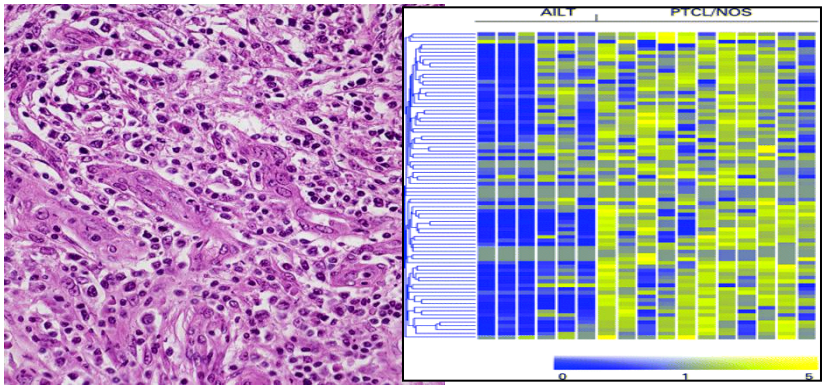
1st POSTGRADUATE Lymphoma Conference
Rome, March 2015

Is There a Specific Rx for Angioimmunoblastic T cell NHL

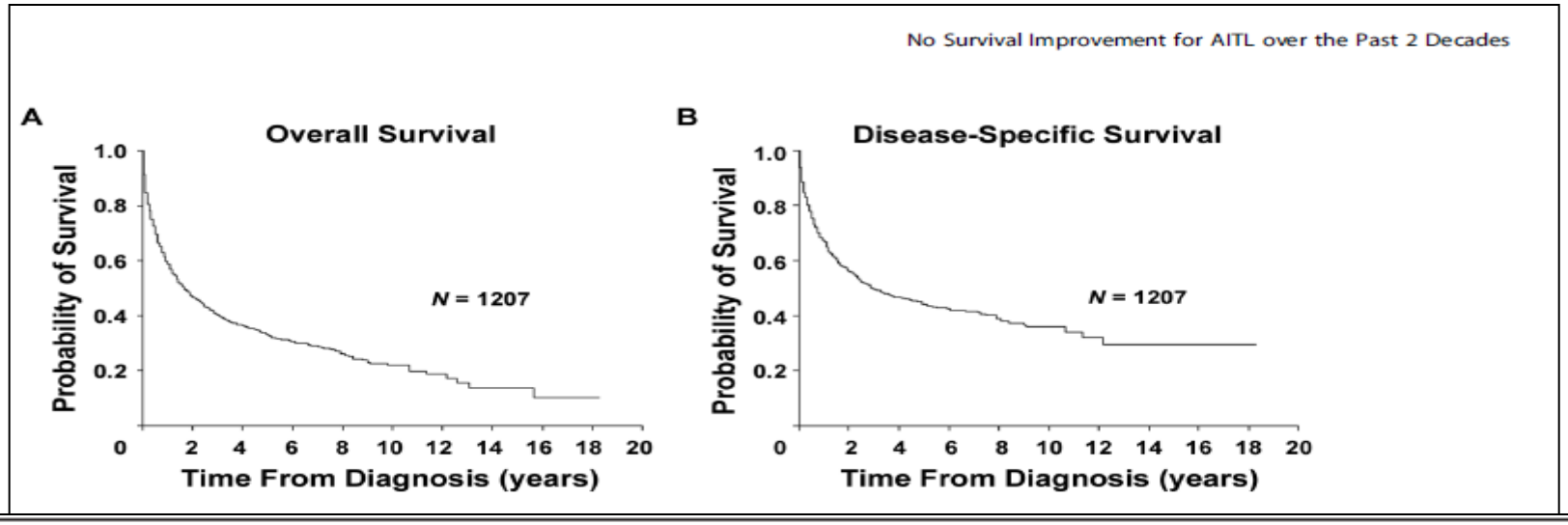
Ranjana Advani MD

Professor of Medicine/Oncology

Stanford University Medical Center



SEER Data
No Survival Improvement for AITL over the past 2 decades



Characteristic	Overall Survival			Disease-Specific Survival		
	2 Year, % (95% CI)	5 Year, % (95% CI)	10 Year, % (95% CI)	2 Year, % (95% CI	5 Year, % (95% CI)	10 Year, % (95% CI)
Year of diagnosis						
1992–1998	44.6 (34.7 to 53.9)	28.7 (20.3 to 37.7)	15.8 (9.5 to 23.6)	53.1 (42.5 to 62.7)	41.7 (31.2 to 51.8)	25.4 (16.2 to 35.6)
1999–2001	51.2 (42.2 to 59.5)	35.4 (27.2 to 43.7)	26.0 (18.7 to 33.8)	60.4 (50.8 to 68.7)	46.7 (37.2 to 55.8)	43.3 (33.7 to 52.5)
2002–2004	42.7 (36.4 to 48.9)	27.8 (22.3 to 33.6)	NR	55.2 (48.3 to 61.5)	41.6 (34.7 to 48.4)	NR
2005–2007	48.9 (43.4 to 54.2)	37.7 (31.9 to 43.6)	NR	59.1 (53.2 to 64.5)	48.5 (41.9 to 54.8)	NR
2008–2010	45.1 (38.8 to 51.2)	NR	NR	51.2 (44.6 to 57.4)	NR	NR

Xu et al PLOS ONE 2014: Adverse #: Older age, advanced-stage disease and male sex

Is There a Specific Rx for Angioimmunoblastic T cell NHL

- Front line therapy
  - Should AILT be treated like PTCL-NOS?
  - Is there an optimal front line regimen?
- Relapsed disease
  - Is there an optimal agent ?

NCCN Guidelines Version 1.2015
Peripheral T-Cell Lymphomas

NCCN Guidelines Index
NHL Table of Contents
Discussion

STAGE | **INDUCTION THERAPY**

Consider prophylaxis for tumor lysis syndrome (See NHODG-B)

ALCL, ALK +

- **Stage I, II** → Multiagent chemotherapy[h] x 6 cycles ± ISRT (30–40 Gy) or Multiagent chemotherapy[h] x 3–4 cycles + ISRT (30-40 Gy)
- **Stage III, IV** → Multiagent chemotherapy[h] x 6 cycles

→ Relapse, See Additional Therapy (TCEL-4)

- PTCL, NOS
- ALCL, ALK -
- AITL[g]
- EATL

→ Stage I–IV → Clinical trial (preferred) or Multiagent chemotherapy[h] 6 cycles ± ISRT (30–40 Gy)

→ At completion of treatment, repeat all positive studies. If PET-CT scan positive, rebiopsy before changing course of treatment.

- Complete response[j] → Clinical trial or Consider high-dose therapy with stem cell rescue[k] or Observe
- Partial response or no response or progressive disease[j]

→ Relapse, See Additional Therapy (TCEL-4)

Breast implant-associated ALCL

- Emerging entity described as development of ALCL around the implant (involving the fibrous capsule and/or seroma only). In this setting, the natural history of this entity appears generally favorable with surgical removal of the implant alone as adequate therapy for most patients.
- However, rare cases with parenchymal breast or nodal involvement may have an aggressive course more in line with systemic ALCL ALK.
- Optimal treatment of these cases is not well defined and management should be individualized.

[g] For selected patients (elderly, comorbid conditions), a trial of single-agent corticosteroid may be considered for symptom management.

[h] See Suggested Treatment Regimens (TCEL-B).

[j] See Lugano Response Criteria for Non-Hodgkin's Lymphoma (NHODG-C).

[k] Localized areas can be irradiated before or after high-dose therapy.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

SUGGESTED TREATMENT REGIMENS[a]

First-line Therapy:

- Clinical trial[b]
- ALCL, ALK+ histology
  - CHOP-21 (cyclophosphamide, doxorubicin, vincristine, prednisone)
  - CHOEP-21 (cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone)
- Other histologies (ALCL, ALK-; PTCL, NOS; AITL; EATL), regimens that can be used include:
  - Preferred regimens (in alphabetical order)
    - CHOEP
    - CHOP-14
    - C
    - D
  - Alte
    - C
      m
    - H
      hi

First-lin

- Consi

Patient

[a] See refe
[b] While C
favorab
[c] CHOP f

Note: A
Clinical

Recommendations largely consensus based
No randomized trials

Other Issues:
Small number of pts
Most studies include all subtypes of PTCL
Outcomes specifically for AITL sparse

Front-line Anthracycline-Based therapy for PTCL Meta-Analysis: OS (Older Series 1999-2005)

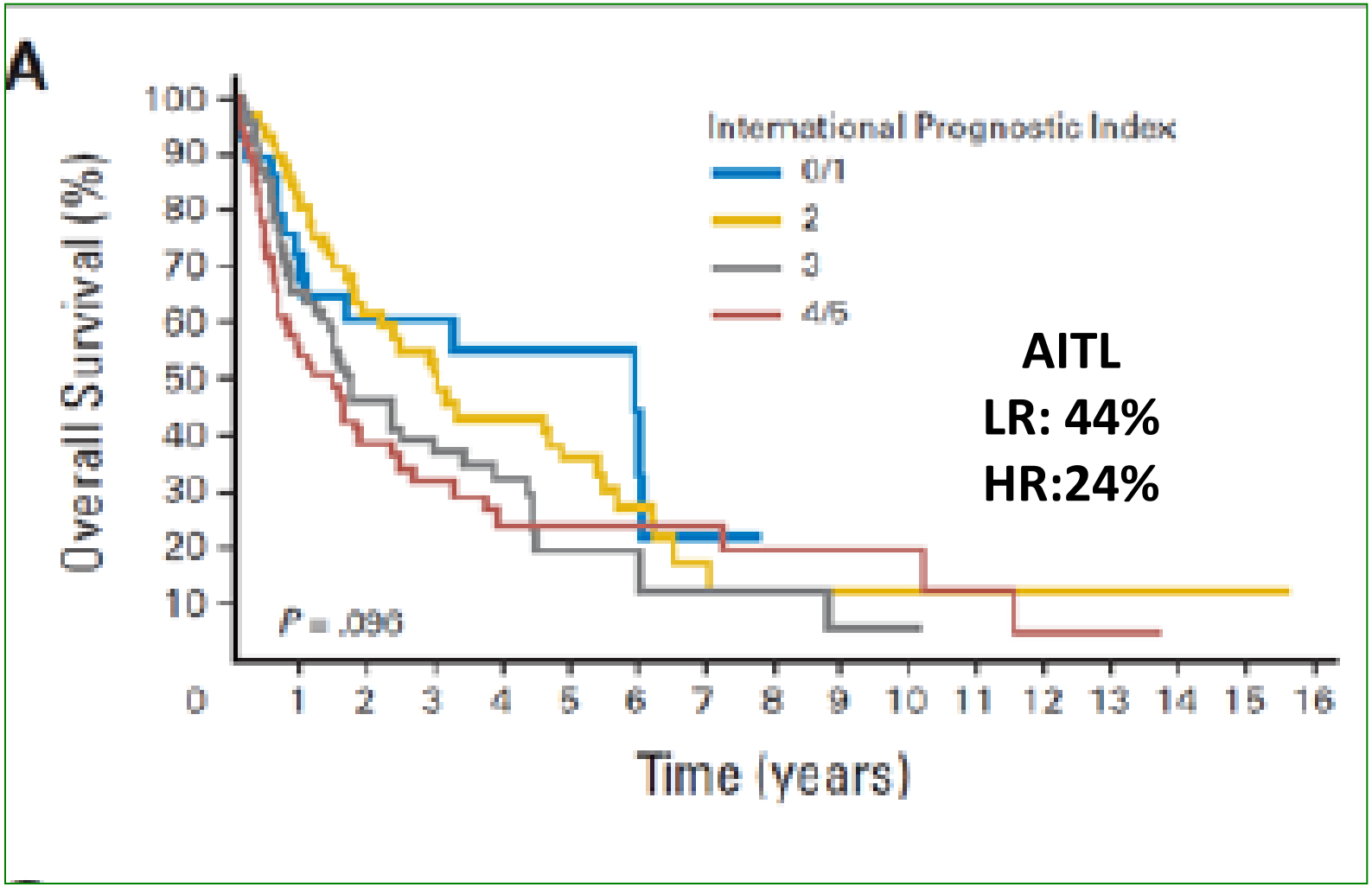
PTCL subgroup	Study, year		5-year OS rate	95% CI		5-year OS rate and 95% CI
AITL	Pautier et al., 1999 [24]		0.360	0.217	0.534	
	Savage et al., 2004 [32]		0.360	0.134	0.672	
	Sonnen et al., 2005 [36]		0.280	0.155	0.451	
	Vose et al., 2008 [1]		0.320	0.264	0.381	
	AITL summary estimate	Fixed	0.321	0.272	0.375	
		Random	0.321	0.272	0.375	
ALCL	Gisselbrecht et al., 1998 [4]		0.640	0.512	0.751	
	Savage et al., 2004 [32]		0.430	0.275	0.600	
Non-ALCL PTCL	Gisselbrecht et al., 1998 [4]		0.350	0.291	0.414	
	Rudiger et al., 2002 [29]		0.260	0.182	0.357	
PTCL-NOS	Savage et al., 2004 [32]		0.350	0.269	0.440	
	Sonnen et al., 2005 [36]		0.450	0.338	0.567	
	Vose et al., 2008 [1]		0.320	0.273	0.371	
PTCL combined	Karakas et al., 1996 [13]		0.480	0.303	0.663	
	Kim et al., 2002 [27]		0.526	0.415	0.633	
	Reiser et al., 2002 [28]		0.550	0.429	0.665	

Older studies with CHOP/like therapy (most pts rx prior to 2000):
5y OS ~ 32%

Estimated 5 Y OS ~ 32 % (95% CI 27%, 38%)

AbouYabis AN et al. ISRN Hematol. 2011

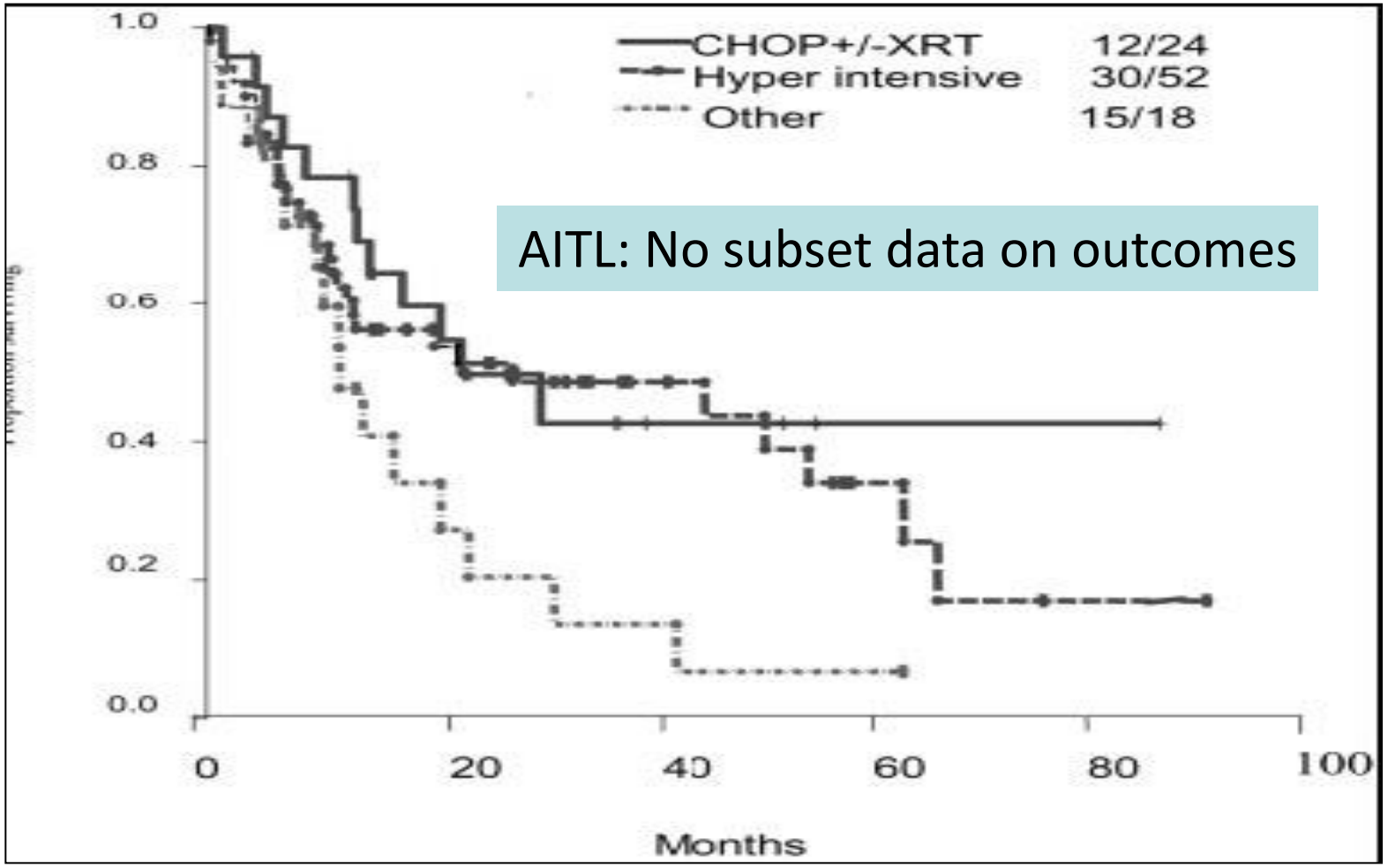
AITL: Outcome (5y OS) Varies According To Risk



Federico M: J Clin Oncol 2012

PTCL: CHOP versus Intensive Regimes

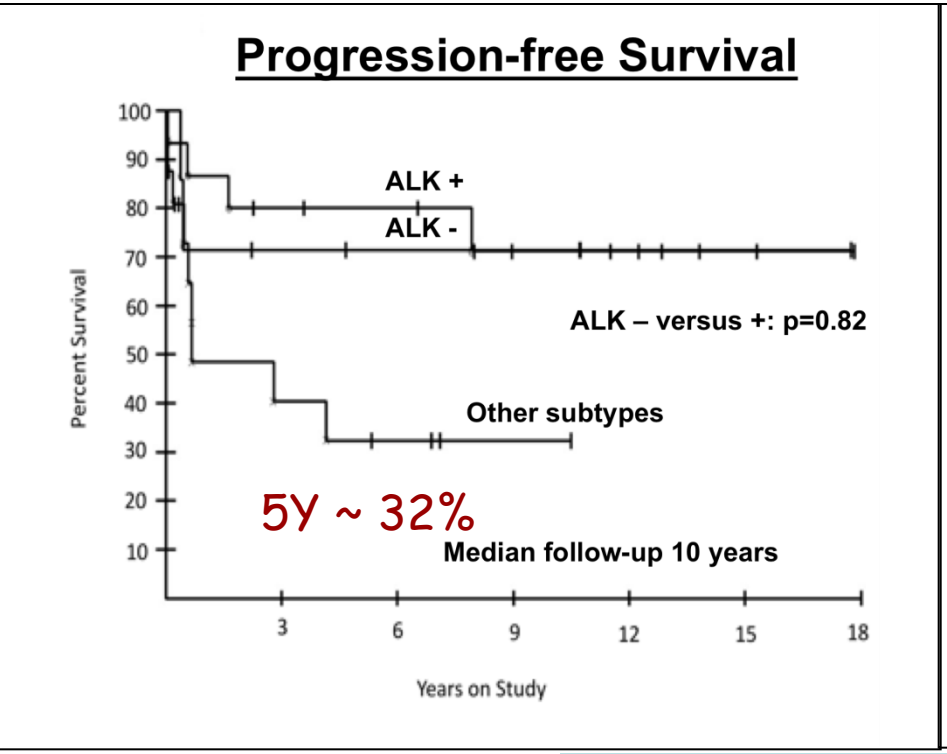
MD Anderson Experience

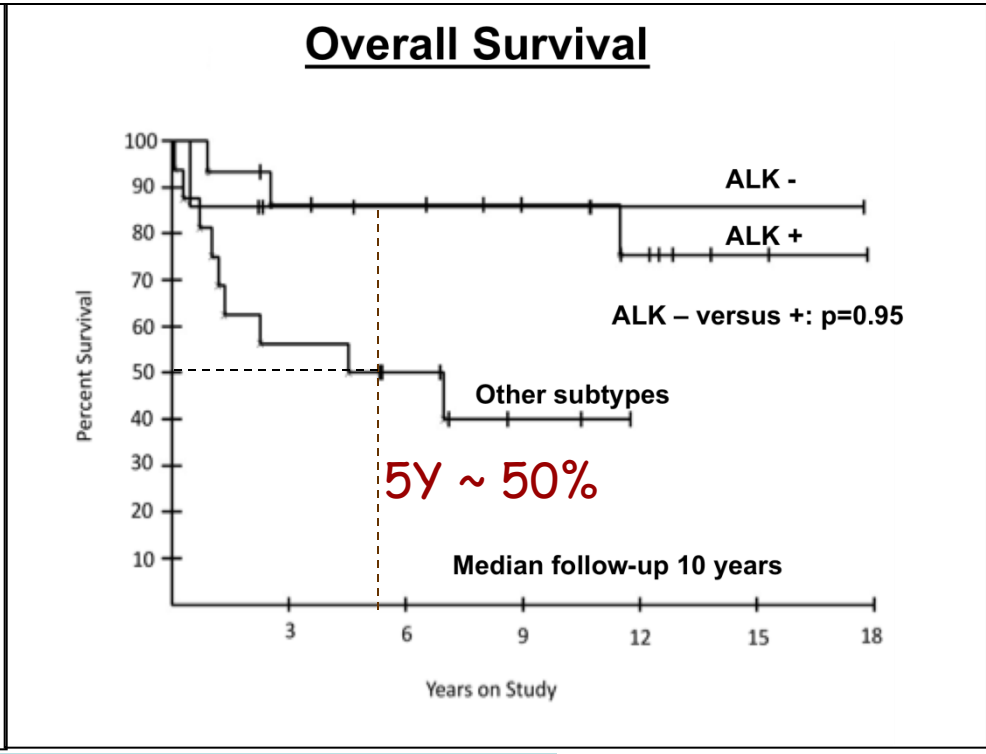


Escadon et al, Cancer 2005

Phase 2 study of Dose Adjusted EPOCH in PTCL

Patients Rx 1999-2009



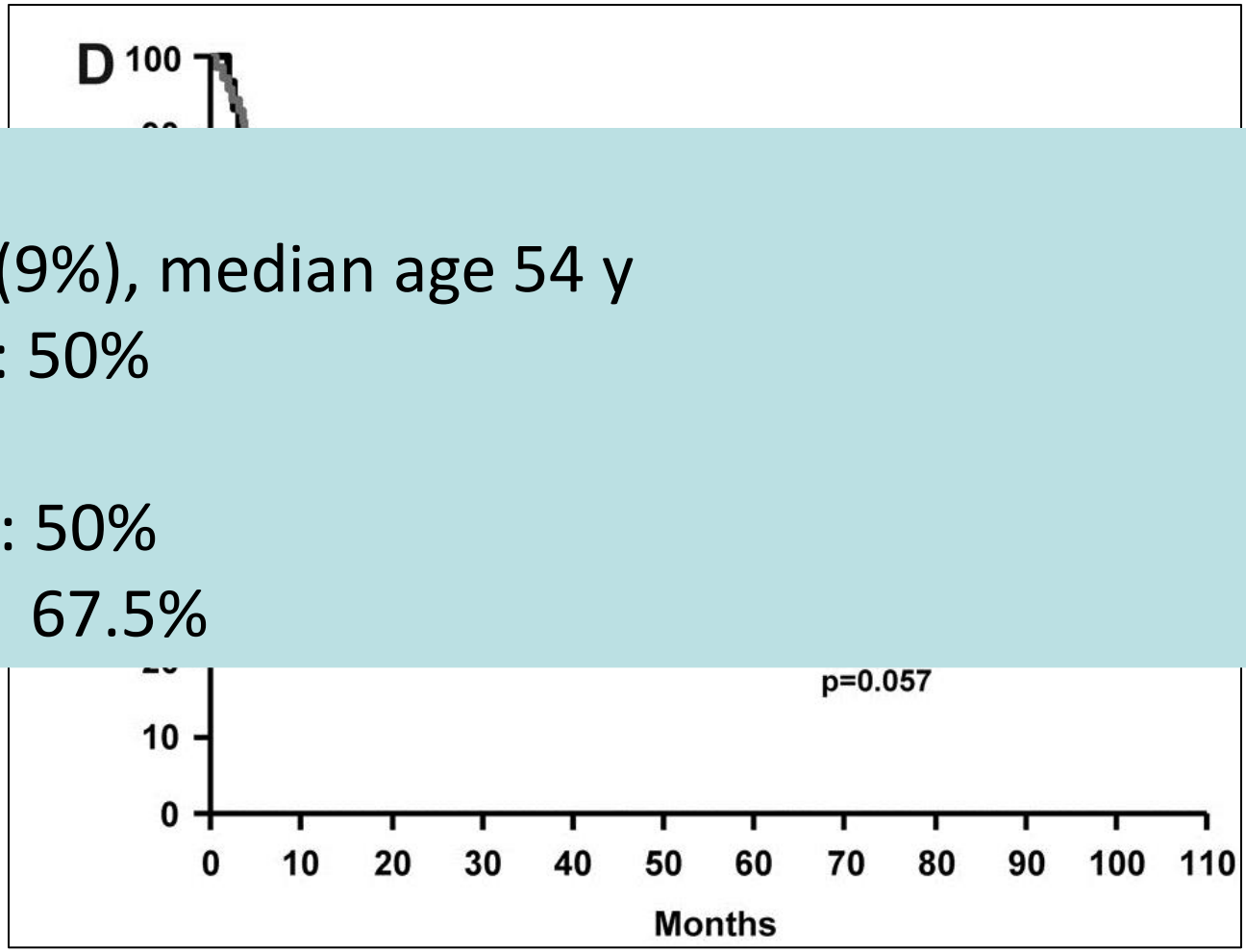


AITL: No subset data on outcomes

DunLeavey et al ASH 2011

German High-Grade NHL Study Group: CHOEP

EFS of younger patients (18-60 years, LDH ≤ UNL).



AITL:
n= 28 (9%), median age 54 y
IPI > 2: 50%

3y EFS: 50%
3y OS: 67.5%

Schmitz N et al. Blood 2010

Multicentre Phase II Study of the CycloBEAP regimen for patients with PTCL

AITL:

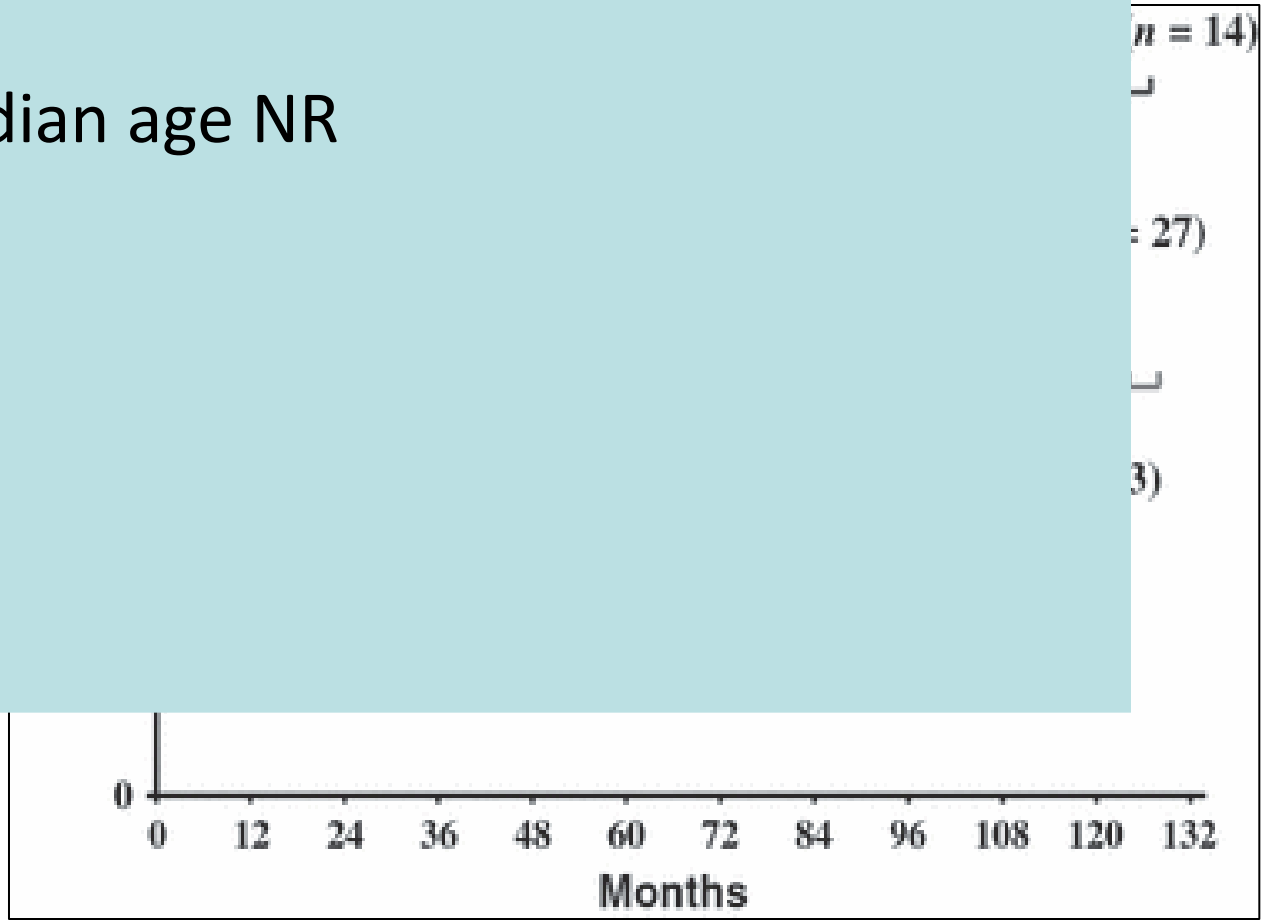
n= 27 (32%), median age NR

IPI > 2: NR

CR rate: 53%

3y EFS/PFS NR

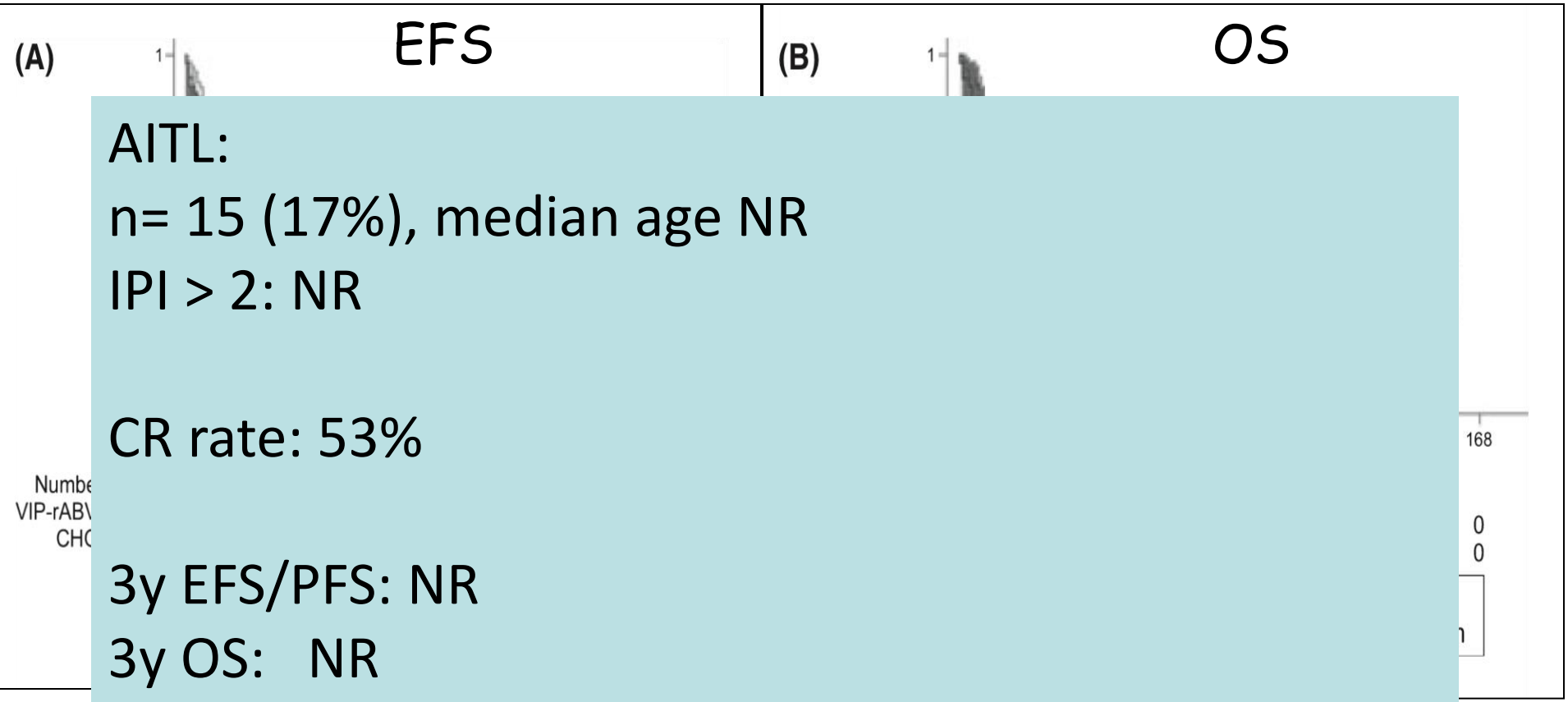
5y OS 74%



Niitsu N et al. Br J Haematology 2011

VIP reinforced ABVD versus CHOP/21 in newly diagnosed PTCL: Randomized phase III trial GOELAMS-LTP95

VIP= Etoposide, Ifosfamide and cisplatinum



AITL:

n= 15 (17%), median age NR

IPI > 2: NR

CR rate: 53%

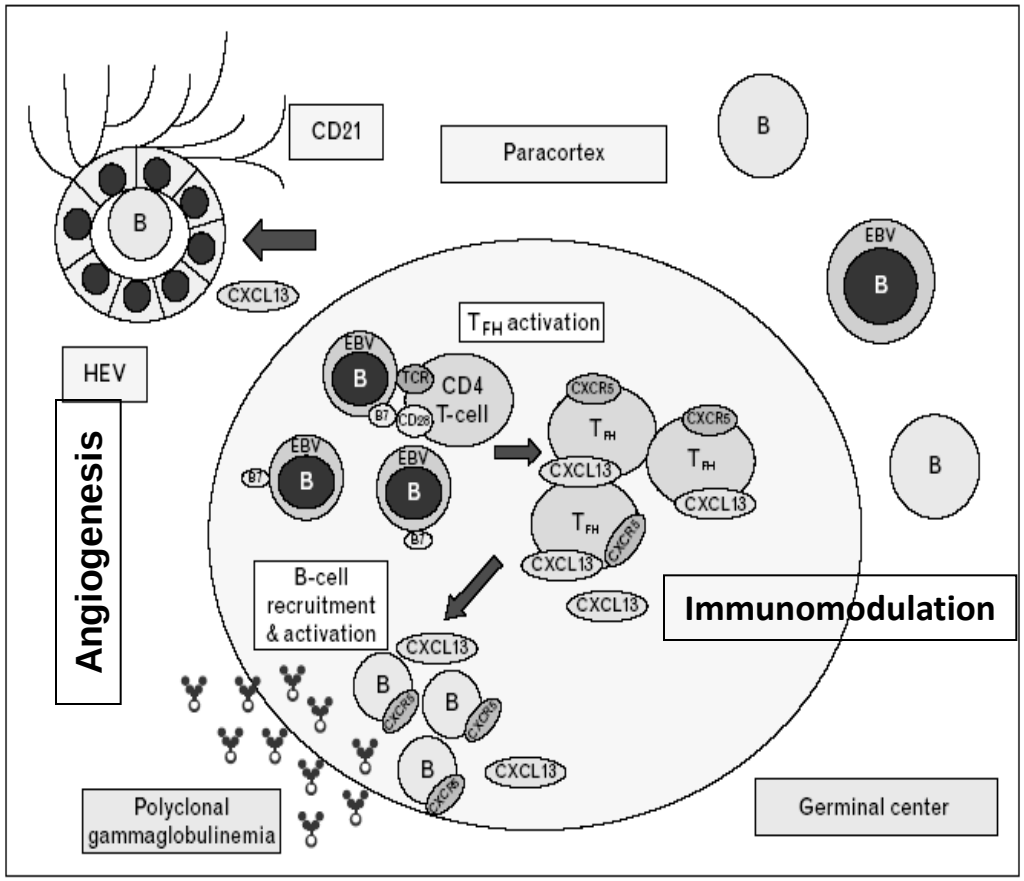
3y EFS/PFS: NR

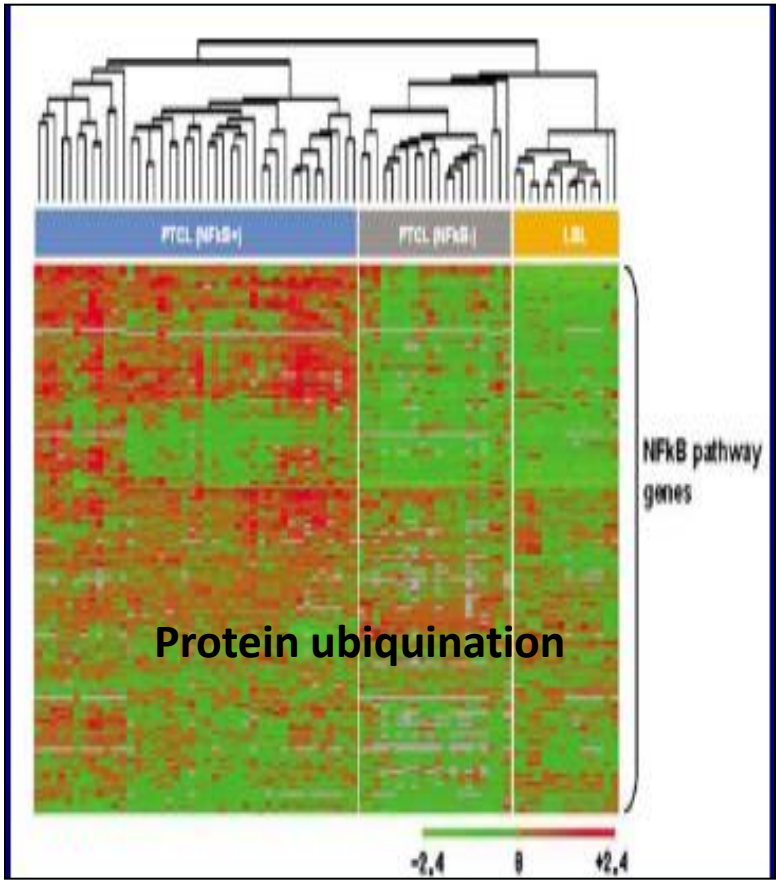
3y OS: NR

Simon et al. Br J Haem 2010

No improvement and increased toxicity.

Angioimmunoblastic T-cell Lymphoma
Novel targets for Intervention



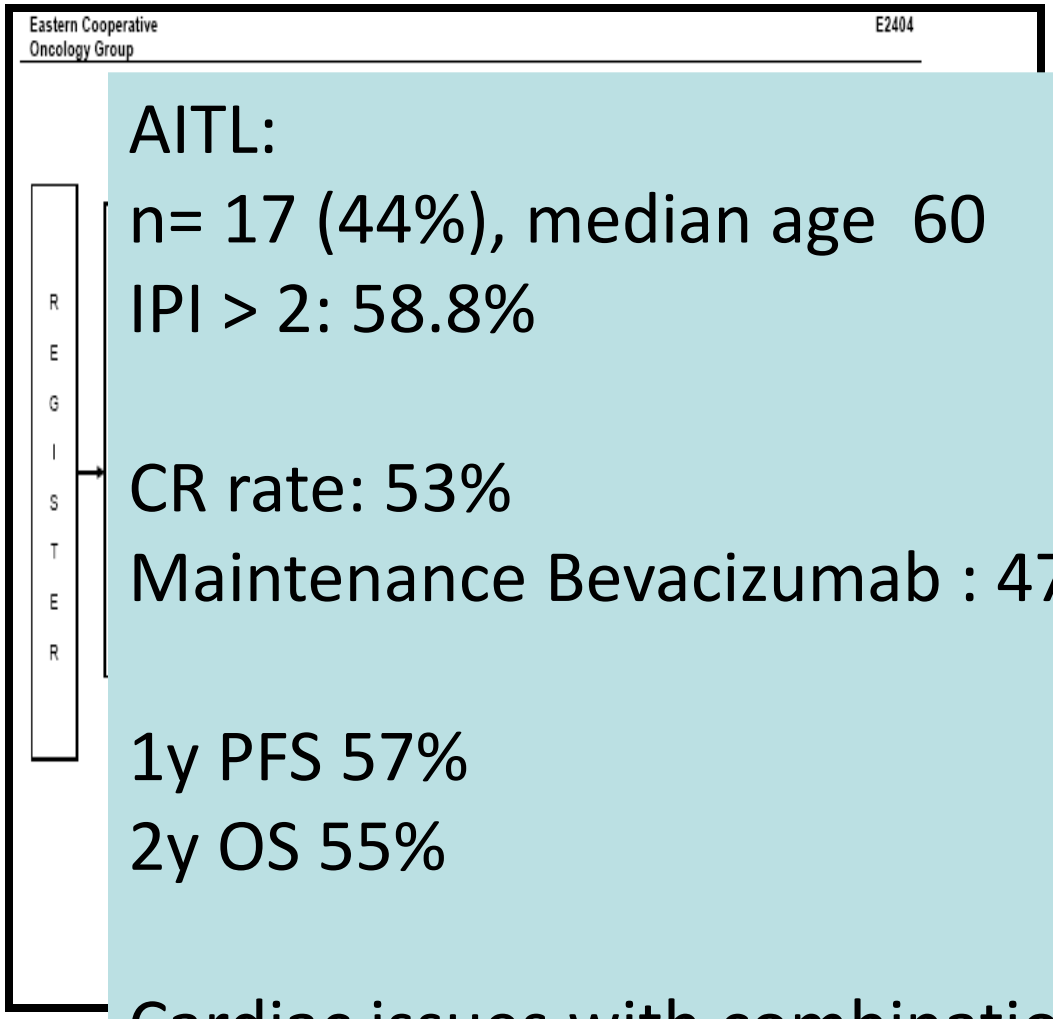


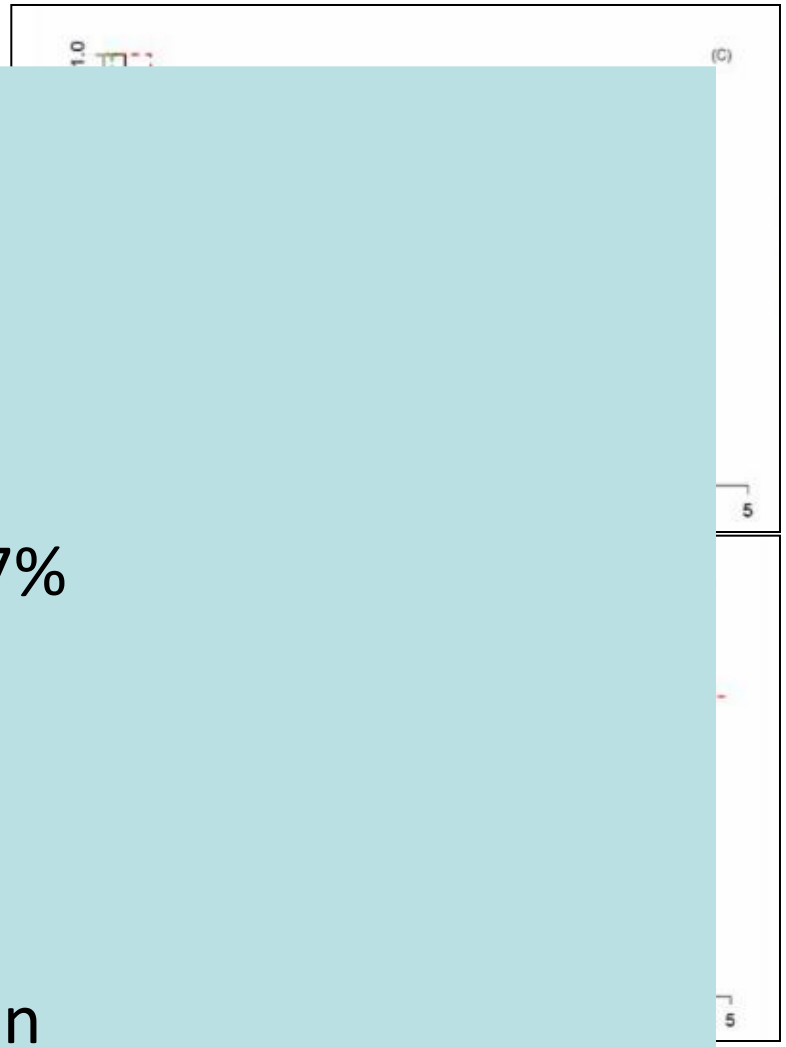
Dunleavy et al Curr Opin Hematol 2007

Martinez Delgado Leukemia 2005

Phase II study of Bevacizumab and CHOP (A-CHOP) for PTCL

ECOG 2404





AITL:

n= 17 (44%), median age 60

IPI > 2: 58.8%

CR rate: 53%

Maintenance Bevacizumab : 47%

1y PFS 57%

2y OS 55%

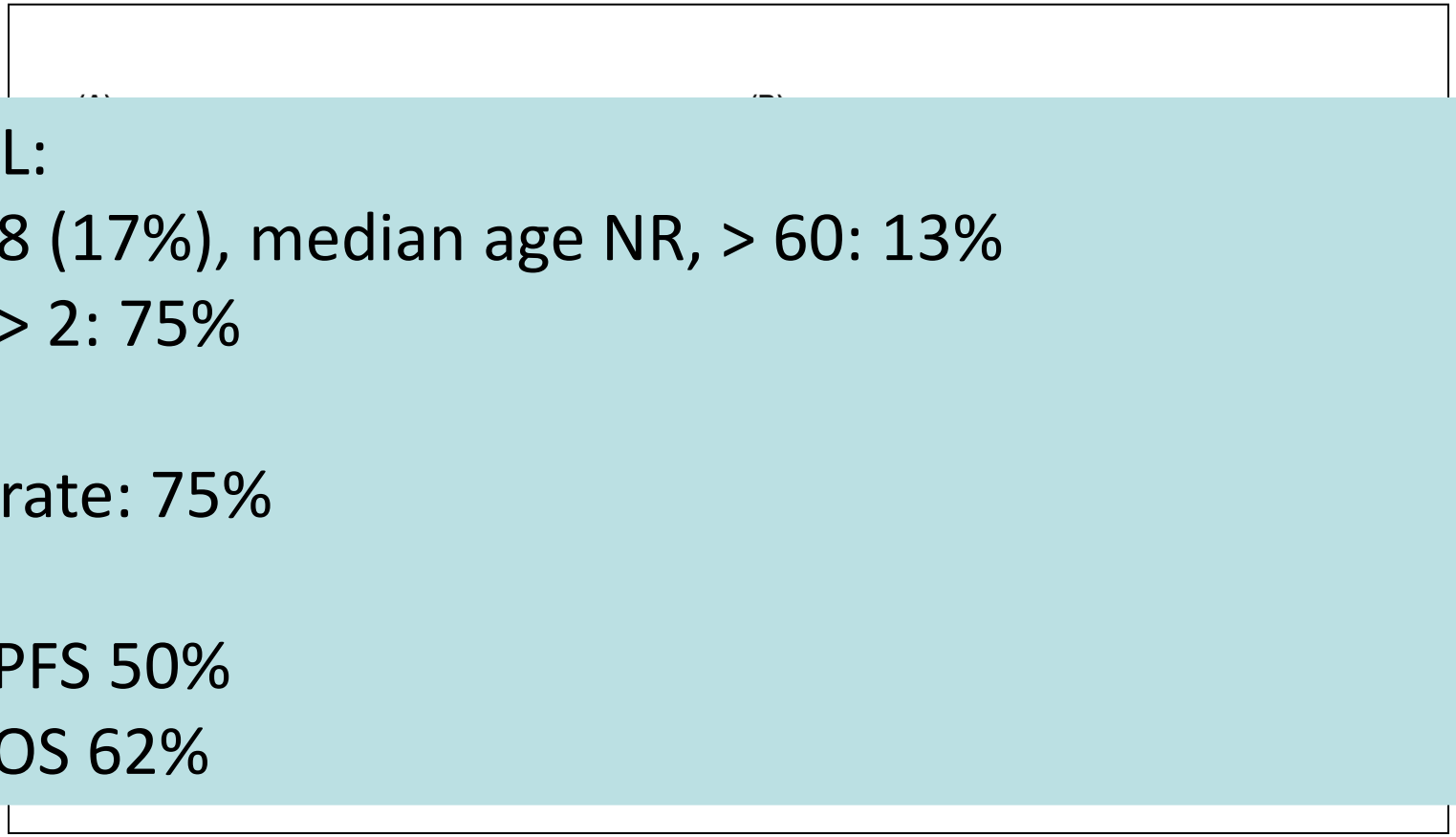
Cardiac issues with combination

cardiac issues. Advanl BJH 2011

Ganjoo BJH 2014

Bortezomib+CHOP in PTCL

CHOP: Standard q 21 days, Bortezomib: 1.8 mg/m2 d 1 and 8



AITL:
n= 8 (17%), median age NR, > 60: 13%
IPI > 2: 75%

CR rate: 75%

3y PFS 50%
3y OS 62%

Kim SJ et al Eur J Ca 2012

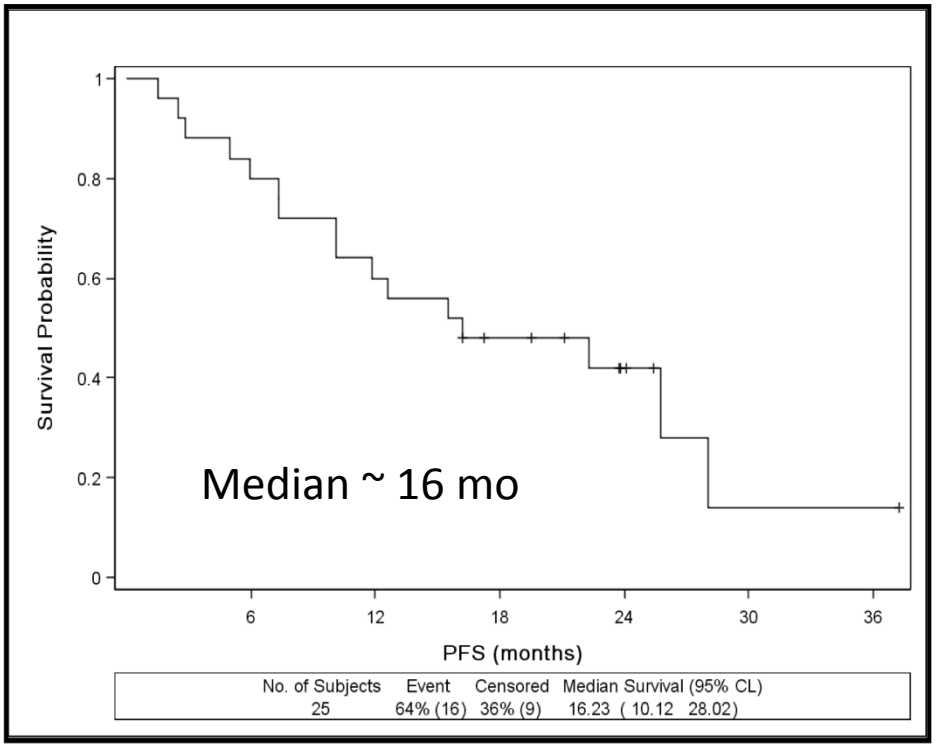
Targeting intratumoral B-cells with Rituximab R+CHOP in AITL: GELA study

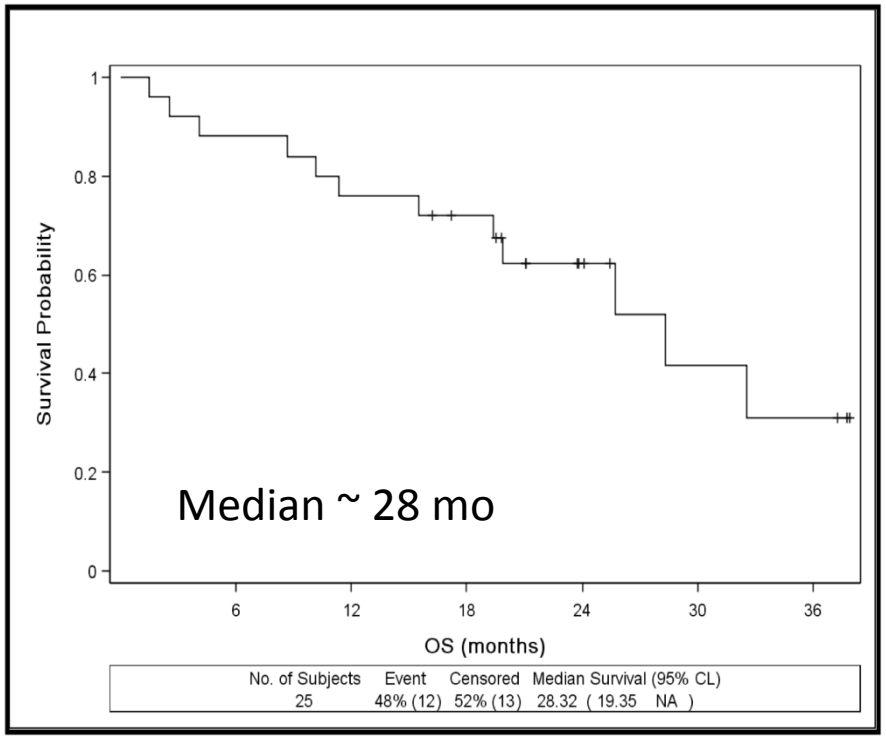
n=25, median age 66 y, IPI> 2: 76%, med fu 24 mo

2y PFS 42%

CR 44%,

2y OS 62%





Delfau-Larueet al. Haematologica 2012

Results: similar to CHOP alone

STAGE | **INDUCTION THERAPY**

Consider prophylaxis for tumor lysis syndrome (See NHODG-B)

ALCL, ALK +

- **Stage I, II** → Multiagent chemotherapy[h] x 6 cycles ± ISRT (30–40 Gy) or Multiagent chemotherapy[h] x 3–4 cycles + ISRT (30-40 Gy)
- **Stage III, IV** → Multiagent chemotherapy[h] x 6 cycles

→ Relapse, See Additional Therapy (TCEL-4)

- **PTCL, NOS**
- **ALCL, ALK -**
- **AITL**[g]
- **EATL**

→ **Stage I–IV** → Clinical trial (preferred) or Multiagent chemotherapy[h] 6 cycles ± ISRT (30–40 Gy)

→ At completion of treatment, repeat all positive studies. If PET-CT scan positive, rebiopsy before changing course of treatment.

- **Complete response**[j] → Clinical trial or Consider high-dose therapy with stem cell rescue[k] or Observe
- **Partial response or no response or progressive disease**[j]

→ Relapse, See Additional Therapy (TCEL-4)

Breast implant-associated ALCL →

- Emerging entity described as development of ALCL around the implant (involving the fibrous capsule and/or seroma only). In this setting, the natural history of this entity appears generally favorable with surgical removal of the implant alone as adequate therapy for most patients.
- However, rare cases with parenchymal breast or nodal involvement may have an aggressive course more in line with systemic ALCL ALK.
- Optimal treatment of these cases is not well defined and management should be individualized.

[g] For selected patients (elderly, comorbid conditions), a trial of single-agent corticosteroid may be considered for symptom management.

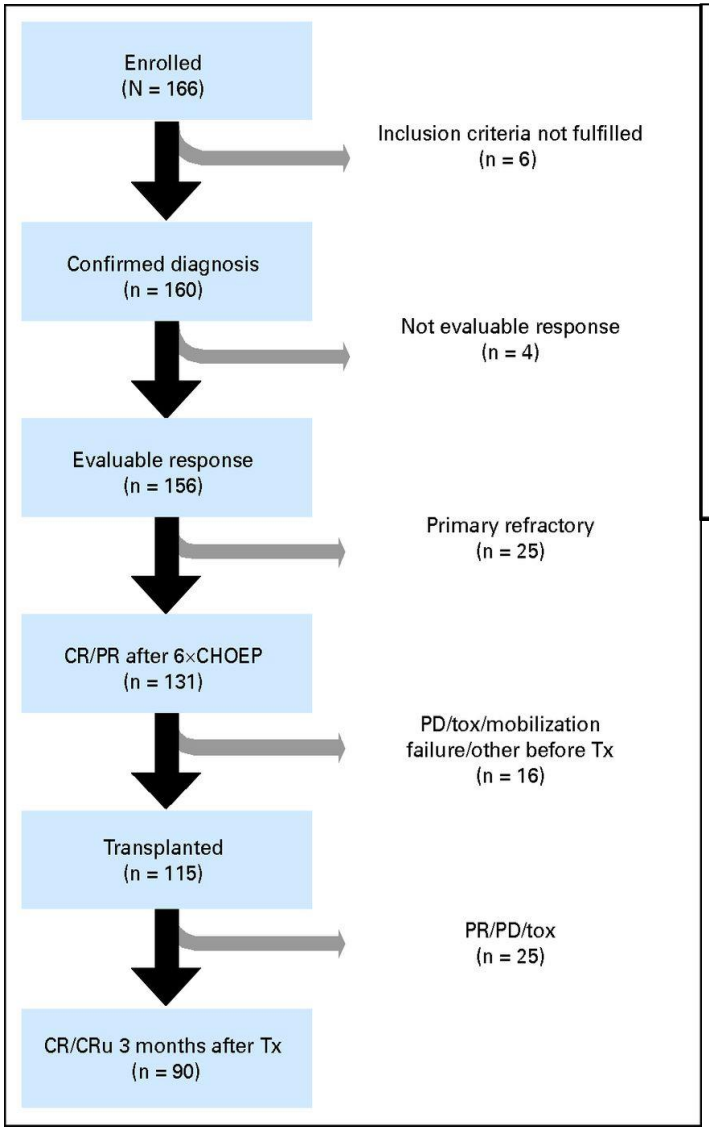
[h] See Suggested Treatment Regimens (TCEL-B).

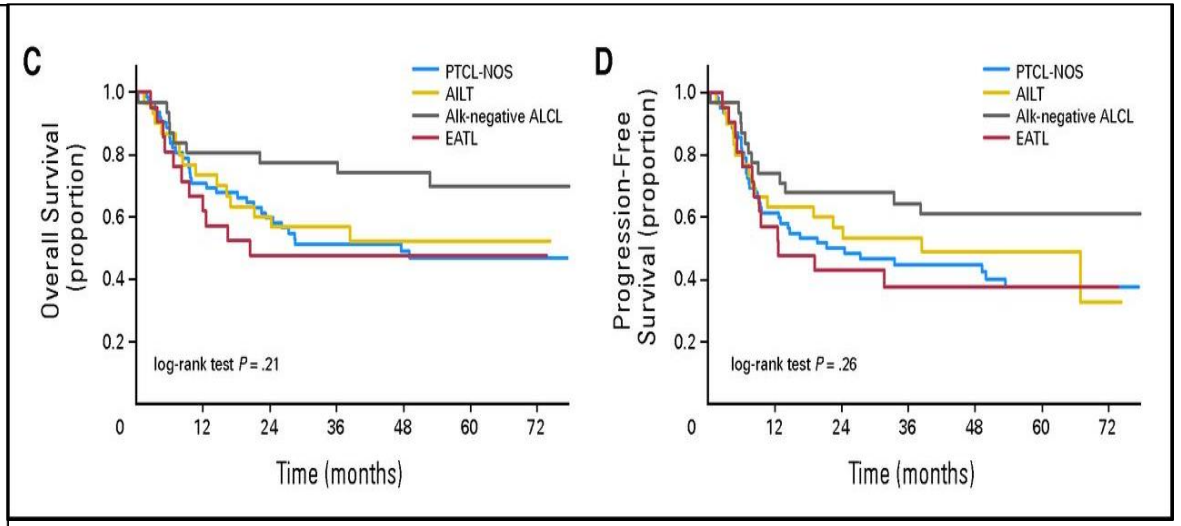
[j] See Lugano Response Criteria for Non-Hodgkin's Lymphoma (NHODG-C).

[k] Localized areas can be irradiated before or after high-dose therapy.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

NLG-T-01 (Nordic Lymphoma Group) study.





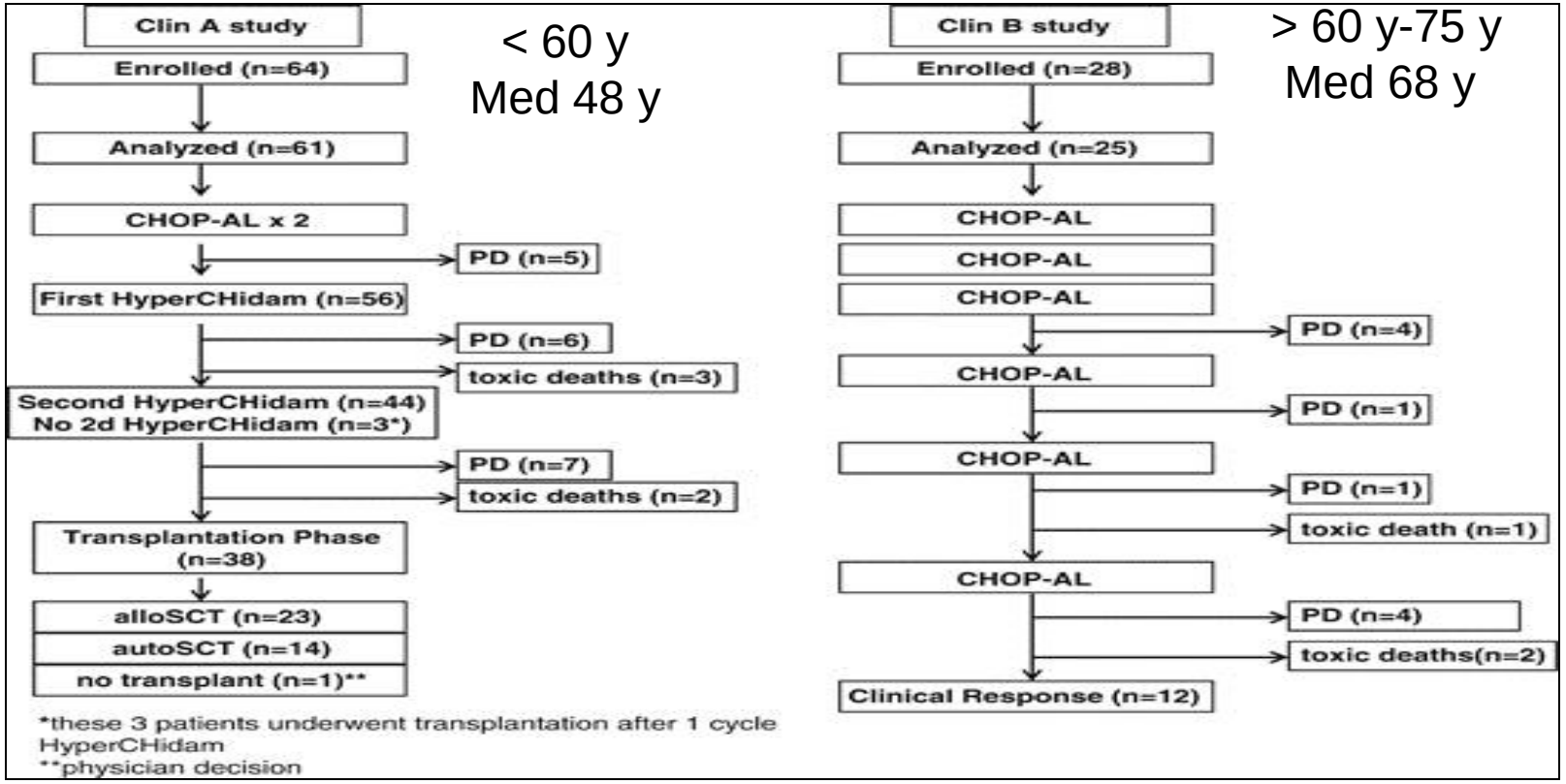
AITL:
n= 30 (19%), median age NR
IPI > 2: NR

CR rate: NR

3y PFS ~ 52%, median ~ 24 mo
3y OS ~ 55%, median ~ 30 mo

d'Amore F et al. JCO 2012

Phase 2 Study of Intensified Chemo-immunotherapy with or without SCT in newly diagnosed pts with PTCL



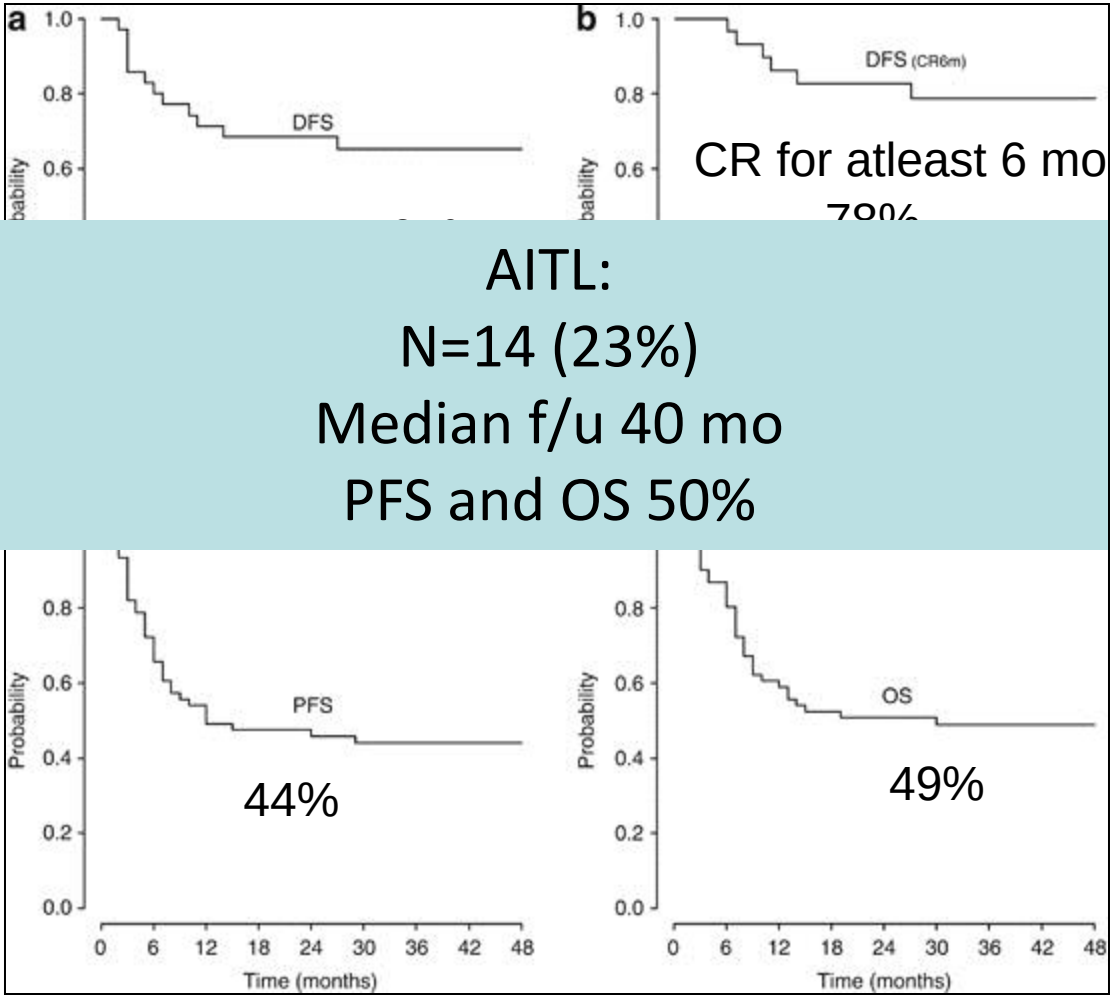
Alemtuzumab 30 mg

Alemtuzumab 10 mg

Arm B: AITL: 7(28%)
No details reported

Corradini et al Leukemia 2014

Results Arm A: Estimated 4 yr outcomes median follow up 40 mo, 62% received SCT



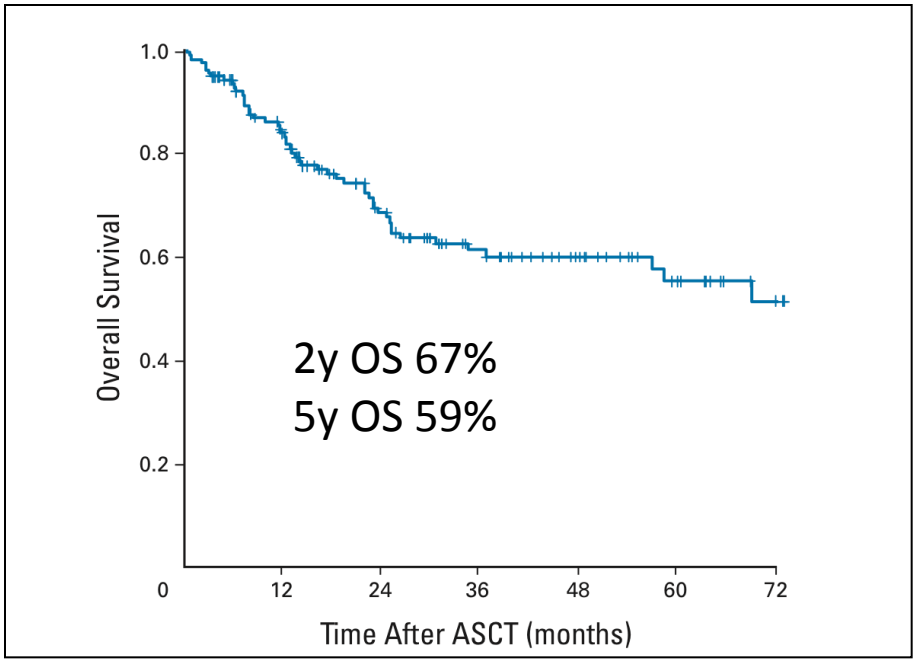
No diff auto vs allo
4 y OS 92% vs 69%
P=0.8
4 y PFS 70% vs 69%
P=0.9

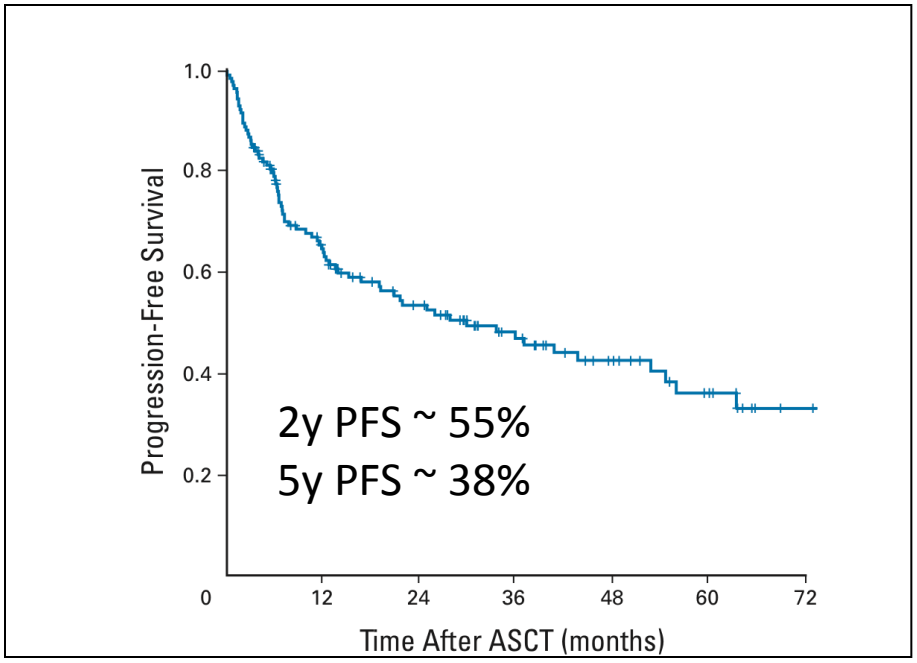
CMV 14%

Corradini et al Leukemia 2014

High-Dose Therapy and ASCT in AITL: European Group for Blood and Marrow Transplantation

N=146 (101 pts front line), 33% in CR, 36% PR at time of ASCT
Median age 53y, median fu 31 mo





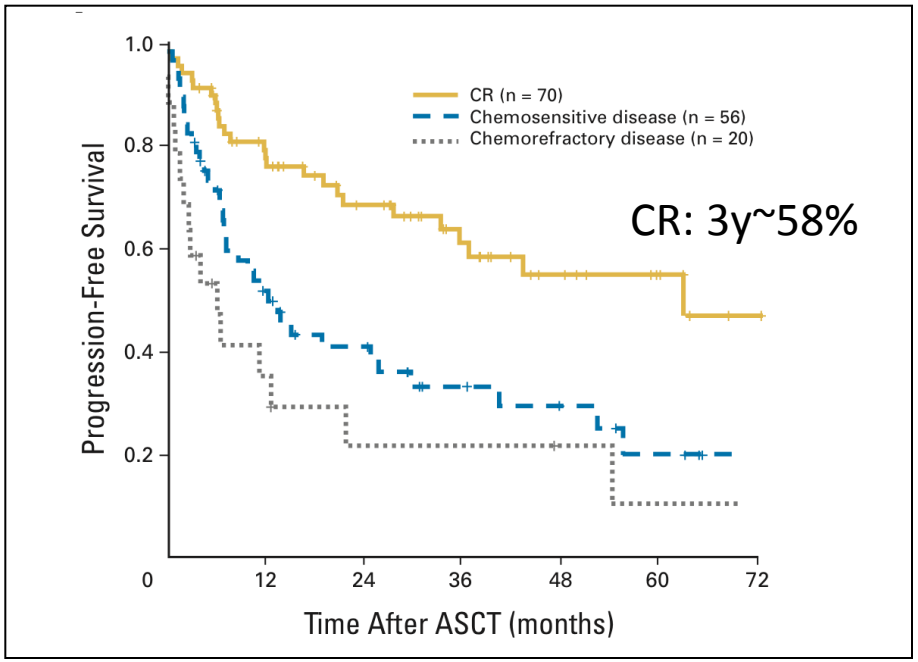
TBI containing regimens less relapse

Kyriakou et al. J Clin Onc 2008

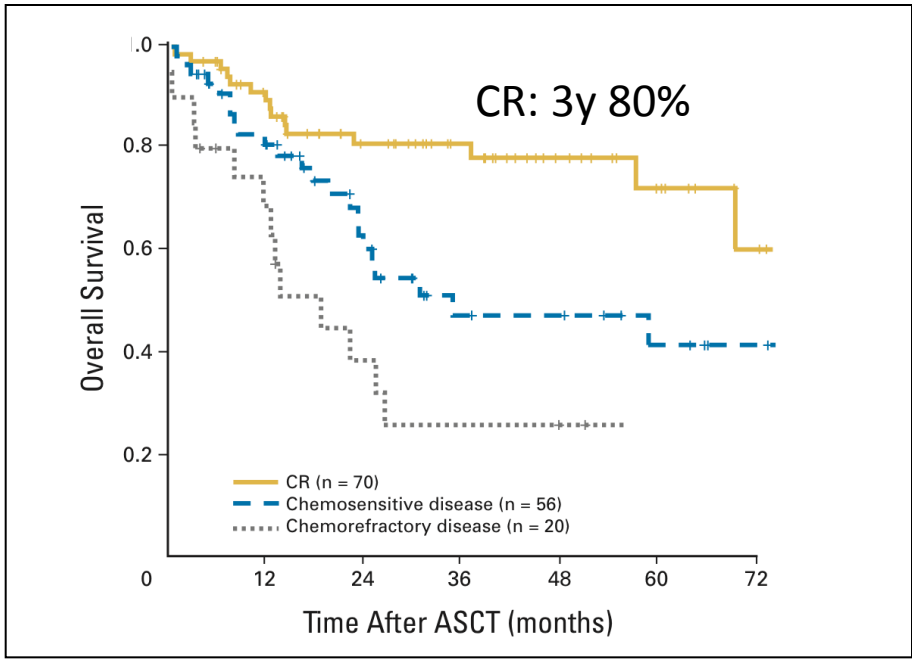
High-Dose Therapy and ASCT in AITL: European Group for Blood and Marrow Transplantation

CR at time of transplant most important determinant of outcome

PFS



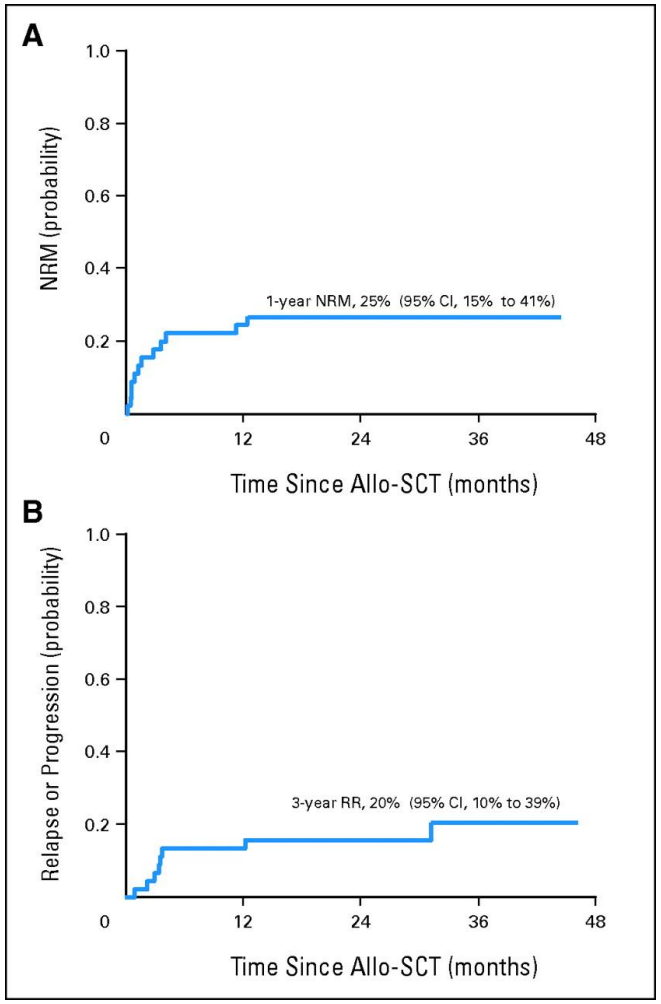
OS

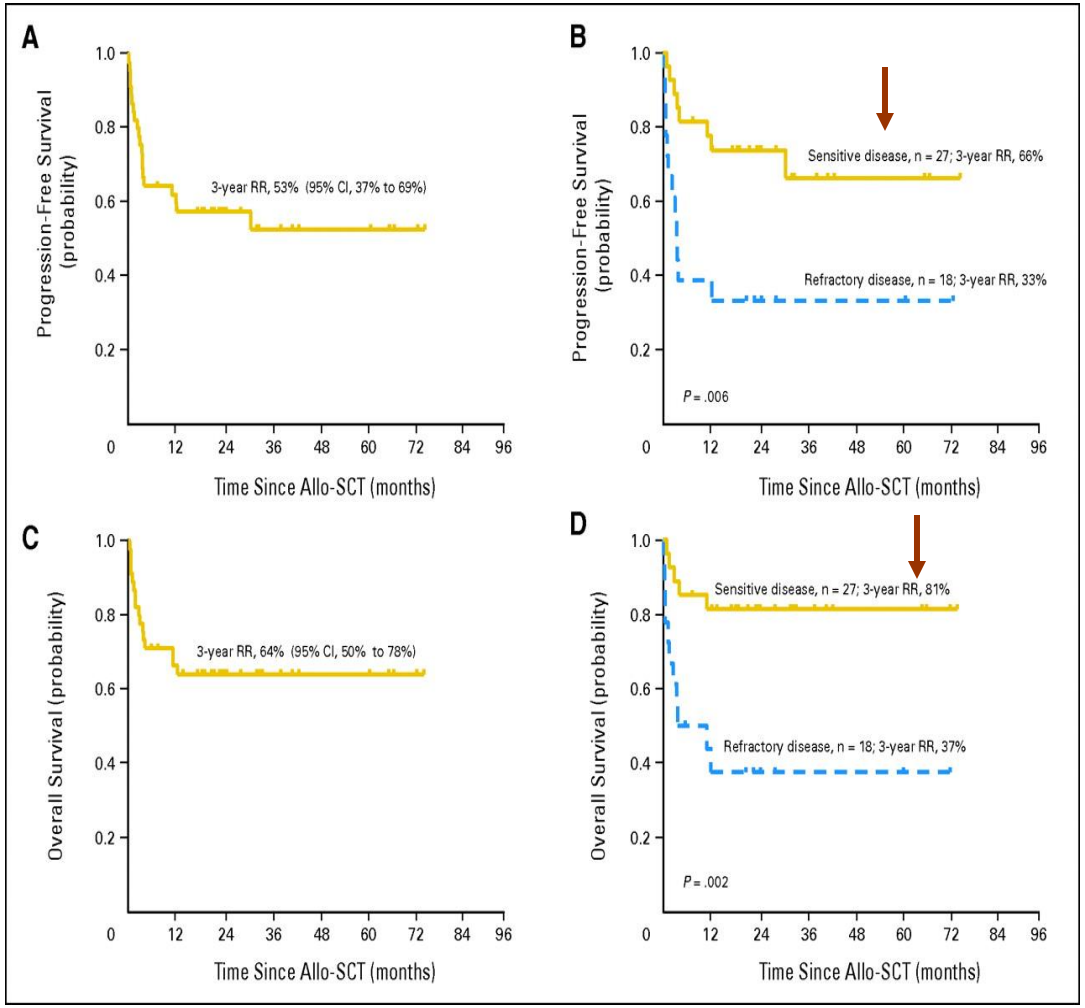


Kyriakou et al. J Clin Onc 2009

Allogenic Transplant in AITL: Retrospective EBMT

N= 45, ~27% CR 1





Kyriakou C et al. J Clin Oncol 2009

AITL: Summary of OS

Older studies
Rx pre 2000 for most pts

Study	% OS
Meta analysis	5y 30
Int T cell	5y 33

Recent studies
Rx post 2000 for most pts

Study	% OS
SEER (mainly CHOP)	3 yr ~33
RCHOP (GELA)	3y ~ 33
CHOEP	3y 67.5
CHOEP+ ASCT	3y 55
Bortezomib+CHOP	3 y 60
Bevacizumab+CHOP	2y 55
ASCT in CR	4y 60
Allo with chemosensitive disease	3y 81

Is there a specific Rx for Angioimmunoblastic T cell NHL

- Front line therapy
  - Should AILT be treated like PTCL-NOS?
    - Currently no data for different approach
  - Is there an optimal front line regimen?
    - Selected data support an etoposide containing regimen
    - Consolidation in first CR/PR slightly better results
      - ? Pt selection bias

SUGGESTED TREATMENT REGIMENS[a]
(in alphabetical order)

Second-line and Subsequent Therapy (intention to proceed to high-dose therapy):
- Clinical trial preferred
- Bendamustine
- Belinostat (category 2B)
- Brentuximab vedotin for systemic ALCL excluding primary cutaneous ALCL
- Brentuximab vedotin for systemic CD30+ PTCL
- DHAP (dexamethasone, cisplatin, cytarabine)
- ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin)
- Dose-adjusted EPOCH
- GDP (gemcitabine, dexamethasone, cisplatin)
- GemOx (gemcitabine, oxaliplatin)
- ICE (ifosfamide, carboplatin, etoposide)
- Pralatrexate[d]
- Romidepsin

Second-line and Subsequent Therapy (non-candidate for high-dose therapy):
- Clinical trial preferred
- Alemtuzumab
- Bendamustine
- Belinostat (category 2B)
- Bortezomib[e] (category 2B)
- Brentuximab vedotin for systemic ALCL excluding primary cutaneous ALCL
- Brentuximab vedotin for systemic CD30+ PTCL
- Cyclosporine for AITL only[f]
- Dose-adjusted EPOCH
- Gemcitabine
- Pralatrexate[d]
- Radiation therapy
- Romidepsin

See First-line Therapy on TCEL-B 1 of 3.

[a] See references for regimens TCEL-B 3 of 3.
[d] In AITL, pralatrexate has limited activity.
[e] Activity has been demonstrated in small clinical trials and additional larger trials are needed.
[f] With close follow-up of renal function.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

New Drugs in PTCL

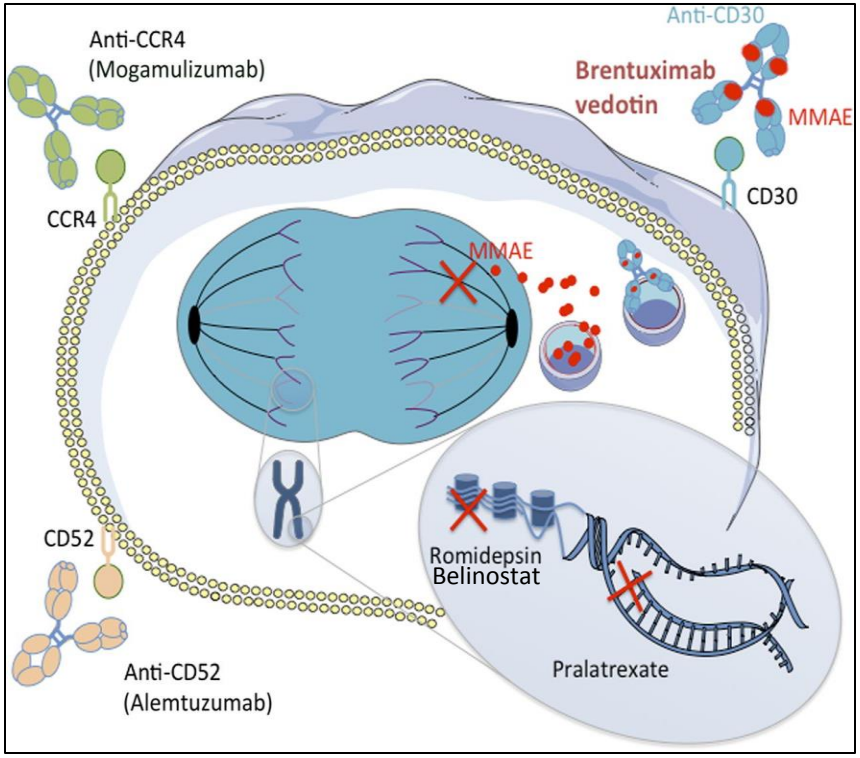


Table 5. Larger phase 2 studies of new agents with response by subtype

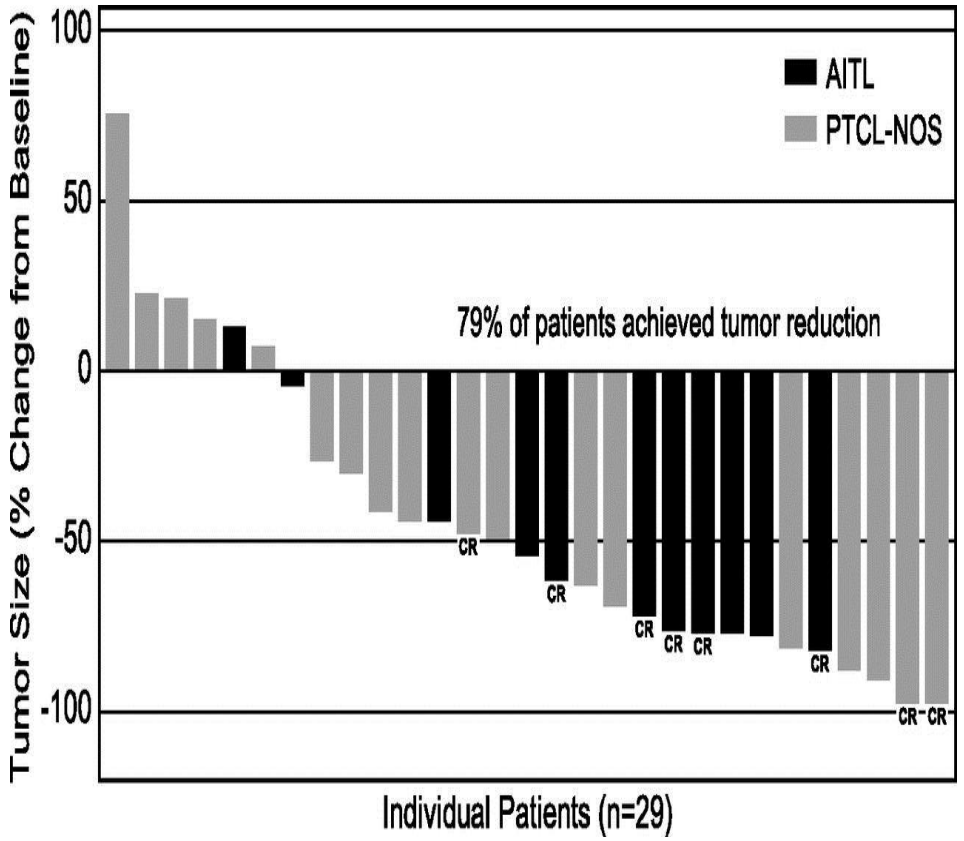
	Overall response rate by common subtype			
Subtype	Pralatrexate[28]	Romidepsin[27]	Belinostat[48,58]	Brentuximab vedotin[28,30]
PTCL-NOS	31%	29%	23%	33%
AITL	8%	30%	46%	54%
ALCL	29%	24%	15%	86%

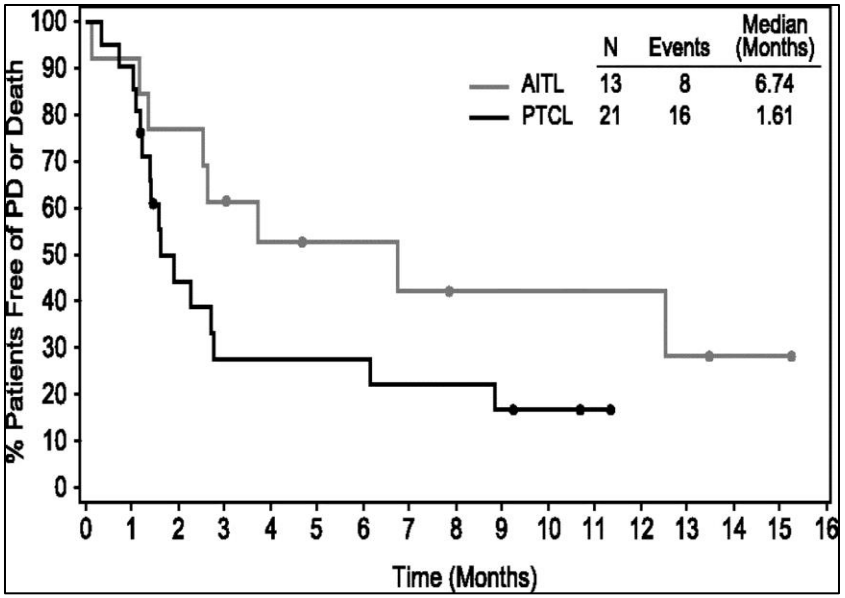
Bachy E , and Coiffier B Blood 2014

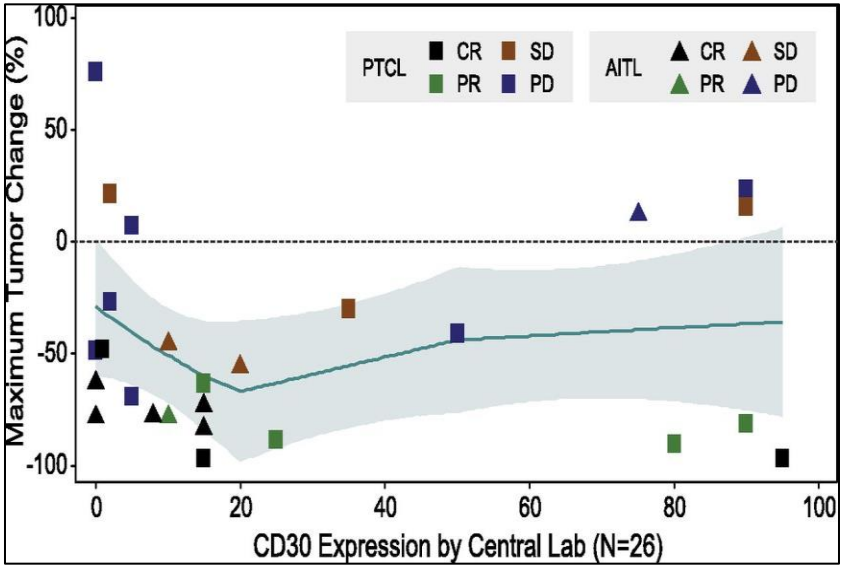
Horwitz et al Blood 2014

Brentuximab Vedotin: Response in CD 30 positive PTCL

Objective responses in relapsed AITL



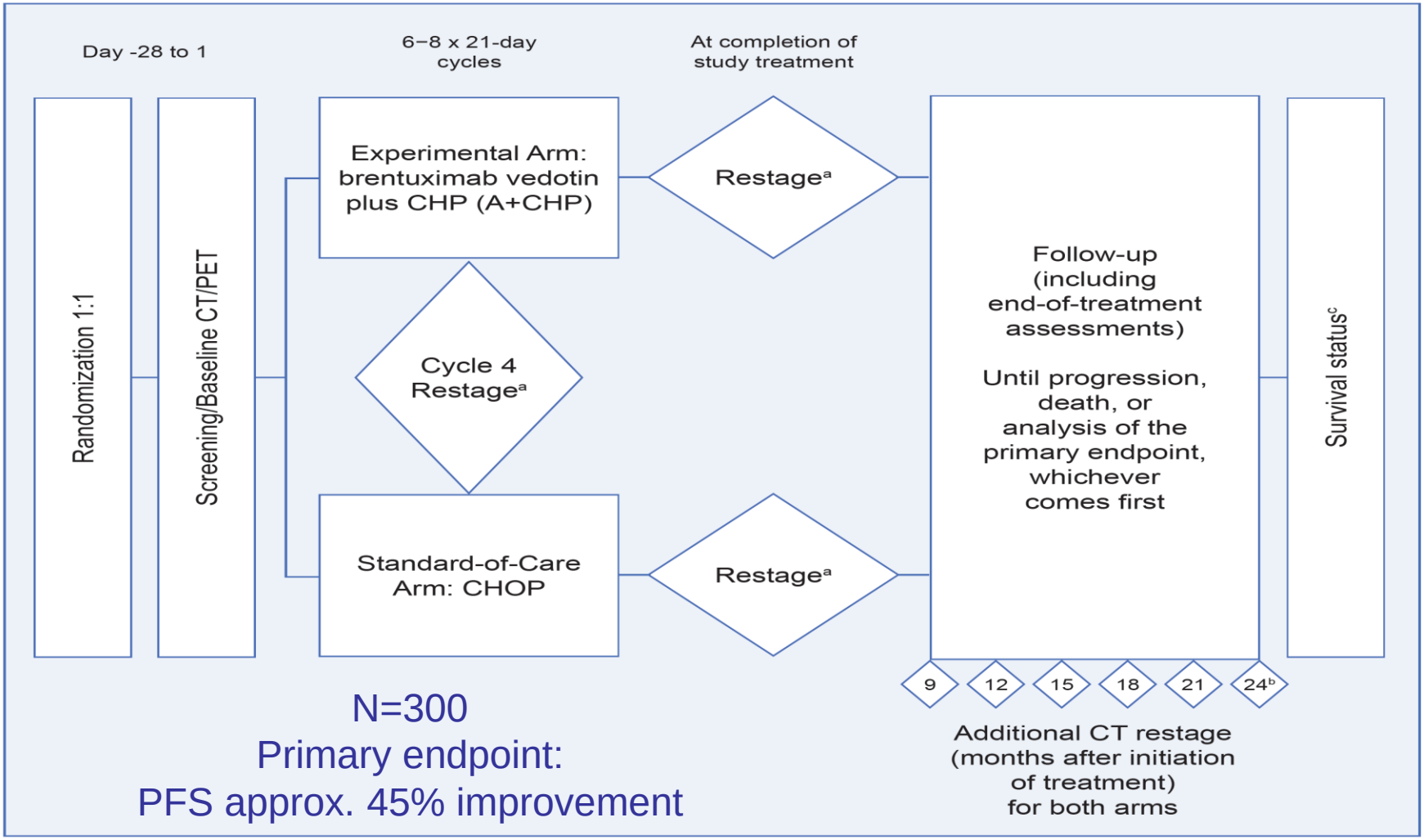




Horwitz S M et al. Blood 2014

Echelon-2 Trial

PTCL-CD30+ (≥ 10%)



a CT and PET scans required
b Additional CT scans every 6 months thereafter until progression per investigator, death, or analysis of the primary endpoint, whichever comes first
c For patients with documented progression, continued follow-up for survival every 6 months until death or study closure, whichever comes first

Recent Advances in AITL

Distribution of mutations in AITL.

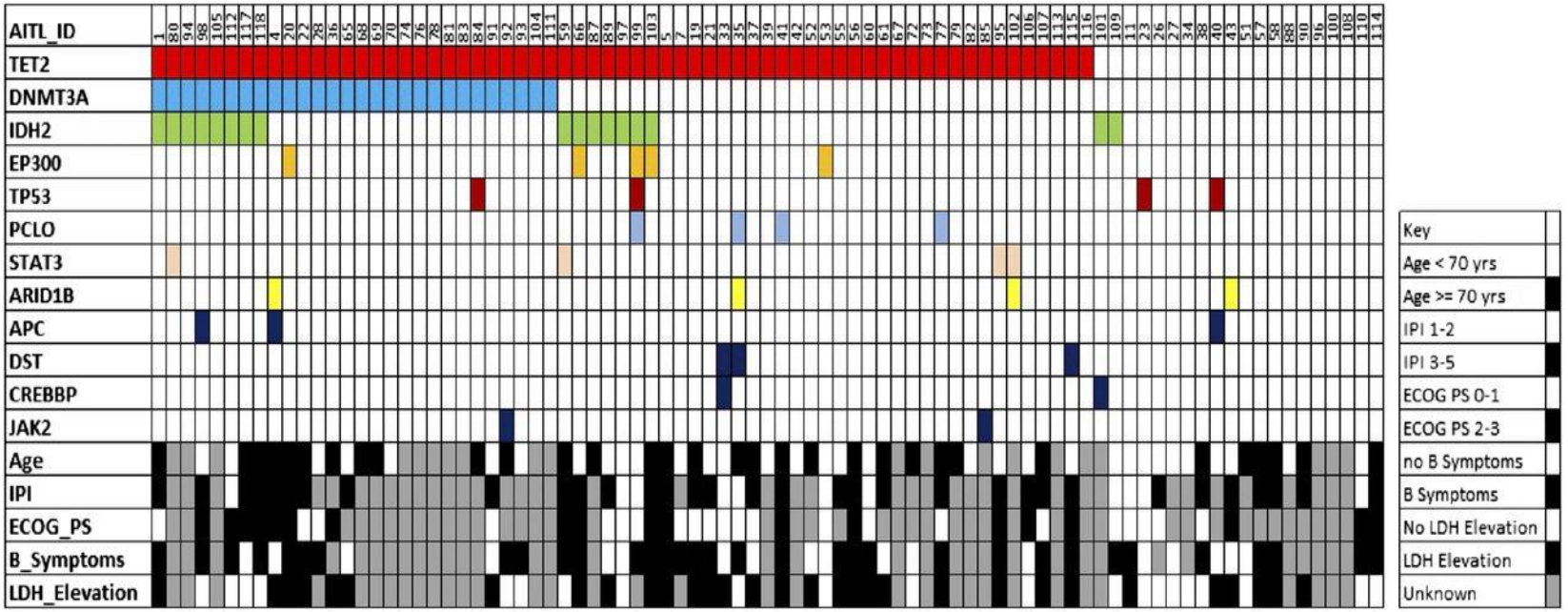


Table I. Summary of mutations in AITL.

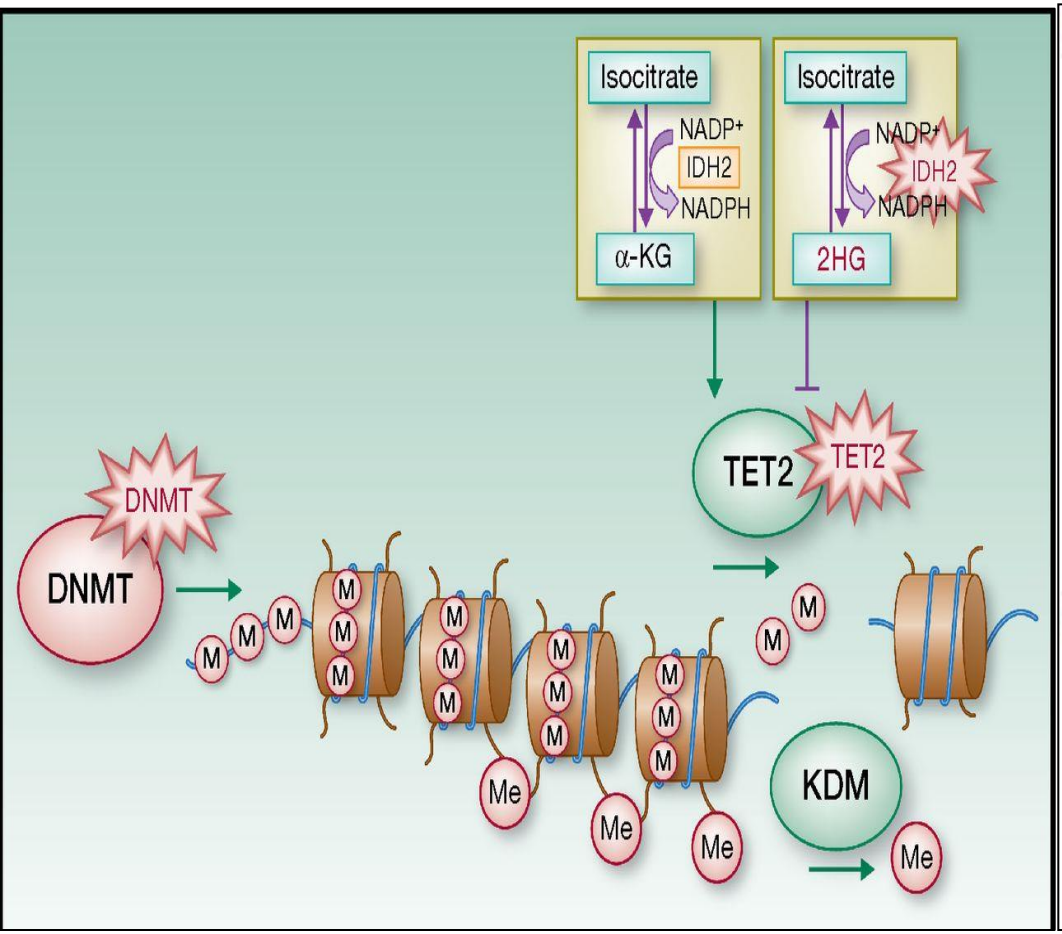
	Reference	% *TET2*	% *RHOA*	% *DNMT3A*	% *IDH2*	Total no. of cases
AITL	Palomero *et al* (2014)	47	67	–	–	35
	Sakata-Yanagimoto *et al* (2014)	82·6	70·8	26	30·4	72
	Odejide *et al* (2014)	76	–	33	20	85
	Cairns *et al* (2012)	–	–	–	20	79
	Yoo *et al* (2014)	–	53.3	–	–	45

Odejide O et al. Blood 2014;

Ahearne et al BJH 2014

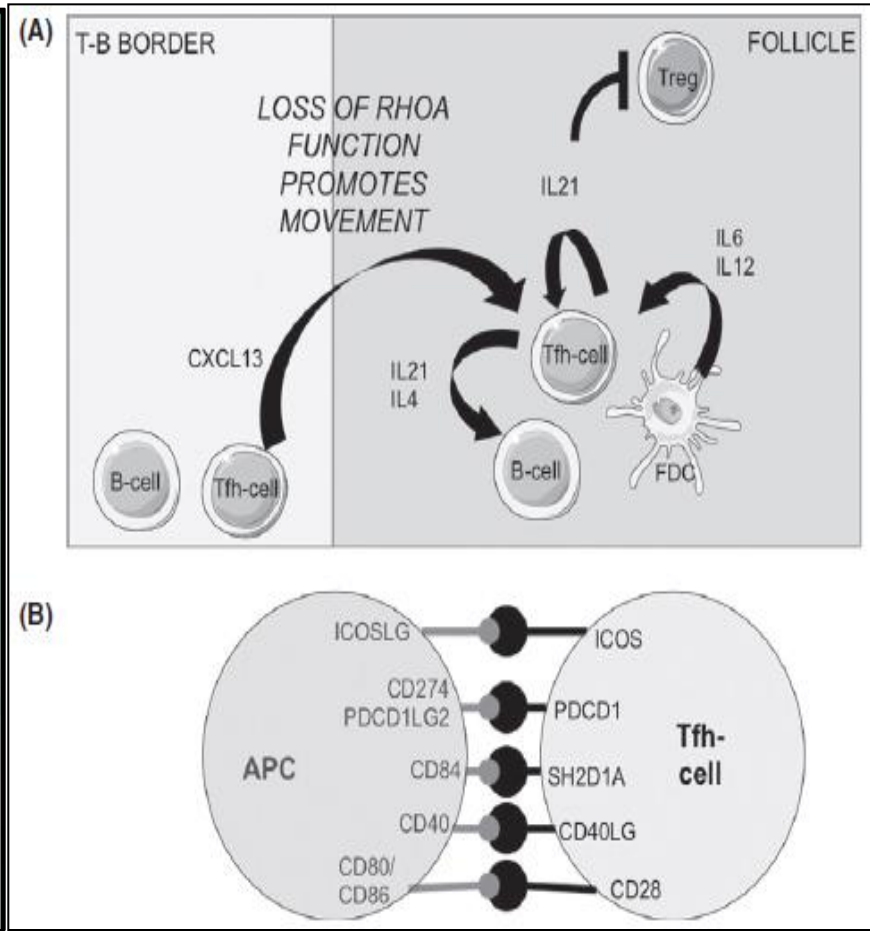
Impact of Mutations

Mutations in epigenetic genes in AILT affect DNA methylation.



O'Connor O A et al. Clin Cancer Res 2014

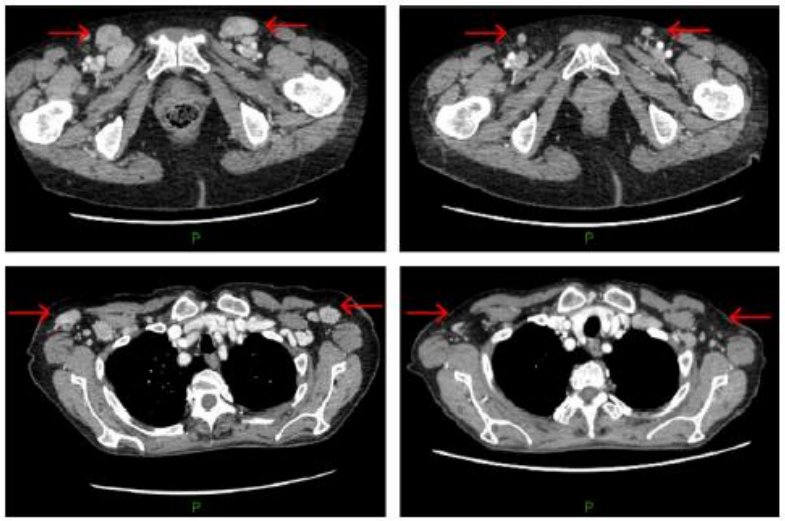
Defects in RHOA promotes TFH cell movement



Ahearne BJH 2014

	Overall	TET2 mutated	TET2 WT	P[a]
Patients (*n*)	86	13	73	
CR	20 (23%)	5 (38%)	15 (21%)	0.17
PR	1 (1%)	0 (0%)	1 (1%)	
mCR	11 (13%)	4 (31%)	7 (10%)	
SD with HI	13 (15%)	2 (15%)	11 (15%)	
SD without HI	23 (27%)	1 (8%)	22 (31%)	
Progression	15 (17%)	1 (8%)	14 (19%)	
Early death (<4 cycles)	3 (4%)	0 (0%)	3 (4%)	
Overall response (CR, PR, mCR)	32 (37%)	9 (69%)	23 (31%)	0.01
Overall response including SD with HI	45 (52%)	11 (85%)	34 (47%)	0.01
Response duration, mos	9.3 (1.7–29.0)	9.2 (2.0–28.2)	7.1 (1.7–29.0)	0.7

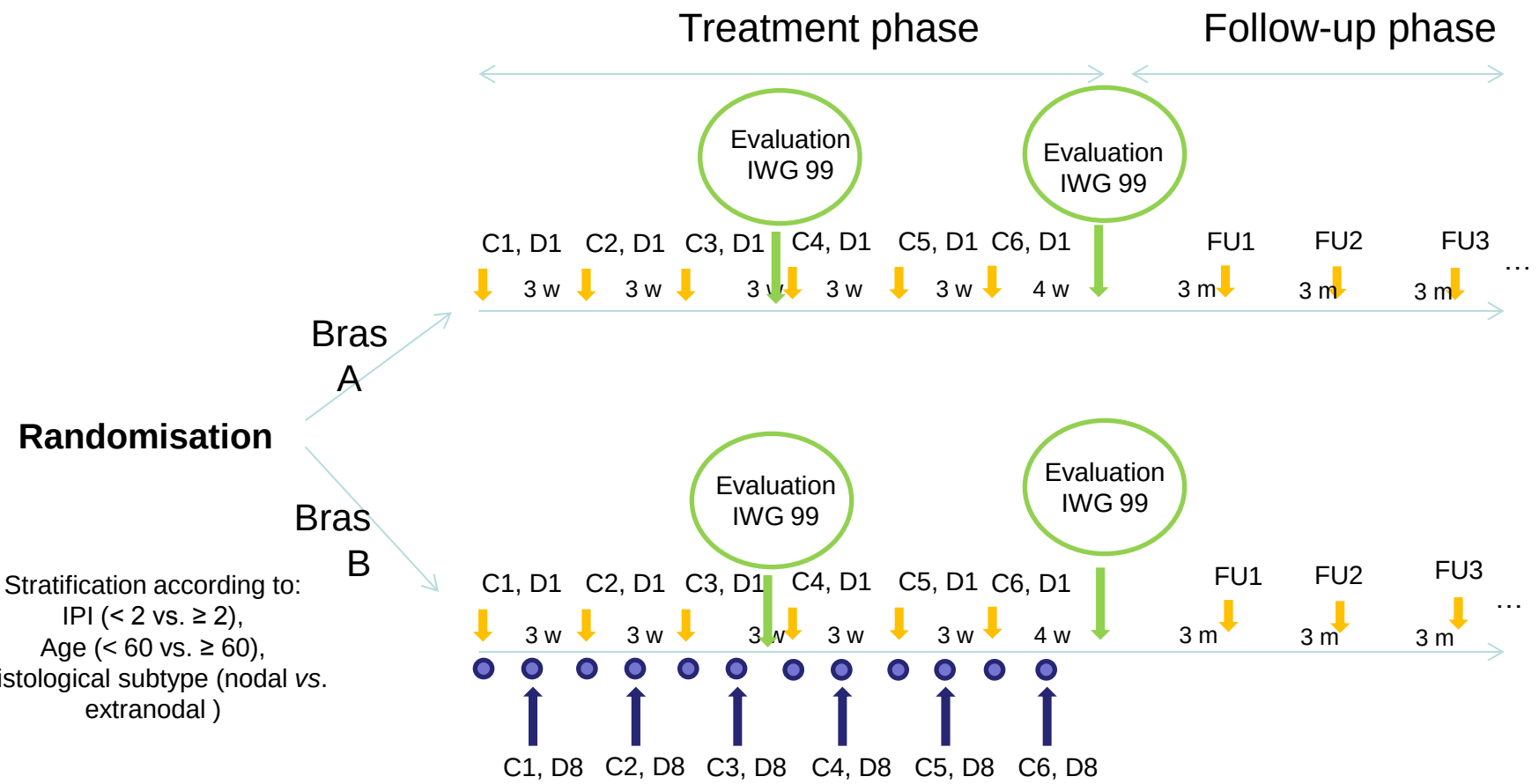
- Small molecule inhibitor specific for mutated IDH-2 enzyme leads to reversal of DNA methylation (Kernytsky et al Blood 2014)
- ? Synergy with other hpomethylating agents



Cheminant M et al. Br J Haem 2014;doi: 10.1111/bjh 13170

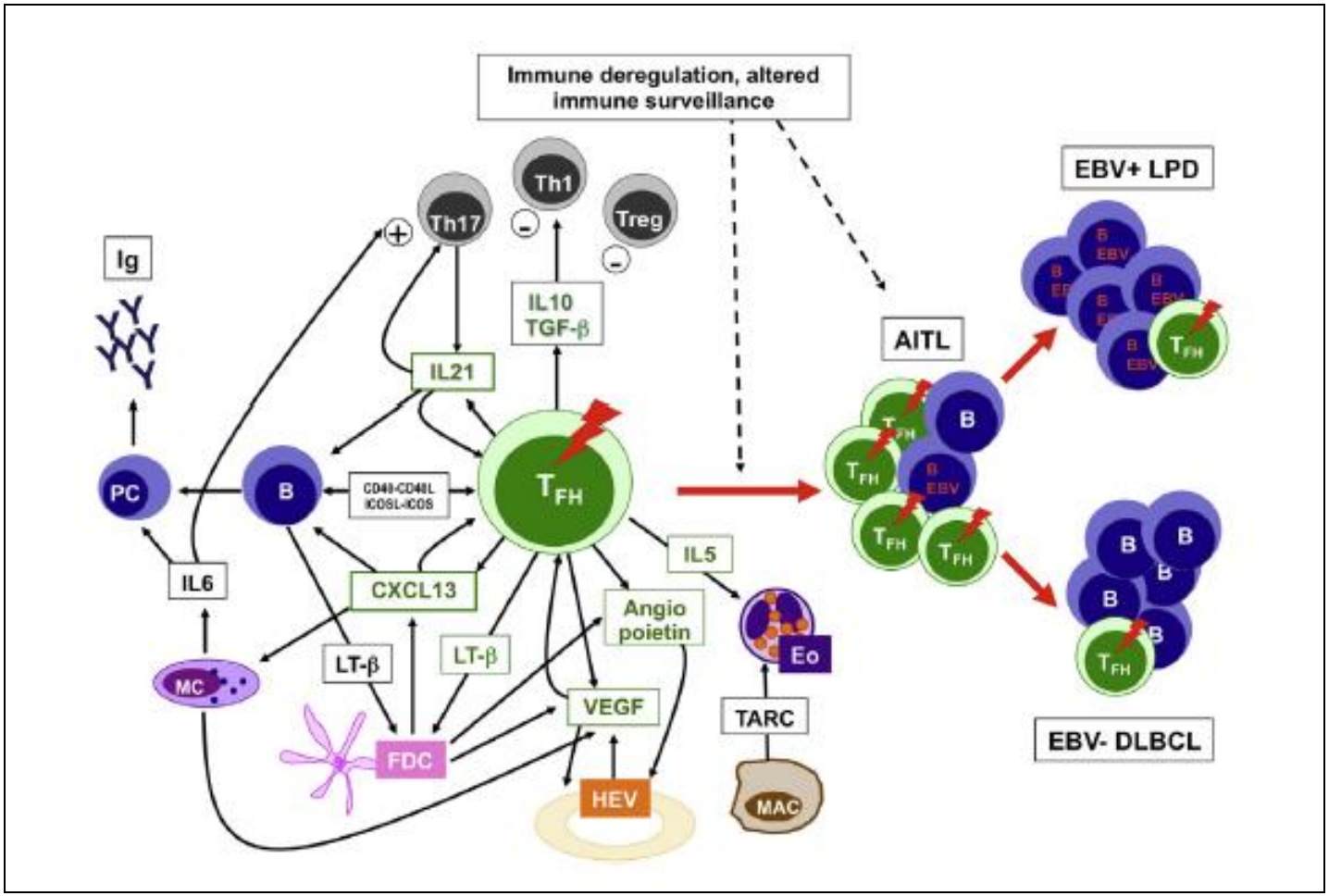
Ro CHOP Phase 3 Study

Results specific to AITL not reported



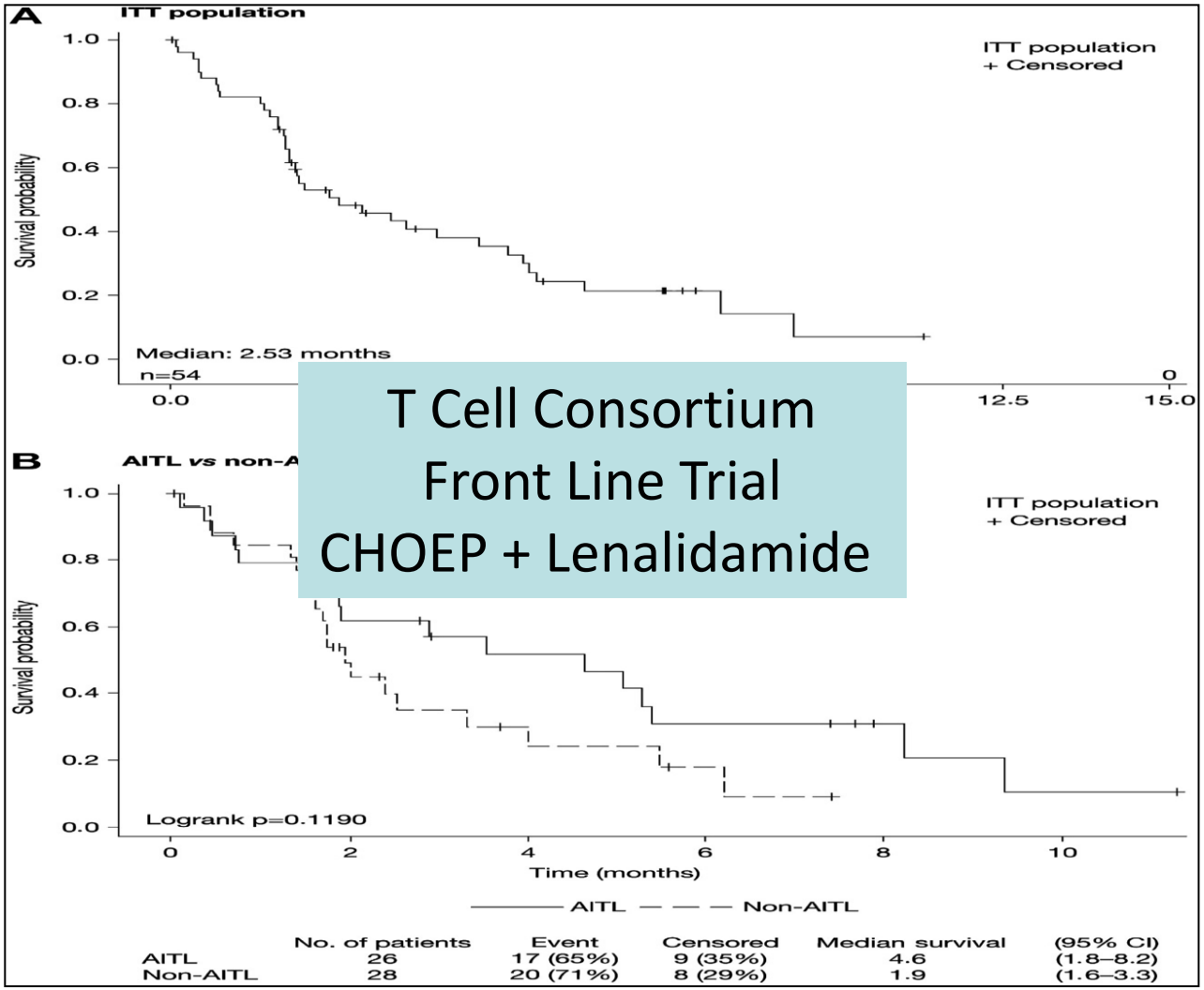
Pathogenic Model for AITL

Interactions of neoplastic cells with cellular components of the microenvoirnment



Gaulard et al Sem in Ca Biol 2014

Lenalidamide in Relapsed AITL
Expect Trial



T Cell Consortium
Front Line Trial
CHOEP + Lenalidamide

Morschhauser EJC 2014

Cyclosporine Experience in AILT

Patient Characteristics and Treatment

N = 12

- Median age 64 y (47 - 83)
- Signs and symptoms
  - Fever 11
  - LN 12
  - H/S 11
  - Anemia 9
- IPI
  - Low/Low Int 0
  - High/High Int 12
- Prior Treatment
  - None 2
  - Prednisone 2
  - Chemo +/- Pred 8

SCHEMA

CsA dose 3-5 mg/kg PO bid X 6-8 wks
Gradual taper by 50-100 mg q 1-3 wks

Responding patients: Maintenance dose 50-100 mg PO bid for ~ 6-12 months

Dose titrated for renal dysfunction or hypertension

Levels NOT monitored

ORR (8/12):66%.
DOR 2-120 mo (9 mo)
Most responses by 4-6 weeks

Advani et al: Leukemia Lymphoma 2007

Is there a specific Rx for Angioimmunoblastic T cell NHL

- Relapsed disease: Is there an optimal agent ?
  - Brentuximab data provocative
  - Mutations identified suggest that hypomethylating agents and histone inhibitors may be active

Future Directions

Is there a specific Rx for Angioimmunoblastic T cell NHL

- Clinical trial should always be the first choice if available
- Outcomes of AITL with novel agents in combination with chemo in front line awaited
- Future challenges:
  - Identifying subsets who may benefit from maintenance strategy
  - Are there subsets where chemotherapy not reqd?
    - Combinations of targeted agents BV/HDAI/Len
- Need a trial of ASCT vs no ASCT