Clinical and biomarker results from Phase I/II study of PI3K inhibitor, BYL719 (Alpelisib) plus Nab-paclitaxel in HER2 negative metastatic breast cancer

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Abstract # 1018

Background

- Mutations/deregulations in the phosphatidylinositol-3-kinase (PI3K) pathway are common in breast cancer. Activation of the PI3K pathway promotes tumor growth and progression, as well as resistance to anticancer therapies like taxanes . [1-4]
- BYL719 (alpelisib) is a potent oral, class I PI3K inhibitor which strongly inhibits the PI3K alpha isoforms. Targeting the alpha isoform of PI3K is expected to improve the therapeutic window over inhibitors with less isoform specificity. [5]
- Alpelisib has shown single agent activity in patients with *PIK3CA*-altered advanced solid tumors, and in combination with endocrine therapy in *PIK3CA*-altered or wild-type estrogen receptor-positive advanced breast cancer . [6-7]
- Efficacy of alpelisib in combination with taxane chemotherapy in PIK3CA-altered or wild-type HER2 negative breast cancer has not been studied.

Aims

- Primary Objectives : 1) Determine the recommended phase II dose (RPTD) of alpelisib + nab-Paclitaxel, 2) Assess Objective Response Rate (ORR).
- Secondary objectives: 1) Progression-free survival , 2) Clinical benefit rate, 3) pharmacokinetics of alpelisib and nab-paclitaxel , 4) Correlation of PI3K pathway aberrations with response.

Methods

- Phase I was a 3+3 dose-escalation design with three dose levels of alpelisib (250mg, 300mg, and 350mg) administered PO once daily (D1-28) with nab-paclitaxel (100 mg/m2 intravenously D 1, 8, 15) every 28 days. Phase II was a Simon's two stage minimax design targeting a ORR of 40% (NCT02379247)
- Eligible criteria:
  - HER2 negative breast cancer that was either locally advanced and not amenable to curative therapy, or stage metastatic. Patients were required to have measurable disease and to have received at least one line of chemotherapy in either the advanced or adjuvant setting
  - No limitations on number of prior chemotherapies for metastatic disease. Treatment with prior taxanes (except nab-paclitaxel) allowed, as long as >6 months since prior taxane exposure
- FFPE tumor tissue was subjected to next-generation sequencing
- Circulating cfDNA was isolated from of plasma. Purified cfDNA was then used to prepare a NGS library targeting 56 genes (SLIMamp™ Pan-Cancer Hot Spots Panel, Pillar Biosciences) followed by paired-end sequencing on a NextSeq 500 instrument
- Response was evaluated using RECIST v 1.1

References

1.TCGA breast (Network 2012); 2. Samuels Y, et al. Science 2004; 3. Isakoff SJ, et al. Cancer Res; 4. Hu L, et al. Cancer Res, 2002; 5. Fritsch C et al, Cancer Ther 2014; 6. Juric D, et al. JCO 2018; 7. Meyer I, et al, CCR 2017

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Results

- Between 4/2015 and 5/2017, 43 total patients were enrolled in the study.
- Phase I: 10 patients treated on three dose levels. There were no DLTs and no PK interactions were detected when BYL719 and nab-paclitaxel were co-administered. 1/10 patients not included in the DLT assessment (stopped treatment within 10 days)
- RPTD=nab-paclitaxel 100 mg/m2 D1,8,15 Q 28 days plus alpelisib 350mg QD. Phase II: Simon's two stage Minimax design targeting ORR of 40%
- Objective response was noted at all dose levels of alpelisib. ORR in 33 patients treated at the RPTD and all 43 patients was 57% and 59%, respectively. Figures/tables outlining response include all 43 patients.
- PI3K pathway activation was defined as the presence of *PIK3CA*-activating or *PTEN*-inactivating mutations in either tumor tissue or cfDNA and was noted in 44% (19/43) of patients. Absence of *PIK3CA*-activating or *PTEN*-inactivating mutations in both tumor tissue and cfDNA (or only cfDNA when tumor tissue not available, n=5) was categorized as absence of PI3K pathway activation (53%, 23/43).
- Hyperglycemia was noted in 76% (G3:27%, G4:0%). 32% patients required metformin for hyperglycemia management. Rash was noted in 63% (G3:7% G4 0%). All patients received second or third generation H_1-anti-histaminic prophylaxis for rash
- Alpelisib dose reductions needed in 26% (11/43) patients (n=1 at 250mg dose, n=10 at 350mg dose). Fatigue/anorexia n=3, Diarrhea n=3, Rash n=2, Hyperglycemia n=1, Hypokalemia n=1, MD choice n=1. Two patients discontinued therapy (after two cycles) due to grade 2 pneumonitis
- Nab-paclitaxel dose reduction in 28%(10/43) patients. Peripheral Neuropathy(n=3), fatigue(n=1), Rash(n=1), Diarrhea(n=1), Thrombocytopenia(n=1), Neutropenia(n=1), MD choice n=2.
- 2 patients stopped Nab-Paclitaxel and continued on single agent alpelisib. Both stopped alpelisib at 12 weeks due to progressive disease (one PIK3CA mutation +ve and one -ve)

Table 1: Toxicities

N=43	CTCAE Grade				All Grades
Event	Grade 1	Grade 2	Grade 3	Grade 4	N(%)
Diarrhea	23 (56%)	11 (27%)	2 (5%)	0 (0%)	36 (88%)
Fatigue	12 (29%)	14 (34%)	2 (5%)	0 (0%)	28 (68%)
Hyperglycemia	9 (22%)	11 (27%)	11 (27%)	0 (0%)	31 (76%)
Peripheral neuropathy	16 (39%)	9 (22%)	1 (2%)	0 (0%)	26 (63%)
Neutropenia	3 (7%)	5 (12%)	10 (24%)	3 (7%)	21 (51%)
Infections	7 (17%)	15 (37%)	2 (5%)	0 (0%)	24 (59%)
Anemia	12 (29%)	4 (10%)	5 (12%)	0 (0%)	21 (51%)
Rash	21 (51%)	2 (5%)	3 (7%)	0 (0%)	26 (63%)
Pneumonitis	1 (2%)	2 (5%)	0 (0%)	0 (0%)	3 (7%)
Musculoskeletal	26 (63%)	10 (24%)	2 (5%)	0 (0%)	38 (93%)
Pulmonary Other	11 (27%)	6 (15%)	1 (2%)	0 (0%)	18 (44%)
Anorexia	17 (41%)	5 (12%)	0 (0%)	0 (0%)	22 (54%)
Nausea	21 (51%)	7 (17%)	0 (0%)	0 (0%)	28 (68%)
Vomiting	6 (15%)	5 (12%)	0 (0%)	0 (0%)	11 (27%)
GI Other	15 (37%)	5 (12%)	0 (0%)	0 (0%)	20 (49%)
Mucositis/Oral Pain	15 (37%)	4 (10%)	1 (2%)	0 (0%)	20 (49%)
Electrolyte imbalance	16 (39%)	2 (5%)	1 (2%)	1 (2%)	20 (49%
Dysgeusia	17 (41%)	2 (5%)	0 (0%)	0 (0%)	19 (46%)
Liver enzyme increase	14 (34%)	1 (2%)	0 (0%)	0 (0%)	15 (37%)
Eye Disorders	11 (27%)	3 (7%)	0 (0%)	0 (0%)	14 (34%)
Nail Changes	11 (27%)	2 (5%)	0 (0%)	0 (0%)	13 (32%)
Myalgia	8 (20%)	2 (5%)	0 (0%)	0 (0%)	10 (24%)
Neurological	8 (20%)	0 (0%)	0 (0%)	0 (0%)	8 (20%)
Dry Mouth/Skin	7 (17%)	1 (2%)	0 (0%)	0 (0%)	8 (20%)
Weight loss	2 (5%)	5 (12%)	0 (0%)	0 (0%)	7 (17%)
Renal	2 (5%)	2 (5%)	1 (2%)	0 (0%)	5 (12%)
Edema	2 (5%)	1 (2%)	0 (0%)	0 (0%)	3 (7%)
Thrombocytopenia	1 (2%)	1 (2%)	0 (0%)	0 (0%)	2 (5%)
Others	10 (24%)	8 (20%) *	0 (0%)	0 (0%)	18 (44%)

Table 2: Patient Demographics

	N=43
Median Age (years, range)	56 (36 – 74)
Subtype HR Positive TNBC	 30/43 (70%) 13/43 (30%)
Measurable disease	43/43 (100%)
Visceral disease	36/43 (84%)
Prior lines of Chemotherapy for mBC 0 1 ≥2	 10 (23%) 20 (69%) 13 (8%)
Prior Taxane	35/43 (81%)
Prior CDK 4/6 inhibitor use	12/42 (28%)

Figure 1
Longitudinal change from baseline

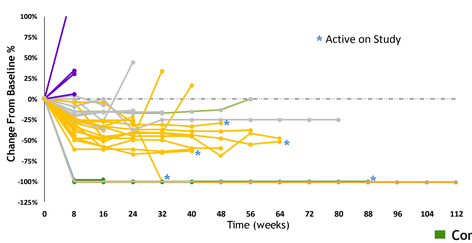


Figure 2
Waterfall Plot for Best Overall Response

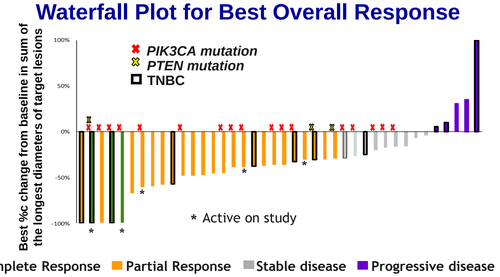


Figure 3: Durability of Response

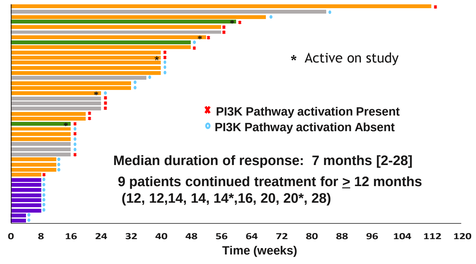


Figure 4A: Progression Free Survival

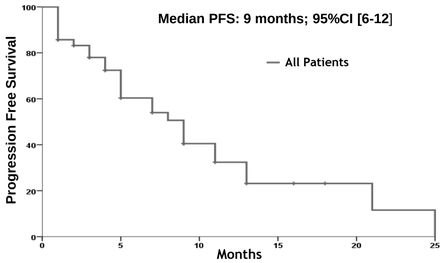


Figure 4B: PFS by PI3K pathway status

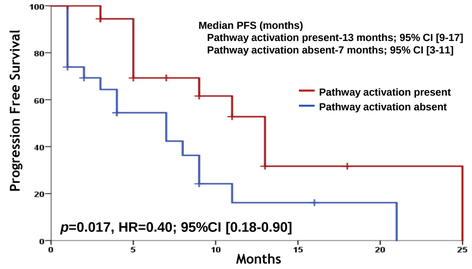


Figure 5: Response by PI3K pathway status

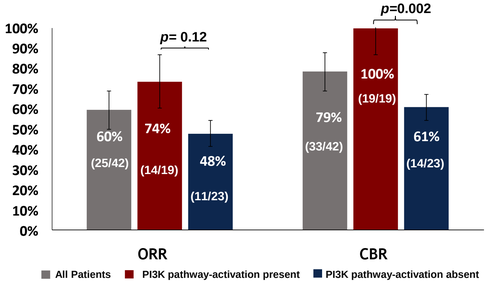
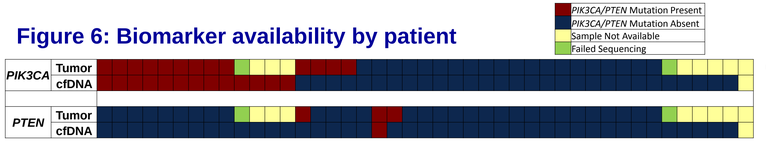


Table 3 : Response by Prior Treatment and Subtype

All Patients (N=42)*		Prior Lines of Chemotherapy			Prior Taxane Exposure		Subtype	
Response	% (n)	0 (n=9) % (n)	1 (n=20) % (n)	≥ 2 (n=13) % (n)	Yes (n=35) % (n)	No (n=7) % (n)	HR+ (n=30) %(n)	TNBC (n=12) % (n)
ORR	59%(25)	56% (5)	65%(14)	46% (6)	60% (21)	57% (4)	60% (18)	58% (7)
CR	7% (3)	0% (0)	10% (2)	8% (1)	9% (3)	0% (0)	3% (1)	16% (2)
PR	52%(22)	56% (5)	60% (12)	38% (5)	51% (18)	57% (4)	57% (17)	42% (5)
Stable Disease (≥16weeks)	19% (8)	22%(2)	15% (3)	23% (3)	17% (6)	29% (2)	27% (8)	0%
CBR	78%	78%	85%	79%	77%	86%	87%	58%

* Response data not available for one TNBC patient

Figure 6: Biomarker availability by patient



Each column represents one patient

Conclusion and Discussion

- Combination of alpelisib and nab-paclitaxel was well tolerated with manageable toxicities. No new toxicity signals were observed
- Encouraging efficacy noted with objective response rate of 59% and CBR of 79%.
  - Efficacy appears similar in patents with Hormone positive and TNBC.
  - Responses noted in patients with previous taxane exposure and beyond first line treatment
  - Efficacy noted in patients with previous CDK 4/6 inhibitor use (ORR of 67%)
- Durability of response observed with several patients continuing treatment for ≥ 1 year.
  - Longest duration of response 26 months in a patient with PIK3CA mutation.
- Tissue and cfDNA NGS analysis provides insights into patients most likely to benefit
  - Although, Clinical benefit was seen in 100% of patients with PI3K pathway activated tumors, activity was also observed in patients without apparent PI3K pathway activation.
  - Further translational studies on tumor and serial cfDNA are ongoing to investigate mechanisms of response in patients without apparent pathway activation and evaluate mechanisms of secondary resistance in patients with durable responses.
- Drugs targeting PI3K pathway are promising new class for breast cancer treatment. Investigation of PI3K inhibitors and AKT inhibitors are on going in Phase II and III trials for patients with hormone positive and triple negative breast cancer.

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