Factors associated With pCR and Distant Recurrence in Patients With Early-Stage TNBC Treated With KN522

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Background

- The KEYNOTE522 (KN522) regimen of neoadjuvant chemotherapy with pembrolizumab yields statistically significant and clinically meaningful improvements in pathologic complete response (pCR) rate, event-free and overall survival compared to chemotherapy alone in patients with early-stage triple-negative breast cancer (eTNBC).
- Despite KN522 results, ~1/3 of patients have residual disease , increasing the likelihood of incurable distant metastatic disease
- Understanding characteristics of high-risk patients with TNBC is a critical unmet need.

(1) What are the clinicopathologic factors associated with residual disease?
(2) Among patients with residual disease, what factors are associated with distant metastatic recurrence?

Methods

Study sample: All patients with early-stage triple negative breast cancer for whom treatment plans were created for the KN522 regimen between 9/2/ 2021 and 12/1/2024 at the Hospital of the University of Pennsylvania.

Data Collection: Retrospective chart review was performed to determine patient demographics, clinical stage, tumor characteristics, treatment related factors including toxicity, and outcomes, including pathologic stage and recurrence

To identify factors associated with pCR : Univariate analyses (Fisher's exact test) and multivariable logistic regressions were performed in R.

To identify factors associated with distance recurrence: univariate analyses (Fisher's exact test) were performed among 1) patients without pCR, and 2) patients with pCR.

Figure 1: Study flow diagram showing inclusion and exclusion criteria

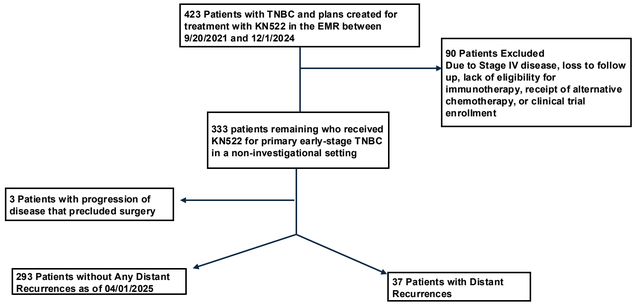
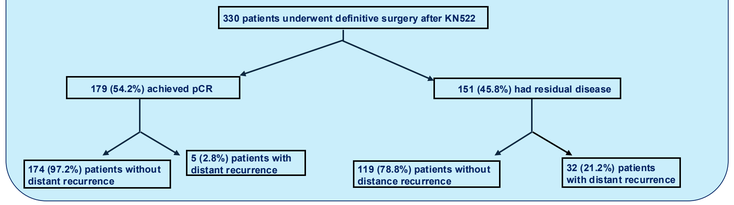


Figure 2: Flow diagram showing breakdown of patients by pCR and distant recurrence status



Results

Factors associated with pCR

Table 1: Univariate analysis of factors associated with pCR among all patients (N=330) using Fisher's exact test

Variable	Category	pCR n (%)	No pCR n (%)	Fisher's p-value
ECOG PS	0	148(56%)	117(44%)	
	1 or greater	31(48%)	34(52%)	0.27
PV/LPV		0 141 (54%)	118 (46%)	
		1 28 (64%)	16 (36%)	0.32
Clinical N stage	N0	108 (56%)	85 (44%)	
	N1–N3	71 (53%)	64 (47%)	0.57
Clinical T stage	T0–T1	46 (67%)	23 (33%)	
	T2–T4	130 (51%)	124 (49%)	**0.029**
Multifocality		0 154 (57%)	114 (43%)	
		1 25 (40%)	37 (60%)	**0.016**
Histology	IDC	163 (56%)	126 (44%)	
	Other	16 (39%)	25 (61%)	**0.044**
ER status	<1%	161 (54%)	138 (46%)	
	≥1%	18 (58%)	13 (42%)	0.71
Tumor grade	Grade 2	8 (24%)	26 (76%)	
	Grade 3	167 (57%)	124 (43%)	**<0.001**
Systemic steroids		0 154 (55%)	128 (45%)	
		1 25 (52%)	23 (48%)	0.76
irAE – Endocrinopathy		0 128 (50%)	128 (50%)	
		1 51 (69%)	23 (31%)	**0.005**
irAE – Non-endocrinopathy		0 138 (55%)	113 (45%)	
		1 41 (52%)	38 (48%)	0.7
irAE (overall)		0 100(51%)	96(49%)	0.178
		1 79(59%)	55(41%)	
BRCA1		0 155 (54.8%)	128 (45.2%)	
		1 15 (71.4%)	6 (28.6%)	0.174
BRCA2		0 167 (55.9%)	132 (44.1%)	
		1 3 (60.0%)	2 (40.0%)	1
PALB2		0 171 (56.4%)	132 (43.6%)	
		1 0 (0.0%)	3 (100.0%)	0.085

Table 2: Multivariate logistic regression of factors associated with pCR among all patients (N=330)

Variable	OR	95% CI (Lower)	95% CI (Upper)	p-value
Age at diagnosis	0.998	0.974	1.022	0.838
Race (Non-white vs White)	1.343	0.788	2.301	0.28
ECOG PS (1-2 vs 0)	1.286	0.623	2.72	0.502
Histology (Other vs IDC)	0.48	0.199	1.113	0.092
Tumor grade (3 vs 2)	**3.441**	**1.409**	**9.129**	**0.009**
ER status (≥1% vs <1%)	0.848	0.355	2.094	0.714
Clinical T stage (T2–T4 vs T0–T1)	0.648	0.324	1.259	0.208
Clinical N stage (N1–N3 vs N0)	0.87	0.507	1.493	0.612
Time from biopsy to chemotherapy initiation	0.989	0.975	1.003	0.117
irAE – Endocrinopathy	**2.321**	**1.216**	**4.581**	**0.012**
irAE – Non-endocrinopathy	0.977	0.498	1.931	0.946
Systemic steroids (Yes vs No)	1.007	0.423	2.413	0.988
PV/LPV (Present vs Absent)	1.387	0.647	3.053	0.406
Multifocality (Present vs Absent)	**0.45**	**0.232**	**0.862**	**0.017**
Cycles of Taxol	1.392	0.851	2.342	0.194
Cycles of Carboplatin	1.054	0.684	1.605	0.806
Cycles of AC	**1.569**	**1.15**	**2.186**	**0.006**
Cycles of Neoadjuvant Pembrolizumab	0.95	0.783	1.145	0.593

Results

Table 3: Among patients who did not achieve pCR (n=151), variables significantly associated with the development of distant recurrence in a univariate analysis

Factor	Category	No recurrence n(%)	Recurrence n(%)	Fisher's p-value
irAE – Endocrinopathy	No	97 (64.2%)	31 (20.5%)	
	Yes	22 (14.6%)	1 (0.7%)	0.0291
Clinical N stage	N0	74 (49.7%)	11 (7.4%)	
	N1–N3	43 (28.9%)	21 (14.1%)	0.0046
Surgery type	Bilateral mastectomy	41 (27.3%)	8 (5.3%)	
	Lumpectomy	55 (36.7%)	8 (5.3%)	
	Unilateral mastectomy	22 (14.7%)	16 (10.7%)	0.0025
Pathologic T stage	T0/Tis, T1	92(60.9%)	15 (9.9%)	
	T2+	27(17.9%)	17 (11.3%)	0.0017
Pathologic N stage	N0	95 (63.8%)	7 (4.7%)	
	N1+	23 (15.4%)	24 (16.1%)	3.22E-09

- **In multivariate logistic regression, higher tumor grade, absence of multifocality, development of an endocrine irAE, and number of cycles of AC were significantly associated with pCR .**
- **Among all patients with irAE, there was no significant association between irAE grade (1-2 vs 3-4, p-value=1), or use of systemic steroids in neoadjuvant setting (p-value=0.436) and development of pCR.**
- **Among patients without pCR, absence of an endocrine IRAE, higher clinical N stage at diagnosis, unilateral mastectomy, and higher pathologic T stage and pathologic N stage were significantly associated with development of distance recurrence.**
- **Among patients with pCR, 5 patients developed distant recurrence. 3 patients had visceral metastases(60%) and 2 patients had CNS metastases (40%).**

Conclusions

- Our real-world study shows that endocrine irAEs are significantly associated with higher rates of pCR in multivariate logistic regression.
- Among patients without pCR, irAE endocrinopathies are significantly associated with lower rates of distant recurrence.
- Our findings are in agreement with studies across solid tumors(NSCLC, SCLC, RCC, gastric cancer, urothelial carcinoma) that show that irAE development generally and endocrinopathies in particular are predictive of improved cancer outcomes.
- Endocrine irAEs appear to be favorable prognostic markers of pCR and recurrence risk, warranting further validation in prospective datasets.
- Among patients with residual disease after KN522, those with clinical and pathologic node positivity, and pT2 or larger tumors may represent target populations for studies investigating enhanced surveillance and treatment strategies.

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