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# KEYTRUDA®

## EXTENDED DOSING OF PEMBROLIZUMAB IN PATIENTS WITH ADVANCED ESOPHAGEAL CANCER

### A comprehensive literature review and expert perspective

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*Over the last decade, the immune checkpoint inhibitor pembrolizumab has become an integral part of the treatment algorithm for a broad range of cancer types. The standard dosing schedule for pembrolizumab is 200 mg every three weeks (Q3W). Considering the widespread use of this agent across multiple indications, an option of extended dosing at 400 mg every six weeks (Q6W) was evaluated to provide greater flexibility and convenience to both patients and healthcare providers. The latter is of particular relevance in the context of advanced esophageal, gastric, or gastro-esophageal junction (GEJ) cancer where pembrolizumab can be combined with a standard chemotherapy backbone that is given every two weeks (e.g., FOLFOX). This report provides a comprehensive summary of the available evidence obtained from modeling and simulation studies, clinical trials and real-world evidence on the efficacy and safety of pembrolizumab at a dose of 400 mg Q6W, and its applicability in patients with advanced esophageal, gastric or GEJ cancer. Additionally, esteemed specialists in digestive oncology share their expert opinion and experience with extended-interval dosing strategies for pembrolizumab in patients with advanced gastro-esophageal cancer.*

## Introduction

Pembrolizumab, a humanized monoclonal antibody targeting the programmed death-1 (PD-1) receptor, has demonstrated significant antitumor activity and a manageable safety profile across various cancer types. Based on the clinical research program, pembrolizumab as monotherapy or in combination with other agents gained approvals from the European Medicines Agency (EMA) in multiple indications, including melanoma, non-small cell lung carcinoma (NSCLC), classical Hodgkin lymphoma, urothelial carcinoma, head and neck squamous cell carcinoma, renal cell carcinoma, triple-negative breast cancer, endometrial carcinoma, cervical cancer, microsatellite instability high (MSI-H) cancers, esophageal carcinoma, and gastric or GEJ adenocarcinoma.[1] Recent studies have highlighted the role of pembrolizumab in combination with standard therapies as first-line treatment for gastro-esophageal cancer. For example, in the phase III KEYNOTE-590 study, pembrolizumab added to first-line chemotherapy was shown to induce a significant benefit in overall (OS) and progression-free survival (PFS) in patients with advanced esophageal or HER2-negative GEJ cancer, whose tumors express PD-L1 with a combined positive score (CPS) ≥10, irrespective of tumor histology.[2] Similarly, the phase III KEYNOTE-811 and KEYNOTE-859 studies established pembrolizumab-

based combination therapies as first-line treatment options for patients with HER2-positive and HER2-negative advanced gastric or GEJ cancer with tumoral PD-L1 expression (CPS≥1), respectively.[3,4]

In the majority of clinical trials evaluating pembrolizumab-based treatment, evidence has been generated with the 200 mg Q3W standard dose regimen. However, in the context of gastro-intestinal cancers, there is an interest to explore less frequent pembrolizumab dosing schedules that align better with the standard chemotherapy backbones used in this setting. Such an extended dosing schedule is also associated with a decreased infusion frequency, which could provide flexibility for patients and time savings for patients and healthcare providers while maintaining therapeutic outcomes.[5] In this light, several research groups have looked into the safety and efficacy of using pembrolizumab at a dose of 400 mg Q6W. Ultimately, these research efforts have resulted in the EMA approval of this alternative pembrolizumab dosing schedule in all adult indications, as monotherapy (2019) or as part of combination therapy (2021).[1]

# Literature review on Pembrolizumab extended dosing schedule

## PHARMACOKINETIC MODELING AND SIMULATION STUDIES

The initial European regulatory approval of the extended dosing schedule for pembrolizumab of 400 mg Q6W as an alternative to the original dosing schedule of 200 mg Q3W was supported by an exposure-response evaluation for both efficacy and safety using pharmacokinetic (PK) modeling and simulation. Overall, the results of the model-based analyses showed that pembrolizumab 400 mg Q6W had a similar predicted exposure as the 200 mg Q3W dose. Furthermore, the predicted exposures for patients who switch from pembrolizumab 200 mg Q3W to 400 mg Q6W were similar to the exposures modeled for continuous pembrolizumab 400 mg Q6W dosing from treatment initiation. The study concluded that the 400 mg Q6W dosing regimen for pembrolizumab is predicted to have a similar efficacy and safety profile as the 200 mg Q3W dosing regimen, which is expected to be applicable across the different tumor types.[6]

## CLINICAL TRIAL DATA: KEYNOTE-555 (COHORT B)

Subsequently, clinical data from cohort B of the KEYNOTE-555 study, an open-label clinical trial in patients with treatment-naïve metastatic melanoma, were used to validate the pharmacokinetic-model-based assessments of pembrolizumab 400 mg Q6W.[6,7] In this study, a total of 101 patients with unresectable stage III or IV melanoma, who did not receive prior systemic therapy for advanced disease, received pembrolizumab at a dose of 400 mg Q6W for up to 18 cycles. Interestingly, the observed pharmacokinetic data from cohort B in this study align with the previously described model-based predictions for pembrolizumab 400 mg Q6W. In terms of efficacy, an objective response rate (ORR) of 50.5% was reported, with a median PFS of 13.8 months.[7] These efficacy results were as expected for pembrolizumab monotherapy as a first line treatment for advanced melanoma.[8] Importantly, the extended dosing of pembrolizumab did not raise any unexpected safety signals. The incidence of grade 3-5 treatment-related adverse events (TRAEs) and immune-mediated adverse events (irAEs) was reported at 6.9% and 1.0%, respectively.[7] As such, these interim results support prior findings from the model-based assessment and indicate that the benefit-risk profile is consistent for pembrolizumab dosed at 400 mg Q6W and 200 mg Q3W.[7]

## REAL-WORLD EVIDENCE & OBSERVATIONAL STUDIES

Further insights into the efficacy and safety of pembrolizumab Q6W come from different real-world data sets, mainly including patients with NSCLC or melanoma.[9-15] Despite some inconsistencies, likely induced by the retrospective nature of these studies and differences in their design and patient population, the efficacy results obtained with pembrolizumab Q6W in these real-world studies were mainly consistent with what has been reported with the standard Q3W pembrolizumab dosing.[9-16] Importantly, extending the dosing interval of pembrolizumab did not seem to increase the risk for irAEs.[11-16] Similarly, also a switch from standard Q3W dosing of pembrolizumab to an extended 6-weekly dosing interval did not seem to increase the probability for (grade ≥3) irAEs.[11] Of note, as a significant proportion of the irAEs in patients who switched from pembrolizumab Q3W to the Q6W schedule occurred shortly after the switch, a more intensive surveillance might be warranted during the first extended dose cycles.[11]

# WHAT DO EXPERTS SAY?

## Pembrolizumab Q6W in the treatment of patients with advanced esophageal or GEJ cancer

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As illustrated above, the available prospective and real-world data on the efficacy and safety of pembrolizumab Q6W are scarce and have mainly been generated in patients with NSCLC or melanoma. To shed some more light on the adoption and outcomes of extended pembrolizumab dosing in patients with advanced gastro-esophageal cancer, we asked Prof. Marc Van den Eynde (Cliniques Universitaires St-Luc, Brussels), Dr. Filip Van Herpe (University Hospitals Leuven, Leuven) and Dr. Veerle Casneuf (OLV Ziekenhuis, Aalst) to share their personal experience with extended pembrolizumab dosing in the treatment of these patients.

Anno 2023, the standard first line treatment for patients with advanced esophageal/GEJ cancer is based on the HER2 status, the result of the MSI test and the level of PD-L1 expression. *Prof. Van den Eynde: "For patients with HER2-negative advanced esophageal/GEJ cancer, the treatment choice is mainly steered by the expression of PD-L1. When the PD-L1 CPS is ≥10 a combination of chemotherapy with pembrolizumab has become standard of care, irrespective of the tumor histology."* As indicated earlier, the clinical basis for this is formed by the phase III KEYNOTE-590 study in which the addition of pembrolizumab to a first line treatment with 5-fluorouracil (5-FU) and cisplatin significantly improved the OS and PFS of patients with advanced esophageal or HER2-negative GEJ cancer.[2] Dr. Van Herpe: "*While the chemotherapy backbone that was used in this clinical trial is popular in Asian countries, it is rarely used in Western countries. In fact, the preferred chemotherapy backbone for patients with advanced esophageal/GEJ cancer in Belgium consists of FOLFOX. In contrast to cisplatin-5-FU, however, this regimen is given every 2 weeks instead of every 3 weeks, making it complex to combine with a 3-weekly administration of pembrolizumab."* According to *Prof. Van den Eynde*, there are two options to better align the chemotherapy and pembrolizumab schedule in this situation: *"You can opt for a chemotherapy backbone that is given every three weeks, or you can extend the pembrolizumab interval to a multiple of 2 weeks."* With respect to the first, a possible chemotherapy regimen could be CAPOX (capecitabine plus oxaliplatin). However, this regimen is not very popular in Belgium for the treatment of patients with esophageal/GEJ cancer. The main reason for this is that these patients often present with dysphagia which makes the high pill intake that comes with CAPOX somewhat challenging. As such, adapting the treatment interval of the immunotherapy component of the treatment seems to be a much more elegant solution. As a result, **all three experts are now routinely opting for the 6-weekly pembrolizumab regimen in the treatment of patients with HER2-negative, PD-L1 positive advanced esophageal/GEJ cancer.** *Dr. Casneuf: "When using pembrolizumab Q3W, patients have to come to the hospital on weeks 2, 3, 4 and 6. This comes with a considerable treatment burden and makes things overly complex for patients. With the 6-weekly schedule, it is clear for patients that they have to come to the hospital every 2 weeks, with a combined administration of chemotherapy and pembrolizumab every 3 visits."*

The choice for pembrolizumab Q6W is supported by the pharmacokinetic model-based, prospective, and real-world data summarized earlier.[6-16] Commenting on this, *Dr. Van Herpe* notes that "*despite the fact that the real-world data largely come from retrospective analyses, it is important to underscore that these studies contained relatively large patient cohorts making the data sufficiently convincing."* In line with these literature findings, the **experts did not encounter any negative experience with pembrolizumab Q6W in their own clinical practice,** indicating an efficacy and safety profile that is consistent with what has been reported with the standard Q3W dose.

Importantly, the fact that these patients need to come to the hospital on a 2-weekly basis to receive their chemotherapy also means that the 6-weekly pembrolizumab dosing does not lead to a suboptimal follow-up. *Dr. Van Herpe: "In patients with esophageal/GEJ cancer we sometimes have to drop the oxaliplatin from the chemotherapy schedule due to neuropathy. However, we rarely have to stop the chemotherapy completely.*

*As a result, we almost never come in a situation where we give pembrolizumab as monotherapy to these patients. This means that we continue to see our patients on a 2-weekly basis."* Also for *Dr Casneuf,* the 2-weekly consultations with patients offer reassurance when it comes to the follow-up of patients who receive pembrolizumab every 6 weeks.

With the available data, *Prof. Van den Eynde* concludes that *"dosing pembrolizumab with a 6-weekly interval does not compromise the treatment efficacy, does not cause any safety concerns and is much more convenient for patients."* Therefore, he believes that it is reasonable to opt for an extended 6-weekly administration when you decide to add pembrolizumab to chemotherapy in patients with HER2-negative advanced esophageal/GEJ cancer.

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MSD is not able to make recommendations on which patients should be treated with Keytruda® (pembrolizumab) 200 mg Q3W versus 400 mg Q6W dosing, nor on switching dosing schedules.


## ABBREVIATIONS

**CAPOX**: Capecitabine plus Oxaliplatin; **CPS**: Combined Positive Score; **EMA**: European Medicines Agency; **FOLFOX**: 5-fluorouracil plus Oxaliplatin; **GEJ**: gastro-esophageal junction; **HER-2**: Human Epidermal Growth Factor Receptor 2; **irAEs**: Immune-related Adverse Events; **MSI-H**: Microsatellite Instability-High; **NSCLC**: Non-Small Cell Lung Cancer; **ORR**: Objective Response Rate; **OS**: Overall Survival; **PD-L1**: Programmed Death-Ligand 1; **PD-1**: Programmed Death 1; **PFS**: Progression-Free Survival; **PK**: pharmacokinetic; **Q3W**: 3-Weekly Dosing; **Q6W**: 6-Weekly Dosing; **TRAEs**: Treatment-Related Adverse Events; **5-FU**: 5-fluorouracil


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