LymphomaHub

CLL/SLL, MCL, MZL

AACR 2017 | Poster 154/21 – Copanlisib is active as monotherapy or in combination in Mantle Cell Lymphoma, Marginal Zone Lymphoma, and Chronic Lymphocytic Leukemia cell lines

Terri Penfold | Apr 04, 2017

This year's American Association for Cancer Research (AACR) annual meeting took place on 1–5 April in Washington, DC, USA. The program committee Chair was Kornelia Polyak, MD, PhD, from the Dana-Farber Cancer Institute, Boston, Massachusetts.

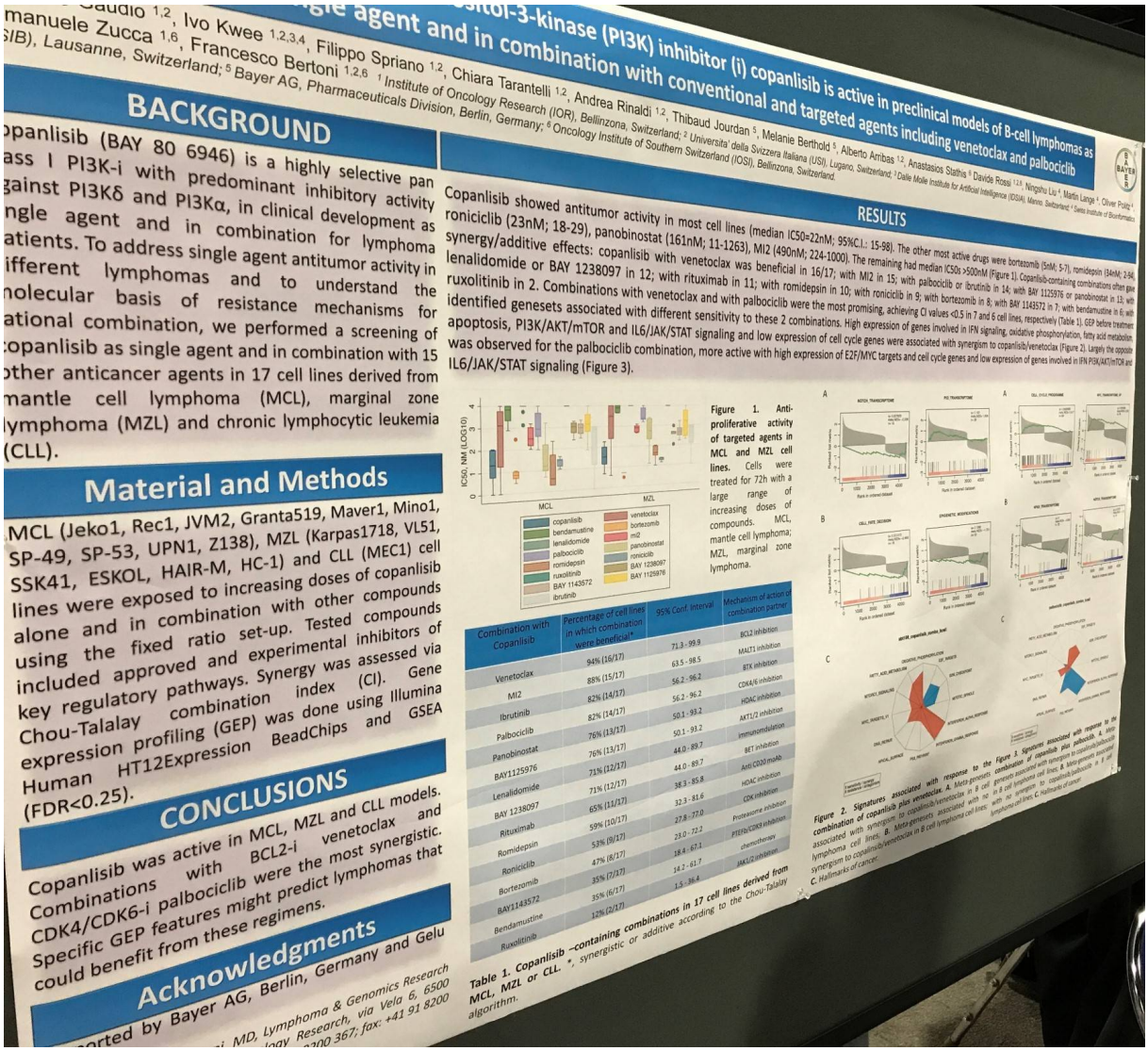
On Sunday 2nd April, a poster (154 / 21) by Eugenio Gaudio, from the Institute of Oncology Research, Bellinzona, Switzerland, *et al.* titled "The phosphatidylinositol-3-kinase (PI3K) inhibitor (i) copanlisib is active in preclinical models of B-cell lymphomas as single agent and in combination with conventional and targeted agents including venetoclax and palbociclib" was presented.

Multiple MCL, MZL, and CLL cell lines were exposed to increasing doses of copanlisib alone and in combination with other compounds using a fixed ratio set-up.

Key Highlights:

- Copanlisib showed anti-tumor activity in the majority of cell lines (median IC50 = 22nM; 95% CI, 15–98)
- The other most efficacious drugs = bortezomib (5nM; 5–7), romidepsin (34nM; 2–94), roniciclib (23nM; 18–29), panobinostat (161nM; 11–1263), and MI2 (490nM; 224–1,000)
- The remaining had median IC50s >500nM
- Combinations with venetoclax and palbociclib were the most promising, achieving CI values <0.5 in 7 and 6 cell lines, respectively
- Gene expression profiling before treatment identified gene sets associated with sensitivity to these two combinations
- Low expression of cell cycle genes as well as high expression of genes involved in interferon signaling, oxidative phosphorylation, fatty acid metabolism, apoptosis, PI3K/AKT/mTOR, and IL6/JAK/STAT signaling were associated with synergism to copanlisib/venetoclax
- The palbociclib combination was more active with high expression of E2F/MYC targets and cell cycle genes and low expression of genes involved in IFN PI3K/AKT/mTOR and IL6/JAK/STAT signaling

The poster concluded by stating that copanlisib is active in MCL, MZL, and CLL cell lines. Combinations with venetoclax (BCL-2 inhibitor) and palbociclib (CDK4/CDK6 inhibitor) were the most synergistic. Using gene expression profiling may identify patients with Lymphoma who would respond well to these combination regimens.



The phosphatidylinositol-3-kinase (PI3K) inhibitor (i) copanlisib is active in preclinical models of B-cell lymphomas as single agent and in combination with conventional and targeted agents including venetoclax and palbociclib

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BACKGROUND

opanlisib (BAY 80 6946) is a highly selective pan ass I PI3K-i with predominant inhibitory activity gainst PI3Kδ and PI3Kα, in clinical development as ngle agent and in combination for lymphoma atients. To address single agent antitumor activity in ifferent lymphomas and to understand the olecular basis of resistance mechanisms for ational combination, we performed a screening of opanlisib as single agent and in combination with 15 ther anticancer agents in 17 cell lines derived from mantle cell lymphoma (MCL), marginal zone ymphoma (MZL) and chronic lymphocytic leukemia (CLL).

Material and Methods

MCL (Jeko1, Rec1, JVM2, Granta519, Maver1, Mino1, SP-49, SP-53, UPN1, Z138), MZL (Karpas1718, VL51, SSK41, ESKOL, HAIR-M, HC-1) and CLL (MEC1) cell lines were exposed to increasing doses of copanlisib alone and in combination with other compounds using the fixed ratio set-up. Tested compounds included approved and experimental inhibitors of key regulatory pathways. Synergy was assessed via Chou-Talalay combination index (CI). Gene expression profiling (GEP) was done using Illumina Human HT12Expression BeadChips and GSEA (FDR<0.25).

CONCLUSIONS

Copanlisib was active in MCL, MZL and CLL models. Combinations with BCL2-i venetoclax and CDK4/CDK6-i palbociclib were the most synergistic. Specific GEP features might predict lymphomas that could benefit from these regimens.

Acknowledgments

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RESULTS

Copanlisib showed antitumor activity in most cell lines (median IC50=22nM; 95%C.I.: 15-98). The other most active drugs were bortezomib (5nM; 5-7), romidepsin (34nM; 3-94), roniciclib (23nM; 18-29), panobinostat (161nM; 11-1263), MI2 (490nM; 224-1000). The remaining had median IC50s >500nM (Figure 1). Copanlisib-containing combinations often gave synergy/additive effects: copanlisib with venetoclax was beneficial in 16/17; with MI2 in 15; with palbociclib or ibrutinib in 14; with BAY 1125976 or panobinostat in 12; with lenalidomide or BAY 1238097 in 12; with rituximab in 11; with romidepsin in 10; with roniciclib in 9; with bortezomib in 8; with BAY 1143572 in 7; with bendamustine in 6; with ruxolitinib in 2. Combinations with venetoclax and with palbociclib were the most promising, achieving CI values <0.5 in 7 and 6 cell lines, respectively (Table 1). GEP before treatment identified genesets associated with different sensitivity to these 2 combinations. High expression of genes involved in IFN signaling, oxidative phosphorylation, fatty acid metabolism, apoptosis, PI3K/AKT/mTOR and IL6/JAK/STAT signaling and low expression of cell cycle genes were associated with synergism to copanlisib/venetoclax (Figure 2). Largely the opposite was observed for the palbociclib combination, more active with high expression of E2F/MYC targets and cell cycle genes and low expression of genes involved in IFN PI3K/AKT/mTOR and IL6/JAK/STAT signaling (Figure 3).

Figure 1. Anti-proliferative activity of targeted agents in MCL and MZL cell lines. Cells were treated for 72h with a large range of increasing doses of compounds. MCL, mantle cell lymphoma; MZL, marginal zone lymphoma.

Combination with Copanlisib	Percentage of cell lines in which combination were beneficial*	95% Conf. Interval	Mechanism of action of combination partner
Venetoclax	94% (16/17)	71.3 - 99.9	BCL2 inhibition
MI2	88% (15/17)	63.5 - 98.5	MALT1 inhibition
Ibrutinib	82% (14/17)	56.2 - 96.2	BTK inhibition
Palbociclib	82% (14/17)	56.2 - 96.2	CDK4/6 inhibition
Panobinostat	76% (13/17)	50.1 - 93.2	HDAC inhibition
BAY1125976	76% (13/17)	50.1 - 93.2	AKT1/2 inhibition
Lenalidomide	71% (12/17)	44.0 - 89.7	immunomodulation
BAY 1238097	71% (12/17)	44.0 - 89.7	BET inhibition
Rituximab	65% (11/17)	38.3 - 85.8	Anti CD20 mAab
Romidepsin	59% (10/17)	32.3 - 81.6	HDAC inhibition
Roniciclib	53% (9/17)	27.8 - 77.0	CDK inhibition
Bortezomib	47% (8/17)	23.0 - 72.2	Proteasome inhibition
BAY1143572	35% (7/17)	18.4 - 67.1	PTEN/CDK3 inhibition
Bendamustine	35% (6/17)	14.2 - 61.7	chemotherapy
Ruxolitinib	12% (2/17)	1.5 - 36.4	JAK1/2 inhibition

Table 1. Copanlisib –containing combinations in 17 cell lines derived from MCL, MZL or CLL. *, synergistic or additive according to the Chou-Talalay algorithm.

Figure 2. Signatures associated with response to the combination of copanlisib plus venetoclax. A. Meta-genesets associated with synergism to copanlisib/venetoclax in 8 cell lymphoma cell lines; B. Meta-genesets associated with synergism to copanlisib/venetoclax in 8 cell lymphoma cell lines; C. Hallmarks of cancer.

Reference:

1. Gaudio E. *et al.* The phosphatidylinositol-3-kinase (PI3K) inhibitor (i) copanlisib is active in preclinical models of B-cell lymphomas as single agent and in combination with conventional and targeted agents including venetoclax and palbociclib [Poster]. In: Proceedings of the 107th Annual Meeting of the American Association for Cancer Research; 2017 Apr 1-5; Washington, DC. Philadelphia (PA): AACR; 2017. Poster nr [154 / 21].