mTOR inhibitor

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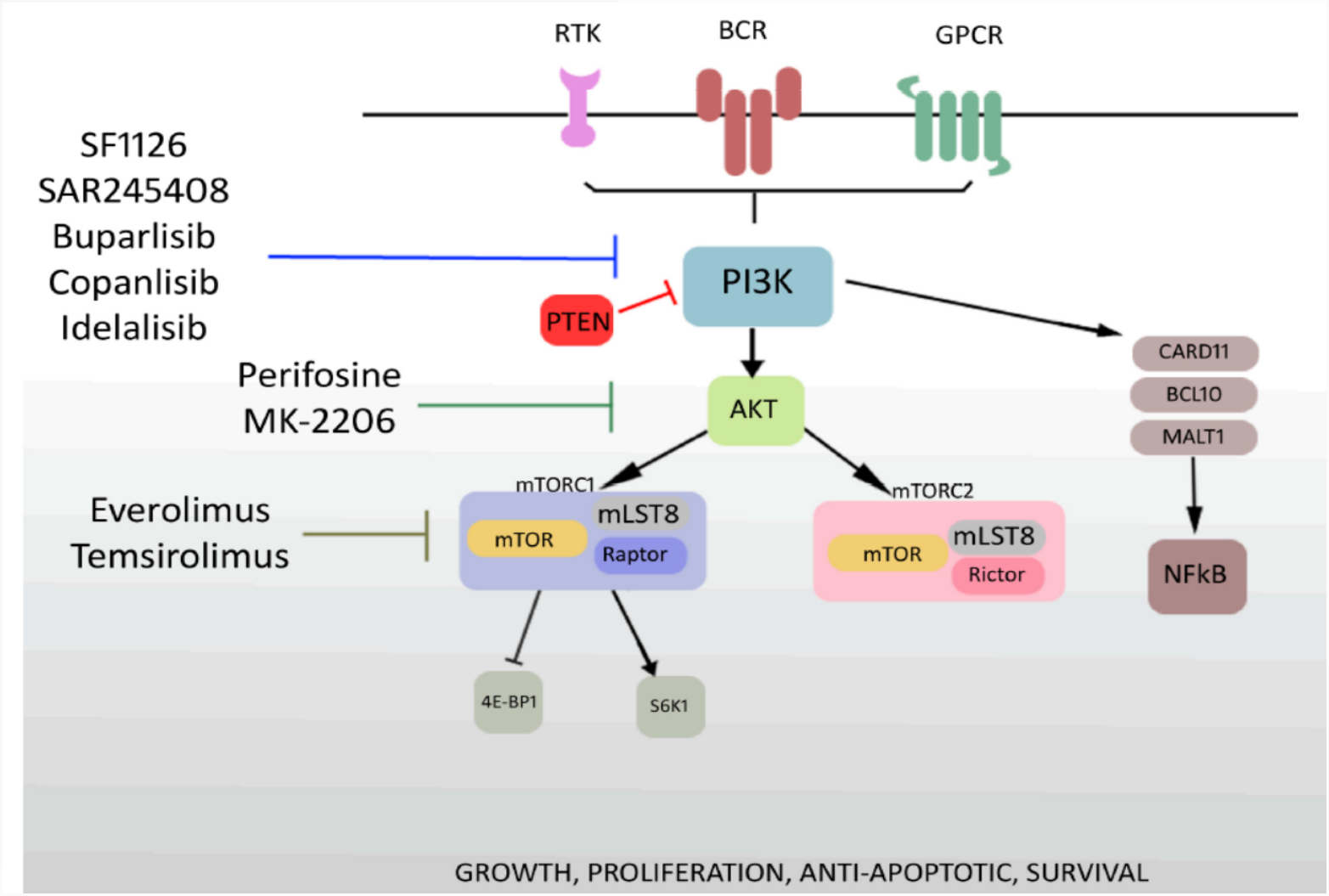
mTOR (Mammalian target of rapamycin)



Lymphoid disease	Agent used	Trial design	Clinical response
Relapsed, refractory MCL	Temsirolimus iv 250 mg weekly	Prospective phase II	ORR 38% (13 of 34 patients; 90% CI, 24–54%), median PFS 6·5 months
	Temsirolimus iv 25 mg weekly	Prospective phase II	ORR 41% (11 of 27 patients; 90% CI, 22–61%), median PFS 6 months
	Everolimus 10 mg po daily	Phase II: subgroup	ORR 32% (6 of 19 patients; 95% CI: 13–57) in subgroup
	Everolimus 10 mg po daily	Prospective phase II	ORR 20% (7 of 35 patients; 95% CI: 8–37), median PFS 5·5 months
	Temsirolimus 175 mg iv 3 weekly followed by 75 mg iv weekly; vs. temsirolimus 175 mg iv 3 weekly followed by 25 mg iv weekly; vs. single agent investigator's choice	162 patients multicentre phase III study	ORR 22% in 175 mg/75 mg vs. ORR 2% with 'investigator's choice' ($P = 0.0019$). Median PFS 4·8 months vs. 3·4 months vs. 1·9 months ($P = 0.0009$). Median OS 13·6 months (175 mg/75 mg) vs. 9·7 months (investigator's choice)
	Temsirolimus 25 mg iv weekly combined with rituximab iv 375 mg/m^2 (weekly for 4 weeks, then 4 weekly)	Phase II multicentre, prospective study	ORR 59% (41 of 69 patients; 19% CR, 41% PR). ORR 63% (30 of 48) for previously rituximab-sensitive; ORR 52% in rituximab-refractory
Relapsed, refractory DLBCL	Temsirolimus 25 mg iv weekly	Phase II: subgroup	ORR 28·1%, median PFS 2·6 months and median OS 7·2 months in subgroup
	Everolimus 10 mg po daily	Phase II: subgroup	ORR 30% (14 of 47 patients; 95% CI 17–45) in subgroup
	Everolimus 10 mg/d with rituximab 375 mg/m^2 iv weekly (4 weeks); then every 4 weeks	Prospective phase II	75% rituximab-refractory at enrolment. ORR 38% (9 of 24 patients; 90% CI: 21–56%), PFS 2·9 months (90% CI 1·8–3·8), OS 37% at 12 months
Relapsed, refractory WM	Everolimus 10 mg po daily		ORR 70% (included 28% 'minimal responses'); other 42% PR. Estimated PFS at 12 months 62%; median PFS not reached
Relapsed, refractory CLL	Everolimus 10 mg po daily	Prospective phase II study	ORR 18% (4 of 22 patients; 95% CI 5–40), median PFS 5·1 months
Relapsed, refractory HL	Everolimus 10 mg po daily	Phase II study, 19 patients	ORR 47% (9 of 19 patients; 95% CI 24–71), median PFS 7·2 months

AKT-mTOR pathway Is it active in PTCL?

✓ **The mTOR pathway is activated in ALK+ALCL**

- mTOR activation is triggered directly by NPM1/ALK
- Rapamycin induces cell-cycle arrest and apoptosis in ALK+ALCL cells.

✓ **mTORC1 activation has been detected in CD4+ T-cells from patien ts with CTCL**

- Rapamycin induces cytostatic rather than cytotoxic effect in CTCL cells.

✓ **EBV-associated PI3K/AKT activation in NKTCL**

✓ **In Japanese Phase I study of everolimus, 1 ALCL patient out of 4 had SD longer than 10mo.**

AKT-mTOR pathway activation in PTCLs

✓ Immunohistochemistry (tissue microarray methods)

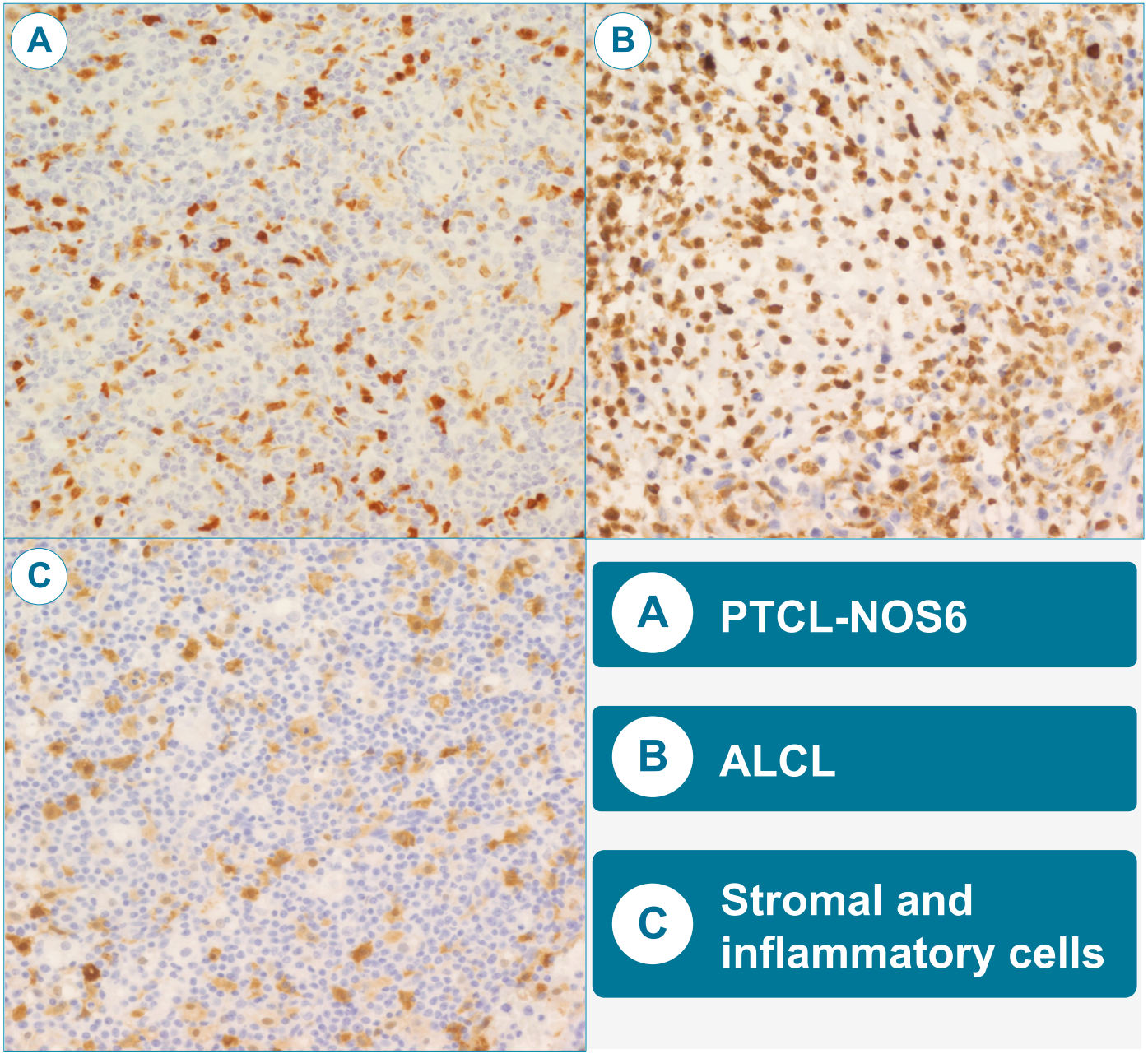
- **semi-quantitative assessment of p-AKT stained cells**
  intensity score as 0, 1+, 2+, 3+
  proportion score from 0% to 100%
- **antibody No. 9275 specific for P-AKT (Thr^{308})**
  (Cell Signaling Technology, Beverly, MA)

✓ Evaluation of p-AKT expression

- p-AKT score expressed as arbitrary units (AUs)
  p-AKT score (AUs) = intensity score* proportion score
  (ranging from 0 to 300)

- **High p-AKT group**
  : patients with p-AKT score above the highest quartile of AUs
- **Low p-AKT group**
  : patients with p-AKT score in lower 3 quartiles of AUs

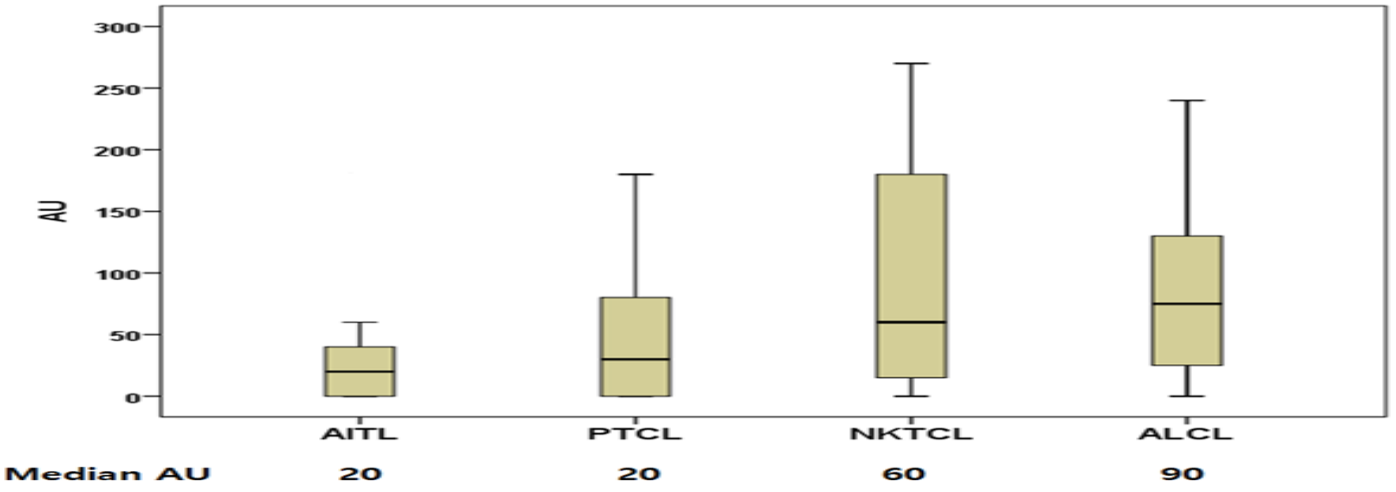
Hong et al ASH 2013



Hong et al ASH 2013

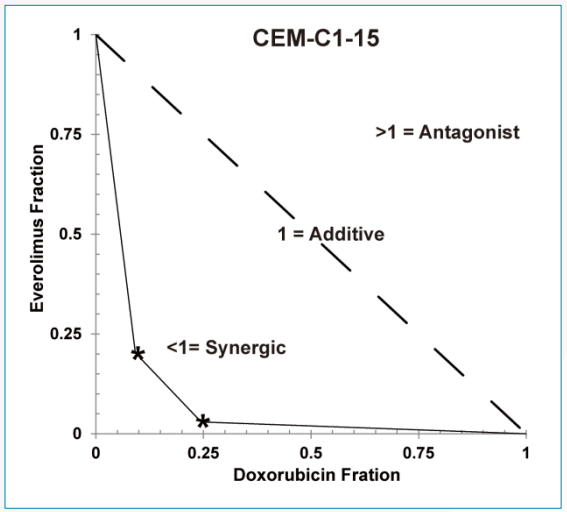
Clinical impact of AKT phosphorylation

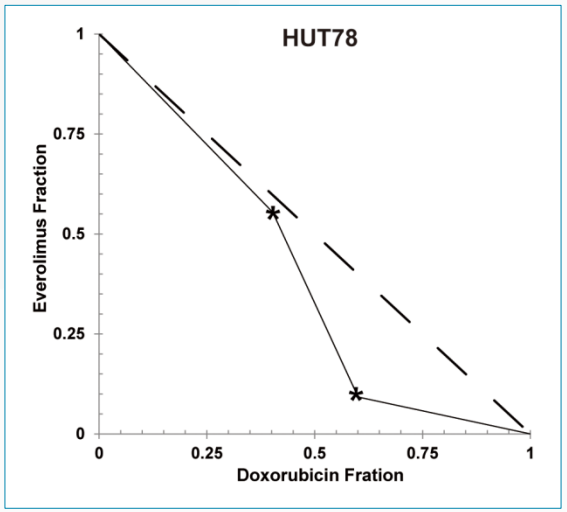
	All patients (N=63)		Low AKT (n=51)		High AKT (n=12)		*P*
Pathology, no. (%)							
PTCL-NOS	16	(25.4)	13		3		**0.02**
AITL	19	(30.2)	19		0		
ALCL	11	(17.5)	7		4		
NKTCL	17	(27.0)	12		5		
Response to front-line Tx, no. (%)							
CR or PR	34	(61.8)	32	(71.1)	2	(20.0)	**0.004**
SD or PD	21	(38.2)	13	(28.9)	8	(80.0)	

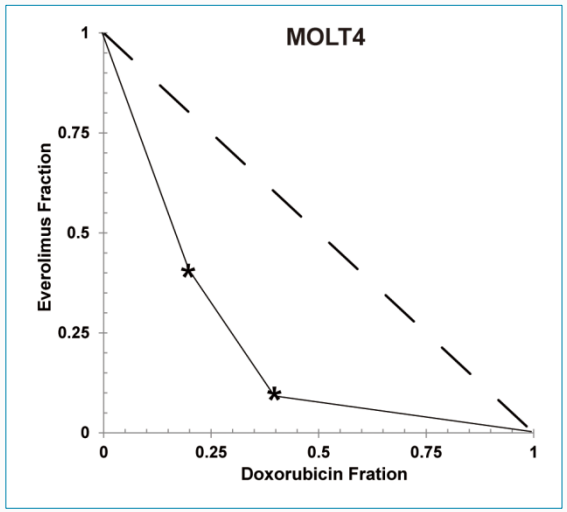


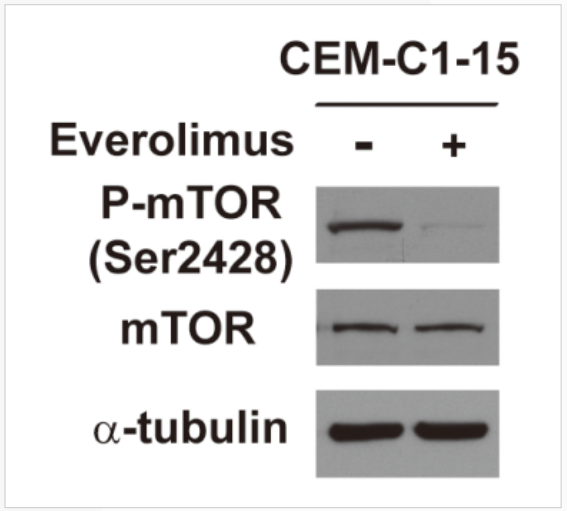
Hong et al ASH 2013

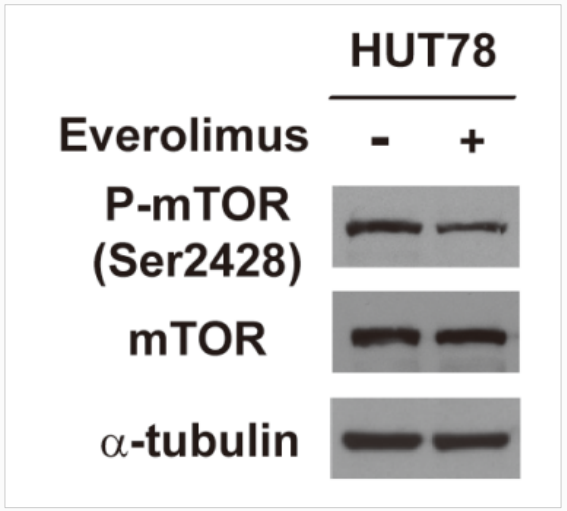
Synergism of everolimus and doxorubicine in T-cell lymphoma cell s

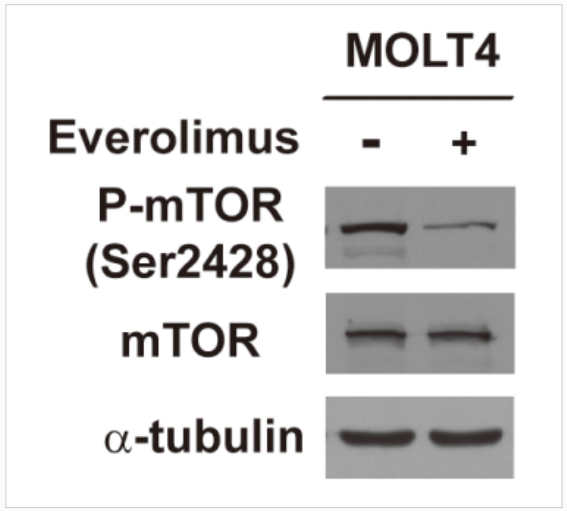












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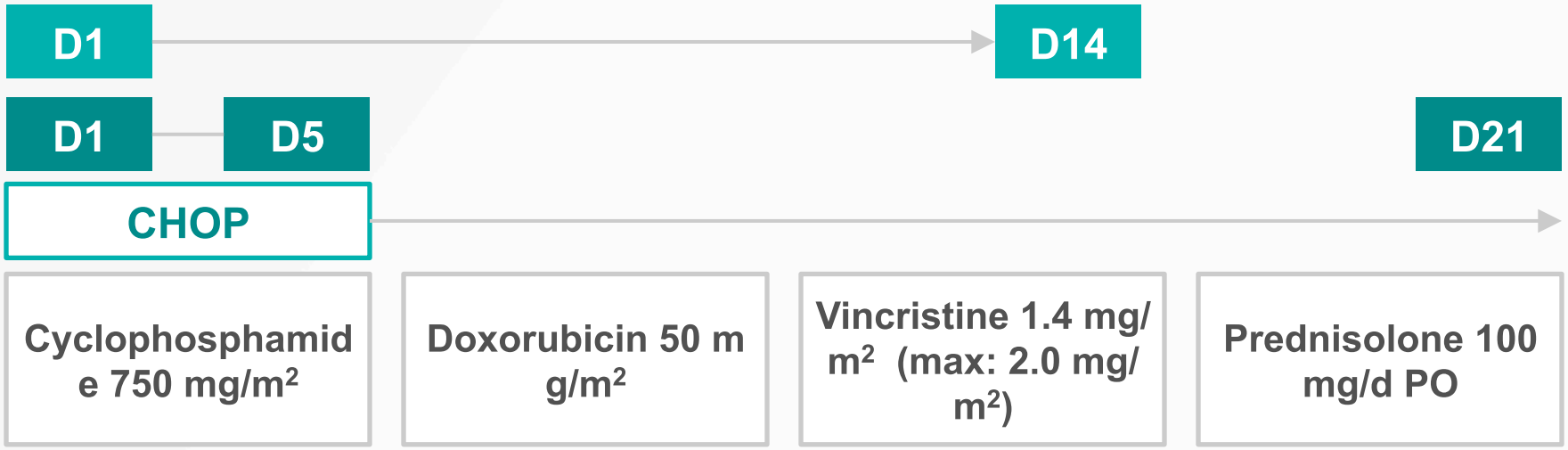
Phase I of everolimus with CHOP in newly diagnosed PTCL

A standard 3 + 3 dose escalation

everolimus: 4 dose levels (2.5, 5, 7.5, and 10 mg)



Kim SJ, et al. Invest New Drugs. 2013;31(6):1514-21

Patient Characteristics

Characteristics		N	%	Characteristics		N	%
Age	≤ 60	11	73	B symptoms	Presence	8	53
	> 60	4	27		Absence	7	47
Sex	Male	5	67	BM invasion	Presence	6	40
	Female	10	33		Absence	9	60
ECOG PS	< 2	14	93	Bulky disease	Bulky	3	20
	2	1	7		Non-bulky	12	80
Ann Arbor stage	III	4	27	Serum LD	Normal	2	13
	IV	11	73		Increase	13	87

Peripheral T-cell lymphoma-unspecified (PTCL-U, n = 8); Angioimmunoblastic T-cell lymphoma (AITL, n = 4); ALK-negative, anaplastic large cell lymphoma (ALCL, n = 1); Cutaneous T-cell lymphoma (CTCL, n = 2)

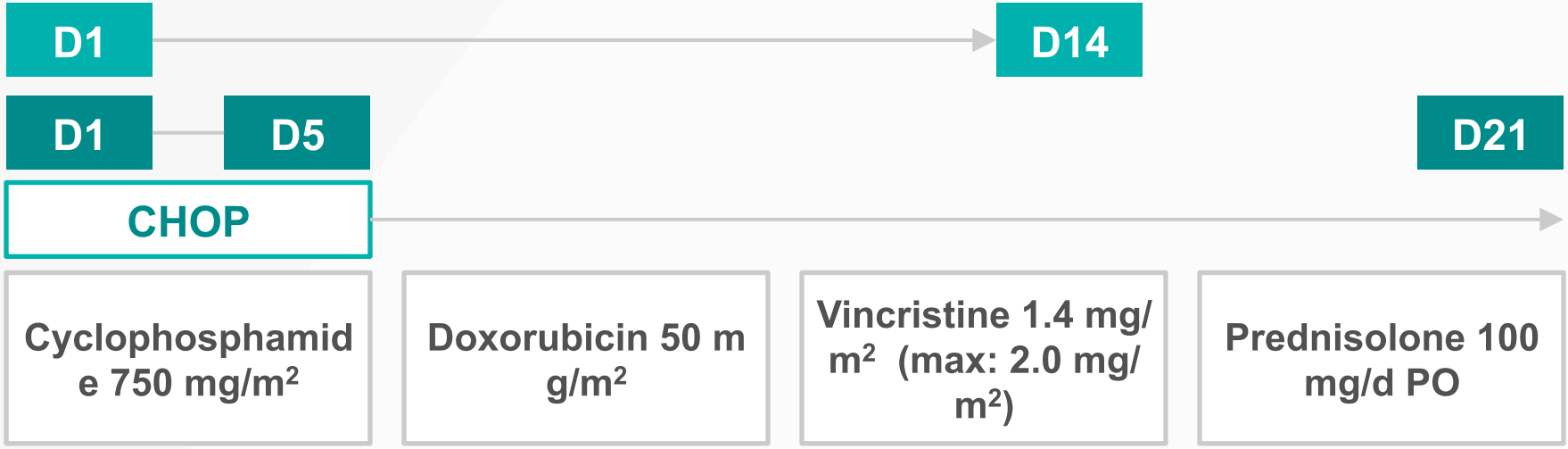
Summary of DLT

Level	No.	Subtype	Sex	Age	Stage	Serum LD	Dose-limiting toxicity	Best Response	Current status
1	001	AITL	M	55	IIIB	Inc		CR	CR
	002	PTCL-U	F	68	IVA	Inc		CR	Relapse
	003	PTCL-U	F	59	IVA	Inc		PR	PD
2	004	AITL	F	59	IVB	N		CR	CR
	005	AITL	M	57	IVB	N		PR	PD
	006	PTCL-U	F	42	IIIA	Inc	G3 LFT abnormality	CR	CR
	007	PTCL-U	F	61	IVB	Inc		PR	PD
	008	CTCL	F	21	IVA	Inc		CR	CR
	009	AITL	F	59	IIIB	Inc		CR	CR
3	010	PTCL-U	F	67	IVB	Inc	G4 Thrombocytopenia	PR	PR
	011	PTCL-U	F	41	IVA	N		CR	Relapse
	012	PTCL-U	M	53	IIIA	N	G4 Thrombocytopenia	CR	CR
	013	PTCL-U	M	45	IVB	Inc	G4 Febrile neutropenia	NE	NE
	014	ALCL	M	68	IVB	Inc		PR	PD
	015	CTCL	F	49	IVA	Inc		PR	PD

ORR 100% (4 CRs and 2 PRs) at level 2

Phase II study of RAD001 combined with CHOP in newly diagnosed peripheral T-cell lymphomas

everolimus: 4 dose levels (2.5, 5, 7.5, and 10 mg)



Patient characteristics

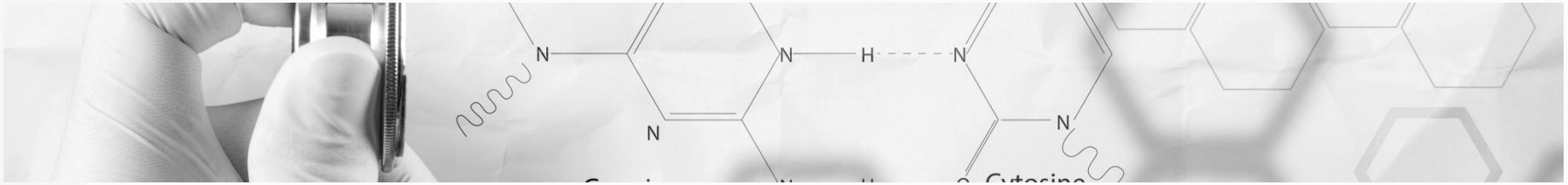
N 30

Characteristics		N	%	Characteristics		N	%
Age	≤ 60	19	63	B symptoms	Absence	16	53
Median 54 (18-71)	> 60	11	37		Presence	14	47
Sex	Male	15	50	BM invasion	Absence	23	77
	Female	15	50		Presence	7	23
ECOG PS	< 2	25	83	Bulky disease	Non-bulky	27	90
	2	5	17		Bulky	3	10
Ann Arbor stage	II	2	7	IPI	L	6	20
	III	10	33		LI	7	23
	IV	18	60		HI	8	27
Serum LD	Normal	12	40		H	9	30
	Increase	18	60				

Unpublished data

Histologic subtype

Subtypes	N	%
Peripheral T-cell lymphoma, not-otherwise specified (PTCL)	19	63
Angioimmunoblastic T-cell lymphoma (AITL)	3	10
ALK-negative Anaplastic large cell lymphoma (ALCL)	7	23
Subcutaneous panniculitis-like T cell (SPTCL)	1	3



Unpublished data

Response

	Final response		Best response	
	N	%	N	%
CR	17	57	17	57
PR	4	13	10	33
PD	7	23	1	3
NE*	2	7	2	7
ORR/CR		70/57		90/57

Causes of not evaluated cases
#1: Early stop due to grade 4 febrile neutropenia after 2nd cycle
#2: Early stop due to grade 3 pulmonary venous thromboembolism after 1st cycle

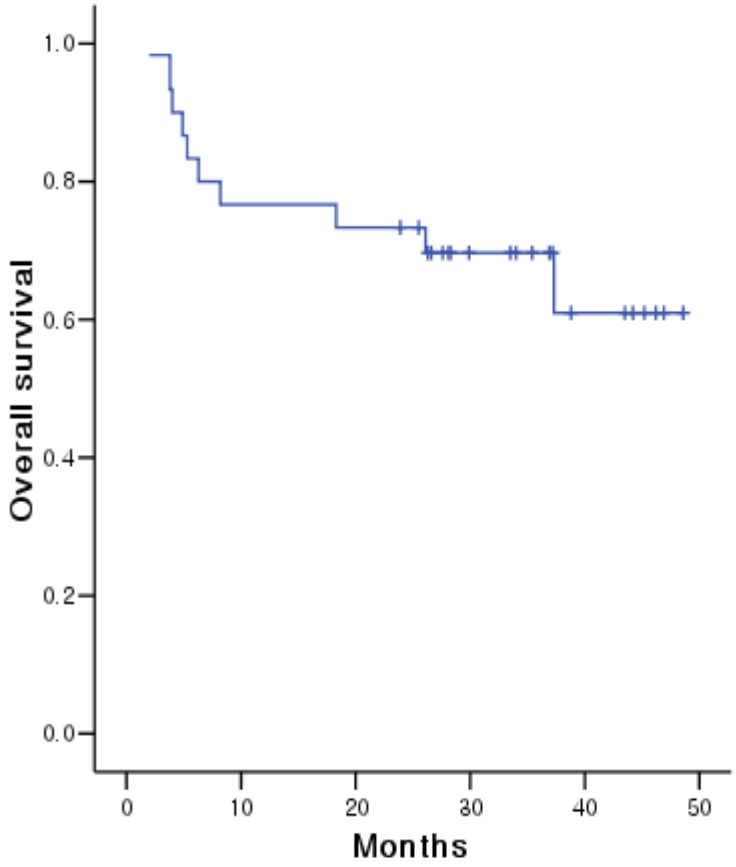
Unpublished data

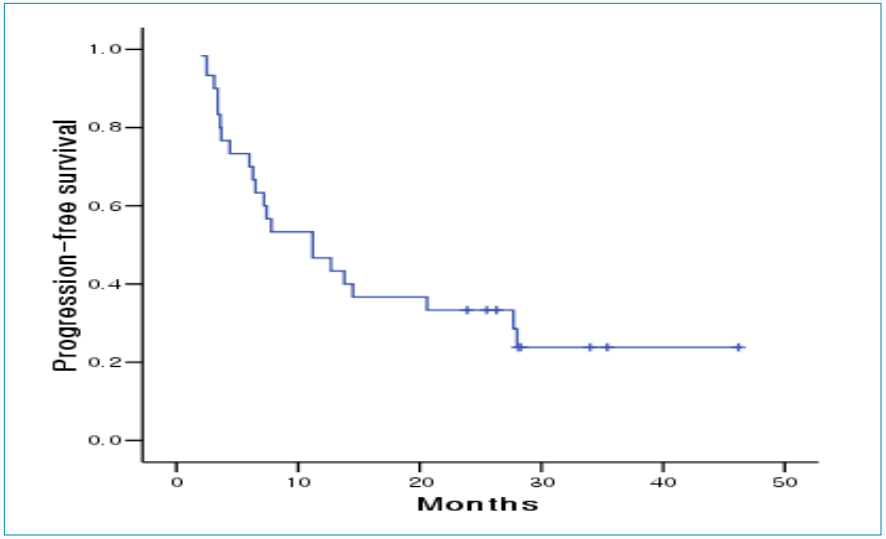
Comparison of Final Response

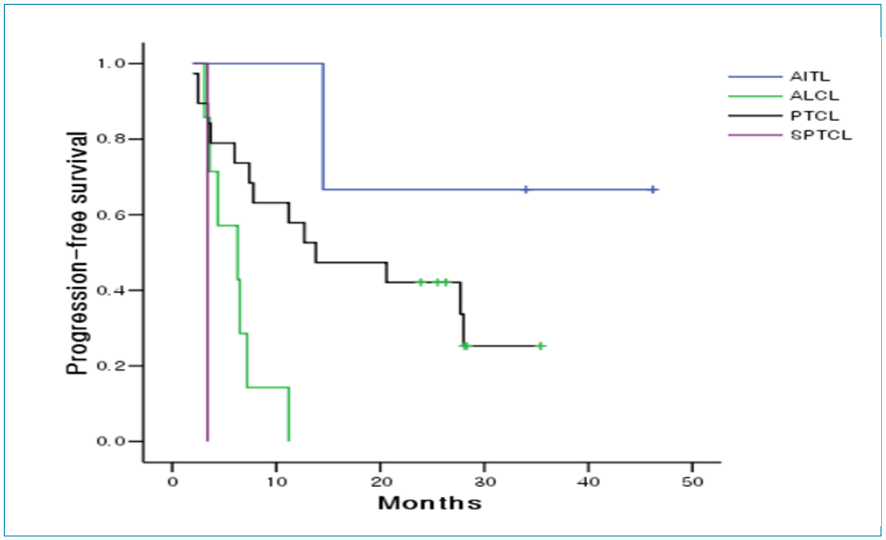
	PTCL (n = 19)	AITL (n = 3)	ALCL (n = 7)	SPTCL (n = 1)
CR	12	3	2	
PR	2		2	
PD	4		2	1
NE	1		1	
ORR/CR (%)	74/63	100/100	47/28.6	0/0

Unpublished data

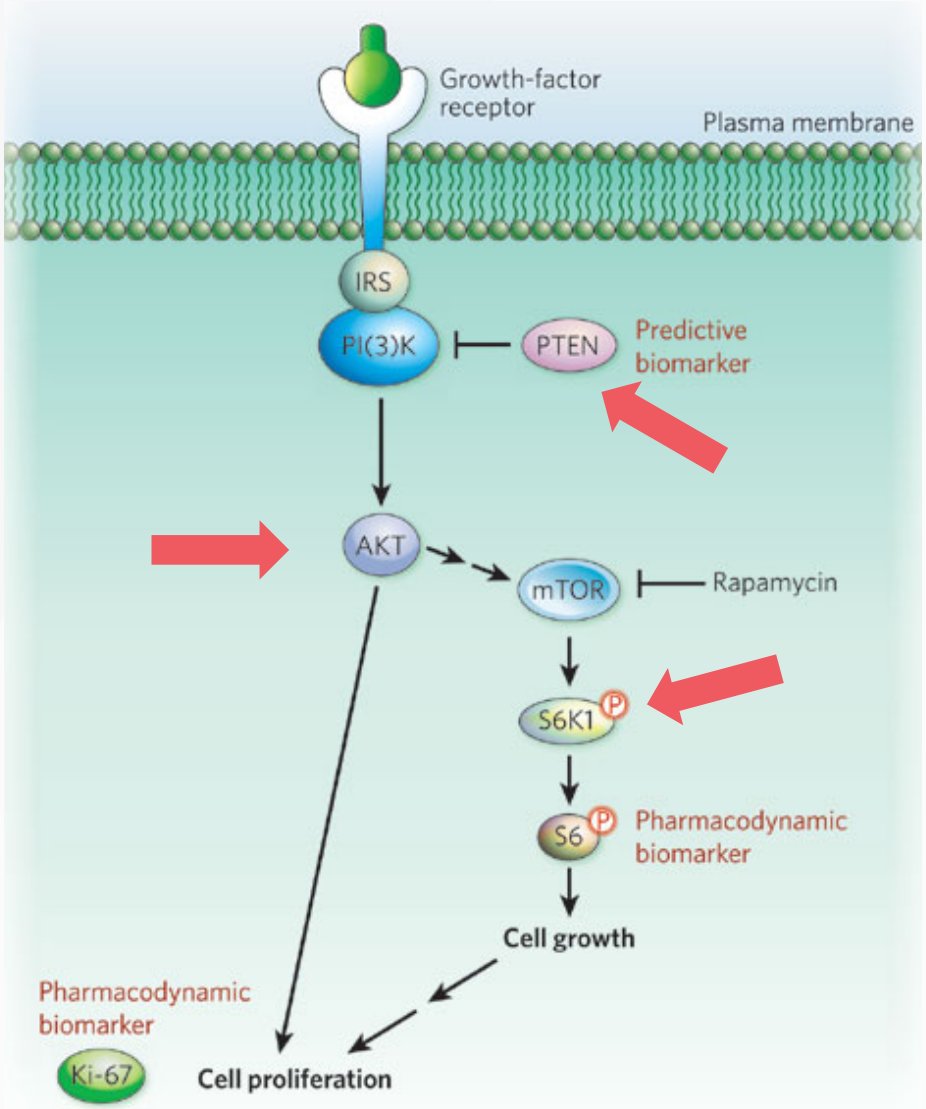
Survival outcomes







mTOR pathway



Phospho-p70 S6 kinase

	PTCL (n = 7)	AITL (n = 2)	ALCL (n = 5)	Total (n=14)
Positive	3	1	3	7
Negative	4	1	2	7

	CR (n = 7)	PR (n = 3)	PD (n = 2)	NE (n=2)	Total (n=14)
Positive	3	1	3	1	7
Negative	4	1	2	1	7

P = 0.450

Definition of positivity

At least 10% of tumor cells should be positive based on the grade from 1+ to 3+

PTEN

	PTCL (n = 7)	AITL (n = 2)	ALCL (n = 6)	Total (n=15)
Positive	6	2	4	12
Negative	1	0	2	3

	CR (n = 8)	PR (n = 3)	PD (n = 2)	NE (n=2)	Total (n=15)
Positive	8 (67%)	1	1	2	12
Negative	0	2	1	0	3

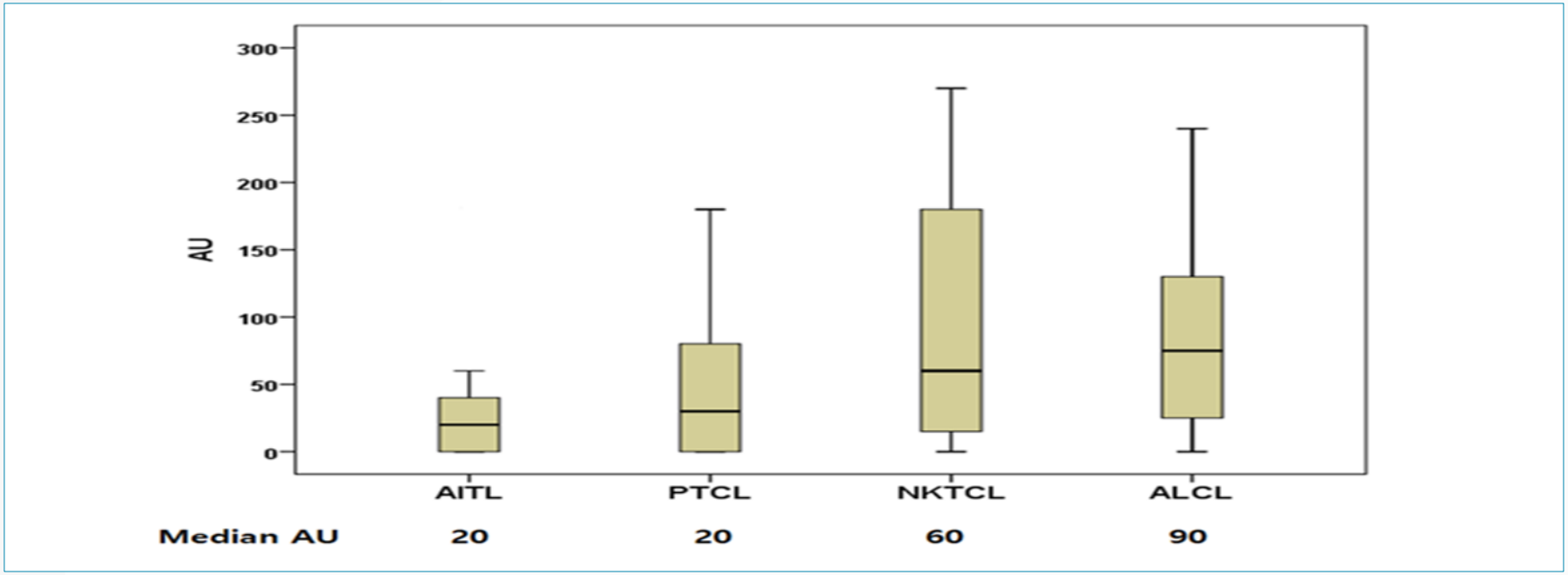
P = 0.05

Definition of positivity

At least 10% of tumor cells should be positive based on the grade from 1+ to 3+

Phopho-AKT


공사중


AU
300
250
200
150
100
50
0
AITL
PTCL
NKTCL
ALCL
Median AU
20
20
60
90

Hematologic Toxicities

	Grade 1	Grade 2	Grade 3	Grade 4
Hematologic toxicity				
Anemia	6	9		2
Neutropenia		3	11	13
Thrombocytopenia	1	8	11	7
Febrile neutropenia			7	4

N 30

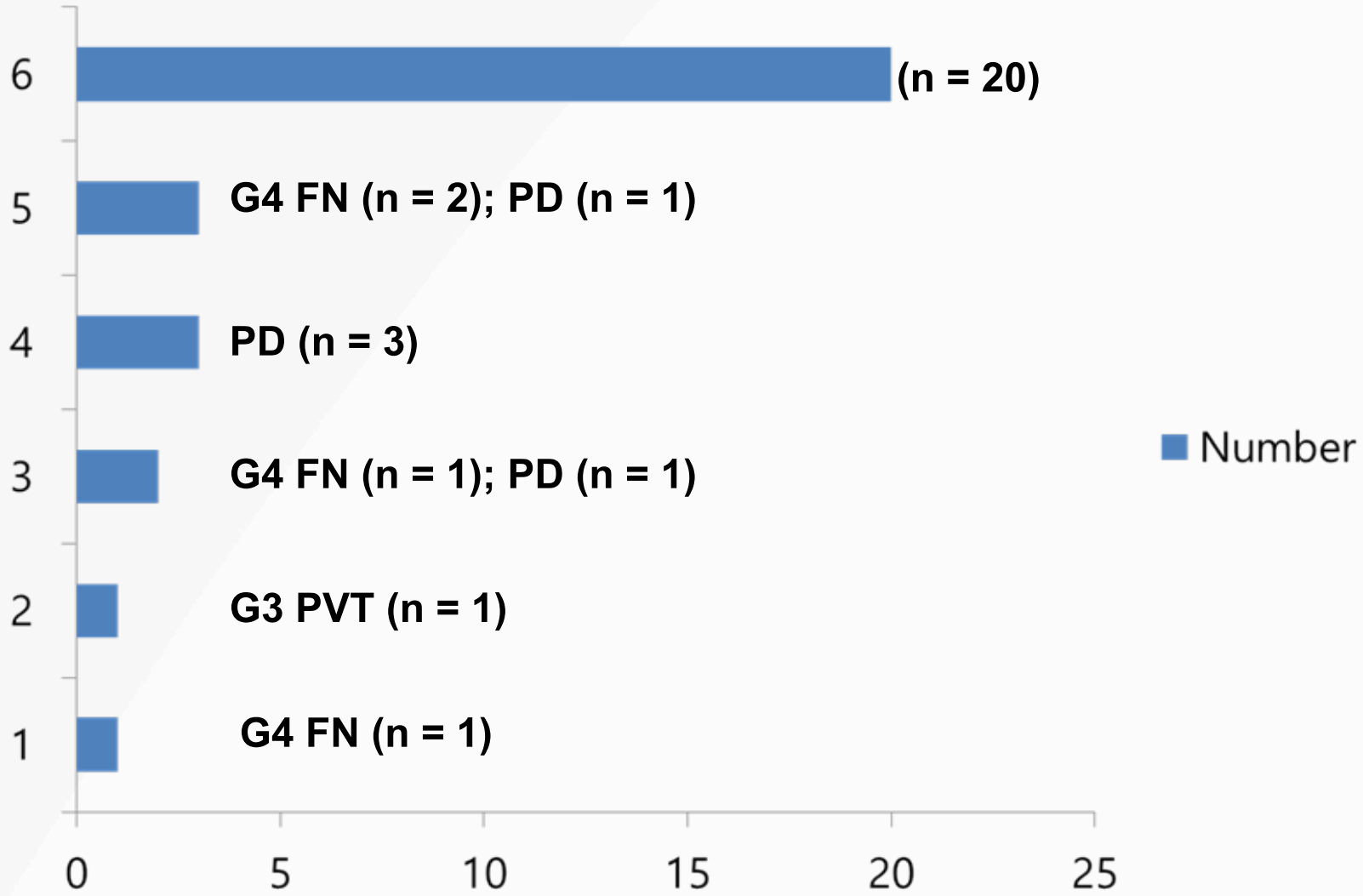
Unpublished data

Non-Hematologic Toxicities

	Grade 1	Grade 2	Grade 3	Grade 4
Nausea	4	1	1	
Vomiting	1			
Mucositis	2	4		
Neuropathy	7			
Abdominal pain	1		1	
Constipation	3			
Diarrhea	1	1	1	
Herpes simplex	2			
Cough	3	1		
Pneumonia			2	
Epistaxis			1	
Pulmonary venous embolism			1	
BK virus			1	
Liver function test			1	
Renal function		1		

Unpublished data

Number of cycles



CHOP+everolimus

Is it effic ient?

Yes,

especially in PTEN+PTCL

No,

especially in PTEN-PTCL

Everolimus dose was low to over come activated mTOR pathyway comparing conventional dose in B-cell lymphoma

Thank You

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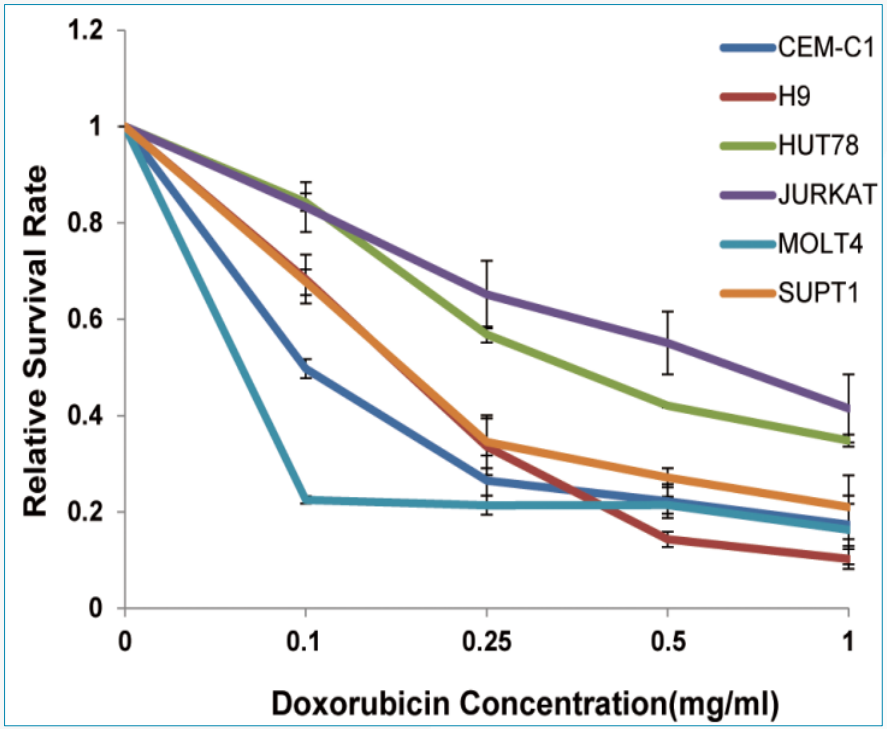
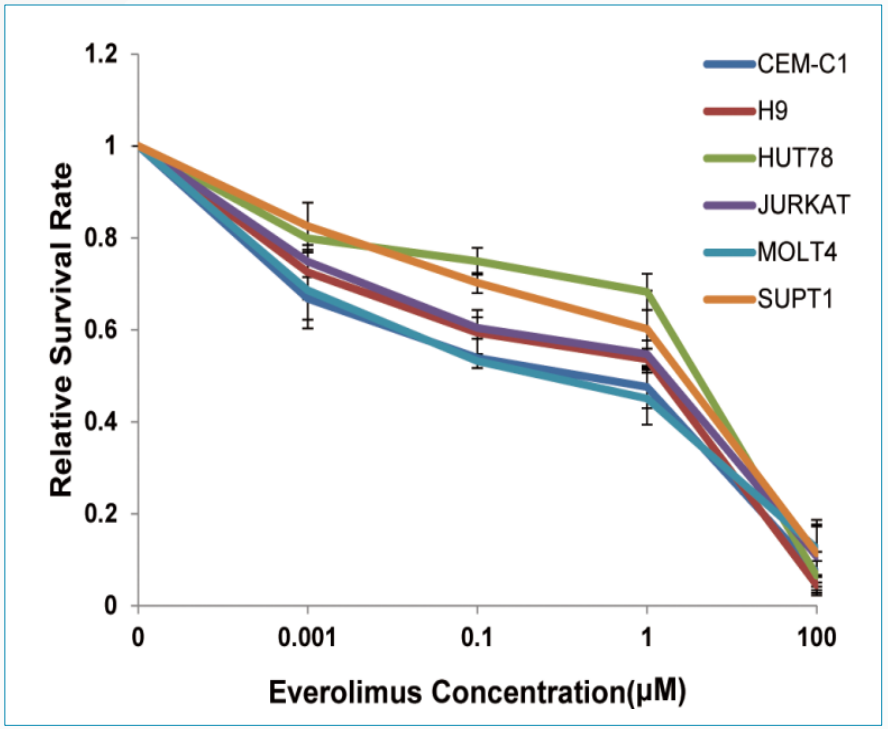
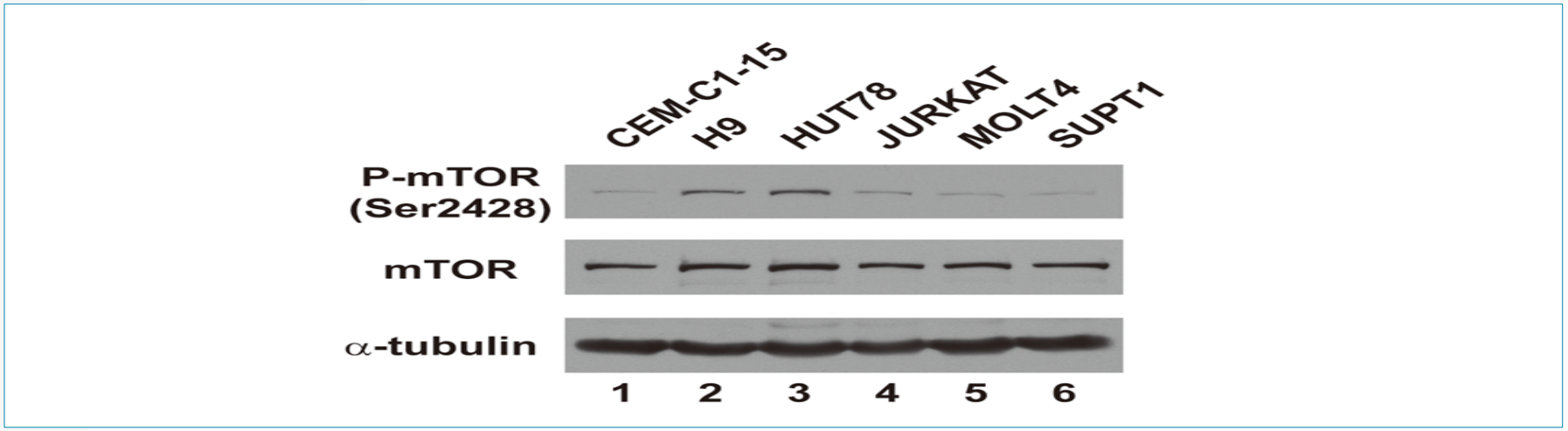
RAD001

- On D8 of RAD001 administration during the first cycle, th e hematologic results must be:
  - Platelet count ≥ 30 x 10^9/L AND
  - ANC ≥ 0.75 x 10^9/L
  - If the above parameters are not met, the remaining schedule of RAD001 dose will be skipped
  - If D8-14 RAD001 were skipped due to hematologic toxicity, the d ose of RAD001 will be reduced in the following cycles

- Dose reduction of RAD001: 5mg → 2.5mg
  - Two patients after 1st cycle
  - One patient after 2nd cycle







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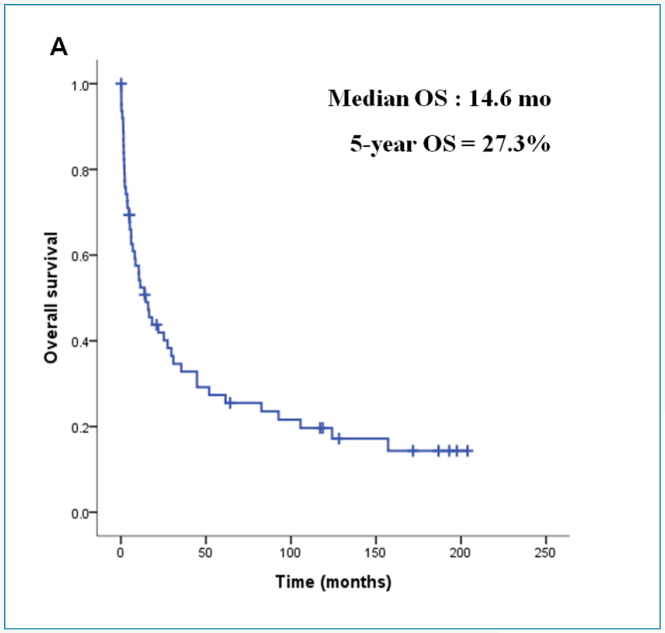
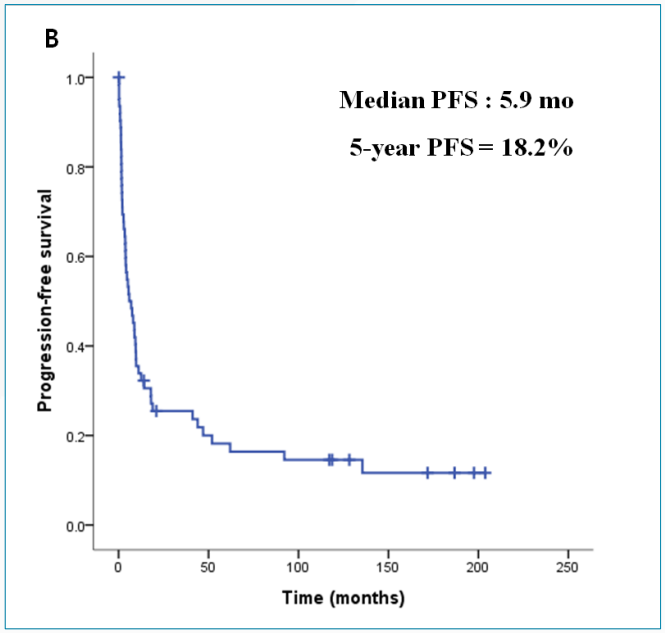
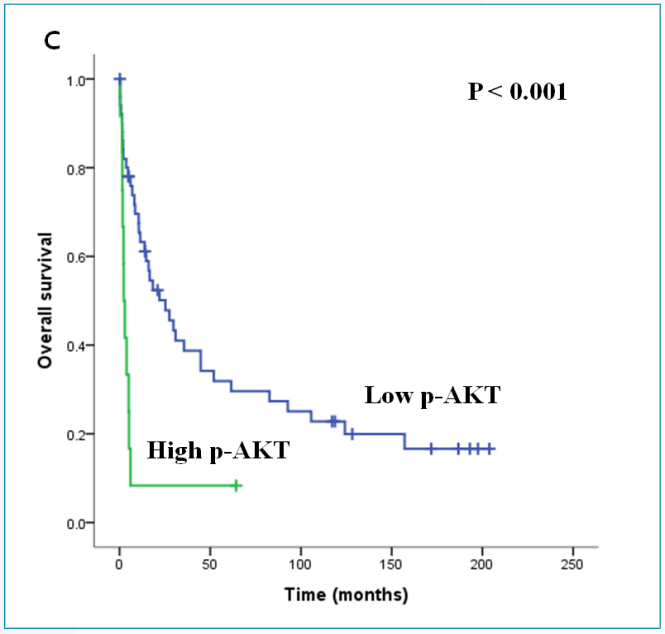
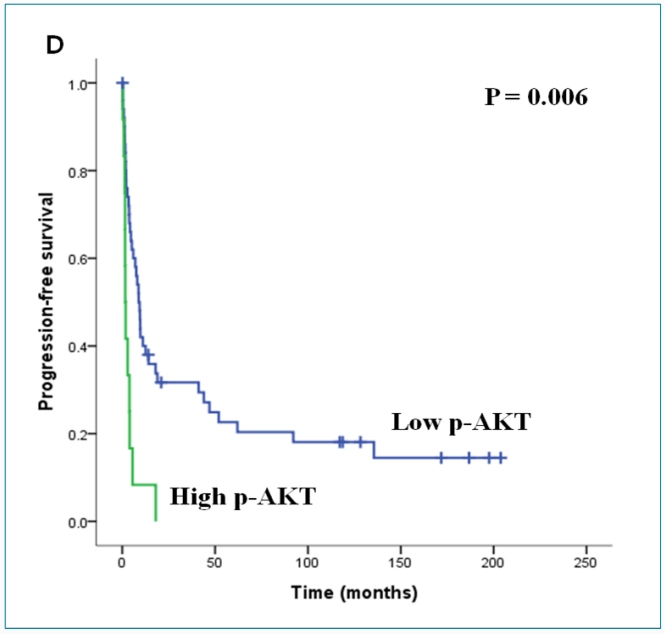

A
Median OS : 14.6 mo
5-year OS = 27.3%
Overall survival
Time (months)


B
Median PFS : 5.9 mo
5-year PFS = 18.2%
Progression-free survival
Time (months)


C
P < 0.001
Low p-AKT
High p-AKT
Overall survival
Time (months)


D
P = 0.006
Low p-AKT
High p-AKT
Progression-free survival
Time (months)