PALLAS
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Predictors of early discontinuation of adjuvant palbociclib in early HR+/ HER2- breast cancer: final analysis of the PALLAS (AFT-05; ABCSG-42) trial integrating patient-reported outcomes

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Background

The PALLAS trial investigates adjuvant palbociclib plus endocrine therapy (ET) versus ET alone in patients (pts) with HR+/HER2− early breast cancer. While palbociclib improves outcomes in the metastatic setting, final analysis from PALLAS did not demonstrate benefit in survival outcomes from the addition of adjuvant palbociclib to ET. A high number of pts discontinued palbociclib before the planned 2-year duration, though degree of palbociclib exposure was not associated with clinical outcomes. This analysis explores factors predictive of palbociclib early discontinuation and dose reductions, including baseline characteristics, toxicities, and patient-reported outcomes (PROs).

Methods

Using the safety population of 5736 pts (2840 receiving palbociclib + ET), we assessed early palbociclib discontinuation within a competing-risks framework (competing events: progression, death). Cumulative incidence curves (Aalen-Johansen estimates) and cause-specific hazard models were used to explore associations with clinical and demographic factors (age, menopausal status, stage, race, endocrine therapy type), toxicities (neutropenia, anemia, nausea), and baseline PROs (patient assessed quality of life (QoL), anxiety, fatigue, pain, frailty/ dependency, depression, and low income. financial difficulties). We performed an automated model selection based on the AIC starting from the cause-specific hazard model incorporating all considered predictors including PROs.

Results

Early discontinuation of palbociclib not due to progression or death occurred in 41.3% of pts; an additional 12.1% stopped due to results of a futility analysis. Median time to early discontinuation was 7.7 months (median IQR 3.45-13.60). Very early discontinuation (≤3 months) occurred in 9.2% of pts. Dose reductions to 100mg and 75mg occurred in 55.2% and 33.6%, respectively. In univariable analyses among others, higher age, lower N-stage, and poor baseline PROs (baseline QoL, fatigue, anxiety, depression, frailty/ dependency and financial difficulties) were linked with increased risk of discontinuation. The best-fitting multivariable model identified age, nodal stage (N-stage), low quality of life (QoL), and financial difficulties as key predictors of early treatment discontinuation.

Conclusions

In the PALLAS trial, older age, lower nodal stage, lower baseline quality of life, and financial difficulties were associated with early discontinuation of adjuvant palbociclib. These findings underscore the value of incorporating patient-reported outcomes into risk stratification. They also support the need for targeted adherence interventions, particularly for more vulnerable patient groups. This aligns with results from the ESMO Breast QoL analysis (Bjelic-Radisic et al.), which demonstrated that patient-reported measures complement clinical parameters in evaluating treatment burden and adherence.

References:

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Table 1: Patients characteristics

Variable	level	Overall	Missing
n		5753	
Sex at birth (%)	Female	5717 (99.4)	0.0
	Male	36 (0.6)	
Randomised treatment (%)	palbociclib + ET	2883 (50.1)	0.0
	only ET	2870 (49.9)	
Actual treatment received (%)	palbociclib + ET	2840 (49.5)	0.3
	only ET	2896 (50.5)	
Treatment started (%)	No	17 (0.3)	0.0
	Yes	5736 (99.7)	
Age at randomisation (%)	<40	587 (10.2)	0.0
	40-49	1776 (30.9)	
	50-59	1763 (30.7)	
	60-64	647 (11.2)	
	65-69	520 (9.0)	
	>=70	459 (8.0)	
Age at randomisation (mean (SD))		53.00 (10.97)	0.0
Menopausal status (%)	Pre-/Perimenopausal	2617 (45.5)	0.0
	Postmenopausal/Male/unknown	3136 (54.5)	
Race (%)	White	5013 (87.1)	0.0
	Asian	279 (4.8)	
	Black	148 (2.6)	
	Other/unknown	313 (5.4)	
N-stage (%)	N0	751 (13.1)	0.0
	N1	2836 (49.3)	
	N2	1406 (24.4)	
	N3	758 (13.2)	
T-stage (%)	T0/T1/Tis/TX	1055 (18.3)	0.0
	T2	3238 (56.3)	
	T3/T4	1459 (25.4)	
Histological grade (%)	G1/G2	3891 (67.6)	0.0
	G3	1604 (27.9)	
	GX	258 (4.5)	
Adjuvant endocrine therapy (%)	Aromatase Inhibitor	3865 (67.4)	0.3
	Tamoxifen	1871 (32.6)	
Prior chemotherapy (%)	No	1004 (17.5)	0.0
	Yes	4748 (82.5)	

Table 1: Baseline characteristics of all patients

Figure 1: Palbociclib treatment discontinuation

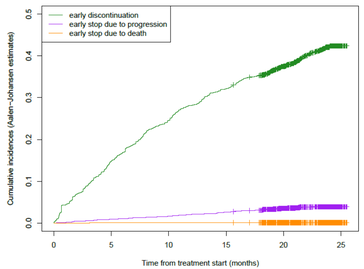


Figure 1: Cumulative incidence curves of competing events (Aalen-Johansen estimates).

Table 2: Univariable cause-specific hazard models

Predictor	Hazard ratio	95% CI	P-value (logrank)
Age at randomisation 40-49	0.95	[0.77, 1.16]	0.12
Age at randomisation 50-59	0.88	[0.72, 1.09]	
Age at randomisation 60-64	1.07	[0.84, 1.36]	
Age at randomisation 65-69	1.13	[0.87, 1.46]	
Age at randomisation >=70	1.09	[0.84, 1.43]	
Age at randomisation	1.01	[1.00, 1.01]	0.043
Menopausal status Postmenopausal/Male/unknown	1.06	[0.95, 1.19]	0.29
Race Asian	1.54	[1.21, 1.94]	0.0017
Race Black	0.77	[0.51, 1.15]	
Race Other/unknown	1.03	[0.79, 1.34]	
N-stage N1	0.93	[0.78, 1.10]	<0.001
N-stage N2	0.84	[0.69, 1.02]	
N-stage N3	0.64	[0.51, 0.81]	
T-stage T2	0.92	[0.79, 1.07]	0.53
T-stage T3/T4	0.96	[0.81, 1.14]	
Histological grade G3	0.82	[0.72, 0.94]	0.014
Histological grade GX	0.94	[0.70, 1.25]	
Adjuvant endocrine therapy Tamoxifen	1.00	[0.88, 1.13]	0.95
Prior chemotherapy Yes	0.87	[0.75, 1.01]	0.073
Poor overall QoL (item 30) Yes	2.13	[1.33, 3.39]	0.0012
Depression (item 24) Yes	1.16	[0.91, 1.46]	0.23
Anxiety (item 22) Yes	1.10	[0.92, 1.32]	0.28
Cognitive impairment (items 20/25) Yes	1.15	[0.87, 1.53]	0.33
Frailty (items 4/5) Yes	2.58	[0.64, 10.32]	0.17
Dependency/frailty (items 4/5) Yes	1.45	[1.10, 1.92]	0.009
Impaired social function (items 26/27) Yes	1.55	[1.10, 2.18]	0.011
Financial difficulties (item 28) Yes	1.32	[1.10, 1.58]	0.0026
Nausea/vomiting (items 14/15) Yes	0.82	[0.20, 3.27]	0.77
Fatigue (items 10/11/12/18) Yes	1.36	[1.08, 1.72]	0.0091
Pain (items 9/19) Yes	1.22	[0.97, 1.54]	0.091
Age at randomisation (per 5 years)	1.027	[1.001, 1.055]	0.043
Age at randomisation (per 10 years)	1.056	[1.002, 1.112]	0.043

Table 2: Estimated HRs from univariable cause-specific hazard models for early discontinuation of palbociclib, considering 1 predictor at a time.