A post-marketing surveillance of the real-world safety and effectiveness of avelumab in patients with curatively unresectable Merkel cell carcinoma in Japan

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SCOPE

- This post-marketing surveillance (PMS) evaluated the safety and effectiveness in patients with curatively unresectable Merkel cell carcinoma (MCC) treated in general clinical practice settings in Japan

CONCLUSIONS

- In this PMS of avelumab in 75 patients with curatively unresectable MCC in general clinical practice settings in Japan:
  - No new safety concerns were identified, with adverse events (AEs) of any grade occurring in 81.3% of patients, and adverse drug reactions (ADRs) occurring in 61.3%
  - The most common ADRs specified in the Risk Management Plan for avelumab were infusion reaction, thyroid dysfunction, hepatic function disorder, and interstitial lung disease (ILD)
  - Effectiveness (objective response rate [ORR] of 45.3%; 12-month overall survival [OS] rate of 59.6%) was broadly similar to that observed in the phase 2 JAVELIN Merkel 200 clinical trial[1-4]

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BACKGROUND

- Avelumab (an anti–PD-L1 antibody) was approved in Japan in September 2017 for the treatment of curatively unresectable MCC[5]
- Because few Japanese patients (n=3) were enrolled in the pivotal JAVELIN Merkel 200 trial;[1-4] this PMS was required as an approval condition
- This PMS evaluated safety and effectiveness in patients with curatively unresectable MCC treated in general clinical practice settings in Japan

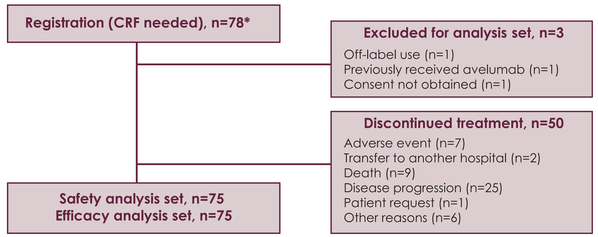
METHODS

- This prospective, noncomparative, observational study included all patients with MCC who started to receive avelumab between 22 November 2017 (avelumab approval date) and 31 October 2019
- The study period for patients was a maximum of 52 weeks from the first administration of avelumab
- The primary objective of the study was to evaluate safety in general clinical practice settings
  - Safety endpoints included the incidence of all AEs and ADRs in addition to safety specifications (ADRs prespecified in the Japanese Risk Management Plan for avelumab)
- The secondary objective was to evaluate effectiveness
  - Effectiveness endpoints included best overall response and ORR based on investigator's assessment and referring to RECIST 1.1, and OS, which was defined as time to all-cause death

RESULTS

- At data cutoff (22 September 2021), 75 patients were included from 53 institutions (**Figure 1**)
- Demographics and baseline characteristics are reported in **Table 1** and **Supplementary Figure 1**
- The median number of avelumab doses patients received was 12.5 (range, 1-27) (**Supplementary Figure 2**)
- 61 patients (81.3%) had an AE, and 46 patients (61.3%) had an ADR (**Supplementary Figure 3**)
- The most common safety specifications of any grade were infusion reaction (28.0%), thyroid dysfunction (9.3%), hepatic function disorder (5.3%), and interstitial lung disease (4.0%) (**Table 2**)
  - 3 patients (4.0%) had grade ≥3 infusion reaction
  - 1 patient each (1.3%) had grade ≥3 ILD, myositis/rhabdomyolysis, type 1 diabetes, or nerve disorder

Figure 1. Patient disposition



CRF, case report form.
*Results are based on the 8th Periodic Safety Report.

Table 1. Demographics and baseline characteristics

Characteristic	N=75
Sex, %	
Male	48.0
Female	52.0
Age, median (range), years	77.0 (42-95)
ECOG PS, %	
0	48.0
1	33.3
2	9.3
3	8.0
4	0
Unknown	1.3
Disease location, %	
Skin	89.3
Lymph node	2.7
Other	8.0
Prior treatment, %	
Surgical resection	76.0
Radiotherapy	62.7
Chemotherapy	9.3

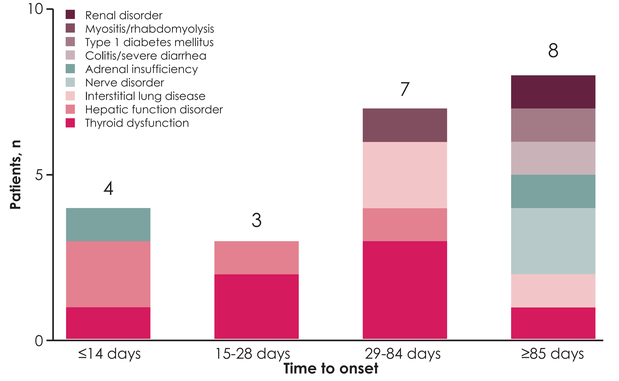
Table 2. Safety specifications by worst grade

N=75	Patients, n (%)				
	Any grade	Grade 1	Grade 2	Grade 3	Grade 4
Infusion reaction	21 (28.0)	13 (17.3)	5 (6.7)	2 (2.7)	1 (1.3)
Thyroid dysfunction	7 (9.3)	4 (5.3)	3 (4.0)	-	-
Hepatic function disorder	4 (5.3)	3 (4.0)	1 (1.3)	-	-
Interstitial lung disease	3 (4.0)	2 (2.7)	-	-	1 (1.3)
Nerve disorder	2 (2.7)	-	1 (1.3)	1 (1.3)	-
Adrenal insufficiency	2 (2.7)	1 (1.3)	1 (1.3)	-	-
Type 1 diabetes mellitus	1 (1.3)	-	-	1 (1.3)	-
Myositis/rhabdomyolysis	1 (1.3)	-	-	1 (1.3)	-
Colitis/severe diarrhea	1 (1.3)	-	1 (1.3)	-	-
Renal disorder	1 (1.3)	-	1 (1.3)	-	-

ADR, adverse drug reaction.

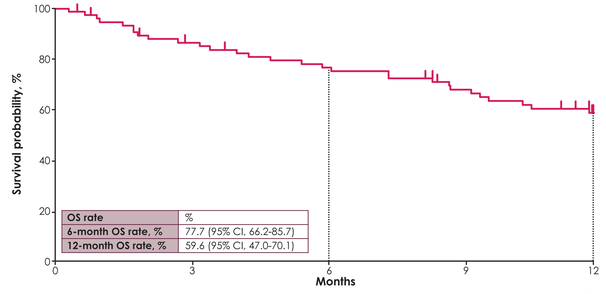
- Time to onset after treatment initiation of safety specifications is shown in **Figure 2** and **Supplementary Figure 4**
  - Onset of thyroid dysfunction and hepatic function disorders tended to occur within 84 and 28 days, respectively; onset of ILD tended to occur after ≥28 days of treatment
  - Adrenal insufficiency occurred in 2 patients (within 14 days and after 84 days, respectively), nerve disorders occurred in 2 patients (both after 84 days), and 1 patient each had myositis/rhabdomyolysis (onset between 28 and 84 days), colitis/severe diarrhea, type 1 diabetes mellitus, and renal disorders (all with onset after 84 days)
  - 19 patients (25.3%) had onset of infusion reaction after the first dose, and the other 2 patients (2.7%) had onset of infusion reaction after the third and seventh doses

Figure 2. Time to onset of safety specifications not including infusion reactions



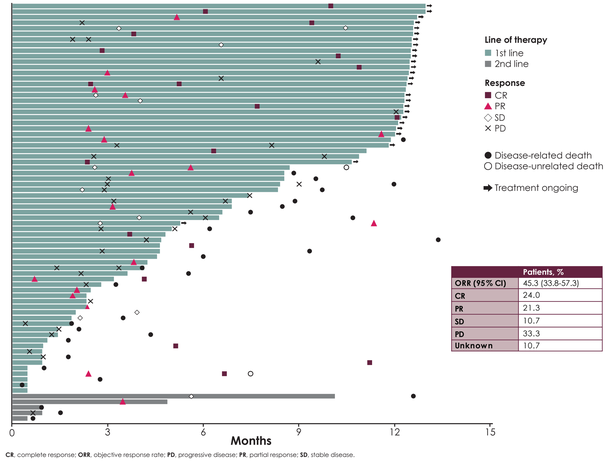
- 6- and 12-month OS rates were 77.7% (95% CI, 66.2%-85.7%) and 59.6% (95% CI, 47.0%-70.1%), respectively (**Figure 3**)
- The best overall response within 52 weeks of first avelumab dose (**Figure 4**) was complete response in 18 patients (24.0%), partial response in 16 patients (21.3%), stable disease in 8 (10.7%), and progressive disease in 25 patients (33.3%)
- Duration of treatment and treatment responses for each patient are shown in **Figure 4**

Figure 3. Overall survival



OS, overall survival.

Figure 4. Duration of avelumab treatment and objective responses



CR, complete response; **ORR**, objective response rate; **PD**, progressive disease; **PR**, partial response; **SD**, stable disease.

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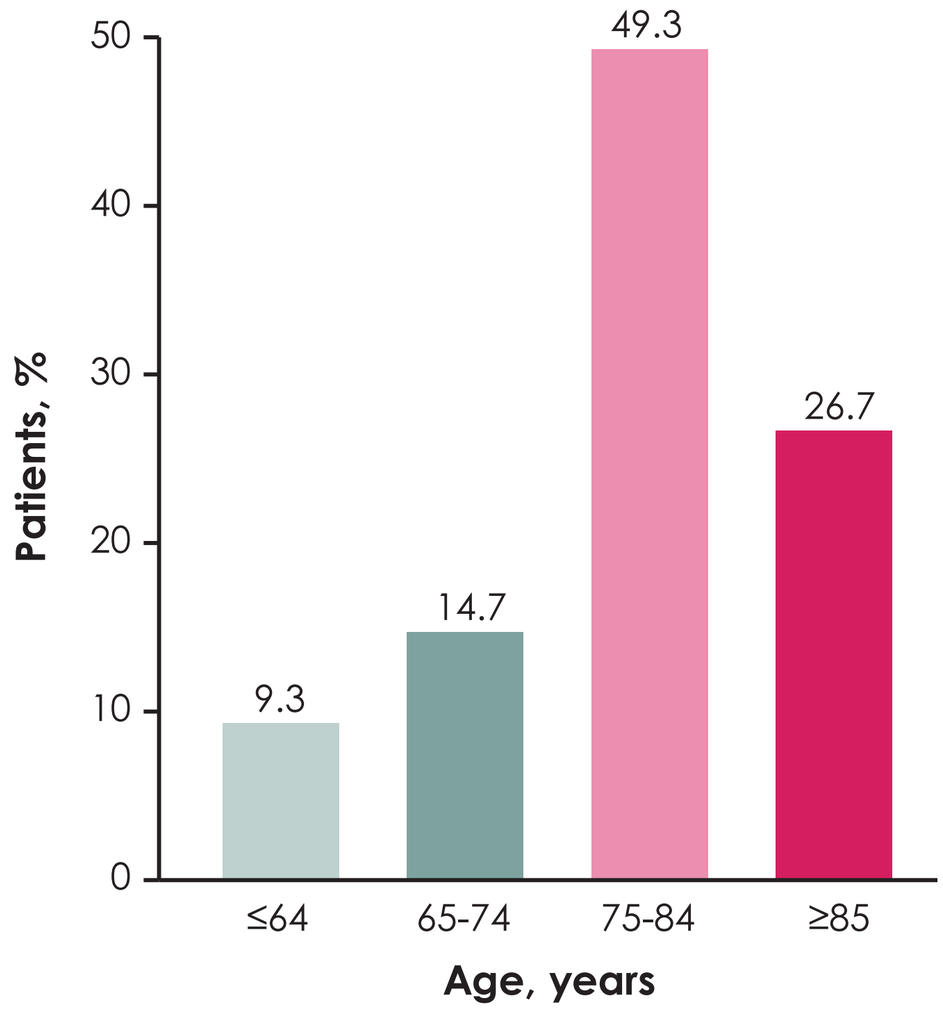
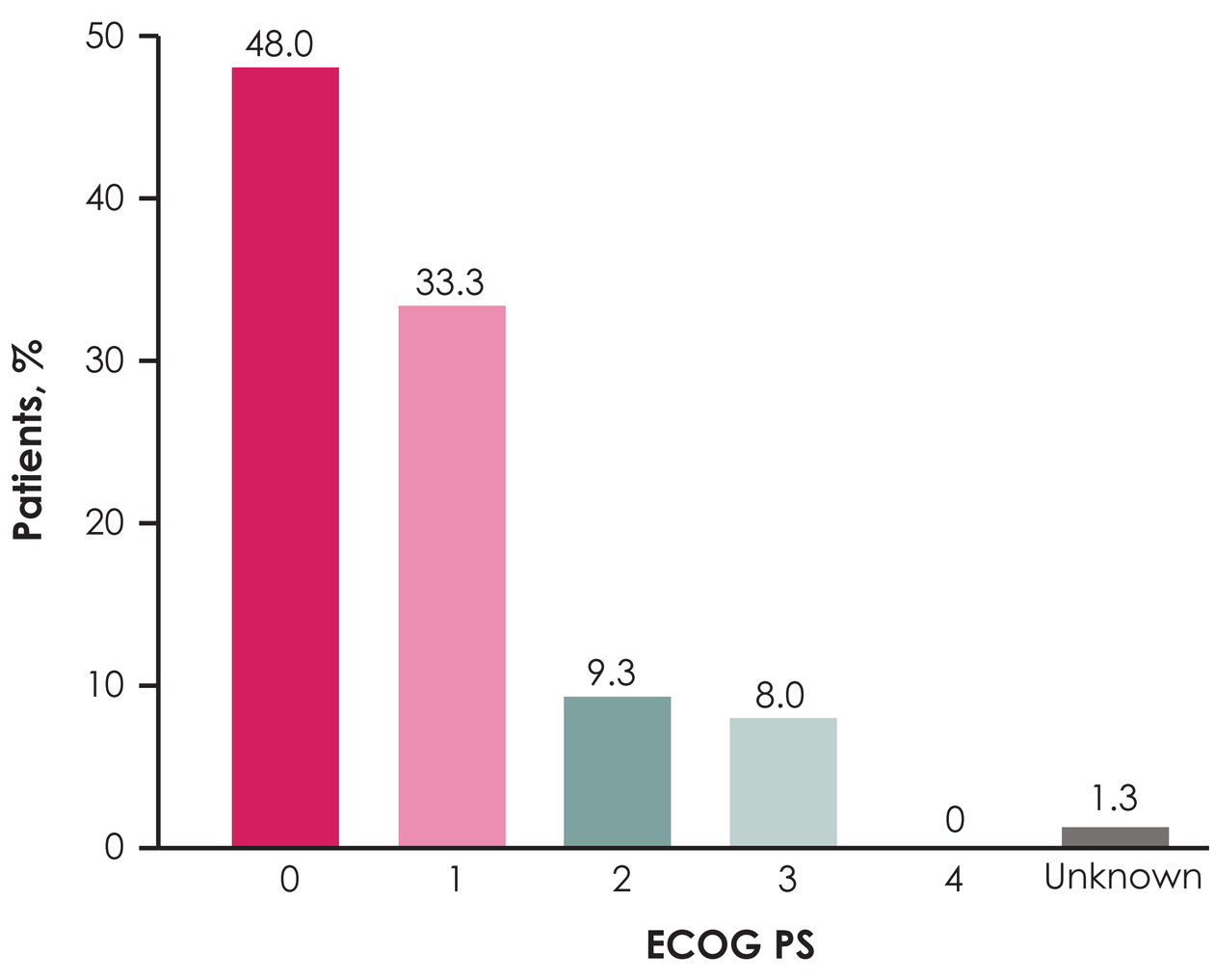
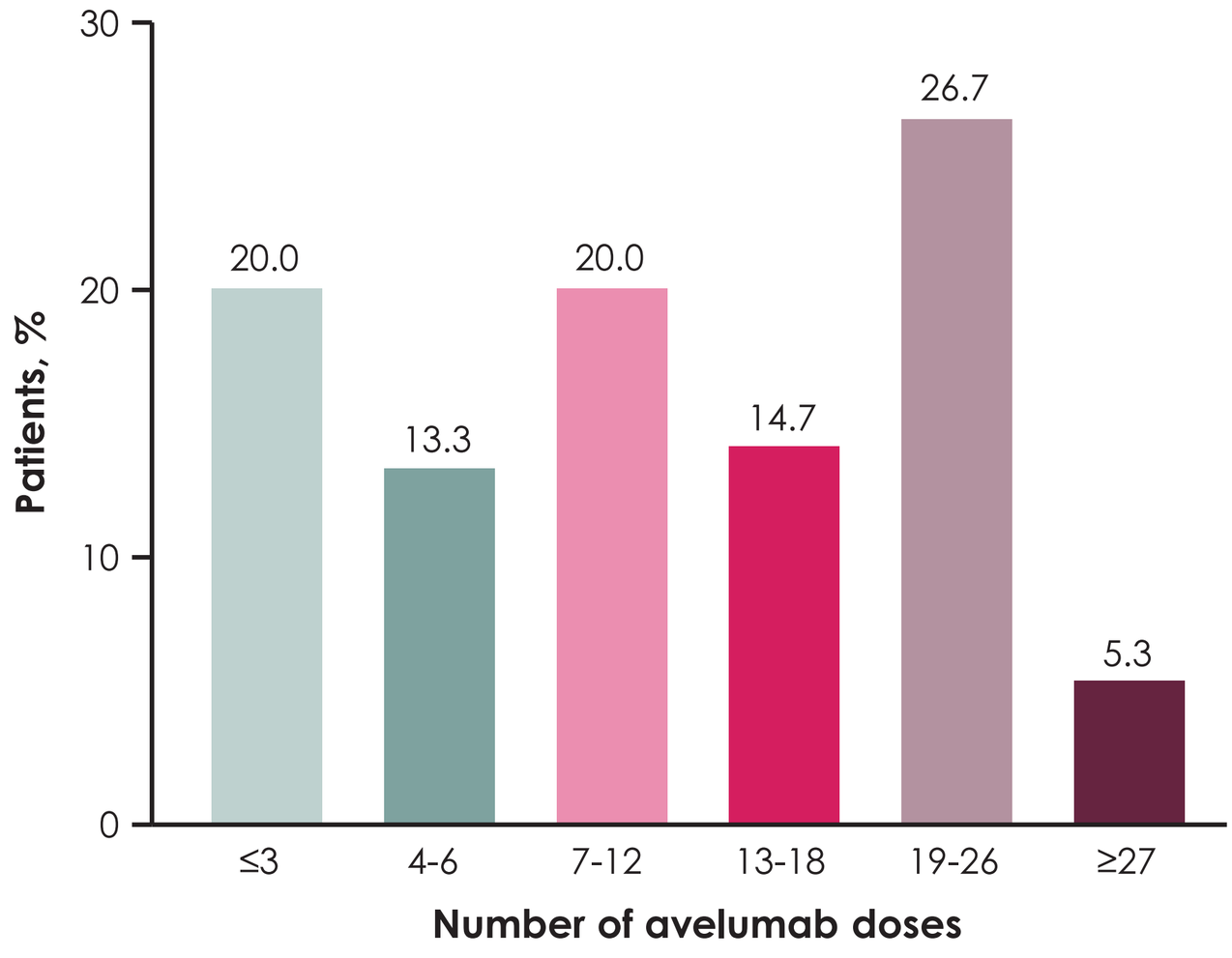
Supplementary Figure 1. Baseline characteristics

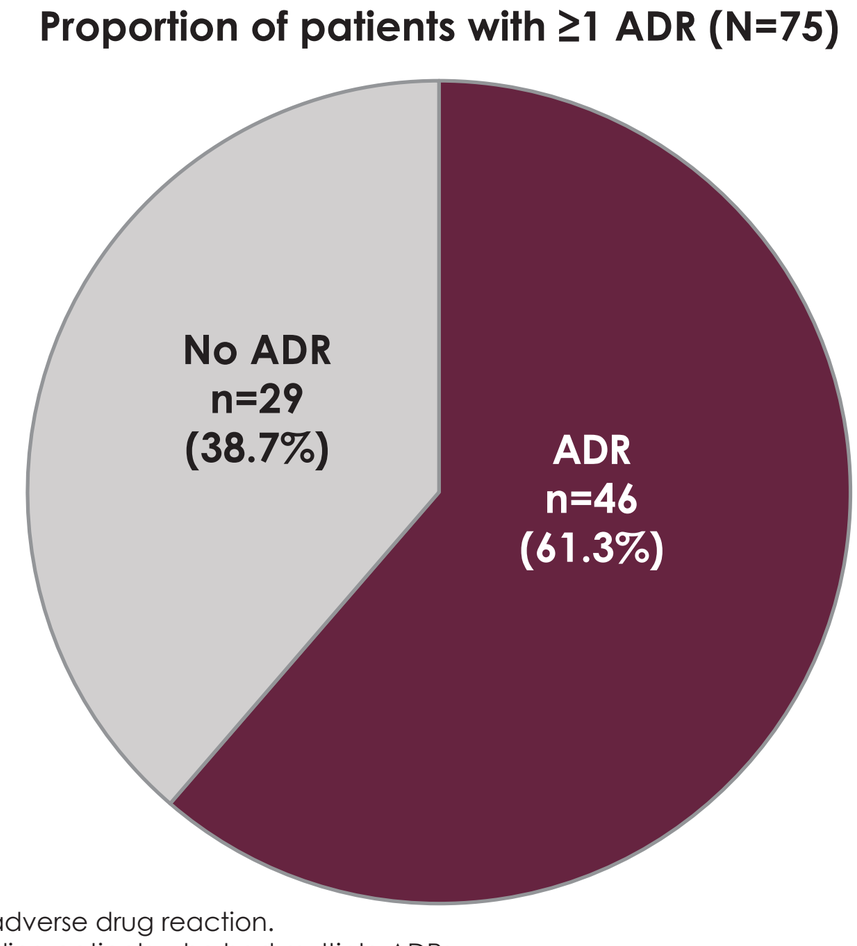


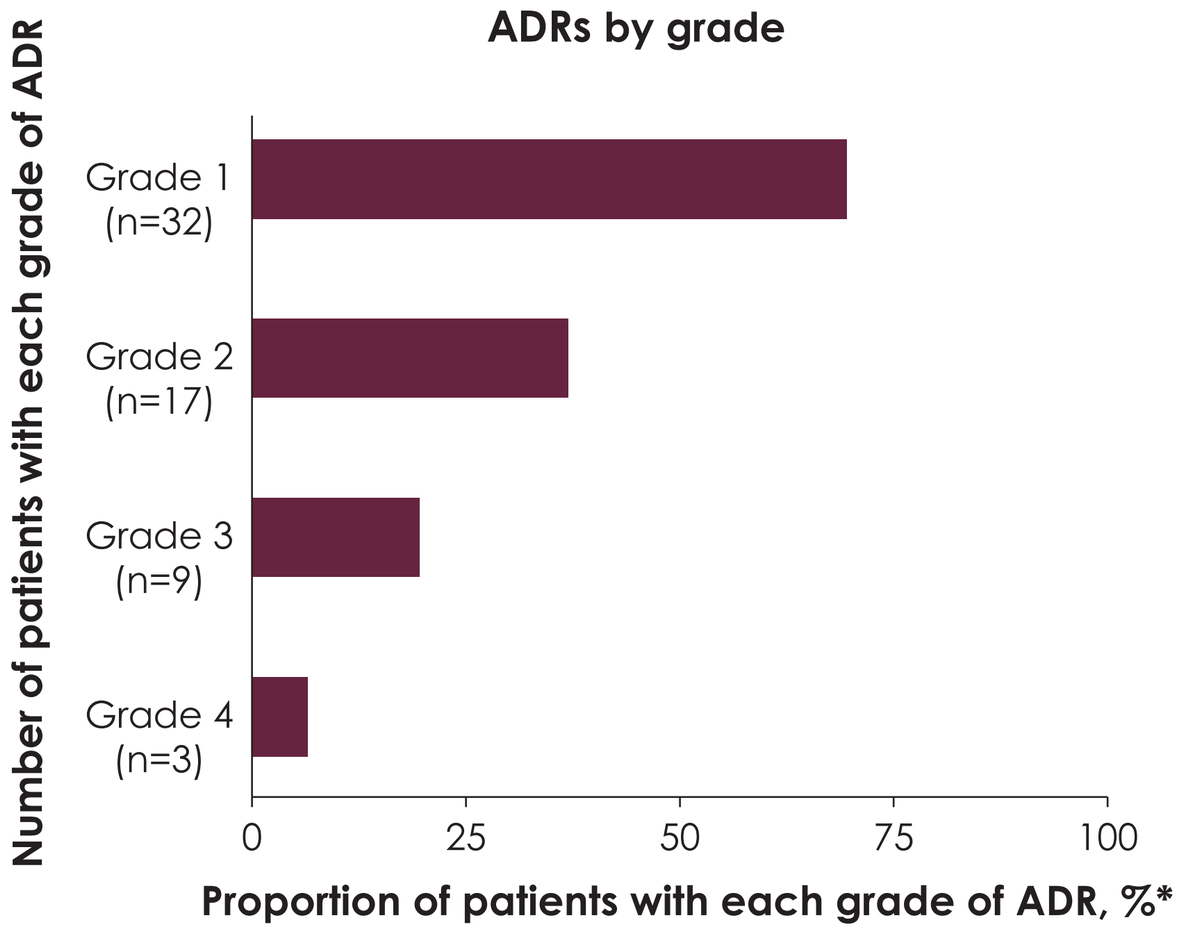


Supplementary Figure 2. Number of doses of avelumab



Supplementary Figure 3. Occurrence and severity of ADRs





ADR, adverse drug reaction.
*Including patients who had multiple ADRs.

Supplementary Figure 4. Onset of infusion reaction by avelumab dose