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ORIGINAL ARTICLE – BREAST ONCOLOGY

Impact of Neoadjuvant Chemoimmunotherapy on Surgical Outcomes and Time to Radiation in Triple-Negative Breast Cancer

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ABSTRACT

Background. We examined the association between immunotherapy-containing and standard chemotherapy regimens with treatment delays and postoperative complications in stage II–III triple-negative breast cancer. The effect of immune-related adverse events (irAEs) was compared.

Patients and Methods. We compared 139 women treated with neoadjuvant pembrolizumab plus chemotherapy (KEYNOTE-522 regimen) from August 2021 to September 2022 with 287 consecutive patients who received neoadjuvant chemotherapy alone prior to July 2021 and underwent surgery. Baseline characteristics, time to treatments, and surgical complications were compared using two-sample nonparametric tests. Linear regression evaluated association of irAEs with time to surgery and radiation. Logistic regression identified factors associated with surgical complications.

Results. Age, body mass index, race, American Society of Anesthesiologists (ASA) class, and mastectomy rates were similar among cohorts. No clinically relevant difference in time from end of neoadjuvant treatment to surgery was observed [KEYNOTE-522: median 32 (IQR 27, 43) days; non-KEYNOTE-522: median 31 (IQR 26, 37) days; $P = 0.048$]. Time to radiation did not differ ($P = 0.7$). A total of 26 patients (9%; non-KEYNOTE-522) versus 11 (8%; KEYNOTE-522) experienced postoperative complications ($P = 0.6$). In the KEYNOTE-522 cohort, 59 (43%) of 137 patients experienced 82 irAEs; 40 (68%) required treatment. Older age ($P = 0.018$) and ASA class 4 ($P = 0.007$) were associated with delays to surgery after adjusting for clinical factors. Experiencing ≥ 1 irAE was associated with delay to radiation ($P = 0.029$). IrAEs were not associated with surgical complications ($P = 0.4$).

Conclusions. We observed no clinically meaningful difference between times to surgery/adjuvant radiation or postoperative complications and type of preoperative chemotherapy. IrAEs were associated with delay to adjuvant radiation but not with postoperative complications or delay to surgery.

Keywords Immune checkpoint blockade · Triple-negative breast cancer · Surgical outcomes

Preoperative chemoimmunotherapy using pembrolizumab, an anti-programmed cell death protein 1 (PD-1) monoclonal antibody, is the standard of care for early triple-negative breast cancers (TNBCs). This treatment regimen is based on findings from the KEYNOTE-522 randomized trial demonstrating increased pathologic complete response (pCR) rate and event-free survival among patients with TNBC who received pembrolizumab and chemotherapy compared with chemotherapy alone.[1,2] Pembrolizumab is an immune checkpoint inhibitor that functions by blocking inhibitory "checkpoint" molecules that prevent host antitumor immunity. These medications activate the immune system, and activation of T cells and their cytokines

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or antibodies may promote autoimmune toxicities, i.e., immune-related adverse events (irAEs).

IrAEs have been observed in nearly all organ systems, and the most common irAEs—endocrinopathies (e.g., thyroid dysfunction, adrenal insufficiency, etc.) and cardiac and pulmonary toxicities—have implications for perioperative care and oncologic therapy.[3,4] IrAEs may be sufficiently severe to dictate cessation of immunotherapy, can be permanent, and may occur up to 1 year after therapy. Although irAEs are a common consequence of immune checkpoint blockade, occurring in 38.9% of patients in the KEYNOTE-522 trial,[2] data on their incidence and impact in patients treated prior to surgery are limited.[4–8] Existing literature from other solid organ malignancies demonstrates considerable variability both in extent and incidence of surgery delays after neoadjuvant immune checkpoint blockade.[9] As a result, the influence of irAEs on surgical outcomes and the timing of adjuvant treatment is not well understood.

Prompted by studies that indicate delays in treatment after preoperative therapy can negatively impact clinical outcomes and disease recurrence rate,[10–13] we describe a retrospective single-institution experience comparing neoadjuvant pembrolizumab plus chemotherapy with chemotherapy alone for TNBC to investigate differences in time to adjunct treatments and surgical complications, and the effect of irAEs on these outcomes. We also sought to explore the effect of neoadjuvant chemoimmunotherapy on postoperative complications and delay in time to surgery and to adjuvant radiation.

PATIENTS AND METHODS

In this retrospective cohort study conducted using data from patients treated at Memorial Sloan Kettering Cancer Center (MSK), we identified 139 women with TNBC who received preoperative chemoimmunotherapy on the basis of the KEYNOTE-522 trial regimen[2] between August 2021 and September 2022. A total of 142 patients were identified who had the KEYNOTE-522 regimen initiated with curative intent, but 3 did not receive surgery; 1 died of a thromboembolic event, 1 declined surgery, and 1 died of an unknown cause. The cohort of 139 patients was compared with 287 consecutive women who received neoadjuvant chemotherapy followed by surgery prior to the US Food and Drug Administration's approval of pembrolizumab for use in early TNBC in July 2021. The published KEYNOTE-522 regimen is administered over 24 weeks, with an anticipated 3- to 6-week lapse between end of treatment and surgery. Most patients at our institution were treated with dose-dense adriamycin, cyclophosphamide, and taxol (ddACT), as opposed to adriamycin and cyclophosphamide every 3 weeks. Of the 287 patients who received a non-KEYNOTE-522 neoadjuvant regimen, 202 (70%) received ddACT.

In addition to patient demographics and tumor characteristics, data relevant to irAEs, postoperative complications, and time to adjuvant therapies were collected. IrAEs were classified according to the Common Terminology Criteria for Adverse Events (CTCAE) rubric.[14] In accordance with guidelines published by the Society for the Immunotherapy of Cancer,[15] patients who receive immunotherapy are monitored for irAEs using assessment of medical history, physical examination, and laboratory testing. Complete blood count and a comprehensive metabolic panel are obtained prior to pembrolizumab dosing. Thyroid function tests and morning cortisol are measured every other cycle or at least every 6 weeks. An echocardiogram is performed at baseline and at completion of treatment if the patient has symptoms of cardiac dysfunction. In this study, thyroid function tests and morning cortisol were obtained in the period between completion of neoadjuvant therapy and surgery. IrAEs of any grade were documented and included adrenal insufficiency, hepatitis/transaminitis, pneumonitis, hypo- and hyperthyroidism, arthritis/myositis, neurological or ophthalmological dysfunction, dermatitis, colitis, myocarditis, diabetes, and nephritis.

Time to surgery or adjuvant treatment was calculated from the final preoperative doses of chemoimmunotherapy or chemotherapy. To evaluate whether time to surgery and adjuvant treatment may have been influenced by inability to tolerate preoperative therapy (resulting in early treatment discontinuation), time to treatment was also calculated from initiation of preoperative therapies for patients who received the KEYNOTE-522 regimen and compared with the standard time duration provided by current guidelines.

Baseline characteristics, time to adjuvant therapies, and surgical complications were compared between patients who received the KEYNOTE-522 regimen (KN-522 cohort) and who did not receive the regimen (non-KN-522 cohort), and among patients who received the KEYNOTE-522 regimen and did and did not experience irAEs, using two-sample non-parametric tests. Continuous variables were described using medians and interquartile ranges, and categorical variables were described using counts and percentages. The Wilcoxon rank sum test was used to compare continuous variables and the Fisher exact test or chi-squared test was used to compare categorical variables. Linear regression was used to evaluate the association of irAEs with time to surgery and adjuvant radiation among patients who received the KEYNOTE-522 regimen. Logistic regression identified factors associated with surgical complications among patients who received the KEYNOTE-522 regimen. R 4.2 statistical software (R Core Development Rema, Vienna, Austria) was used for all analyses, and $P < 0.05$ was considered significant. Institutional review board approval was obtained prior to initiation of this study.

RESULTS

Age, body mass index, race, American Society of Anesthesiology (ASA) Physical Status Classification, and mastectomy rate were similar among the KN-522 ($n = 139$) and non-KN-522 ($n = 287$) cohorts (Table 1). Median patient age was 52 years in both cohorts. Most patients in both cohorts were white (58% in non-KN-522 and 62% in KN-522 cohorts; $P = 0.072$). Mastectomy rate was similar between the non-KN-522 (45%) and the KN-522 (40%) cohorts ($P = 0.3$), and fewer patients in the KN-522 cohort underwent axillary lymph node dissection (21% versus 33%; $P = 0.009$). Significantly more patients in the KN-522 cohort had clinical T1 disease (18% versus 8.7%), and there was no difference in preoperative nodal status ($P = 0.18$). Compared with the non-KN-522 cohort, patients in the KN-522 cohort presented with earlier disease stage at diagnosis; 79% versus 88% had clinical stage II disease at diagnosis ($P = 0.006$). In the entire cohort, 115 (63%) of 184 patients who underwent mastectomy and 238 (98%) of 242 patients who received breast-conserving surgery had postoperative radiation. pCR occurred in 99 (35%) of 287 patients in the non-KN-522 cohort and in 80 (58%) of 139 patients in the KN-522 cohort ($P < 0.001$). Of patients who had clinically node-positive disease, axillary pCR occurred in 85 (51%) of 167 patients in the non-KN-522 cohort and in 44 (66%) of 67 patients in the KN-522 cohort ($P = 0.04$).

IrAEs

Of the 137 patients with complete preoperative chemoimmunotherapy records in the KN-522 cohort, 59 (43%) experienced 82 irAEs; 40 (68%; 29% of entire cohort) required treatment (Table 2). A total of 22 patients (37%) who experienced an irAE were prescribed steroids (Table 3). Pembrolizumab was held in 20 patients (34% who experienced an irAE; 15% of entire cohort) and discontinued permanently in 18 patients (31% who experienced an irAE; 13% of entire cohort). The most common irAE was hypothyroidism, which affected 13 patients (22%) who experienced an irAE. No irAE-associated deaths occurred.

Time to Surgery and Adjuvant Therapy

Median interval from end of neoadjuvant treatment until surgery was statistically significant but not clinically meaningful; the median interval was 32 (IQR 27, 43) days in the KN-522 cohort versus 31 (IQR 26, 37) days in the non-KN-522 cohort ($P = 0.048$). Compared with the published 24-week KEYNOTE-522 regimen, the median interval from the beginning of the KEYNOTE-522 regimen to surgery was 170 (IQR 159, 185) days, or 24.2 weeks. Experiencing an irAE did not impact the timing of surgery relative to initiation of preoperative therapy (Fig. 1), and this relationship remained after excluding 16 patients who had surgery earlier than anticipated due to permanent discontinuation of pembrolizumab secondary to an irAE (Fig. 2). In both the KN-522 and non-KN-522 cohorts, older age [coeff. 0.38, 95% CI 0.07–0.69, $P = 0.018$ (KN-522 cohort); coeff. 0.16, 95% CI 0.01–0.30, $P = 0.032$ (non-KN-522 cohort)] and ASA class 4 [coeff. 53, 95% CI 15–91, $P = 0.007$ (KN-522 cohort); coeff. 57, 95% CI 43–71, $P < 0.001$ (non-KN-522 cohort)] were associated with delays to surgery from end of preoperative therapy after adjusting for relevant clinical factors. Experiencing an irAE was not significantly associated with time to surgery for patients in the KN-522 cohort on univariate analysis ($P = 0.13$), and therefore was not included in multivariable analysis. Patients in the non-KN-522 cohort who received a partial mastectomy were less likely to have delay to surgery on multivariable analysis (coeff. −4.6; 95% CI −8.1 to −1.1; $P = 0.01$).

Time to initiation of radiation from surgery did not differ between the KN-522 [median 49 (IQR 42, 60) days] and non-KN [median, 52 (IQR 42, 63) days; $P = 0.7$] cohorts (Fig. 3). Experiencing an irAE was associated with delay to radiation (coeff. 11, 95% CI 1.2–21, $P = 0.029$). Overall, 38 patients (27%) in the KN-522 cohort and 99 (34%) in the non-KN-522 cohort received adjuvant capecitabine. No difference was observed in the median time to initiating capecitabine after the end of preoperative therapy [149 (IQR 111, 176) days in the non-KN-522 cohort versus 135 (IQR 103, 167) days in the KN-522 cohort; $P = 0.3$]. In the KN-522 cohort, time to capecitabine did not differ by irAE occurrence; median time to capecitabine treatment in patients who experienced an irAE was 127 (IQR 92, 159) days compared with 140 (IQR 117, 177) days among those without an irAE ($P = 0.5$).

Postoperative Complications

Postoperative complications occurred in 26 patients (9.1%) in the non-KN-522 cohort versus 11 patients (7.9%) in the KN-522 cohort ($P = 0.6$; Table 4). The most common complication in the non-KN-522 cohort was surgical site infection/abscess, whereas ischemia of mastectomy flaps occurred most frequently in the KN-522 cohort. Patients who required intervention for complications were most often managed with antibiotics alone; 3 (2.2%) of 139 patients in the KN-522 cohort versus 12 (4.2%) of 287 patients in the non-KN-522 cohort received antibiotics, and 2 (1.4%) of 139 patients in the KN-522 cohort and 6 (2.1%) of 287 in the non-KN-522 cohort required reoperation.

On univariate analysis, history of autoimmune disease was the only comorbid condition associated with higher odds of postoperative complication (Table 5). Lumpectomy compared with mastectomy was associated with lower odds

TABLE 1 Patient, tumor, and treatment characteristics

Characteristic	Non-KN-522 *N* = 287	KN-522 *N* = 139	*P*-value
Days to surgery, median (IQR)	31 (26, 37)	32 (27, 43)	0.048
Age, median years (IQR)	52 (41, 61)	52 (42, 65)	0.5
BMI, median (IQR)	26.7 (23.6, 32.5)	26 (23.1, 30.1)	0.092
Race, *n* (%)			0.072
Asian/Far East/Indian Subcontinent	24 (9.1%)	19 (14%)	
Black	62 (24%)	25 (19%)	
Native American/American Indian/Alaskan	0	1 (0.7%)	
White	152 (58%)	83 (62%)	
Other	25 (9.5%)	6 (4.5%)	
Unknown	24	5	
Ethnicity, *n* (%)			0.15
Hispanic	36 (13%)	9 (7.6%)	
Non-Hispanic	250 (87%)	109 (92%)	
Unknown	1	21	
ASA classification, *n* (%)			0.4
2	86 (30%)	33 (24%)	
3	193 (68%)	103 (75%)	
4	5 (1.8%)	2 (1.4%)	
Unknown	3	1	
Comorbidities, *n* (%)			
Renal	5 (1.7%)	0	0.2
Hepatic	10 (3.5%)	3 (2.2%)	0.6
Previous malignancy	11 (3.8%)	9 (6.5%)	0.2
Hematologic	14 (4.9%)	8 (5.8%)	0.7
Autoimmune	23 (8.0%)	13 (9.4%)	0.6
Cardiovascular	20 (7.0%)	8 (5.8%)	0.6
Pulmonary	21 (7.3%)	11 (7.9%)	0.8
Diabetes	42 (15%)	9 (6.5%)	0.016
Clinical T stage, *n* (%)			0.003
T1/Tis	25 (8.7%)	25 (18%)	
T2	193 (67%)	97 (70%)	
T3	47 (16%)	11 (8.0%)	
T4	20 (7.0%)	5 (3.6%)	
Unknown	0	1	
Clinical N stage, *n* (%)			0.2
N0	120 (42%)	72 (52%)	
N1	146 (51%)	62 (45%)	
N2	7 (2.4%)	1 (0.7%)	
N3	14 (4.9%)	4 (2.9%)	
Histology, *n* (%)			0.006
Invasive ductal carcinoma	258 (90%)	135 (98%)	
Invasive lobular carcinoma	4 (1.4%)	1 (0.7%)	
Other	25 (8.7%)	2 (1.4%)	
Unknown	0	1	
Surgery, *n* (%)			0.3
Mastectomy	129 (45%)	55 (40%)	
Partial mastectomy	158 (55%)	84 (60%)	
Postoperative radiation, *n* (%)	240 (84%)	113 (81%)	0.5
Axillary lymph node dissection, *n* (%)	92 (33%)	28 (21%)	0.009

Table 1 (continued)

Characteristic	Non-KN-522 $N = 287$	KN-522 $N = 139$	*P*-value
Unknown	8	3	
Days to radiation, median (IQR)	52 (42, 63)	49 (42, 60)	0.7
Postoperative complication, *n* (%)			0.6
Cardiac arrest	1 (0.4%)	0	
Hematoma	3 (1.1%)	2 (1.5%)	
Implant loss	0	1 (0.7%)	
Flap ischemia	8 (2.8%)	5 (3.6%)	
Pneumothorax	1 (0.4%)	0	
Surgical site infection	13 (4.6%)	3 (2.2%)	
None	259 (91%)	126 (92%)	
Unknown	2	2	
Intervention for surgical complication, *n* (%)			0.3
Antibiotics	12 (27%)	3 (12%)	
Antibiotics with drainage procedure	1 (2.3%)	1 (3.8%)	
CPR/ACLS	1 (2.3%)	0	
Operative debridement/hematoma evacuation	6 (14%)	2 (7.7%)	
Wound care/hyperbaric oxygen	2 (4.5%)	0	

KN-522 KEYNOTE-522, *IQR* Interquartile range, *BMI* Body mass index, *ASA* American Society of Anesthesiology, *CPR* Cardiopulmonary resuscitation, *ACLS* Advanced cardiovascular life support, *Tis* Carcinoma in situ

TABLE 2 Type and frequency of immune-related adverse events (irAEs)

IrAE	No. of irAEs (%) ($N = 82$)*
Hypothyroidism	13 (15.9%)
Hepatitis/transaminitis	12 (14.6%)
Adrenal insufficiency	8 (9.8%)
Dermatitis	8 (9.8%)
Pneumonitis	7 (8.5%)
Arthritis/myositis	7 (8.5%)
Neurologic/opthalmologic	6 (7.3%)
Hyperthyroidism	4 (4.9%)
Colitis	4 (4.9%)
Nephritis	3 (3.7%)
Diabetes	2 (2.4%)
Myocarditis	1 (1.2%)
Other	2 (2.4%)

*A total of 82 irAEs were experienced by 59 patients.

TABLE 3 Interventions required for immune-related adverse events (irAEs) among the 59 patients who received the KEYNOTE-522 (KN-522) regimen

Intervention type	No. of patients (%) $N = 59$
Steroids alone	22 (37.3%)
Synthroid alone	5 (8.5%)
Steroids and hospitalization	3 (5.1%)
Steroids and antibiotics	3 (5.1%)
Steroid and synthroid	1 (1.7%)
Calcium channel blocker	1 (1.7%)
IVIG and steroids	1 (1.7%)
Antibiotics alone	1 (1.7%)
Insulin/hypoglycemics	1 (1.7%)
Synthroid and antibiotics	1 (1.7%)
Synthroid and atenolol	1 (1.7%)

IVIG Intravenous immunoglobulin

of postoperative complication. IrAEs were not associated with surgical complications ($P = 0.4$).

DISCUSSION

In this study, no significant associations were observed between type of neoadjuvant therapy received and postoperative complications or delays to surgery or adjuvant radiation. IrAEs were not significantly associated with delays to surgery but were associated with delays to adjuvant radiation. While there is a concern that adverse events related to immunotherapy may confer a heightened risk of experiencing postoperative side effects, our data provide reassurance that the benefits of improved pCR rates as a result of adding immunotherapy to the standard preoperative chemotherapy regimen[2] did not occur at the expense of a concomitant increase in surgical complications.

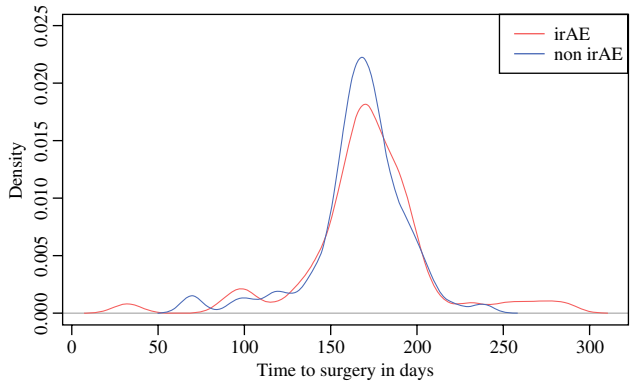

FIG. 1 Distribution of time to surgery (days) from initiation of KEYNOTE-522 regimen among patients with and without immune-related adverse events (irAEs)

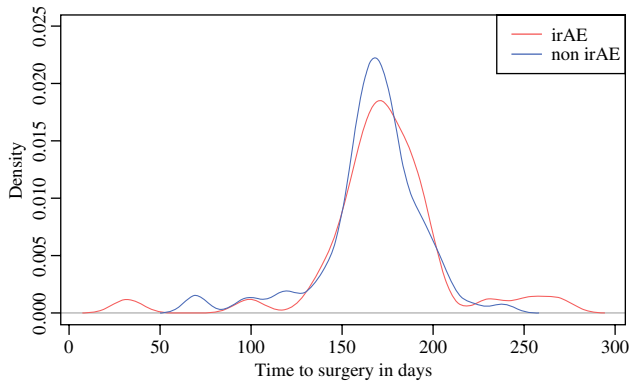

FIG. 2 Distribution of time to surgery (days) from initiation of KEYNOTE-522 regimen among patients with and without immune-related adverse events (irAEs) after excluding patients who had pembrolizumab discontinued permanently

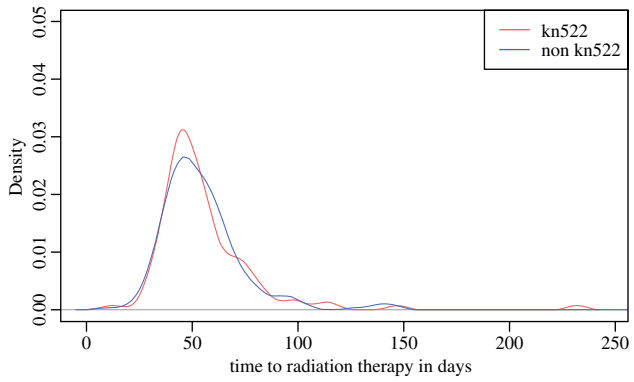

FIG. 3 Distribution of time to radiation (days) from surgery among patients who did and did not receive the KEYNOTE-522 regimen; *KN-522* KEYNOTE-522

TABLE 4 Postoperative complications and interventions among patients who did and did not receive the KEYNOTE-522 (KN-522) regimen

Complication	KN-522, *n* (%) (*N* = 139)	Non-KN-522, *n* (%) (*N* = 287)
Cardiac arrest	0	1 (0.3%)
Hematoma	2 (1.4%)	3 (1%)
Implant loss	1 (0.7%)	0
Skin-flap ischemia	5 (3.6%)	8 (2.8%)
Pneumothorax	0	1 (0.3%)
Infection/abscess	3 (2.2%)	13 (4.5%)

KN-522 KEYNOTE-522

TABLE 5 Factors associated with postoperative complications in patients who received preoperative immunotherapy

Characteristic	Univariate	
	OR (95% CI)	*P*-value
Race		
Asian	Not estimable	
Black	–	–
Native American	Not estimable	
White	3.67 (0.66, 68.8)	0.2
Other	Not estimable	
ASA		
2	–	–
3	0.69 (0.21, 2.71)	0.6
4	Not estimable	
Surgery type		
Mastectomy	–	–
Lumpectomy	0.26 (0.07, 0.83)	0.030
BMI	1.04 (0.94, 1.15)	0.4
Age	0.97 (0.93, 1.01)	0.2
ALND	1.83 (0.47, 6.16)	0.3
Number of irAE	0.75 (0.30, 1.27)	0.5
Any irAE	0.59 (0.15, 1.92)	0.4
Comorbidities		
Renal disease	–	–
Hepatic disease	Not estimable	
Previous malignancy	1.08 (0.06, 6.54)	
Hematologic	3.09 (0.43, 14.8)	0.2
Autoimmune	5.78 (1.36, 22.0)	0.011
Cardiovascular	Not estimable	
Pulmonary	Not estimable	
Diabetes	Not estimable	

Understanding of the incidence and severity of irAEs is evolving. While irAEs of any grade occurred in 304 (38.9%) of 781 patients in the KEYNOTE-522 trial, only 101 (12.9%) had severe events (grade ≥ 3). Although our

institutional experience reported a comparable rate of irAEs (41.3%), the frequency of specific irAEs differed. We observed a higher rate of adrenal insufficiency and a lower rate of hypo- and hyperthyroidism; however, the rate of immune-related endocrine toxicities was similar at 19% in our study compared with 20.4% in the KEYNOTE-522 trial. As existing evidence demonstrates that patient-specific, tumor-specific, and agent-specific risk factors contribute to irAE incidence, differences in the study cohorts may explain this variability.[16] Younger patients have been shown to more frequently have severe adverse events, and there are data to suggest age-related organ specificity. Endocrinopathies and gastrointestinal toxicities more commonly occur among younger patients, whereas older adults are disproportionately affected by dermatologic and rheumatologic events.[17,18] Investigations to identify risk factors and biomarkers that may help predict irAEs are ongoing.

IrAEs can be severe enough to justify discontinuing further administration of immune checkpoint inhibitors. More than 30% of the patients in this study who experienced irAEs required permanent discontinuation of pembrolizumab. For comparison, in the KEYNOTE-522 trial, treatment-related adverse events, irAEs, or other toxicities prompted discontinuation of pembrolizumab in 13.4% of patients during the neoadjuvant period.[2] In some patients, immune checkpoint inhibitors can be reinitiated concurrently with steroid taper after symptoms of adverse events have resolved.[15,19,20] Although data regarding how pause, termination, and rechallenging impact survival and oncologic outcomes after surgical resection are lacking,[21] Watson et al. recently demonstrated that among patients with metastatic melanoma, resumption of immune checkpoint blockade was associated with longer overall survival than cessation of treatment.[22]

While there is little evidence regarding delays in surgery and adjuvant treatment after preoperative immunotherapy, delays in treatment after neoadjuvant therapy have been shown to impact clinical outcomes and disease recurrence rate. Al-Masri et al. observed in their retrospective analysis of 468 women, the majority of whom had stage II–III breast cancer, that overall survival was adversely affected in women whose surgery was delayed beyond 4 weeks after neoadjuvant anthracycline-based chemotherapy.[10] Other groups have observed similar adverse impacts on oncologic outcomes following delays to surgery of greater than 6 or 8 weeks after completion of neoadjuvant chemotherapy.[12,13] Additionally, delays in initiation of adjuvant radiation were found to be associated with increased locoregional recurrence, which in turn was associated with increased rate of distant metastases and death.[11] These findings and other data motivated our primary objective to determine whether irAEs are associated with delays in treatment that may result in differences in clinical outcomes. We found a delay of 11 days to initiation of adjuvant radiation in patients who experienced an irAE; however, whether this delay was clinically significant is not known given the lack of long-term follow-up, although it may reflect the timing of irAE occurrence.

Surgical outcomes data from the KEYNOTE-522 trial, which were presented at the 2023 St. Gallen International Breast Cancer Conference and are consistent with our findings, demonstrated no difference in median time from end of preoperative therapy to surgery between patients who received pembrolizumab [median 1.2 (range 0.4–6.7) months] and those who received chemotherapy with placebo [median 1.2 (range 0.5–9.6) months].[23,24]

In contrast, data from MD Anderson Cancer Center analyzing 87 patients with clinical stage I–III TNBC who received preoperative pembrolizumab and chemotherapy showed that 48.3% of patients experienced delays in surgical care and 24.1% had postoperative complications (i.e., wound complications or infection).[25] Although our study defined delays according to deviation from standard duration of time between preoperative therapy and surgery provided by current guidelines, others may classify delays according to an alternative criteria. Patient-level factors such as comorbidities may have contributed to differences in rates of postoperative complications between our investigation and the MD Anderson experience. Institutional variability in rates of postoperative complications may also reflect whether surgical site infections were classified according to the Centers for Disease Control and Prevention/National Healthcare Safety Network (CDC/NHSN) criteria.[26] When adjusting for these and other clinically relevant variables, it is unclear whether a discrepancy would also be noted between institutional data in postoperative complications or treatment delays among patients who did not receive immunotherapy. In our study, when comparing these outcomes between patients who received preoperative immunotherapy to those who received neoadjuvant chemotherapy alone, no clinically relevant difference was observed. Screening for irAEs allows for early intervention and likely a decrease in the severity of irAEs. The potential impact of irAEs on oncologic and surgical outcomes justifies the standardization of screening for irAEs during both active treatment and the perioperative period.

In this study, postoperative complications were similar among patients who received neoadjuvant chemoimmunotherapy compared with those who received chemotherapy alone. Neither experiencing an irAE nor the number of irAEs were associated with postoperative complications. To our knowledge, this study is the first to evaluate surgical complications by irAE occurrence and type. While there are data to suggest that adrenal insufficiency and hyperthyroidism might be associated with perioperative morbidity,[27,28] existing studies in patients with lung cancer,[4,29,30] melanoma,[5,6,8] and urothelial and bladder cancers[31] have shown postoperative complications are comparable in patients who

receive neoadjuvant immunotherapy and those who receive neoadjuvant chemotherapy without immune checkpoint inhibitors.

This study has several limitations. First, in contrast to KEYNOTE-522, there were differences in tumor characteristics, and specifically proportion of T1 disease, among KN-522 and non-KN-522 cohorts in this retrospective review. This likely is attributed to the KEYNOTE-522 study being restricted to patients with T1c disease or higher. The grade of adverse events was variably documented, making it difficult to distinguish clinically relevant irAEs from those identified on routine biochemical testing. This study considered only irAEs that occurred within the period of preoperative therapy. Therefore, it is unclear whether delays in radiation among patients who experienced irAEs could be attributed to postoperative irAEs. Follow-up was not sufficiently mature to make conclusions regarding long-term recurrence and survival; therefore, it is unclear whether alterations in perioperative treatment (e.g., changes in surgical planning, postoperative complications) impacted long-term clinical outcomes. Power calculations were not performed for this retrospective study, and therefore we are not able to evaluate whether there was sufficient power to make conclusions of non-inferiority. Nevertheless, our findings provide important qualitative information and can inform future prospective studies.

CONCLUSIONS

We did not find clinically significant associations between times to surgery or adjuvant treatment, postoperative complications, and type of preoperative chemotherapy. IrAEs were not associated with delays to surgery or postoperative complications but were associated with longer time to adjuvant radiation. To our knowledge, this is one of the first investigations to explore the effect of irAEs on subsequent oncologic treatment and clinical outcomes. Our findings are reassuring in the context of literature highlighting that irAEs are common and can be severe.

DISCLOSURE G.P. reports professional services and activities with Merck & Co Inc., Paige.AI, Inc., Tizona Therapeutics, and Trishula Therapeutics, Inc. and intellectual property rights from Takeda Pharmaceuticals. The other authors do not have potential conflicts of interest to declare.

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