PIK3CA MUTATIONS IN HER2-POSITIVE BREAST CANCER PATIENTS ENROLLED IN THE ADJUVANT RANDOMIZED SHORT-HER STUDY.

Valentina Guarneri[1,2], Maria Vittoria Dieci[1,2], Giancarlo Bisagni[3], Alba A. Brandes[4], Antonio Frassoldati[5], Luigi Cavanna[6], Antonino Musolino[7], Francesco Giotta[8], Anita Rimanti[9], Ornella Garrone[10], Elena Bertone[11], Katia Cagossi[12], Oriana Nanni[13], Federico Piacentini[14], Enrico Orvieto[15], Matteo Curtarello[2], Nuria Chic[16,17], Roberto D'Amico[14], Aleix Prat[16-18], Pierfranco Conte[1,2].

[1]University of Padova, Italy; [2]IOV-IRCCS, Padova, Italy; [3]USL-IRCCS Reggio Emilia, Italy; [4]AUSL Bologna, Italy; [5]University hospital, Ferrara, Italy; [6]G. Da Saliceto Hospital, Piacenza, Italy; [7]University Hospital, Parma, Italy; [8]IRCCS Istituto Tumori, Bari, Italy; [9]Azienda Ospedaliera, Mantova, Italy; [10]AOS Croce and Carle Teaching Hospital, Cuneo, Italy; [11]S. Anna Hospital, Torino, Italy; [12]Ramazzini Hospital, Carpi, Italy; [13]IRST-IRCCS, Meldola, Italy; [14]University Hospital, Modena, Italy; [15]Ulss 5, Rovigo, Italy; [16]H. Clinic de Barcelona, Spain; [17]IDIBAPs, Spain; [18]SOLTI Breast Cancer Research Group, Spain

Background and aim

PIK3CA gene mutations are a source of heterogeneity in HER2+ BC.

We explored the frequency and prognostic impact of *PIK3CA* mutations in the randomized adjuvant ShortHER trial.

Methods

The ShortHER trial randomized 1254 patients with HER2+ early BC to 9 weeks or 1 year of adjuvant trastuzumab combined with chemotherapy. Non-inferiority of the short arm was not demonstrated with the frequentist approach[1].

PIK3CA hot-spot mutations in exon 9 (E542K, E545K-A-G, Q546E-K) and exon 20 (M1043I, H1047R-L-Y, G1049R-S) were analysed by using Pyrosequencing method on DNA extracted from centralized FFPE tumor samples.

Intrinsic molecular subtypes from tumor samples were determined using PAM50 from nCounter.

References: 1. Conte PF et al., Ann Oncol 2018

Results

A *PIK3CA* mutation was found in 22% out of 803 patients.

Table 1 shows the association between *PIK3CA* mutation and clinicopathological characteristics.

Characteristics	*PIK3CA* mut N (%)	*PIK3CA* wt N (%)	TOT N (%)	*P*
Total	174 (22%)	629 (78%)	803 (100%)	-
Age (y) median (Q1-Q3)	57 (50-64)	56 (48-64)	56 (48-64)	0.169
Postmenopausal	49 (28)	227 (36)	276 (34)	
Premenopausal	125 (72)	401 (64)	526 (66)	0.050
AJCC Stage I	70 (40)	259 (41)	329 (41)	
AJCC Stage II	77 (44)	277 (44)	354 (44)	
AJCC Stage III	27 (16)	91 (15)	118 (15)	0.936
N0	85 (49)	343 (55)	428 (53)	
N1-N2	61 (35)	191 (30)	252 (31)	
N3	28 (16)	95 (15)	123 (15)	0.393
Hormone rec Neg	41 (24)	195 (31)	236 (29)	
Hormone rec Pos	133 (76)	434 (69)	567 (71)	0.057
Grade 1-2	54 (31)	172 (28)	226 (28)	
Grade 3	118 (69)	448 (72)	566 (72)	0.348
TILs Median (Q1-Q3)	5 (1-15)	5 (1-15)	5 (1-15)	0.637
PAM50 LumA	22 (24)	64 (19)	86 (20)	
PAM50 LumB	8 (9)	34 (10)	42 (10)	
PAM50 HER2-E	49 (53)	183 (54)	232 (54)	0.358
PAM50 Basal	2 (2)	25 (7)	27 (6)	
PAM50 Normal	11 (12)	35 (10)	46 (11)	

PIK3CA mutation had no impact on DFS in the whole study cohort (**Figure 1**) and in subgroups defined by hormone receptor status (HR=0.87, 95%CI 0.39-1.95 for hormone receptor negative and HR=0.84, 95%CI 0.52-1.36 for hormone receptor positive).

Figure 1. KM DFS curves by *PIK3CA* status in the whole study cohort.

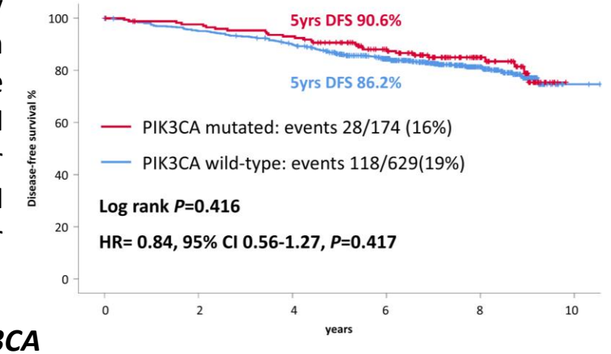
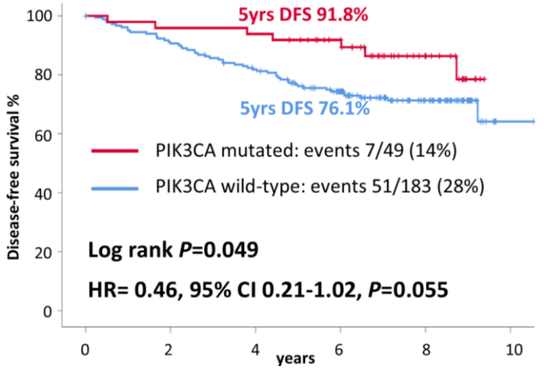


Figure 2. KM DFS curves by *PIK3CA* status in the HER2-enriched subtype.



PIK3CA mutation was associated with better DFS as compared to *PIK3CA* wild-type in the HER2-enriched intrinsic subtype (**Figure 2**). No prognostic impact in non-HER2-enriched patients was observed (HR=1.29, 95%CI 0.57-2.89).

Conclusions

Within the HER2-enriched molecular subtype, *PIK3CA* mutated patients showed better DFS as compared to *PIK3CA* wild-type patients.

These results highlight the need to integrate multiple biomarkers in order to dissect the heterogeneity of HER2-positive breast cancer.