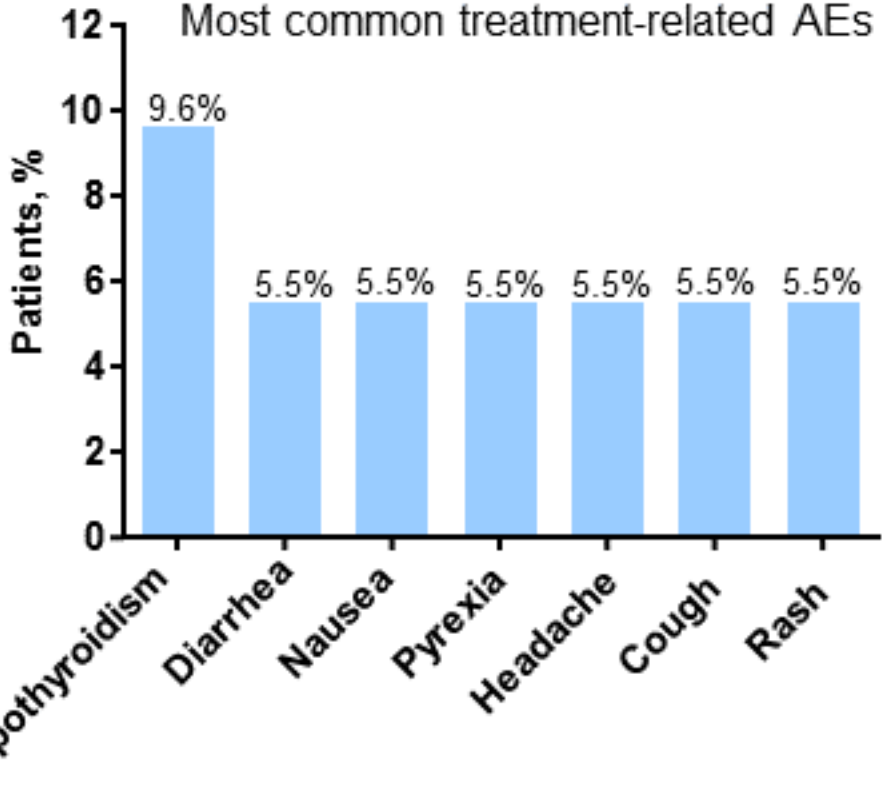
- Low toxicities in relapsed/refractory HL
- Less than 5% of grade 3 toxicities, major toxicities are:

- Fatigue
- Diarrhoea
- Infections
- hypothyroidism
- Hepatitic cytolysis
- Cutaneous Rash
- pneumonia

Younes Lancet oncol 2016
Moskowitz JCO 2017

Treatment-Related Adverse Events

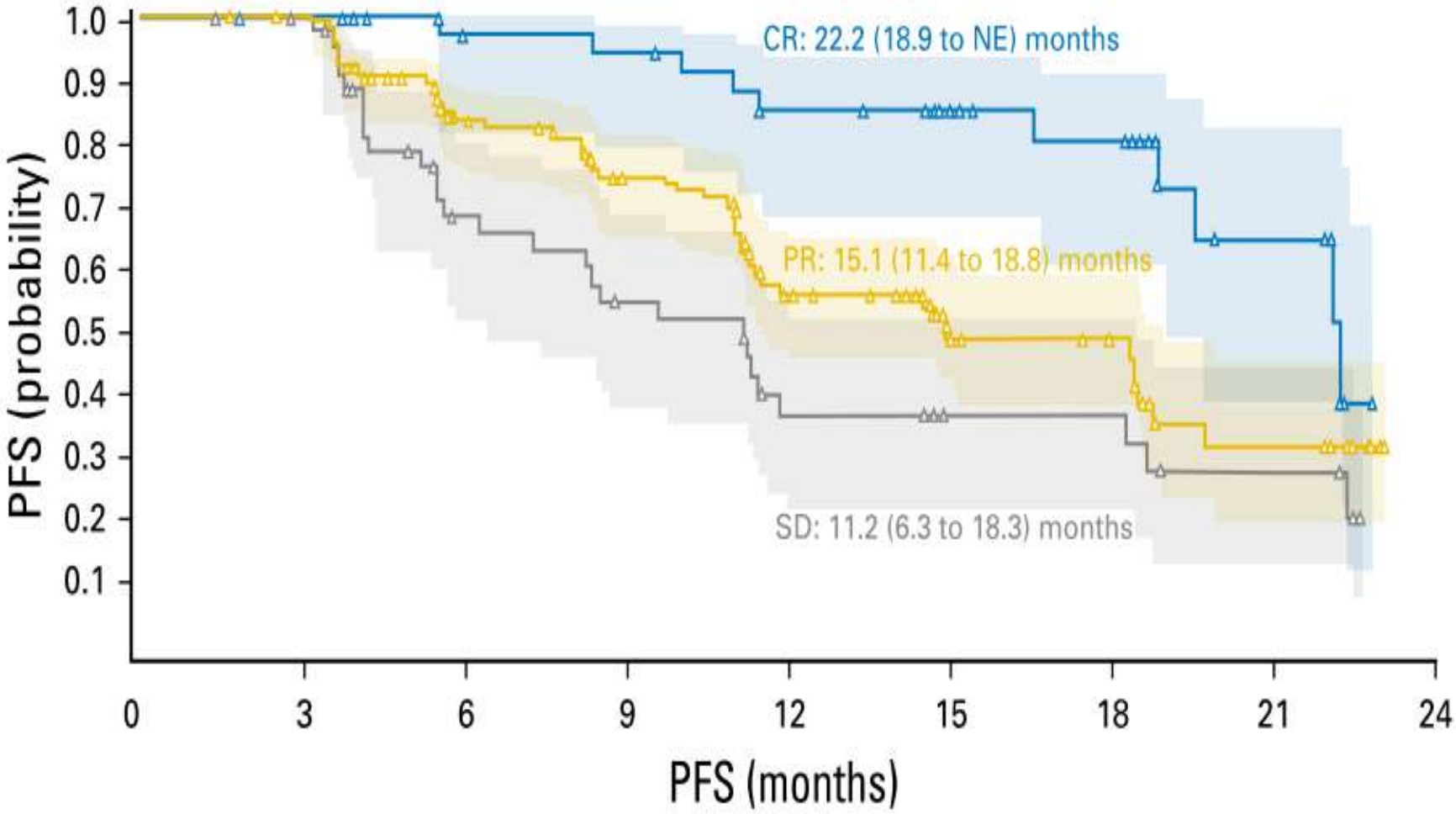
Treatment-related AE	n (%)
Any grade	46 (63.0)
Grade 3/4	6 (8.2)
Grade 5	0
Led to discontinuation	3 (4.1)



- Treatment-related AEs were similar between the primary refractory subgroup and total population
- Treatment-related AEs leading to discontinuation: myocarditis, cytokine release syndrome, infusion-related reaction, and pneumonitis
- Death unrelated to treatment: 1 (during safety follow-up, graft vs host disease)

Data cutoff: September 25, 2016.

Duration of response is linked to CR or not (Nivolumab)

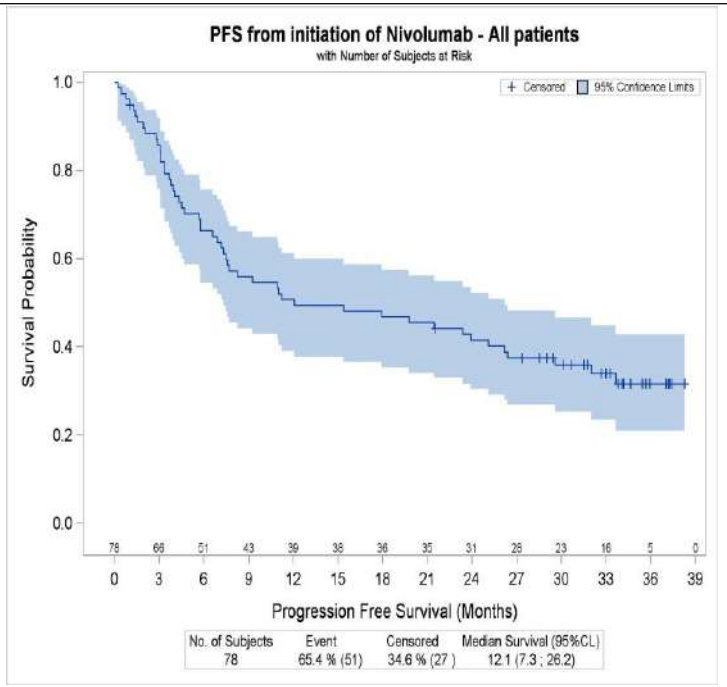


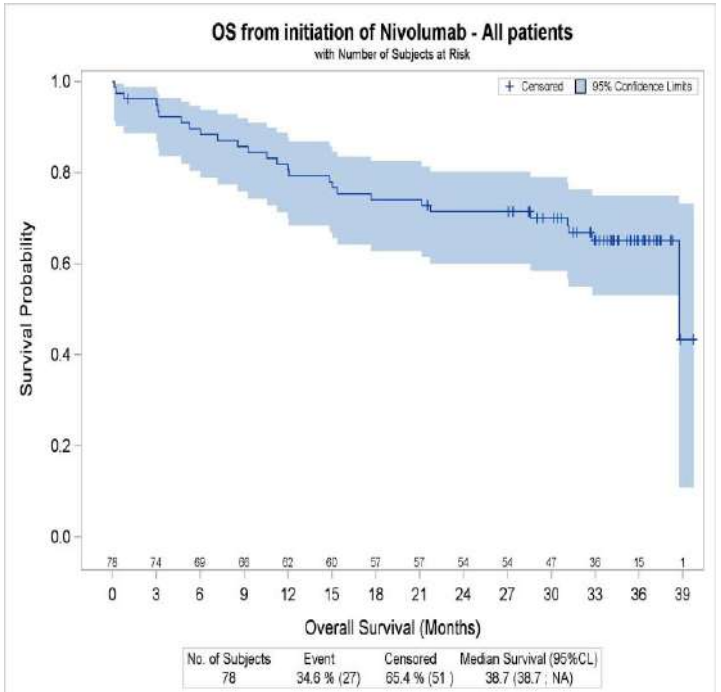
Etude ATU-nivo

Results French ATU Nivolumab

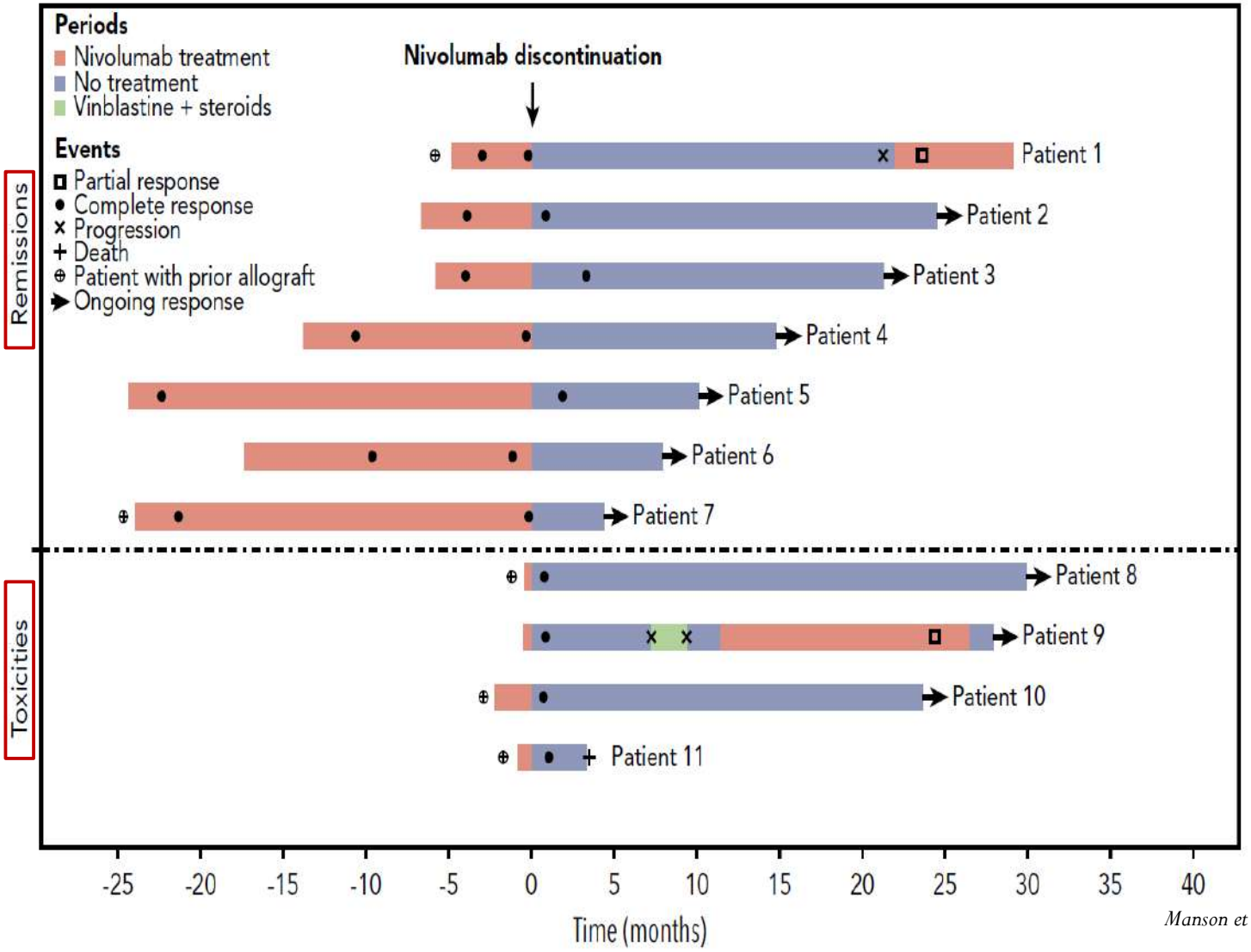
Efficacy

N	76
Médian FU, months	34.3
ORR	65.8%
CR	38.2%
PR	27.6%
PFS, médian mo	12.1 [0,2 – 38.3]
3 years OS	65%



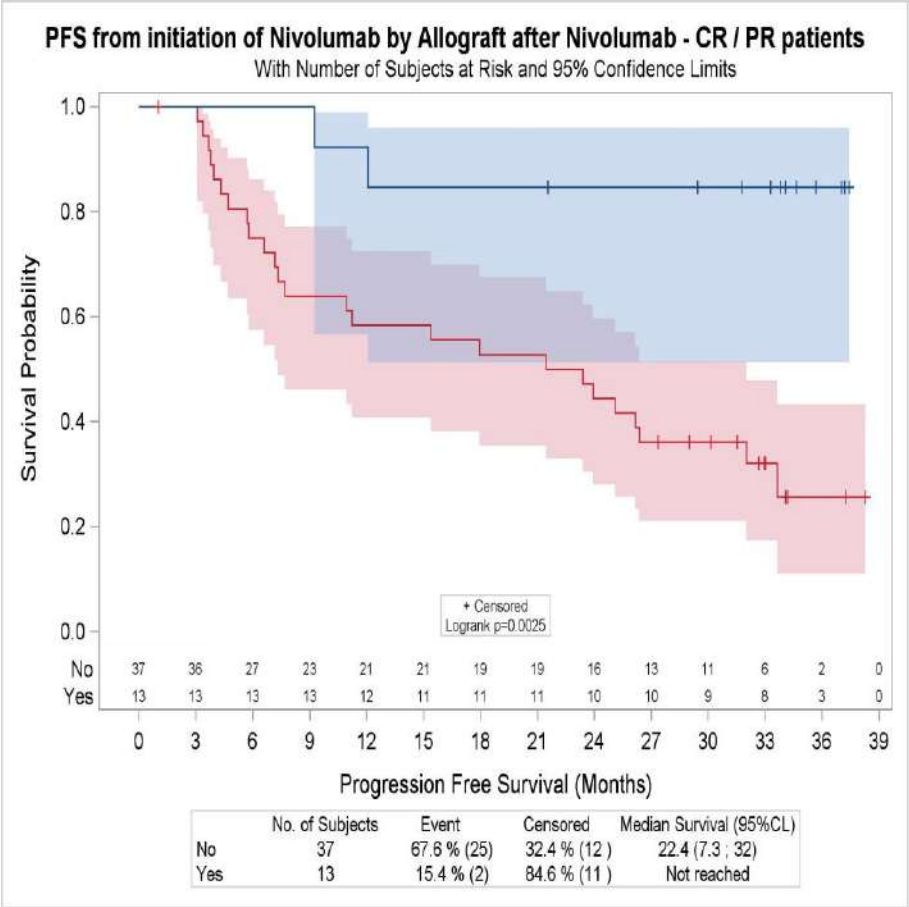


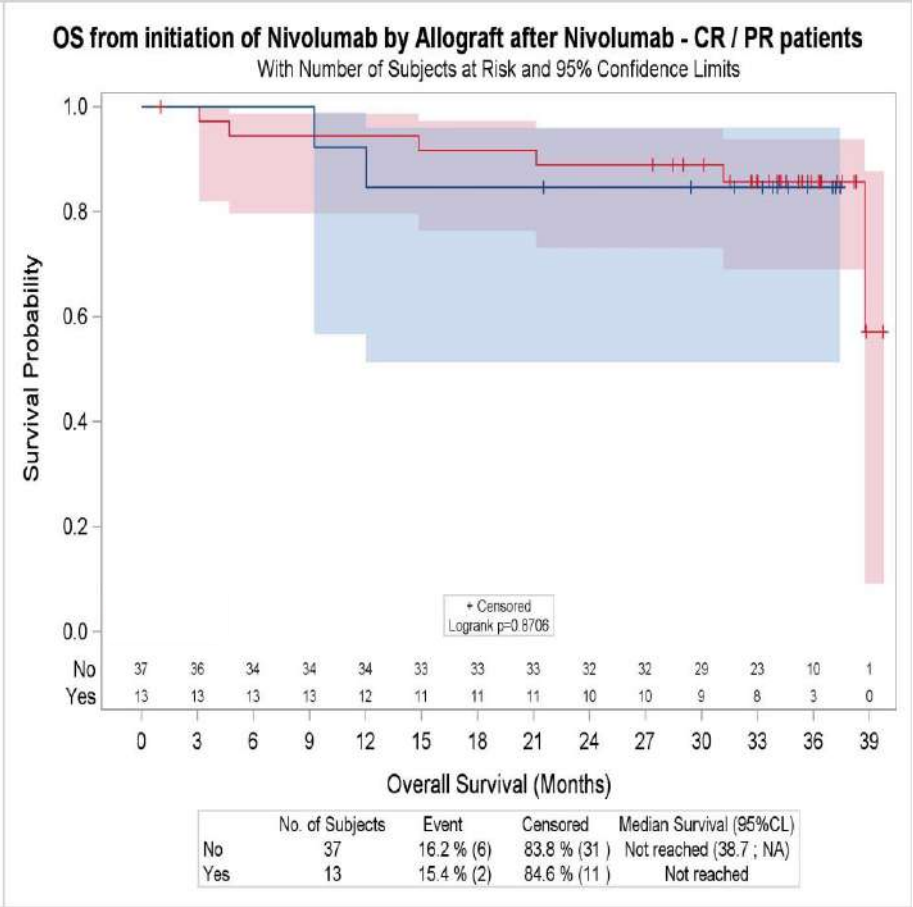
Nivolumab discontinuation in 11 patients in CR



Manson et al. Blood 2018

Responding patients receiving or not allogeneic transplantation





Allogreffe après antiPD1 : taux de GVH et risque de rechute

- GVH :
  - Aigüe : 44%
  - Chronique : 41%
- NRM 1 an : 11%
- Rechute à 1 an : 14% (plus faible que études sans antiPD1)
- PFS 1 an : taux de 76% encourageant
- OS 1 an : 89%

Série Post Cy (n=19)
Incidence attendue de GVH 2-4
Pas de GVH grade 3-4
Pas de GVH chronique

Schoch et al. Blood Advance 2018

Herbaux et al. 2016

Questions

- Les anti PD1 doivent ils être un bridge pour l'allogreffe ou la remplacer ?
- Efficacité avec la radiotherapie ?
- Peux t on arrêter pour les patients en RC ?
- Retraitement

- *Merryman et al blood 2016*

REPRISE DE TRAITEMENT PAR ANTIPD1

- 20 Patients en RC après nivolumab (NB median de cycles à 25)
- RC obtenue en médiane apres 6 cycles [6-18]
- 8 patients en rechute délai median de 11 mois dont 4 confirmées par biopsie
- 50% de RC apres retraitement apres 6 cycles
- Apparition d'effets secondaires immuns chez 3 patients

Fedorova et al abstr465
ICML 2019

Recommandations de l'utilisation des antiPD1

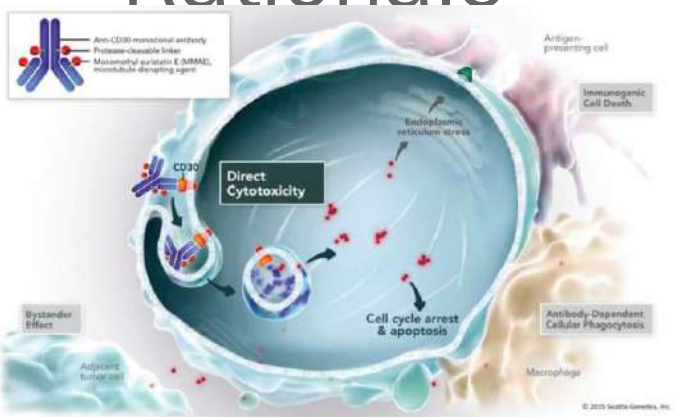
- En monothérapie avec évaluation aux alentours de trois mois et continuer tant qu'il y a un bénéfice clinique (pas de signes B si de syndrome inflammatoire et syndrome tumoral modéré)
- Essayer de faire de la radiotherapie si possible sur un site réfractaire (Quero et al cancer Radiother 2019)
- Arrêter au bout d'un an si RC (reprendre si rechute et discuter allogreffe selon age)
- Proposer allogreffe pour RP avec masse tumorale minime et si éligible (comorbidités)

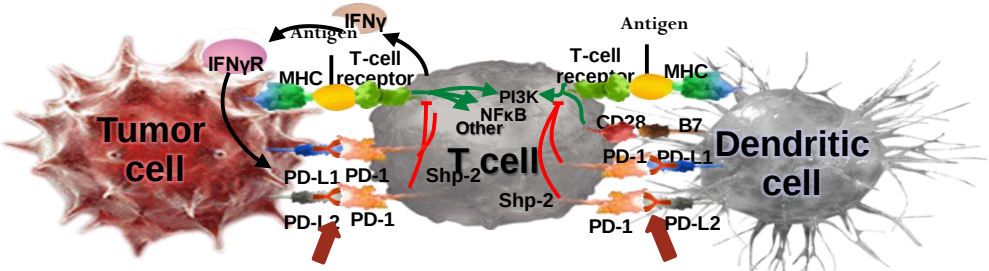
Sensibilité chimio post anti-PD1

Patient	Regimens performed before anti-PD-1	Response reached	Treatment Line	CT performed after anti-PD-1 monotherapy	Response reached	Time lapse[a] (months)
1[b]	Vinblastine-novantrone	PD	9	Vinblastine	PR	60
2[b]	Gemcitabine- vinblastine-liposomal doxorubicine	CR	10	Vinblastine	PR	47
3[b]	Vinblastine-novantrone	PD	6	Vinblastine	CR	11
4[b]	Vinblastine	PD	5	Vinblastine	PD	12
5	Bendamustine- BV	CR	6	Bendamustine	CR	45
6	Bendamustine	CR	7	Bendamustine	CR	6
7[b]	Gemcitabine	PR	3	Gemcitabine	PR	23
8	BV	CR	6	Bendamustine-BV	CR	47
9	Vinblastine-novantrone	PD	4	Liposomal anthracycline	PD	25
10	Bendamustine- BV	CR	13	Bendamustine	CR	10
11	BV	PD	5	Gemcitabine- BV	CR	23
12	ABVD	PR	1	BEACOPP	CR	68
13[b]	BV-GVD	PD	4	BV	CR	9
14	BV	CR	3	Bendamustine-BV	PD	49
15	BV	PR	5	Bendamustine-BV	PR	23

Rossi et al. AJH 2018

Nivolumab and BV Combination: Rationale





Nivolumab blocks the PD-1 receptor

Brentuximab vedotin disrupts the microtubule network and triggers an immune response through the induction of endoplasmic reticulum stress[1]

Nivolumab targets the programmed death-1 (PD-1) immune checkpoint pathway and restores antitumor immune responses

*Per investigator. BV, brentuximab vedotin; CR, complete response; HL, Hodgkin lymphoma; ORR, overall response rate; PD-1, programmed death 1; R/R, relapsed/refractory.

1. Gardai SJ, et al. AACR 2015; Abstract 2469. 2. Gopal AK, et al. *Blood* 2015;125:1236-1243. 3. Younes A, et al. *Lancet Oncol* 2016;17:1283-1294.

Brentuximab & nivolumab

- First Refractory/relapsed HL:
- 102 patients (42 % primary refractory)

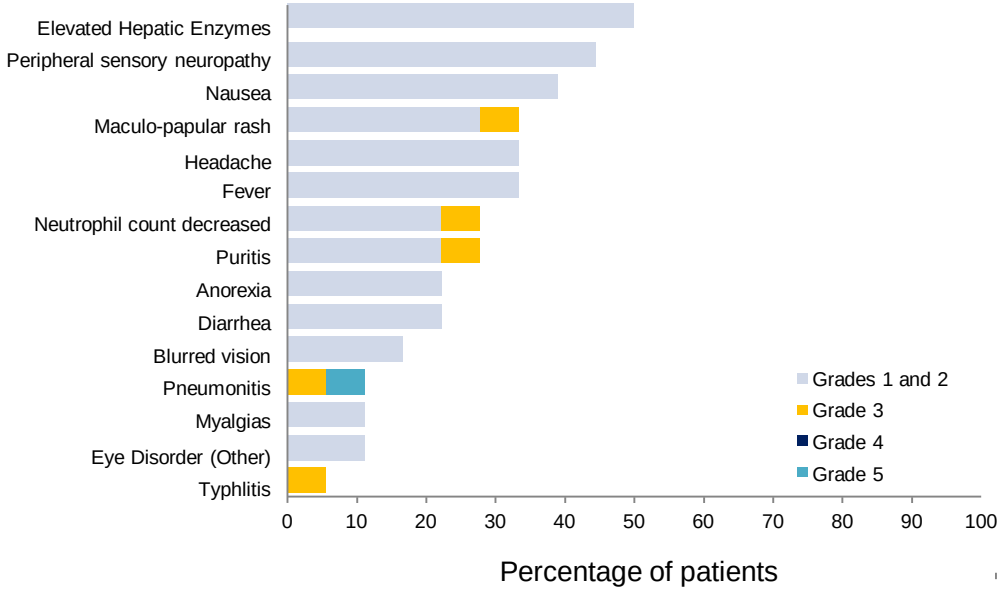
- Brentuximab 1,8 mg/kg & Nivolumab 3mg/kg every 3weeks
- Patients recived 4 cycles in median
- No dose reduction or interruption for AE
- Some infusion related reaction
- Overall response rate at 90 % with 62% complete metabolic response

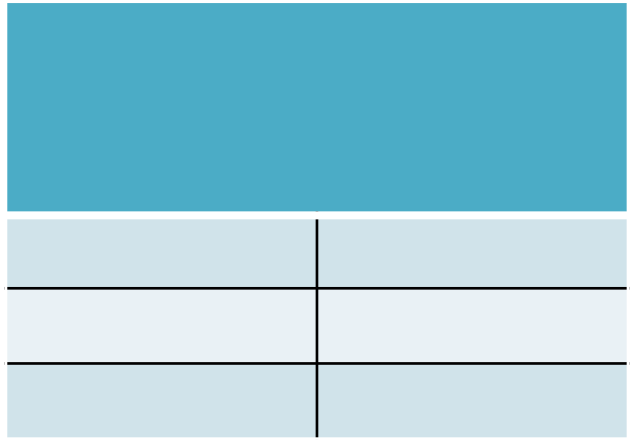
Herrera blood 2018

E4412: Safety

BV+Nivo: R/R HL after SCT, or 1L chemo or primary refractory, prior BV or immunotherapy allowed but not within 6 months

Common and immune adverse events with Nivolumab and BV (N=18)





- Elevated hepatic enzymes most common: transient primarily cycle 1 no impact on treatment
- Peripheral sensory neuropathy common in BV re-treatment patients
- BV dose was reduced or delayed in 3 patients; nivolumab dose was delayed in 2 patients

Diefenbach CS et al. Presented at: *The 58th American Society of Hematology (ASH) Annual Meeting & Exposition*; December 3–6, 2016; San Diego, CA.

Autres LNH pour antiPD1

- PD-1 blockade with nivolumab in relapsed/refractory primary central nervous system and testicular lymphoma *BLOOD, 8 JUNE 2017 x VOLUME 129, NUMBER 23* *5 réponses sur 5*
- Pembrolizumab in patients with CLL and Richter transformation or with relapsed CLL,
- *BLOOD, 29 JUNE 2017 x VOLUME 129, NUMBER 26* *ORR à44% pour RT*

Efficacité des CI dans les LNH

- **PD-1 Blockade in Mediastinal Gray-Zone Lymphoma** *June 28, 2017, at NEJM.org.*
- **LNH T NK extranasal: 2 RC/7** **Kwong Blood 2017**
- **Protocole ACSE**

- **PMBL 41 % de réponses sur 18 patients** **Zinzani blood 2017**
- **PMBL Brentuximab et nivolumab** 73 % de réponses et 37 % de RC sur 30 patients
- **Zinzani JCO 2019**

Conclusions

- Efficacité remarquable dans les LH et dans certains sous entités de Lymphome (PMBL)
- Actuellement des associations sont en devt:
- - NIVO + VELBE (LYSA)
- - Atezolizumab et tamezostat
- - Atezolizumab et Obinutuzumab et venetoclax
- - NIVO et DTIC
- - NIVO et AVD
- NIVO + GEMOX (R)