Copanlisib (BAY 80-6946) in peripheral T cell lymphomas

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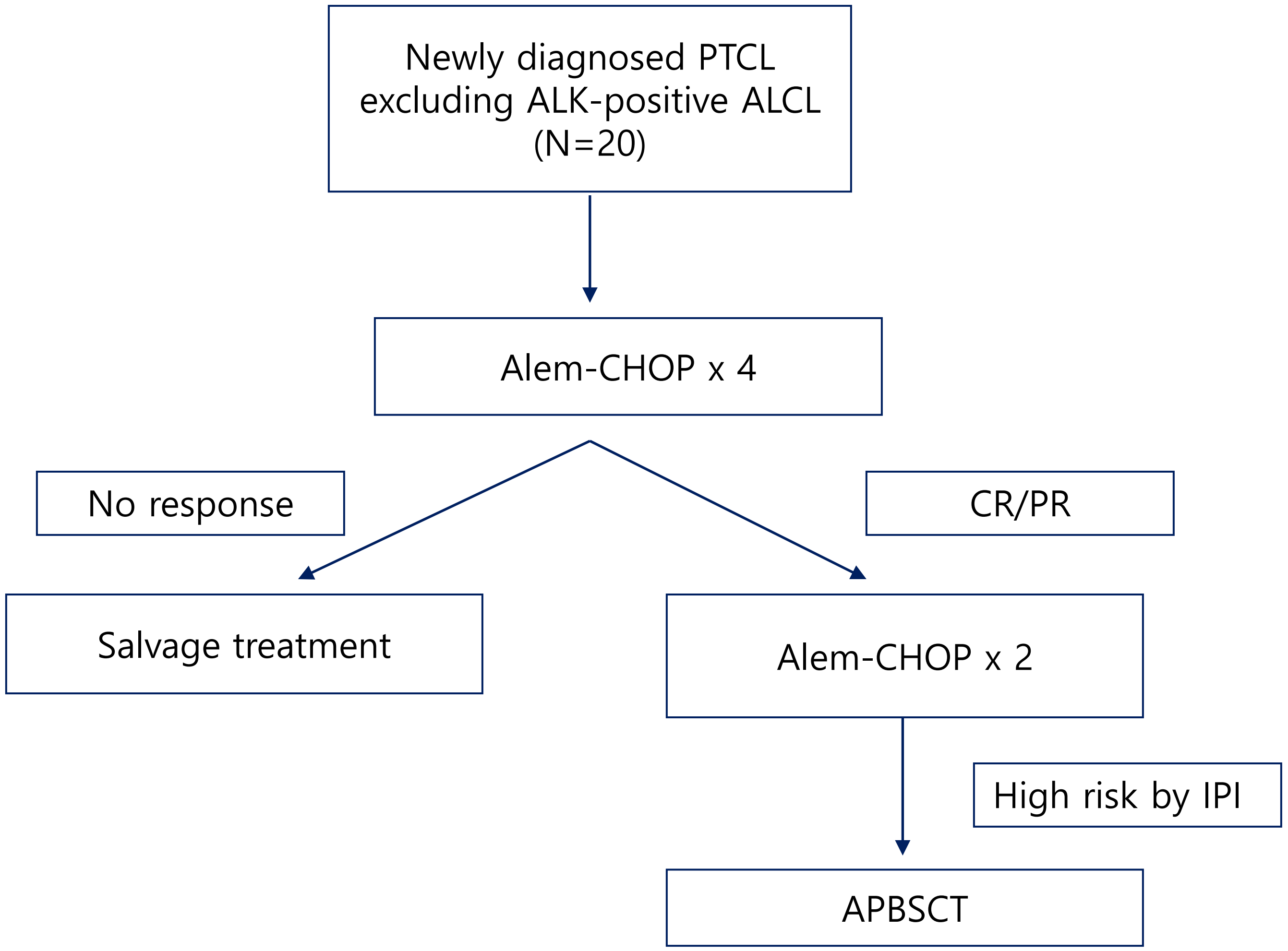
Alem-CHOP in Korea

Treatment scheme



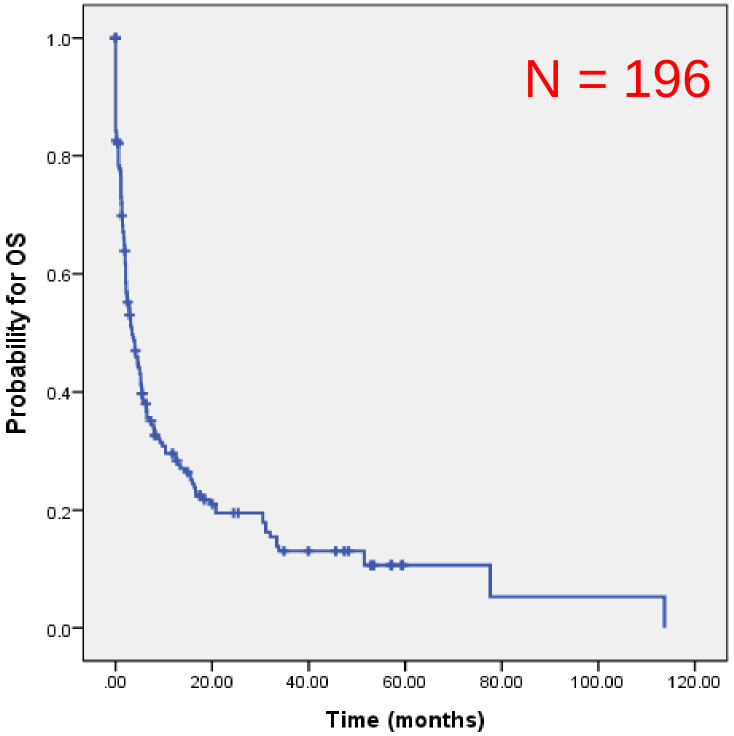
ORR: 80%
13 complete responses (65.0%) and three partial responses (15.0%)

Febrile neutropenia was observed in 11 patients (55.0%). Five patients (25%) experienced cytomegalovirus (CMV) reactivation

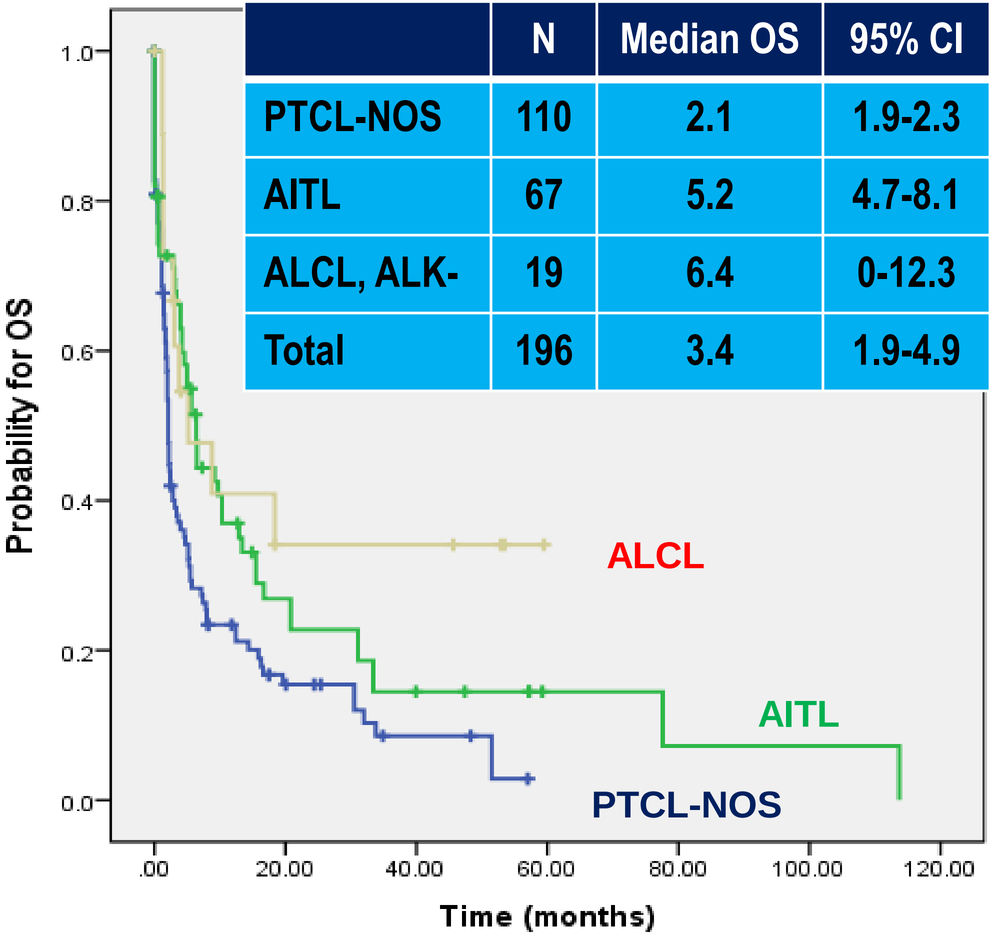
Cancer chem pharma 2007 Jun;60(1):129-34

Poor outcome of RR nodal PTCL – Korean data

Median follow-up duration: 50.4 months (IQR; 21.8 – 70.9 months)



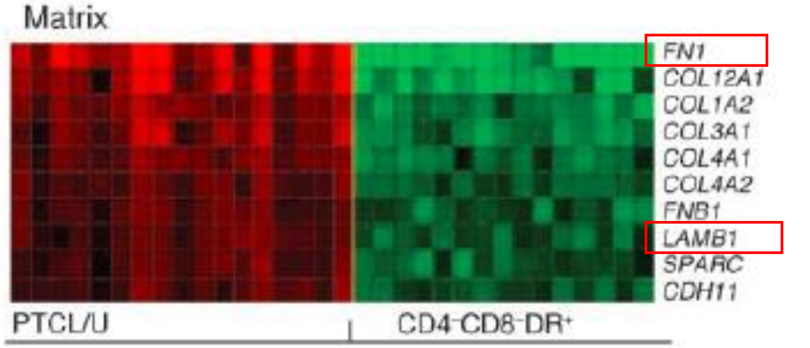
Median OS : 3.4 months (95% CI, 1.9 – 4.9)

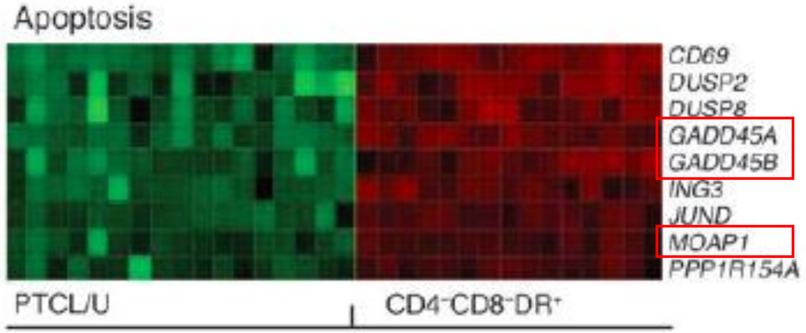


	N	Median OS	95% CI
PTCL-NOS	110	2.1	1.9-2.3
AITL	67	5.2	4.7-8.1
ALCL, ALK-	19	6.4	0-12.3
Total	196	3.4	1.9-4.9

Gene expression profiles of PTCLs

Overexpressed genes in PTCLs
(cell adhesion and matrix remodeling)
: FN1 and LAMB1 also regulate the apoptotic process
- through the PI3K/AKT and MEK/ERK pathways, respectively



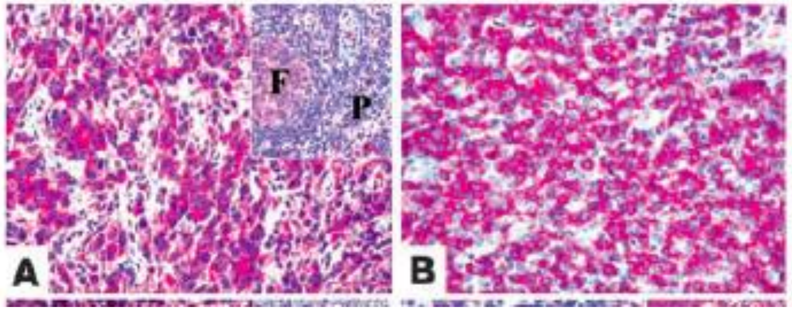


The group of Down-regulated genes (apoptosis)
1) GADD45A and 45B : growth arrest and DNA damage-inducible α and β
   - control of apoptosis
2) MOAP1 : a Bcl-2 homology 3-like motif (BH3)
   - interact with Bax, mediating caspase-dependent apoptosis

Table 1
Immunohistochemical analysis on TMAs

Marker	Evaluable cases	Positive cases (>30% positive elements)	Percentage of positive cases
Caldesmon	129	128[A]	99
BCL10	75	15	20
IGFBP7	120	68	57
p27	114	53[B]	46
PDGFRα	133	121	91
p-PDGFRα	110	105	95
CYR61	137	132	96
LIFR-1	116	36	31

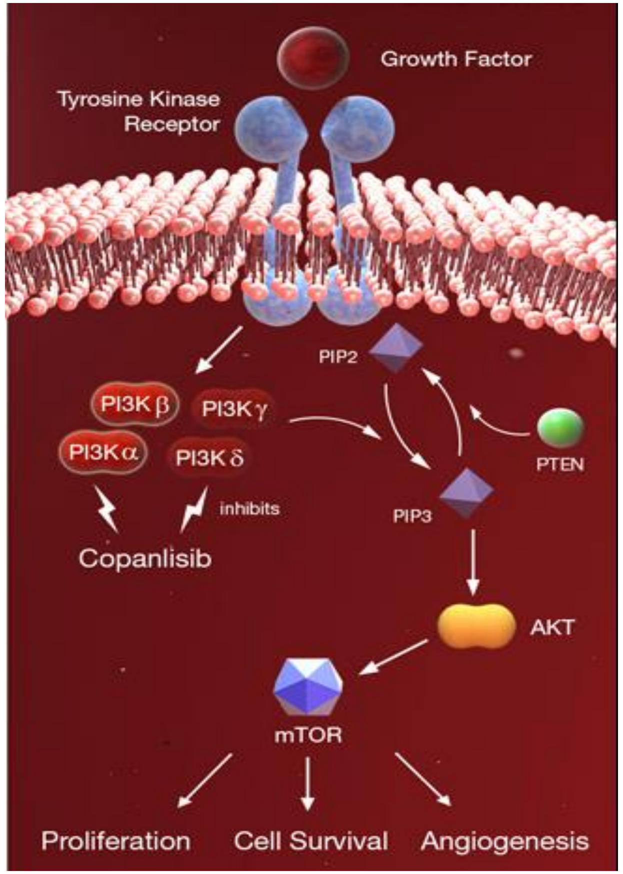
[A]Stromal reactivity. [B]In most cases, p27 was expressed but by less than 30% of the neoplastic elements.

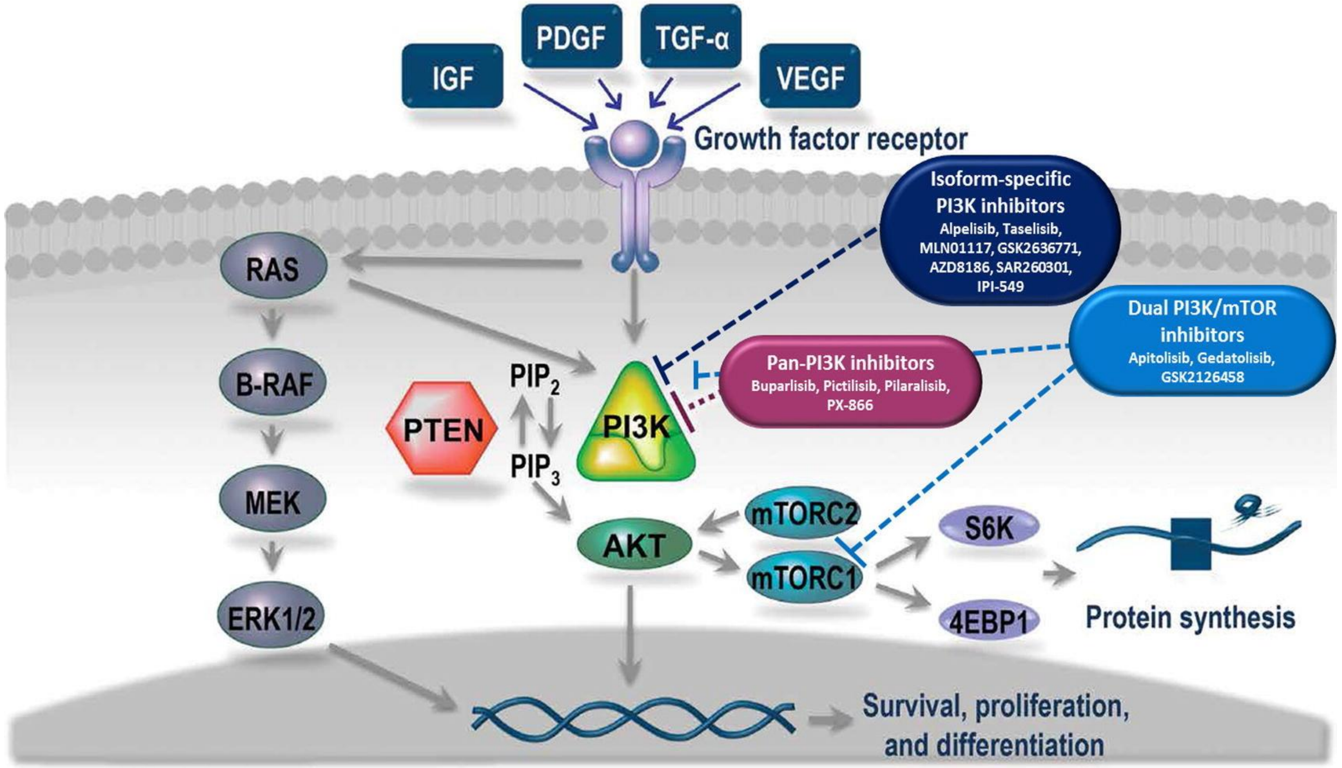


PDGFRa and p-PDGFRa : strongly expressed in PTCL

Copanlisib could induce the apoptosis of T cell lymphoma cells

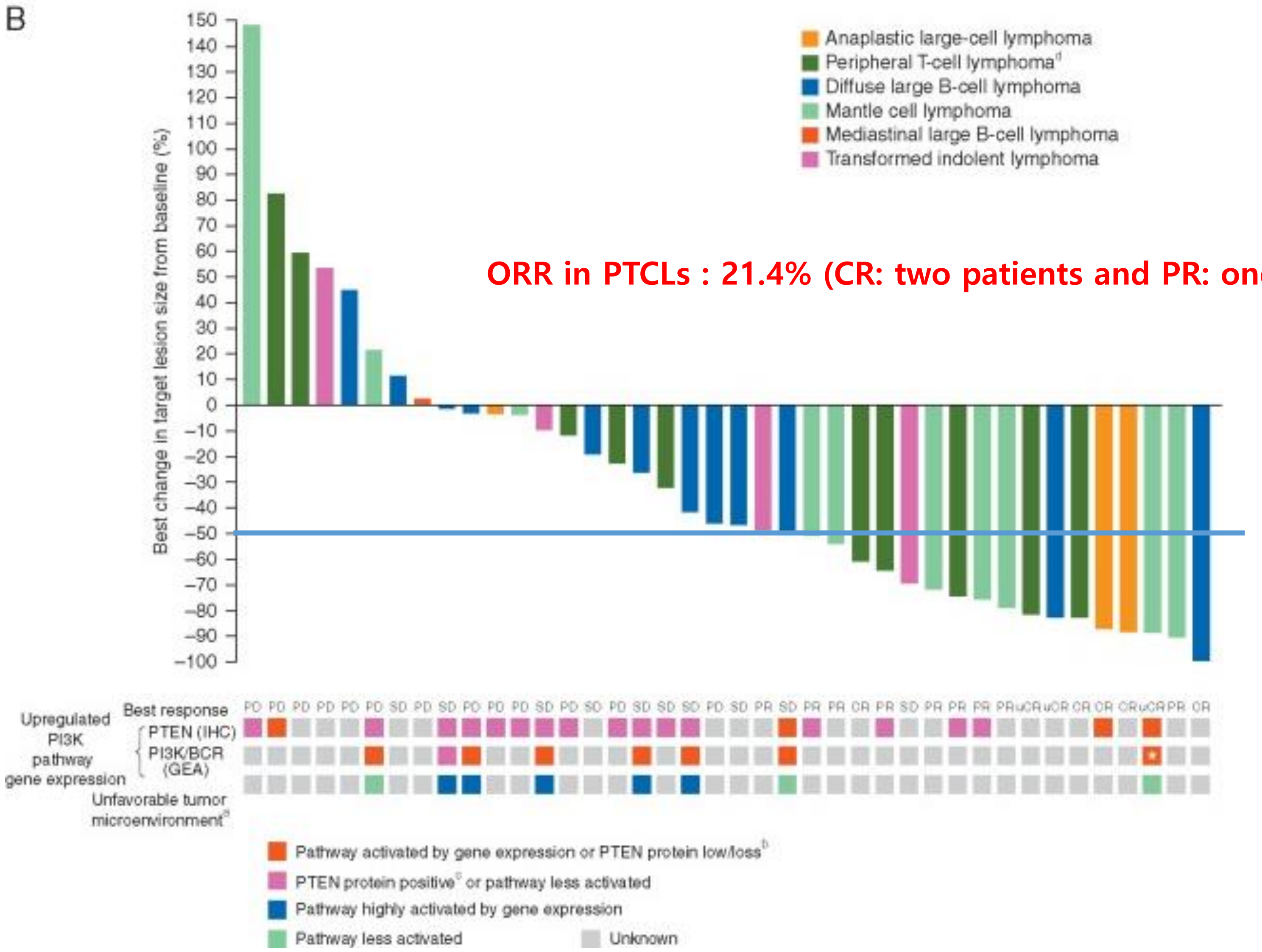
- **Copanlisib** : class I, pan kinase inhibitor of PI3K α/β/γ/δ, which has demonstrated a potency to treat not only solid cancer but hematologic malignancy
  - *PI3Kδ:* Key factor to BCR(B Cell Receptor) and TCR(T Cell Receptor)-induced intracellular signaling
  - the p110α catalytic isoform is essential for the growth of tumors driven by *PIK3CA* mutations and/or oncogenic *RAS* and receptor tyrosine kinases
  - targeting p110δ may result **in immunomodulatory side effects**





Cancer Treatment Reviews 2017

Phase II study of copanlisib, a PI3K inhibitor, in relapsed or refractory, indolent or aggressive lymphoma



ORR in PTCLs : 21.4% (CR: two patients and PR: one)

Ann Oncol 2017 Sep 1;28(9):2169-2178

Open-labeled, multicenter phase I and II study of combined chemotherapy with Gemcitabine and Copanlisib (BAY 80-6946) in relapsed or refractory peripheral T cell lymphomas

Study design

CG regimen (Phase I study : 3 + 3 study)

Copanlisib	**Level I-II** mg 1-hr infusion rate	**D1, D8, D15**
Gemcitabine	**1000 mg/m^2** in fixed infusion rate of 40 minutes	**D1, D8**

Be repeated every 28 days

Dose level will be determined as escalating dose level schedule as followed.

	Level - I	Level I	Level II
Gemcitabine (mg/m^2)	1000	1000	1000
Copanlisib (mg)	30	45	60

c.f.) Referenced to maximum tolerable dose (MTD) of Copanlisib (0.8 mg/kg D1, D8, D15) in Western study,

phase I study of CG combined chemotherapy in adult East ASIAN patients with PTCLs will start with low MTD dose.

Treatment period

Total number of administration: **CG 6 cycles + Copanlisib Monotherapy for 12 months**

Inclusion criteria

① Histologically confirmed **relapsed or refractory PTCLs excluding ALK-positive anaplastic large cell T-cell lymphomas (ALCL), primary cutaneous T cell lymphoma, and Sezary Syndrome.**

② performance status (ECOG) ≤2

③ age > 18

④ At least one or more unidimensionally measurable lesion(s)

- ≥1.5 cm by conventional CT
- ≥ 1 cm by spiral CT
- skin lesion (photographs should be taken)
- measurable lesion by physical examination

⑤ Laboratory values

–Cr ≤ 1.5 mg/dL or Ccr ≥ 50 ml/min

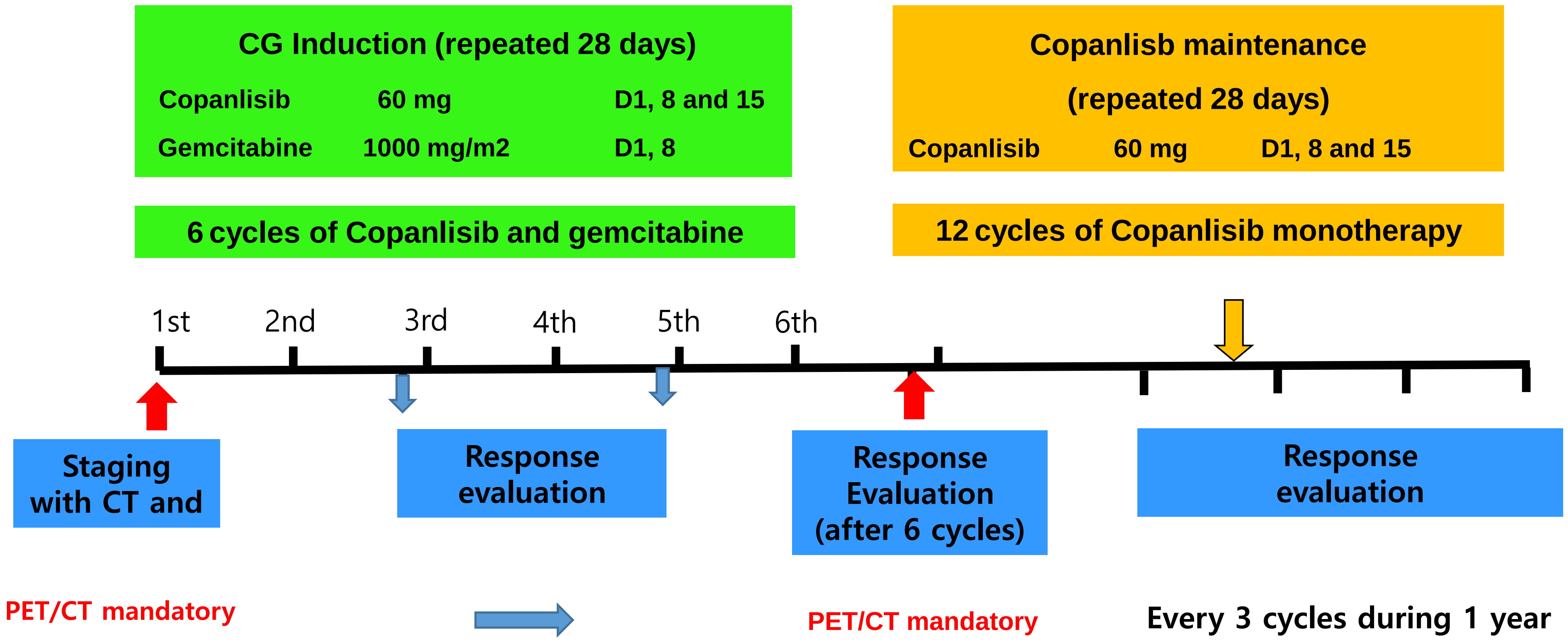
–Transaminase < 3 X upper normal value

–Bilirubin < 2.0 mg/dl

–ANC ≥ 1,500/ul, platelet ≥ 75,000/ul

② Informed consent

Response assessment



Study status and comments

- **Phase I : N= total 6 patients (started from 28th Mar. 2018)**

  → Level I (N=3) and Level II (N=3) : No DLT happened

- **Phase II : N=25 patients including 3 patients of Level II (closed the enrollment at May 2019)**

  → **25 patients** are enrolled recently including 3 patients of Level I

- **Prophylactic antibiotics with trimethoprim-sulfamethoxazole** (Bactrim, 1 tablet) once a day

- **Allogenic stem cell transplantation : one patients** who achieve ≥ PR after 4 cycles of CG combination.

- **No treatment-related mortality reported**

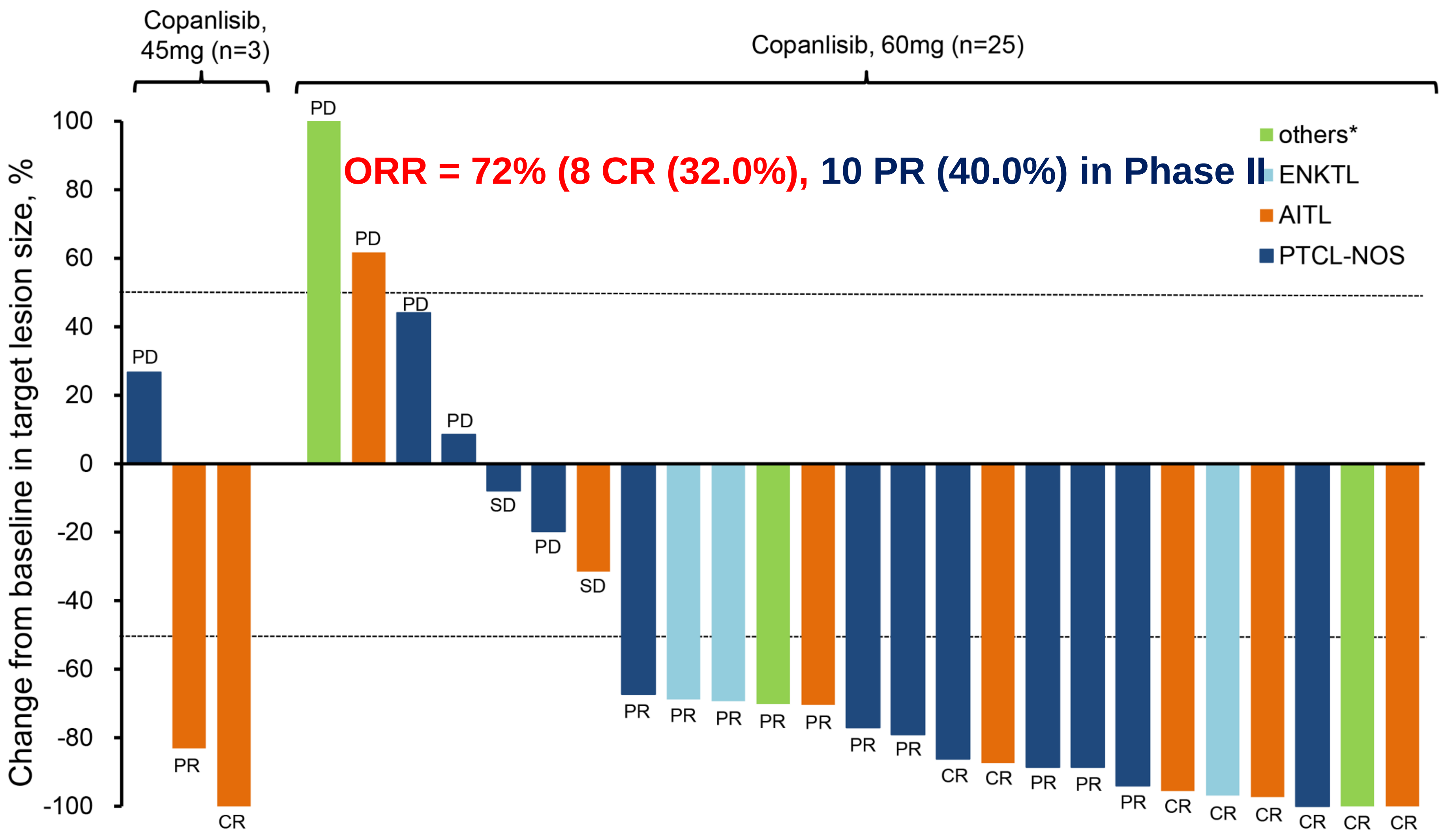
Demographic & clinical characteristics, (N=28)

	Total (N=28, %)
Age, years median, range >60	 62.5 (22-79) 16 (57.1)
Male Sex	16 (57.1)
Histologic subtype	
PTCL, NOS	13 (46.4)
AITL	9 (32.1)
ENKTL	3 (10.7)
ALCL, ALK-	1 (3.6)
EATL	1 (3.6)
SPLTL	1 (3.6)
Ann Arbor Stage 3-4	23 (82.1)
ECOG PS of 2	3 (10.7)
B symptoms	8 (28.6)
Elevated LDH level	15 (53.6)
BM involvement	6 (21.4)

	Total (N=28, %)
Extranodal sites >1	5 (17.9)
Sec-IPI, at relapse	
low	7 (25.0)
low-intermediate	9 (32.1)
HI or high	12 (42.9)
No. of prior regimens	
1	17 (60.7)
2	10 (35.7)
3	1 (3.6)
Prior ASCT	6 (21.4)
Response to prior Tx relapsed disease refractory disease*	 7 (25.0) 21 (75.0)

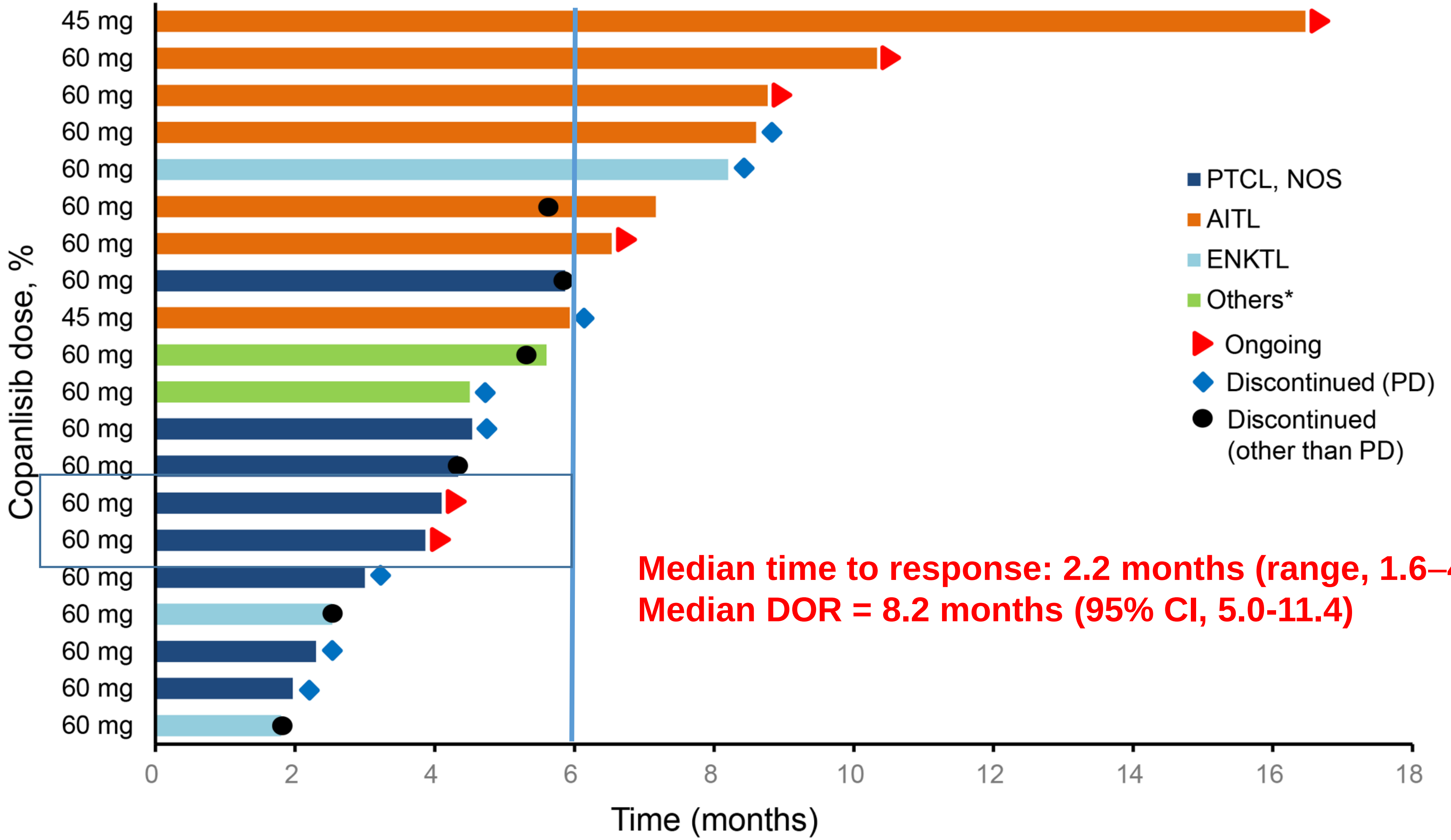
*Refractory disease was defined as PD as best response to previous chemotherapy, SD after ≥4 cycles (first-line), or 2 cycles (later-line), or relapse ≤12 months after ASCT
.

Best treatment responses (N=28)



*Others included ALCL-ALK neg (n=1), subcutaneous panniculitis-like T-cell lymphoma (n=1), and enteropathy-associated T-cell lymphoma (n=1).

Duration of responses (N=20)



Median time to response: 2.2 months (range, 1.6–4.4)
Median DOR = 8.2 months (95% CI, 5.0-11.4)

Discontinuation other than disease progression included recurrent low-grade non-hematologic AEs (N=4), in particular fatigue, proceeding to allo-SCT (n=1), and consent withdrawal (n=1)

*Others included ALCL-ALK neg (n=1) and subcutaneous panniculitis-like T-cell lymphoma (n=1).

Hematologic and non-hematologic toxicity profiles

Adverse Event (≥grade III or IV), n (%)	N = 307
Any treatment-emergenet AE	274 (89)
Hyperglycemia	173 (56)
Anemia	14 (5)
Nausea	2 (1)
Hypertension	122 (40)
Neutropenia	48 (16)
Thrombocytopenia	7 (2)
Cough	14 (22)
Pneumonitis	8 (3)
Pneumonia	18 (6)

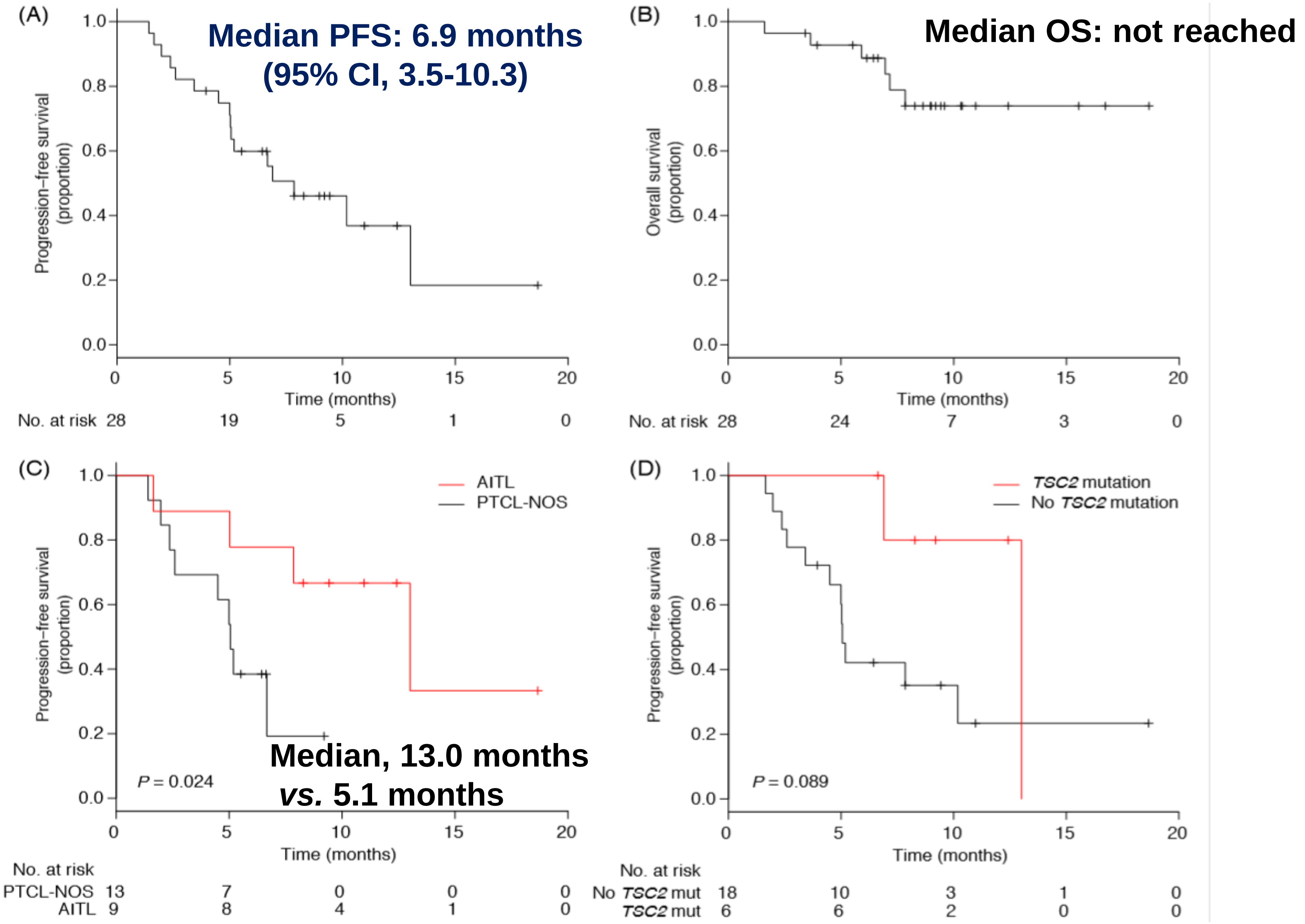
Toxicities	Total adverse events*	Grade 1–2	Grade 3	Grade 4
		N, %	N, %	N, %
Her				
N			31 (23.5)	28 (21.2)
A			2 (1.5)	2 (1.5)
T			35 (26.5)	14 (10.6)
Me				
H			70 (53.0)	5 (3.8)
H			25 (18.9)	0 (0)
Infe				
F			5 (3.8)	0 (0)
H			0 (0)	0 (0)
L			2 (1.5)	0 (0)
Gas				
N			0 (0)	0 (0)
F			1 (0.8)	0 (0)
C			0 (0)	1 (0.8)
Lab				
Elevated AST	15 (11.4)	14 (10.6)	1 (0.8)	0 (0)
Elevated ALT	13 (9.8)	11 (8.3)	1 (0.8)	1 (0.8)
Cutaneous				
Skin rash	7 (5.3)	7 (5.3)	0 (0)	0 (0)

Values are expressed as number of patients and percentage, unless otherwise indicated.

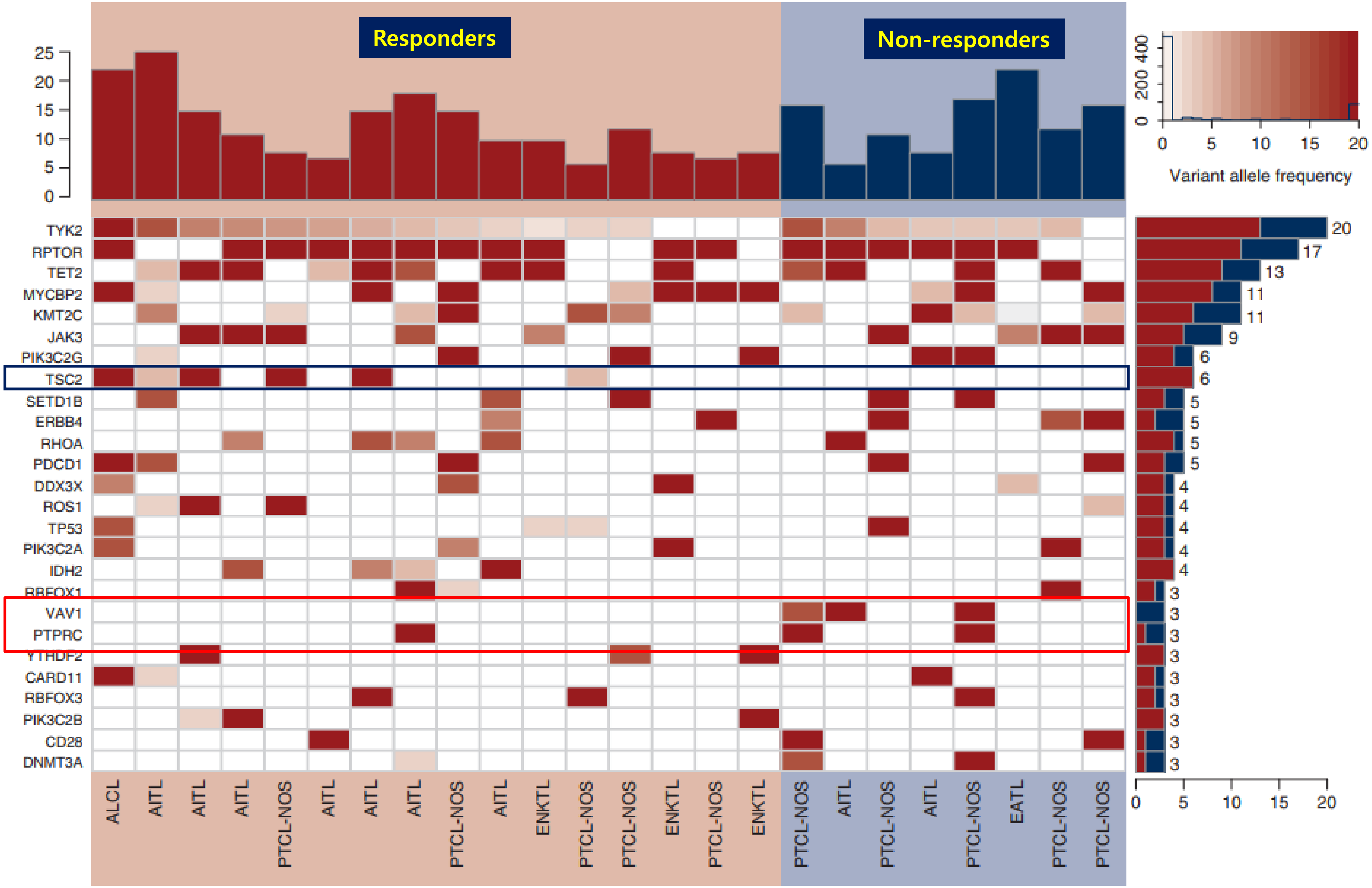
* Toxicities were assessed in 132 cycles of copanlisib and gemcitabine combination in 28 patients

PFS and OS (N=28)

Median follow-up duration : 8.9 months (IQR, 6.3-12.1)



NGS assessment



Summary

- ORR = 72% (8 CR (32.0%), 10 PR (40.0%) in Phase II
- 8 patients relapsed or progressed after best ORR
- 12 patients with CR or PR (42.8%) at the time of analysis (30th Nov. 2019) : may be ORR

  (Statistical P1 = 45%) → 9 patients remained CR state at the time of re-analysis (Oct. 2022)
- **Responder** : 5 out of 9 patients with AITL, 8 of 13 patients with PTCL-NOS, all 3 patients with NK/T
- **NGS assessment** : **TSC2** mutation in responder

  VAV1 in non-responder

Activating mutations and translocations in the guanine exchange factor VAV1 in peripheral T-cell lymphomas

PNAS January 24, 2017 114 (4) 764-769

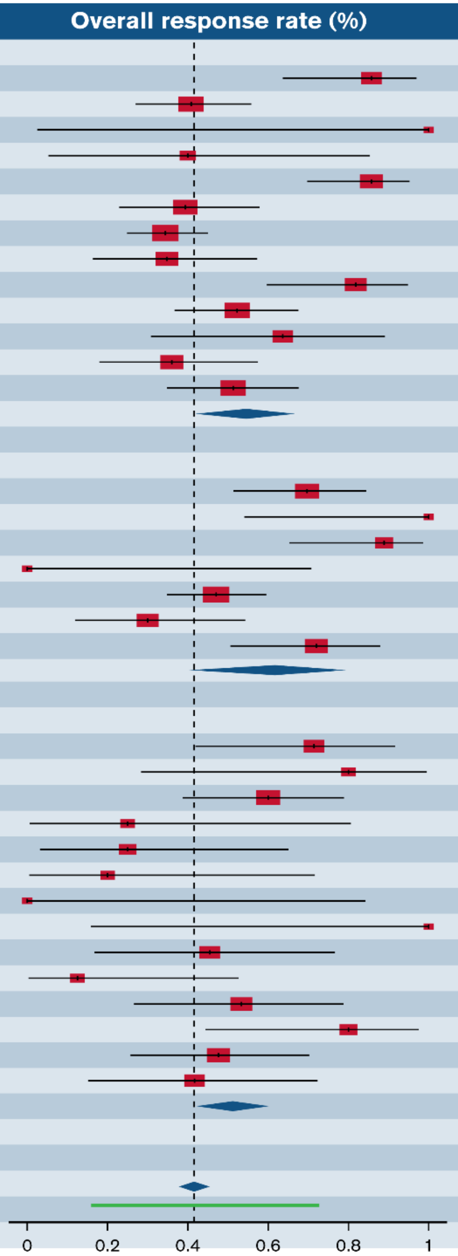
PTPRC may be a tumor suppressor in more mature T-cell neoplasms

Molecular heterogeneity in peripheral T-cell lymphoma, not otherwise specified revealed by comprehensive genetic profiling

Leukemia (2019) 33:2867–2883

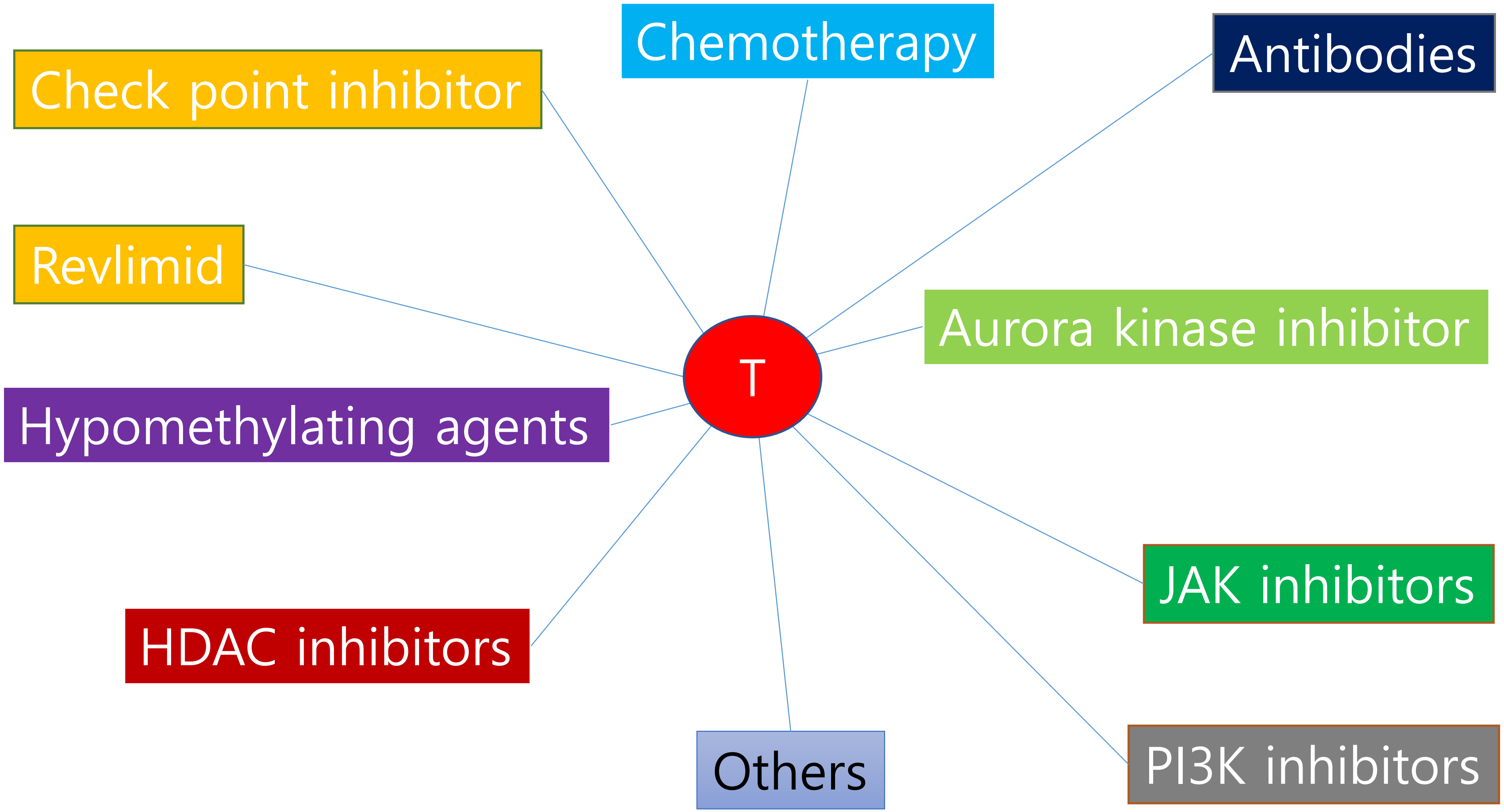
Comparative efficacy and tolerability of novel agents vs chemotherapy in relapsed and refractory T-cell lymphomas: a meta-analysis

Study	Events	Total	Proportion	95%−CI	Weight
Therapy = combination chemotherapy					
Corazzelli 2010	18	21	0.86	[0.64; 0.97]	0.8%
Dummer 2010	20	49	0.41	[0.27; 0.56]	1.2%
Dumontet 2001	1	1	1.00	[0.03; 1.00]	0.2%
Emmanouilides 2004	2	5	0.40	[0.05; 0.85]	0.5%
Kwong 2010	30	35	0.86	[0.70; 0.95]	1.0%
Mahadevan 2013	13	33	0.39	[0.23; 0.58]	1.1%
O'Connor 2011	32	93	0.34	[0.25; 0.45]	1.3%
O'Connor 2015	8	23	0.35	[0.16; 0.57]	1.0%
Park 2015	18	22	0.82	[0.60; 0.95]	0.9%
Tssimberidou 2004	23	44	0.52	[0.37; 0.68]	1.2%
Tsukune 2010	7	11	0.64	[0.31; 0.89]	0.8%
Yao 2013	9	25	0.36	[0.18; 0.57]	1.0%
Zinzani 2010	20	39	0.51	[0.35; 0.68]	1.2%
Random effects model		**401**	**0.55**	**[0.42; 0.67]**	**12.2%**
Heterogeneity: $I^2 = 74\%$, $p < 0.01$					
Therapy = combination of novel agent + traditional chemo					
Advani 2016	23	33	0.70	[0.51; 0.84]	1.1%
Cai 2020	6	6	1.00	[0.54; 1.00]	0.2%
Johnston 2015	16	18	0.89	[0.65; 0.99]	0.6%
Lansigan 2010	0	3	0.00	[0.00; 0.71]	0.2%
Lunning 2018	32	68	0.47	[0.35; 0.60]	1.3%
Pellegrini 2016	6	20	0.30	[0.12; 0.54]	0.9%
Yhim 2021	18	25	0.72	[0.51; 0.88]	1.0%
Random effects model		**173**	**0.62**	**[0.40; 0.79]**	**5.5%**
Heterogeneity: $I^2 = 74\%$, $p < 0.01$					
Therapy = combination of novel agents					
Amengual 2018	10	14	0.71	[0.42; 0.92]	0.8%
Barta 2020	4	5	0.80	[0.28; 0.99]	0.4%
Falchi 2021	15	25	0.60	[0.39; 0.79]	1.1%
Fanale 2014	1	4	0.25	[0.01; 0.81]	0.4%
Hopfinger 2014	2	8	0.25	[0.03; 0.65]	0.6%
Lee 2016	1	5	0.20	[0.01; 0.72]	0.4%
Marchi 2020	0	2	0.00	[0.00; 0.84]	0.2%
Marchi 2020	2	2	1.00	[0.16; 1.00]	0.2%
Mehta−Shah 2017	5	11	0.45	[0.17; 0.77]	0.8%
Moskowitz 2017	1	8	0.12	[0.00; 0.53]	0.4%
Moskowitz 2017	8	15	0.53	[0.27; 0.79]	0.9%
Porcu 2020	8	10	0.80	[0.44; 0.97]	0.6%
Tan 2015	10	21	0.48	[0.26; 0.70]	1.0%
William 2019	5	12	0.42	[0.15; 0.72]	0.8%
Random effects model		**142**	**0.51**	**[0.42; 0.60]**	**8.6%**
Heterogeneity: $I^2 = 28\%$, $p = 0.15$					
Random effects model		**3158**	**0.42**	**[0.38; 0.45]**	**100.0%**
Prediction interval				**[0.16; 0.73]**	
Heterogeneity: $I^2 = 68\%$, $p < 0.01$					
Test for subgroup differences: $\chi^2_3 = 16.20$, df = 3 ($p < 0.01$)					



Blood Adv 2022

Effective combination



Future directions

- **Better characterization of disease**
  - Classification
  - Molecular analysis
  - Determine the way to describe microenvironment
  - Preclinical model…
- **Salvage**
  - Combination therapy with target + chemotherapy
  - Targeted + Targeted
    - Effective doublet / triplet to be pushed to salvage
  - Immune therapy (PD1/PDL1/CART?)

Nothing ever goes my Way………