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ORIGINAL ARTICLE

Phase I dose escalation study of the PI3kinase pathway inhibitor BKM120 and the oral poly (ADP ribose) polymerase (PARP) inhibitor olaparib for the treatment of high-grade serous ovarian and breast cancer

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Background: Based upon preclinical synergy in murine models, we carried out a phase I trial to determine the maximum tolerated dose (MTD), toxicities, pharmacokinetics, and biomarkers of response for the combination of BKM120, a PI3K inhibitor, and olaparib, a PARP inhibitor.

Patients and methods: Olaparib was administered twice daily (tablet formulation) and BKM120 daily on a 28-day cycle, both orally. A 3 + 3 dose-escalation design was employed with the primary objective of defining the combination MTD, and secondary objectives were to define toxicities, activity, and pharmacokinetic profiles. Eligibility included recurrent breast (BC) or ovarian cancer (OC); dose-expansion cohorts at the MTD were enrolled for each cancer.

Results: In total, 69 of 70 patients enrolled received study treatment; one patient never received study treatment because of ineligibility. Twenty-four patients had BC; 46 patients had OC. Thirty-five patients had a germline *BRCA* mutation (g*BRCA*m). Two DLTs (grade 3 transaminitis and hyperglycemia) were observed at DL0 (BKM120 60 mg/olaparib and 100 mg b.i.d.). The MTD was determined to be BKM120 50 mg q.d. and olaparib 300 mg b.i.d. (DL8). Additional DLTs included grade 3 depression and transaminitis, occurring early in cycle 2 (DL7). Anticancer activity was observed in BC and OC and in g*BRCA*m and g*BRCA* wild-type (g*BRCA*wt) patients.

Conclusions: BKM120 and olaparib can be co-administered, but the combination requires attenuation of the BKM120 dose. Clinical benefit was observed in both g*BRCA*m and g*BRCA*wt pts. Randomized phase II studies will be needed to further define the efficacy of PI3K/PARP-inhibitor combinations as compared with a PARP inhibitor alone.

Key words: BKM120, olaparib, ovarian cancer, breast cancer, PARP-inhibitors

Introduction

The Cancer Genome Atlas has revealed shared genomic alterations of high-grade serous OC (HGSC) and triple negative BC (TNBC) including extensive copy number alterations, *p53* mutations, PI3K pathway activation, and deficiencies in DNA damage repair and homologous recombination (HR) [1, 2] providing a rationale for

examining similar treatment concepts in both diseases. Poly (ADP ribose) polymerase (PARP) inhibitors interfere with DNA damage repair and exhibit single agent activity in recurrent g*BRCA*m and g*BRCA*wt OC and BC [3–6]. However, despite the presence of *PIK3CA* amplification in HGSC and PIK3CA mutations in endometrial and breast cancer (BC), treatments with single agent PI3K inhibitors have had limited efficacy [7, 8]. Preclinical data supporting the combination and synergy of a PI3K and PARP inhibitor was derived from genetically engineered and patient-derived xenograft (PDX) mouse models and both demonstrated substantial improvement over single agent activity when the PI3K inhibitor BKM120 and PARP inhibitor olaparib were co-administered [9–11]. The underlying rationale is that PI3K inhibitors enhance the efficacy of PARP inhibitors through their antimetabolic activity [9, 10]. PI3K inhibition leads to decreased flux through the non-oxidative pentose phosphate pathway (PPP) that produces ribose-5-phosphate required for nucleoside synthesis [10]. Thus, PI3K inhibitors lower nucleotide pools required for DNA synthesis and S-phase progression, sensitizing BC cells to PARP inhibitor treatments [10]. Additionally, in g*BRCA*wt breast tumors, PI3K inhibition is thought to decrease *BRCA*1 expression through transcriptional regulation [11].

The pan-PI3K inhibitor BKM120 has been examined in phase I studies [8, 12–14] that reported disease stability in 30%–40% of patients as best responses, and a partial response (PR) was seen in one patient with TNBC [8]. Olaparib has single agent activity with response rates of 41% in g*BRCA*m and 24% in g*BRCA*wt OC; objective responses in BC were not seen in this study [6]. Notably, only one of 26 patients with platinum-resistant g*BRCA*wt OC (4%) had a response to olaparib [6]. In different series [4, 15], 13%–41% of *BRCA*m BC patients achieved objective responses.

The primary objective of this phase I dose escalation study was to determine the MTD and recommended phase 2 dose (RP2D) of the combination of BKM120 and olaparib. Secondary objectives were to define the safety and toxicity, anticancer activity and pharmacokinetic interactions of the combination.

Methods

Study design and treatment

The phase I study used a 3 + 3 design, dose escalating if 0/3 or 1/6 participants experienced a DLT during the first cycle of therapy (first 28 days) (see supplementary data, available at *Annals of Oncology* online). Once the MTD and RP2D were determined, up to 12 patients were entered into two separate expansion cohorts, one for OC and another for BC. BKM120 and olaparib were administered p.o., daily (q.d.) and continuously; BKM120 was given q.d. and olaparib b.i.d. Tumor assessment by RECIST 1.1 occurred every two cycles. PK blood samples were collected for BKM120 and olaparib on Day 1, time 0 and then days 8 and 15 at time 0, 1, 2, 4, and 8 h of cycle 1.

Eligibility

Patients were eligible if they had a confirmed diagnosis of either recurrent ovarian, fallopian tube, or primary peritoneal cancer (collectively referred to as 'OC'), HGSC or TNBC histology; diagnosis of BC or ovarian other than HGSC or TNBC but with known g*BRCA*m; RECIST 1.1 measurable or evaluable (BC only) disease, normal organ function, and ability to provide informed consent. Prior PARP inhibitor use was allowed for patients in dose escalation but not in the dose expansion cohort; no prior PI3K inhibitor use was allowed. Only patients with a known deleterious *BRCA* mutation were classified as *BRCA*m positive.

Table 1. Patient and tumor characteristics

Characteristic	Ovarian cancer	Breast cancer
Number of patients	46	24
Age, years		
Median (range)	60 (34–78)	48 (27–70)
Histology		
High-grade serous	41 (89%)	–
High-grade endometrioid	1 (2%)	–
Carcinosarcoma	2 (4%)	–
Poorly differentiated carcinoma	2 (4%)	–
Platinum status		
Platinum resistant	26 (57%)	–
Platinum sensitive	20 (43%)	–
Breast cancer subtype[a]		
Triple negative	–	13 (54%)
Hormone receptor positive	–	11 (46%)
ECOG performance status		
0	32 (70%)	17 (71%)
1	14 (30%)	7 (29%)
Germline *BRCA* status		
g*BRCAm*	32 (70%)	15 (63%)
wt *BRCA*	9 (20%)	7 (29%)
Unknown	5 (10%)	2 (8%)

[a]All breast cancer patients tested Her2-negative by FISH or IHC standard criteria.

Results

Seventy patients were enrolled into the study between October 2012 and November 2014. During the dose-escalation, 47 patients were enrolled: 35 patients with OC (26 ovarian, six fallopian tube, three primary peritoneal) and 12 patients with BC. Twenty-three patients were enrolled in the dose-expansion cohorts: 11 patients with OC and 12 patients with BC. One patient was deemed ineligible after signing the informed consent and never received study drug. The cutoff date for analysis was 5 April 2015 when 60 of 69 patients (78%) had stopped study treatment.

Patient characteristics are summarized in Table 1. Of the 46 women with OC, 89% had HGSC, and 70% were g*BRCA*m positive, 20% were g*BRCA*wt, and 10% were unknown/not tested. Of the BC patients, 54% had a diagnosis of TNBC, and 46% were hormone receptor positive (either ER+ and/or PR+); 63% were g*BRCA*m, 29% g*BRCA*wt, and 8% unknown/not tested. Median ages of the OC and BC patients were 60 and 48 years of age, respectively. In those patients who were negative for a known deleterious germline mutation in *BRCA*1 or *BRCA*2, no somatic mutations or mutations of unknown significance were found in patients whose DNA was available for WES or MSKImpact [17].

Ten dose combinations were evaluated (supplementary Table S1, available at *Annals of Oncology* online). The starting dose, DL0, was BKM120 60 mg q.d. and olaparib 100 mg b.i.d. Two

DLTs occurred during DL0, one patient with grade 3 hyperglycemia and another with grade 3 transaminitis who was found to have liver metastases after undergoing repeat diagnostic imaging after cycle 1. The doses were then decreased to BKM120 40 mg q.d. and olaparib 50 mg b.i.d. (DL-1) which were deemed safe. Doses were then escalated (supplementary Table S1, available at *Annals of Oncology* online) to BKM120 60 mg q.d. and olaparib 300 mg b.i.d. (DL7). At DL7, there were no DLT's during cycle 1, but grade 4 transaminase elevation occurred in one patient on cycle 2, day 8 as well as grade 3 depression in another patient on cycle 2, day 10, both episodes resulting in hospitalization and both considered dose-limiting; doses were then de-escalated to BKM120 50 mg q.d. and olaparib 300 mg b.i.d. (DL8) which were subsequently deemed safe and selected as the MTD. Patients on the expansion cohort were treated at this dose level.

Related non-hematologic and hematologic toxicities occurring in ≥10% of all treated patients ($n = 69$) are listed in Table 2. There were no unexpected toxicities observed based on the known toxicities of olaparib and BKM120. Nausea and fatigue were the most common toxicities occurring in 78% and 65% of patients respectively, mostly grades 1 and 2. Hyperglycemia, an expected toxicity of PI3K-inhibitors, was seen in 39% of patients, mostly grades 1 and 2. Transaminase elevations, a known toxicity of PI3K inhibitors, were also observed in 20% of patients and were responsible for two DLT's as described above. Depression and anxiety, which were observed in 36% and 28% of patients, respectively are known toxicities of BKM120; these toxicities were reversible with either dose reductions or cessation of BKM120 based on the toxicity grade. Anemia, an expected toxicity of olaparib, occurred at an incidence of 23%, mostly grades 1 and 2 (Table 2). Neutropenia was observed in 12% of patients, and thrombocytopenia and lymphopenia were each observed in 10% of patients.

Best overall response using RECIST 1.1 criteria was assessable in 59 of 69 treated patients (86%) (Table 3). All patients had measurable disease at baseline. Tumor measurements at restaging were not available for seven non-responders who came off study before first restaging. Nine of 17 PRs were confirmed, confirmation of response was not required. Activity of the combination was similar for both cancer types, with a 29% response rate for OC (90%CI: 18%–43%) irrespective of platinum-sensitivity status and a 28% response rate for BC (90%CI: 12%–50%); all PRs. Slightly less than half of patients with both cancers had stable disease (SD) as best overall response. The median duration of SD for assessable patients without progressive disease as best overall response ($n = 45$) was 6.9 months (90%CI: 5.5–7.5 months). Among all treated patients, 16 of 45 OC patients (36%) and 8 of 24 BC patients (33%) achieved disease stability for >6 months.

Thirty-seven of 52 assessable patients with restaging radiographic imaging showed tumor shrinkage from baseline (Figure 1A). Among the 17 patients with PR's, 12 progressed while on treatment, one discontinued treatment of intolerability, and four remain on study treatment, with a median duration of response of 4.8 months by Kaplan–Meier estimation (Figure 1B). In the OC cohort, all of the patients with a PR had HGSC histology, and 8 of the 12 patients who achieved a PR were known g*BRCA*m carriers; we were not able to obtain sufficient quality DNA in those four ovarian cancers (OCs) that achieved partial remissions and were g*BRCA*wt. In the patients with BC who exhibited a tumor response, four out of the five patients with a PR had a g*BRCA*m; one patient who had a PR had TNBC and was g*BRCA*wt. Supplementary Figure S1, available at *Annals of Oncology* online, describes a patient with a g*BRCA2*m and ER+/PR+ HER2 negative BC who achieved a PR.

Table 2. Study treatment-related toxicities occurring in ≥10% of patients

Toxicity	Grade 1 *N* (%)	Grade 2 *N* (%)	Grade 3 *N* (%)	Grade 4 *N* (%)	Total *N* (%)
Non-hematologic toxicities					
Nausea	42 (61%)	10 (14%)	2 (3%)	0	54 (78%)
Fatigue	30 (43%)	13 (19%)	2 (3%)	0	45 (65%)
Hyperglycemia	18 (26%)	8 (12%)	1 (1%)	0	27 (39%)
Anorexia	17 (25%)	8 (12%)	1 (1%)	0	26 (38%)
Depression	15 (22%)	6 (9%)	3 (4%)	1 (1%)	25 (36%)
Diarrhea	21 (30%)	3 (4%)	0	0	24 (35%)
Anxiety	13 (19%)	5 (7%)	1 (1%)	0	19 (28%)
Mucositis	12 (17%)	4 (6%)	0	0	16 (23%)
Vomiting	13 (19%)	1 (1%)	1 (1%)	0	15 (22%)
↑ALT	7 (10%)	3 (4%)	3 (4%)	1 (1%)	14 (20%)
↑AST	8 (12%)	2 (3%)	4 (6%)	0	14 (20%)
Dysgeusia	9 (13%)	3 (4%)	0	0	12 (17%)
Dyspepsia	5 (7%)	4 (6%)	0	0	9 (13%)
Constipation	7 (10%)	0	0	0	7 (10%)
↑Creatinine	7 (10%)	0	0	0	7 (10%)
Dizziness	6 (9%)	0	1 (1%)	0	7 (10%)
Hematologic toxicities					
Anemia	10 (14%)	3 (4%)	2 (3%)	1 (1%)	16 (23%)
Neutropenia	0	6 (9%)	1 (1%)	1 (1%)	8 (12%)
Thrombocytopenia	6 (9%)	1 (1%)	0	0	7 (10%)
Lymphopenia	2 (3%)	5 (7%)	0	0	7 (10%)

To identify potentially predictive markers for this combination, we examined archival tumor tissue from 40 patients enrolled in this study by Next Generation Sequencing (NGS, MSKImpact panel [17]); of these 36 were also subjected to Whole Exome Sequencing (WES) (supplementary Figure S2, available at *Annals of Oncology* online). Sixty-four percent were germline mutation carriers for *BRCA*1 (42%) or *BRCA*2 (22%) (Figure 1B). Forty-four percent of patients had a genetic alteration that could activate the PI3K pathway, but there was no apparent relationship between the presence of these and response to the treatment combination (Figure 2).

PK results for BKM120 and olaparib are located in supplementary Tables S2 and S3, available at *Annals of Oncology* online. Steady state C_{max} values determined on day 8, 2 h post dosing for both olaparib and BKM120 appear comparable to values when testing both of these agents as single agents in the phase I setting, i.e. drug exposures increased appropriately with increasing dose [3, 14]. BKM120 C_{max} results appeared unaffected by olaparib dosing, and olaparib C_{max} results appeared unaffected by BKM120 dosing. However, at the higher doses, PKs varied as much as fivefold for each drug (supplementary Tables S2 and S3, available at *Annals of Oncology* online). None of the patients with DLT toxicities had abnormally elevated steady state C_{max} levels of either olaparib or BKM120.

Despite the molecular similarities of TNBC and HGSOC [1, 2], there are notable differences, namely the greater genomic instability of OC and the predominance of PIK3CA amplifications

Table 3. Response to treatment

RECIST 1.1 Response	Ovarian cancer *N* (%)	Breast cancer *N* (%)	Total *N* (%)
Number treated[a]	45	24	69
Not assessable	4 (9%)	6 (25%)	10 (14%)
Non-measurable disease	3 (7%)	6 (25%)	9 (13%)
Discontinued cycle 1 without PD	1 (2%)	0	1 (1%)
Number assessable	41	18	59
Complete response	0	0	0
Partial response	12 (29%)	5 (28%)	17 (29%)
Stable disease	20 (49%)	8 (44%)	28 (47%)
Progressive disease	9 (22%)	5 (28%)	14 (24%)
Response by BRCA status			
gBRCAm	28	12	40
Partial response	8 (29%)	4 (33%)	12 (30%)
Stable disease	13 (46%)	5 (42%)	18 (45%)
Progressive disease	7 (25%)	3 (25%)	10 (25%)
gBRCAwt	8	5	13
Partial response	1 (12%)	1 (20%)	2 (15%)
Stable disease	5 (62%)	2 (40%)	7 (54%)
Progressive disease	2 (25%)	2 (40%)	4 (31%)
Unknown	5	1	6
Partial response	3 (60%)	0	3 (50%)
Stable disease	2 (40%)	1 (100%)	3 (50%)
Progressive disease	0	0	0
Response by platinum status			
Platinum resistant	22	–	–
Partial response	6 (27%)	–	–
Stable disease	11 (50%)	–	–
Progressive disease	5 (23%)	–	–
Platinum sensitive	19	–	–
Partial response	6 (32%)	–	–
Stable disease	9 (47%)	–	–
Progressive disease	4 (21%)	–	–

Response to treatment of all patients based on RECIST 1.1 and BRCA status. One patient was deemed ineligible before initiating treatment.
[a]Of the originally consented 46 patients, one withdrew consent before treatment.

rather than activating mutations. We carried out preclinical experiments with OC PDX to examine if the PI3K-inhibitor enhanced the efficacy of the PARP inhibitor olaparib similar to what was found in BC [9, 11, 16]. We used PDX derived from 10 different OC patients, none of whom were enrolled on this study) (supplementary files 'Murine ovarian cancer PDX models' and Figures S3 and S4, available at *Annals of Oncology* online). In 7/10 PDX-models, the combination of BKM120 with olaparib showed better outcomes than the PARP inhibitor alone (supplementary Figure S4, available at *Annals of Oncology* online). There was, however, no obvious correlation between baseline status of PIK3CA or DNA damage repair parameters and response to the BKM120 and olaparib combination in these PDX models.

Discussion

The rationale for this phase I study of the oral PI3K inhibitor BKM120 and the oral PARP inhibitor olaparib was based on preclinical work showing *in vivo* synergy of this combination [9, 11]. Both agents were able to be combined in this study with RECIST 1.1 responses occurring in both recurrent ovarian and BC patients; the MTD was BKM120 50 mg q.d. and olaparib 300 mg b.i.d. Overall, the combination was well tolerated, but toxicities prevented further escalation of BKM120 which included CNS toxicity, specifically grade 3 depression and grade 3 transaminase elevation, both known toxicities of BKM120. In addition, no predictive genotypic markers using NGS were identified in this study for the combination.

Though the PK's of both olaparib and BKM120 did not show any drug drug interactions (DDI), we were not able to dose escalate BKM120 beyond 50 mg; the single agent MTD of BKM120 is 100 mg. Therefore, there are likely DDI between BKM120 and olaparib possibly leading to cumulative BKM120 drug levels given the delayed DLT toxicities observed early in cycle 2 in two patients (grade 3 transaminase elevations and grade 3 depression), providing rationale for extended PK testing beyond completion of cycle 1. An amendment to this phase I study adding dose escalation testing

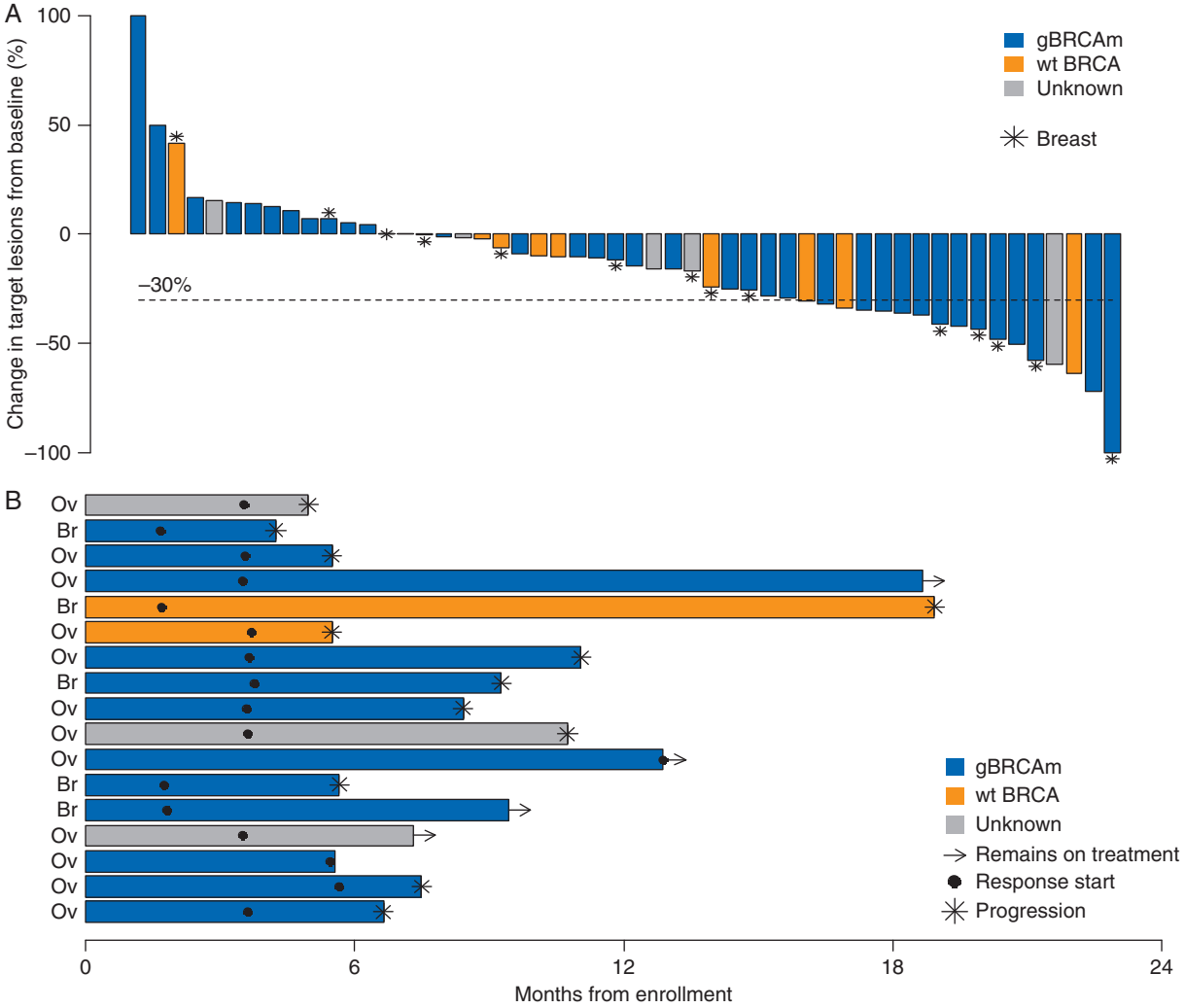

Figure 1. Response to study treatment. (A) Summary of the maximum reduction in target lesion size in $n = 52$ patients with measurable disease and restaging scans. (B) Summary of the duration of response for the 17 patients who achieved a partial response by RECIST 1.1 criteria labeled by cancer type. The interval from date of enrollment to date of either progression or date of last disease assessment is displayed along with the first disease assessment to achieve partial response. Median duration of response was 4.8 months (maximum 17.2 months).

for the alpha specific PI3K inhibitor BYL719 combined with olaparib is now underway given this PI3K inhibitor's selectivity on the PI3K pathway and absence of CNS toxicities.

Our group has previously established and characterized a group of OC PDX models that faithfully model the clinical spectrum and responsiveness to standard-of-care chemotherapy [18]. In this mouse model system of HGSC, the addition of BKM120 improved responses over olaparib monotherapy in both *BRCA*-related and unrelated OC (supplementary Figure S4, available at *Annals of Oncology* online), similar to what was seen previously in BC [9, 11]. Our approach, using human OC PDX models rather than select cell lines, models the inter-individual variability of patients tumors, and as expected, responses were also highly variable (supplementary Figure S4, available at *Annals of Oncology* online). However, we did not identify any biomarkers that predicted response, thus underscoring the complexity of the biology underlying responses to this regimen even in a mouse model; this raises the possibility that a constellation of genomic or proteomic markers might be predictive.

Our study demonstrated a response rate of 29% in advanced OC and 28% in BC patients with measurable disease. Of the women with OC, all of the patients who responded had HGSC histology, and the majority (8 out of 12 responders) had a known g*BRCA*m. There was no difference in response to the BKM120 + olaparib regimen between OC patients with platinum-sensitive versus platinum-resistant disease. In previous studies overall response rates to olaparib in g*BRCA*mt OC was 28% [5], and response rates of olaparib in platinum-resistant patients is usually lower than observed with platinum-sensitive patients [5, 6]. Within the group of BC patients with g*BRCA*m, 4 out of 12 patients had a PR and 5 out of 12 patients had SD, which translates into a clinical benefit for the majority of these patients; even more remarkably, one out of five patients with g*BRCA*wt had a prolonged PR and two out of five BC patients with g*BRCA*wt had SD and continued on study at the time of the data lock. These observations in a small cohort of patients do raise the possibility that the PI3K and PARP inhibitor combination might improve outcomes over olaparib alone for BC patients. For OC patients who are g*BRCA*m, it is impossible to determine the benefit of the combination of olaparib and BKM120, given the known activity of olaparib in this patient population; in fact, the U.S. Food and Drug Administration (FDA) granted

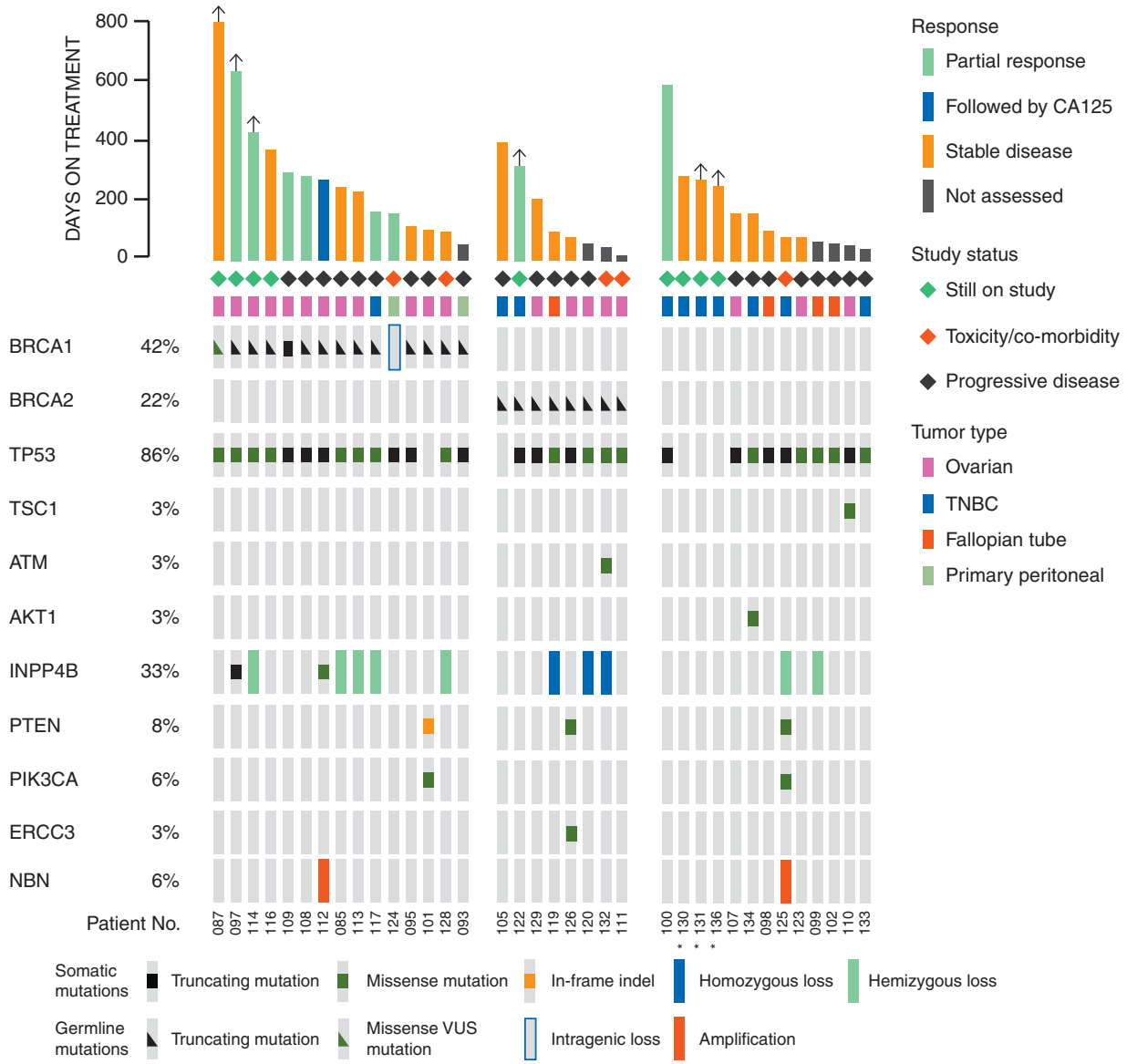

Figure 2. Genomic aberrations in the PI3K pathway or in DNA damage repair in patients with metastatic breast or ovarian cancer on this study. Data are shown for the 36 patients who could be evaluated for a response and in whom sufficient material was available as described in supplementary Figure S1, available at *Annals of Oncology* online. Mutations and were identified through next-generation sequencing (MSK-IMPACT panel). Not shown are FANCA, CHEK2, PALB2, HDAC2, RAD51, MLH3, and MRE11 (no mutations), ERCC3 (mutated in one patient) and NBN (amplified in two patients). An asterisk marks cases with low DNA purity, and low frequency mutations may be present.

accelerated approval to olaparib in December 2014 for patients with g*BRCA*m recurrent OC. Additional biomarker strategies besides presence of a g*BRCA*m or a somatic *BRCA*m will be needed to select patients who could benefit from the combination versus single agent olaparib given the activity of olaparib in both g*BRCA*m and g*BRCA*wt ovarian and BC.

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Disclosure

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