Traitements des Rechutes de Lymphomes T Périphériques

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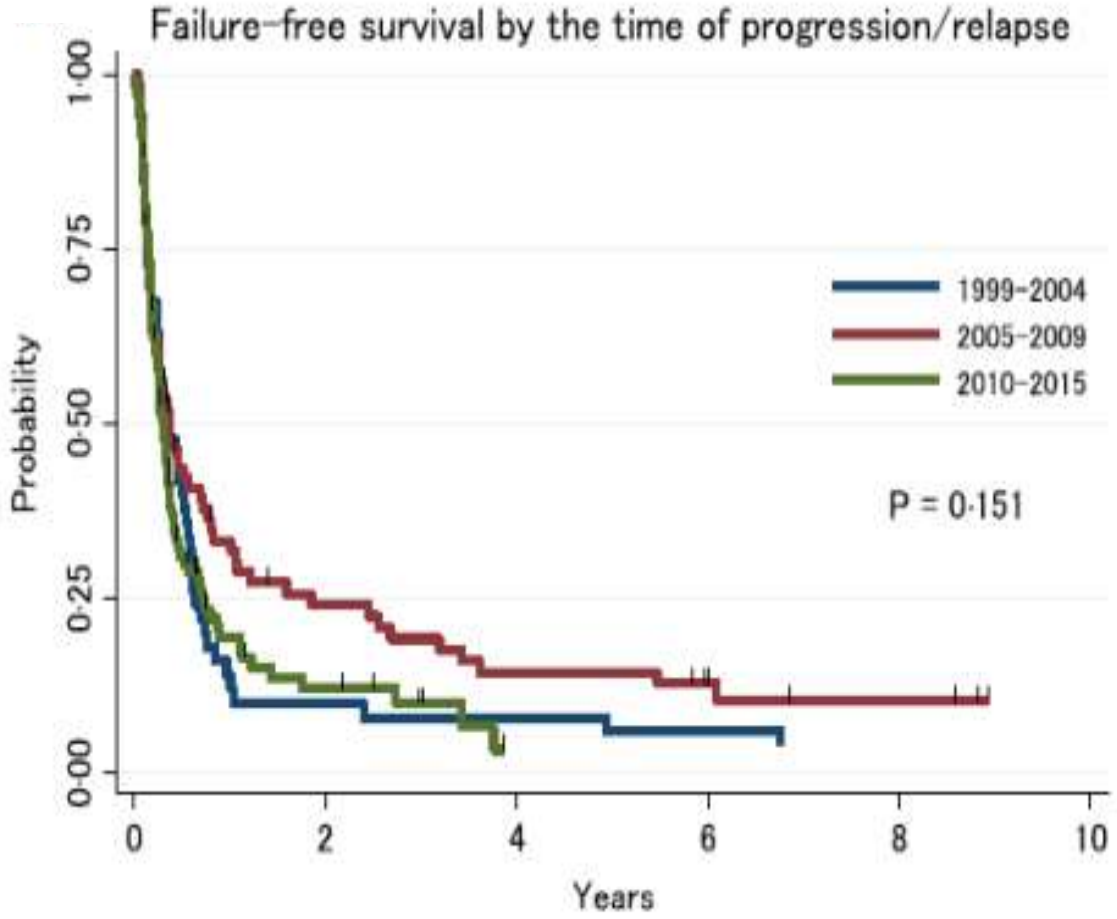
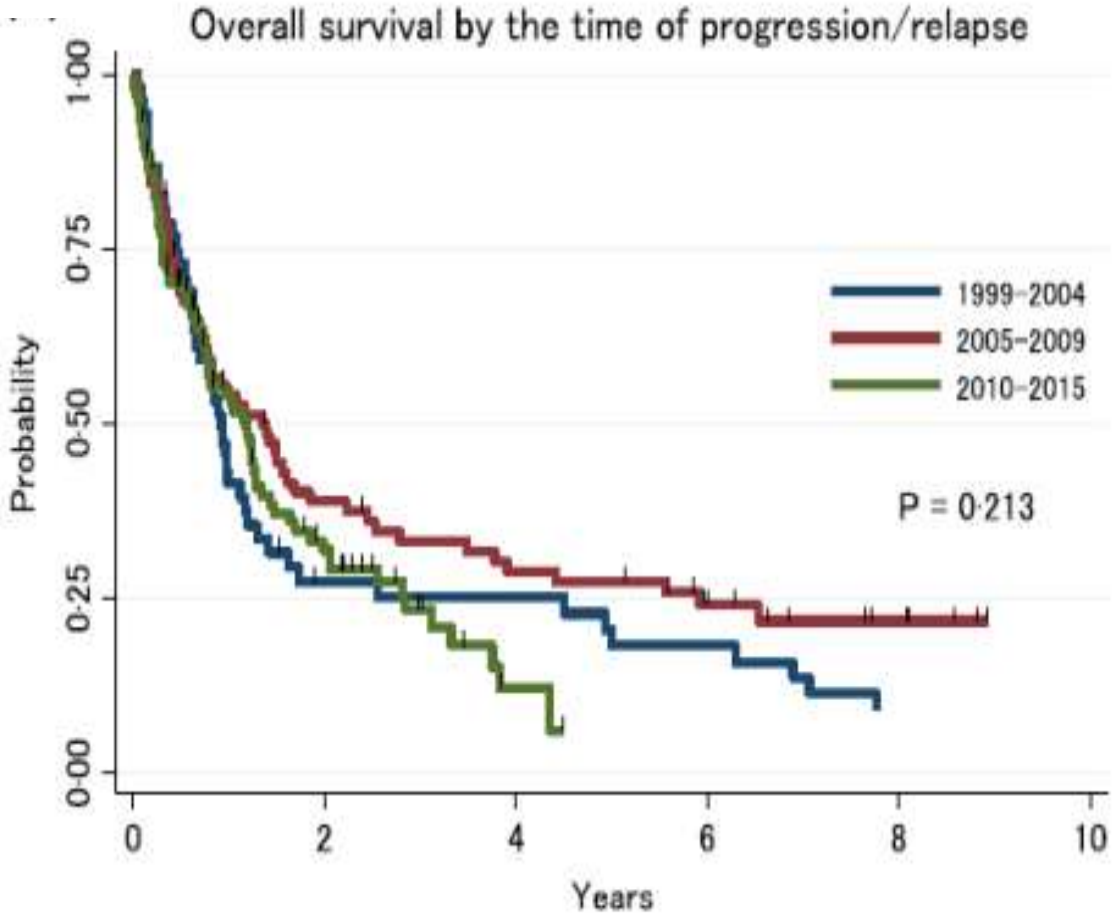
PTCL : an unmet medical need !

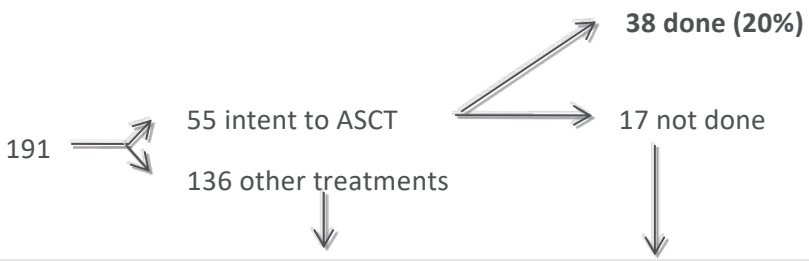
Long term OS: 20-30%





Chihara et al, BJH 2017

Median time from PTCL diagnosis to relapse or progression : 6 – 7 months
Progression Free Survival[1] : 3.7 months
Poor overall survival[1] : 6.5 months

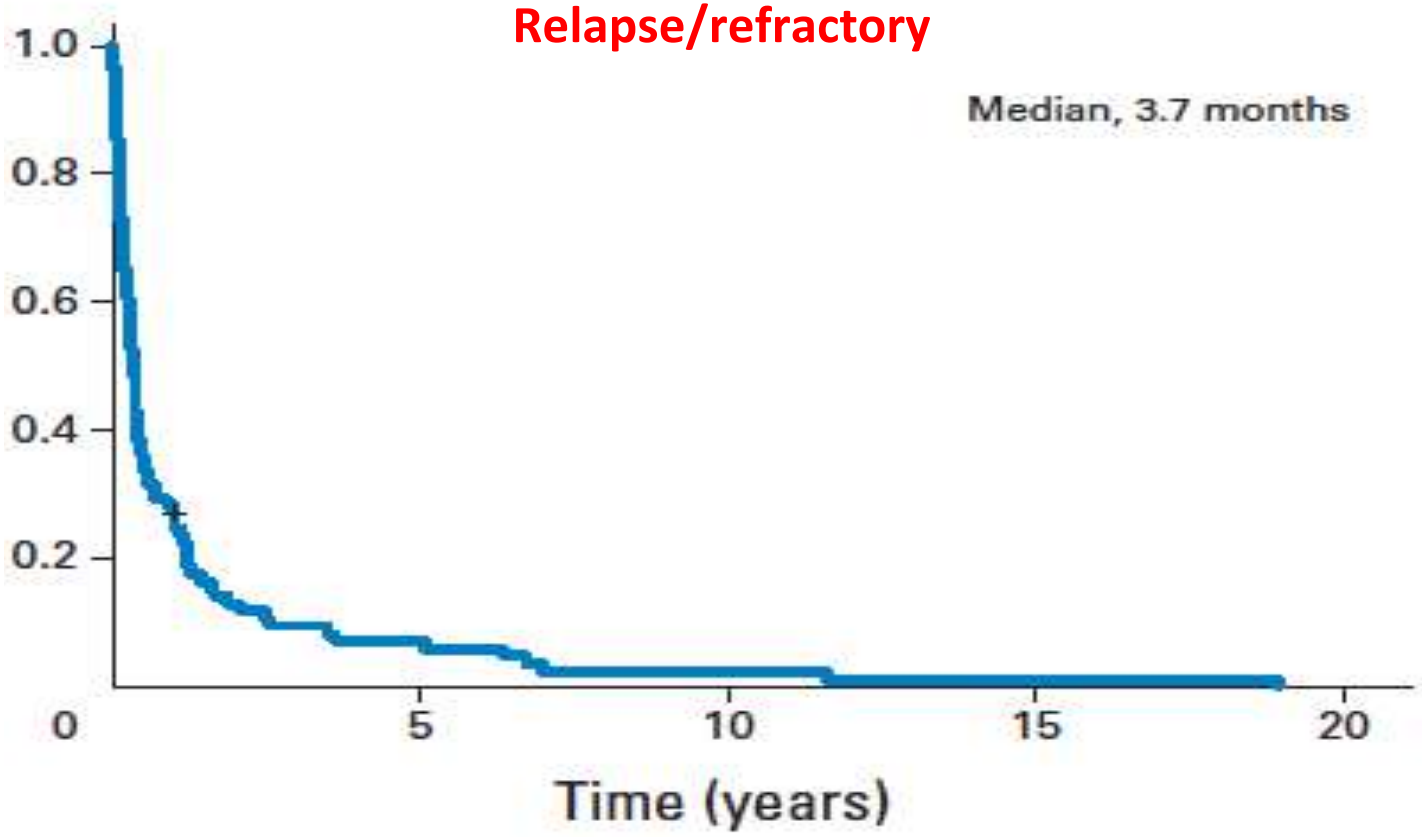


Total : 153 patients : PTCL-NOS 52% ALCL 23,5%
AITL 25%

Treatments : active 76%
non active 24%

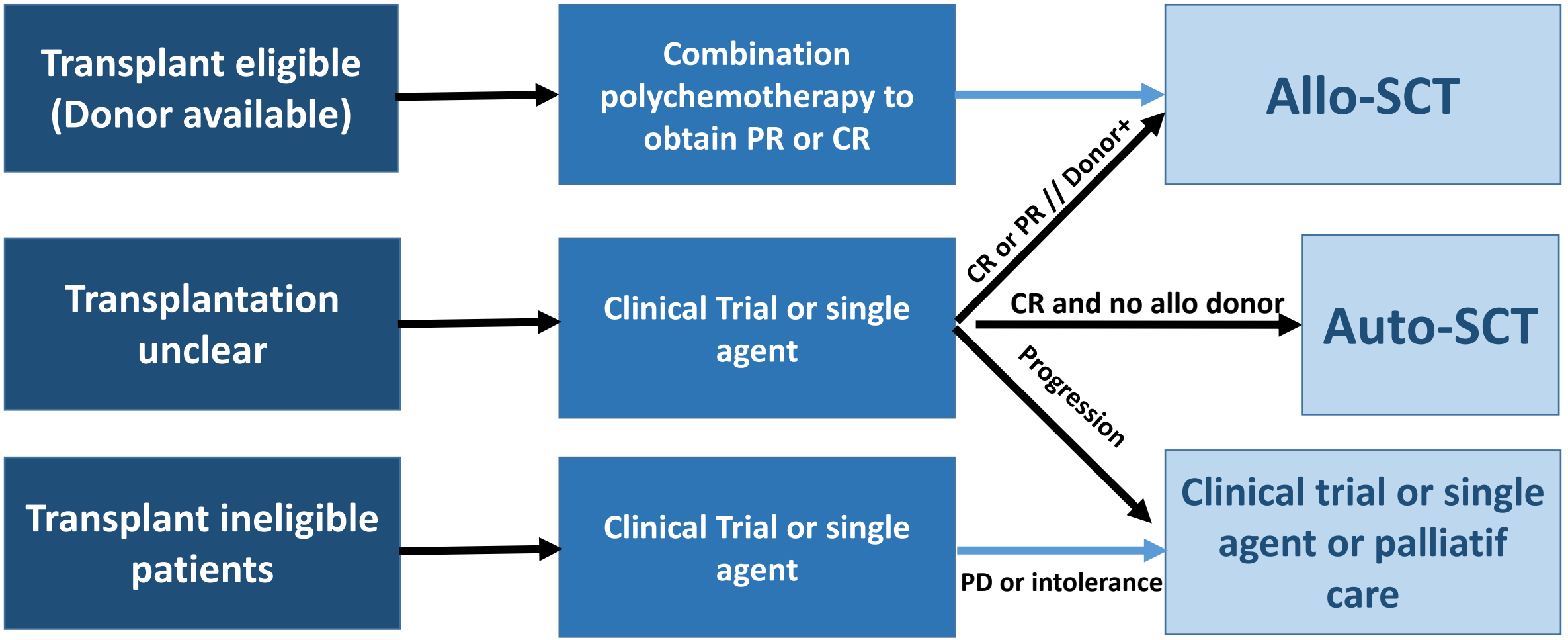
New drugs ?
New strategies ?

Relapse/refractory



Mak et al, JCO 2013

Treatment Strategy for Patients with R/R PTCL



Adapted from Luning et al; JCO 2013

Résultats des polychimiothérapies : R/R PTCL

	ORR (CR)	Median PFS
1. ICE(n=40)	70% (35)	6 m
2. GemDexCis (n=51)	80% (47)	4 m
3. ESHAP (n=22)	32% (18)	2.5 m

Results of single agents in the R/R setting !

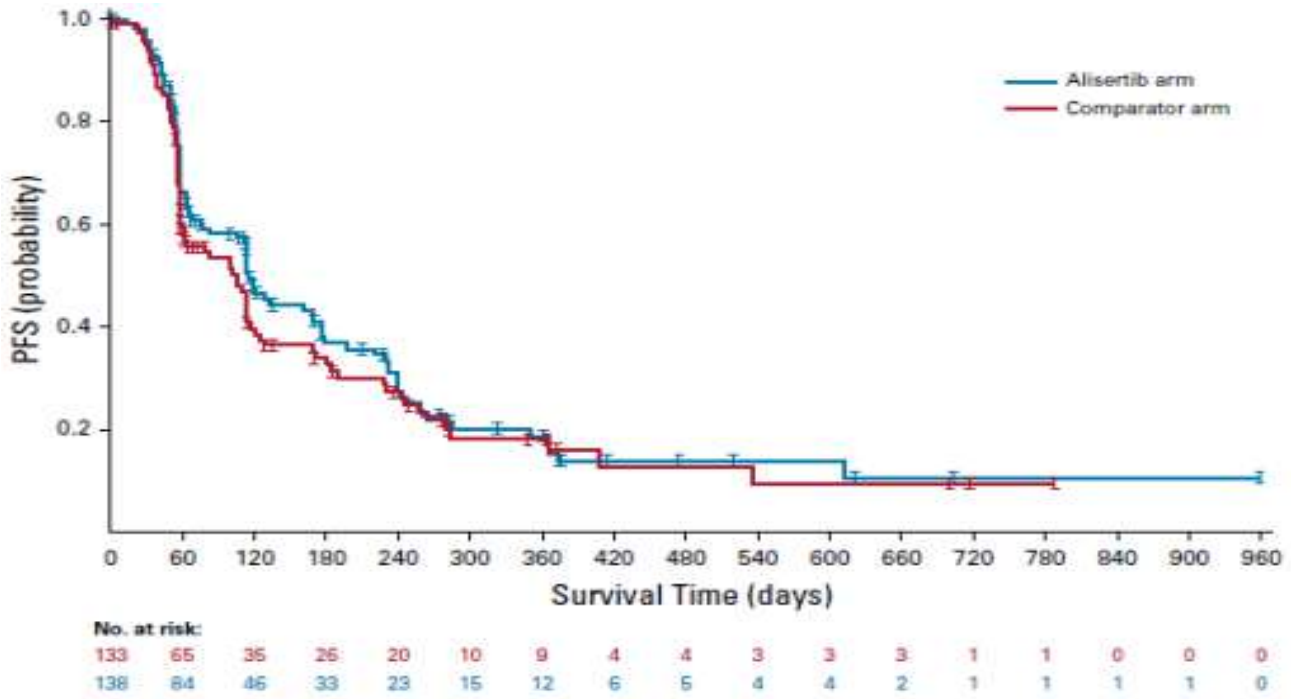
	ORR (CR)	Median PFS
1. Pralatrexate; (n=111)	29% (15)	3.5 m
2. Romidepsine; (n=130)	25% (15)	4 m
3. Bendamustine; (n=60)	50% (28)	3.6 m
4. Belinostat; (n=129)	25% (11)	1.6 m
5. Brentuximab Vedotin; (n=39)*	69% (44)	6.7m
6. Alisertib; (n=102)	34%	4 m
7. Gemcitabine (n=30)	35% (22)	3 m
8. Azacytidine+romidepsine (n=11)	73%	

* anaplastic large cell lymphoma

1.O'Connor, JCO 2011; 2. Coiffier, JCO 2012; 3. Damaj, jco 2012; 4. Horwitz, Blood 2014; 5. O'Connor, JCO 2015, 6.&7. O'Connor, JCO 2019

LUMIERE: Randomized Phase III Study of Alisertib or Investigator's Choice

Response	Alisertib (n = 102)	Comparator (n = 92)	Gemcitabine (n = 30)	Pralatrexate (n = 80)	Romidepsin (n = 23)
CR	18 (18; 11 to 26)	25 (27; 18 to 37)	5 (22; 7 to 44)	14 (27; 16 to 42)	6 (33; 13 to 59)
PR	16 (16; 9 to 24)	16 (17; 10 to 27)	3 (13; 3 to 34)	8 (16; 7 to 29)	5 (28; 10 to 53)
CR + PR	34 (33; 24 to 43)	41 (45; 34 to 55)	8 (35; 16 to 57)	22 (43; 29 to 58)	11 (61; 36 to 83)
SD	34 (33; 24 to 43)	19 (21; 13 to 30)	3 (13; 3 to 34)	13 (25; 14 to 40)	3 (17; 4 to 41)
PD	34 (33; 24 to 43)	32 (35; 25 to 45)	12 (52; 31 to 73)	16 (31; 19 to 46)	4 (22; 6 to 48)



O'Connor et al, JCO 2019

Addition of Brentuximab vedotin to gemcitabine in Relapsed or Refractory T-cell Lymphoma: Results of a LYSA Multicenter, Phase II Study. "The TOTAL Trial"

Olivier Tournilhac (1), Maya Hacini (2), Kamal Bouabdallah (3), Kamel Laribi (4), Marie Maerevoet (5), Loic Ysebaert (6), Stephanie Guidez (7), Steven Le Gouill (8,9), Marc André (10), Jehan Dupuis (11), Catherine Thieblemont (12), Emmanuel Bachy (13), Nicolas Daguindau (14, Franck Morschhauser (15, Sabine Tricot (16, Pierre Feugier (17), Anne Banos (18), Thierry Lamy De La Chapelle (19, Adrien Chauchet (20), Emmanuel Gyan (21), Guillaume Cartron (22), Hassan Farhat (23), Vincent Camus (24), Bernard Drenou (25), Hacene Zerazhi (26), David Sibon (27), Emmanuelle Nicolas-Virelizier (28, Caroline Delette (29), Sylvia Snauwaert (30), Nicole Straetmans (31), Richard Delarue (32), Marie Parrens (33), Céline Bossard (34), Laurence De Leval (35), Philippe Gaulard (36) and Gandhi Laurent Damaj (37)

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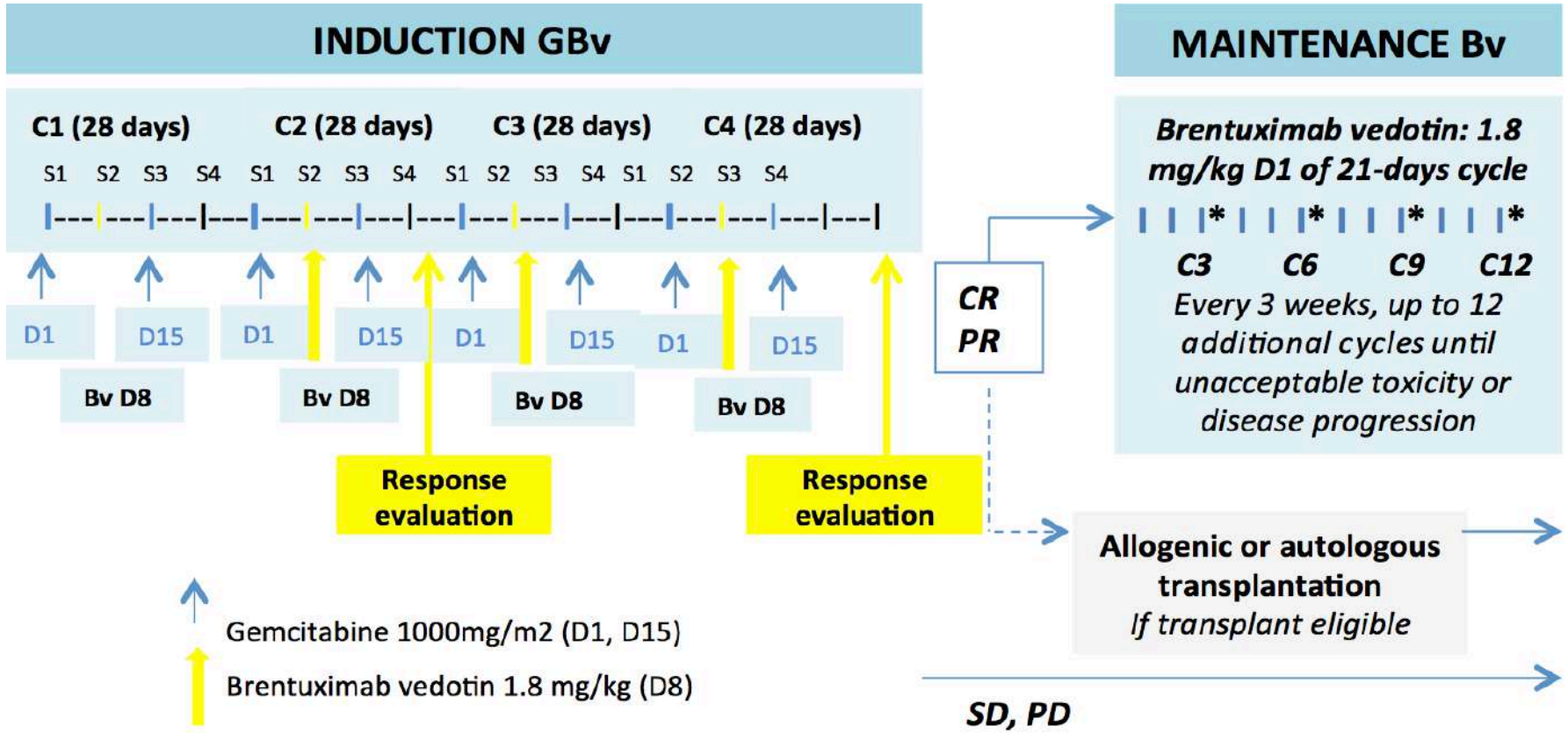
Session 624. Hodgkin Lymphoma and T/NK Cell Lymphoma
Saturday, December 5, 2020

Abstract #1161

Study objective and methods



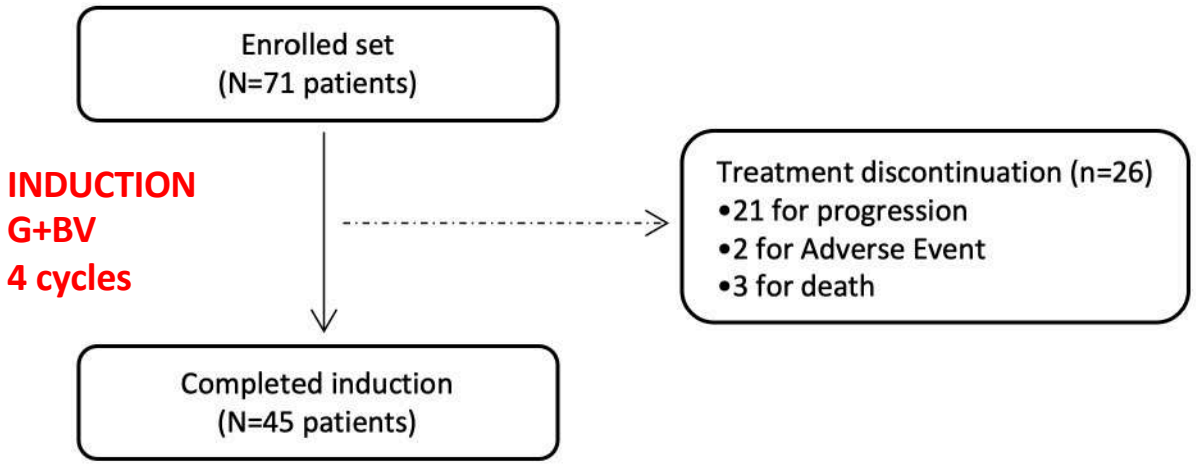
Results – patients' characteristics

Age , median (range; years)	**66 (20-79)**
Male/female (n)	47/24
Histology (%)	
AILT	31
PTCL-TFH	7
PTCL-nos	7
ALCL-Alk negative	14
ALCL-Alk positive	6
EATL	3
PTCL unclassified	3
PTCL (pending histology review)	29
Disease stage (%)	
Stage I-II	8
Stage III-IV	92
ECOG (%)	
0	31
1-2	69

71 included patients
From April 2018 to October 2019

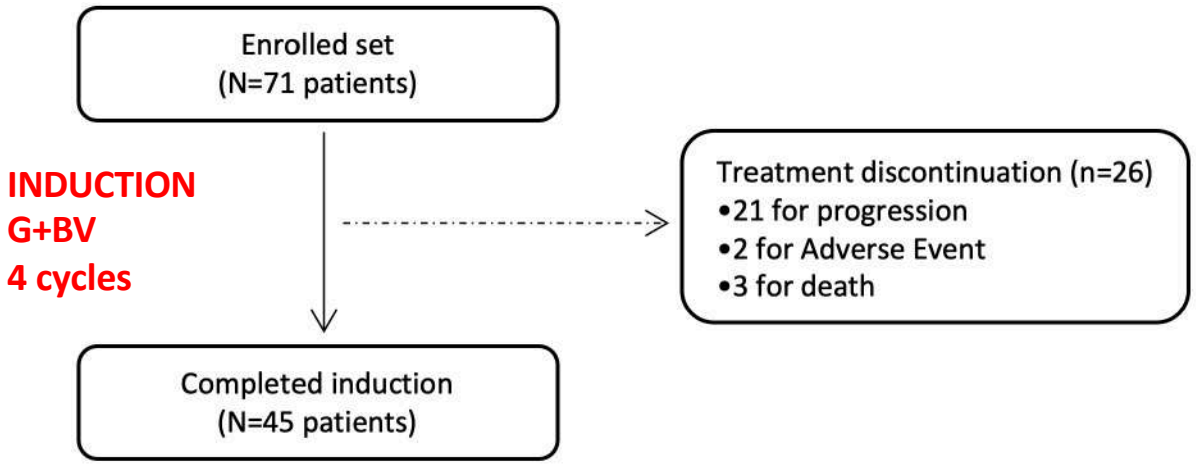
Previous line of treatment (%)	
1 line	80
2 lines	16
3 lines	4
Prior therapy* (%)	
CHOP/CHOP like regimen	100
ASCT transplantation	16
Epigenetic modifiers	7
Time from diagnosis to enrollment months; median (range)	9.4 (2-131)
Refractory to last prior therapy (%)	39

Results – @ 4 cycles of G+BV



Response (n= 71) Intention-to-treat as by Local Investigator	N	%
CR+PR	34	47.9
CR	14	19.7
PR	20	28.2

Safety – @ 4 cycles of G+BV



Adverse events of Grade ≥3	%
Neutropenia	67
Thrombocytopenia	17
Anemia	26
Infection	16
Peripheral neuropathy*	5
Cardio-vascular	5
Gastro-intestinal	7
Liver	3
Skin	5

*Peripheral neuropathy of any grade was recorded in 11%

Brentuximab – bendamustine in R/R PTCL

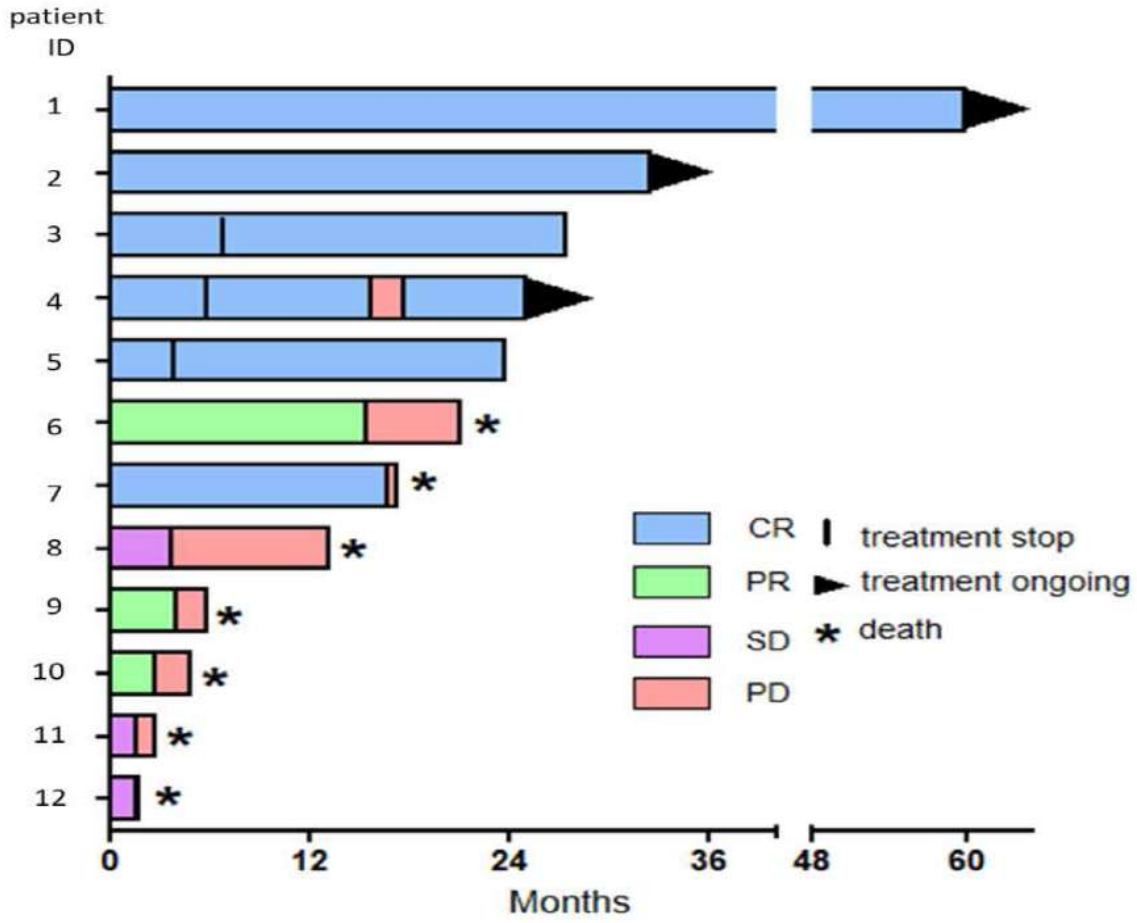
- **Travail en cours**
- **Raphaëlle AUBRAIS**
- **> 100 cas en cours d’analyse**

5-Azacytidine and AITL: A promising therapy !

- Treatment:
  - Aza 75 mg/m2 sc daily x 7 q28d
  - Median number of 5.5 cycles

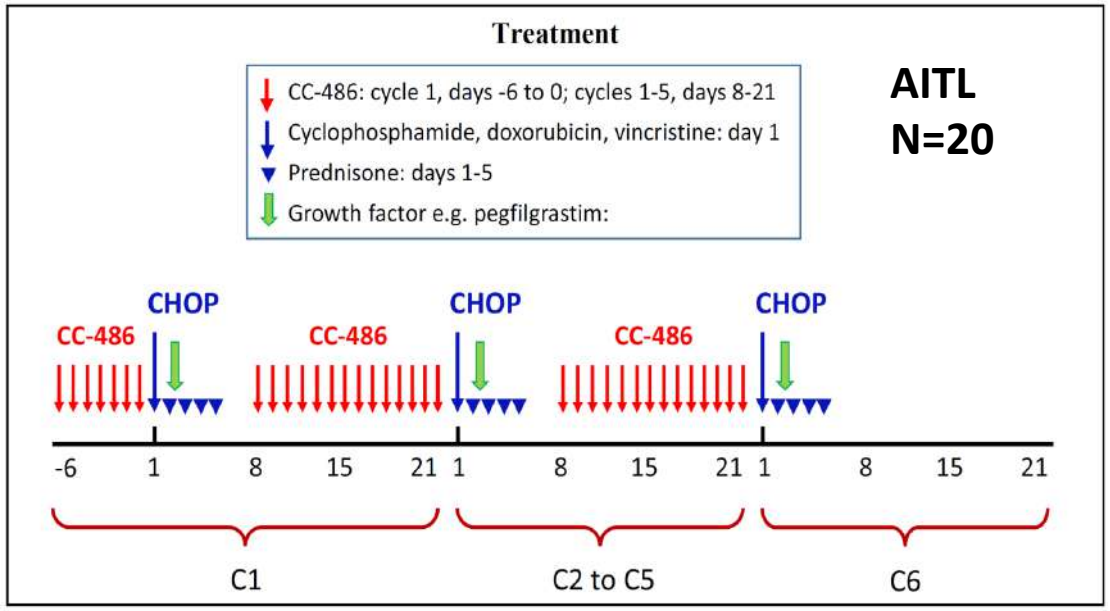
- Patients:
  - 12 AITL, median age 71 years
  - 5/12 (41%) with MDS/CMML

- Efficacy:
  - **ORR 75% (9/12), CR/CRu 50% (5/12)**
  - mPFS 15 months, mOS 21 months
  - Mutations: *TET2* 100%, *DNMT3A* 33%, *RHOA* 41%



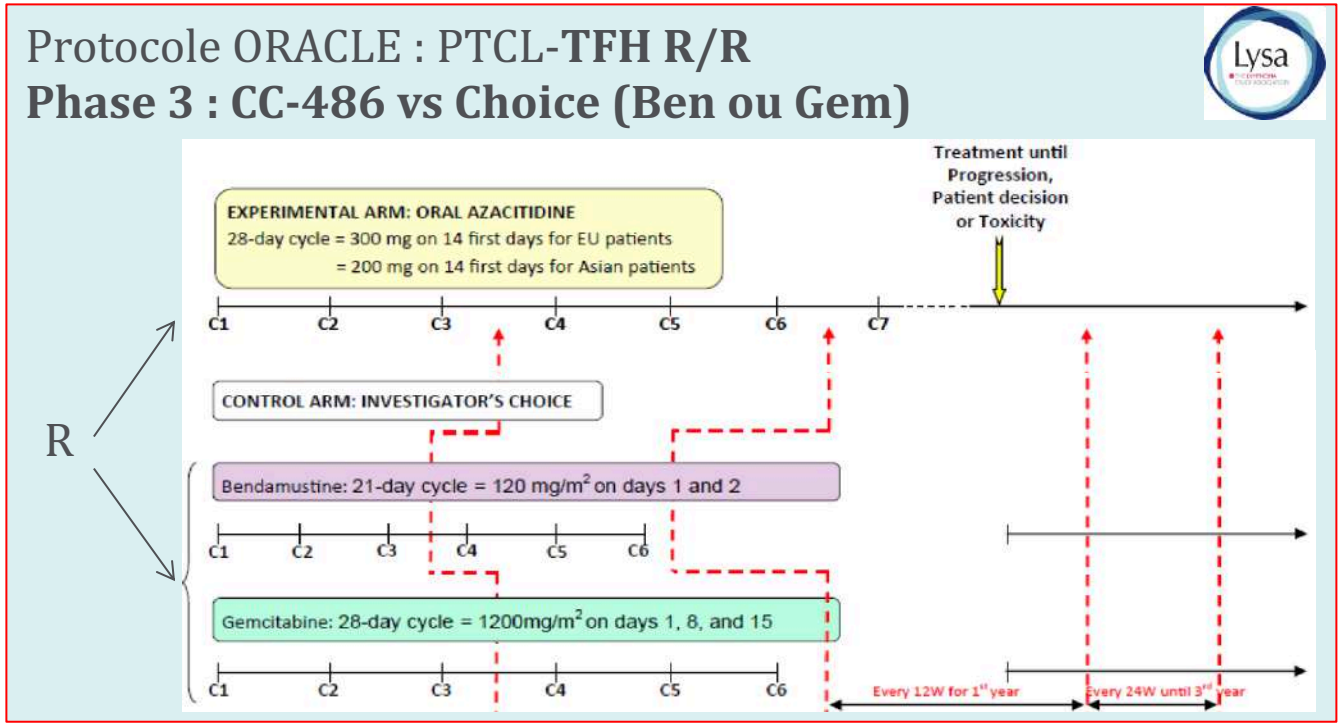
5-Azacytidine et PTCL TFH

Phase II Frontline Study of Oral Azacitidine plus CHOP: *Weill Cornell Medicine Consortium (NCT03542266)*



AITL
N=20

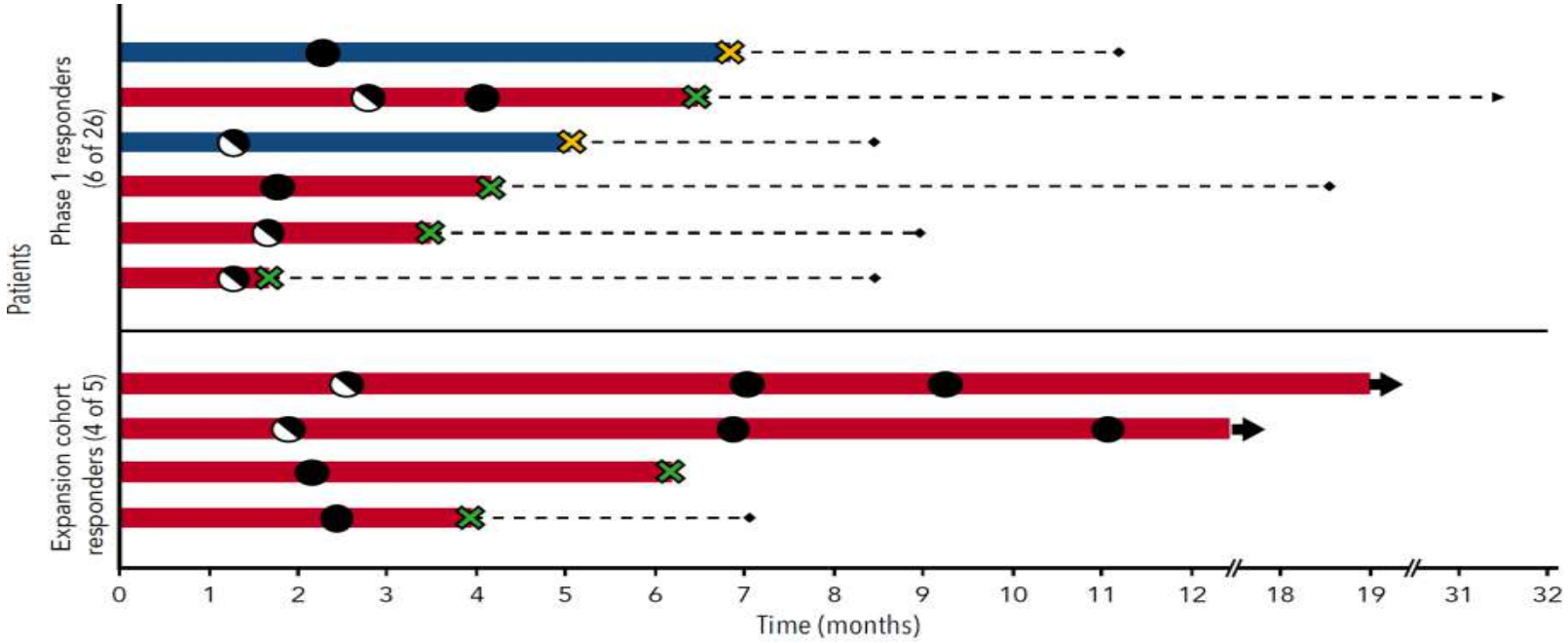
ORACLE Study. "Closed to inclusion



Oral 5-azacytidine and romidepsin exhibit marked activity in patients with PTCL

T-cell lymphoma (n = 11)	
Anthracycline-based (CHOP, CHOEP, EPOCH±bortezomib)	8 (26)
Gem-based (gem, *p*-gemox, gem+liposomal cytarabine)	4 (13)
HDAC inhibitor (vorinostat, ROMI)	3 (10)
Bv	2 (6)
Pralatrexate	1 (3)
Experimental drug or other therapy, n (%)‖	6 (20)

Response type	All patients (N = 31), n (%)	Phase 1 population (n = 26), n (%)	Expansion cohort (n = 5), n (%)	Non–T-cell lymphoma (n = 20), n (%)	T-cell lymphoma (n = 11), n (%)
Overall response	10 (32)	6 (23)	4 (80)	2 (10)	8 (73)
Complete response	7 (23)	3 (12)	4 (80)	1 (5)	6 (55)
Partial response	3 (10)	3 (12)	0	1 (5)	2 (18)
Stable disease	7 (23)	7 (27)	0	7 (35)	0
Progressive disease	11 (35)	10 (38)	1 (20)	9 (45)	2 (18)
Not evaluable	3 (10)	3 (12)	0	2 (10)	1 (9)



Autres molécules en développement

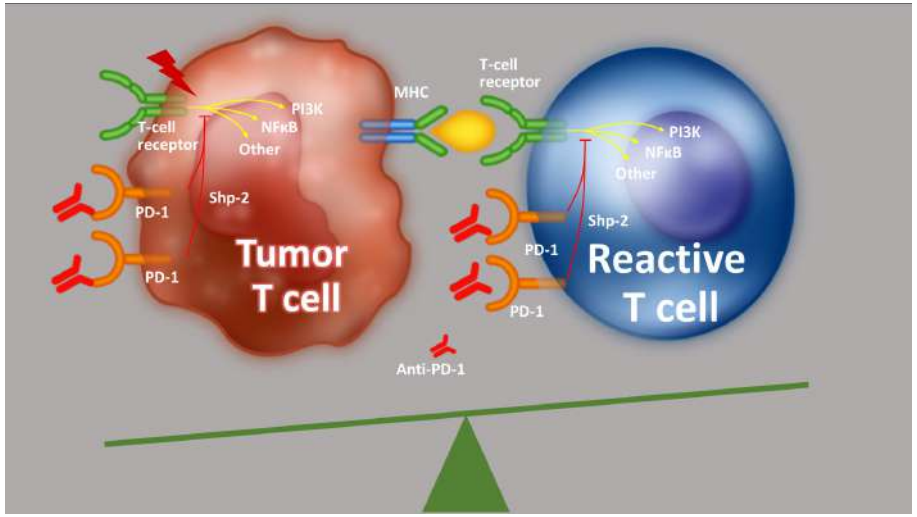
Drugs	ORR	PFS
Tipifarnib (blood 2019)	27-50%	
Ruxolitinib (Blood 2019)	11-30%	
Duvelisib (blood 2018)	50%	8.3 mo
Romi-Len	50%	
Romi-Len-carlfilzomib		
….		

Cerdulatinib: SYK and JAK inhibitors

- **SYK and JAK signaling pathways may be critical mediators in the pathogenesis of peripheral T-cell lymphoma (PTCL) and cutaneous T-cell lymphoma (CTCL).**
- **Transgenic expression of constitutively active SYK in CD4+ T cells in mice results in a lethal T-cell proliferative disease**
- **Cerdulatinib single-agent 30 mg BID in a phase 2a dose expansion study in patients with PTCL and CTCL**

Response	AILT/TFH	PTCL-NOS	PTCL-other	Total
N	27	11	26	64
ORR	52	0	31	22
CR	37	0	15	22%
PR	15	0	15	12%
SD	15	27	23	55%
DOR (months), (range)	9+ (1-20)		5 (1-12)	8 (1-20)

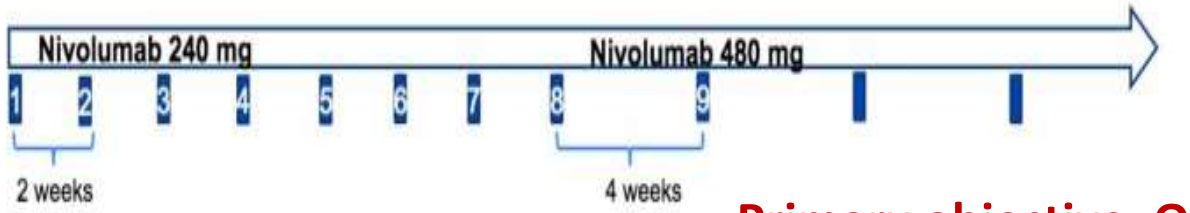
Immunotherapy in PTCL: Devil or Angel?



Subtype	Agent	Phase	ORR	CR	DOR
PTCL	Nivo	Ib (n=5)	40%	0	NR
NK/TCL	Pembro	Cohort (n=7)	100%	71%	NR
ATLL	Nivo	2 (n=3)	Rapid Progression		NR

Lesokhin et al, J Clin Oncol 2016;34:2698-2704
Kwong YL et al, Blood 2017;129(17):2437-2442
Ratner et al, N Engl J Med 2018; 378:1947-1948

Anti-PD1 in R/R PTCL: no major efficacy !



Primary objective: ORR

Key Inclusion Criteria

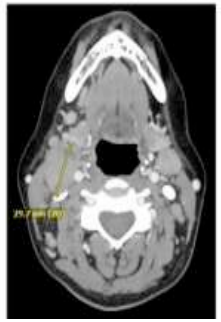
1. Biopsy confirmation of relapsed or refractory PTCL
2. Measurable disease on cross-sectional imaging that is ≥ 1.5 cm
3. Prior systemic chemoimmunotherapy including ASCT

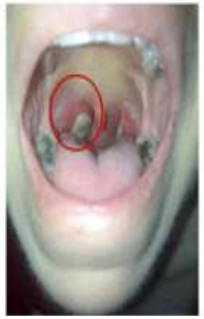
Key Exclusion Criteria

1. Prior therapy with anti-PD-1/PD-L1/2 or anti-CTLA-4 antibodies
2. Prior allogeneic SCT
3. Known central nervous system involvement
4. Interstitial lung disease or autoimmune disease

HYPERPROGRESSION

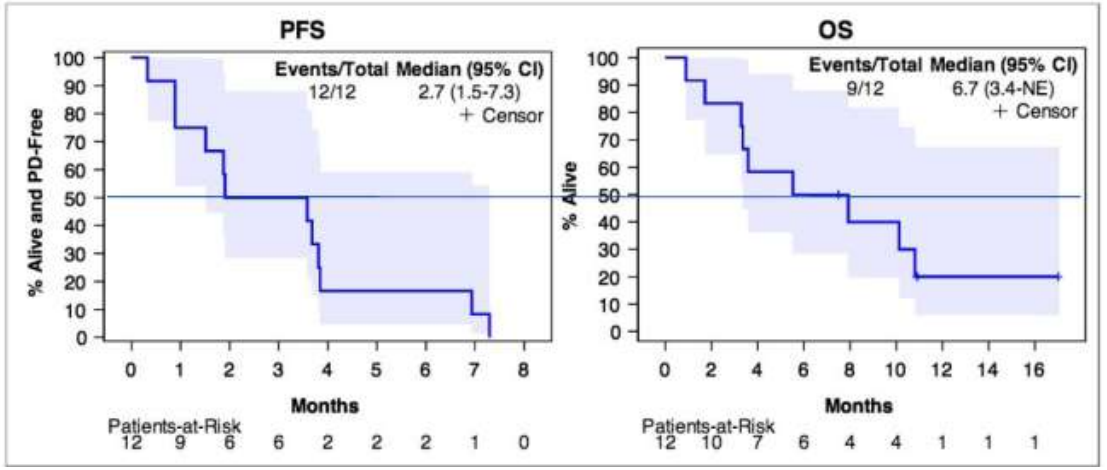
- Hyperprogressive disease, defined as dramatic progression within **1 cycle** of treatment, occurred in 1 pt with AITL
- Significant progression in tonsilar and cervical lymphadenopathy **within 7-10 days of infusion**, biopsy proven involvement with AITL





	Total N=12
T-cell Lymphoma Subtype, n (%)	
Angioimmunoblastic T-Cell Lymphoma	6 (50)
Peripheral T-cell Lymphoma, not otherwise specified	3 (25)
Anaplastic Large Cell Lymphoma, ALK negative	1 (8)
Enteropathy-associated T-Cell Lymphoma	1 (8)
Hepatosplenic Gamma Delta T-Cell Lymphoma	1 (8)
Ann Arbor Stage, III/IV n (%)	12 (100)
Extranodal Involvement, n (%)	11 (92)

	Total N=12
Overall Response Rate, n (%) (95% CI)	4 (33) (12.3 - 63.7)
Complete Response : - 1 ALK-ALCL - 1 AITL	2
Partial Response : - 1 PTCL-NOS - 1 EATL	2



The addition Pembrolizumab 200 mg Fixed Dose Q3W in Combination with Romidepsin 14 mg/m^2 on days 1, 8

Demographics	PTCL (n=15)
Age (Range)	(52-81)
Gender Male, n (%)	 10 (66%)
Race Caucasian n (%) African-american n (%) hispanic/latino n (%) Asian n (%)	 7 (46) 2 (13) 5 (33) 1 (6)
Bone Marrow involvement n (%)	11 (73)
Prior therapies, (Range) </= 2 therapies, n (%) >/= 3 therapies, n (%)	1-5 3 (60) 2 (40)
Prior Radiation n (%)	
Elevated LDH n (%)	13 (86)
Stage 3 or 4, n (%)	9 (60)
ECOG >2 n (%)	12(80)
* Disease status Relapse, n (%) Refractory, n (%)	 1 (33) 4 (80)
Pathology PTCL, NOS, n (%) Transformed mycosis fungoides, n (%) ALCL, n (%)	 12 (80) 2 (13) 1 (6)
* Disease status defined as refractory to or relapsed after ≥ 1 prior treatment lines.	

- **DLT hypotension and renal insufficiency**
- **Phase II is ongoing with 9 pts enrolled**

- **ORR = 44%; (CR 3; PR 2)**
- **The median follow-up was 6 months (3 weeks- 12 months)**
- **DoR for CR > 10 months.**

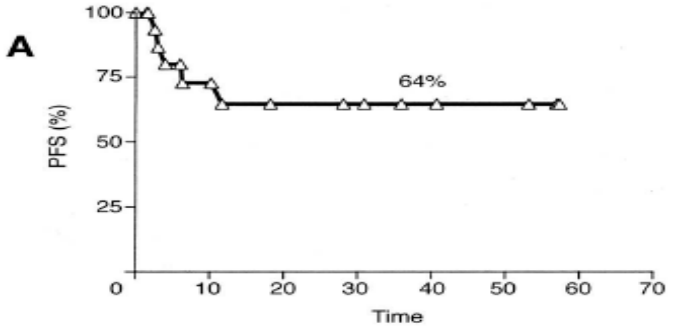
- **TEAEs ≥ grade 3 Nausea/vomiting and fatigue**

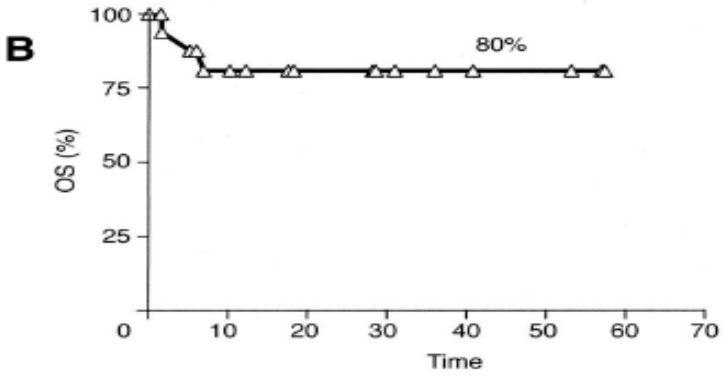
- **Two patients experienced hyperprogression within the first 10 days after the treatment.**

Swami et al, ASH, 2019

Allogeneic SCT is a curative option for PTCL

- **Prospective study**
- **N°= 17 patients**
- **Induction therapy: DHAP x 4-6**
- **Disease status before Allo-SCT**
  - CR 2
  - PR 11
  - Progressive 2
- **RIC conditioning** **100%**
- **Follow-up** **28 m (3-57)**





Corradini, JCO, 2004

Allo-SCT: Retrospective studies in R/R PTCL

	N°	MAC/RIC (%)	Disease status prior allo	NRM	m-PFS/EFS	OS
Murashige, 2005	28	82/18	CR = 57%	MAC 30% RIC 20%	34% (3y)	40% (3y)
Le Gouill, 2008	77	74/26	CR=21 PR=30	33%	53% (5y)	57% (5y)
Kyriakou, 2011	45	56/44	CR=27 PR=22	MAC 29% RIC 24%	53% (3y)	64% (3y)
*Jacobsen, 2012**	52	60/40	CR=44 PR=31	27%	39% (3y)	59% (3y)
Kanakry, 2012	44	45/55	CR/PR=75%	MAC 10% RIC 8%	40% (2y)	43% (2y)
*Smith,2013**	126	59/36	Cx sensitive 75%	MAC 32% RIC 27%	37% (3y)	46% (3y)

NRM
MAC : 30%
RIC : 20%

PFS 30-50%
OS 40-60%

retro & prosp

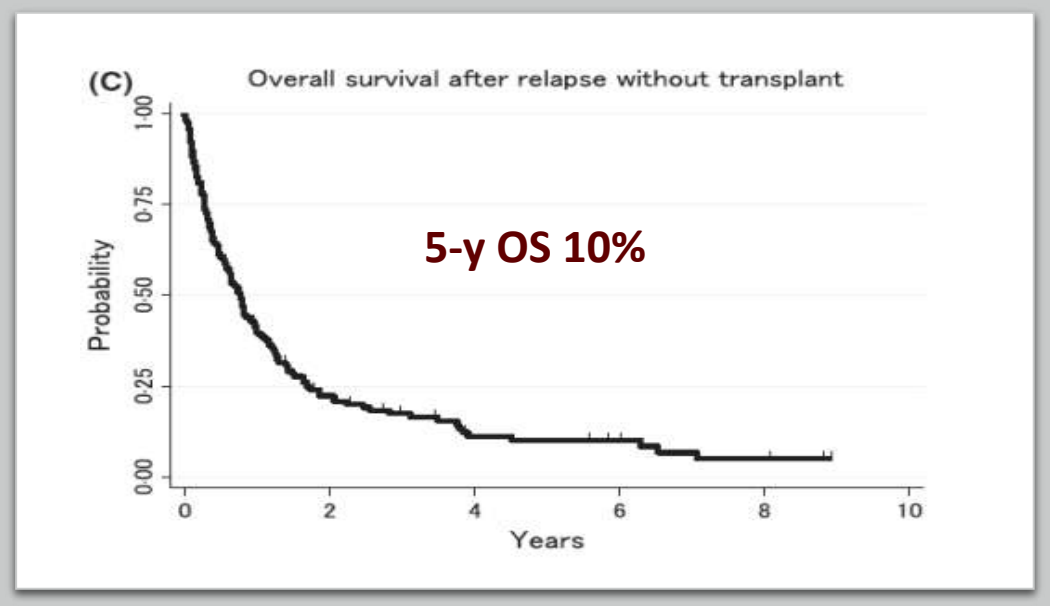
Allogeneic SCT is a curative option for PTCL

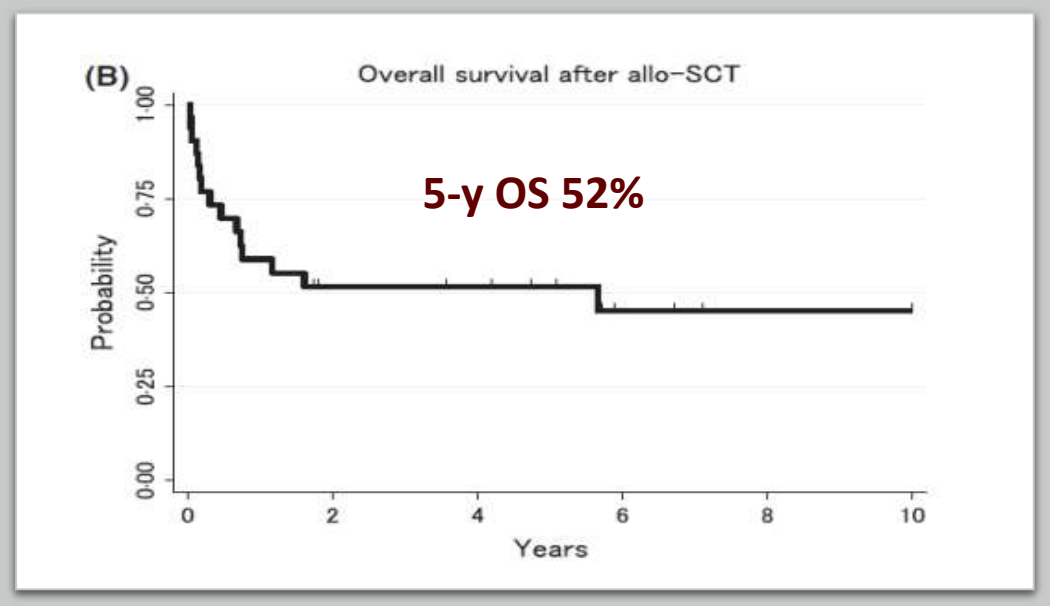
- **Effective immunotherapy**
- **Plateau after 2-years**

- **Retrospective study : 321 patients**
- **Relapse or refractory disease**

- **PTCL-nos; n=180; AILT, n=141**

- **Treatment at relapse before SCT**
  Romidepsine, pralatrexate, gemcitabine, ICE, ESHAP,…





Chihara et al, BJH, 2017

Allo-SCT: a good curative option for PTCL patients

N = 285 patients (2006-2014)

Lymphoma subtypes

- PTCL-nos 39%
- AILT 29%
- ALCL 17%
- Others 17%

Front-line: 48%

- CR1= 33%
- PR1 = 15%

Relapsed/refractory: 147 pts

- ≥ CR2/PR2 (116pts) 41%
- Progressive (31pts) 11%

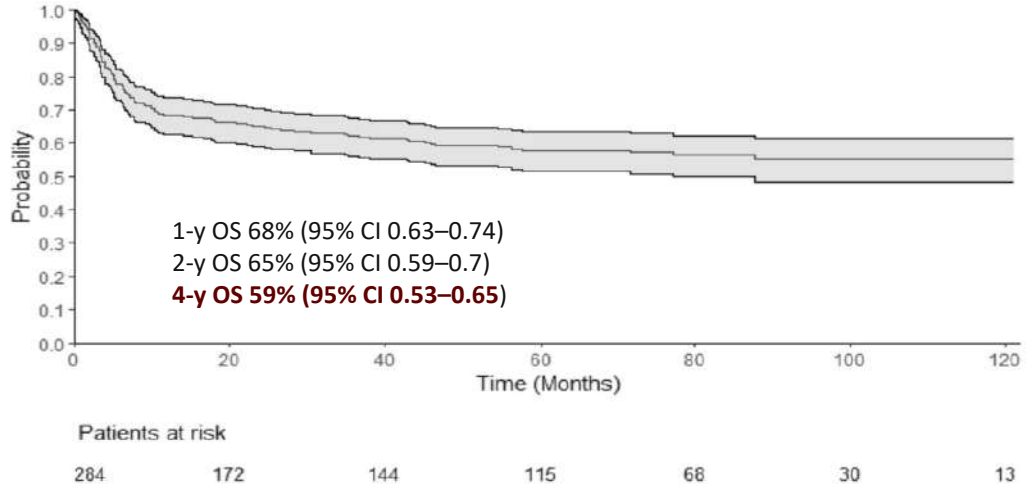
conditioning

- MAC = 38%
- **RIC = 62%**

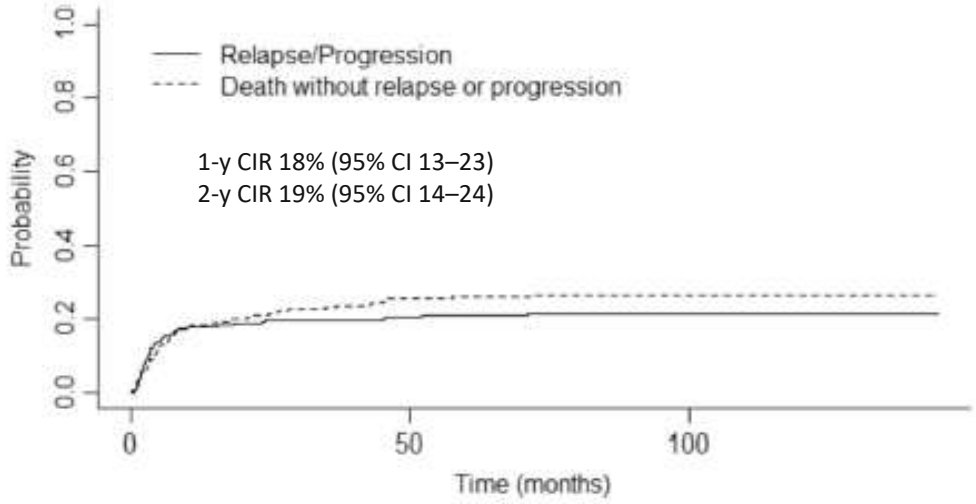
Source of stem cells

- identical sibling 45%
- Matched-unrelated 36%

median follow-up 72.4 months



Overall survival. Kaplan-Meier curve represents the probability of overall survival for the all cohort



Mamez et al, J Hematol & Oncol, 2020

ITT analysis versus only transplanted patients !

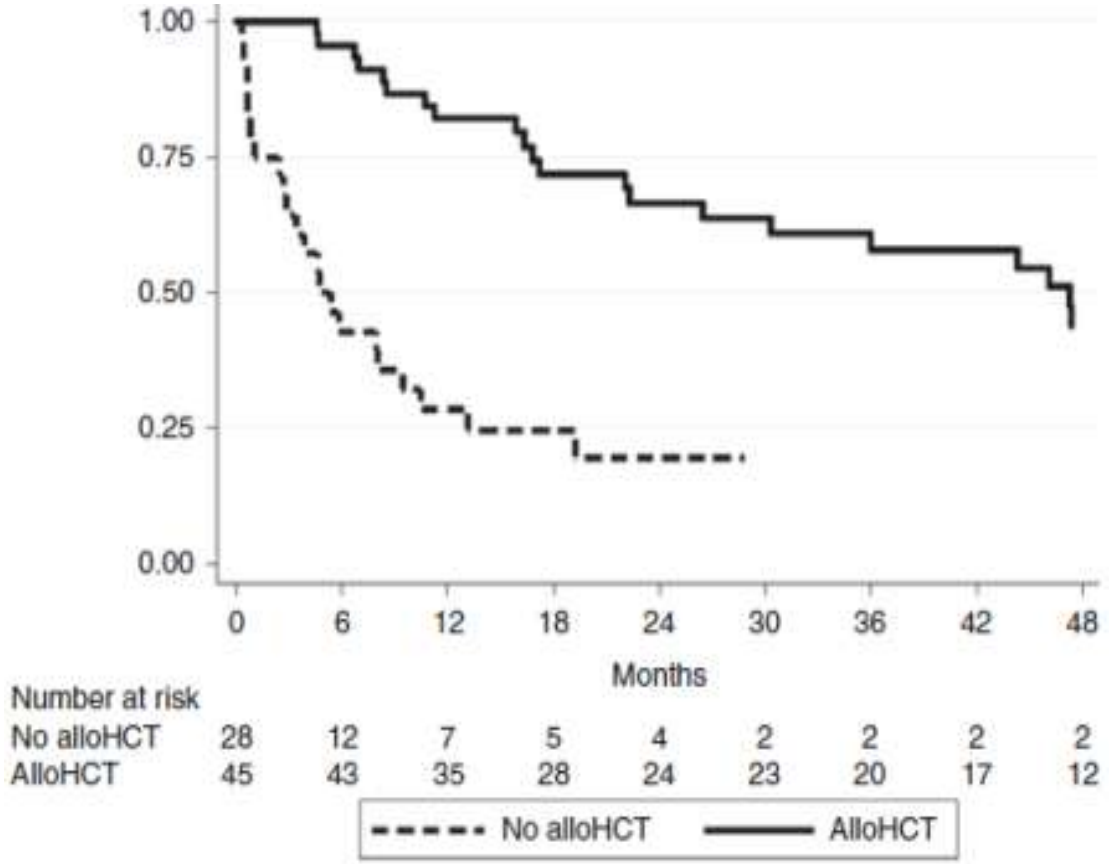
Mussetti et al, Bone Marrow Transplantation, 2019

- **73 consecutive R/R PTCL patients eligible for Allo transplant at Relapse or Progression**
  - **Refractory disease 48%**
  - **Chemo sensitive disease 37%**
- **Intent to Treat analysis: median PFS 2: 14%**
  median OS 2: 34%
- **62% of patients received allo-SCT: 4y-OS 51%**
- **OS for refractory transplanted patients : 25%**

Allo-SCT
versus
non allo-SCT

- **73 consecutive R/R PTCL patients eligible for Allo transplant at Relapse or Progression**

OS from time of 1st relapse/progression



Mussetti et al, Bone Marrow Transplantation, 2019

ITT analysis versus transplanted patients !

Selberg et al, Bone Marrow Transplantation, 2020

- **N° PTCL: 53 patients eligible for Allo-transplant**

- **The median time from diagnosis to donor search was 0.5 year**
- **Successful donor search 88%**
  (MRD, MUD, MMRD, MMUD)
- **The Median time to donor identification was 47 days (28 – 70)**

- **% of patients who undergo allo-SCT: 77%**
  main cause to not undergo allotransplant was disease progression

- **5-y OS was 62% (from 3 mo landmark after diagnosis)**
  overestimation by a factor of 1.24

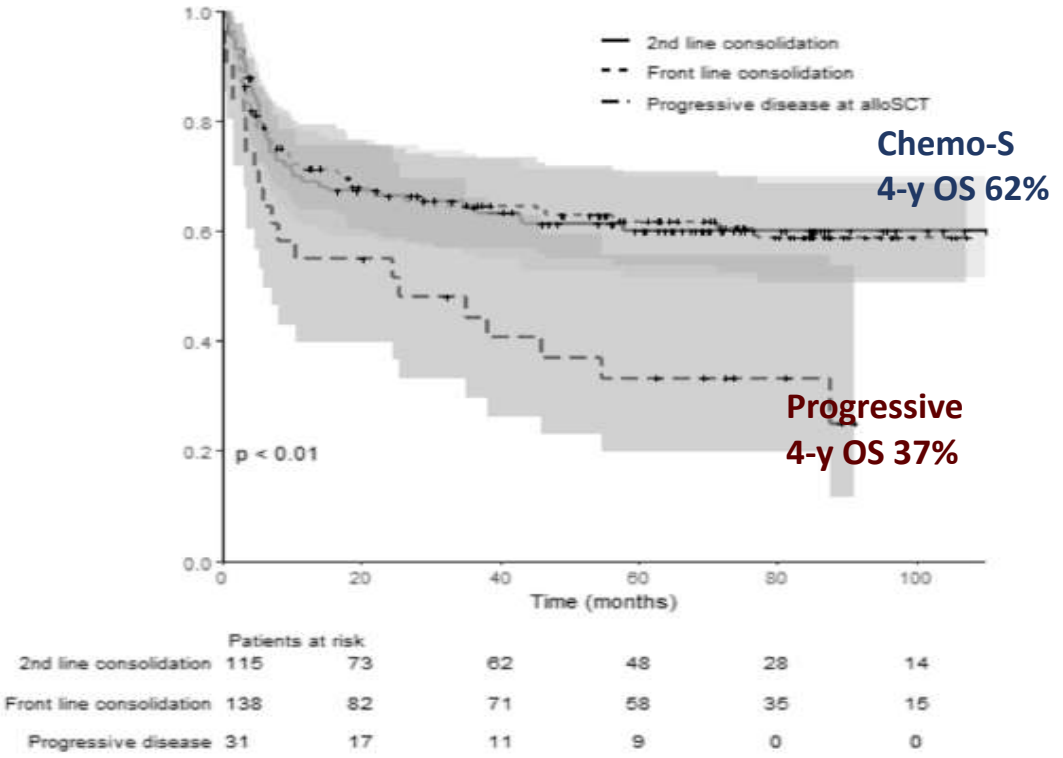
- **OS in Intent to Treat analysis is 50%**

Allo-SCT: a good curative option for R/R PTCL patients

What is the impact of the disease status before allo-SCT on the outcome ?

Chemo-sensitive disease > Refractory or progressive prior to Allo

N = 285 patients (2006-2014)
Lymphoma subtypes
PTCL-nos 39%, AILT 29%
ALCL 17%, Others 17%
Front-line: 48%
CR1= 33%
PR1 = 15%
Relapsed/refractory: 147 pts
≥ CR2/PR2 (116pts) 41%
Progressive (31pts) 11%
conditioning
MAC = 38%; RIC = 62%

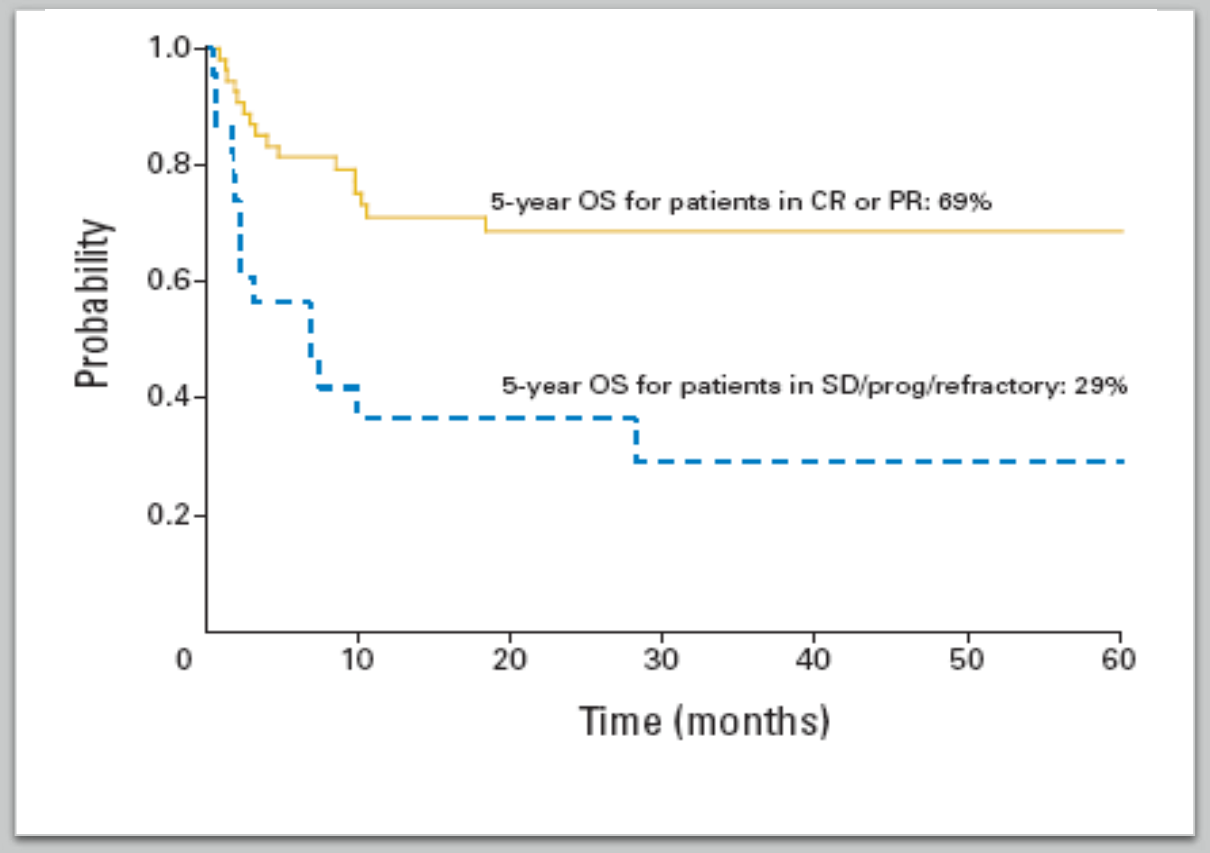


Multivariate	5-year OS	NRM
PD vs CR before SCT	HR = 2.21, p 0.0062	-

Mamez et al, J Hematol & Oncol, 2020

Impact of the disease status before Allo-SCT

- N = 77 patients
- Disease Status prior to transplant: CR/PR = 51%; Refractory = 49%
- Conditioning : MAC = 74%; RIC = 26%
- 5-y NRM 33%;
- 5-y PFS 53% 5-y OS 57%



Multivariate	
Disease status	(OS & EFS)
HLA mismatch	(OS, EFS & TRM)

Le Gouill et al, JCO, 2008

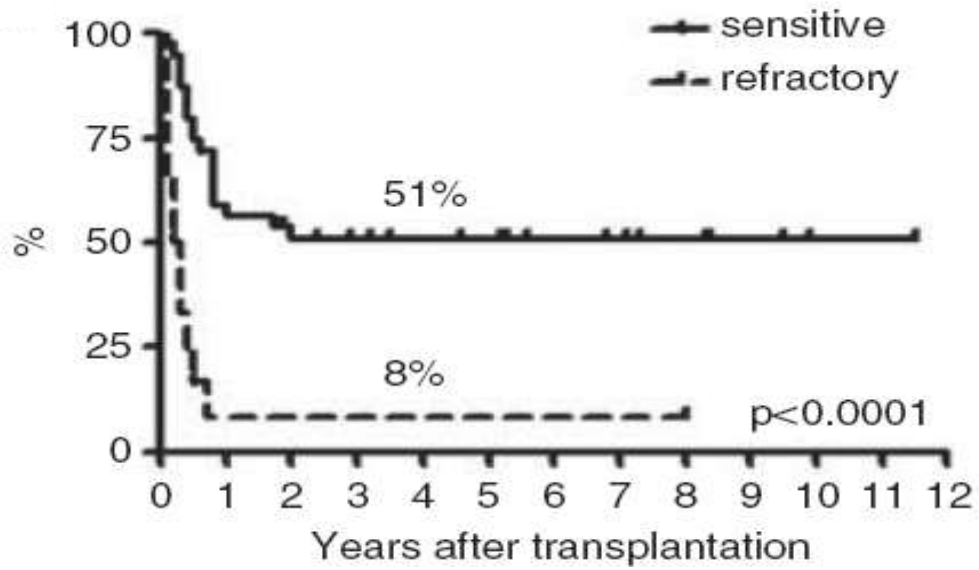
Impact of the disease status before Allo-SCT

N = 52 patients
Retrospective= ; prospective=
Lymphoma subtypes

Disease Status prior to transplant
CR/PR = 75%
Refractory = 25%

RIC conditioning = 100%

5-y NRM = 12%
5-y PFS = 40%
5-y OS = 50%



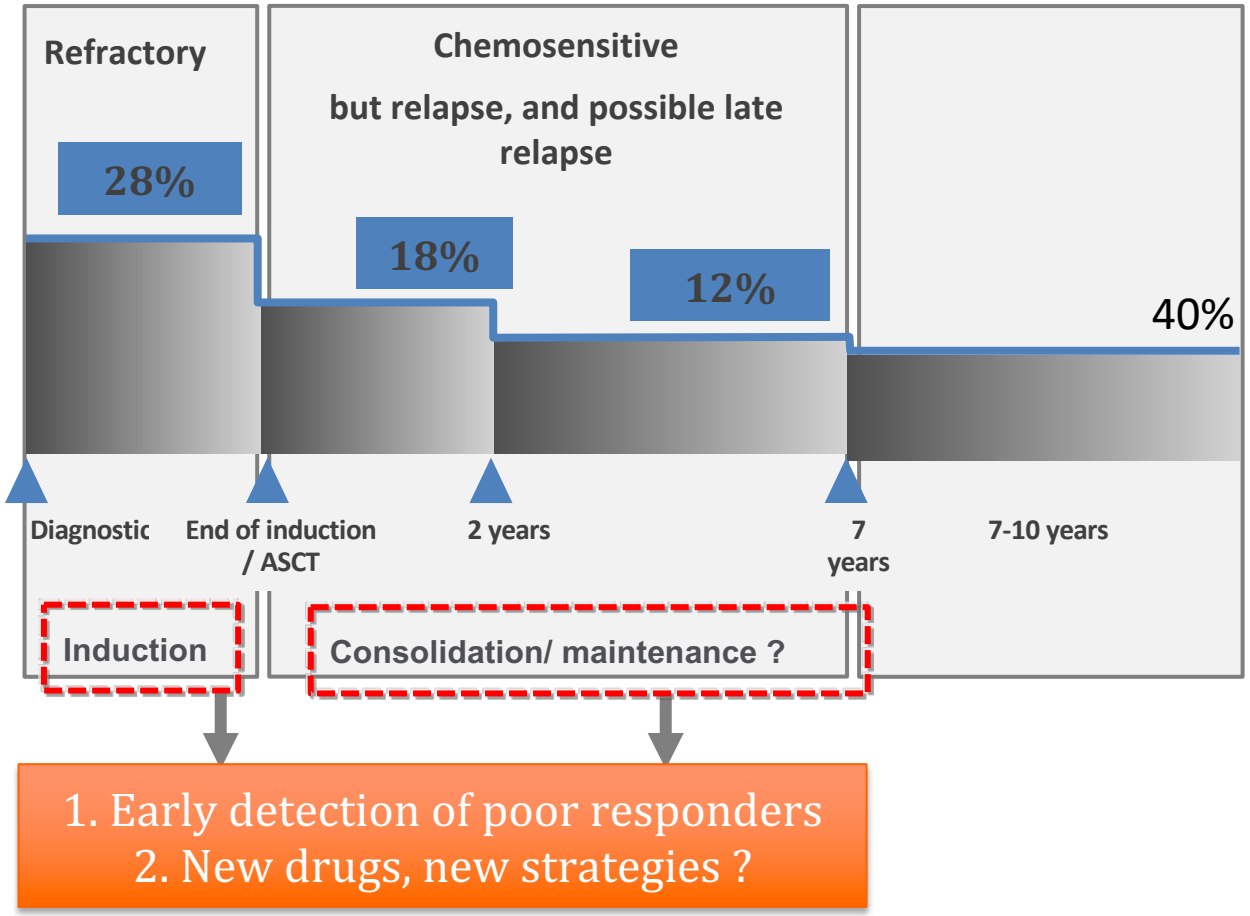
RIC = 100%

Multivariate	
Disease status	(OS et PFS)
Age > 45 y	(OS et PFS)

Dodero et al, Leukemia, 2012

How to improve the outcome ?

Global outcome of PTCL



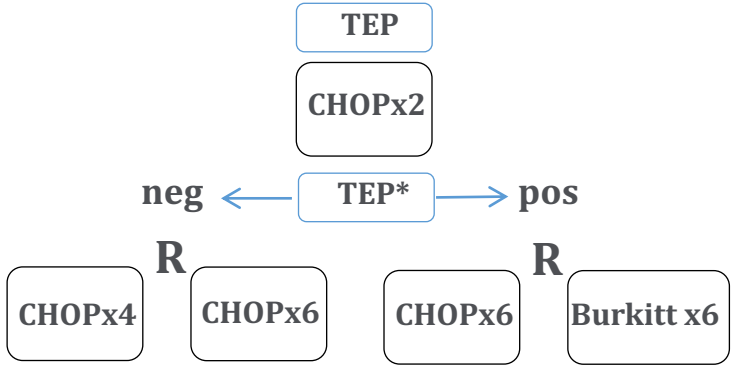
D'Amore, F. abstract #74, *ICML 2015;*

Early detection of poor responders

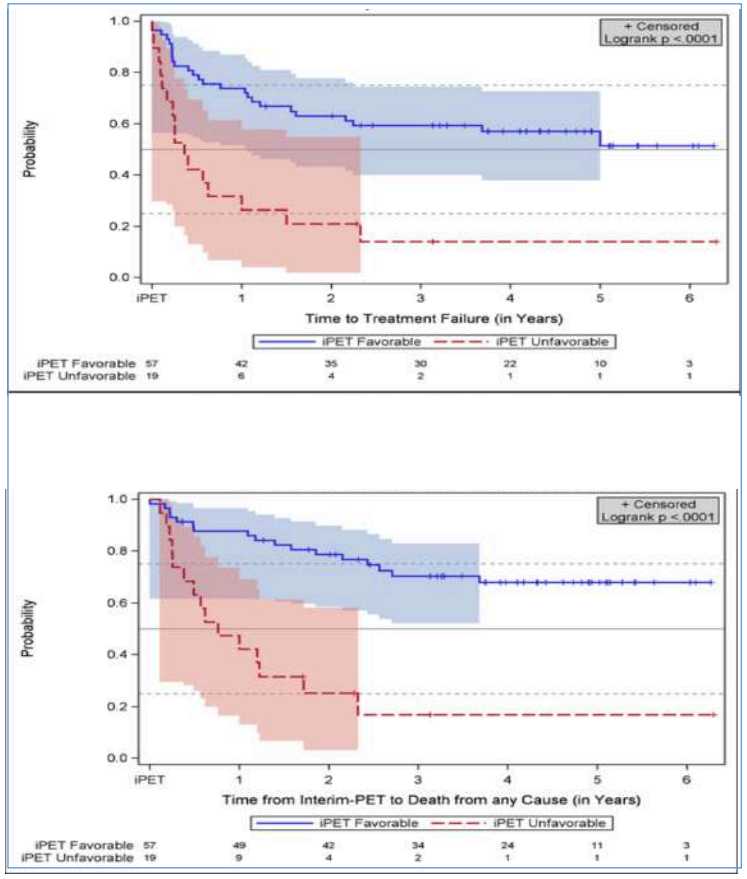
PETAL

(Essen)

PTCL n = 76
Age > 60 (43%)



*3 weeks post C2, DSUV -66%, No G-CSF

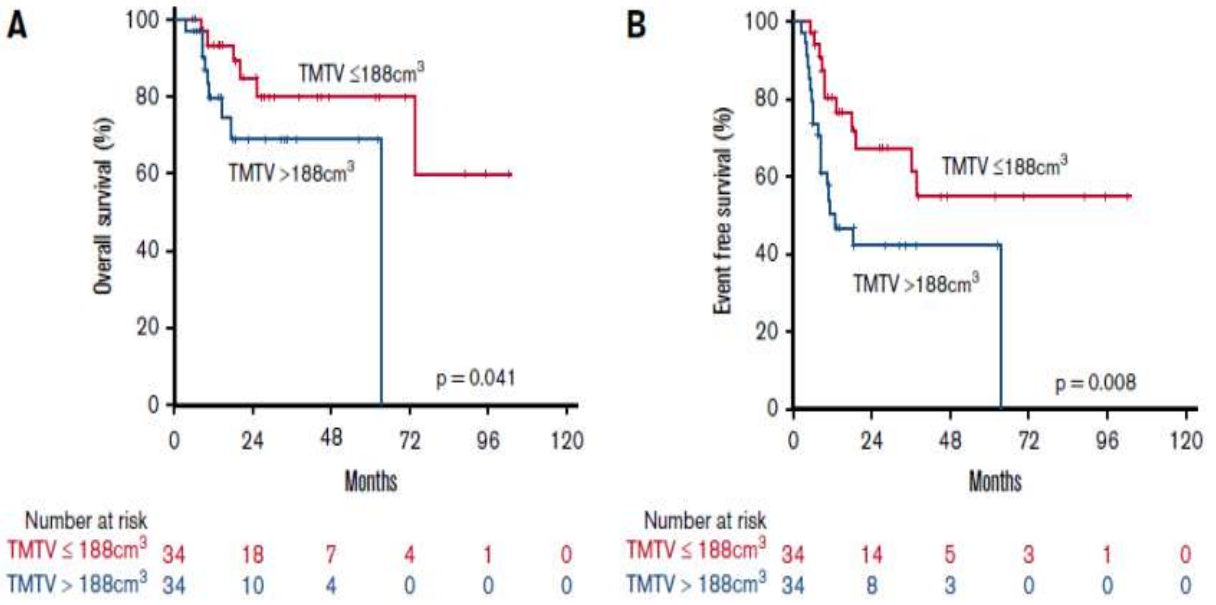


2-y TTTF: 63 % vs. 21 %
HR = 3.4 (95 % CI 1.8 - 6.4) , p<0.0001;

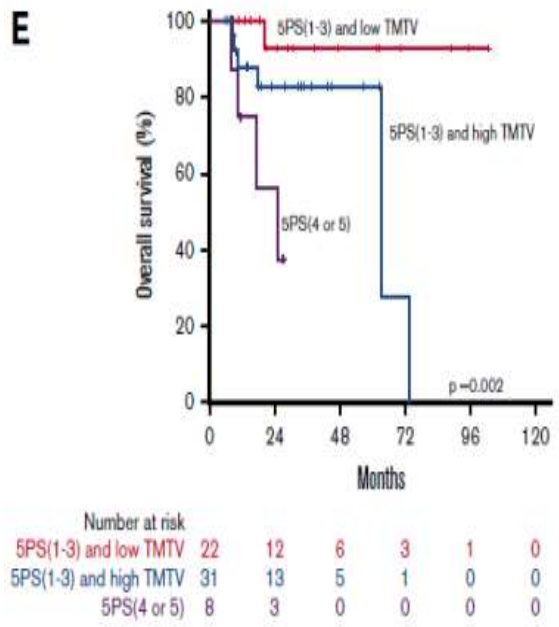
2-y OS: 79 % vs. 25 %
HR = 5.0 (95 % CI 2.4 - 10.3), p<0.0001;

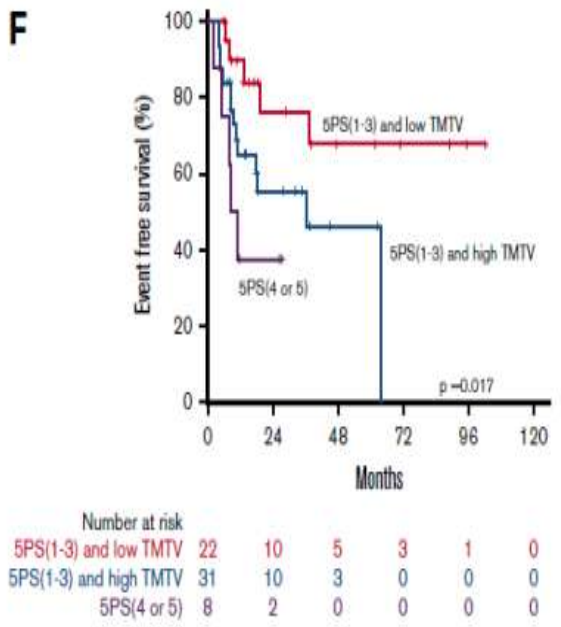
Prognostic value of iPET in PTCL

OS and EFS by TMTV. OS (A) and EFS (B) curves by median (188 cc)



OS (E) and EFS (F) curves of combined 5PS with TMTV





Mehta-Shah et al, Blood Adv, 2019

Conclusion

- **Many progress in the molecular comprehension of PTCL: Targeting therapies ?**
  Epigenetics; SYK/JAK
- **Predictive factors of poor response or early relapses could improve the outcome**
  TEP; iTEP (TMTV)
- **New therapeutic agents such as Aza, Cerdulatinib are promising**
- **Allo-SCT represents the only curative therapy for PTCL**
  - **The Overall survival rate > OS obtained with other strategies**
- **Relevant fraction of patients will not be able to enter the transplant procedure**
  - **Considering allo-SCT early in the course of the disease**
  - **Allo-SCT should be decided for patients who obtained less than CR1 or in R/R disease**
  - **Allo-SCT is superior if chemo-sensitive disease (CR/PR) > refractory disease**

In conclusion

- **Allo-SCT represents the only curative therapy for PTCL**
  - **The Overall survival rate > OS obtained with other strategies**
- **Relevant fraction of patients will not be able to enter the transplant procedure**
  - **Considering allo-SCT early in the course of the disease**
- **Allo-SCT could not be recommended in first line chemo sensitive PTCL based on the AATT trial**
  - **Allo-SCT should be decided for patients who obtained less than CR1 or in R/R disease**
  - **Allo-SCT is superior if chemo-sensitive disease (CR/PR) > refractory disease**

Thank you for your attention