Safety and Clinical Outcomes of Pembrolizumab Standard-Interval Dosing Versus Extended-Interval Dosing in Patients with Breast Cancer

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Introduction

- Extended-interval (EI) dosing of IV pembrolizumab 400 mg every 6 weeks is more convenient for patients compared to standard-interval (SI) dosing, decreasing the number of clinic and infusion visits.
- However, the impact of EI dosing of pembrolizumab on toxicity and clinical outcomes in patients with breast cancer has not been well studied.
- EI dosing of IV pembrolizumab received U.S. FDA approval across all adult solid tumor indications based on pharmacokinetic (PK) modeling and exposure-response analyses, as well as an interim analysis of patients with advanced melanoma in the KEYNOTE-555 trial.[1-3]
- Retrospective studies in other cancer types, primarily non-small cell lung cancer (NSCLC) and melanoma, are mixed regarding whether EI dosing of pembrolizumab increases the rate of immune-related adverse events (irAE), although efficacy of the two regimens appear similar.[4-7]
- We performed a retrospective study aimed to investigate the safety and clinical efficacy of EI compared to SI dosing of pembrolizumab in patients with breast cancer.

Methods and Materials

- This was a retrospective cohort study of patients with breast cancer who received pembrolizumab per standard-of-care between August 2017 to January 2024.
- Toxicity data pertaining to irAE was manually collected via chart review according to CTCAE v.5.
- Clinical outcomes including event-free survival (EFS), progression-free survival (PFS), objective response rate (ORR), disease control rate (DCR), and overall survival (OS) were collected.
- Safety and clinical outcomes were compared between patients who received only SI pembrolizumab and those who received at least one dose of EI.

Results

Table 1. Patient and treatment characteristics according to pembrolizumab dosing regimen received.

Patient and Treatment Characteristics	All Patients (n=355)	Pembrolizumab Dosage		
		Standard-Interval Dosing Only (n=296)	≥1 Cycle of Extended-Interval Dosing (n=59)	P-value
Age at ICI start (years), median (IQR)	55.4 (45.7 - 64.9)	55.3 (46.0 - 65.1)	55.9 (45.0 - 62.0)	0.9
Stage				
Early	252 (71.0%)	207 (69.9%)	45 (76.3%)	0.3
Metastatic/recurrent	103 (29.0%)	89 (30.1%)	14 (23.7%)	
Total ICI cycles, median (IQR)	12 (5 – 17)	11 (5 – 17)	12 (8 – 15)	0.8
Number of 200 mg doses received, median (IQR)	10 (4 – 17)	11 (5 – 17)	8 (4 – 12.5)	**0.0008**
Number of 400 mg doses received, median (IQR)	0 (0 – 2)	0 (0 – 0)	4 (2 – 6)	**<0.0001**
Any grade irAE	185 (52.1%)	158 (53.4%)	27 (45.8%)	0.3
Any grade 3 or higher irAE	57 (16.1%)	55 (18.6%)	2 (3.4%)	**0.004**

Table 2. Safety and clinical outcomes according to pembrolizumab dosing regimen received in patients with early-stage breast cancer.

	All Patients with Early-Stage Breast Cancer (n=252)	Pembrolizumab Dosage		
		Standard-Interval Dosing Only (n=207)	≥1 Cycle of Extended-Interval Dosing (n=45)	P-value
Follow-up (months), median (95% CI)	25.2 (24.3, 27.9)	26.2 (24.3, 27.9)	25.0 (23.1, 29.2)	0.8
irAE				
Any grade	148 (58.7%)	125 (60.4%)	23 (51.1%)	0.3
Grade 3 or higher	44 (17.5%)	42 (20.3%)	2 (4.4%)	**0.01**
Recurrence Type				
None	215 (85.3%)	176 (85.0%)	39 (86.7%)	0.6
Localized	4 (1.6%)	4 (1.9%)	0 (0.0%)	
Metastatic	33 (13.1%)	27 (13.0%)	6 (13.3%)	
2-year EFS estimates (95%CI)	79.3% (73.1, 84.2)	79.1% (72.2, 84.5)	80.2% (64.0, 89.6)	0.8
Median OS (95%CI)	NR (NR, NR)	NR (NR, NR)	NR (NR, NR)	0.5

Table 3. Safety and clinical outcomes according to pembrolizumab dosing regimen received in patients with metastatic breast cancer.

	All Patients with Metastatic Breast Cancer (n=103)	By Pembrolizumab Dosage		
		Standard-Interval Dosing Only (n=89)	≥1 Cycle of Extended-interval Dosing (n=14)	P-value
Follow-up months, median (95%CI)	29.6 (26.2, 39.0)	29.6 (27.1, 39.0)	33.7 (23.4, NR)	1.0
irAE				
Any grade	37 (35.9%)	33 (37.1%)	4 (28.6%)	0.5
Grade 3 or higher	13 (12.6%)	13 (14.6%)	0 (0.0%)	0.1
Best response				
Complete response	8 (7.8%)	4 (4.5%)	4 (28.6%)	**0.01**
Partial response	17 (16.5%)	16 (18.0%)	1 (7.1%)	
Stable disease	13 (12.6%)	11 (12.4%)	2 (14.3%)	
Progressive disease	46 (44.7%)	39 (43.8%)	7 (50.0%)	
Unknown	19 (18.4%)	19 (21.4%)	0 (0.0%)	
ORR (95%CL)	28.1% (18.6, 37.6)	26.7% (16.4, 36.9)	35.7% (7.0, 64.4)	0.5
DCR (95%CL)	42.7% (32.2, 53.2)	41.3% (30.0, 52.7)	50.0% (20.0, 80.0)	0.6
PFS (months), median (95%CI)	4.4 (3.5, 5.8)	4.1 (3.4, 5.6)	7.8 (3.3, 12.5)	0.8
OS (months), median (95%CI)	16.2 (12.8, 20.7)	15.4 (11.7, 22.2)	17.8 (7.2, NR)	0.5

Figure 1. Kaplan-Meier estimates of EFS for patients with early-stage breast cancer according to pembrolizumab dosing regimen received.

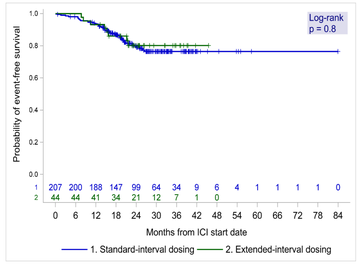
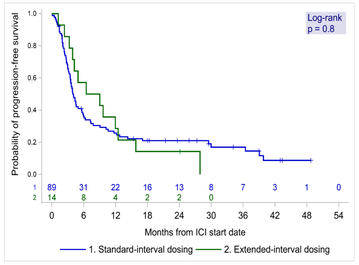


Figure 2. Kaplan-Meier estimates of PFS for patients with metastatic breast cancer according to pembrolizumab dosing regimen received.



Discussion

- In patients with early-stage disease, comparing EI dosing to SI dosing showed that:
  - The incidence of any-grade irAE was similar
  - Grade 3 or higher irAE was less frequent in EI dosing compared to SI dosing
  - EFS and OS were similar
- In patients with metastatic disease, comparing EI dosing to SI dosing showed that:
  - The incidence of any-grade irAE and grade 3 or higher irAE were similar
  - PFS and OS were similar
- Limitations of this study include the small sample size of patients who received only EI dosing, limiting the ability to compare patients who received only EI dosing to those who received only SI dosing
- Patients who received EI dosing may have been a selected patient population who were already tolerating SI dosing, possibly leading to the lower rates of grade 3 or higher irAE in early-stage disease
- A prospective, randomized trial (NCT04295863) is ongoing to compare the safety and efficacy between the two dosing regimens in patients with locally advanced or metastatic cancer

Conclusions

- This study suggests comparable rates of any-grade irAE and clinical outcomes in patients with breast cancer treated with pembrolizumab EI dosing compared to SI dosing.
- As more patients are treated with EI dosing, this data provides new evidence that safety and efficacy are maintained while improving medication burden for patients.

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