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EDITORIAL

Optimal treatment for aromatase inhibitor-resistant metastatic breast cancer patients: lessons from the PEARL study

Hormone receptor-positive (HR+), HER2-negative (HER2−) tumors represent ∼70% of metastatic breast cancer (mBC) patients. Endocrine treatment (ET) in combination with cyclin-dependent kinase 4-6 inhibitors (CDK4/6is) is the standard of care in first line, and an effective treatment option in second and subsequent lines.[1] Palbociclib was the first-in-class CDK4/6i to be approved, both in combination with letrozole as first-line treatment for HR+/HER2− mBC, based on the results of PALOMA-2, and in combination with fulvestrant in patients with HR+/HER2− mBC after progression to ET, based on the results of PALOMA-3.[2,3] In the PALOMA-3 study, palbociclib, in combination with fulvestrant, improved progression-free survival (PFS) compared with fulvestrant plus placebo. However, the poor performance of the control arm [median PFS (mPFS) of 4.6 months, 95% confidence interval (CI) 3.5-5.6] raised the need to compare the combination of palbociclib and ET with other standard treatment strategies in the same population.[3]

In the PEARL trial, palbociclib in combination with exemestane (cohort 1) or in combination with fulvestrant (cohort 2) was compared with capecitabine in postmenopausal, HR+/HER2− mBC patients, after progression on aromatase inhibitors (AIs).[4] Originally, the study was designed to compare the combination of palbociclib plus exemestane to capecitabine. In 2016, however, the study design was modified, based on evidence that *ESR1* mutation was a mechanism of resistance to AIs and that fulvestrant, differently from tamoxifen and AIs, could be active also on *ESR1*-mutated tumors. Therefore, a second cohort of patients was enrolled to compare the combination of palbociclib plus fulvestrant with capecitabine. Co-primary endpoints were PFS in cohort 2 and PFS among patients with *ESR1* wild-type tumors in both cohorts. Palbociclib did not improve PFS, neither in cohort 2 [mPFS of 7.5 versus 10.0 months, adjusted hazard ratio (HR) 1.13; 95% CI 0.85-1.50], nor among *ESR1* wild-type patients (mPFS of 8.0 versus 10.6 months, adjusted HR 1.11, 95% CI 0.87-1.41).

When the PEARL trial was designed, it was not known whether CDK4/6i should be given as a first- or second-line treatment. Since then it has been demonstrated that the absolute PFS benefit was higher when CDK 4/6i was given as first-line[2,5-7] compared with second-line treatment.[3,8,9] This has been also confirmed in the PEARL trial, where the mPFS of ET plus palbociclib in the combined cohort was only 7.4 months. Moreover, three studies have shown that CDK4/6is improve overall survival.[6,9,10] Based on the aforementioned data, there is an increasing use of this class of drugs in the first-line setting. The results of the ongoing randomized SONIA study (NCT03425838) will answer the question of whether CDK4/6i is superior when given as first- compared to second-line treatment.[11] Moreover, if the recent positive data about the CDK4/6i abemaciclib in the adjuvant setting for high-risk, early HR+/HER2− BC[12] will be confirmed after a longer follow-up, the use of CDK4/6i in the early setting of disease will further affect treatment strategies in the metastatic setting.

However, today there are still mBC patients who have not been exposed to CDK4/6i and are resistant to ET. Several reported studies have evaluated different treatments for these patients (Table 1). How can the PEARL trial, reported in this issue of *Annals of Oncology*, help us refine treatment in this setting? Fulvestrant and CDK4/6i is mostly used for these patients based on the PALOMA-3 results.[3] Moreover, exemestane in combination with the mechanistic target of rapamycin inhibitor everolimus is approved for AI-resistant patients based on the results of the Breast Cancer Trials of Oral Everolimus-2 (BOLERO-2) study.[15] More recently, the PIK3CA-specific inhibitor alpelisib in combination with fulvestrant has been also approved for *PIK3CA*-mutant, AI-resistant patients based on the SOLAR-1 study results.[18] However, the aforementioned two regimens are now mostly reserved for patients progressing after ET + CDK4/6i. Another option for AI-resistant patients is chemotherapy, such as capecitabine. The PEARL trial did not demonstrate that ET + palbociclib was superior in PFS compared with capecitabine. These results are in line with the BOLERO-6 trial results in failing to demonstrate that the combination of exemestane with everolimus was better than capecitabine,[17] but discordant from those reported from the Young-PEARL (KCSG-BR15-10) trial.[14] In the Young-PEARL trial, ET plus palbociclib showed a significant increase in PFS, compared to capecitabine in premenopausal women.[14] The different results between the PEARL and the Young-PEARL trials can be at least partly explained by the different patient populations (postmenopausal women progressing on AIs versus premenopausal women progressing on tamoxifen) and different study designs (phase III versus II) for the PEARL and Young-PEARL trials, respectively.

Then, should PEARL trial results change the current standard of care for AI-resistant patients of fulvestrant and CDK4/6i? The answer is no. Although ET + palbociclib did not improve PFS compared to capecitabine, it was associated with a lower rate of treatment discontinuation due to

Table 1. Selected studies in metastatic breast cancer patients treated with prior endocrine treatment

	PALOMA-3[3,13]		PEARL[4]				Young-PEARL (KCSG-BR15-10)[14]		BOLERO-2[15,16]		BOLERO-6[17]			SOLAR-1[18,19] (*PIK3CA*-mutated cohort)	
	Palbociclib + fulvestrant	Placebo + fulvestrant	Cohort 1		Cohort 2		Palbociclib + ET	Capecitabine	Everolimus + exemestane	Placebo + exemestane	Everolimus + exemestane	Everolimus	Capecitabine	Alpelisib + fulvestrant	Placebo + fulvestrant
			Palbociclib + exemestane	Capecitabine	Palbociclib + fulvestrant	Capecitabine									
Number of patients	347	174	153	143	149	156	92	86	485	239	104	103	102	169	172
Median age, years (range)	57 (30-88)	56 (29-80)	60 (31-89)	60 (38-87)	62 (38-86)	60 (33-85)	44 (40-48)	44 (40-48)	62 (34-93)	61 (28-90)	61 (32-86)	61 (38-88)	60 (35-84)	63 (25-87)	64 (38-92)
Menopausal status (pre/postmenopausal)	72 (21%)/275 (79%)	36 (21%)/138 (79%)	0/153 (100%)	0/143 (100%)	0/149 (100%)	0/156 (100%)	92 (100%)/0	86 (100%)/0	0/485 (100%)	0/239 (100%)	0/104 (100%)	0/103 (100%)	0/102 (100%)	0/168 (99%)	0/172 (100%)
Visceral disease	206 (59%)	105 (60%)	103 (67%)	94 (66%)	97 (65%)	102 (65%)	45 (49%)	43 (50%)	56%	56%	69 (66%)	66 (64%)	63 (62%)	93 (55%)	100 (58%)
≥2 metastatic sites	234 (67%)	112 (64%)	106 (69%)	110 (77%)	93 (62%)	121 (78%)	42 (40%)	48 (47%)	67%	71%	—	—	–	106 (63%)	119 (69%)
Sensitivity to prior ET[a]	274 (79%)	136 (78%)	107 (70%)	104 (73%)	119 (80%)	122 (78%)	—	—	84%	84%	—	—	–	140 (83%)	146 (85%)
Previous CT for metastatic disease	113 (33%)	64 (37%)	48 (31%)	41 (29%)	41 (27%)	41 (26%)	22 (24%)	18 (21%)	26%	26%	24 (23%)	35 (34%)	21 (21%)	0	0
Line at study entry															
First	84 (24%)	45 (26%)	27 (18%)	31 (22%)	38 (25%)	43 (28%)	46 (50%)	45 (51%)	0	0	—	—	—	88 (52%)	89 (52%)
Second	132 (38%)	70 (40%)	61 (40%)	50 (35%)	76 (51%)	79 (50%)	30 (33%)	30 (52%)	16%	18%	—	—	—	79 (47%)	82 (48%)
Third or more	131 (38%)	59 (34%)	62 (40%)	62 (43%)	35 (23%)	34 (22%)	16 (17%)	11 (13%)	84%	83%	—	—	—	—	—
Discontinuation due to AEs	14 (4%)	3 (2%)	8 (5%)	25 (18%)	3 (2%)	16 (10%)	1 (1%)	2 (2%)	19%	4%	8 (8%)	20 (19%)	19 (19%)	71 (25%)	12 (4%)
mPFS (experimental arm versus control arm)[b]	9.5 ersus 4.6 months (HR 0.46, 95% CI 0.36-0.59, $P < 0.0001$)		Cohort 2: 7.5 versus 10.0 months (adjusted HR 1.13, 95% CI 0.85-1.50) Wild-type *ESR1* patients: 8.0 versus 10.6 months (adjusted HR 1.11, 95% CI 0.87-1.41)				20.1 versus 14.4 months (HR 0.66, 95% CI 0.44-0.99, $P = 0.023$)		6.9 versus 2.8 months (HR 0.43, 95% CI 0.35-0.54, $P < 0.001$)		8.4 months with everolimus plus exemestane versus 6.8 months with everolimus alone (HR 0.74, 90% CI, 0.57-0.97) versus 9.6 months with capecitabine (HR 1.26, 90% CI 0.96-1.66)			11.0 versus 5.7 months (HR 0.65, 95% CI 0.50-0.85, $P < 0.001$)	
QoL assessment	On treatment, overall global QoL scores 66.1 in palbociclib + fulvestrant group versus 63.0 in the placebo + fulvestrant group ($P = 0.0313$)		Median time to deterioration in global health status 8.6 months in palbociclib + ET arm versus 6.2 months in capecitabine arm (adjusted HR 0.67, 95% CI 0.53-0.85, $P = 0.001$)				—		Median time to definitive deterioration in health-related QoL 8.3 months with everolimus + exemestane versus 5.8 months with placebo + exemestane (HR 0.74, $P = 0.0084$)		—			No difference between arms in time to 10% deterioration in global health/QoL status (HR 1.03, 95% CI 0.72-1.48)	

AEs, adverse events; CI, confidence interval; CT, chemotherapy; ET, endocrine therapy; HR, hazard ratio; mPFS, median progression-free survival; QoL, quality of life.

[a] Sensitivity to prior ET was defined as relapse after 24 months of adjuvant ET or response (complete or partial) or stabilization after 24 weeks of the most recent ET in the context of advanced disease.

[b] Assessed by local investigators.

adverse events compared to capecitabine (3.6% versus 13.7%, respectively) and with better quality of life. This makes it a more attractive option for second-line treatment. Capecitabine can be reserved for later lines. In the PEARL trial, there was no patient subgroup that benefited more from one treatment over the other with the exception of patients with non-luminal tumors (basal-like and HER2 enriched) by the Prediction Analysis of Microarray 50 classification who seemed to benefit more from capecitabine. In a recent analysis of the MONALEESA trials evaluating the association of intrinsic BC subtypes with efficacy outcomes in patients treated with ribociclib, the HER2-enriched subtype showed the greatest benefit from adding ribociclib to ET, while the basal-like was the only subtype showing no benefit.[20] The above analyses are hypothesis-generating that need to be further confirmed. At the moment, apart from estrogen receptor status, no other biomarkers exist to select patients for CDK4/6i, although several studies are investigating the mechanisms of response/resistance to CDK4/6 inhibition.[21-23] Studies aimed to select patients who will not benefit from CDK4/6i are needed.

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