Safety and Efficacy of Pembrolizumab in Advanced, Programmed Death Ligand 1–Positive Cervical Cancer: Results From the Phase Ib KEYNOTE-028 Trial


ABSTRACT

Purpose
The KEYNOTE-028 trial (ClinicalTrials.gov identifier: NCT02054806) was designed to assess the safety and efficacy of pembrolizumab in 20 programmed death ligand 1–positive, advanced solid tumor cohorts. Here, we present the results from the cohort of patients with advanced cervical cancer.

Methods
Patients were treated with pembrolizumab 10 mg/kg every 2 weeks for up to 24 months. Response was assessed every 8 weeks for the first 6 months and every 12 weeks thereafter. The primary end point was overall response rate per Response Evaluation Criteria in Solid Tumors, version 1.1, by investigator review. Safety was a secondary end point.

Results
Twenty-four patients were enrolled in the cervical cancer cohort. The median age was 42 years (range, 26 to 62 years), 22 patients (92%) had received prior radiation therapy, and 15 patients (63%) had received two or more lines of therapy, including bevacizumab (10 of 24 patients), for advanced disease. At the data cutoff, median follow-up duration was 11.0 months (range, 1.3 to 32.2 months). Overall response rate was 17% (95% CI, 5% to 37%); four patients (17%) achieved a confirmed partial response, and three patients (13%) had stable disease. Median duration of response for the four patients who achieved a partial response was 5.4 months (4.1 to 7.5 months). Treatment-related adverse events (AEs) were experienced by 18 patients (75%); only rash (n = 5; 21%) and pyrexia (n = 4; 17%) occurred in $10% of patients. Five patients experienced grade 3 treatment-related AEs. No grade 4 treatment-related AEs or deaths were observed.

Conclusion
In patients with programmed death ligand 1–positive advanced cervical cancer, pembrolizumab demonstrated antitumor activity and exhibited a safety profile consistent with that seen in other tumor types.

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INTRODUCTION

Although the use of screening programs and the introduction of vaccines protecting against the human papillomavirus (HPV) have dramatically reduced the incidence of cervical cancer, the disease remains a problem in populations without access to adequate health care. Consequently, cervical cancer is the second most commonly diagnosed malignancy in women in the developing world, with 87% of all cervical cancer deaths occurring in developing regions. In the United States, 46% of patients diagnosed with cervical cancer will present with localized disease. The prognosis for these patients is good, with a 5-year survival rate of 91%. In contrast, the prognosis for patients with advanced disease is poor, with a 5-year survival rate of only 17%. For recurrent or metastatic disease, cisplatin-based therapy has been a common treatment option; however, outcomes are disappointing, with response rates ranging from 13% with cisplatin alone to 36% with cisplatin-containing doublet therapy. Recently, bevacizumab in combination with chemotherapy...
compared with chemotherapy alone was found to provide an overall survival (OS) advantage (17 months v 13 months) and a higher response rate (48% v 36%). However, after progression, only limited treatment options exist, including single-agent therapies and palliative care.5–7

Programmed death 1 (PD-1) is a T-cell coinhibitory receptor that under normal conditions functions in an immunoregulatory manner.12 PD-1 is known to play a significant role in cancer by contributing to the ability of a tumor to avoid immunosurveillance.13,14 Pembrolizumab is a highly selective, fully humanized monoclonal antibody that prevents the interaction between PD-1 and its ligands, programmed death ligand 1 (PD-L1) and programmed death ligand 2 (PD-L2).15,16 Pembrolizumab is currently approved for the treatment of melanoma in more than 60 countries, in the United States and Europe for metastatic non–small-cell lung cancer, urothelial carcinoma, and adults with relapsed/refractory classic Hodgkin lymphoma, and in the United States for recurrent or metastatic head and neck squamous cell carcinoma (HNSCC), pediatric patients with relapsed/refractory classic Hodgkin lymphoma, and microsatellite instability high or mismatch repair deficient cancer.15,17 The recent identification of PD-L1 expression in cervical intraepithelial neoplasias and cervical cancers suggests that PD-1 may be an attractive therapeutic target for patients with advanced cervical malignancies.18,19 Pembrolizumab is currently under investigation as a treatment of PD-L1–positive solid tumors in the phase Ib KEYNOTE-028 trial (ClinicalTrials.gov identifier: NCT02054806). Here, we report the results from the cervical cancer cohort.

**METHODS**

**Study Design and Patient Population**

KEYNOTE-028 (Data Supplement) is a multicenter, phase Ib, single-arm trial investigating the safety and efficacy of pembrolizumab in 20 different PD-L1–positive advanced solid tumors. Within this report, we present results from the cohort of patients with advanced cervical cancer. Informed consent was obtained for all patients, and the trial was conducted in compliance with local and national regulations and in accordance with the ethical principles that have their origin in the Declaration of Helsinki. Patients were required to be ≥18 years of age and have histologically or cytologically documented, locally advanced, or metastatic PD-L1–positive cervical cancer that had progressed after prior standard therapy, for which no standard therapy existed, or for whom standard therapy was not considered appropriate. PD-L1 positivity, determined using an archived formalin-fixed paraffin-embedded tumor sample or newly obtained core or excisional biopsy sample, was defined as membranous staining on ≥1% modified proportion score or interface pattern as assessed using a laboratory-developed prototype immunohistochemistry assay (QuaTek Molecular Laboratories, Goleta, CA)20 and the 22C3 antibody (Merck & Co., Inc., Kenilworth, NJ).21 Additional eligibility criteria included measurable disease per Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST v1.1); Eastern Cooperative Oncology Group performance status of 0 or 1; and adequate organ function. Patients were excluded if they had received chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks before treatment initiation; if they had received a prior antinecancer monoclonal antibody or any investigational agent within 4 weeks before treatment initiation; or if they had previously received any anti–PD-1, anti–PD-L1, or anti–PD-L2 therapy. Patients with an active infection requiring systemic therapy, evidence of interstitial lung disease, a diagnosis of immunodeficiency, known additional malignancies, active central nervous system metastases, or an active autoimmune disease requiring systemic treatment within the past 2 years were also excluded.

**Treatment and Assessments**

Patients received pembrolizumab 10 mg/kg as a 30-minute intravenous infusion every 2 weeks. Treatment was continued for up to 24 months or until withdrawal of consent, confirmed radiographic progression, unacceptable toxicity, or investigator decision. Participants with stable disease (SD) or better on treatment discontinuation could be eligible to restart pembrolizumab treatment of up to 1 year if they exhibited subsequent disease progression. Treatment could be withheld for patients exhibiting intolerable or persistent grade 2 treatment-related adverse events (AEs) and was permanently discontinued if the toxicity did not resolve to grade 0 to 1 within 12 weeks.

Safety was monitored throughout the study and for 30 days after treatment discontinuation (90 days for serious AEs and immune-mediated AEs). AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0). Immune-mediated AEs were defined as events with potentially drug-related immunologic causes that were consistent with an immune phenomenon, regardless of attribution to treatment or immune relatedness by the investigator. Response was assessed by computed tomography or magnetic resonance imaging every 8 weeks for the first 6 months, and every 12 weeks thereafter. If radiologic imaging indicated progressive disease, a repeat assessment was required ≥4 weeks later. If the follow-up scan confirmed progression, treatment was discontinued. Patients were given the option to continue treatment until progression was confirmed.

**End Points**

The primary end point was overall response rate (ORR). ORR was defined as the proportion of patients achieving either a confirmed complete response or partial response (PR), per RECIST v1.1, by investigator review. Secondary end points included safety and tolerability, progression-free survival (PFS; time from allocation to first documented disease progression according to RECIST v1.1 or death from any cause), OS (time from enrollment to death from any cause), and duration of response (DOR; time from first observation of response according to RECIST v1.1 to radiographic disease progression in patients who had achieved PR or better).

**Statistical Analyses**

A sequential monitoring procedure was used to evaluate efficacy and futility after at least six patients had at least one postbaseline response assessment. Enrollment continued provided at least one of the first six patients exhibited a response. A sample size of 22 patients per cohort was calculated using the binomial exact method to provide 80% power to demonstrate that the best ORR induced by pembrolizumab exceeded 10% at an overall one-sided 8% α level, if the true best ORR was 35%. For ORR, the point estimate, repeated CI, and adjusted P value for testing whether the RECIST v1.1 response rate was greater than 10% was provided using a truncated sequential probability ratio test. DOR, PFS, and OS were estimated using the Kaplan-Meier method. Efficacy was assessed in all patients who had measurable disease at baseline per RECIST v1.1 and who received at least one dose of pembrolizumab. Safety, analyzed using descriptive statistics, was assessed in all patients who received at least one dose of pembrolizumab. The data cutoff for this analysis was February 20, 2017.

**RESULTS**

**Baseline Patient Characteristics**

Of the 46 patients with cervical cancer who were screened, 39 were PD-L1 positive and 24 were ultimately enrolled in the study.
These 24 patients had a median age of 42 years (range, 26 to 62 years; Table 1). All patients (n = 24; 100%) presented with metastatic disease, which was most frequently located in the lymph nodes (n = 16; 67%), lung (n = 9; 38%), pelvis (n = 9; 38%), and liver (n = 6; 25%). Patients were pretreated, with 92% (n = 22) having received prior radiation therapy and 63% (n = 15) having received two or more lines of chemotherapy for advanced disease. All but one patient had received platinum-based chemotherapy before study start, and 10 of 24 patients (42%) had received prior bevacizumab. All patients discontinued treatment during the study, four (17%) because of AEs, one (4%) because of physician decision, and 19 (79%) because of progressive disease (Fig 1). Among the 24 PD-L1–positive patients enrolled in this cohort, 18 (75%) were PD-L1 positive in the tumor only and six (25%) were positive in the tumor and stroma.

Safety

At the time of the data cutoff, median follow-up duration was 11.0 months (range, 1.3 to 32.2 months). AEs considered related to the study drug (treatment-related AEs) were observed in 18 patients, with only rash (n = 5; 21%) and pyrexia (n = 4; 17%) occurring in ≥ 10% of patients (Table 2). Grade 3 treatment-related AEs were experienced by five patients and included neutropenia, rash, colitis, Guillain-Barré syndrome, and proteinuria. No grade 4 treatment-related AEs were observed, and no treatment-related deaths occurred. Four patients (17%) experienced serious AEs that were considered treatment related, which included one case each of rash (grade 3), colitis (grade 3), Guillain-Barré syndrome (grade 3), and pyrexia (grade 2). Two patients discontinued treatment because of grade 3 treatment-related AEs (colitis and Guillain-Barré syndrome). After discontinuation, the patient with Guillain-Barré syndrome received tegeline and recovered. Immune-mediated AEs were observed in six patients and included rash (n = 2; grade 3), colitis (n = 1; grade 3), Guillain-Barré syndrome (n = 1; grade 3), hyperthyroidism (n = 1; grade 2), and hypothyroidism (n = 1; grade 2).

Antitumor Activity

ORR was 17% (95% CI, 5% to 37%; n = 4) on the basis of RECIST v1.1 by investigator review, with four patients (17%; 95% CI, 5% to 37%) achieving a confirmed PR (Table 3). In these four patients, only rash (n = 5; 21%) and pyrexia (n = 4; 17%) occurring in ≥ 10% of patients (Table 2). Grade 3 treatment-related AEs were experienced by five patients and included neutropenia, rash, colitis, Guillain-Barré syndrome, and proteinuria. No grade 4 treatment-related AEs were observed, and no treatment-related deaths occurred. Four patients (17%) experienced serious AEs that were considered treatment related, which included one case each of rash (grade 3), colitis (grade 3), Guillain-Barré syndrome (grade 3), and pyrexia (grade 2). Two patients discontinued treatment because of grade 3 treatment-related AEs (colitis and Guillain-Barré syndrome). After discontinuation, the patient with Guillain-Barré syndrome received tegeline and recovered. Immune-mediated AEs were observed in six patients and included rash (n = 2; grade 3), colitis (n = 1; grade 3), Guillain-Barré syndrome (n = 1; grade 3), hyperthyroidism (n = 1; grade 2), and hypothyroidism (n = 1; grade 2).

Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (N = 24)</th>
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<tr>
<td>Median age, years (range)</td>
<td>42 (26-62)</td>
</tr>
<tr>
<td>Race</td>
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</tr>
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<td>0</td>
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<td>1</td>
<td>18 (75)</td>
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<tr>
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<tr>
<td>Squamous cell carcinoma</td>
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<td>Adenocarcinoma</td>
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<td>Metastatic stage</td>
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<tr>
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<td>Lung</td>
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<tr>
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<tr>
<td>Liver</td>
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<td>Bone</td>
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<td>Prior lines of therapy for advanced disease</td>
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<td>Prior platinum</td>
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</tr>
<tr>
<td>Prior bevacizumab</td>
<td>10 (42)</td>
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</table>

NOTE: Data presented as No. (%) unless otherwise indicated. Abbreviation: ECOG PS, Eastern Cooperative Oncology Group performance status.
patients, the predominant site of responding disease was the lymph nodes in all four patients (not in a previously radiated field), cervix uteri in one patient (who received prior radiation to the pelvis), and the lungs and liver in one patient. Three patients had SD (13%; 95% CI, 3% to 32%), and 16 patients had progressive disease (67%; 95% CI, 45% to 84%) as best response. Median time to response in the four patients who achieved PR was 1.9 months (range, 1.7 to 8.2 months), and median DOR for responders was 5.4 months (range, 4.1 to 7.5 months; Fig 2A). Two of the four patients achieving PR exhibited a response for over 6 months. Tumor samples from all four patients with PRs had PD-L1 expression in the tumor only.

A decrease in the sum of diameters of target lesions from baseline was observed in 8 (36%) of 22 evaluable patients by computed tomography scan (Fig 2B); these decreases in patients with PRs were maintained over time (Fig 2C). Median PFS in all patients was 2 months (95% CI, 2 to 3 months), and median DOR for responders was 5.4 months (range, 4.1 to 7.5 months; Fig 2A). Two of the four patients achieving PR exhibited a response for over 6 months. Tumor samples from all four patients with PRs had PD-L1 expression in the tumor only.

The results from the phase 1b KEYNOTE-028 trial presented herein suggest that pembrolizumab has promising antitumor activity in PD-L1–positive advanced cervical cancer. The ORR in this population was 17%, with four patients achieving PR and an additional three patients exhibiting SD. Of note, one patient did respond on a previously irradiated site. A median OS of 11 months and a 6-month OS rate of 67% further indicate the potential of pembrolizumab for treating advanced cervical cancer. The safety profile for pembrolizumab was consistent with that seen in other tumor types,6,16 with two patients discontinuing treatment because of grade 3 treatment-related AEs, and no grade 4 treatment-related AEs or treatment-related mortality occurred.

Cisplatin is widely recognized as the primary treatment of patients with advanced cervical cancer, either in combination with radiotherapy or as a first-line option for patients with disease that is not amenable to local treatment.6 However, the efficacy of cisplatin-based regimens is limited, and toxicity remains a concern.8-10 Furthermore, many patients with advanced cervical cancer have previously received cisplatin as treatment of primary disease and may have developed resistance to platinum-based chemotherapy.22 Several single-arm, phase II clinical trials evaluating the treatment of advanced cervical cancer in the second-line setting have been previously conducted by the Gynecologic Oncology Group.7,14 ORRs in these studies ranged from 0% to 19%,23-33 with only three regimens providing an ORR of > 10% (topotecan, vinorelbine, and bevacizumab).24,26,31 In addition, only three regimens (oxaliplatin, cisplatin plus pentoxifylline, and bevacizumab) were associated with 6-month PFS rates of > 20%.23,25,31 Taken together, these findings further support the promising antitumor activity of pembrolizumab in the current study, which was associated with an ORR of 17% and a 6-month PFS rate of 21%.

The most significant shift in the treatment paradigm for advanced cervical cancer has been the recent inclusion of bevacizumab as part of first-line chemotherapy combinations.6 The addition of the antivascular endothelial growth factor antibody to treatment guidelines was based on the results of the Gynecologic Oncology Group 240 trial, in which the addition of bevacizumab to
a standard chemotherapeutic combination significantly improved median OS to 17 months compared with an OS of 13 months with chemotherapy regimens alone. However, increased toxicity was observed with bevacizumab in this trial, with a higher incidence of grade 3 thromboembolism and grade 3 gastrointestinal and genitourinary fistula, which both remain a significant concern for patients and physicians. These results demonstrate the value of nonchemotherapeutic agents in that context, and there remains a need for new alternative agents that are well tolerated and that improve clinical outcomes.

The PD-1–PD-L1 pathway is known to play a significant role in oncogenesis, aiding tumor escape from immunosurveillance by negatively regulating the proliferation and function of tumor-directed T cells. Agents that target the PD-1–PD-L1 axis have been approved for several solid tumor indications, including melanoma, non–small-cell lung cancer, HNSCC, renal cell carcinoma, classic Hodgkin lymphoma, and urothelial carcinoma.

In recent years, interest in the role of the PD-1–PD-L1 pathway in the development of virally driven cancers has been growing. In HNSCC, PD-L1 expression is thought to play a role in the initiation and persistence of HPV infection by providing an immune-privileged site where T-cell activity is downregulated. PD-L1 is also highly expressed within HPV-positive HNSCC tumors. Because virtually all cervical cancers are associated with HPV infection, the role of the PD-1–PD-L1 pathway in HPV-driven tumorigenesis is of particular interest within this indication. Although an association between HPV infection and PD-L1 expression in cervical tumor cells has previously been identified, additional investigation is required to elucidate the specific contribution of the PD-1–PD-L1 pathway to HPV-driven cervical tumorigenesis.
results of the phase I/II study of nivolumab in patients with virus-associated tumors (CheckMate 358) have been presented for the recurrent or metastatic cervical, vaginal, and vulvar cancers cohort. PD-L1 expression was not mandatory for inclusion and was known in less than 50% of patients. In a cohort of 19 patients with cervical cancer, the ORR was 26% (95% CI, 9% to 51%). Of note, fewer patients in this population had prior treatment: 30% of patients were receiving front-line treatment for advanced disease, and only 29% of patients had received two lines or more of treatment, compared with 63% of patients in our study who received two or more lines of treatment. Other PD-1–PD-L1 inhibitors, such as atezolizumab (ClinicalTrials.gov identifier: NCT02921269), durvalumab (ClinicalTrials.gov identifiers: NCT02291055, NCT01975831, NCT02725489), and nivolumab (ClinicalTrials.gov identifier: NCT02257528), are currently being investigated for the treatment of cervical cancer.

In conclusion, results from this analysis of the phase Ib KEYNOTE-028 trial suggest that pembrolizumab is well tolerated and has durable antitumor activity in patients with PD-L1–positive advanced cervical cancer. The safety and clinical benefit of pembrolizumab in advanced cervical cancer is currently under investigation in the open-label, phase II, multicohort KEYNOTE-158 trial (ClinicalTrials.gov identifier: NCT02628067). Additionally, the predictive value of PD-L1 immunohistochemistry, as well as other biomarkers, is being assessed, with enrollment of patients with PD-L1–positive as well as PD-L1–negative tumors, and will provide additional analyses of the role of PD-L1 expression in cervical cancer.

References


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Author contributions

Conception and design: Patrick A. Ott

Provision of study materials or patients: Jean-Sebastien Frenel, Christophe Le Tourneau, Bert O’Neil, Sarina A. Piha-Paul, Hope S. Rugo

Collection and assembly of data: Jean-Sebastien Frenel, Bert O’Neil, Patrick A. Ott, Sarina A. Piha-Paul, Carlos Gomez-Roca, Emilie M.J. van Brummelen, Sanatan Saraf, Reshma Rangwala

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors
Efficacy of Pembrolizumab in PD-L1–Positive Cervical Cancers

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Affiliations
Jean-Sebastien Frenel, Institut de Canerologie de l’Ouest, Centre René Gauducheau, Saint-Herblain; Christophe Le Tourneau, Institut Curie, Paris and Saint-Cloud, and Institut National de la Santé et de la Recherche Médicale U900 Research Unit, Saint-Cloud; Carlos Gomez-Roca, Institut Claudius Regaud, Toulouse; Andrea Varga, Gustave Roussy, Villejuif, France; Bert O’Neil, Indiana University Health University Hospital, Indianapolis, IN; Patrick A. Ott, Dana-Farber Cancer Institute, Boston, MA; Sarina A. Piha-Paul, The University of Texas MD Anderson Cancer Center, Houston, TX; Emilie M.J. van布鲁门, The Netherlands Cancer Institute, Amsterdam, Netherlands; Hope S. Rugo, University of California, San Francisco, San Francisco, CA; and Shari Thomas, Sanatan Saraf, and Reshma Rangwala, Merck & Co., Inc., Kenilworth, NJ.

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Jean-Sebastien Frenel
Consulting or Advisory Role: Pfizer, Roche, Eli Lilly, AstraZeneca
Travel, Accommodations, Expenses: Roche, Pfizer

Christophe Le Tourneau
Honoraria: Merck Sharp & Dohme
Consulting or Advisory Role: Merck Sharp & Dohme

Bert O’Neil
Honoraria: Bayer
Consulting or Advisory Role: Amgen, Genentech/Roche, Bayer
Travel, Accommodations, Expenses: Merck KGaA, Bayer

Patrick A. Ott
Consulting or Advisory Role: Amgen, Bristol-Myers Squibb, Alexion Pharmaceuticals, CytomX Therapeutics, Celldex, Genentech, Neon Therapeutics
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Sarina A. Piha-Paul
Consulting or Advisory Role: Genentech,
Research Funding: GlaxoSmithKline, XuanZhu, Puma Biotechnology, Novartis, Merck Sharp & Dohme, Curis, Principia Biopharma, Biomarin, Helix BioPharma, Bayer, Abbvie, Incyte, Five Prime Therapeutics, Cerulean Pharma, MedImmune, Medivation

Carlos Gomez-Roca
Consulting or Advisory Role: Bristol-Myers Squibb, Novartis, AstraZeneca
Travel, Accommodations, Expenses: Bristol-Myers Squibb

Emilie M.J. van Brummelen
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Hope S. Rugo
Honoraria: Biotheranostics
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Shari Thomas
Employment: Merck

Sanatan Saraf
Employment: Merck

Reshma Rangwala
Employment: Genmab A/S
Stock or Other Ownership: Merck
Travel, Accommodations, Expenses: Genmab A/S

Andrea Varga
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