# **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

## **Poor outcome of RR nodal PTCL – Korean data**



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



Time (months)

## **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

Matrix



Apoptosis



The group of Down-regulated genes (apoptosis) 1) GADD45A and 45B : growth arrest and DNA damage-inducible α and β control of apoptosis

- control of apoptosis
- 2) MOAP1 : a Bcl-2 homology 3-like motif (BH3)
  - interact with Bax, mediating caspasedependent apoptosis

#### Table 1

Immunohistochemical analysis on TMAs

Marker	Evaluable cases	Positive cases (>30% positive elements)	Percentage of positive cases
Caldesmon	129	128 <sup>A</sup>	99
BCL10	75	15	20
IGFBP7	120	68	57
p27	114	53 <sup>8</sup>	46
PDGFRa	133	121	91
p-PDGFRa	110	105	95
CYR61	137	132	96
LIFR-1	116	36	31

AStromal reactivity. 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  $\alpha/\beta/\gamma/\delta$ , 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**



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



# 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

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

Copanlisib	Level I-II mg 1-hr infusion rate	D1, D8, D15
Gemcitabine	1000 mg/m <sup>2</sup> 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 <sup>2</sup> )	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)  $\leq 2$
- ③ age > 18
- ④ At least one or more unidimensionally measurable lesion(s)
  - $\geq$ 1.5 cm by conventional CT
  - $\geq$  1 cm by spiral CT
  - skin lesion (photographs should be taken)
  - measurable lesion by physical examination
- (5) Laboratory values

-Cr  $\leq$  1.5 mg/dL or Ccr  $\geq$  50 ml/min

-Transaminase < 3 X upper normal value

–Bilirubin < 2.0 mg/dl

 $-ANC \ge 1,500/ul$ , platelet  $\ge 75,000/ul$ 

② Informed consent



### Study status and comments

- Phase I : N= total 6 patients (started from 28<sup>th</sup> 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  $\geq$ 4 cycles (first-line), or 2 cycles (later-line), or relapse  $\leq$ 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)**



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

Tavisitias	Total adverse	Grade 1–2	Grade 3	Grade 4	
Toxicities	events*	N, %	N, %	N, %	
Hei Adverse Event (≥grade III or IV), n (%)		N = 307	31 (23.5)	28 (21.2)	
Any treatment-emergen	et AE	274 (89)	2 (1.5)	2 (1.5)	
Me <sup>Hyperglycemia</sup>		173 (56)	35 (20.5)	14 (10.6)	
H Anemia		14 (5)	70 (53.0)	5 (3.8)	
⊢ InfeNausea		2 (1)	25 (18.9)	0 (0)	
F Hypertension		122 (40)	5 (3.8)	0 (0)	
- Neutropenia		48 (16)	0 (0) 2 (1 5)	$\begin{array}{c} 0 \\ 0 \\ 0 \end{array}$	
Gas Thrombocytopenia		7 (2)	2 (1.3)	0 (0)	
N Cough		14 (22)	0 (0)	0 (0)	
C Pneumonitis		8 (3)	0 (0)	1 (0.8)	
Lab Elevated AST	12 (11.4)	<b>18 (6)</b>	1 (0.8)	0 (0)	
Elevated ALT	13 (9.8)	11 (8.3)	1 (0.8)	1 (0.8)	
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%)  $\rightarrow$  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

Therapy combination chemotherapy         0         <	Study	Events	Total	Overall response rate (%) Proportion	95%-CI	Weight
Canzenti 2010         18         21	Therapy = combination chemotherapy					
Damner 2010 1 20 40 102; 0.68 12% Damner 2020 20 2 6 40 102; 0.68 10% Damner 2020 20 2 6 40 100; 0.88 102; 0.89 10% Damner 2020 20 2 8 2 4 2 4 2 4 2 4 4 4 4 4 4 4 4 4 4 4	Corazzelli 2010	18	21	0.86	[0.64; 0.97]	0.8%
Dumonet 2001 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	Dummer 2010	20	49	0.41	[0.27; 0.56]	1.2%
Emmanulation 2004         2         5	Dumontet 2001	1	1		[0.03; 1.00]	0.2%
Kwong 2010       30       35 $\bullet$ <	Emmanouilides 2004	2	5	0.40	[0.05; 0.85]	0.5%
Mahadowa 2013       13       33       0.29	Kwong 2010	30	35	0.86	[0.70; 0.95]	1.0%
O'Connor 2011       32       93	Mahadevan 2013	13	33		[0.23; 0.58]	1.1%
O'Connor 2015       8       23	O'Connor 2011	32	93	0.34	[0.25; 0.45]	1.3%
Park 2015       18       22       0.62       0.062       0.061       0.061       0.061       0.062       0.064       0.031:0.062       0.063       0.064       0.031:0.064       0.035       0.064       0.035       0.064       0.035       0.064       0.035       0.064       0.035       0.064       0.035       0.064       0.022       0.064       0.022       0.064       0.023       0.00       0.00       0.00       0.024       0.024       0.042       0.035       0.064       0.035       0.064       0.035       0.064       0.035       0.064       0.035       0.064       0.035       0.064       0.042       0.064       0.042       0.064       0.042       0.064       0.042       0.064       0.042       0.064       0.042       0.064       0.042       0.064       0.042       0.064       0.042       0.064       0.042	O'Connor 2015	8	23	0.35	[0.16; 0.57]	1.0%
Tasime 2004       23       44	Park 2015	18	22	0.82	[0.60; 0.95]	0.9%
Taskane 2010       7       11       Image: Constraint of the	Tssimberidou 2004	23	44	0.52	[0.37; 0.68]	1.2%
Yao 2013       9       25       0.36 $[0.18], 0.57]$ $1.04e$ Random effects model       401       0.55 $[0.42], 0.57]$ $12.24e$ Random effects model       401       0.55 $[0.42], 0.57]$ $12.24e$ Random effects model       401       0.55 $[0.42], 0.57]$ $12.24e$ Random effects model       23       33       0.00 $[0.55], (0.84]$ $1.11e$ Advan 2016       23       33       0.00 $[0.55], (0.84]$ $1.11e$ Lunning 2018       32       68       0.00 $[0.05], (0.84]$ $1.11e$ Lunning 2018       32       68       0.047 $[0.55], (0.84]$ $1.31e$ Lunning 2018       32       68       0.047 $[0.55], (0.84]$ $1.31e$ Lunning 2018       32       68       0.047 $[0.55], (0.84]$ $1.39e$ Random effects model       173       0.42 $[0.42], (0.21], 0.49e$ $[0.42], 0.21], 0.49e$ Random effects model       10       14       0.42 $[0.42], 0.22], 0.49e$ $[0.42], 0.22], 0.49e$ Barla 2016       10       14       0.25       0.66 <t< td=""><td>Tsukune 2010</td><td>7</td><td>11</td><td>0.64</td><td>[0.31; 0.89]</td><td>0.8%</td></t<>	Tsukune 2010	7	11	0.64	[0.31; 0.89]	0.8%
Zinzari 2010       20       39       0.51       [0.55]       [0.42]       0.55       [0.42]       0.57       [1.2%]         Readom effects model       401       0.55       [0.42]       0.57       [1.2%]         Hetrogenety: $f^* = 74\%$ , $p < 0.01$ 1       0.55       [0.42]       0.51       [0.54]       1.1%         Cai 2020       6       6       0.00       [0.54]       1.00       [0.54]       1.00       [0.54]       0.09       0.68       0.09       0.69       0.49       0.55       0.68       0.51       0.64       0.25       0.01       0.58       0.09       0.49       0.59       0.49       0.49	Yao 2013	9	25	0.36	[0.18; 0.57]	1.0%
Random effects model       401       0.55 $[0.42; 0.67]$ 12.2%         Heterogeneity: $f^2 = 74%_{0.5} \rho < 0.01$ 23       33       0       0.051; 0.84]       1.1%         Cai 2020       6       6       0       0.051; 0.84]       1.1%         Cai 2020       0       3       0.00       0.651; 0.84]       1.0%         Johaton 2015       16       18       0.00       0.00; 0.71]       0.2%         Johaton 2016       6       20       0.03       0.12; 0.54]       0.9%         Pellegrini 2016       6       20       0.03       0.12; 0.54]       0.9%         Random effects model       173       0.30       0.12; 0.54]       0.9%         Random effects model       173       0.68       0.02; 0.09]       0.4%         Fatch 2020       4       5       0.68       0.02; 0.09]       0.4%         Fatch 2021       15       25       0.60       0.89; 0.09]       0.4%         Fatch 2021       15       25       0.00       0.00; 0.00; 0.00;       0.4%         Fatch 2021       14       0.02       0.00; 0.00; 0.00; 0.00;       0.4%       0.2%       0.00       0.00; 0.00; 0.00; 0.00;       0.4%       0.	Zinzani 2010	20	39	0.51	[0.35; 0.68]	1.2%
Heterogeneity: $f^2 = 74\%, p < 0.01$ Therapy = combination of novel agent + traditional chemo Advani 2016 23 33	Random effects model		401	0.55	[0.42; 0.67]	12.2%
Therapy = combination of novel agent + traditional chemo         Advani 2016       23       33       0.70 $0.51$ ; $0.84$ 1.1%         Cai 2020       6       6       0.70 $0.51$ ; $0.84$ 1.1%         Johnston 2015       16       18       0.89 $0.050$ ; $0.99$ $0.6\%$ Lunning 2018       32       68       0.00 $0.000$ ; $0.71$ $0.2\%$ Lunning 2018       62       0.33 $0.120$ ; $0.54$ $0.9\%$ Random effects model       173       0.62 $0.47$ $0.51$ ; $0.84$ $0.9\%$ Random effects model       173       0.62 $0.47$ $0.52$ ; $0.9\%$ $0.55$ Barta 2020       4       5       0.62 $0.49\%$ $0.9\%$ $0.4\%$ Hetrogenetity: $^{17}$ ar $4\%$ , $p < 0.01$ 14       0.62 $0.22$ ; $0.9\%$ $0.4\%$ Hetrogenetity: $^{17}$ ar $4\%$ 0.62 $0.02$ ; $0.99$ $0.4\%$ Hetrogenetity: $^{17}$ ar $4\%$ 0.60 $0.39$ ; $0.79$ $1.1\%$ Amengual 2018       15       0.60 $0.39$ ; $0.79$ $1.1\%$ Hetrogenetity: $^{17}$ ar $4\%$ 0.25 $0.001$ ; $0.41$	Heterogeneity: $l^2 = 74\%$ , $p < 0.01$					
Advani2016       23       33	Therapy = combination of novel agent + traditional chem	0				
Cai 2020       6       6	Advani 2016	23	33	0.70	[0.51; 0.84]	1.1%
Johnson 2015       16       18       0.89       [0.65; 0.89]       0.6%         Lansigan 2010       0       3       0.00       [0.00; 0.71]       0.2%         Pellegrini 2016       6       20       0.72       [0.51; 0.88]       0.9%         Yhm 2021       18       25       0.72       [0.51; 0.88]       1.0%         Random effects model       173       0.82       [0.47; 0.72]       0.55%         Heterogeneity: $f^* = 74%$ , $p < 0.01$	Cai 2020	6	6	1.00	[0.54; 1.00]	0.2%
Lansigan 2010 0 0 3 4 0.000 [0.00; 0.71] 0.2% [0.00; 0.00] 0.2% [0.00; 0.2] 0.2% [0.00;	Johnston 2015	16	18	0.89	[0.65; 0.99]	0.6%
Lunning 2018       32       68        0.47       [0.35; 0.60]       1.3%         Pellegrin 2016       6       20       0.30       [0.12; 0.54]       0.9%         Random effects model       173       0.62       [0.40; 0.79]       5.5%         Heterogeneity: $I^* = 74\%$ , $p < 0.01$	Lansigan 2010	0	3	0.00	[0.00; 0.71]	0.2%
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: $l^2$ = 74%, $\rho < 0.01$ 0.62       (0.40; 0.79)       5.5%         Amengual 2018       10       14       0.71       [0.42; 0.92]       0.8%         Barta 2020       4       5       0.80       [0.28; 0.99]       0.4%         Faich 2021       15       25       0.60       [0.39; 0.79]       1.1%         Fanale 2014       1       4       0.25       [0.01; 0.72]       0.4%         Hetrogeneity: 2014       2       8       0       0.25       [0.01; 0.72]       0.4%         Marchi 2020       0       2       2       0.00       [0.00; 0.65]       0.6%         Marchi 2020       2       2       0.00       [0.00; 0.65]       0.4%       0.2%         Marchi 2020       2       2       0.00       [0.00; 0.65]       0.4%       0.2%         Moskowitz 2017       1       8       15       0.53       [0.27; 0.7]       0.8%	Lunning 2018	32	68	0.47	[0.35; 0.60]	1.3%
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: $\int^{h} = 74\%, p < 0.01$ Therapy = combination of novel agents         Amengual 2018       10       14 $0.62$ $[0.40; 0.79]$ $0.8\%$ Barta 2020       4       5 $0.80$ $[0.28; 0.99]$ $0.4\%$ Fanale 2014       1       4 $0.25$ $[0.01; 0.81]$ $0.4\%$ Hopfinger 2014       2       8 $0.20$ $[0.01; 0.27; 0.8\%]$ $0.4\%$ Marchi 2020       0       2 $0.25$ $[0.01; 0.81]$ $0.4\%$ Marchi 2020       0       2 $0.25$ $[0.01; 0.81]$ $0.4\%$ Marchi 2020       2 $0.20$ $[0.00; 0.53]$ $0.4\%$ Marchi 2020       2 $0.10$ $[0.16; 1.00]$ $0.29\%$ Meta-Shah 2017       5       11 $0.45$ $[0.77; 0.8\%]$ $0.29\%$ Moskowitz 2017       8       15 $0.53$ $[0.27; 0.79]$ $0.9\%$ $0.445$ $0.27; 0.79]$ $0.9\%$	Pellegrini 2016	6	20		[0.12; 0.54]	0.9%
Random effects model       173       0.62       [0.40; 0.79]       5.5%         Heterogeneity: $l^2 = 74\%$ , $p < 0.01$ Therapy = combination of novel agents       Amengual 2018       10       14       0.71       [0.42; 0.92]       0.8%         Barta 2020       4       5       0.60       [0.38; 0.79]       1.9%         Faichi 2021       15       25       0.60       [0.38; 0.79]       1.9%         Hopfinger 2014       2       8       0.25       [0.01; 0.81]       0.4%         Lee 2016       1       5       0.20       [0.00; 0.72]       0.4%         Marchi 2020       0       2       0.00       [0.00; 0.84]       0.29%         Marchi 2020       0       2       0.00       [0.00; 0.84]       0.29%         Marchi 2020       0       2       0.00       [0.00; 0.53]       0.4%         Moskowitz 2017       1       8       0.53       [0.27; 0.79]       0.9%         Porcu 2020       8       10       0.53       [0.27; 0.79]       0.9%         Villiam 2019       5       12       0.48       [0.42; 0.60]       8.6%         Villiam 2015       10       21       0.48       [0.42; 0.60]       8.6%	Yhim 2021	18	25	0.72	[0.51; 0.88]	1.0%
Heterogeneity: $l^2 = 74\%$ , $p < 0.01$ Therapy = combination of novel agents         Amengual 2018       10       14         Barta 2020       4       5         Faichi 2021       15       25         Fanale 2014       1       4         Hopfinger 2014       2       8         Lee 2016       1       5         Marchi 2020       0       2         Marchi 2020       0       2         Marchi 2020       0       2         Marchi 2020       0       2         Marchi 2020       2       0.00       100.00; 0.84]       0.296         Moskowitz 2017       1       8       0       0.12       10.079       0.896         Moskowitz 2017       1       8       0       0.53       0.497       0.896         Moskowitz 2017       1       8       0       0.53       0.497       0.696         Tan 2015       10       21<	Random effects model		173	0.62	[0.40; 0.79]	5.5%
Therapy = combination of novel agents         Amengual 2018       10       14         Barta 2020       4       5         Falchi 2021       15       25         Fanale 2014       1       4         Hopfinger 2014       2       8         Lee 2016       1       5         Marchi 2020       0.000       0.000         Marchi 2020       2       0.000         Moskowitz 2017       1       8       0.12         Moskowitz 2017       1       8       0.12       0.000         Porcu 2020       8       10       0.448       0.22       0.47         William 2019       5       12       0.448       0.22       0.70       0.8%         William 2019       5       12       0.448 <t< td=""><td>Heterogeneity: <math>l^2 = 74\%</math>, <math>p &lt; 0.01</math></td><td></td><td></td><td></td><td></td><td></td></t<>	Heterogeneity: $l^2 = 74\%$ , $p < 0.01$					
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%         Hopfinger 2014       1       4       0.25 $[0.01; 0.81]$ 0.4%         Hopfinger 2014       2       8       0.25 $[0.01; 0.81]$ 0.4%         Lee 2016       1       5       0.25 $[0.01; 0.81]$ 0.4%         Marchi 2020       0       2       0.00 $[0.00; 0.84]$ 0.2%         Marchi 2020       2       0.00 $[0.00; 0.84]$ 0.2%         Mehta-Shah 2017       5       11       0.12 $[0.00; 0.53]$ 0.4%         Moskowitz 2017       1       8       15       0.45 $[0.17; 0.77]$ 0.8%         Porcu 2020       8       10       0.53 $[0.27; 0.79]$ 0.9%         Porcu 2020       8       10       0.48 $[0.64; 0.70]$ 1.0%         Random effects model       142       0.51 $[0.42; 0.60]$ 8.6%         Heterogeneity: $f^2 = 28\%, p < 0.01$ 0	Therapy = combination of novel agents					
Barta 2020       4       5       0.80 $[0.28; 0.99]$ 0.4%         Falch 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 $[0.01; 0.81]$ 0.4%         Lee 2016       1       5       0.25 $[0.01; 0.72]$ 0.4%         Marchi 2020       0       2       0.00 $[0.00; 0.84]$ 0.2%         Marchi 2020       2       0.00 $[0.00; 0.84]$ 0.2%         Marchi 2020       2       0.00 $[0.00; 0.83]$ 0.4%         Moskowitz 2017       1       8       0.53 $[0.27; 0.79]$ 0.9%         Moskowitz 2017       8       15       0.53 $[0.27; 0.79]$ 0.9%         Porcu 2020       8       10       0.48 $[0.26; 0.70]$ 1.0%         William 2019       5       12       0.44       0.51 $[0.42; 0.60]$ 8.6%         Heterogeneity: $I^2 = 28\%, p = 0.15$ 142       0.42 $[0.38; 0.45]$ $100.0\%$ Test for subgroup differences: $\chi_2^2 = 16.20, df = 3(p$	Amengual 2018	10	14	0.71	[0.42; 0.92]	0.8%
Falchi 202115250.60 $[0.39; 0.79]$ 1.1%Fanale 2014140.25 $[0.01; 0.81]$ 0.4%Hopfinger 2014280.25 $[0.03; 0.65]$ 0.6%Lee 2016150.20 $[0.01; 0.72]$ 0.4%Marchi 2020020.00 $[0.00; 0.084]$ 0.2%Marchi 2020210.00 $[0.00; 0.58]$ 0.4%Marchi 2020210.00 $[0.00; 0.53]$ 0.4%Moskowitz 20171810.12 $[0.00; 0.53]$ 0.4%Moskowitz 20178150.53 $[0.27; 0.79]$ 0.8%Porcu 20208100.680 $[0.44; 0.97]$ 0.6%Tan 201510210.48 $[0.26; 0.70]$ 1.0%William 20195120.42 $[0.15; 0.72]$ 0.8%Random effects model31580.42 $[0.38; 0.45]$ 100.0%Heterogeneity: $P^2 = 88\%$ , $p < 0.01$ 1420.51 $[0.42; 0.60]$ 8.6%Prediction interval1420.660.81Heterogeneity: $P^2 = 68\%$ , $p < 0.01$ 0.020.40.60.81	Barta 2020	4	5	0.80	[0.28; 0.99]	0.4%
Fanale 2014140.25 $[0.01; 0.81]$ 0.4%Hopfinger 2014280.25 $[0.03; 0.65]$ 0.6%Lee 2016150.20 $[0.01; 0.72]$ 0.4%Marchi 2020020.00 $[0.00; 0.84]$ 0.4%Marchi 202020.00 $[0.00; 0.84]$ 0.2%Mehta-Shah 20175110.45 $[0.17; 0.77]$ 0.8%Moskowitz 2017180.12 $[0.00; 0.53]$ 0.4%Moskowitz 20178150.53 $[0.27; 0.79]$ 0.9%Porcu 20208100.68 $[0.44; 0.97]$ 0.6%Tan 201510210.48 $[0.26; 0.70]$ 1.0%William 20195120.42 $[0.511]$ $[0.42; 0.60]$ Random effects model31580.42 $[0.512]$ $[0.38; 0.45]$ 100.0%Prediction interval10.020.40.60.81Heterogeneity: $f^2 = 66\%$ , $p < 0.01$ 0.010.60.81Test for subgroup differences: $\chi_3^2 = 16.20$ , df = 3 ( $p < 0.01$ )0.020.40.60.81	Falchi 2021	15	25	0.60	[0.39; 0.79]	1.1%
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       0.00 $[0.00; 0.84]$ $0.2\%$ Marchi 2020       2       0.00 $[0.00; 0.84]$ $0.2\%$ Mehta-Shah 2017       2       1       0.45 $[0.17; 0.77]$ $0.8\%$ Moskowitz 2017       8       15       0.45 $[0.17; 0.77]$ $0.8\%$ Moskowitz 2017       8       15       0.12 $[0.00; 0.53]$ $0.4\%$ Porcu 2020       8       10       0.53 $[0.27; 0.79]$ $0.9\%$ Villiam 2019       5       12       0.48 $[0.26; 0.70]$ $1.0\%$ William 2019       5       12       0.42 $0.51$ $[0.42; 0.60]$ $8.6\%$ Heterogeneity: $l^2 = 28\%, p = 0.15$ 3158       0.42 $[0.16; 0.73]$ $[0.16; 0.73]$ Heterogeneity: $l^2 = 68\%, p < 0.01$ 0.6       0.6       0.8       1         Test for subgroup diff	Fanale 2014	1	4	0.25	[0.01; 0.81]	0.4%
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       1.00 $[0.16; 1.00]$ 0.2%         Marchi 2020       2       1.00 $[0.16; 1.00]$ 0.2%         Metha-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       0.53 $[0.27; 0.79]$ 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       3158       0.42 $[0.16; 0.73]$ 0.6%         Prediction interval       (0.16; 0.73]       (0.16; 0.73]       (0.16; 0.73]         Heterogeneity: $l^2 = 68\%, p < 0.01$ 0.44       0.66       0.8	Hopfinger 2014	2	8	0.25	[0.03; 0.65]	0.6%
Marchi 2020       0       2       0.00 $[0.00; 0.84]$ 0.2%         Marchi 2020       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       0.48 $[0.26; 0.70]$ 1.0%         Random effects model       142       0.51 $[0.42; 0.60]$ 8.6%         Heterogeneity: $l^2 = 28\%, p = 0.15$ 8       0.42 $[0.16; 0.73]$ Heterogeneity: $l^2 = 68\%, p < 0.01$ 0.02       0.4       0.6       0.8       1         Test for subgroup differences: $\chi_3^2 = 16.20, df = 3 (p < 0.01)$ 0.02       0.4       0.6       0.8       1	Lee 2016	1	5	0.20	[0.01; 0.72]	0.4%
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       0.44       [0.15; 0.72]       0.8%         Random effects model       142       0.51       [0.42; 0.60]       8.6%         Heterogeneity: $l^2 = 28\%$ , $p = 0.15$ 8.6%       0.42       [0.38; 0.45]       100.0%         Prediction interval       0.42       [0.38; 0.45]       100.0%       10.0%       100.0%	Marchi 2020	0	2	• 0.00	[0.00; 0.84]	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       0.680 $[0.44; 0.97]$ 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: $l^2 = 28\%, p = 0.15$ 3158       0.42 $[0.38; 0.45]$ $100.0\%$ Prediction interval       0.42 $[0.38; 0.45]$ $100.0\%$ $[0.16; 0.73]$ Heterogeneity: $l^2 = 68\%, p < 0.01$ 0.02       0.4       0.6       0.8       1	Marchi 2020	2	2	<b>—</b> 1.00	[0.16; 1.00]	0.2%
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: $l^2 = 28\%, p = 0.15$ 9       0.42 $[0.38; 0.45]$ 100.0%         Prediction interval       0.42 $[0.16; 0.73]$ 0.12       0.12 $[0.16; 0.73]$ Heterogeneity: $l^2 = 68\%, p < 0.01$ 0.02       0.4       0.6       0.8       1	Mehta-Shah 2017	5	11	0.45	[0.17; 0.77]	0.8%
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: $l^2 = 28\%, p = 0.15$ 3158       0.42 $[0.38; 0.45]$ 100.0%         Prediction interval       0.42 $[0.16; 0.73]$ $[0.16; 0.73]$ $[0.16; 0.73]$ Heterogeneity: $l^2 = 68\%, p < 0.01$ 0.02       0.4       0.6       0.8       1	Moskowitz 2017	1	8	0.12	[0.00; 0.53]	0.4%
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: $l^2 = 28\%, p = 0.15$ 0.42 $[0.38; 0.45]$ 100.0%         Prediction interval       0.42 $[0.16; 0.73]$ $[0.16; 0.73]$ Heterogeneity: $l^2 = 68\%, p < 0.01$ 0.2       0.4       0.6       0.8       1	Moskowitz 2017	8	15	0.53	[0.27; 0.79]	0.9%
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: $l^2 = 28\%, p = 0.15$ 3158       0.42 $[0.38; 0.45]$ $100.0\%$ Prediction interval       (0.16; 0.73)       (0.16; 0.73)       (0.16; 0.73)       (0.16; 0.73)         Heterogeneity: $l^2 = 68\%, p < 0.01$ 0.42, 0.66       0.8       1	Porcu 2020	8	10	0.80	[0.44; 0.97]	0.6%
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: $l^2 = 28\%, p = 0.15$ 3158       0.42 $[0.38; 0.45]$ 100.0%         Prediction interval       0.42 $[0.38; 0.45]$ 100.0%         Heterogeneity: $l^2 = 68\%, p < 0.01$ 0.0       0.2       0.4       0.6       0.8       1	Tan 2015	10	21	0.48	[0.26; 0.70]	1.0%
Random effects model       142       0.51       [0.42; 0.60]       8.6%         Heterogeneity: $l^2 = 28\%, p = 0.15$ 3158       0.42       [0.38; 0.45]       100.0%         Prediction interval       Image: constraint of the state of the	William 2019	5	12	0.42	[0.15; 0.72]	0.8%
Heterogeneity: $l^2 = 28\%$ , $p = 0.15$ 0.42       [0.38; 0.45]       100.0%         Prediction interval       [0.16; 0.73]       [0.16; 0.73]         Heterogeneity: $l^2 = 68\%$ , $p < 0.01$ 0       0.2       0.4       0.6       0.8       1	Random effects model		142	0.51	[0.42; 0.60]	8.6%
Random effects model       3158       0.42       [0.38; 0.45]       100.0%         Prediction interval       [0.16; 0.73]       [0.16; 0.73]         Heterogeneity: $l^2 = 68\%$ , $p < 0.01$ 0       0.42       [0.16; 0.73]         Test for subgroup differences: $\chi_3^2 = 16.20$ , df = 3 ( $p < 0.01$ )       0       0.2       0.4       0.6       0.8       1	Heterogeneity: $l^2 = 28\%$ , $p = 0.15$					
Prediction interval       [0.16; 0.73]         Heterogeneity: $l^2 = 68\%$ , $p < 0.01$ [0.16; 0.73]         Test for subgroup differences: $\chi_3^2 = 16.20$ , df = 3 ( $p < 0.01$ )       [0.2, 0.4, 0.6, 0.8, 1]	Random effects model		3158	0.42	[0.38; 0.45]	100.0%
Heterogeneity: $l^2 = 68\%$ , $p < 0.01$ Test for subgroup differences: $\chi_3^2 = 16.20$ , df = 3 ( $p < 0.01$ )	Prediction interval			÷	[0.16; 0.73]	
Test for subgroup differences: $\chi_3^2 = 16.20$ , df = 3 ( $p < 0.01$ )	Heterogeneity: $l^2 = 68\%$ , $p < 0.01$					
	Test for subgroup differences: $\chi_3^2 = 16.20$ , df = 3 ( $p < 0.01$ )					

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# **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.....