Actualités Lymphomes

Reunion ADHET
5 octobre 2018

Dr Lucie Oberic

Service hématologie

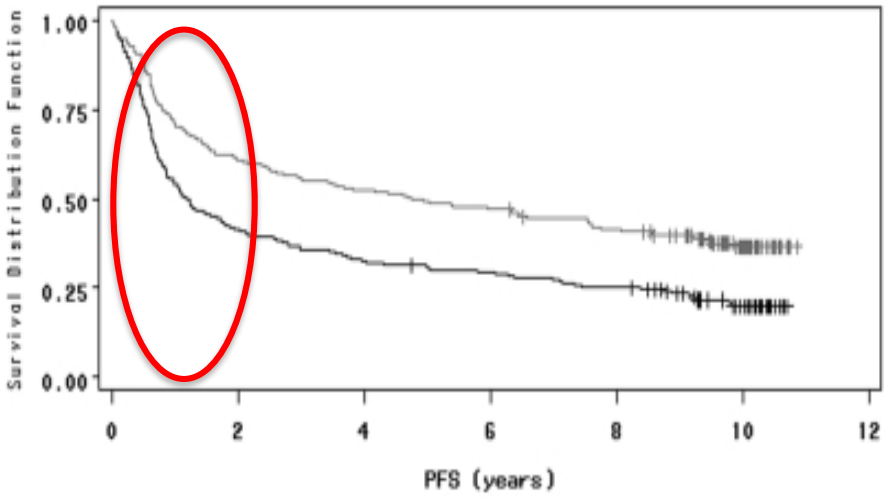
IUC Toulouse Oncopole

- DLBCL
  - Première ligne: améliorer le RCHOP? GaINeD
  - Rechute/réfractaire: , Polatuzumab vedotin, CAR T cell

- Lymphome de hodgkin:
  - Brentuximab Vedotin: stades localisés, stades avancés
  - stratégie thérapeutique guidée par le Petscan : AHL2011
  - Immunothérapie

En première ligne: le standard reste le RCHOP

CHOP versus R CHOP



Coiffier B , Blood2010

X+R CHOP

1. **Phase 1 Azacitidine orale (CC486) –RCHOP**
   N=33, 97% IPI >3, 91% stade III-IV,
   TRG 97%, Pet- 85%

2. **Phase 1-2 Lenalidomide-Ga101-CHOP**
   N=51, TRG 90%

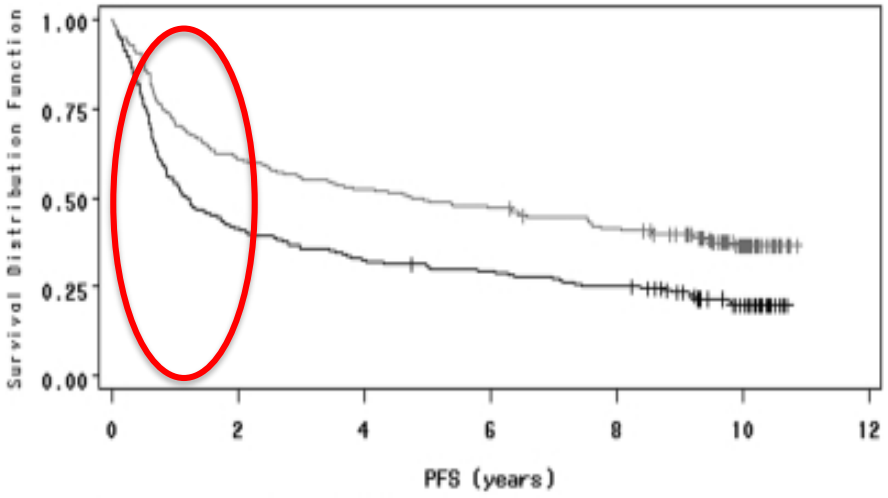
3. **Phase 1-2 Brentuximab Vedotin-R-CHP**
   N=31, SSP à 1 an 92%, SG 1 an 100%

4. Phase III Obinutuzumab

Martin P abs192 ASH2017
Westin JR, abs189, ASH2017
Svoboda J, abs191, ASH2017

En première ligne: le standard reste le RCHOP

CHOP versus R CHOP



X+R CHOP

1. Phase 1 Azacitidine orale (CC486) –RCHOP
2. Phase 1-2 Lenalidomide-Ga101-CHOP
3. Phase 1-2 Brentuximab Vedotin-R-CHP
4. **Phase III Obinutuzumab**

Coiffier B , Blood2010

Martin P abs192 ASH2017
Westin JR, abs189, ASH2017
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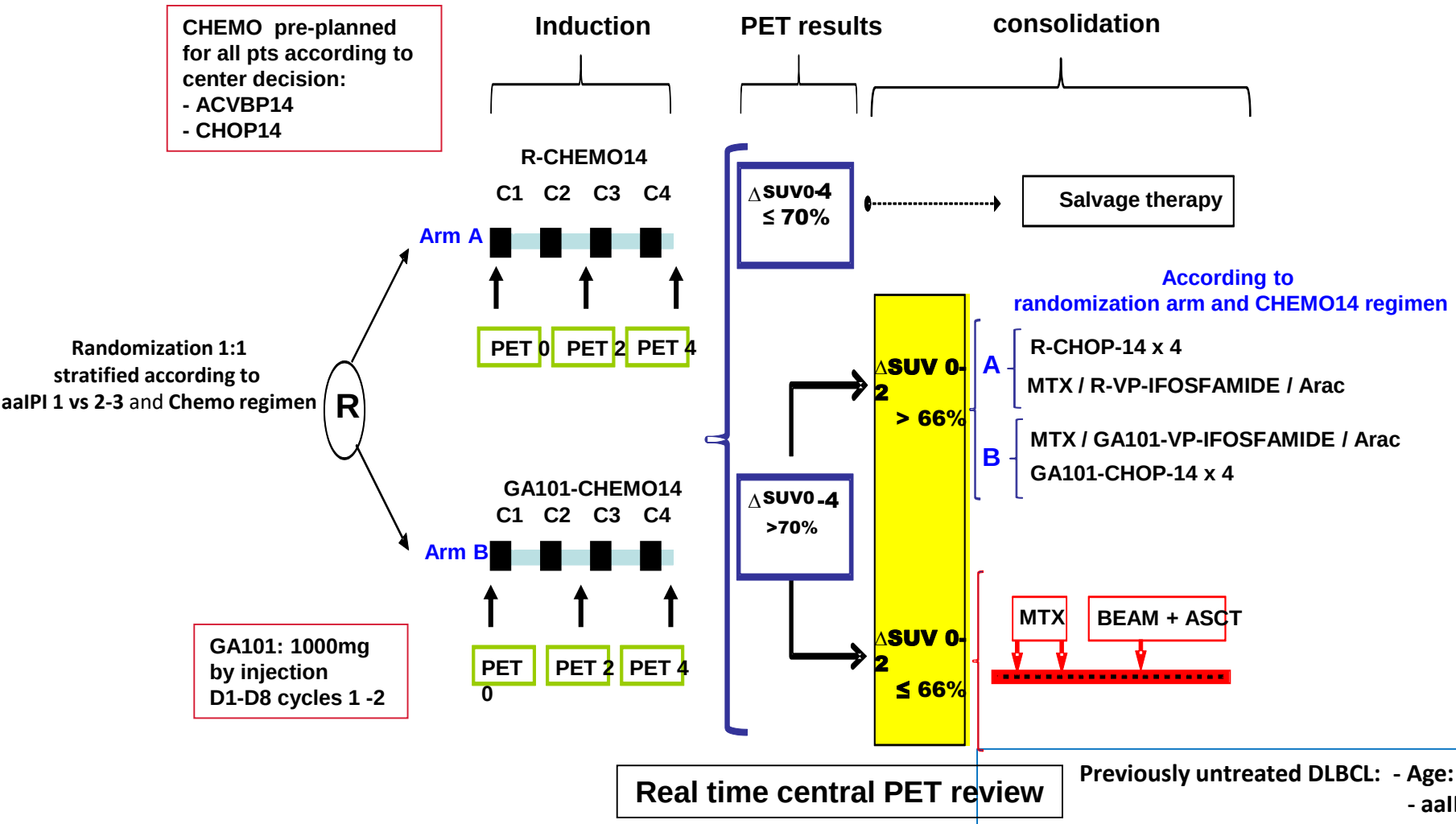
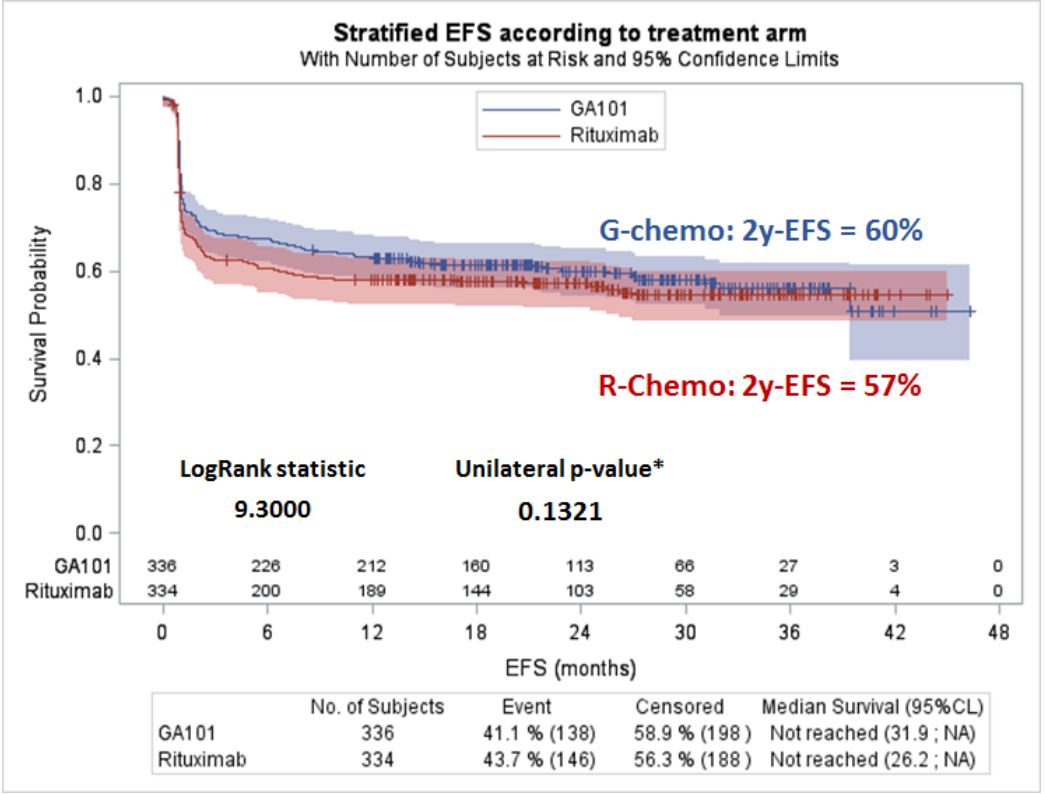
Lymphome B diffus à grandes cellules (LBDGC)
GA In NEwly Diagnosed DLBCL - GAINED



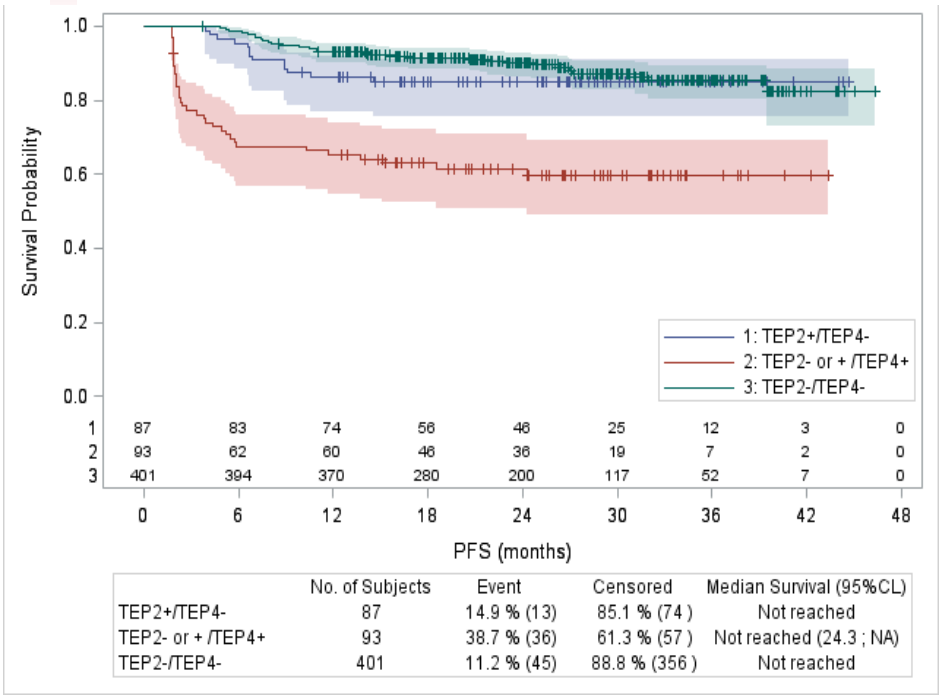
GAINED: Interim PET response according to ΔSUVmax

	G-Chemo n = 292		R-Chemo n = 289		
	N	%	N	%	p
PET2-/PET4-	215	**73**	186	**64**	**<0.02**
PET2+/PET4-	40	14	47	16	0.4
PET4+	37	**13**	56	**19**	**<0.04**



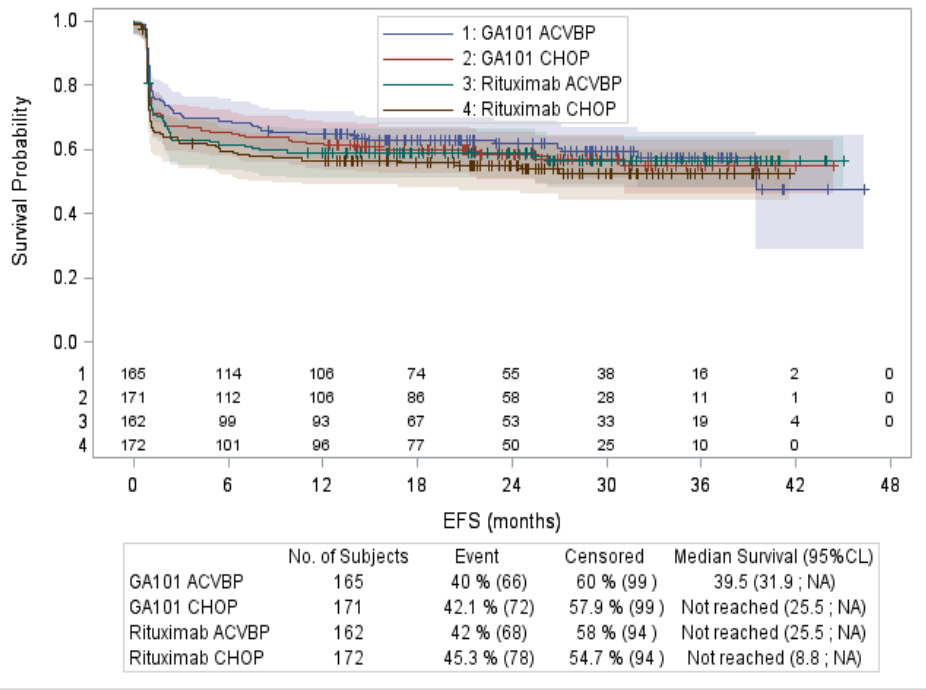
Casasnovas RO, ASH, 2017, Abstract 190

Survie sans évènement selon la TEP



	No. of Subjects	Event	Censored	Median Survival (95%CL)
TEP2+/TEP4-	87	14.9 % (13)	85.1 % (74)	Not reached
TEP2- or + /TEP4+	93	38.7 % (36)	61.3 % (57)	Not reached (24.3 ; NA)
TEP2-/TEP4-	401	11.2 % (45)	88.8 % (356)	Not reached

Survie sans évènement selon le traitement d'induction



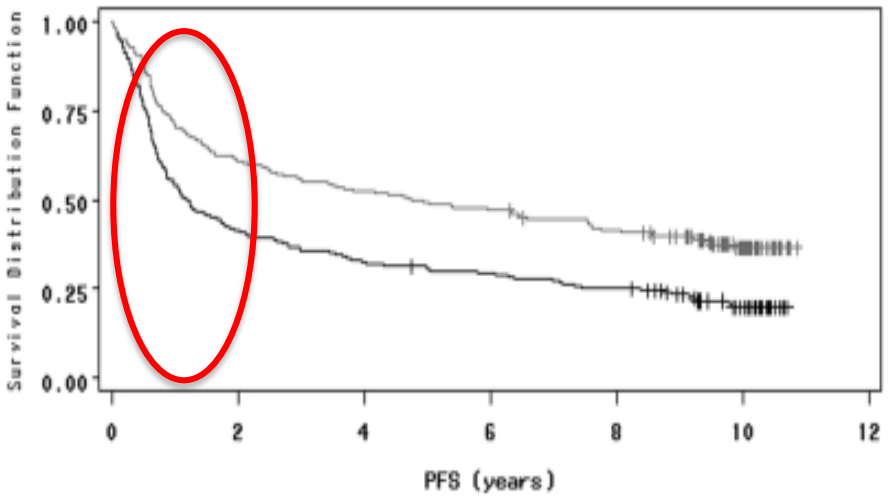
	No. of Subjects	Event	Censored	Median Survival (95%CL)
GA101 ACVBP	165	40 % (66)	60 % (99)	39.5 (31.9 ; NA)
GA101 CHOP	171	42.1 % (72)	57.9 % (99)	Not reached (25.5 ; NA)
Rituximab ACVBP	162	42 % (68)	58 % (94)	Not reached (25.5 ; NA)
Rituximab CHOP	172	45.3 % (78)	54.7 % (94)	Not reached (8.8 ; NA)

	Nb de sujets	Evènements	Censurés	Survie mediane (IC 95%)
TEP2+/TEP4-	87	14,9 %(13)	85,1%(74)	Non atteinte
TEP2-ou+/TEP4+	93	38,7%(36)	61,3%(57)	Non atteinte (24,3;NA)
TEP2-/TEP4-	401	11,2%(45)	88,8%(356)	Non atteinte

Casasnovas RO, ASH, 2017, Abstract 190

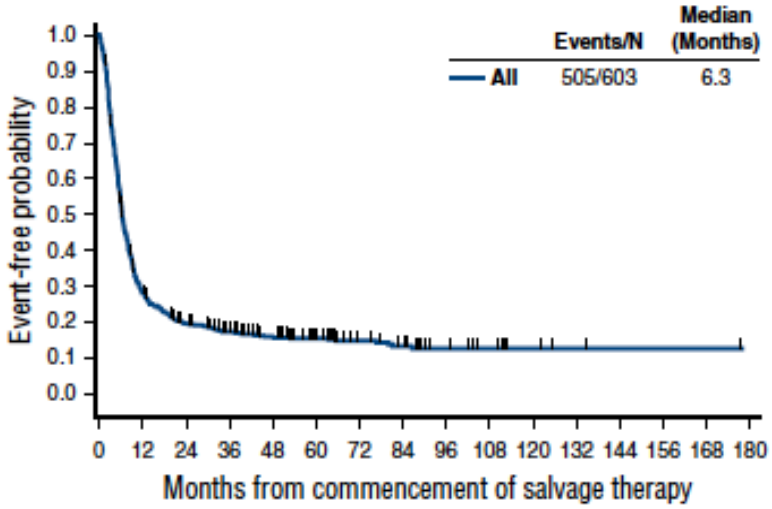
En première ligne: le standard reste le RCHOP…

CHOP versus R CHOP



Mais…

SCHOLAR Study



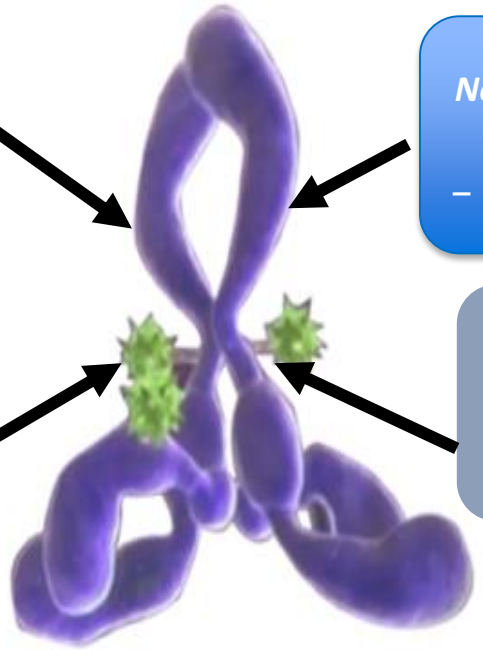
Coiffier B , Blood2010

Crump M, Blood2017

LBDGC R/R: Polatuzumab vedotin

Anti-CD79b[2]
Targets to B-Cell Malignancies
- Not expressed on vital tissue
- Highly internalized

Modified Fc portion
Not recognized by FcγR of immune cells
- No ADCC, like anti-PD1/PDL1 mAbc

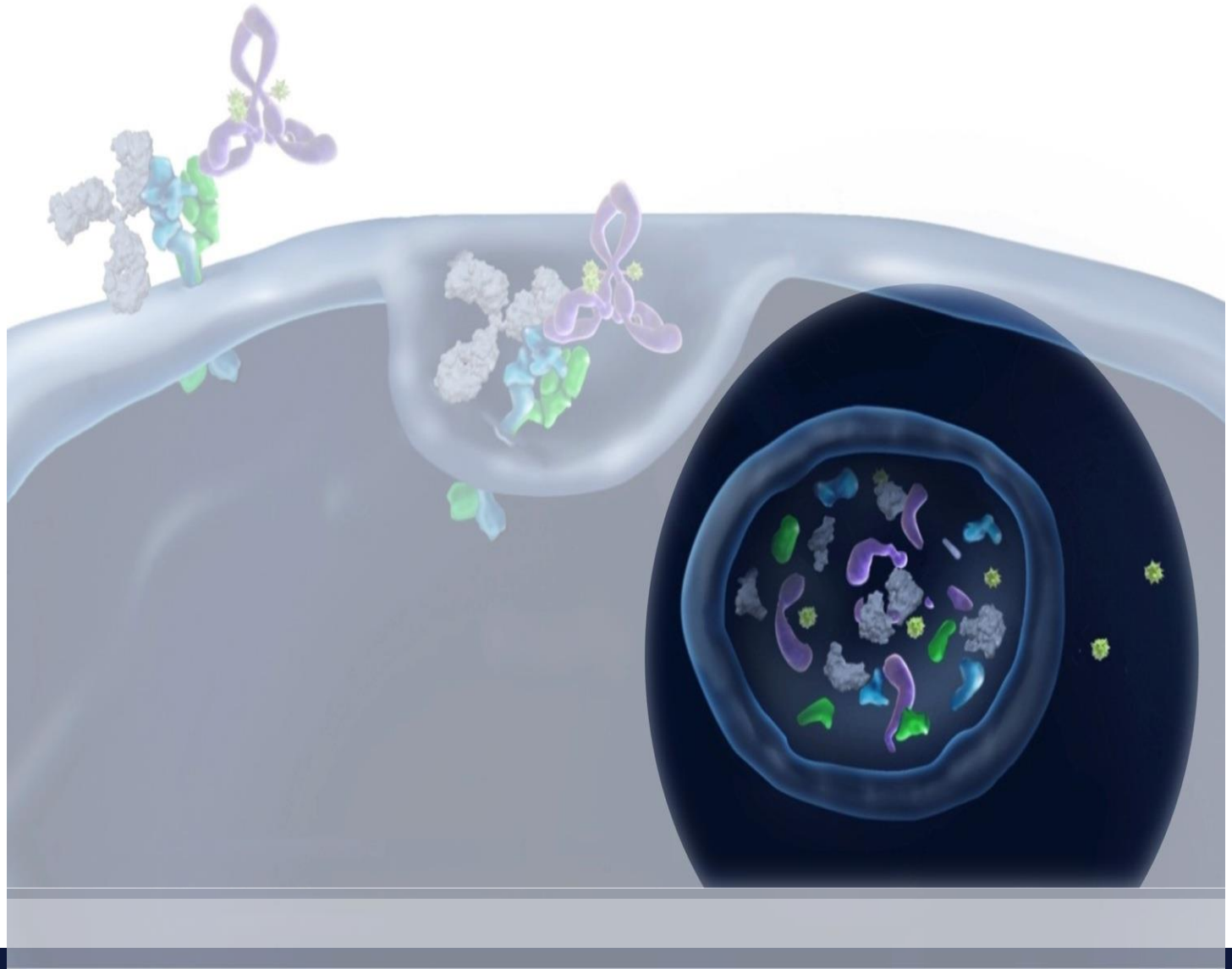


VC Linker[1]
Cleaved by lysosomal proteases
- Stable in circulation

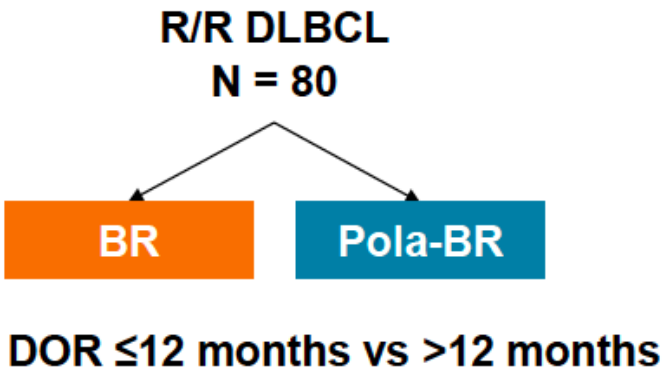
Monomethyl auristatin E (MMAE)[3,4]
Microtubule disrupter
- Highly potent (same as Brentuximab vedotin)
- Non-immunogenic

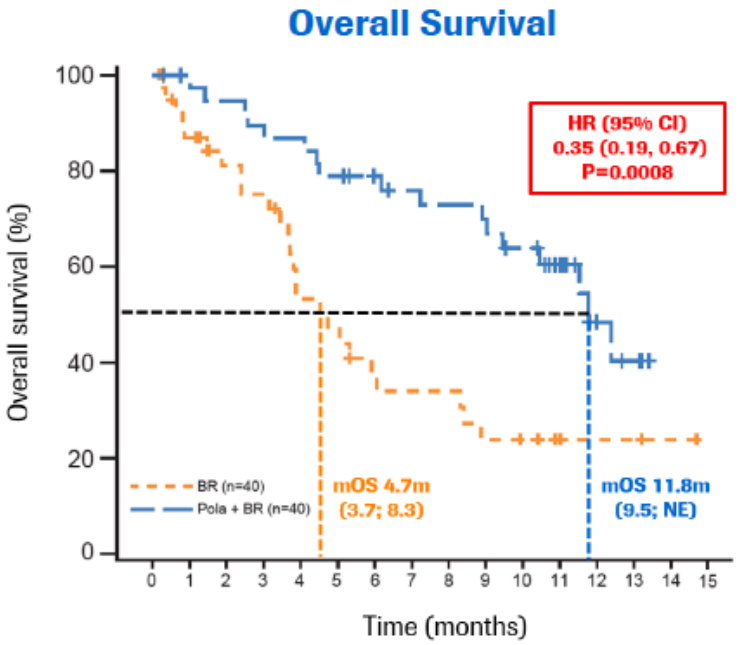
Polatuzumab vedotin: anticorps antiCD79a couplé à MMAE

LBDGC R/R: Polatuzumab vedotin



Polatuzumab Vedotin dans LBDGC R/R





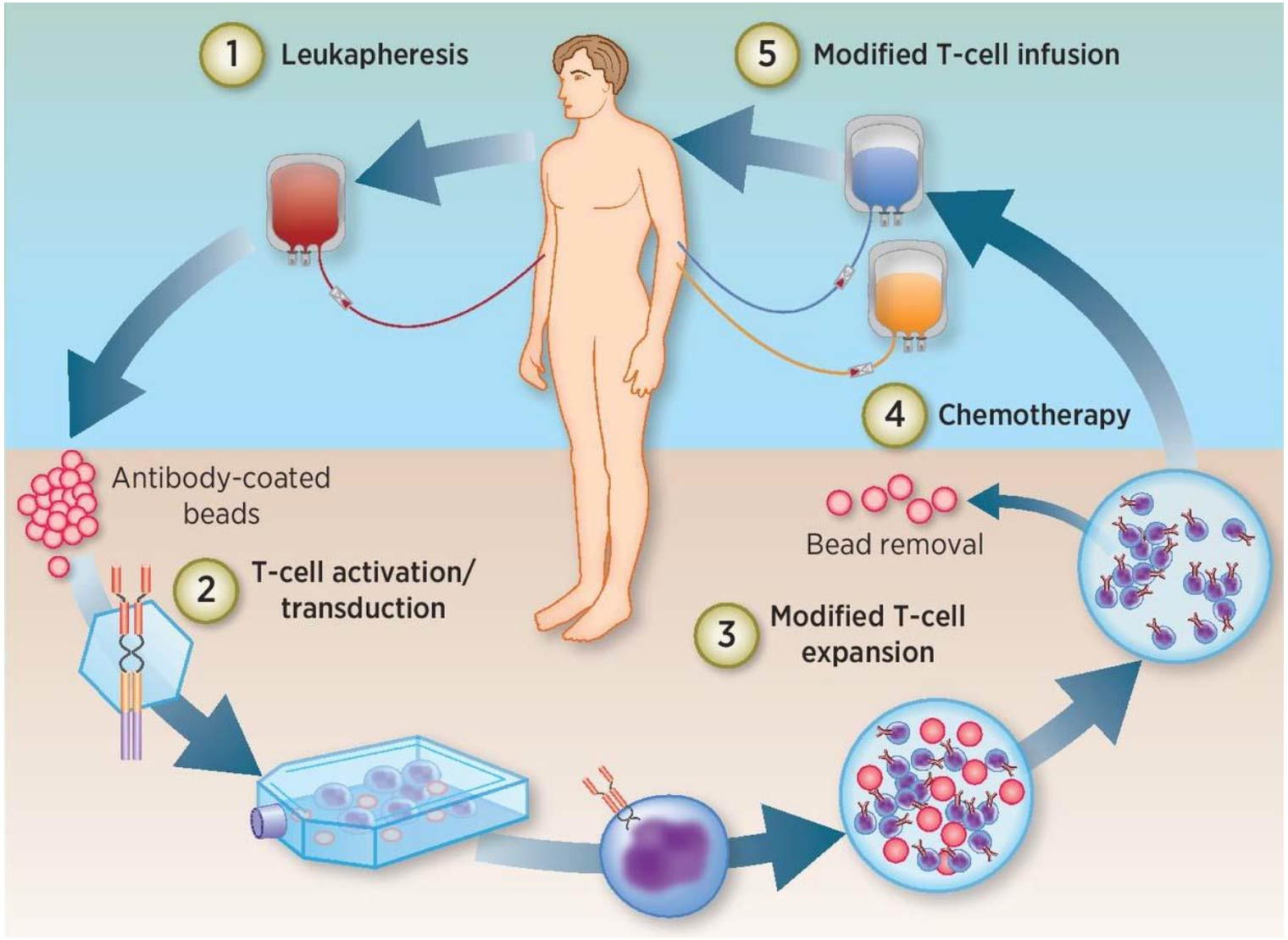
N(%)	Pola+BR (n=40)	BR (n=40)
ORR (EOT)	18 (45%)	7 (18%)
CR	16 (40%)	6 (15%)
mDOR	8,8 mo (4,5-NR)	3,7 (2,6-7,8)
mPFS	6,7 mo (4,9-11,1)	2 (1,5-3,7)
mOS	11,8 (9,5-NR)	4,7 (3,7-8,3)

p<0,0001

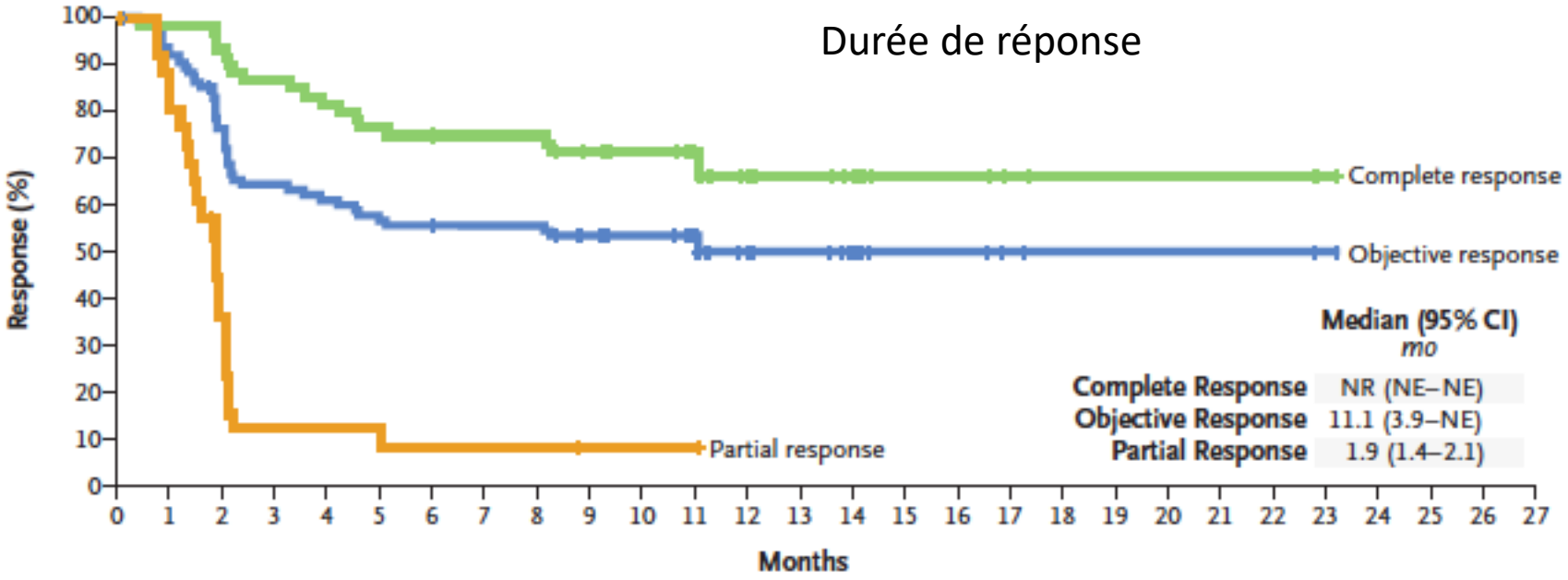
p<=0,0008

Sehn L, abs S802, EHA2018

CAR T Cell


1 Leukapheresis
5 Modified T-cell infusion
4 Chemotherapy
Antibody-coated beads
2 T-cell activation/ transduction
Bead removal
3 Modified T-cell expansion

ZUMA 1
axicabtagene ciloleucel (axi-cell)

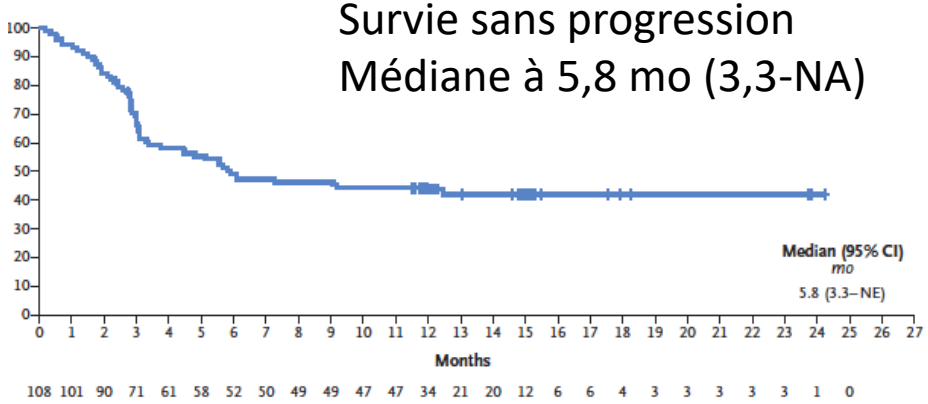


N= 111 patients inclus; 101 patients traités
Suvi médian 15,4 mois
Taux de RG : 82%, RC 54%

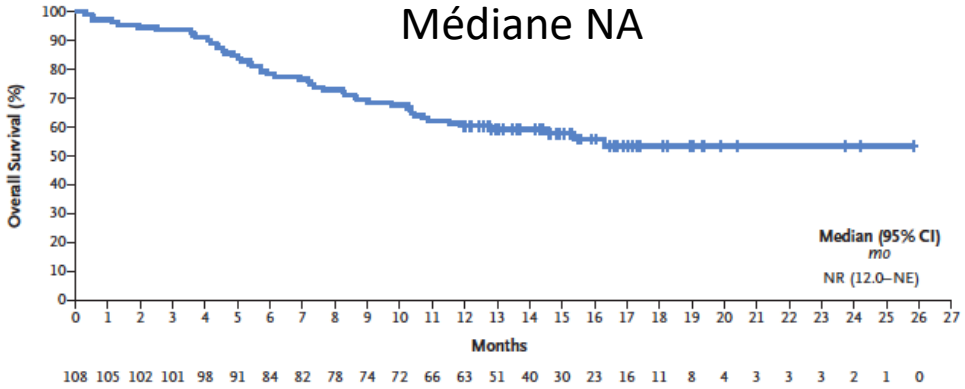
Neelapu S, abs578 ASH2017

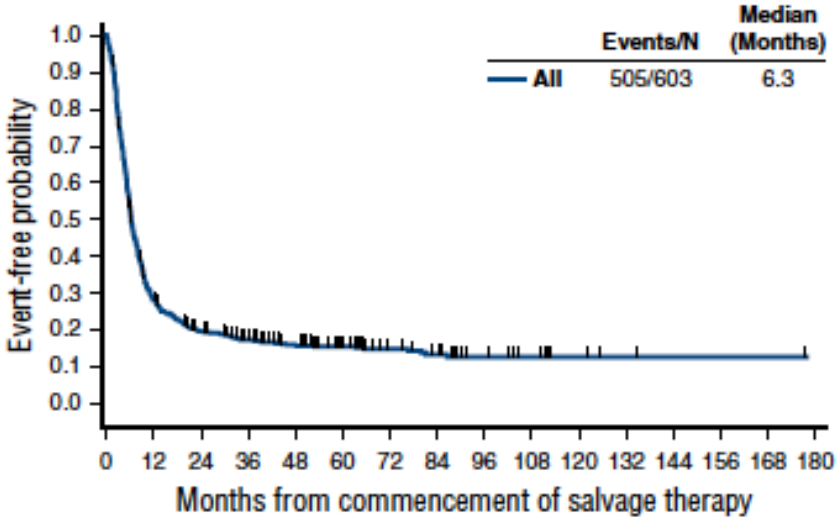
ZUMA 1
axicabtagene ciloleucel (axi-cell)

Survie sans progression
Médiane à 5,8 mo (3,3-NA)



Survie Globale
Médiane NA

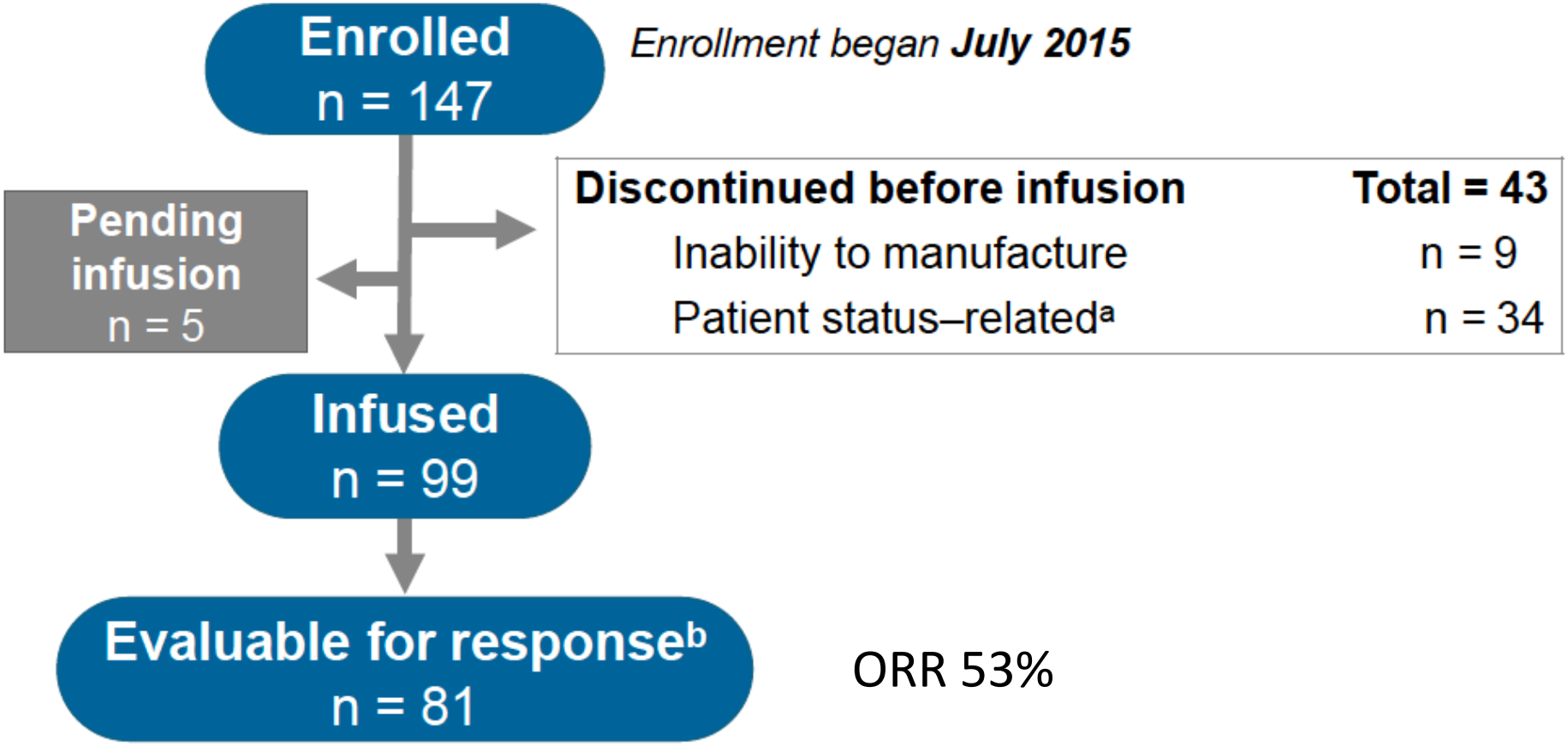




Crump M, Blood2017

Neelapu S, abs578 ASH2017

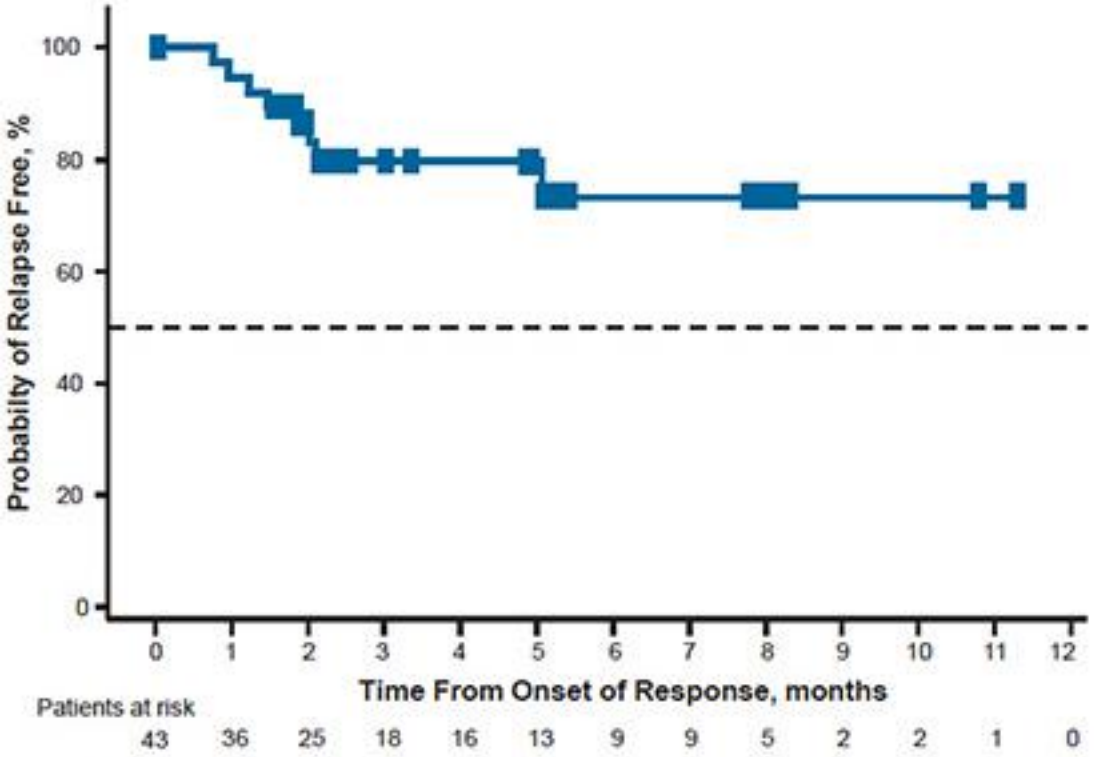
JULIET
tisagenlecleucel



ORR 53%

Schuster S, abs 577, ASH2017

JULIET
tisagenlecleucel



Efficacy analysis set = all patients who received a tisagenlecleucel infusion ≥ 3 months prior to data-cut date.

- **Median DOR and OS not reached**
- Almost all patients in CR at month 3 remained in CR
- No patients proceeded to transplant while in response

CR, complete response; DOR, duration of response; OS, overall response.

Schuster S, abs 577, ASH2017

Syndrome de relargage de cytokine (CRS)

	Patients N = 99
Time to onset, median (range), days[a,b]	3 (1-9)
Duration, median (range), days[a]	7 (2-30)
Hypotension that required intervention, %	28
High-dose vasopressors	6
Intubated, %	8
Anticytokine therapy, %	16
Tocilizumab	15
Corticosteroids	11

Schuster S, abs 577, ASH2017

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- Lymphome de hodgkin:
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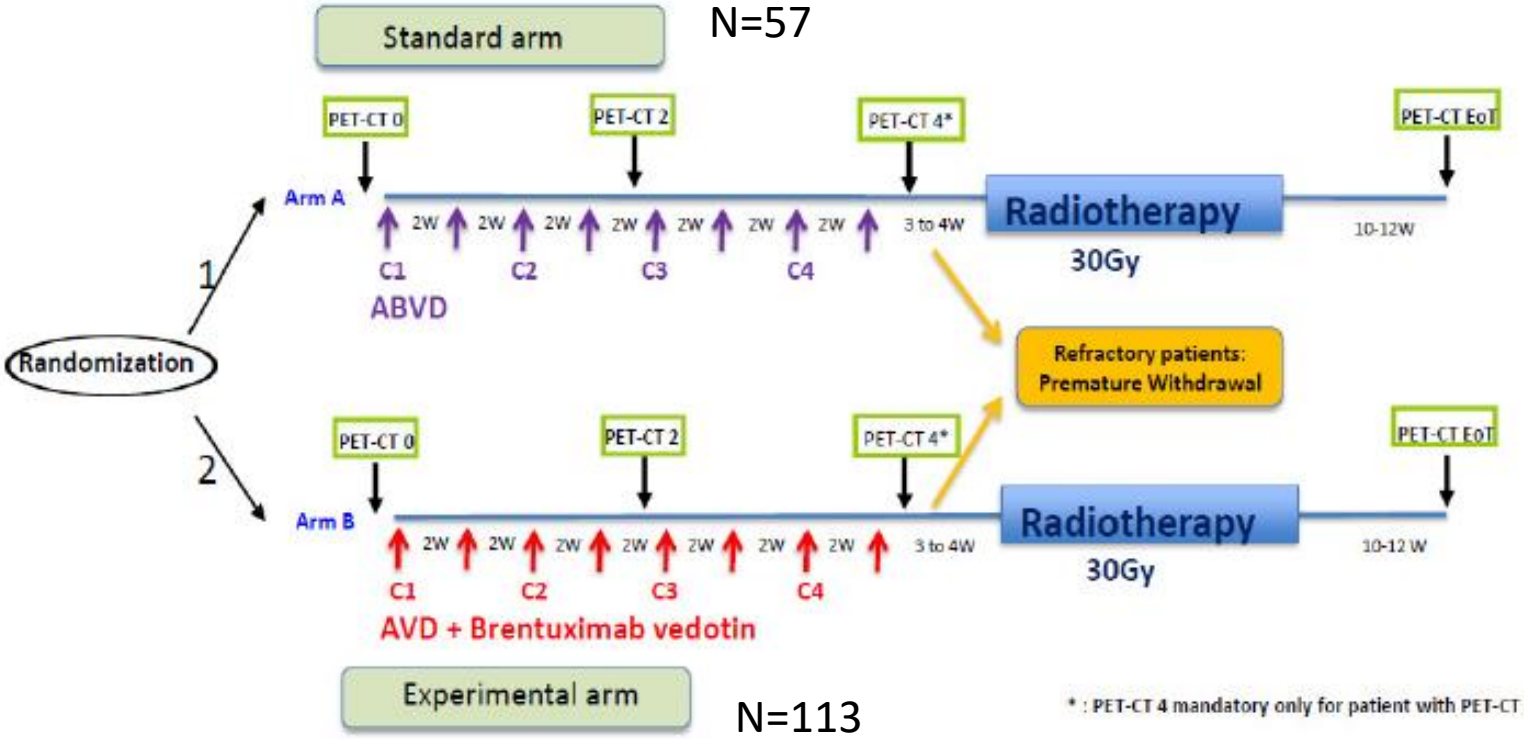
  - stratégie thérapeutique guidée par le Petscan : AHL2011
  - Immunothérapie

Lymphome de Hodgkin: stade localisé
Etude Breach



Experimental arm :

- **BV 1.2 mg/kg every 2 weeks**
- **G-CSF mandatory**

Fornecker L, abs ASH

PET Scan based response after 2 cycles (IRC assessment)

PET-response after 2 cycles, n(%)	BV-AVD *n=113*	ABVD *n=57*
Negative	93 (82.3)	43 (75.4)
95% confidence interval	(75.3% ; 88.0%)	(64.3% ; 84.5%)

The primary objective was met with a lower boundary of the 90% CI greater than 75% in the experimental arm.

Fornecker L, abs ASH2017

Adverse events (cycles 1 et 2)

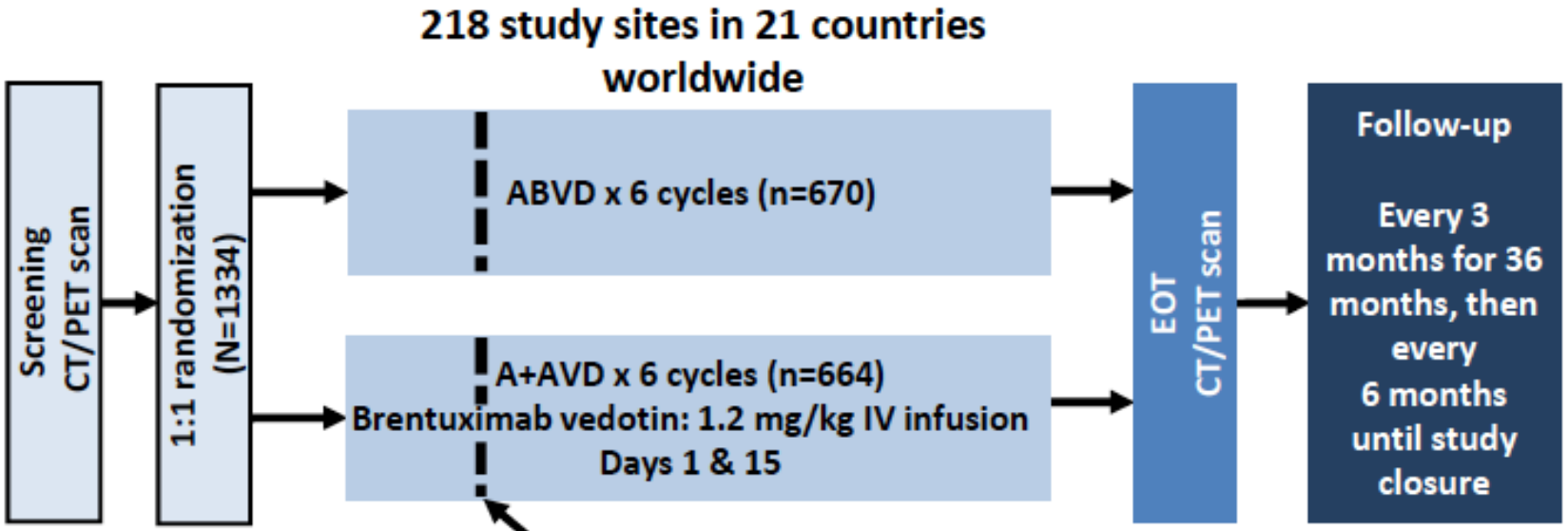
n(%) of pts reporting ≥ 1 event	BV-AVD *n=113*	ABVD *n=55**
Any AE	113 (100)	55 (100)
Grade 3-4 AE	84 (74)	31 (56)
SAE	24 (21)	4 (7)
Grade 3-4 SAE	21 (19)	4 (7)
Treatment-related SAE	19 (17)	1 (2)
SAE leading to permanent BV treatment discontinuation	7 (6)	-

**2 patients with no study drug administration due to consent withdrawal*

Reasons for permanent BV discontinuation were loss of weight, hyponatremia, febrile neutropenia, epileptic seizure, peripheral neuropathy, hepatitis and cutaneous rash.

Fornecker L,oral abs ASH2017

Étude ECHELON



- **Inclusion criteria**
  - cHL stage — III or IV
  - ECOG PS — 0, 1 or 2
  - Age — ≥18 years
  - Measurable disease
  - Adequate liver and renal function

End-of-Cycle-2 PET scan

- Deauville 5; could receive alternate therapy per physician's choice (not a modified PFS event)

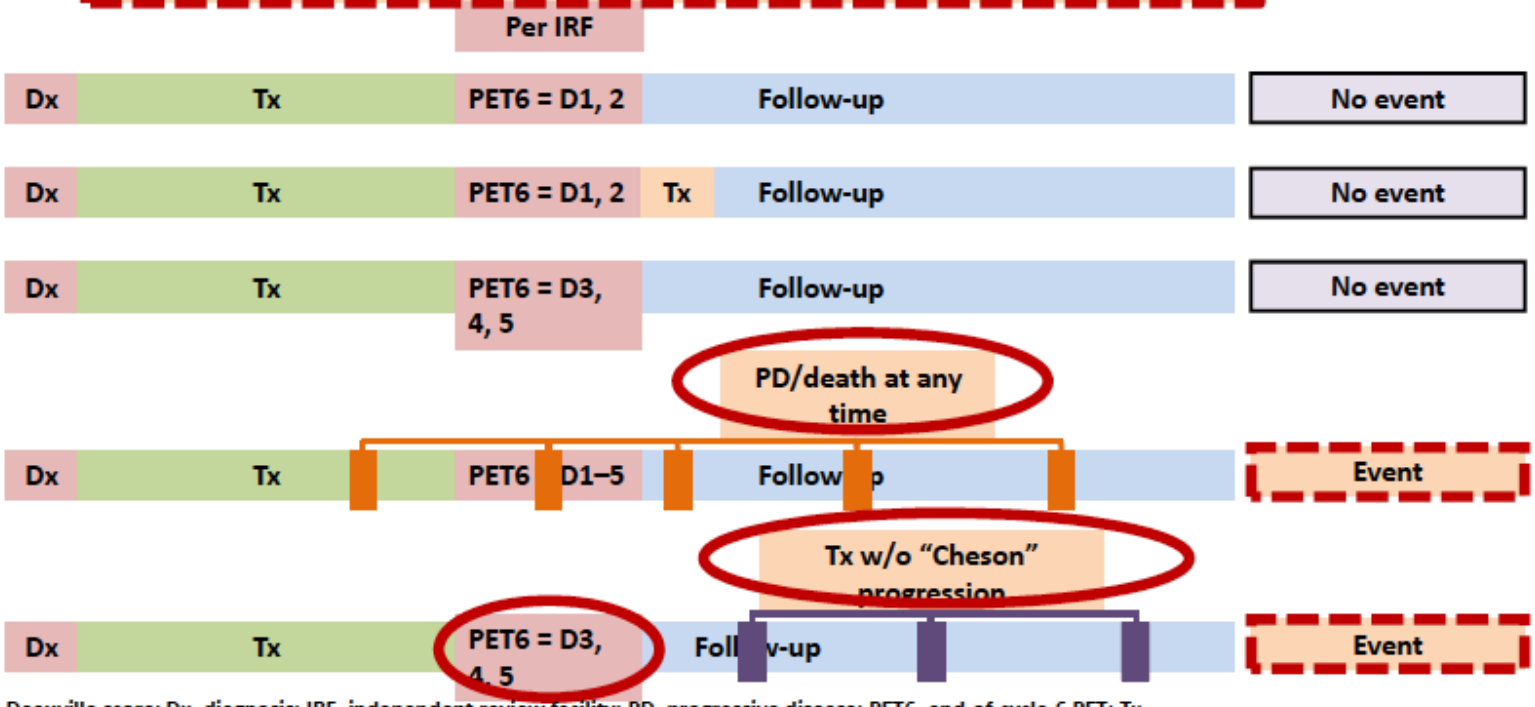
cHL, classic Hodgkin lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; EOT, end-of-treatment; PFS, progression-free survival

Connors M, NEJM2017

Étude ECHELON

- **Primary endpoint: modified PFS per IRF**
  - **A modified PFS event was defined as the first of:**
    - **Progression**
    - **Death from any cause**

- **PET6 = D3, 4, 5 after completion of frontline therapy followed by subsequent anticancer therapy**

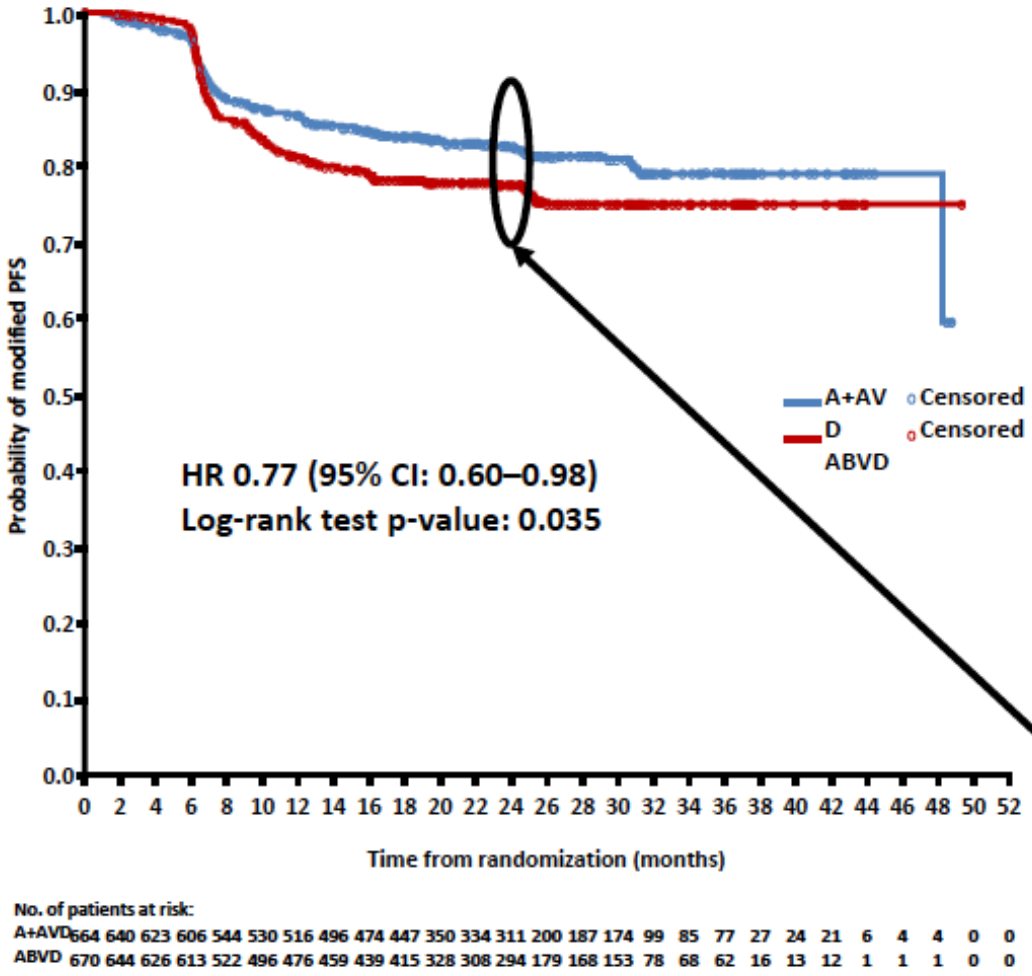


D, Deauville score; Dx, diagnosis; IRF, independent review facility; PD, progressive disease; PET6, end-of-cycle-6 PET; Tx, treatment

Connors M, NEJM2017

Étude ECHELON

Modified PFS per independent review



Number of events

Category	A+AVD N=117	ABVD N=146
Progression	90	102
Death	18	22
Modified progression	9	22
Chemotherapy	7	15
Radiotherapy	2	7

Modified PFS estimates

Time	A+AVD (95% CI)	ABVD (95% CI)
2-year	82.1 (78.7–85.0)	77.2 (73.7–80.4)

Median follow-up (range): 24.9 months (0.0–49.3)

Connors M, NEJM2017

Étude ECHELON

Most clinically important treatment-emergent adverse events

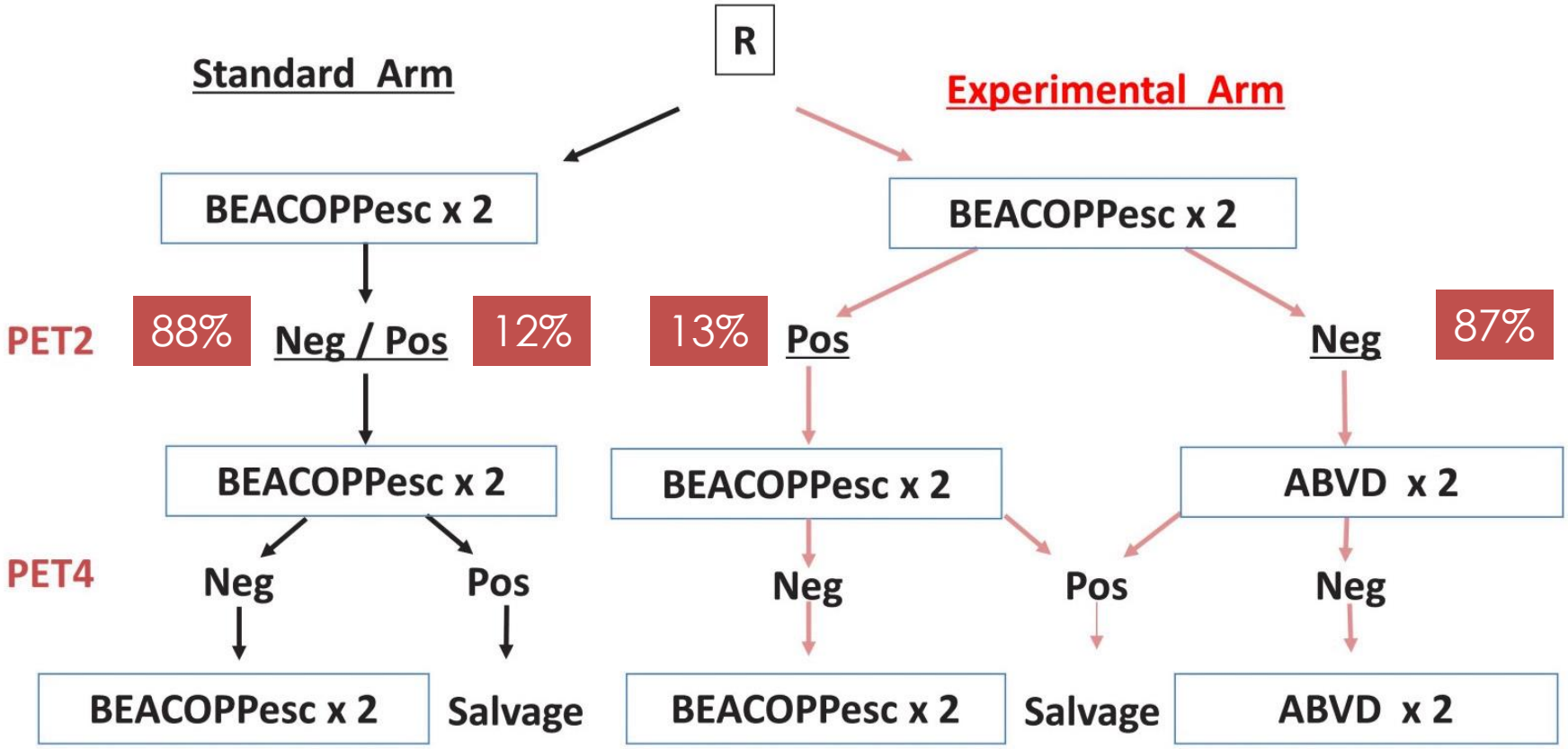
Incidence (any grade) ≥20% + febrile neutropenia

Common adverse events, %*	A+AVD (N=662) Any grade	A+AVD (N=662) Grade ≥3	ABVD (N=659) Any grade	ABVD (N=659) Grade ≥3
Neutropenia	58	54	45	39
Constipation	42	2	37	<1
Vomiting	33	3	28	1
Fatigue	32	3	32	1
Peripheral sensory neuropathy	29	5	17	<1
Diarrhea	27	3	18	<1
Pyrexia	27	3	22	2
Peripheral neuropathy	26	4	13	<1
Abdominal pain	21	3	10	<1
Stomatitis	21	2	16	<1
Febrile neutropenia	19	19	8	8

*Partial list focusing on the most clinically important adverse events. Adverse events (≥20% any grade in either arm) excluded from the table include nausea, alopecia, weight decreased, and anemia

Connors M, NEJM2017

AHL2011

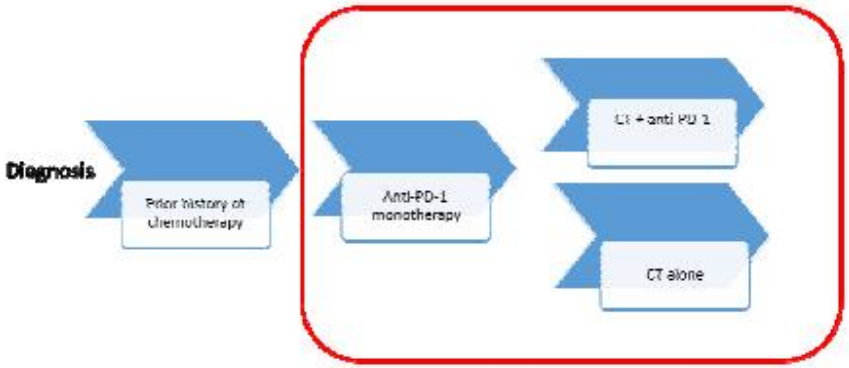


4y PFS 94% 4y PFS 75% 4y PFS 70,8% 4y PFS 91,6%

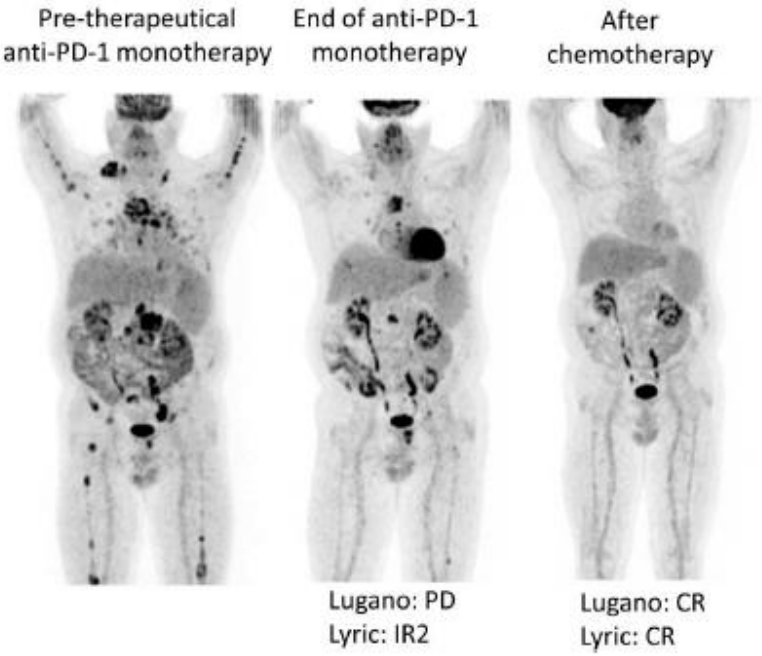
Estimated 4y PFS 87,4% versus 87,1%

Casasnovas RO, absS577, EHA2018

Combinaison antiPD1 et chimiothérapie



	All patients (n=30)	Group 1: chemo only (n=19)	Group 2: Chemo-Anti-PD-1 combination (n=11)
Complete response	**11 (37%)**	6 (32%)	5 (45.5%)
Partial response	**10 (33%)**	5 (26%)	5 (45.5%)
Stable disease	2 (7%)	1 (5%)	1 (9%)
Progression	6 (20%)	6 (32%)	0
Not evaluated	1 (3%)	1 (5%)	0
Improvement of the sequence	**22 (73%)**	**13 (68%)**	**9 (81%)**



- Soutient le concept d'une synergie [anti PD-1 + chimiothérapie]

C. Rossi ASH2017 abstract #652

- Lymphome B à grandes cellules
  - Amélioration de la première ligne:
    - challenger le RCHOP (Polatuzumab Vedotin?)
  - En rechute: Car T cell
    - Accessibilité
    - Sélection des patients
    - Gestion des toxicités
    - Coût

- Lymphome de Hodgkin:
  - Stratégie guidée par le petscan
  - Incorporation nouvelles molécules en première ligne de traitement
  - Futur: immunothérapie