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Peripheral T-Cell Lymphoma: Novel Agents & New Horizons

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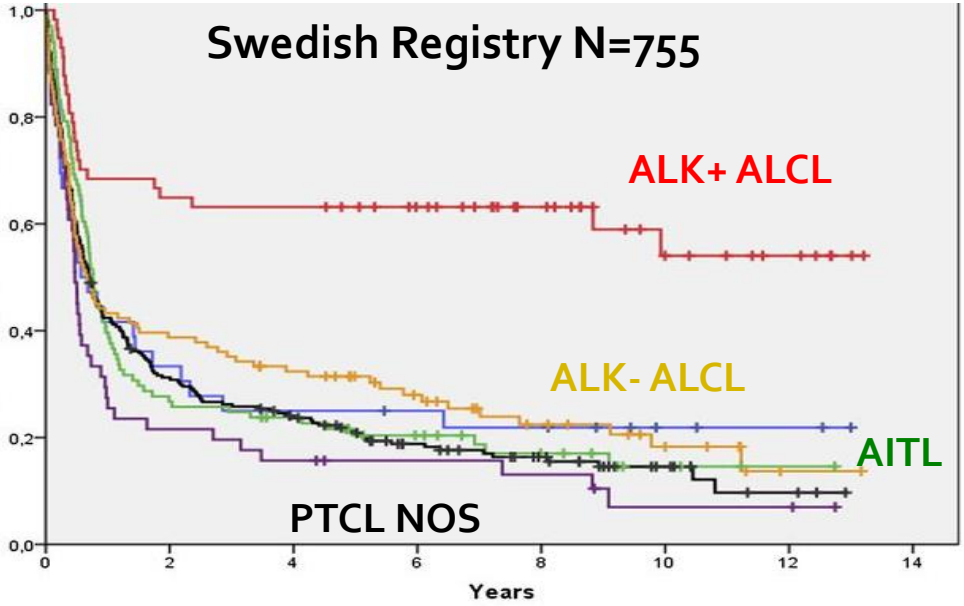
Disclosures for Steven M. Horwitz, MD

Conflict of Interest Disclosure

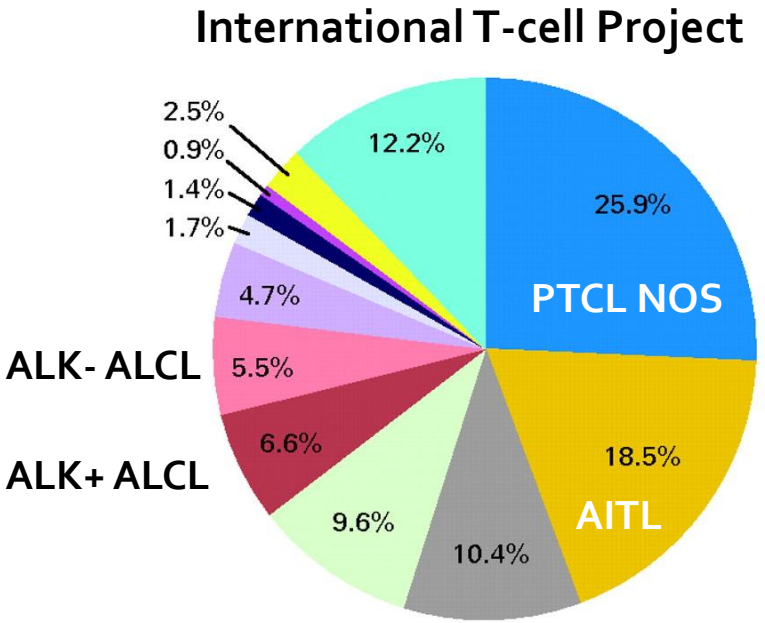
I hereby declare the following potential conflicts of interest concerning my presentation:

- **Consultancy:** ADC Therapeutics, Aileron,Seattle Genetics, Takeda, Kyowa Hakka Kirin, Verastem, Portola, Corvus
- **Research Funding:** Aileron, Celgene, Seattle Genetics, Takeda, Kyowa Hakka Kirin, Verastem, ADCT Therapeutics, Spectrum, Forty-Seven

PTCL: PFS by Subtypes



Fredrik Ellin et al. Blood 2014;124:1570-1577



Vose JM, et al. *J Clin Oncol.* 2008;26:4124-4130

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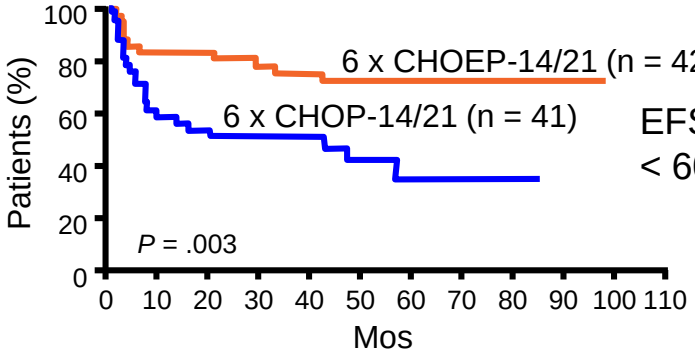
Frontline Treatment of Peripheral T-Cell Lymphoma

Current Common approaches
- Maximizing cytotoxic chemotherapy

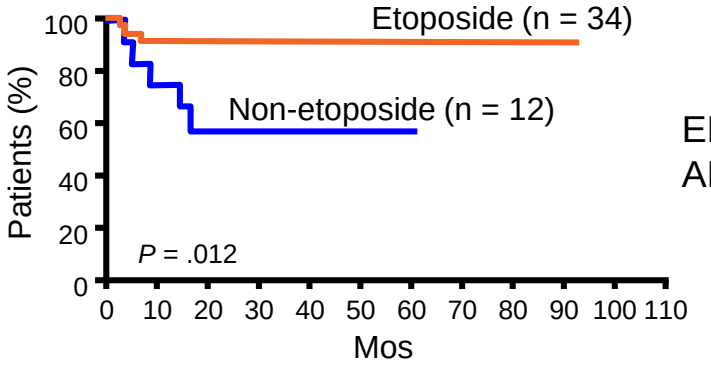
New Data for Frontline Therapy
- New drug X + CHOP

More Tailored Therapy
- New Targets
- Identifying new targets/therapies

Adding Etoposide to CHOP: German Prospective High-Grade NHL Studies

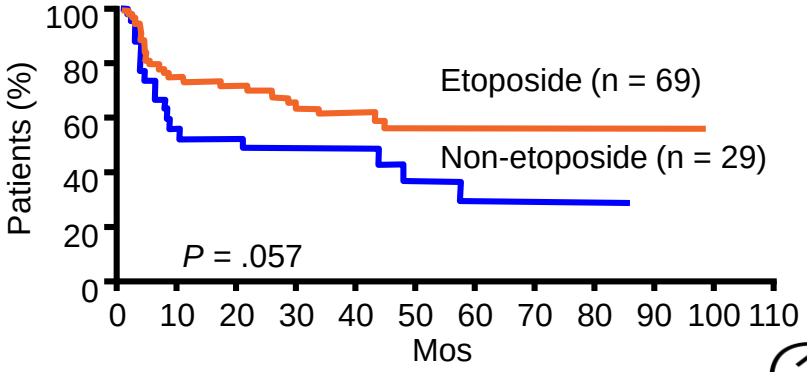


EFS, aged < 60 yrs



EFS, ALCL, ALK+

PTCL Subtype	n
ALCL, ALK+	78
ALCL, ALK-	113
PTCL-NOS	70
AITL	28
Other	31
Total	320



EFS, other subtypes

Schmitz N, et al. Blood. 2010;116:3418-3425.

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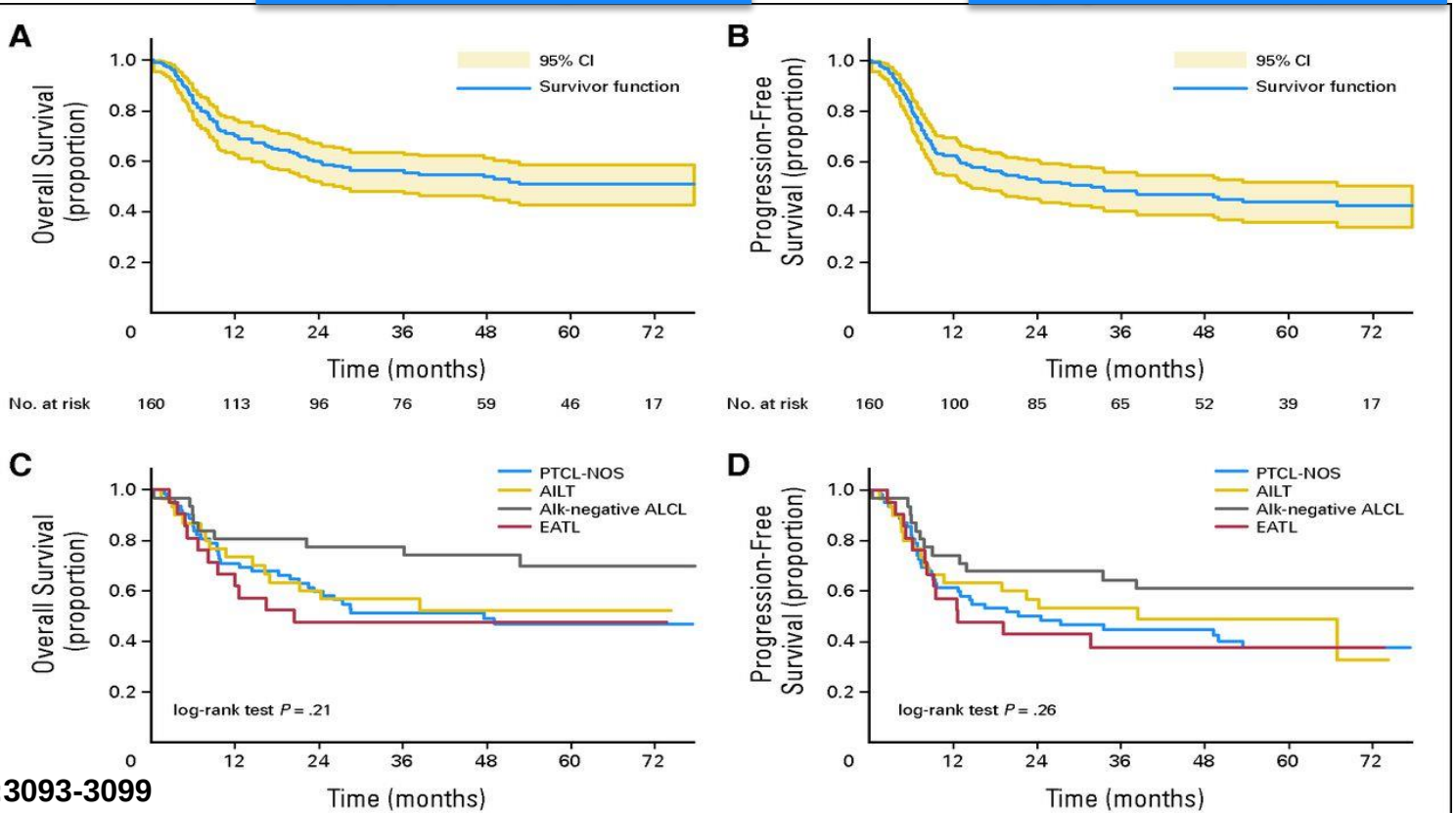
CHOEP -> autoSCT - Nordic Trial

CHO(E)P-14 x 6
n=160
ORR 82%
CR 51%

BEAM or BEAC
auto-SCT
n=115 (72%)

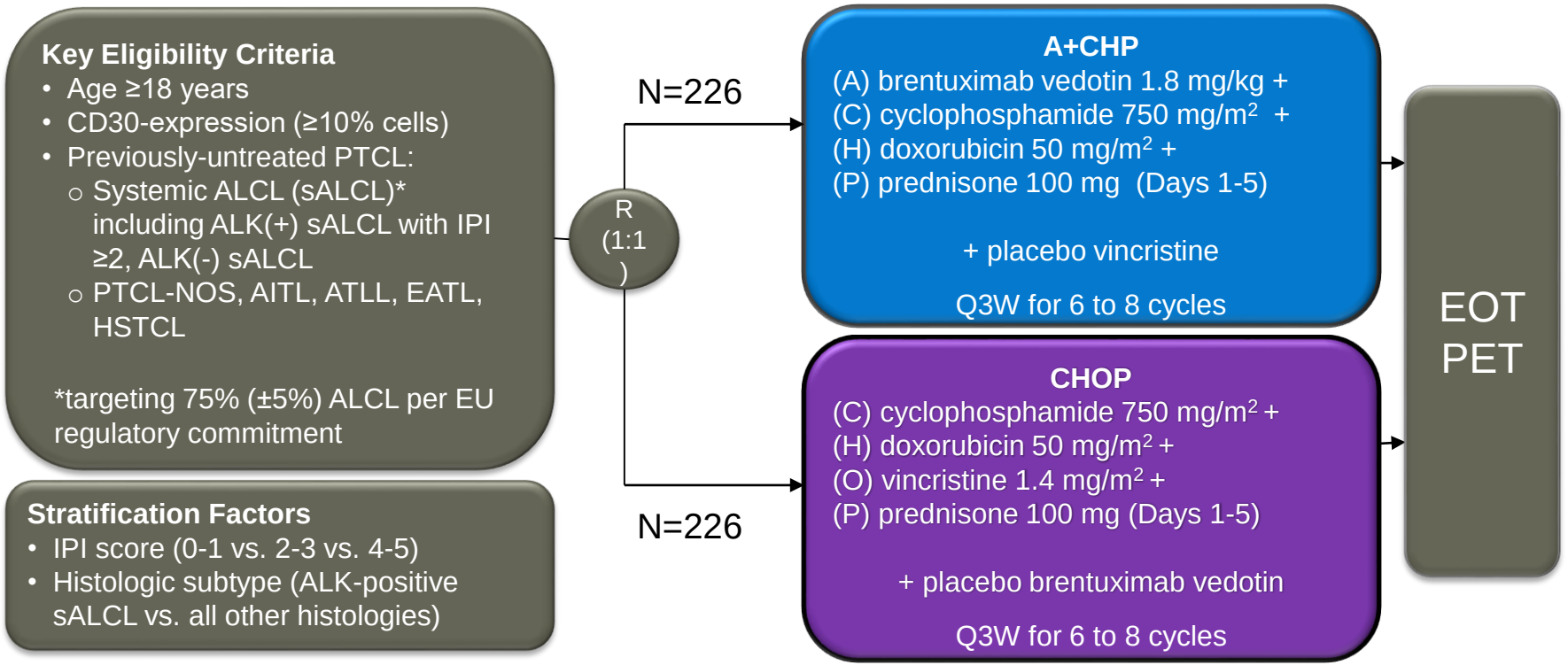
5 yr OS 51%

5 yr PFS 44%



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

ECHELON-2 Study Design (NCT01777152)



Primary Endpoint

PFS per BICR, ASCT or RT consolidation not an event

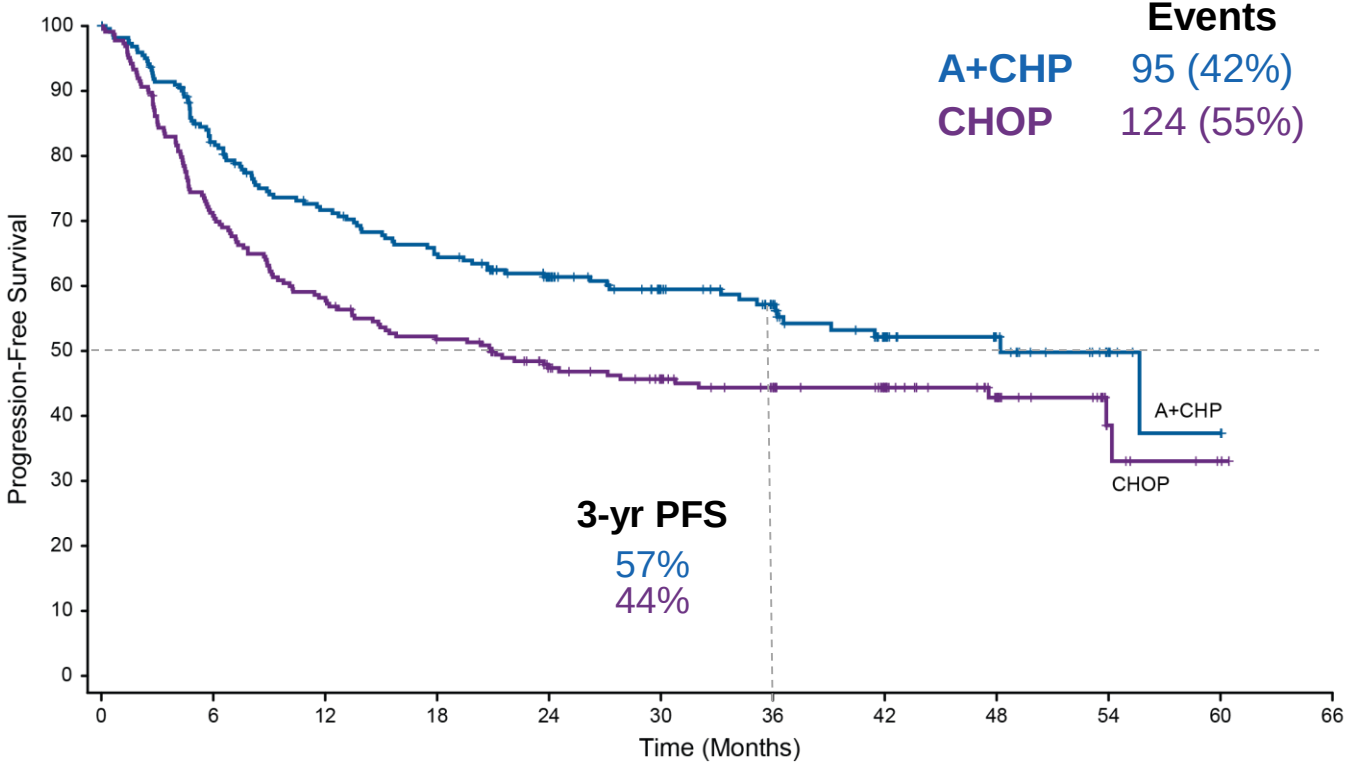
Horwitz et al. Lancet

Baseline Characteristics

	A+CHP (N=226)	CHOP (N=226)
Male, n (%)	133 (59)	151 (67)
Age in years, median (range)	58 (18-85)	58 (18-83)
IPI score, n (%)		
0-1	53 (23)	48 (21)
2-3	140 (62)	144 (64)
4-5	33 (15)	34 (15)
Stage III/IV, n (%)	184 (81)	180 (80)

	A+CHP (N=226)	CHOP (N=226)
Disease diagnosis, n (%)		
sALCL	162 (72)	154 (68)
ALK+	49 (22)	49 (22)
ALK-	113 (50)	105 (46)
PTCL-NOS	29 (13)	43 (19)
AITL	30 (13)	24 (11)
ATLL	4 (2)	3 (1)
EATL	1 (0)	2 (1)

Progression-free Survival



	Events	HR (95% CI)	*P*
A+CHP	95 (42%)	0.71 (0.54, 0.93)	0.011
CHOP	124 (55%)		

Median PFS (95% CI)

48.2 mo (35.2, NE)
20.8 mo (12.7, 47.6)

Median Follow-up

36.2 months

N at Risk (Events)

A+CHP	226(0)	175(39)	149(61)	134(75)	108(82)	81(85)	64(88)	38(93)	24(93)	9(94)	3(95)	0(95)
CHOP	226(0)	157(65)	129(93)	112(107)	87(116)	75(119)	63(121)	44(121)	26(122)	7(123)	2(124)	0(124)

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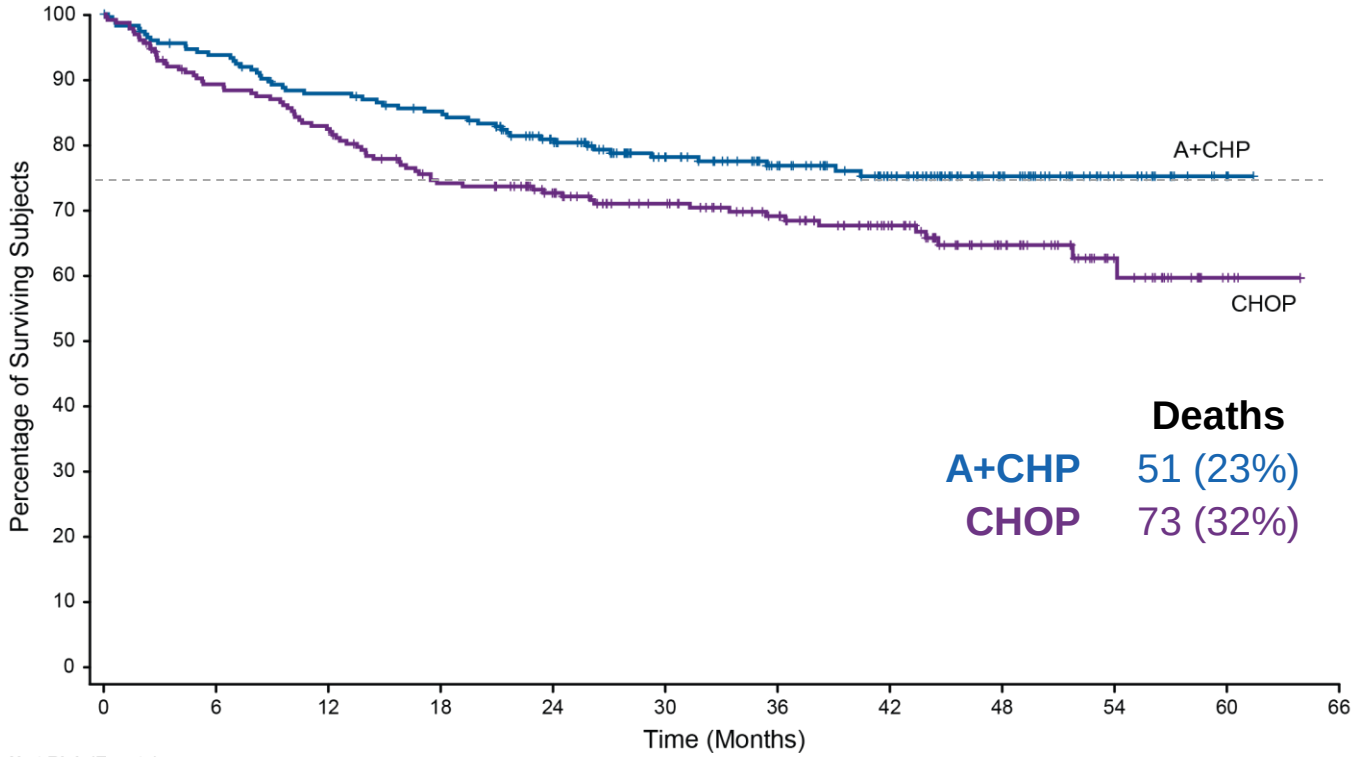
Overall Survival



75th Percentile

Not reached
17.5 mo

	Deaths	HR (95% CI)	*P*
A+CHP	51 (23%)	0.66 (0.46, 0.95)	0.0244
CHOP	73 (32%)		

Median Follow-up
42.1 months

N at Risk (Events)

A+CHP	226(0)	208(14)	193(27)	184(33)	159(42)	128(47)	108(49)	83(51)	45(51)	20(51)	4(51)	0(51)
CHOP	226(0)	196(24)	181(39)	158(57)	140(60)	121(63)	103(66)	79(68)	46(71)	22(72)	4(73)	0(73)

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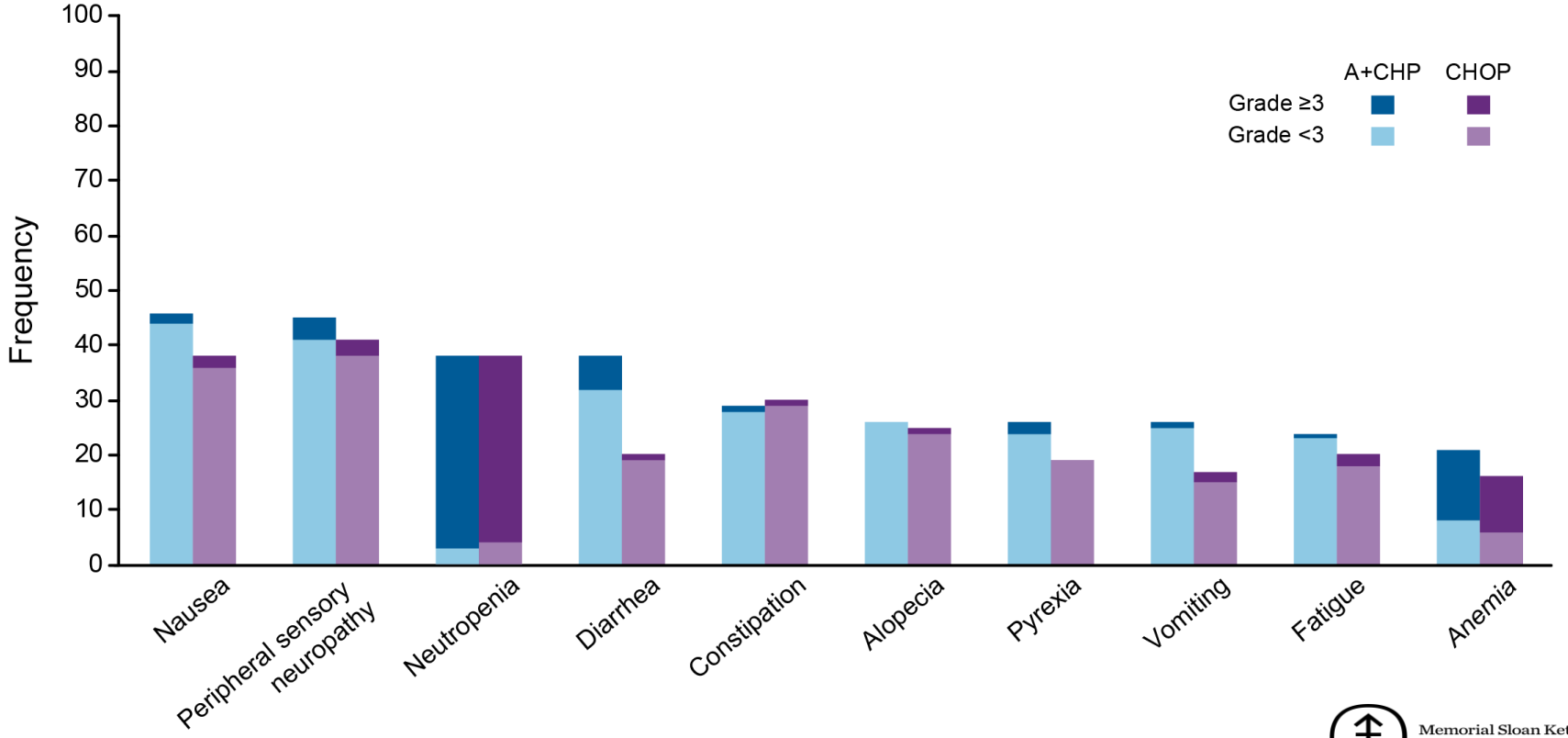
Adverse Events in ≥20% of Subjects



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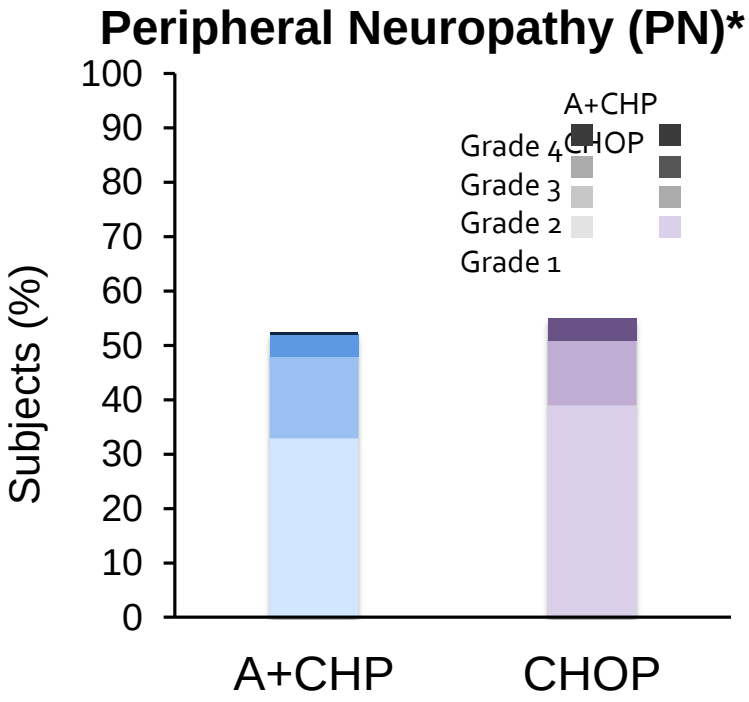
Treatment-Emergent Peripheral Neuropathy



Subjects, n (%)	A+CHP (N=223)	CHOP (N=226)
Treatment-emergent PN, n	117	124
Resolution† of all PN events	58 (50)	79 (64)
Ongoing PN at last follow-up	61 (52)	45 (36)
Grade 1	44 (72)	32 (71)
Grade 2	15 (25)	12 (27)
Grade 3	2 (1)	1 (1)

†Resolution was defined as resolved/recovered with or without sequelae; or return to baseline or lower severity as of the latest assessment for pre-existing events

*Includes the preferred terms of peripheral sensory neuropathy, paraesthesia, peripheral motor neuropathy, muscular weakness, peripheral sensorimotor neuropathy, hypoaesthesia, dysaesthesia, areflexia, burning sensation, peroneal nerve palsy, polyneuropathy, autonomic neuropathy, gait disturbance, muscle atrophy, and neuralgia.

Summary and Conclusions

- ECHELON-2 first prospective trial in PTCL to show OS benefit over CHOP
- A+CHP provided clinically meaningful improvement in PFS and OS versus CHOP
  - 29% reduction in the risk of a progression event
    - 3-yr PFS: A+CHP 57% versus CHOP 44%
  - 34% reduction in the risk of death
- A+CHP has a comparable safety profile to CHOP
- 70% of subjects had ALCL (similar to CHOEP data)
- US FDA approved brentuximab vedotin in combination with CHP for adults with previously-untreated sALCL or other CD30-expressing PTCL, including AITL and PTCL-NOS

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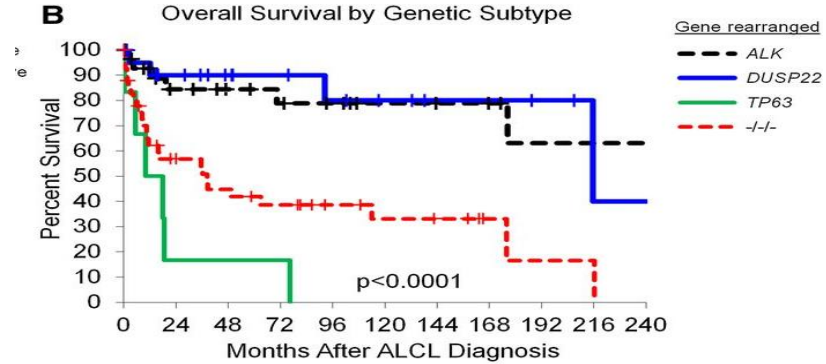
ALCL

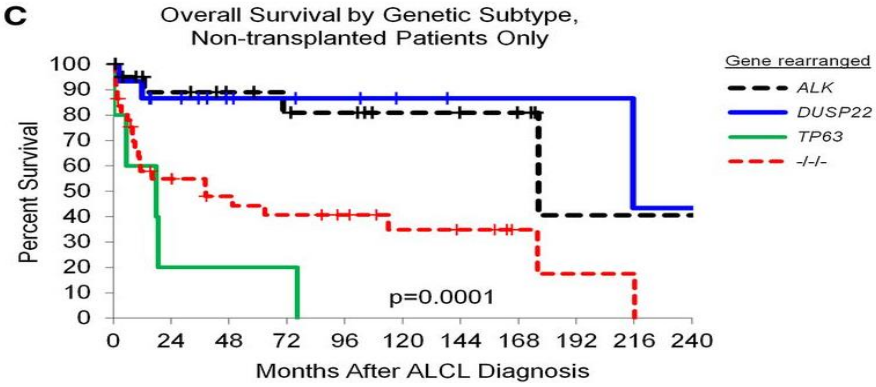
Other Secondary Efficacy Endpoints

	A+CHP (N=226)	CHOP (N=226)	P value
Remission rates in ITT population at EOT			
CR rate	68%	56%	0.0066
ORR	83%	72%	0.0032
sALCL subset analysis, n	163	151	
Subjects with a PFS event, n (%)	56 (34)	73 (48)	
Hazard ratio	0.59 (95% CI: 0.42, 0.84)		0.0031

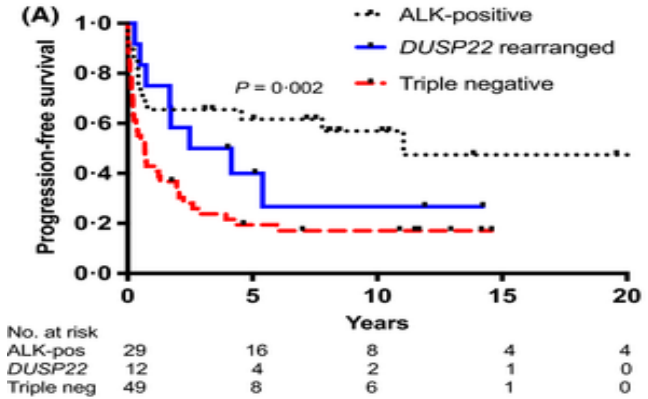
- All secondary endpoints were statistically significant; type I error controlled

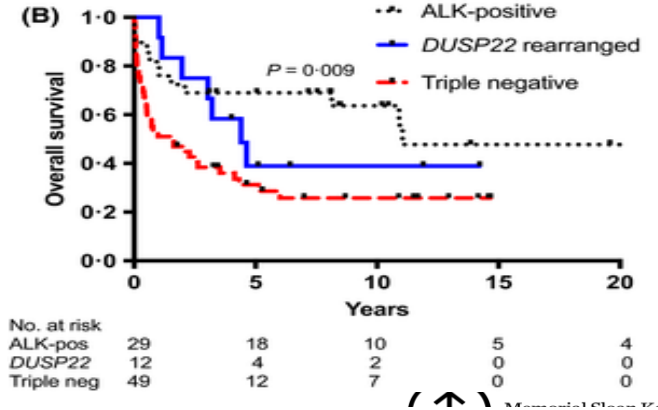
ALK-neg ALCL – recurrent chromosomal rearrangements with DUSP22 and TP63





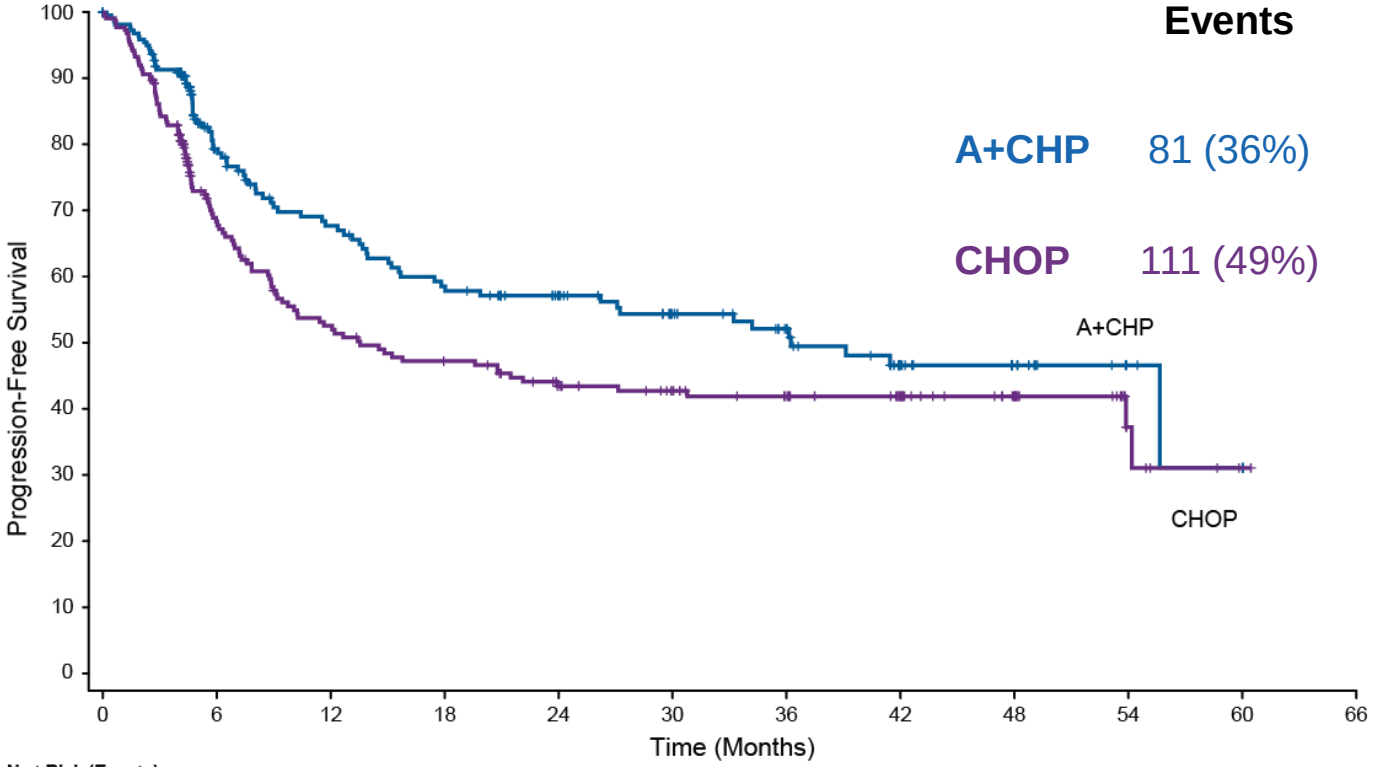
Edgardo R. Parrilla Castellar et al. Blood 2014;124:1473-1480





Hapgood et al. British Journal of Haematology,: 14 March 2019, DOI: (10.1111/bjh.15860)

PFS: censored at time of consolidative ASCT or RT



	Events	HR (95% CI)	*P*
A+CHP	81 (36%)	0.71 (0.53, 0.94)	0.017
CHOP	111 (49%)		

N at Risk (Events)

A+CHP	226(0)	120(39)	97(56)	83(69)	67(71)	52(74)	42(76)	23(80)	14(80)	4(80)	2(81)	0(81)
CHOP	226(0)	118(65)	89(92)	78(101)	64(107)	56(108)	48(109)	37(109)	23(109)	6(110)	1(111)	0(111)

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PTCL-post Echelon 2

BV-CH-P-OS benefit!

- ALCL
  - ALCL ALK+ (?IPI) , ALCL ALK-,
  - Consolidation? E2 doesn't really address this
  - ALK+ -rare, was already unclear
  - DUSP22 rearranged-maybe?

- PTCL-NOS, AITL
  - Part of ITT of E2-PFS, OS, on label
  - Subset size precludes statistical conclusions for individual subtypes
  - Other than CHOP
    - BV-CHP vs CHOEP (similar issues interpretation)
    - ASCT

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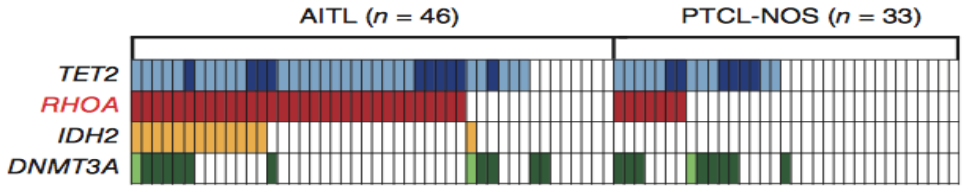
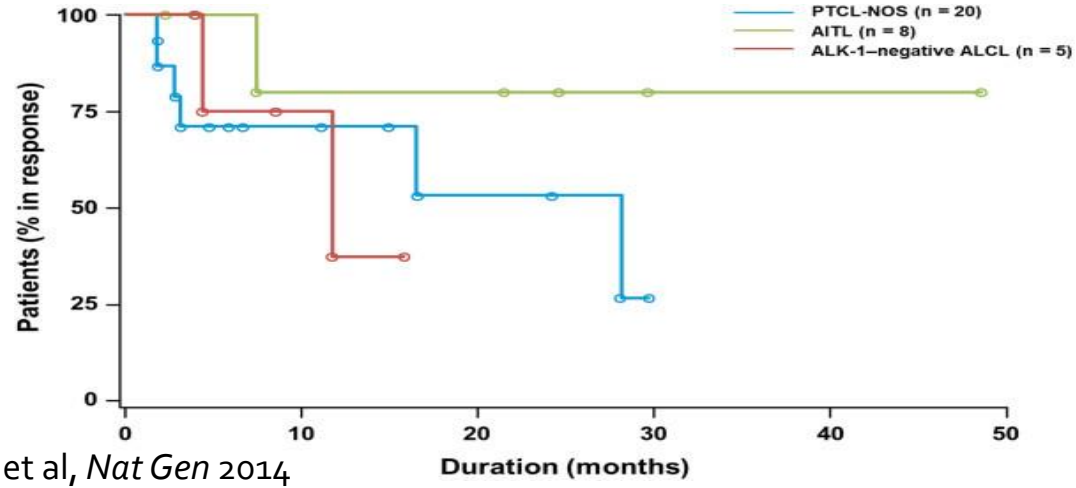
Other Subtypes of PTCL

Molecular and clinical distinctions of AITL/follicular helper T-cell lymphoma

IDH2 Mutations in TFH-like lymphoma (AITL and some PTCL-NOS)



Duration of response to Romidepsin



Sakata-Yanagimoto et al, *Nat Gen* 2014
Coiffier et al, Journal of Hematology & Oncology2014**7**:11

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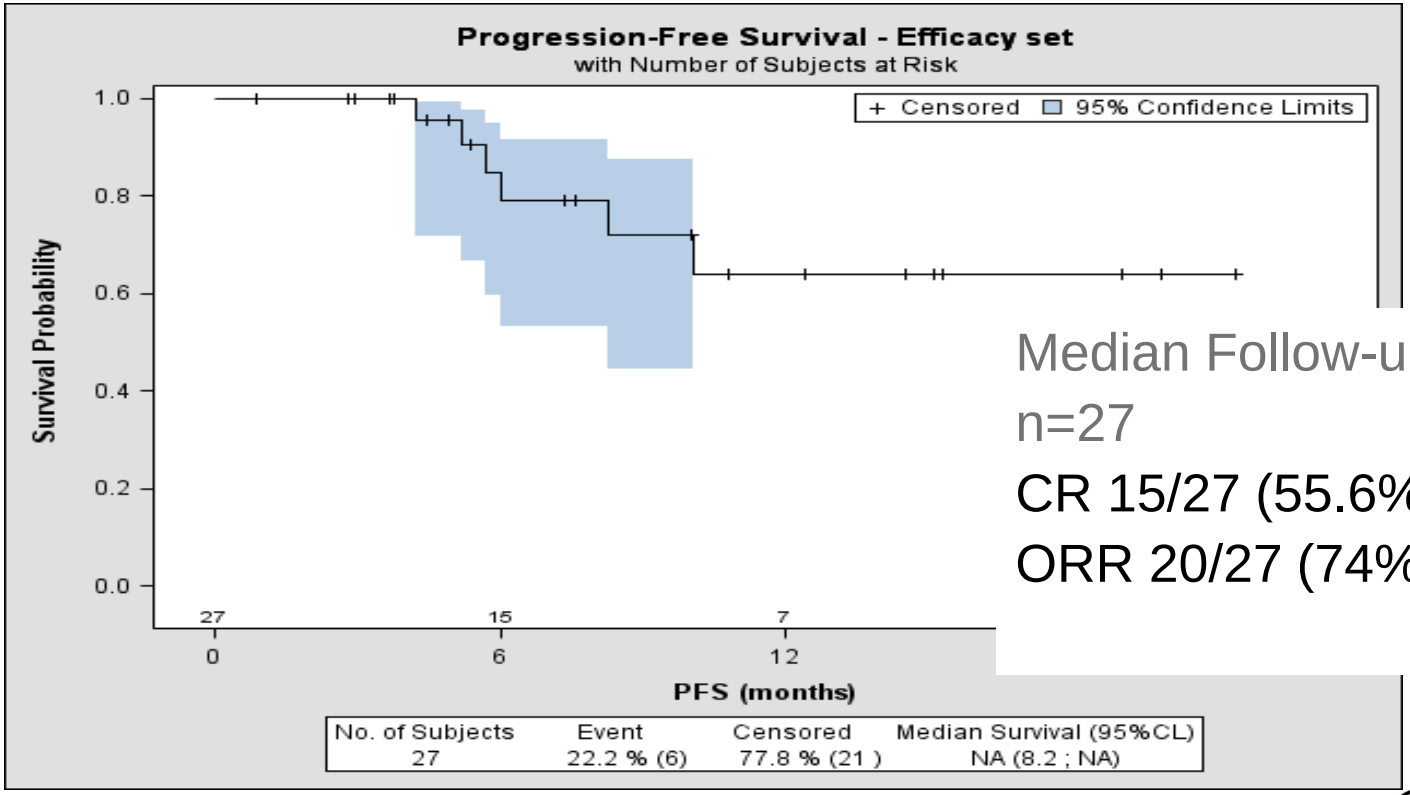
Response to Romidepsin Tfh/AITL vs Non-Tfh

	TFH(n=24)		Non TFH(n=17)		p
Gender (M/F)	10 (42%)/14 (58%)		4 (23%)/13 (77%)		0.32
Age	67 years (36–75)		58 years (32–83)		0.21
Median prior therapies	1 (1-5)		1 (1-5)		NS
Median time-from-diagnosis, months	8 (3-38)		9 (3-67)		0.91
Ann Arbor					
I-II	4 (16%)		2 (12%)		0.99
III-IV	20 (84%)		15 (88%)		
IPI at romidepsin start					
0-2	9 (37%)		7 (41%)		>0.99
3-5	15 (63%)		10 (59%)		
Response	**ORR**	**CR**	**ORR**	**CR**	
Overall	14 (58%)	7 (29%)	5 (30%)	2 (12%)	0.11
Single agent (n=21)	4 (36%)	1 (9%)	1 (10%)	1 (10%)	0.31
Combinations (n=20)	10 (77%)	6 (46%)	4 (57%)	1 (14%)	0.61

Ghione et al. *ASCO 2018*

Romidepsin-CHOP Phase I-II PFS



Median Follow-up 10 months

n=27

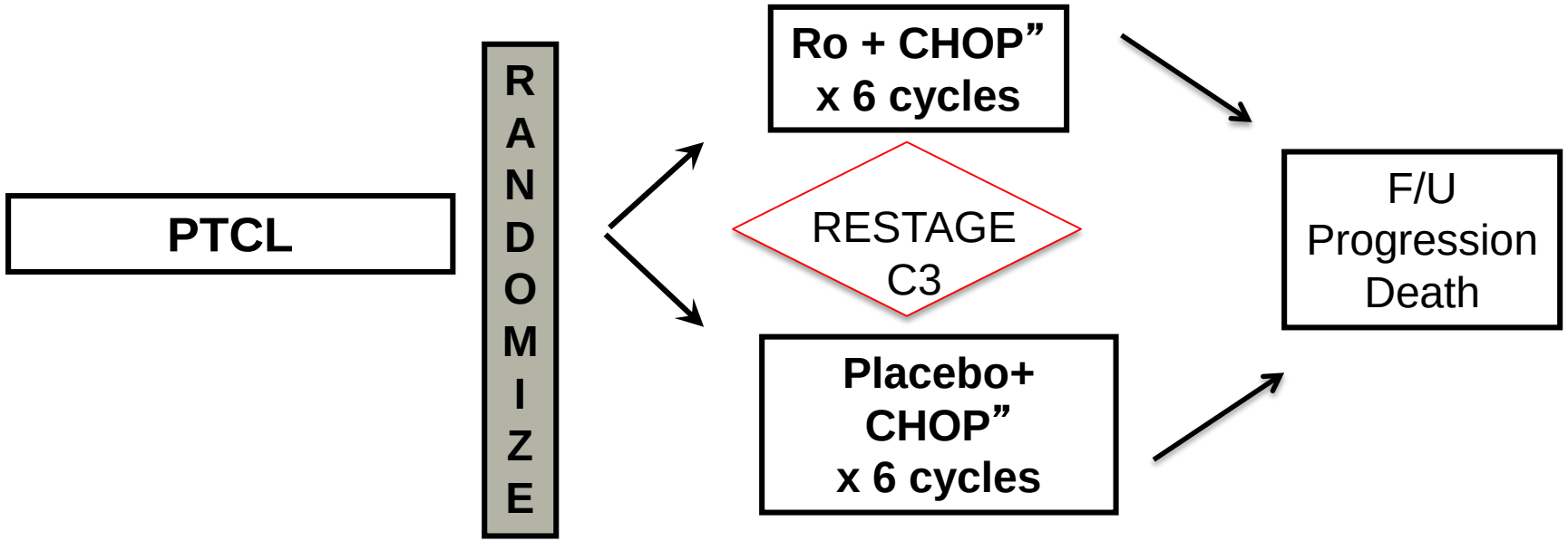
CR 15/27 (55.6%)

ORR 20/27 (74%)

1 year estimated PFS 63.9% (95%CI 35.4 – 82.5)

Delarue et al ASH 2014

Phase III Ro-CHOP Study



Romidepsin D1,8 each cycle
International randomized, open-label study
Principal objective: PFS improvement
Planned accrual: 420 patients

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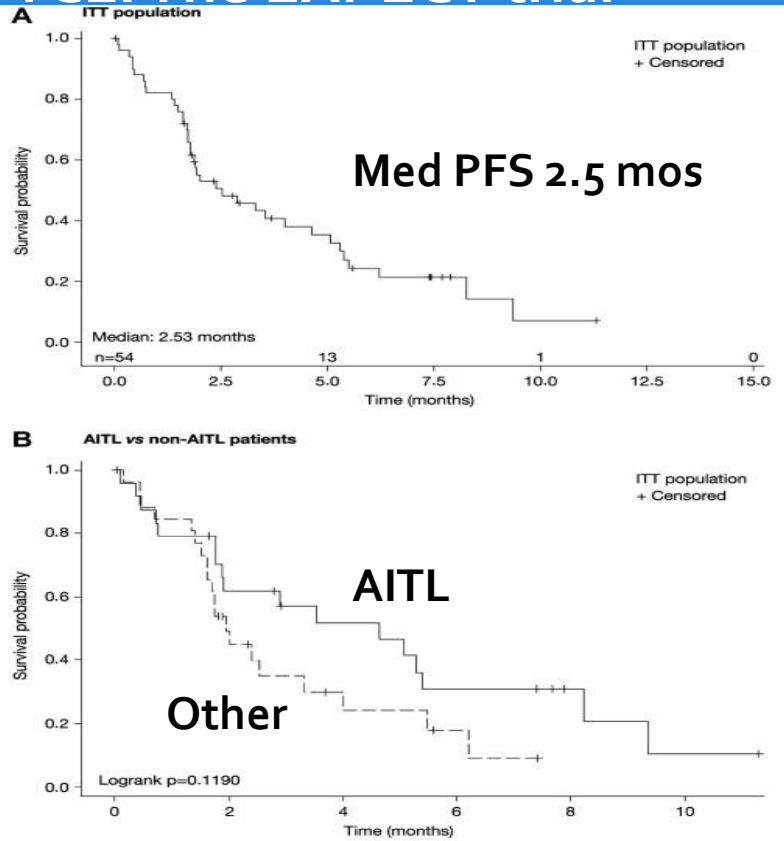
A phase 2, multicentre, single-arm, open-label study of lenalidomide in relapsed or refractory PTCL: The EXPECT trial

	ITT (N=54)	AITL (N=26)
Tumor Control	52% (28)	58% (15)
ORR	22% (12)	31% (8)
CR/Cru	11%(6)	15% (4)
PR	11%(6)	15% (4)
Stable disease	30% (16)	27%(7)
POD	33% (18)	23% (6)
D/C without response assesment	15% (8)	19% (5)



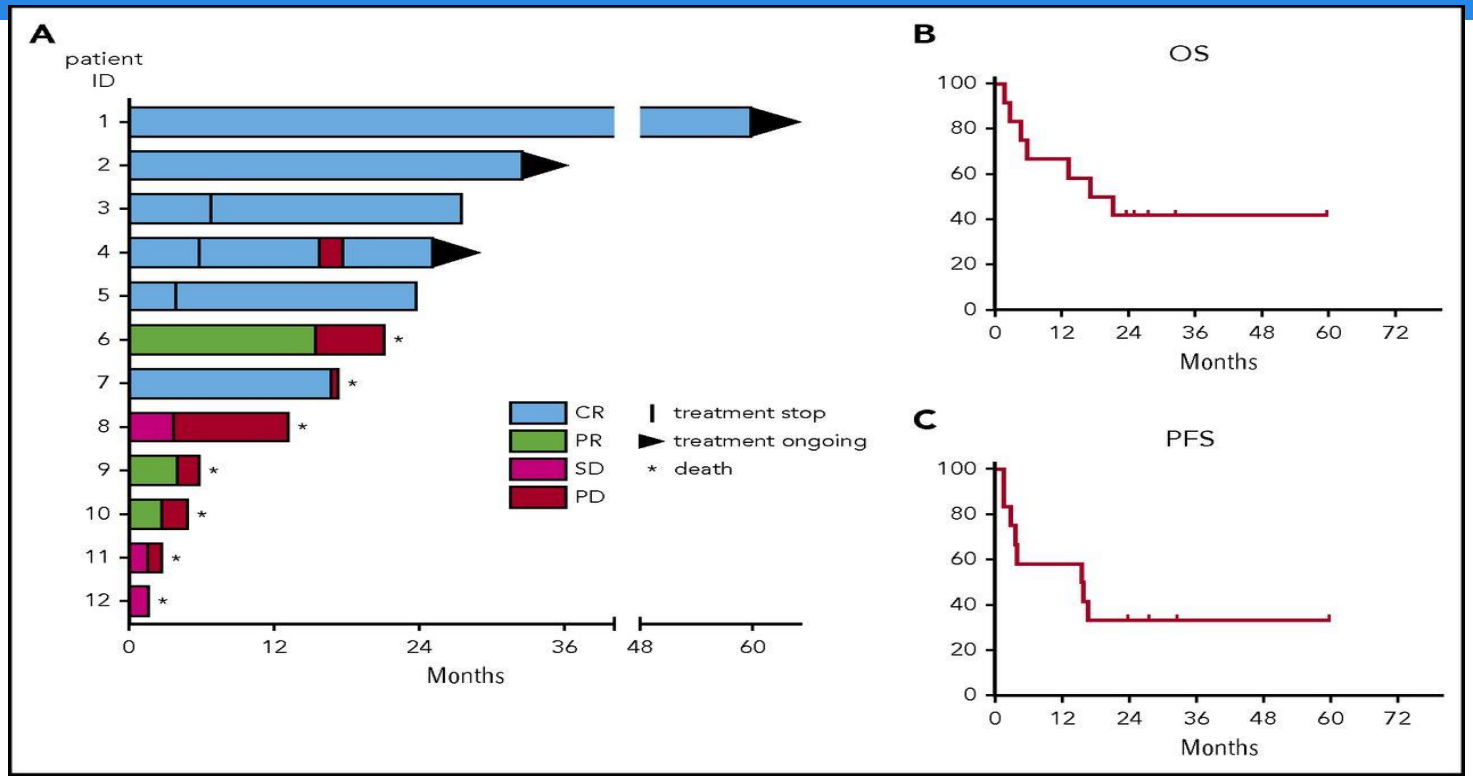
Morschhauser et al European Journal of Cancer, Volume 49, Issue 13, 2013, 2869

Other Combinations for Newly Diagnosed T-Cell Lymphoma

CHOP/CHOP-like +

- **Lenalidomide**
  - CHOEP + Len –increased toxicity, unclear improved efficacy (Lunning et al ASH 2018)
  - CHOP+ Len AITL only, increased tox, no increase efficacy (Lemonnier et al ASH 2018
    - Chemo resistance in DNMT3A^{R882H} mutants?
- **Alemtuzumab**
  - ACT 1 and 2-increased toxicity outweighed any apparent increased efficacy
    - D'amore et al ASH 2018
- **Romidepsin**- Romi-CHOP Data pending

Patient outcomes after 5-azacytidine treatment.

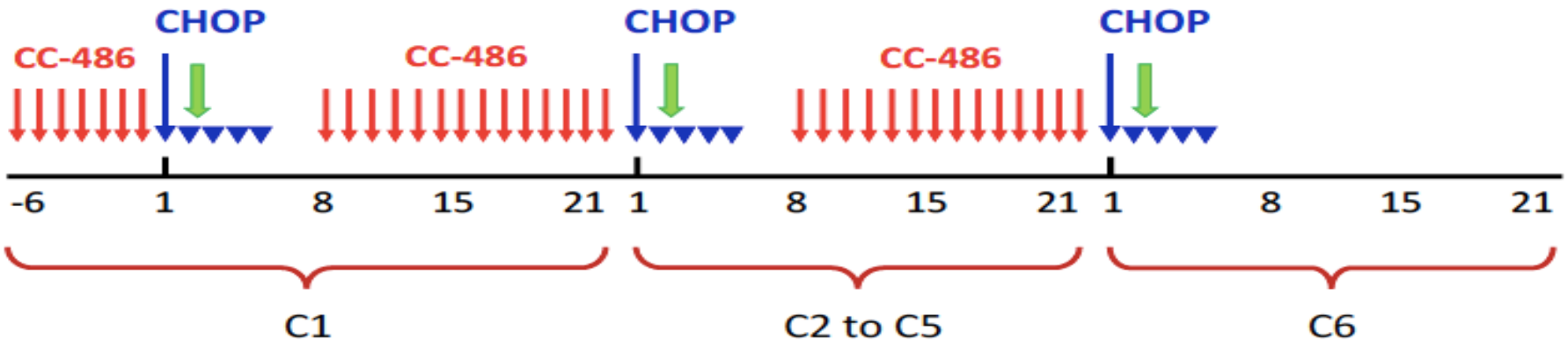


François Lemonnier et al. Blood 2018;132:2305-2309

A Multi-center Phase II Study of CC486-CHOP in Patients with Previously Untreated Peripheral T-cell lymphoma

Treatment

- CC-486: cycle 1, days -6 to 0; cycles 1-5, days 8-21
- Cyclophosphamide, doxorubicin, vincristine: day 1
- Prednisone: days 1-5
- Growth factor e.g. pegfilgrastim:



PI Jia Ruan
WCMC

NCT03542266

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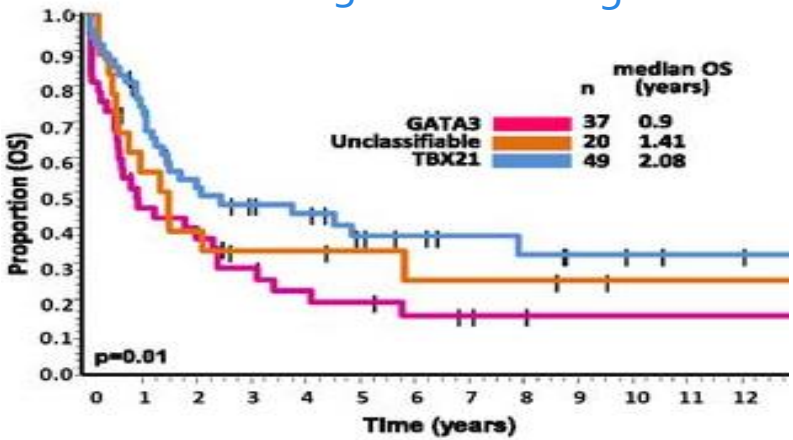
Other Targets in T Cell Lymphoma

JAK/STAT in TCL

TCL subtype	% with JAK/STAT activating mutations
ALCL	38%
Extranodal NK/TCL	5.9%
T-PLL	36%
γδ-T cell lymphomas	33%
MEITL	36.8%
LGL	28-40%
Sezary Syndrome	11%

PTCL: Gata3 high tumors show a worse OS enriched for PI3K-induced signatures



Kucuk C et al. Nature communications 2015;6:6025.
Kiel MJ et al. Nature communications 2015;6:8470.
Kiel MJ et al. Blood 2014;124:1460-72.
Crescenzo R et al Cancer cell 2015;27:516-32.
Koskela HL et al. N Engl J Med 2012;366:1905-13.
Jerez A et al. Blood 2012;120:3048-57.
Iqbal J et al. Blood 2014;123:2915-2923

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Cerdulatinib (syk, jak1/3, tyk 2): Best Overall Response by PTCL Subtype

Response	AITL / TFH	PTCL-NOS	Gamma-delta[1]	ALCL (ALK-)	ATLL	T-PLL	Total
N evaluable (%)	14	13	7	3	3	1	41
ORR	**8 (57)**	**2 (15)**	**1 (14)**	**1 (33)**	**2 (67)**	**0**	**14 (34)**
CR	7 (50)	2 (15)	1 (14)	0	1 (33)	0	11 (27)
PR	1 (7)	0	0	1 (33)	1 (33)	0	3 (7)
SD	1 (7)	3 (23)	3 (44)	1 (33)	0	1 (100)	9 (22)

Gamma-delta includes: HSTCL (3), cGD-TCL (3), MEITL (1).
CR was in HSTCL patient.

Horwitz et al ASH 2018

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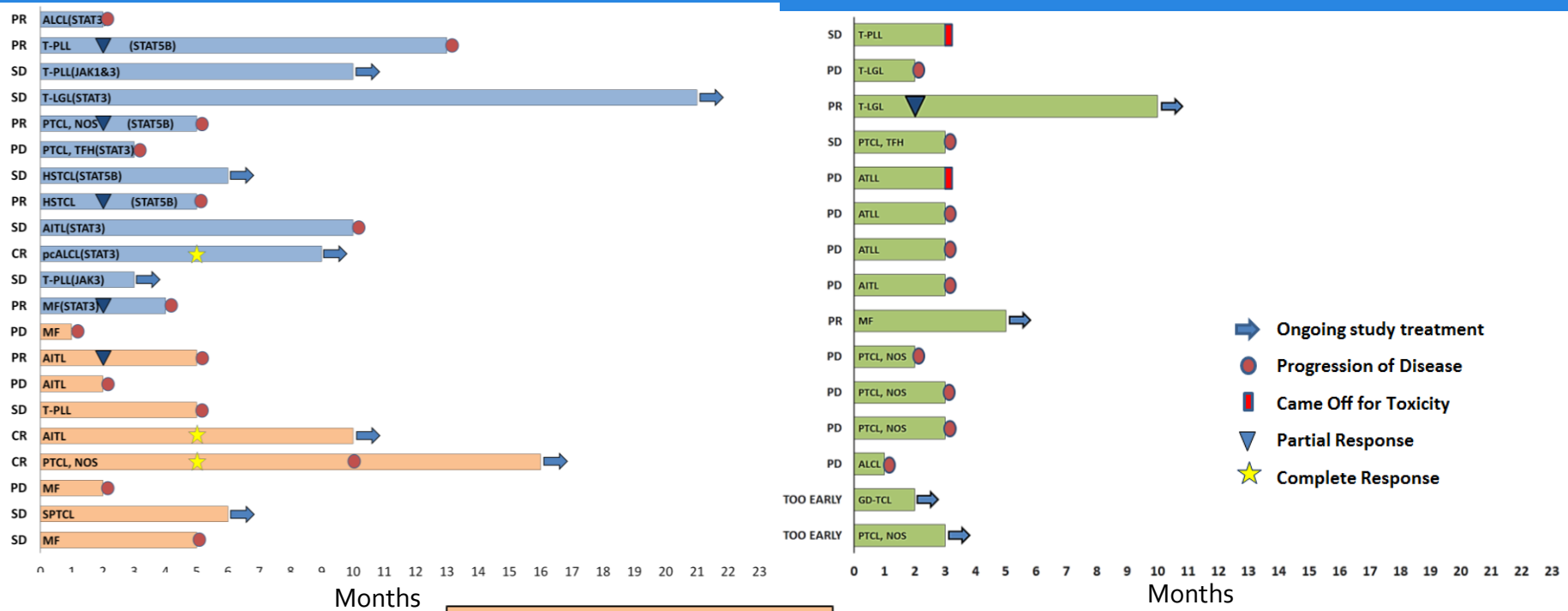
A Phase II Multicenter Study of Ruxolitinib in Relapsed or Refractory T-cell Lymphomas



JAK/STAT mutations

Cohort 1

Phospho-STAT3 expression

Cohort 2

Neither

Cohort 3

Moskowitz et al ASH 2018

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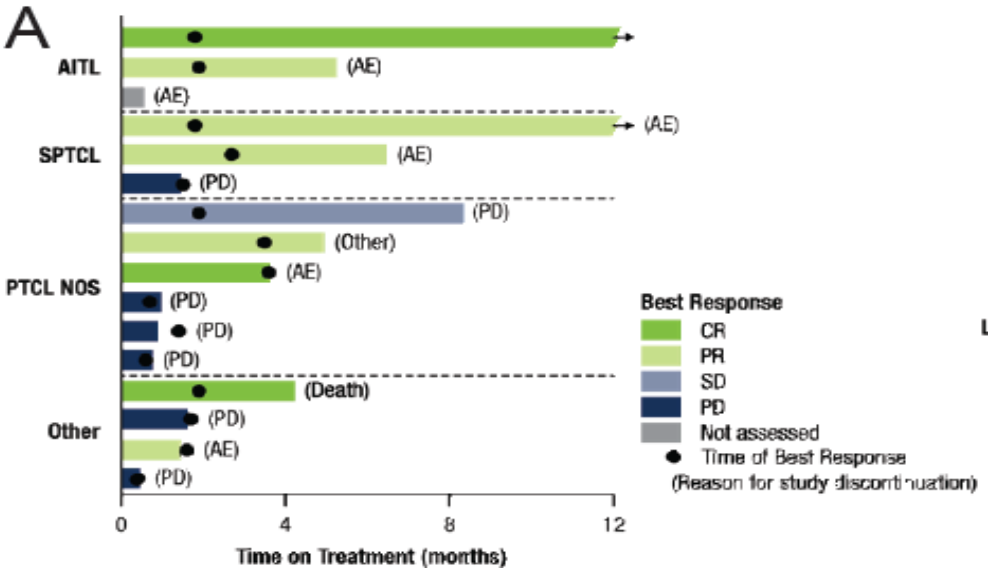
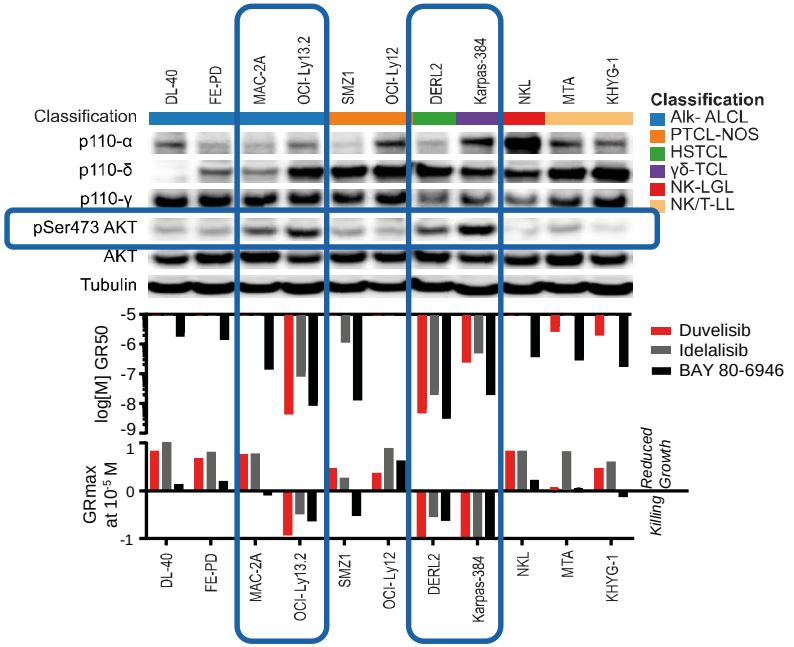
Duvelisib, PI3K-δγ Inhibitor, in T-cell Lymphoms

ORR in PTCL (N=16) : 50%
CR 3 (19%)
Median PFS 8.3 months

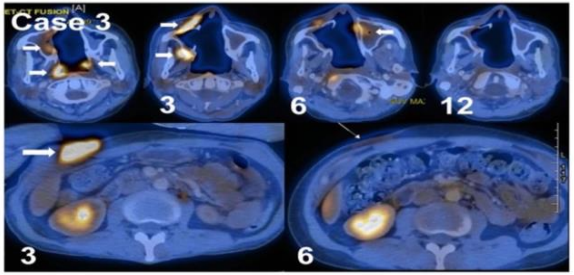


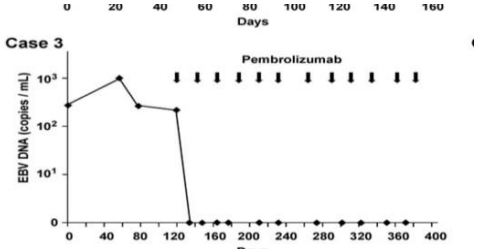


Most patients treated at 75 mg BID

Horwitz et al. Blood. 2018 Feb 22;131(8):888-898

Checkpoint Inhibitors in NK/T-cell Lymphoma





Pembrolizumab in NK/T

- 7 pts rel/ref (not on a trial) 5 CR, 2 PR[1]

Phase II study of the PD1-inhibitor pembrolizumab for PTCL[2]

- Response rate was 27% (4/15 pts; All 4 responders achieved a CR

Nivolumab [3]

- PTCL 40% (2/5) PRs, 1 durable
- MF 15% (2/13) PRs

Hyper-progression

1 Kwong et al. Blood 2017 129:2437-2442; 2 Barta et al ASCO 2018,
3 Lesokhin et al. Journal of Clinical Oncology 34, no. 23 2016 2698-2704.

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Other Therapies in Development in TCL/other targets

Clinical Trials are frequently available for relapsed patients

- **Other doublets**
  - **Pralatrexate-Romidepsin**
  - **Romidepsin-5-AZA**
- **Tipifarnib**
- **MDM2 inhibitors**
- **EZH1/2 inhibitors**
- **New ADCs**
- **Mogamulizumab**-Anti CCR4 Ab-CTCL, ATLL
- **Anti CD47 strategies**
  - Don't eat me signal
  - Studies of 3 compounds underway or planned including PTCL and CTCL
- **ICOS**

Amengual et al Blood 2018 131:397-407; Falchi et al ASH 2017; Hamlin et al ASCO 2018
Witzig et al ICML 2017; Kim et al Lancet Oncol 2018

Peripheral T-Cell Lymphoma: What is New on the Horizon

ECHELON-2

- Discussed-PFS, OS benefit
  - Overall
  - ALCL
  - Others, Consolidation

For those not being treated with an E2 strategy

- CHOEP, CHOP
- Others targets-
  - CHOP + X strategy +/-
    - Len-meh
    - HDAC, Hypomethylating-awaiting data
  - PI3K, jAK/STAT, Checkpoint inhibitors, Others