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Pooled analysis of the BrighTNess, CALGB 40603 (Alliance), and GeparSixto clinical trials identifies the impact of neoadjuvant carboplatin on pCR and survival in early-stage triple-negative breast cancer

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Disclosure Information

Brooke Felsheim

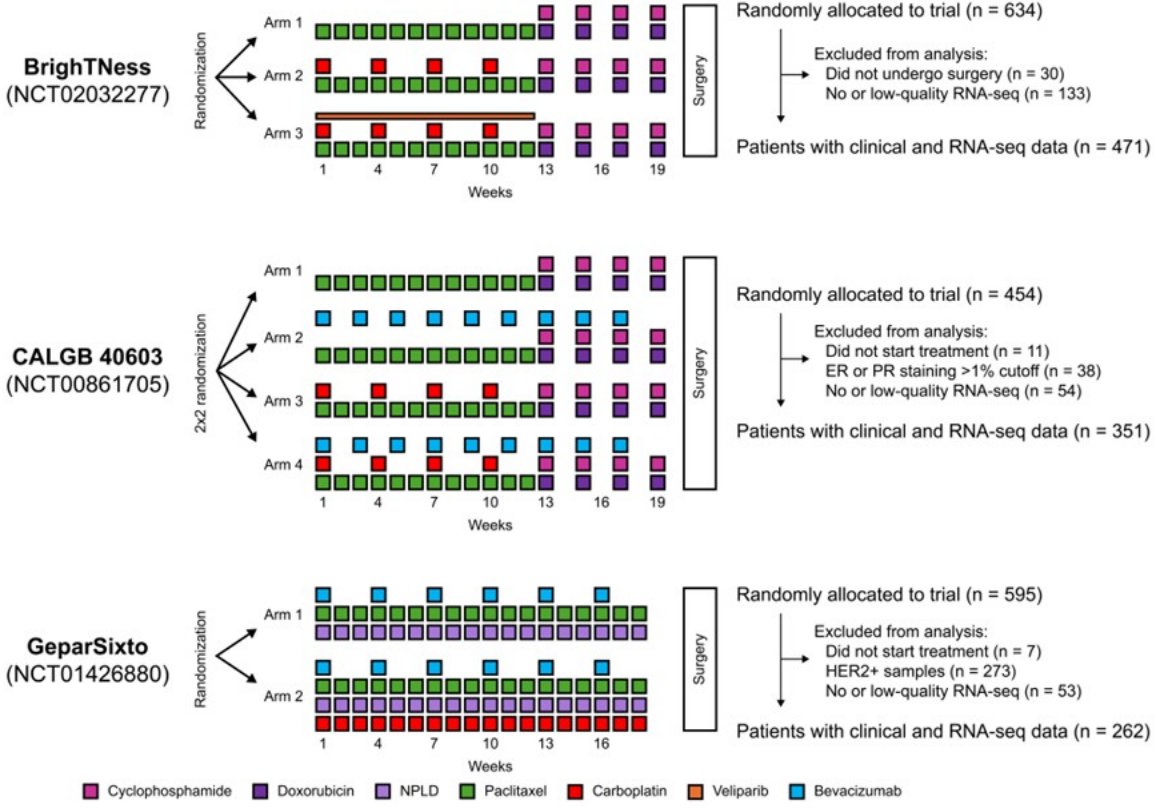
I have no financial relationships to disclose.

Background and motivation

Neoadjuvant carboplatin for early-stage triple-negative breast cancer (TNBC)

- Results from the phase III KEYNOTE-522 trial established a new standard of care for stage II-III triple-negative breast cancer
- The addition of carboplatin to neoadjuvant chemotherapy was not widely adopted as part of standard of care until its incorporation into both arms of KEYNOTE-522
- Given its toxicities, there remains a need to better define the therapeutic benefit of the addition of carboplatin to neoadjuvant chemotherapy

Pooled analysis of the BrighTNess, CALGB 40603, and GeparSixto clinical trials



- Three randomized clinical trials that tested the addition of carboplatin to neoadjuvant chemotherapy in early-stage triple-negative breast cancer
- **Data from a combined total of 1,084 patients**
- Evaluated the impact of neoadjuvant carboplatin on pathologic complete response (pCR), event-free survival (EFS), and overall survival (OS)
- Examined the predictive value of published gene expression signatures

Clinical characteristics of pooled cohort

	Patients, No. (%[1])				
	Overall N = 1,084	**BrighTNess** N = 471	**CALGB 40603** N = 351	**GeparSixto** N = 262	***P* value[2]**
Age, median (IQR)	49 (41, 57)	50 (41, 59)	49 (41, 57)	47 (40, 55)	0.073
Clinical tumor size					<0.001
T0-T2	853 (80.8%)	396 (84.1%)	222 (68.7%)	235 (89.7%)	
T3-T4	203 (19.2%)	75 (15.9%)	101 (31.3%)	27 (10.3%)	
Unknown	28	0	28	0	
Clinical status of lymph nodes					0.060
N negative	585 (56.1%)	261 (55.4%)	165 (52.4%)	159 (62.1%)	
N positive	457 (43.9%)	210 (44.6%)	150 (47.6%)	97 (37.9%)	
Unknown	42	0	36	6	
Tumor grade					<0.001
G1-G2	233 (23.7%)	120 (29.7%)	41 (13.0%)	72 (27.5%)	
G3	749 (76.3%)	284 (70.3%)	275 (87.0%)	190 (72.5%)	
Unknown	102	67	35	0	
Germline *BRCA1*/*BRCA2* status					0.031
Mutant	137 (14.4%)	75 (15.9%)	22 (9.2%)	40 (16.6%)	
Wildtype	813 (85.6%)	396 (84.1%)	216 (90.8%)	201 (83.4%)	
Unknown	134	0	113	21	
Carboplatin	664 (61.3%)	349 (74.1%)	184 (52.4%)	131 (50.0%)	<0.001
pCR breast + axilla (ypT0/is ypN0)	526 (48.7%)	232 (49.3%)	168 (48.6%)	126 (48.1%)	0.952
Unknown	5	0	5	0	

[1] Valid percent; [2] Kruskal-Wallis rank sum test; Pearson's Chi-squared test with continuity correction for 2 by 2 tables

- Baseline clinical characteristics differed slightly by clinical trial
- Accounted for trial in all models

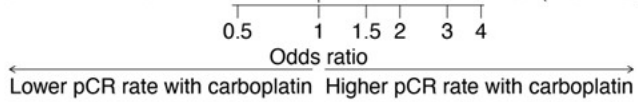
  (pCR: binomial generalized linear mixed models with trial as a random effect)

  (EFS, OS: Cox proportional hazards models stratified by trial)
- Multivariate models included age, cT, cN, tumor grade, and germline *BRCA1* or *BRCA2* mutation status as covariates

The addition of carboplatin to neoadjuvant chemotherapy is associated with higher pCR rates

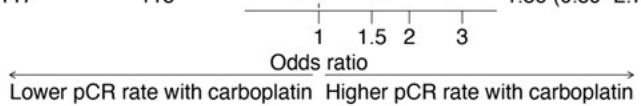
Univariate analysis, pCR

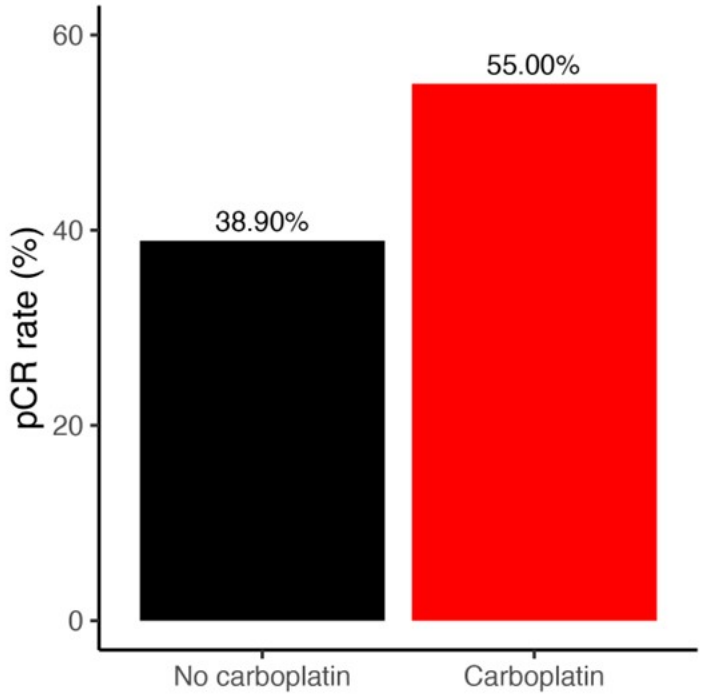
Subgroup	No carbo	Carbo	OR (95% CI)	*P* value
All patients	420	664	1.92 (1.50–2.47)	< 0.001
gBRCA status				
Mutant	41	96	1.01 (0.48–2.10)	0.987
Wildtype	313	500	2.13 (1.59–2.85)	< 0.001
Study				
BrighTNess	122	349	2.63 (1.71–4.10)	< 0.001
CALGB 40603	167	184	1.72 (1.12–2.64)	0.013
GeparSixto	131	131	1.64 (1.01–2.67)	0.048



Multivariate analysis, pCR

Subgroup	No carbo	Carbo	OR (95% CI)	*P* value
All patients	309	525	1.89 (1.41–2.55)	< 0.001
gBRCA status				
Mutant	37	89	1.35 (0.57–3.25)	0.495
Wildtype	272	436	2.00 (1.45–2.75)	< 0.001
Study				
BrighTNess	101	303	2.38 (1.47–3.90)	< 0.001
CALGB 40603	91	104	1.63 (0.90–2.97)	0.109
GeparSixto	117	118	1.56 (0.89–2.75)	0.118





The addition of carboplatin is associated with higher pCR rates in patients with wildtype (but not mutant) germline *BRCA1* and *BRCA2*

Univariate analysis, pCR

Subgroup	No carbo	Carbo	OR (95% CI)	*P* value
All patients	420	664	1.92 (1.50–2.47)	< 0.001
gBRCA status				
Mutant	41	96	1.01 (0.48–2.10)	0.987
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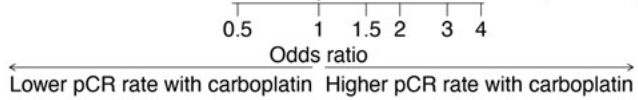

Multivariate analysis, pCR

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All patients	309	525	1.89 (1.41–2.55)	< 0.001
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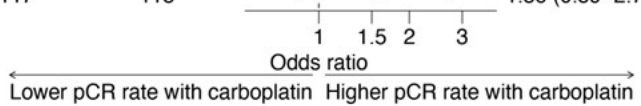
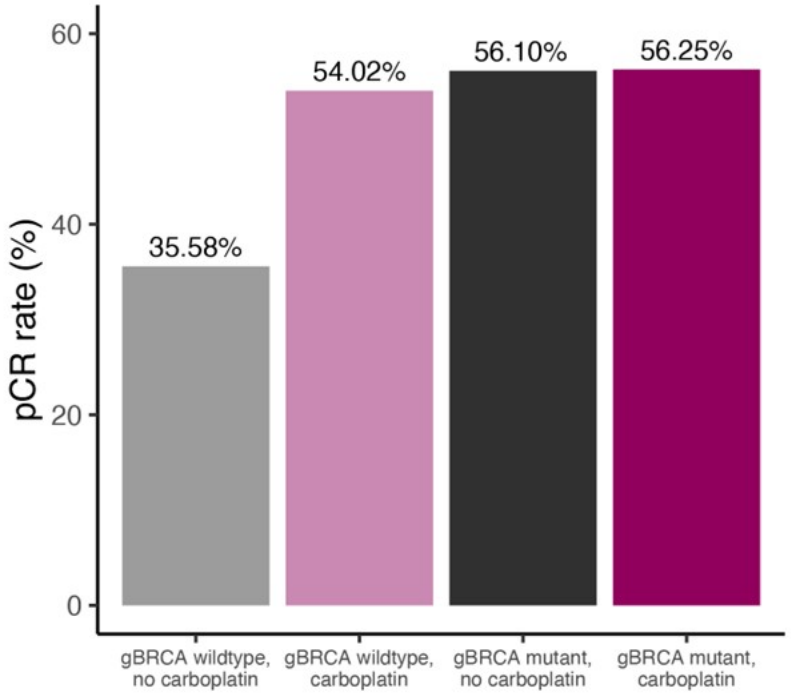
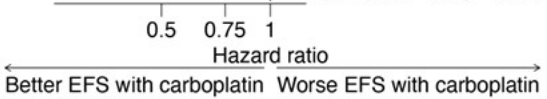




The addition of carboplatin to neoadjuvant chemotherapy is associated with better EFS

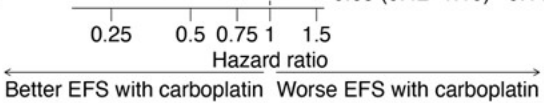
Univariate analysis, EFS

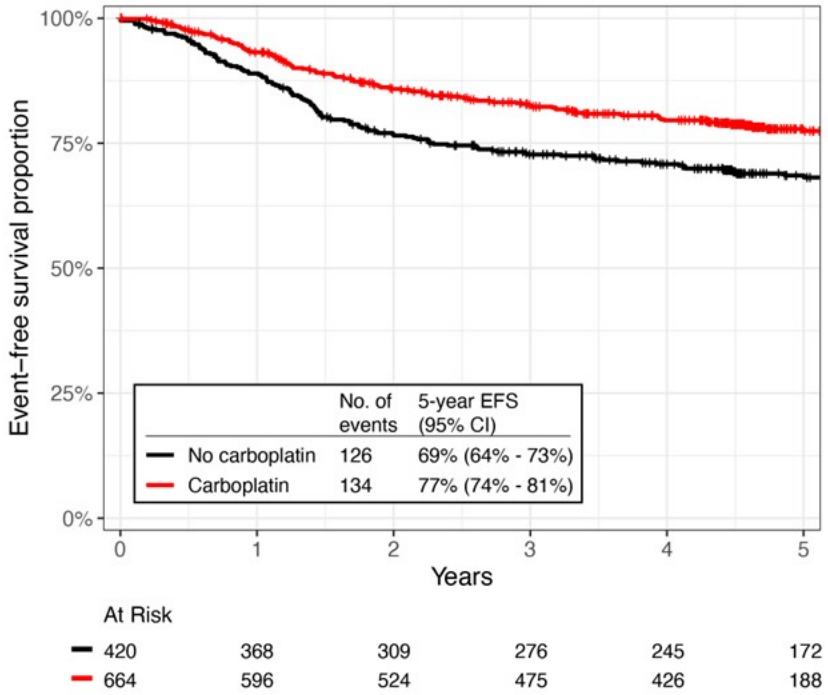
Subgroup	No carbo	Carbo	HR (95% CI)	*P* value
All patients	420	664	0.70 (0.55–0.89)	0.003
gBRCA status				
Mutant	41	96	0.50 (0.25–1.00)	0.050
Wildtype	313	500	0.73 (0.55–0.96)	0.024
Study				
BrighTNess	122	349	0.58 (0.38–0.88)	0.010
CALGB 40603	167	184	0.86 (0.59–1.26)	0.439
GeparSixto	131	131	0.63 (0.40–1.00)	0.050



Multivariate analysis, EFS

Subgroup	No carbo	Carbo	HR (95% CI)	*P* value
All patients	310	526	0.71 (0.54–0.93)	0.014
gBRCA status				
Mutant	37	89	0.37 (0.18–0.79)	0.010
Wildtype	273	437	0.77 (0.57–1.03)	0.079
Study				
BrighTNess	101	303	0.56 (0.36–0.88)	0.012
CALGB 40603	92	105	0.97 (0.59–1.60)	0.912
GeparSixto	117	118	0.68 (0.42–1.10)	0.113

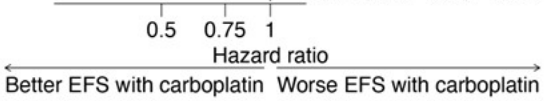




The addition of carboplatin is associated with better EFS in patients with wildtype and mutant germline *BRCA1* and *BRCA2*

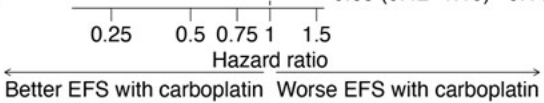
Univariate analysis, EFS

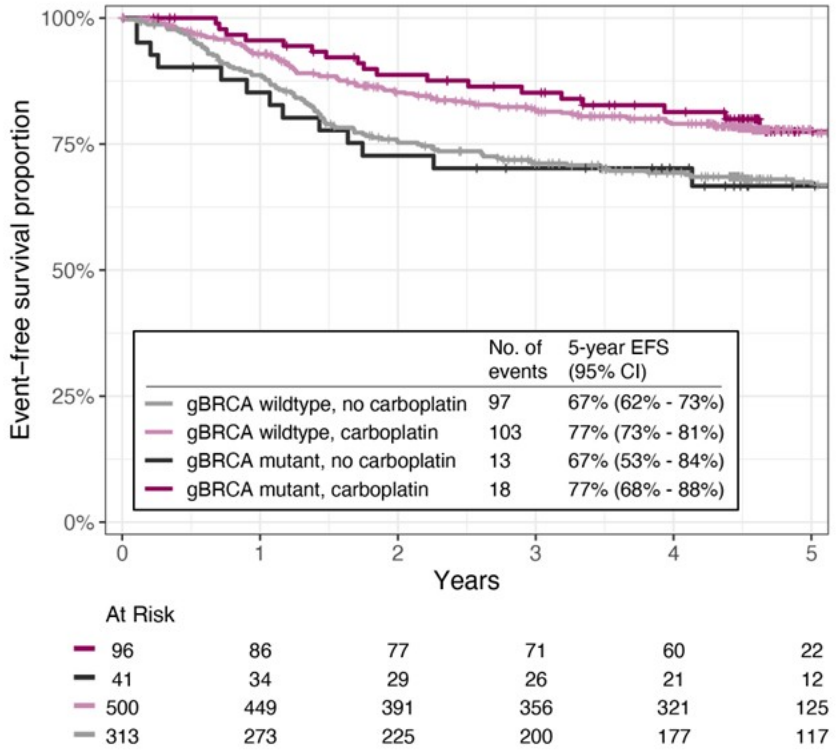
Subgroup	No carbo	Carbo	HR (95% CI)	*P* value
All patients	420	664	0.70 (0.55–0.89)	0.003
gBRCA status				
Mutant	41	96	0.50 (0.25–1.00)	0.050
Wildtype	313	500	0.73 (0.55–0.96)	0.024
Study				
BrighTNess	122	349	0.58 (0.38–0.88)	0.010
CALGB 40603	167	184	0.86 (0.59–1.26)	0.439
GeparSixto	131	131	0.63 (0.40–1.00)	0.050



Multivariate analysis, EFS

Subgroup	No carbo	Carbo	HR (95% CI)	*P* value
All patients	310	526	0.71 (0.54–0.93)	0.014
gBRCA status				
Mutant	37	89	0.37 (0.18–0.79)	0.010
Wildtype	273	437	0.77 (0.57–1.03)	0.079
Study				
BrighTNess	101	303	0.56 (0.36–0.88)	0.012
CALGB 40603	92	105	0.97 (0.59–1.60)	0.912
GeparSixto	117	118	0.68 (0.42–1.10)	0.113

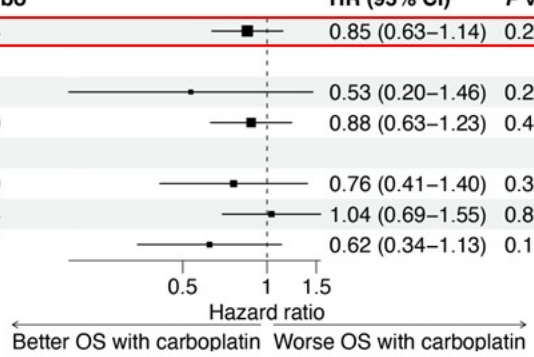




The addition of carboplatin to neoadjuvant chemotherapy is not significantly associated with OS

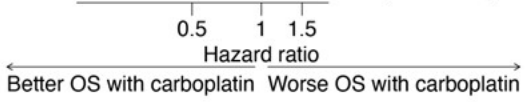
Univariate analysis, OS

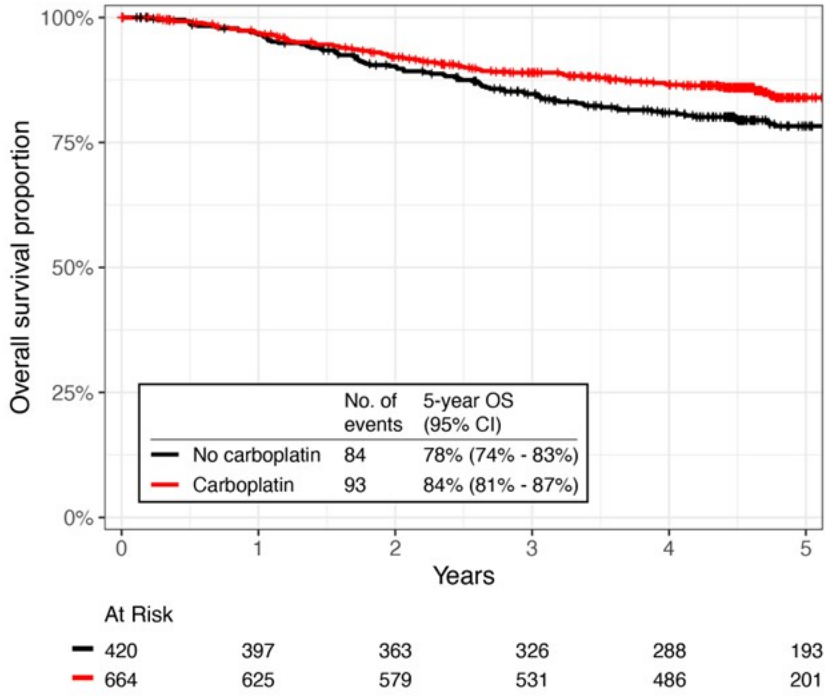
Subgroup	No carbo	Carbo	HR (95% CI)	*P* value
All patients	420	664	0.85 (0.63–1.14)	0.279
gBRCA status				
Mutant	41	96	0.53 (0.20–1.46)	0.221
Wildtype	313	500	0.88 (0.63–1.23)	0.444
Study				
BrighTNess	122	349	0.76 (0.41–1.40)	0.376
CALGB 40603	167	184	1.04 (0.69–1.55)	0.860
GeparSixto	131	131	0.62 (0.34–1.13)	0.118



Multivariate analysis, OS

Subgroup	No carbo	Carbo	HR (95% CI)	*P* value
All patients	310	526	0.93 (0.65–1.31)	0.662
gBRCA status				
Mutant	37	89	0.45 (0.16–1.27)	0.130
Wildtype	273	437	1.00 (0.69–1.44)	0.980
Study				
BrighTNess	101	303	0.92 (0.46–1.83)	0.815
CALGB 40603	92	105	1.13 (0.65–1.95)	0.668
GeparSixto	117	118	0.75 (0.40–1.40)	0.365





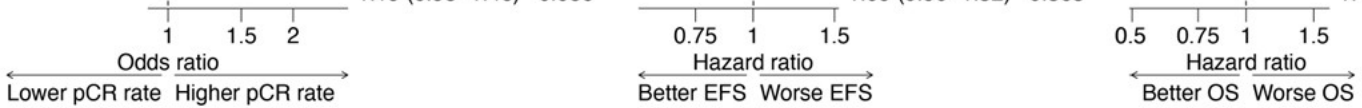
Gene expression analysis

Eight published gene expression signatures were pre-selected to evaluate their predictive ability over pCR, EFS, and OS endpoints

Signature	Literature
CD8+ T cell signature	PMID 24916698: Iglesia et al, CCR 2014
IgG signature	PMID 21214954: Fan et al, BMC Med Genomics 2011
Immune1 TCGA breast signature	PMID 32573490: Garcia-Recio et al, J Clin Invest 2020
CD274 single gene expression	PMID 31730857: Hollern et al, Cell 2019
B-cell/T-cell cooperativity signature	PMID 31730857: Hollern et al, Cell 2019
Follicular helper CD4+ T cell signature	PMID 24138885: Bindea et al, Immunity 2013
VEGF signature	PMID 19291283: Hu et al, BMC Med 2009
Hypoxia-core signature	PMID 31932495: Karn et al, CCR 2020; PMID 19291283: Hu et al. MBC Med 2009

Four immune gene expression signatures are associated with higher pCR rates, better EFS, and better OS in multivariate models

Signature	pCR OR (95% CI)	pCR *P* value	EFS HR (95% CI)	EFS *P* value	OS HR (95% CI)	OS *P* value
CD8+ T cell signature	1.30 (1.15–1.47)	< 0.001	0.85 (0.76–0.95)	0.003	0.82 (0.72–0.95)	0.006
Immunoglobulin G signature	1.26 (1.14–1.40)	< 0.001	0.88 (0.81–0.97)	0.007	0.82 (0.73–0.92)	< 0.001
Immune1 TCGA breast signature	1.24 (1.14–1.36)	< 0.001	0.89 (0.82–0.96)	0.002	0.83 (0.76–0.91)	< 0.001
CD274 single gene expression	1.42 (1.25–1.62)	< 0.001	0.83 (0.73–0.93)	0.002	0.83 (0.71–0.96)	0.015
B–cell/T–cell cooperativity signature	1.18 (1.07–1.30)	0.001	0.93 (0.85–1.02)	0.106	0.90 (0.80–1.01)	0.064
Follicular helper CD4+ T cell signature	1.84 (1.26–2.71)	0.002	0.79 (0.57–1.11)	0.170	0.74 (0.50–1.11)	0.150
VEGF signature	1.13 (0.89–1.43)	0.300	1.23 (1.00–1.53)	0.055	1.27 (0.97–1.65)	0.077
Hypoxia signature	1.19 (0.98–1.46)	0.086	1.09 (0.90–1.32)	0.363	1.13 (0.89–1.44)	0.314



Signature expression values were calculated as the median RNA-seq expression (upper-quartile normalized, log2 transformed, limma batch-adjusted by study) of the published gene list; OR and HR values shown per one unit increment of continuous signature expression

No tested gene expression signature was significantly predictive of pCR, EFS, or OS benefit from the addition of neoadjuvant carboplatin (data not shown)

Conclusions

- In a pooled analysis of the BrighTNess, CALGB 40603, and GeparSixto clinical trials, the addition of carboplatin to neoadjuvant chemotherapy was associated with a higher pCR rate and better EFS
- In patients with germline *BRCA1* or *BRCA2* mutations, the addition of carboplatin significantly improved EFS, but not pCR rate or OS
- Many immune-related gene expression signatures were predictive of a pCR benefit and were prognostic for survival

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