Angioimmunoblastic T-cell lymphoma (AITL)

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Case

50yo male visited clinic because of weakness, fatigue, night sweating.
He complaints severe shortness of breath during exercise.

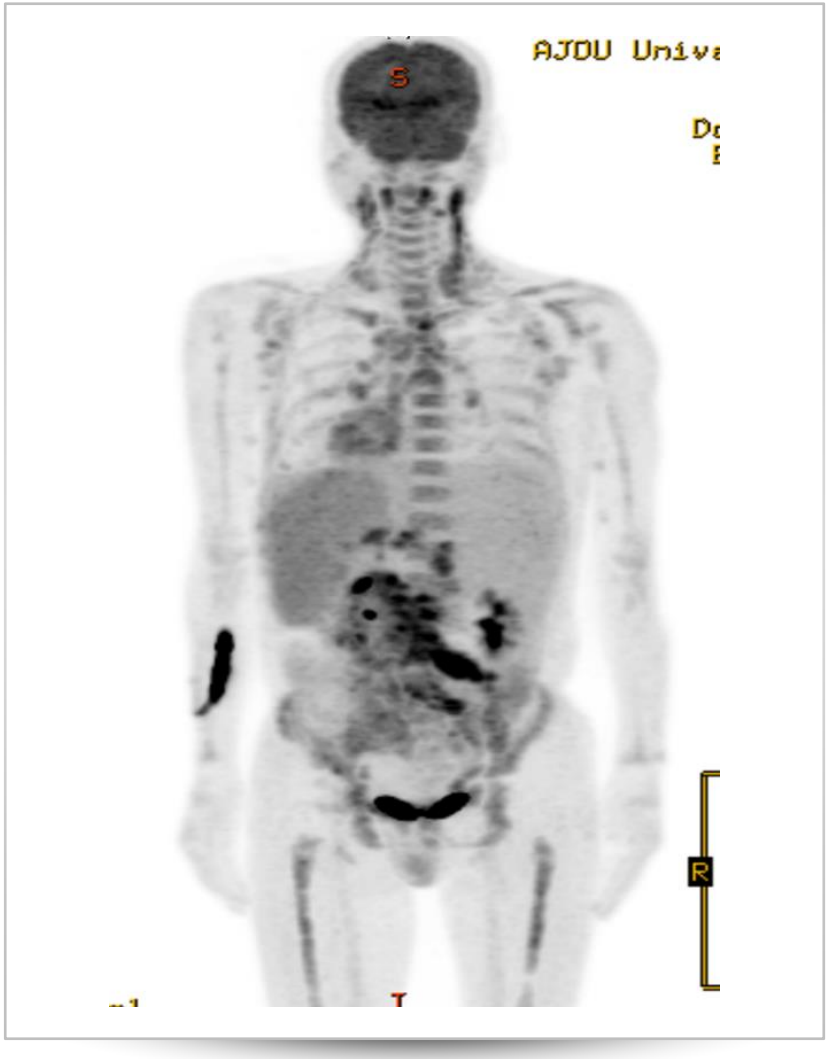
P/E : pale and anemic conjunctiva,
Multiple lymphadenopathy in neck , axillar

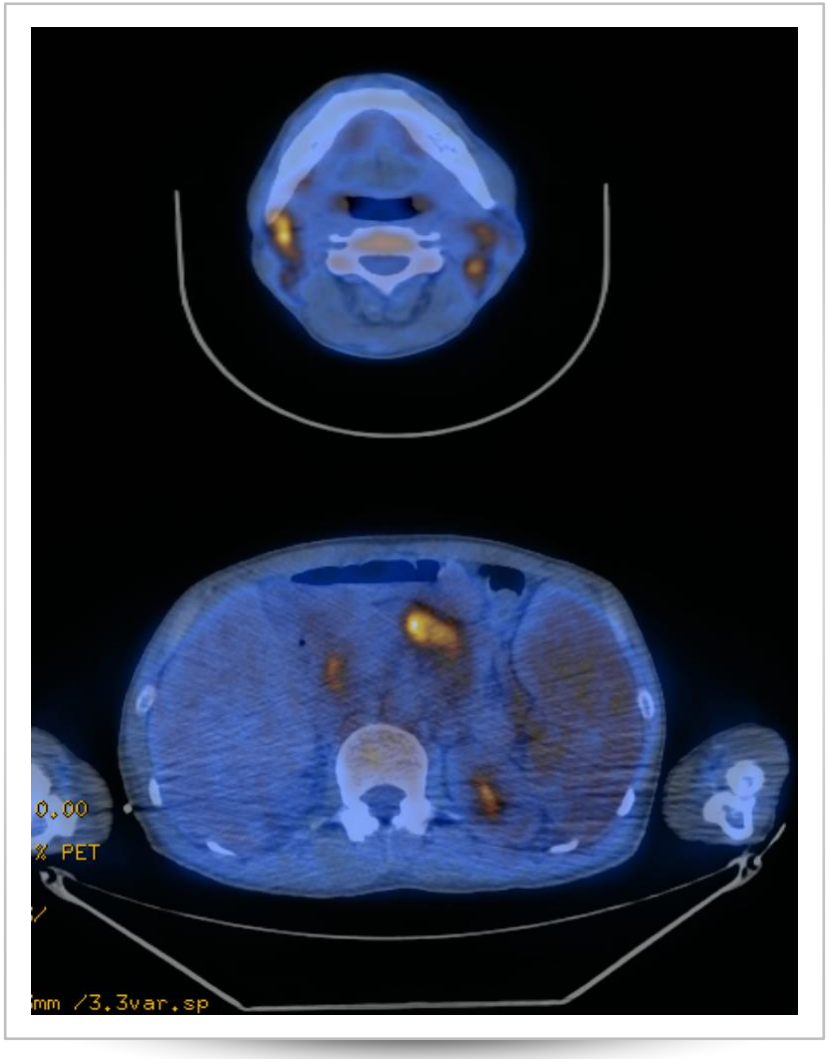
Bx : Angioimmunoblastic T-cell lymphoma
- CD3+/ CD20-/ CD21+/ PD-1+
- Ki-67 : Positive in 40% of tumor cells
- CXCL13: Focal positive in tumor cells

Laboratory findings
- CBC : WBC 10.30×10^3/ul Hb 5.5. g/dl PLT 264×10^3/ul
- Peripheral Blood Cell Morphology : Normocytic and Normochromic Anemia
- AST/ALT 16/9 U/l, Bilirubin 0.5mg/dl, LDH 971IU/l

BM report
- Normocellular marrow with three lineage hematopoiesis
- involvement of AITL

Images





Angioimmunoblastic T-cell lymphoma

In 1970s, it was reported nonneoplastic lymphoproliferation and hyperimmune reaction

- Aingioimmunoblastic lymphademopathy with dysproteinemia (AILD)
- Lymphogranulomatosis
- Immunoblastic lymphadenopathy

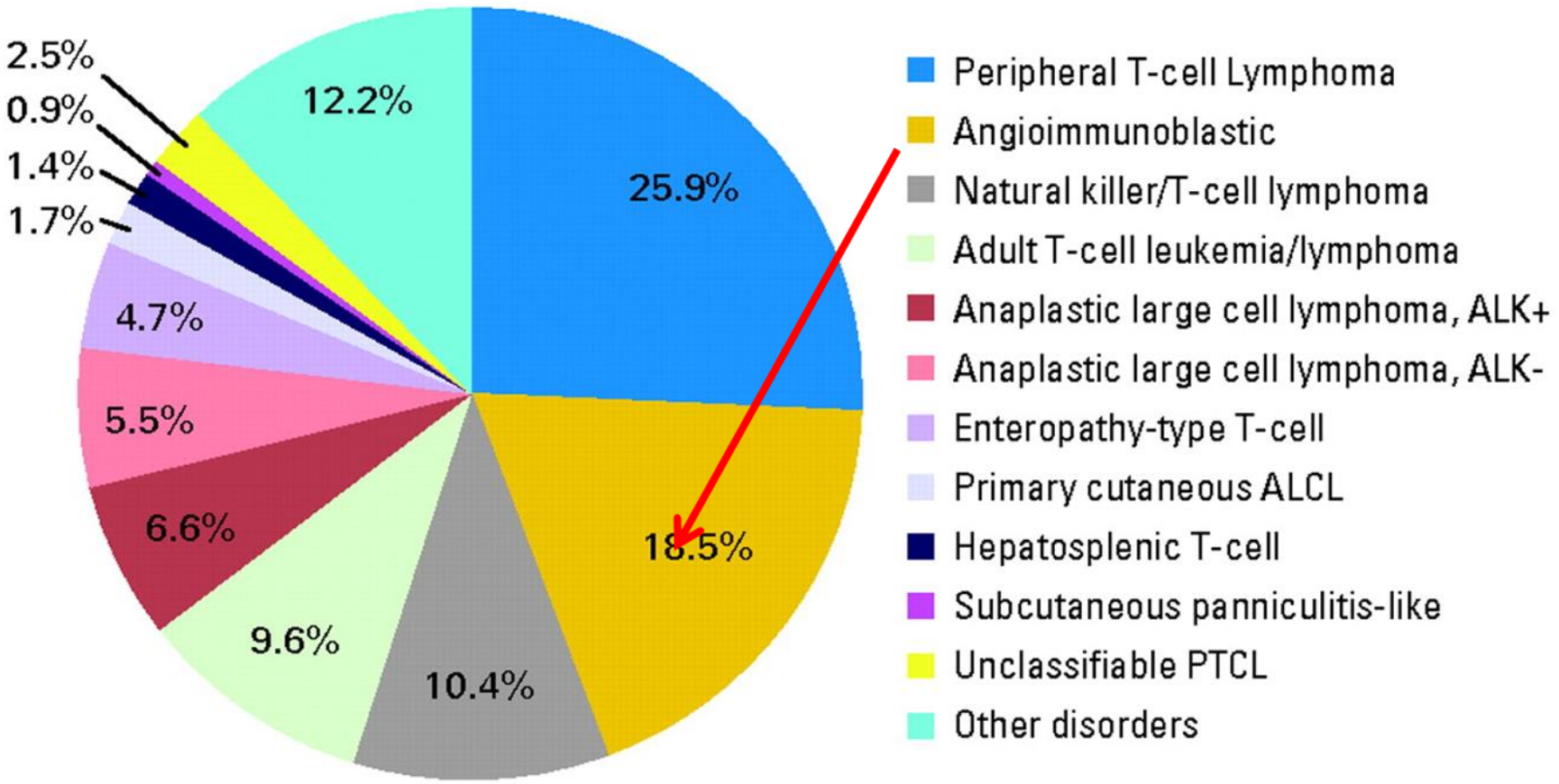
In 1980s, definitely established the neoplastic nature by TCR rearrangement

In REAL and WHO classification, it was recognized as one of common PTCL

In International T-cell lymphoma project

- 18.5% of PTCLs
- More common in EU 29% (Asia 18%, NA 16%)

International T-cell lymphoma project: 1,314 cases



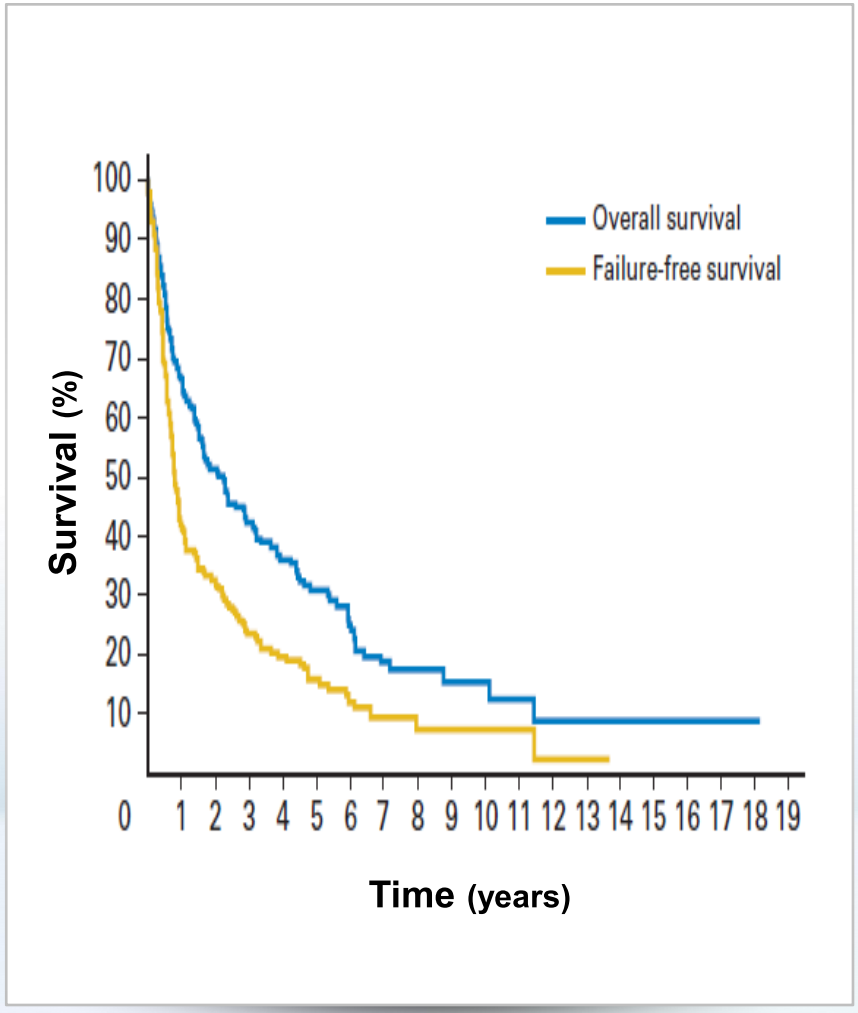
J Clin Oncol 2008

Distribution by geographic area (%)

	Overall	Europe	USA	South America	Asia
PTCL-NOS	37	38	37	43	26
AITL	17	**20**	**22**	7	15
ALCL, ALK-	15	15	13	**26**	6
ALCL, ALK+	7	8	9	7	3
NKTCL	11	7	8	10	**31**
TCR-γδ T-cell lymphoma	8	9	7	4	7
Other histologies	5	3	4	3	12

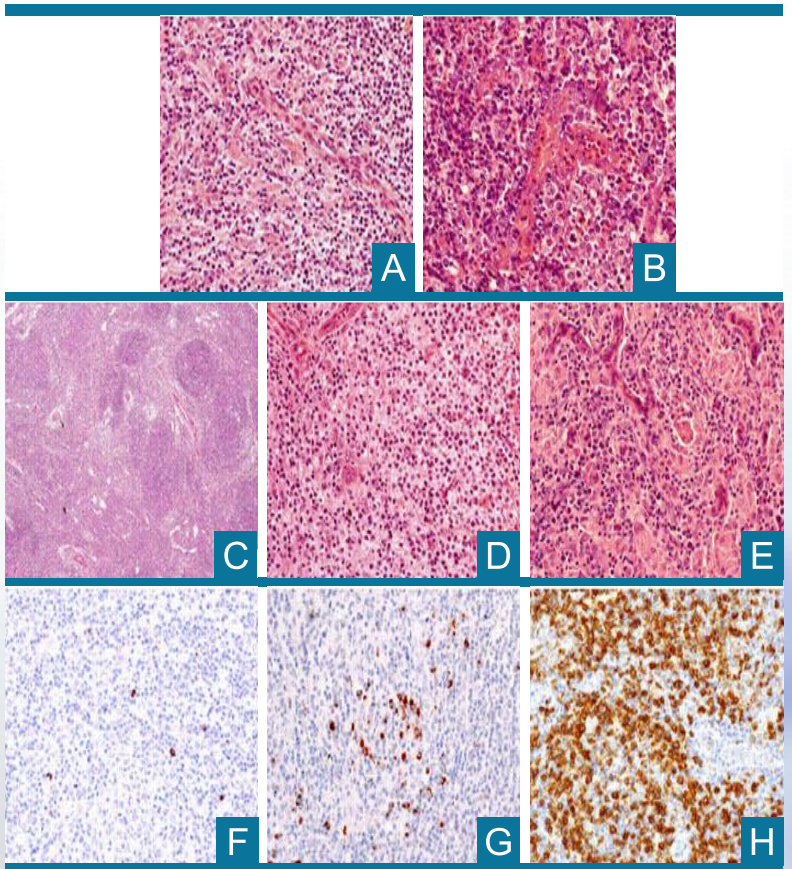
Clinical features of AITL

Characteristic	No.	%
Age Years		
Median	**65**	
Range	20-86	
Male sex	137	56
ECOG PS ≥	89 of 239	37
Stages Ⅲ to Ⅳ	**214 of 241**	**89**
Extranodal sites ≥ two	66	27
BM invovement	67 of 228	28
Systemic symtoms	**168**	**69**
Hemolytic anemia	32 of 205	13
Anemia	81 of 205	33
Platelet count < 150,000/cmm	60	25
Elevated LDH	**146 of 223**	**60**
Elevated β_2-microglobulin	53 of 92	22
Elevated CRP	84 of 127	35
Hypercalcemia	3 of 184	1
Hypergammaglobulinemia	74 of 166	30
HTLV-1 positive	6 of 89	2
HIV positive	2 of 151	1
Immunossuppressive drugs	13 of 211	5
Immune system disorder	3 of 210	1
IPI ≥ 2	**192 of 222**	**79**
PIT ≥ 2	154 of 233	63



Federico M et al. JCO 2013

Clinical, biologic and pathologic features : GELA



(A) classic-type, (B) rich in large cells,
(C) with hyperplastic germinal centers,
(D) rich in clear cells, (E) rich in epithelioid cells

	N 157
Median age	62
Advanced stage	72%
B Sx	72%
Anemia	50%
Hypergamma-globulinemia	50%
7Yr OS	30%

High level of CD10 and CXCL13

no impact on survival

Intensive chemo-regime

no impact on survival

Mourad N et al Blood 2008

Variety of abnormal laboratory test

B-cell immunological activation

- Coombs+ HA, polyclonal hyper-gammaglobulinemia, hypereosinophylia
- various auto-antibodies
  (RF, anti-nuclear factor, anti-smooth muscle)

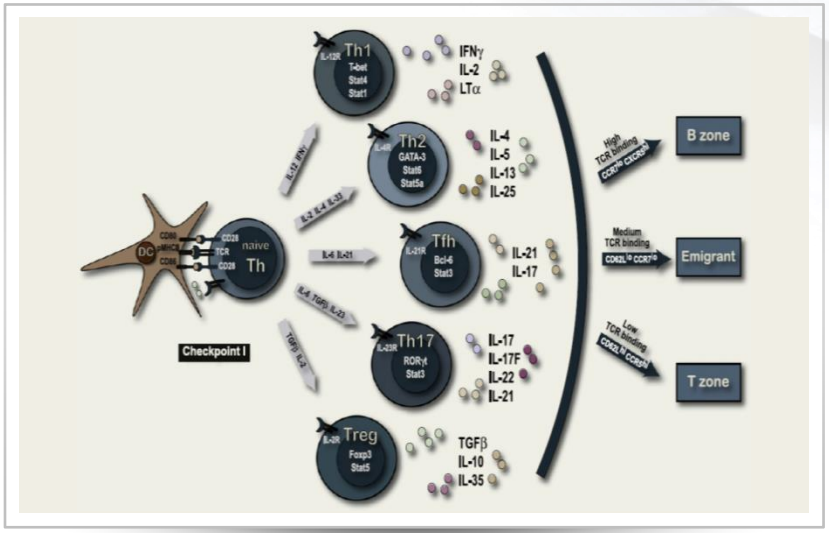
Morphology

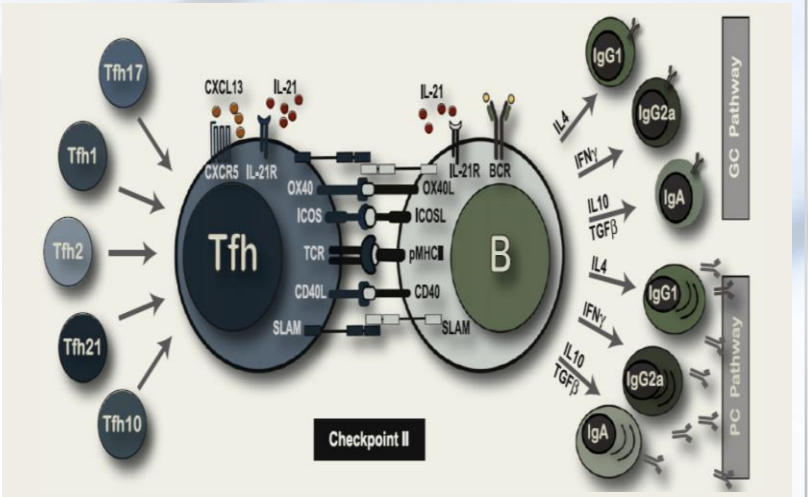
Diffuse LN architecture defeating, clear cell cytology, abundant FDC hyperplasia, complex arborizing vascular structure

Numerous B-lymphocytes are observed, sometimes with EBV integration

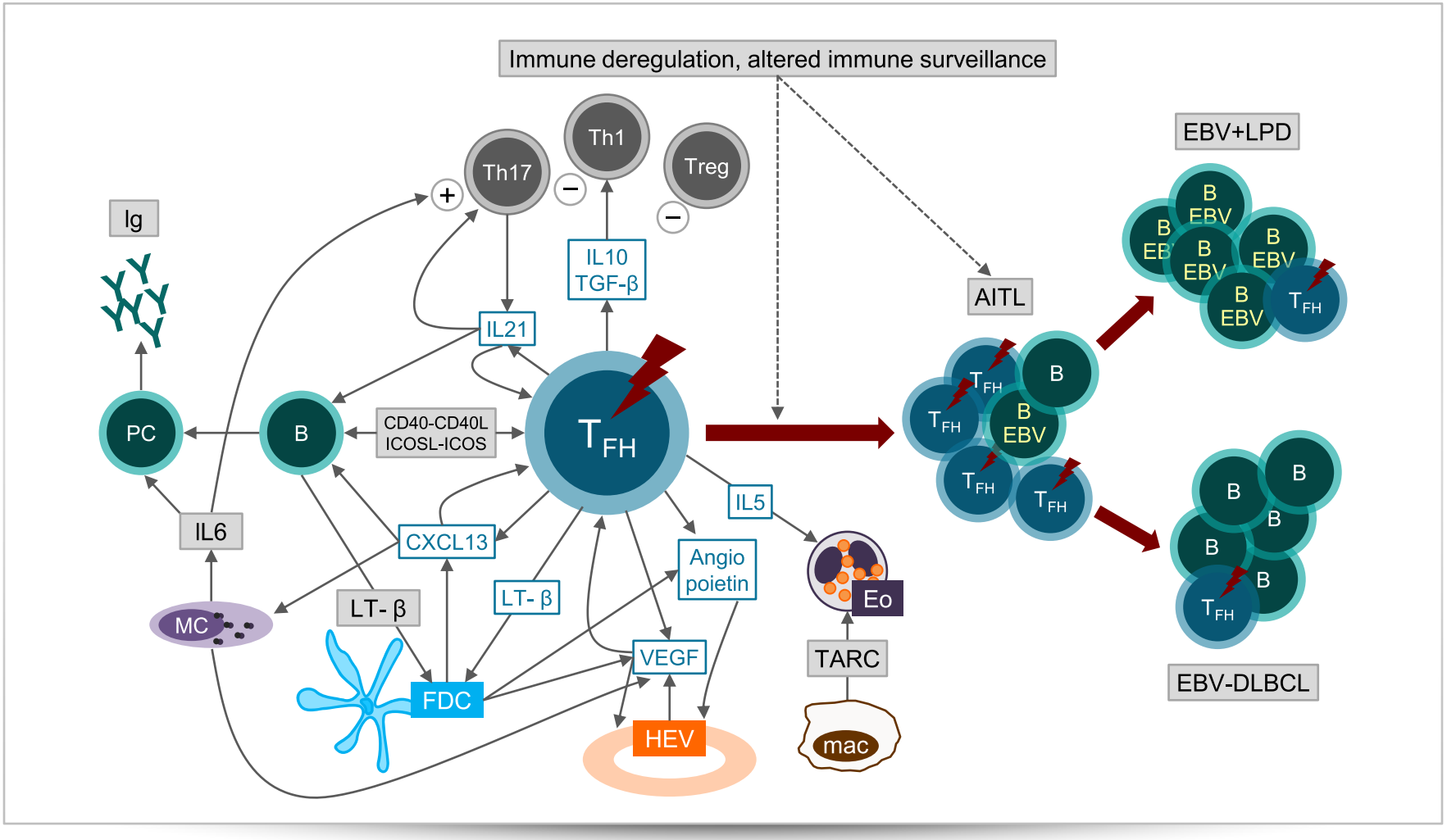
CD3+, CD4+

Carry T-follicular helper (TFH) phenotype
- BCL6, CD10, CXCL13, PD1, SAP and ICOS





Microenvironment



Gaulard P et al. Seminars in cancer biol 2014

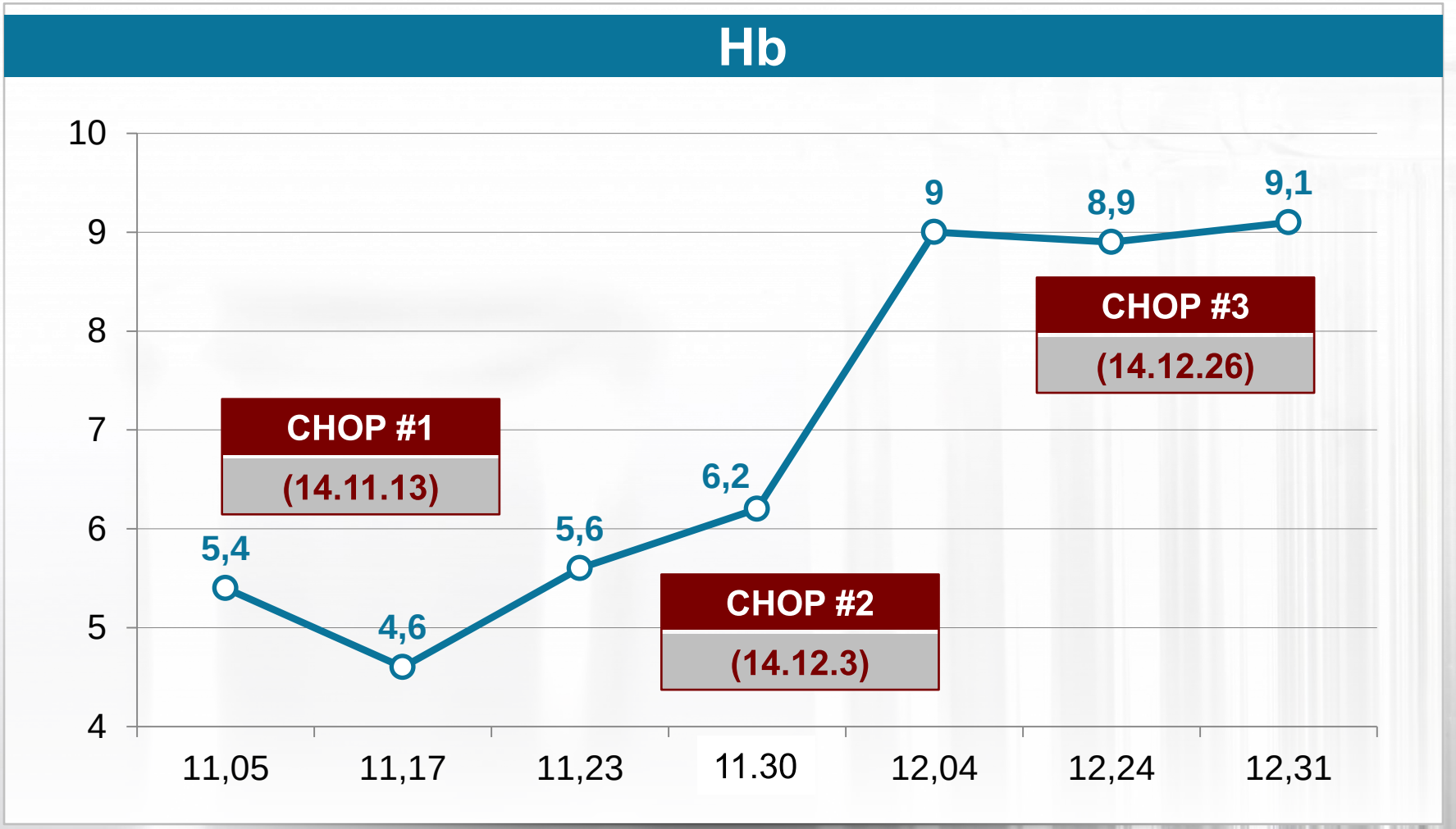
Hospital course

Initial

CHOP#3

CHOP#6

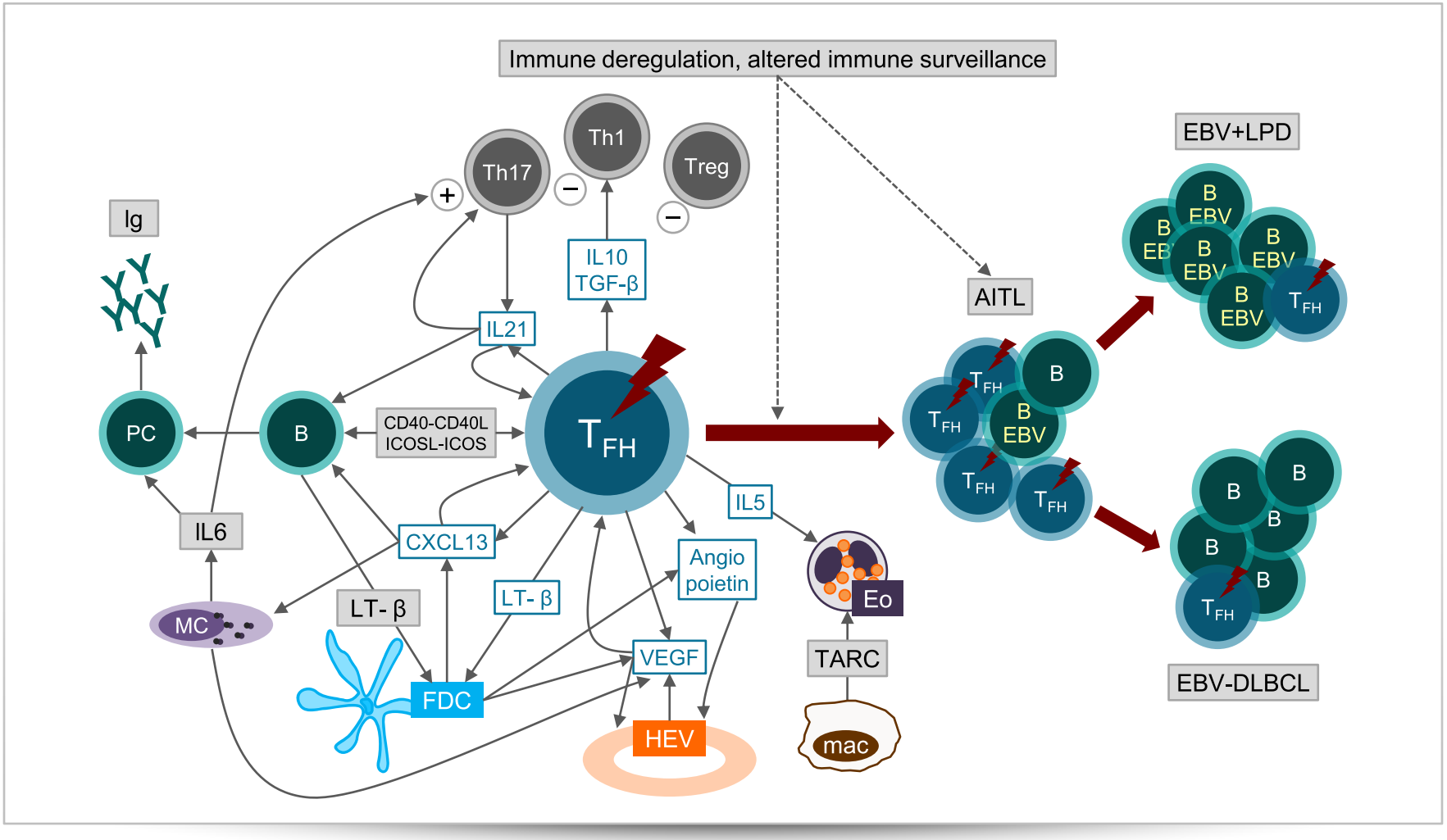
Hospital course



Is CHOP enough ?

1. Addition of novel compound
2. Addition of microenvironment targeting agent
3. High dose chemotherapy followed by stem-cell transplantation

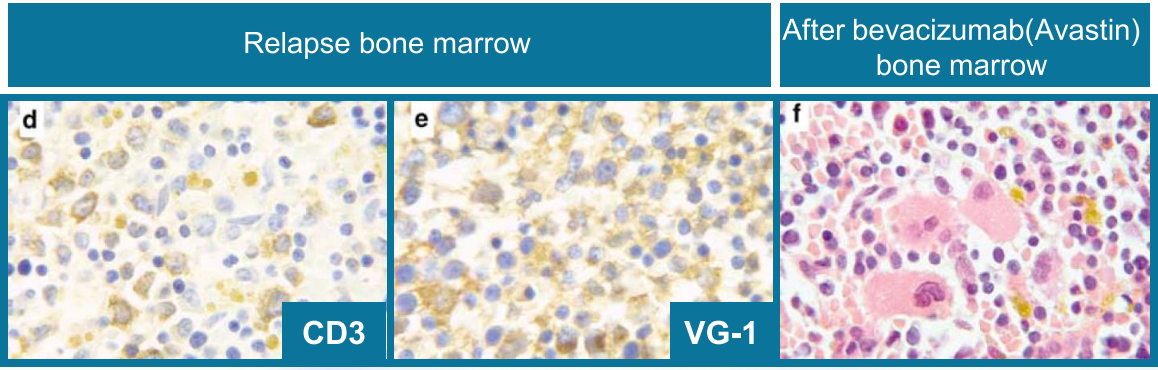
Microenvironment



Gaulard P et al. Seminars in cancer biol 2014

Bevacizumab

A 44 yo heavily treated female achieved CR

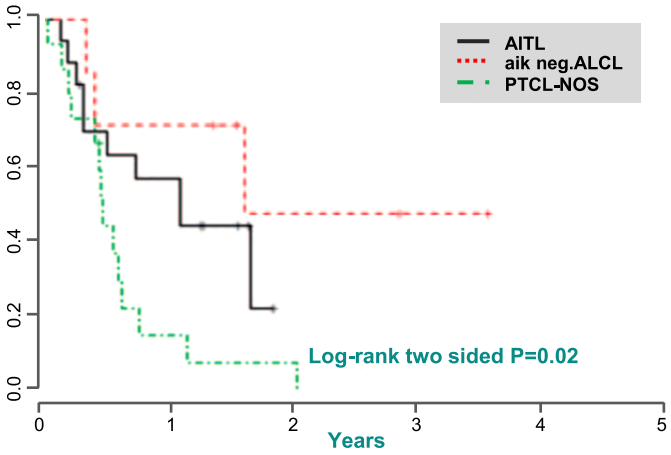


Bruns I Leukemia 2005

Avastin+CHOP for PTCLs (E2404)

- N 30 PTCLs without ALK+ALCL
- ORR 90%, CR 49%
- Gr3-4 congestive heart failure in 4,
- Gr3-4 GI hemorrhage /perforation in 2
- In AITL N 17
  - 9 CRs/17 (53%)

Progression-Free Survival (PFS) based on histology



Ganjoo K et al Leukemia&lymphoma 2014

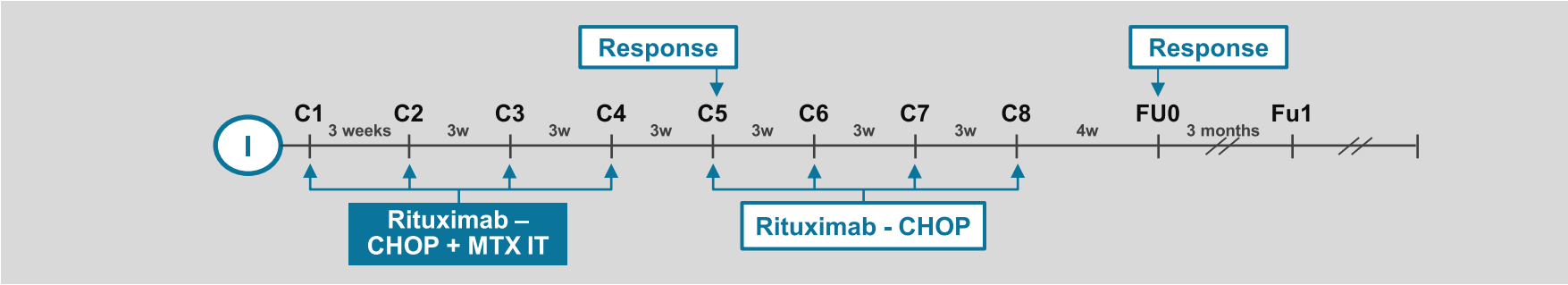
Alemtuzumab

- Hypothetically, it can target both tumor cells and microenvironment
- Pilot study for R/R PTCLs N 14
  - ORR 36% (5/14), 3CRs
  - AITL N 2, 1CR, 1PD
- Alemtuzumab + CHOP

Response Parameter		Histopathology, proportion	Total no. (%)
CR	PTCL-U	7/14	17(70.8)
	AILD-T	6/6	-
	ALCL	3/3	-
	EATCL	1/1	-
PR	PTCL-U	1/14	1(4.2)
Minor response	PTCL-U	1/14	1(4.2)
Disease progression	PTCL-U	5/14	5(20.8)
Patients alive	PTCL-U	5/14	14(58.3)
	AILD-T	6/6	-
	ALCL	3/3	-
	Median follow-up, mo (range)	-	16(5-42)
Patients alive in CCR	PTCL-U	5/14	13(54.2)
	AILD-T	5/6	-
	ALCL	3/3	-
	Median follow-up, mo (range)	-	11(5-42)

Gallamini A et al. Blood 2007

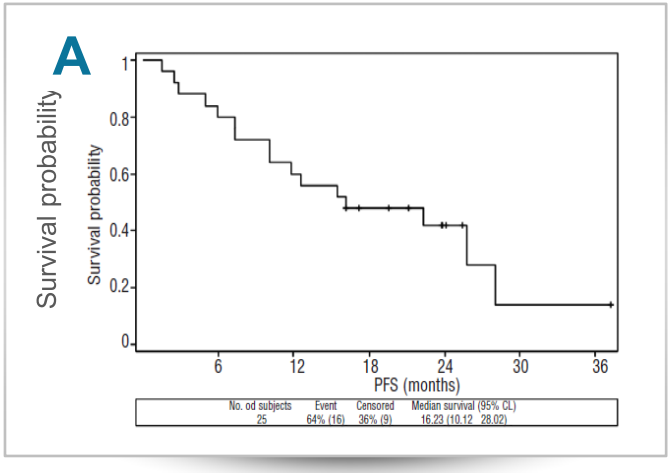
R-CHOP for AITL



	Total number	CR/CRu	Fisher's exact test	Median PFS (months) (95% CI)	Log rank
T-cell density in tumor					
<30%:Score 1	3	1		7.4(2.5-25.8)	
30-50%:Score 2	13	8		16.2	(10.1-)
>50%:score3	9	2	0.2	22.3(7.3-2.8)	0.44
Circulating tumor cells					
Yes	12	3		11(6-28)	
No	10	7	**0.08**	26(16-NR)	**0.17**
B blast density in tumor					
<15(Score 1)	5	1		NA(7.4-NR)	
15-50 (Score 2)	11	6		15.5(10.1-NR)	
>50(Score 3)	9	4	0.5	22.3(5-28)	0.7
EBV load in tissue					
<5(score 1)	16	7		22(12-28)	
≥5(score2 and 3)	9	4	1	10(6-NR)	0.2
EBV load PBMC					
<100cp/μg	11	6		25(15-NR)	
>100cp/μg	11	4	0.6	10(5-28)	0.06
EBV in plasma					
<100 cp/mL	13	7		26(10-28)	
>100cp/mL	7	1	0.15	10(6-22)	0.11

NR : not reached; CR:complete response; Cru:unconfirmed complete response;PFS:Progression-free survival

- N 25
- ORR 80% , CRR 44%

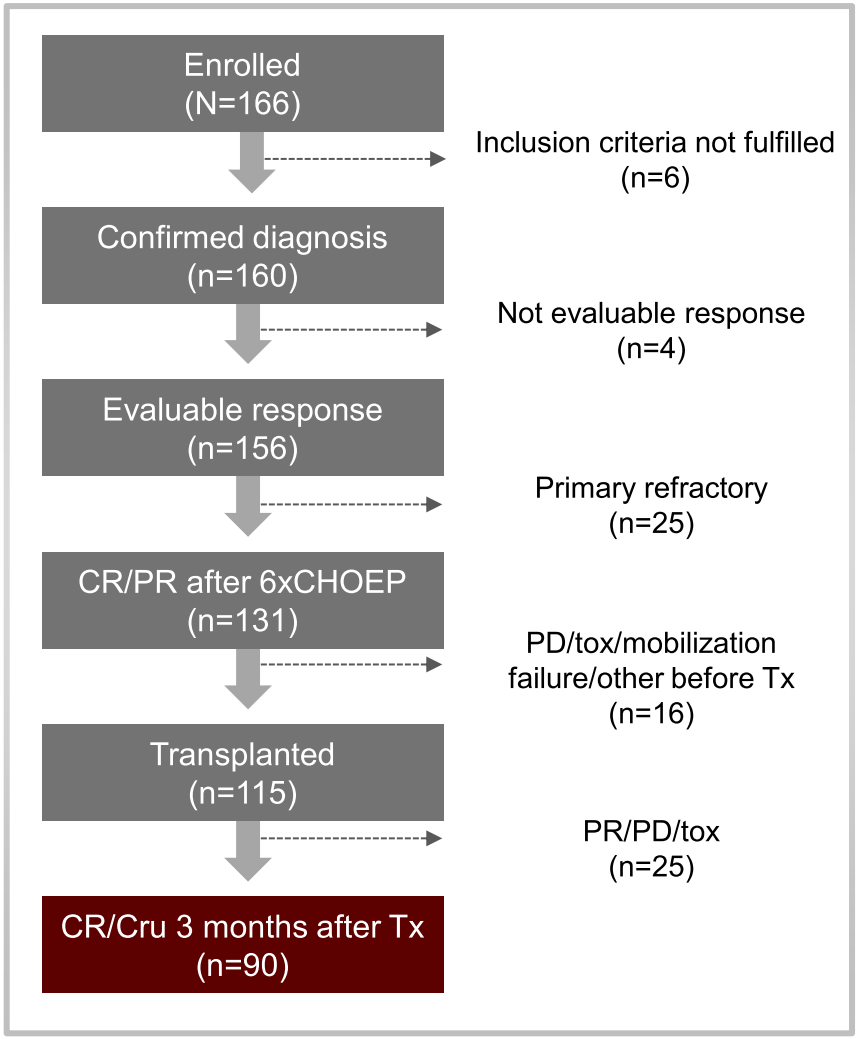


Delfau-Larue et al. Haematologica 2012

After achieving CR, what can be the next treatment?

1. High dose chemotherapy with auto-HSCT
2. RIC with allo-HSCT
3. Maintenance

Flow chart of the NLG-T-01 (Nordic Lymphoma Group) study cohort showing the numbers and types of treatment failures and responding patients throughout the different stages of the protocoled treatment algorithm.



Prospective phase II study in untreated systemic PTCL with a 5-year median follow-up

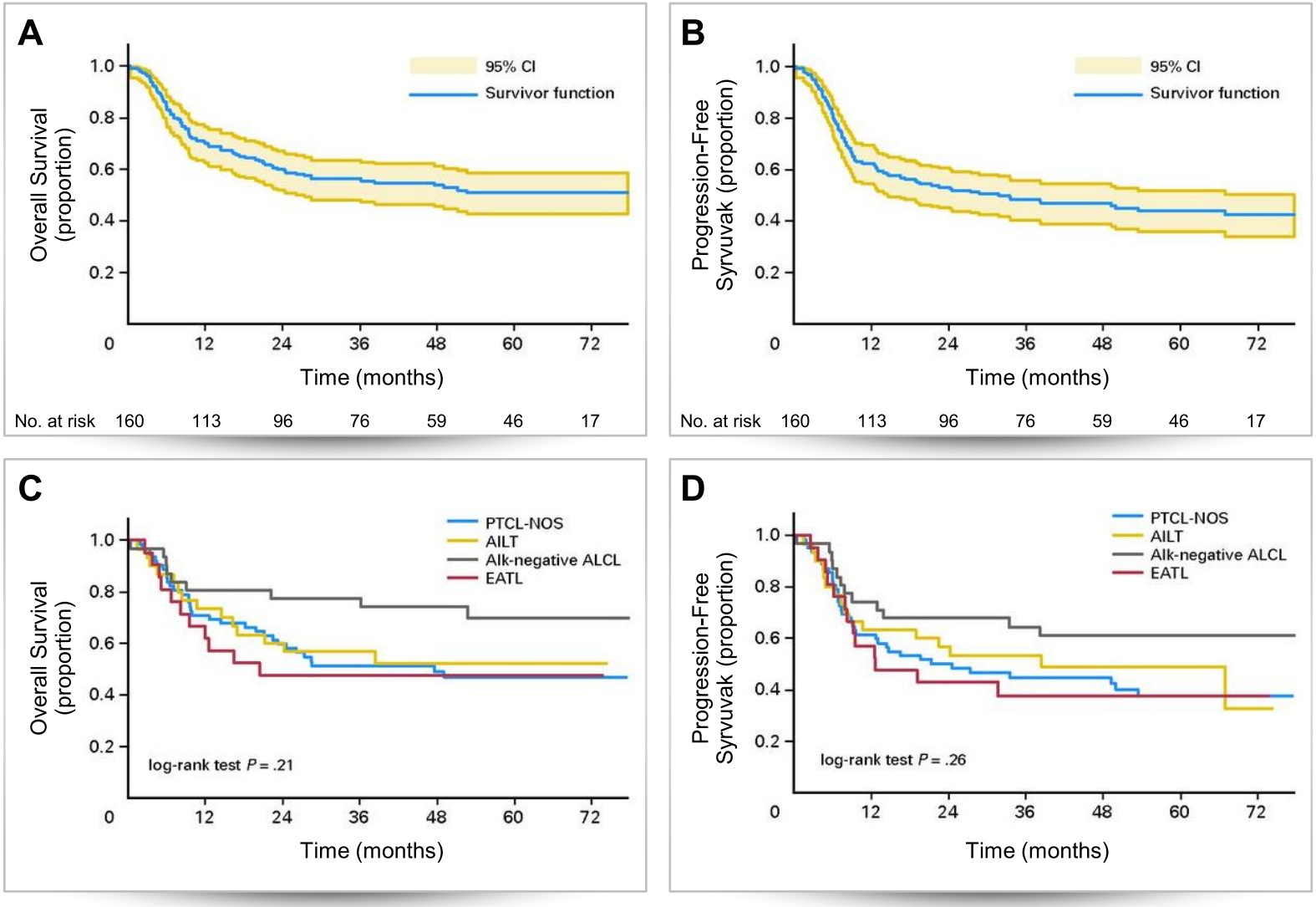
- biweekly CHOEP #6
- CR/PR → HDT/ASCT

HDT/ASCT (n = 115)

- CR 90 at 3 months post-ASCT

Early failures 26%

d'Amore F et al. JCO 2012;30:3093-3099



d'Amore F et al. JCO 2012;30:3093-3099

Frontline ASCT for PTCLs

Current data does not support routine use of ASCT in all patients with PTCL

Chemosensitive patients with high risk may be good candidates

Only 40-50% of patients enjoy a prolonged survival due to relapse even after frontline ASCT : Who are at high risk?

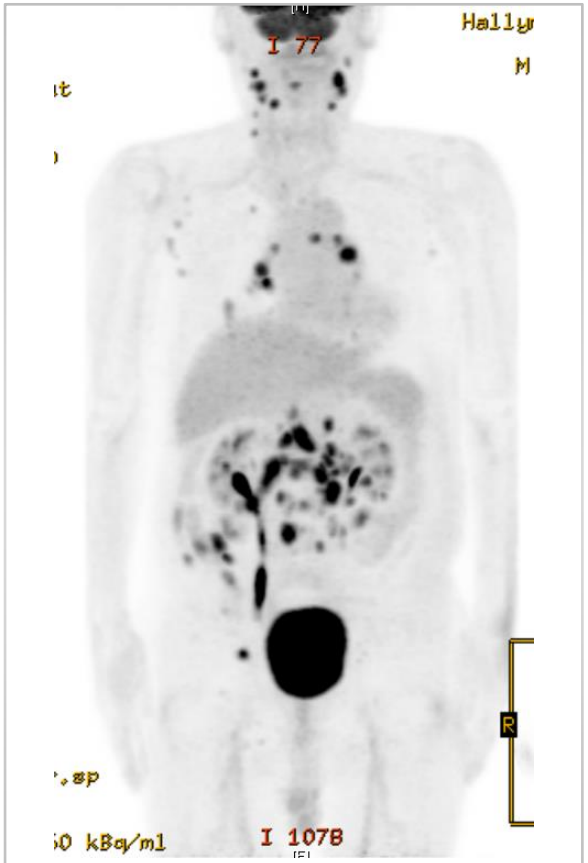
More effective induction treatment strategy prior to ASCT should be required

Case

79yo male visited ER because of fever upto 39°C.
He complained abdominal pain.

- P/E : Multiple lymphadenopathy in neck
- Bx : Angioimmunoblastic T-cell lymphoma
  - CD3+/ CD20-/ CD21+/ PD-1+
  - Ki-67 : Positive in 70% of tumor cells
- Laboratory findings
  - CBC : WBC 7.46x10^{3}/ul Hb 13.4 g/dl PLT 356x10^{3}/ul
  - AST/ALT 26/42 U/l , Bilirubin 0.4mg/dl, LDH 623IU/l
- BM report
  - Normocellular marrow with three lineage hematopoiesis
  - No evidence of malignancy

Hospital course



Initial

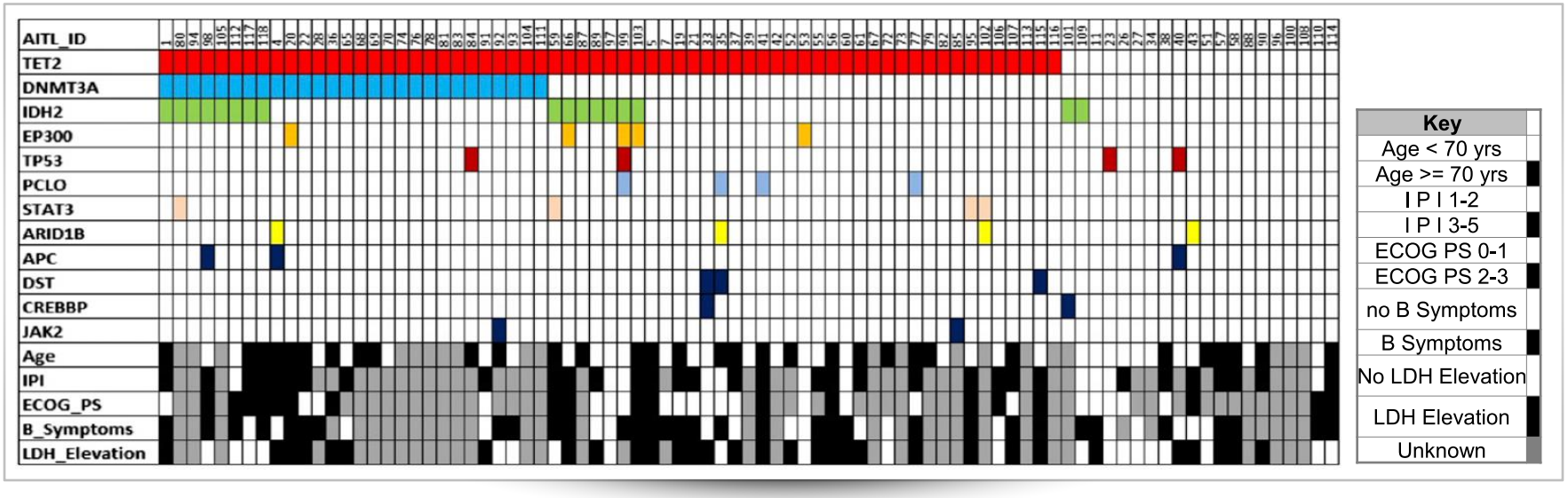
after CHOP#6

Bx of neck LN

<< Results of immunohistochemistry (S15-31917) >>
. CXCL 13: Positive in a few cells
. PD-1 : Positive in tumor cells
. CD3 : Positive in tumor cells
. CD21 : Positive in tumor cells

What can be the treatment choice?

Generic Changes in AITL



TET2 mutation	76%
DNMT3A	33%
IDH2	20%

High frequencies of overlapping mutations in epigenetic modifiers.

Odejide O et al Blood 2014

HDACi

Romidepsin	▪ ORR 25%(33/130) CR/CRu 15%(19/130) ▪ AITL ORR 30%(5CRs, 3 PRs) CRR 19% ▪ PTCL-NOS ORR 29% CRR 14% ▪ ALCL-ALK- ORR 24% CR19%
Belinostat	▪ ORR 25.8%(31/120) CR 10.8%(13/120) ▪ AITL ORR 45.5% ▪ PTCL-NOS ORR 23.3% ▪ ALCL-ALK- ORR 15.3%
Chidamide	▪ ORR 28%(22/79) CR 14%(11/79) ▪ AITL ORR 50% CRR 40% ▪ PTCL-NOS ORR 22% CRR 7% ▪ ALCL-ALK- ORR 45% CRR 36%

Coiffier Bet al JCO 2012
O'connor OA JCO 2015
Shi Y et al Ann Oncol 2015

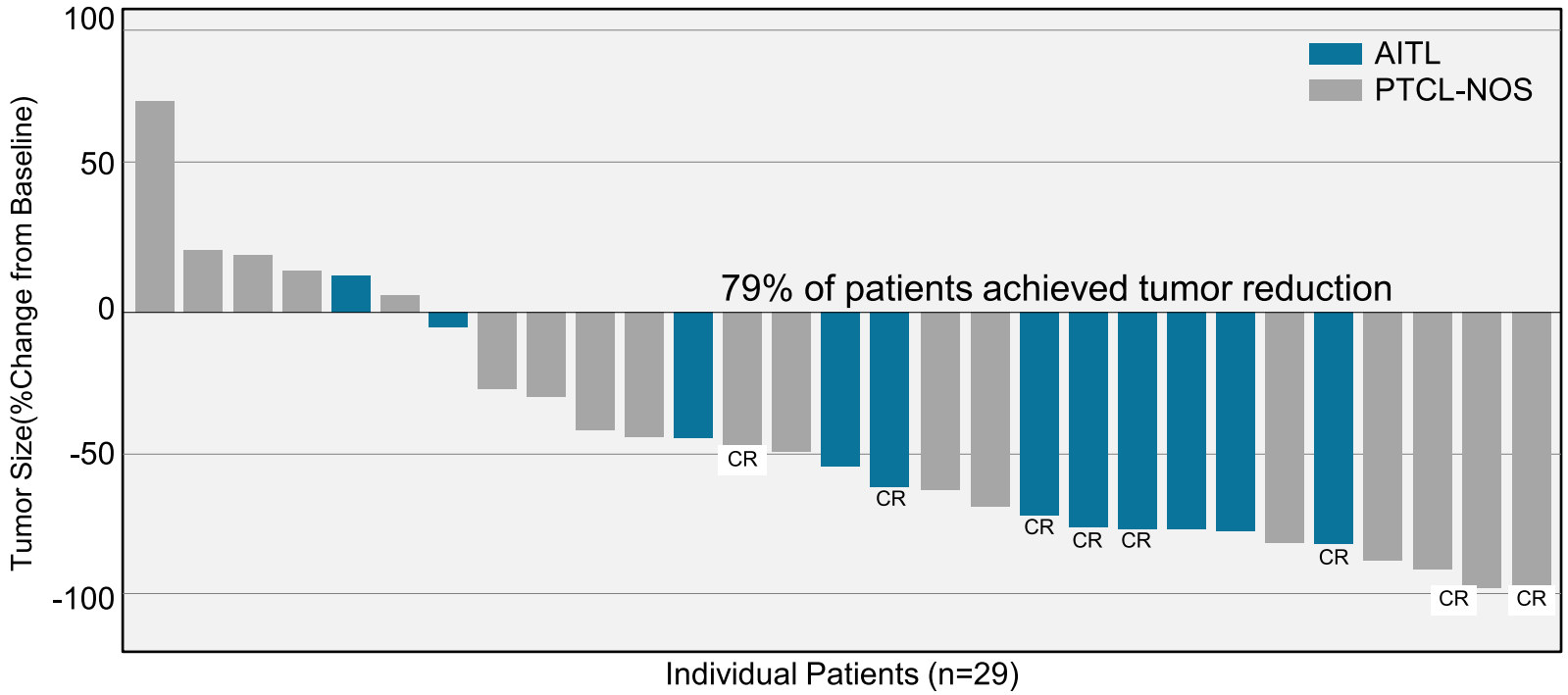
Pralatrexate

- N 115 (Evaluable 109)
- ORR 29% (32/109 , with 12CRs) / median DoR 10.1mo
- Gr3/4 toxicities : thrombocytopenia 32%, mucocits 22%, neutropenia 18%, anemia 18%
- AITL : response 1/13 (8%)

O'Connor OA et al. JCO 2011

Brentuximab vedotin

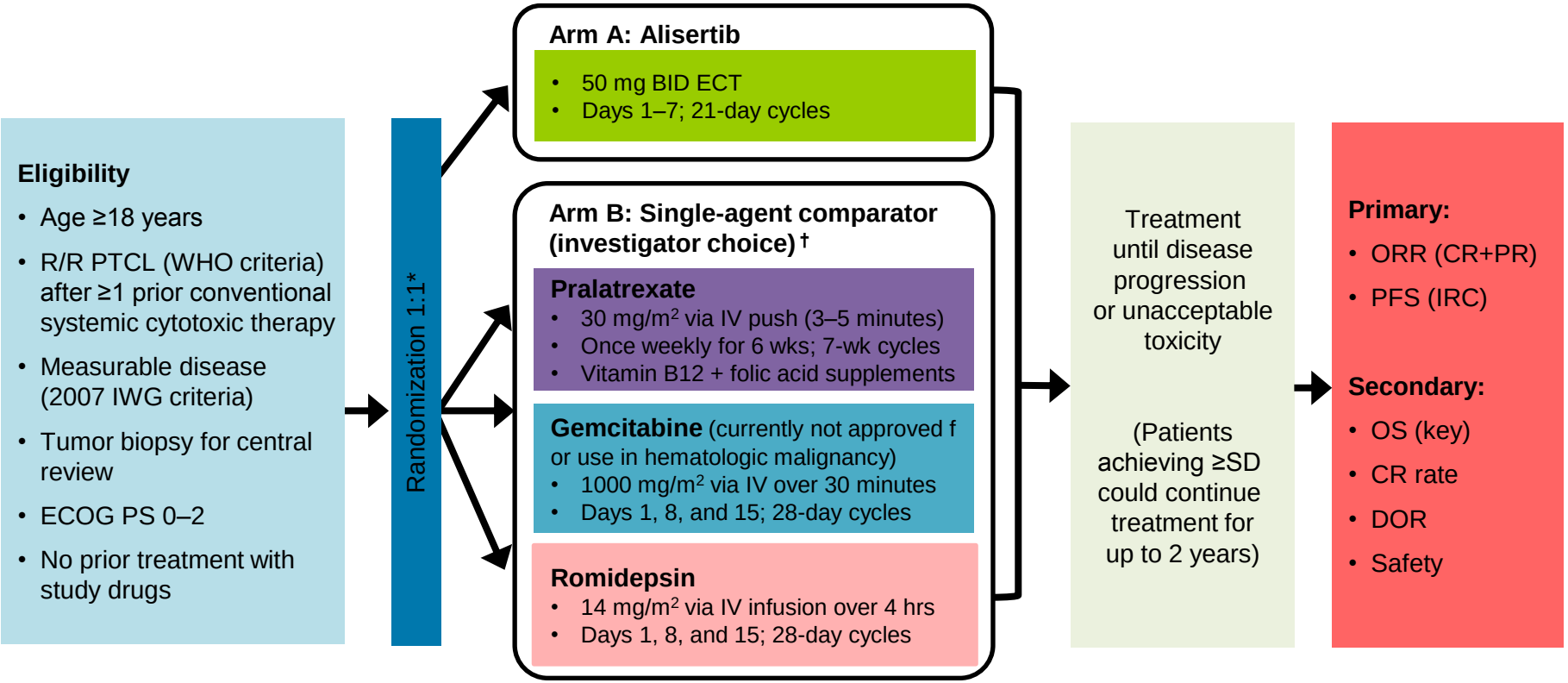
CD30 positive in 63% (61/97) , strong positive in 5% (5/97)



- ORR N 34 41% (8CRs, 6PRs)
- AITL N 13 ORR 54% (5CRs, 2PRs)

Horwitz SM et al. Blood 2014
Bossard C et al Blood 2014

LUMIERE Study design



*Stratified by:
- Nodal vs extranodal disease
- IPI score (0/1/2 vs 3/4/5)
- Region (North America + EU vs Rest of World)

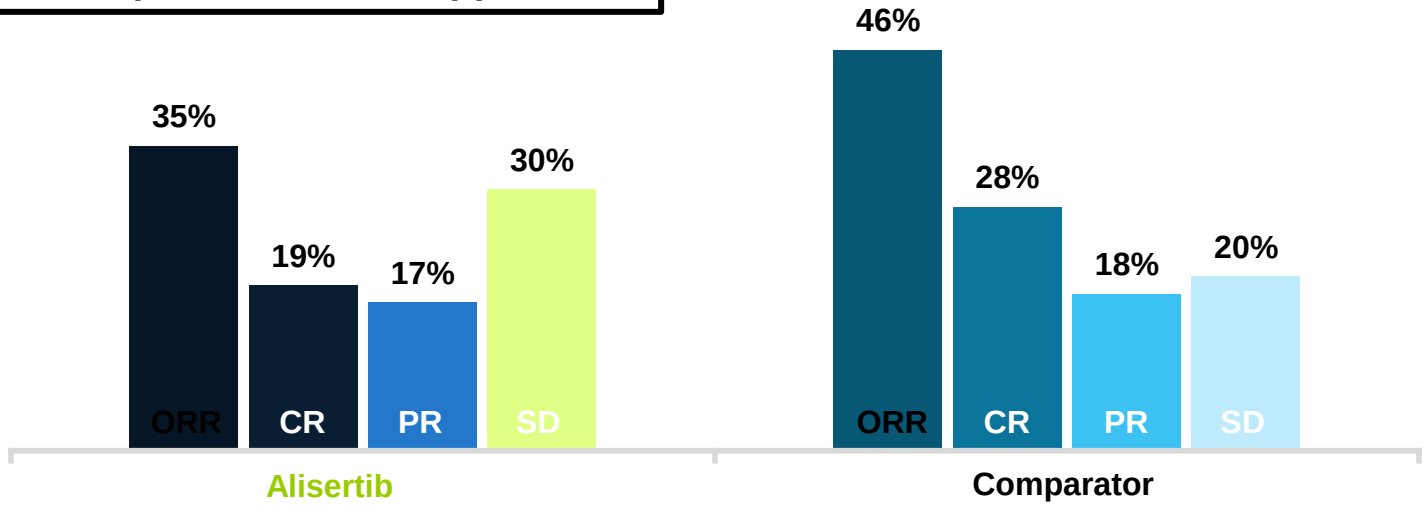
†Crossover to alisertib after comparator arm was not permitted.

BID, twice daily; CR, complete response; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; ECT, enteric-coated tablet; IPI, International Prognostic Index; IRC, independent review committee; IV, intravenous; IWG, International Working Group; OS, overall survival; PFS, progression-free survival; PR, partial response; SD, stable disease; WHO, World Health Organisation

Owen O et al ASH 2015

Best Overall response rate*

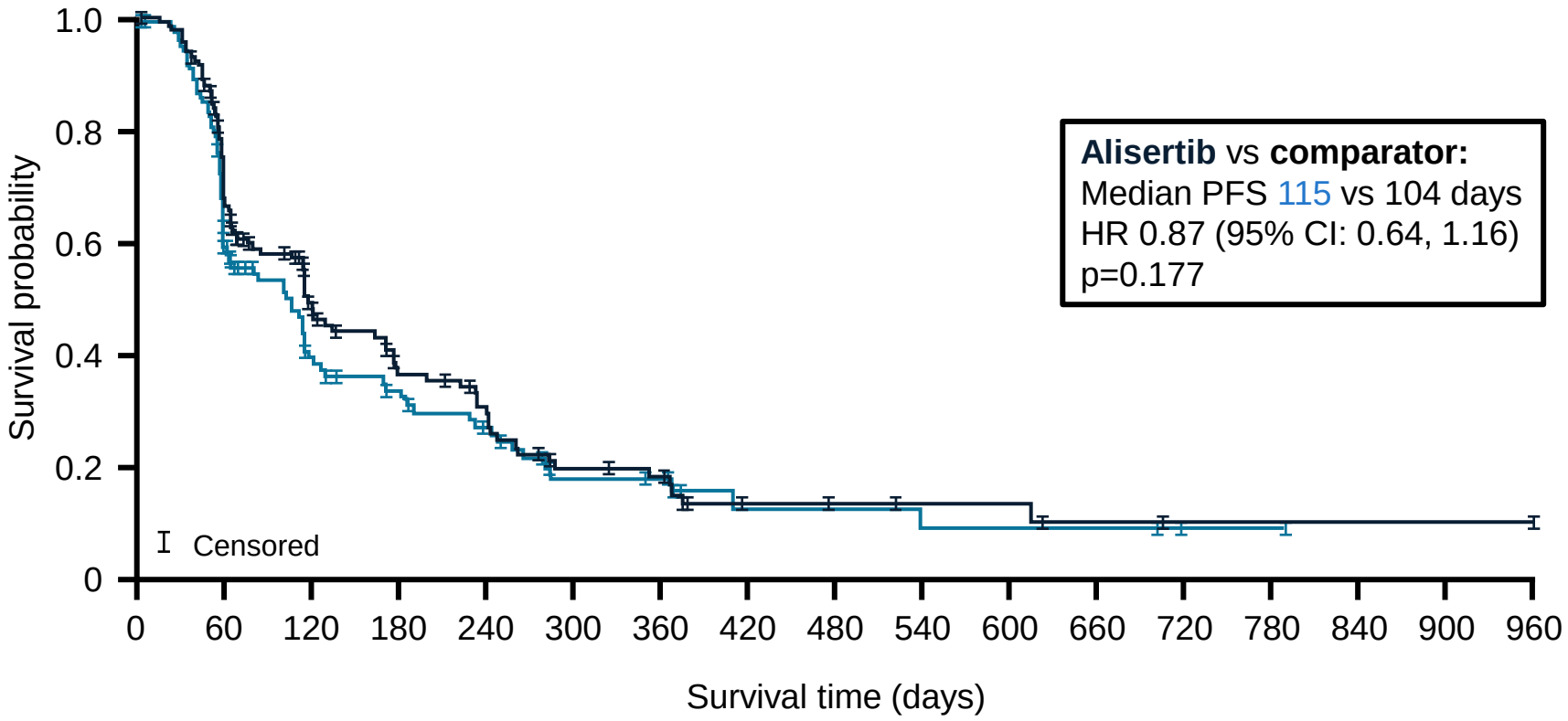
ORR (Alisertib vs Comparator): 35% vs 46%
Odds Ratio 0.65 (95% CI: 0.36, 1.18) p=0.077



		Comparator			
Response, n (%)	**Alisertib (n=96)**	**All (n=85)**	**Pralatrexate (n=45)**	**Gemcitabine (n=22)**	**Romidepsin (n=18)**
ORR (CR + PR)	**34 (35)**	**39 (46)**	**20 (44)**	**8 (36)**	**11 (61)**
CR	18 (19)	24 (28)	13 (29)	5 (23)	6 (33)
PR	16 (17)	15 (18)	7 (16)	3 (14)	5 (28)
SD	29 (30)	17 (20)	11 (24)	3 (14)	3 (17)
PD	33 (34)	29 (34)	14 (31)	11 (50)	4 (22)

*Response-evaluable population, excluding tMF
CI, confidence interval; OR, odds ratio; PD, progressive disease; tMF, transformed mycosis fungoides

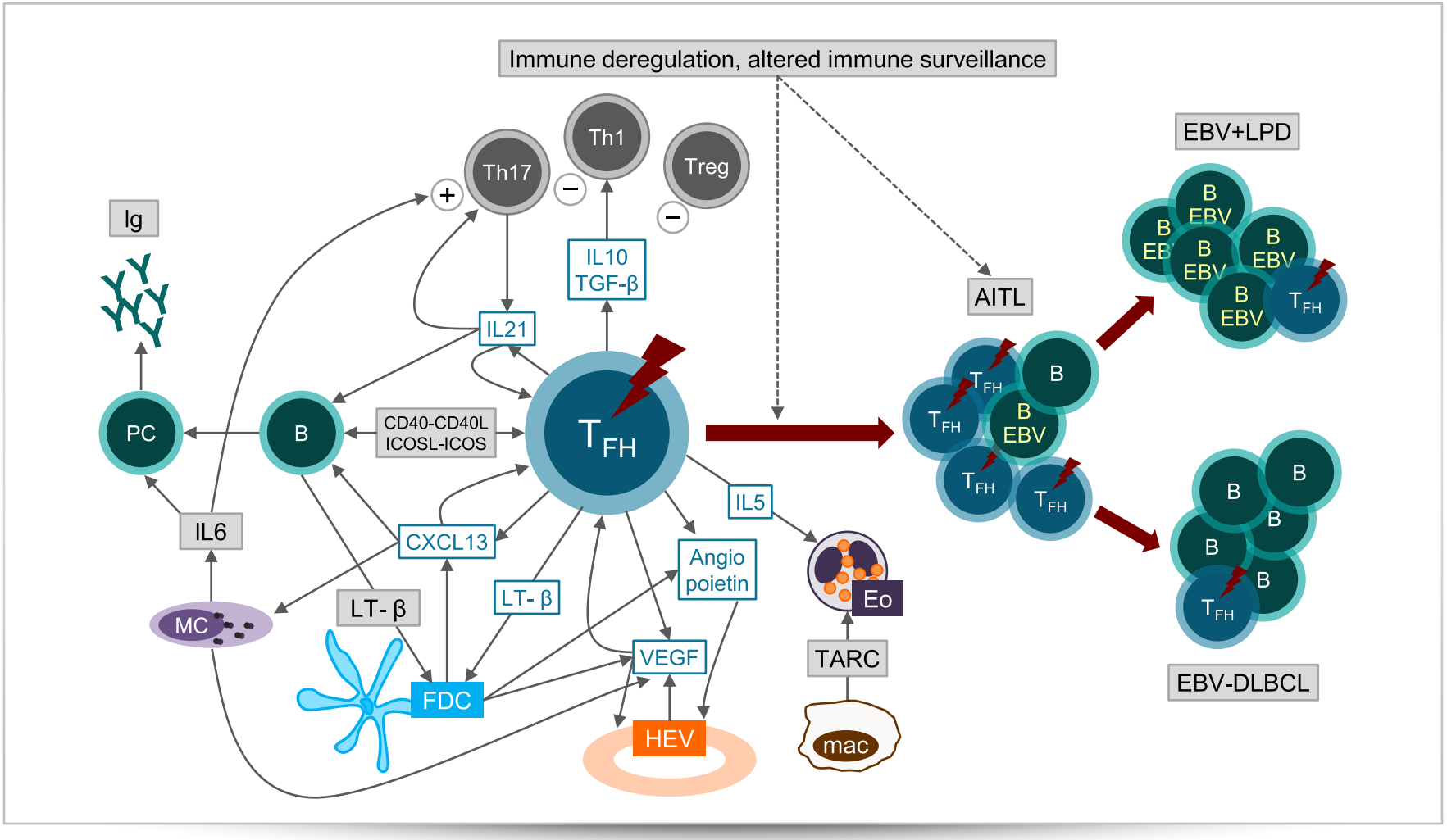
Progression-free survival by irc (ITT)



133	65	35	26	20	10	9	4	4	3	3	3	1	1	0	0	0
138	84	46	33	23	15	12	6	5	4	4	2	1	1	1	1	0

PFS is defined as the time from the date of randomization to the date of first documentation of PD or death due to any cause, which ever occurs first.

Microenvironment



Gaulard P et al. Seminars in cancer biol 2014

Immune modulation

IFN-a	▪ 3M IU qd → if CR , x3/wk ▪ 4CRs,4PRs out of 12pts ▪ DoR 3.5mo

Siegert W et al Leukemia 1991

Cyclosporine A	▪ 8 responders (3CRs , 5PRs) out of 12pts ▪ CR maintained >10yr, 2mo, and 44+mos ▪ Dose reduction in 6 pts due to renal insufficiency, fatigue, hypertension ▪ 2 acute infection , I sudden death ▪ Stopped because of low accrual rate

Advani R et al Leukemia &lymphoma2007

iMID

Thalidomide

- Immune modulatory for both B-and T-cell by inhibition TNF,VEGF, IL-6 and NFkB
- A 32 yo heavily treated man achieved CR and maintained over 28mos.

Ramasamy K Haematologica 2006

Phase II CHOP and Lenalidomide in First Line in AITL (NCT01553786)

under LYSA

Summary

AITL is a common subtype of PTCLs.

Usually affect elderly patients with presentation of advanced disease.

Laboratory abnormalities are commonly associated due to hyper-immune status.

CHOP or CHOP-like regimens are most widely used for young patients.

Optimal treatment is not determined for unfit patients.