PS2-07-14 Characterization of long-term responders for first-line CDK4/6 inhibitors in HR+/HER2- advanced breast cancer

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Background

- CDK4/6 inhibitors (CDK4/6i) plus endocrine therapy (ET) have reshaped first-line treatment of HR+/HER2- metastatic breast cancer (MBC), achieving median progression-free survival (PFS) of 24-33 months and significant overall survival (OS) benefits in pivotal trials[1-4].
- However, **real-world outcomes remain heterogeneous**: while some patients progress early, most benefit for about two years, and a subset maintain prolonged disease control for several years[5].
- Identifying **robust predictors of long-term response** is crucial to optimize patient selection and maximize benefit.
- **We aimed to characterize factors associated with sustained benefit in this setting.**

Material and Methods

- We analyzed **166 patients (pts)** with HR+/HER2- MBC treated with first-line CDK4/6i between March 2014 and April 2022 at Clinic Barcelona Comprehensive Cancer Center with a minimum follow-up (FU) of 36 months.
- Clinical and molecular characteristics were compared between long-term responders (**LR, defined as PFS ≥ 36 months**) and **non-long responders (nLR)**.
- Intrinsic subtype (IS) was determined at baseline, in samples collected prior to CDK4/6i initiation, using research-based PAM50 assay in 123 pts. Gene expression data from the Breast Cancer 360™ nCounter panel were available for 119 pts.

Results

- **Median FU was 60.5 months** (95% CI: 54.0–67.43). Median **PFS and OS** for the cohort were **21.9 months** (95% CI: 18.3–26.5) and **57.9 months** (95% CI: 44.8–74.6), respectively.
- By data cutoff, 133 patients (80.1%) had progression events and 87 (52.4%) had died. Of the total**, 53 (31.9%) were classified as LR** *(fig 1)*.
- Most patients received ribociclib (62.7%), followed by palbociclib (34.9%) and abemaciclib (2.4%), with **no differences between LR and nLR groups** (p=0.626). **Endocrine-resistant disease** was less frequent in LR (p=0.009), as were **liver metastases** (p<0.001), while **high PR>20%** was more common (p=0.005) *(table 1)*.
- **IS distribution differed significantly** (p = 0.038): 82.1% of LR were luminal vs. 63.1% in nLR *(fig 2)*. Specifically, **Luminal A** (LUMA) was more frequent in LR (51.3% vs. 31.0%, p = 0.045), while H**ER2-enriched (HER2-E)** was less frequent (5.1% vs. 19.0%, p = 0.054) *(fig 3)*.
- In univariate analysis, **endocrine resistance, liver metastases, PR >20%, Luminal IS, and LUMA were significantly associated with LR** *(fig 4)*. In **multivariate analysis** including endocrine resistance, liver metastases, PR >20% and luminal IS, **only liver metastases remained independently associated with a lower probability of being** *(fig 5)*. The remaining variables were not independently significant, likely reflecting overlapping biological information related to hormone sensitivity and luminal phenotype.
- Multivariate logistic regression models adjusted for endocrine resistance, liver metastases, PAM50 subtype, and PR >20%, **identified high expression of several immune-related genes (including *HLA-A, HLA-B, HLA-C, HLA-E, CD274, STAT1, CCL5, CXCL10, TAP1, PSMB10, and GZMA*) independently associated with LR**, highlighting the potential contribution of immune-related pathways to durable benefit from CDK4/6i *(fig 6)*.

Results

Table 1. Baseline Patient Characteristics

PATIENT CHARACTERISTICS	Overall Population N=166	Long Responders N=53	Non-Long Responders N=113	p-value	p-value
Age					
Median (range)	63 (34-87)	64 (42-87)	63 (34-87)		
0-40	8 (4.82)	0 (0.00)	8 (7.08)	0.056	
>40-50	29 (17.47)	9 (16.98)	20 (17.70)	1.000	
>50	129 (77.71)	44 (83.02)	85 (75.22)	0.320	0.132
Sex, n (%)					
Female	165 (99.40)	52 (98.11)	113 (100.0)	0.319	
Male	1 (0.60)	1 (1.89)	0 (0.0)	0.319	0.319
Menopausal Status, n(%)					
Premenopausal	40 (24.24)	11 (21.15)	29 (25.66)	0.562	
Postmenopausal	125 (75.76)	41 (78.85)	84 (74.34)	0.705	0.665
Endocrine Resistant, n(%)					
Primary	16 (9.64)	3 (5.66)	13 (11.50)	0.275	
Secondary	43 (25.90)	7 (13.21)	36 (31.86)	**0.013***	
Non-resistant	107 (64.46)	43 (81.13)	64 (56.64)	**0.003***	**0.009****
De Novo Metastatic, n(%)					
Yes	59 (35.54)	22 (41.51)	37 (32.74)	0.299	
No	107 (64.46)	31 (58.49)	76 (67.26)	0.299	0.354
ECOG, n(%)					
0	68 (40.96)	24 (45.28)	44 (38.94)	0.499	
1	90 (54.22)	28 (52.83)	62 (54.87)	0.869	
≥2	8 (4.82)	1 (1.89)	7 (6.19)	0.438	0.412
Bone Only Disease, n(%)					
Yes	45 (27.11)	15 (28.30)	30 (26.55)	0.852	
No	121 (72.89)	38 (71.70)	83 (73.45)	0.852	0.960
Liver Metastases, n(%)					
Yes	48 (28.92)	4 (7.55)	44 (38.94)	**<0.001***	
No	118 (71.08)	49 (92.45)	69 (61.06)	**<0.001***	**<0.001*****
≥3 Sites of Metastases, n(%)					
Yes	48 (28.92)	11 (20.75)	37 (32.74)	0.142	
No	118 (71.08)	42 (79.25)	76 (67.26)	0.142	0.160
Type of CDK4/6i, n(%)					
Palbociclib	58 (34.94)	16 (30.19)	42 (37.17)	0.485	
Ribociclib	104 (62.65)	36 (67.92)	68 (60.18)	0.391	
Abemaciclib	4 (2.41)	1 (1.89)	3 (2.65)	1.000	0.626
Type of Endocrine Therapy,n (%)					
AI	121 (72.89)	42 (79.25)	79 (69.91)	0.262	
Fulvestrant	45 (27.11)	11 (20.75)	34 (30.09)	0.262	0.283
Best Overall Response , n(%)					
CR	19 (11.45)	12 (22.64)	7 (6.19)	**0.003***	
PR	62 (37.35)	21 (39.62)	41 (36.28)	0.732	
SD	65 (39.16)	18 (33.96)	47 (41.59)	0.396	
PD	17 (10.24)	0 (0.00)	16 (14.16)	**0.003***	
UK	3 (1.81)	2 (3.77)	2 (1.77)	0.593	**0.002****
Estrogen Receptor, n (%)					
>50%	108 (65.06)	38 (71.70)	70 (61.95)	0.295	
>10-50%	7 (4.22)	1 (1.89)	6 (5.31)	0.432	
0-10%	6 (3.61)	2 (3.77)	4 (3.54)	1.000	
UK	45 (27.11)	12 (22.64)	33 (29.20)	0.455	0.5502
Progesterone Receptor, n (%)					
>20%	47 (28.31)	23 (43.40)	24 (21.24)	**0.005***	
>1-20%	33 (19.88)	7 (13.21)	26 (23.01)	0.152	
0-1%	37 (22.29)	11 (20.75)	26 (23.01)	0.843	
UK	49 (29.52)	12 (22.64)	37 (32.74)	0.206	**0.025***
HER2, n(%)					
0	64 (38.55)	20 (37.74)	44 (38.94)	1.000	
1+	35 (21.08)	15 (28.30)	20 (17.70)	0.153	
2+	26 (15.66)	8 (15.09)	18 (15.93)	1.000	
UK	41 (24.70)	10 (18.87)	31 (27.43)	0.254	0.388
Ki67, n(%)					
1-10%	27 (16.27)	7 (13.21)	20 (17.70)	0.509	
>10-20%	29 (17.47)	9 (16.98)	20 (17.70)	1.000	
>20%	52 (31.33)	20 (37.74)	32 (29.32)	0.281	
UK	58 (34.94)	17 (32.08)	41 (36.28)	0.727	0.645
Histology, n (%)					
Ductal	31 (18.67)	12 (22.64)	19 (16.81)	0.397	
Lobular	4 (2.41)	2 (3.77)	2 (1.77)	0.593	
Others	2 (1.20)	0 (0.00)	2 (1.77)	1.000	
UK	129 (77.71)	39 (73.58)	90 (79.65)	0.426	0.500

Fig 1. Distribution of LR and nLR

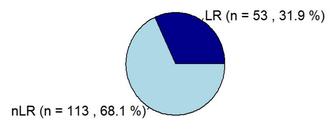


Fig 2. Luminal vs Non-Luminal Intrinsic Subtype Distribution (Overall, LR and nLR)

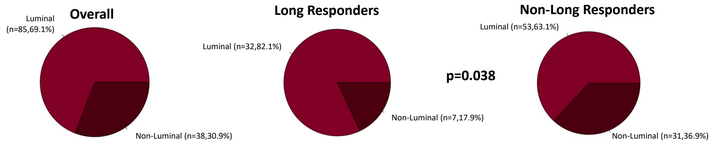


Fig 3. PAM50 Intrinsic Subtype Distribution (Overall, LR and nLR)

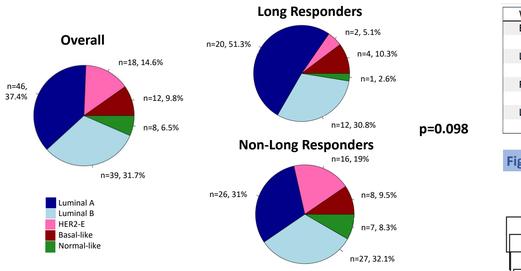


Fig 4. Forest Plot – Univariate Predictors of Long-Term Response

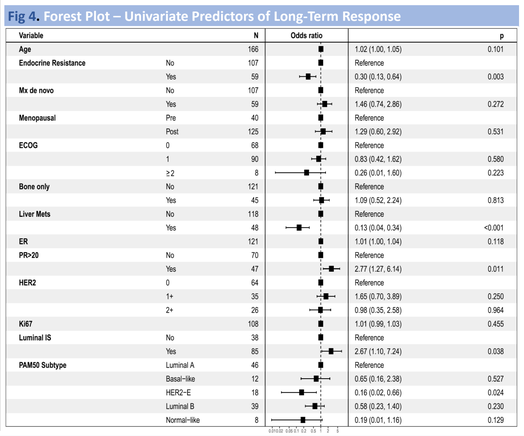


Fig 5. Forest Plot – Multivariate Predictors of Long-Term Response

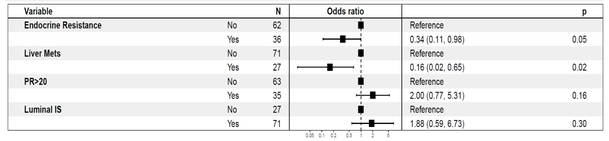
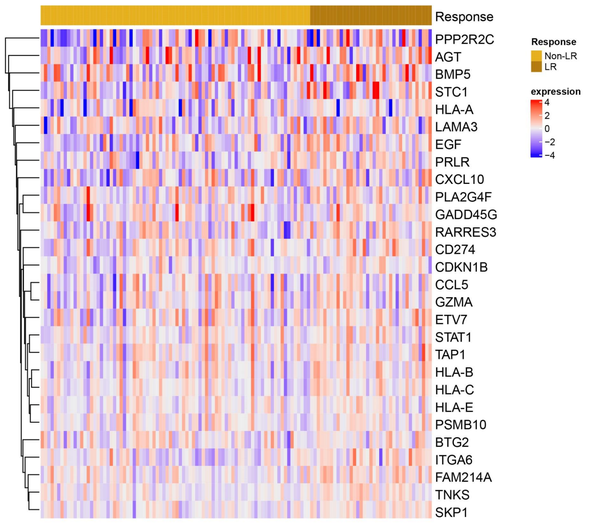


Fig 6. Heatmap – Genes Associated with Long-Term Response



Conclusions

In HR+/HER2- MBC, long-term benefit from first-line CDK4/6i was associated with absence of liver metastasis, hormone-sensitivity, luminal features, and upregulation of immune-related genes, highlighting a potential role of the tumor immune microenvironment in durable response.

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