Prognostic Significance of Liver Metastasis in Durvalumab-Treated Lung Cancer Patients

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Abstract

The prognostic value of baseline liver metastases (LMs) was evaluated in 569 patients with advanced/metastatic non–small-cell lung cancer receiving the programmed cell death ligand 1 (PD-L1) inhibitor durvalumab. LMs were an independent negative prognostic factor for survival and were associated with significantly lower objective response rates. However, PD-L1 as an independent factor predicted benefit from durvalumab.

Introduction: Two clinical studies (Study 1108 and ATLANTIC) were analyzed to evaluate the prognostic value of baseline liver metastases (LMs) in advanced/metastatic non–small-cell lung cancer patients treated with durvalumab 10 mg/kg every 2 weeks. Patients and Methods: A multivariate Cox proportional hazards analysis was conducted; covariates included performance status, tumor stage, histology, sex, age, smoking status, and programmed cell death ligand 1 (PD-L1) status. Results: In all, 569 patients were included. LMs were present in 31.6% (96/304) of Study 1108 patients and 17.9% (47/263) of ATLANTIC patients. Median overall survival (OS) was shorter in patients with LMs than in those without in both studies. In both studies, LMs were an independent negative prognostic factor for OS and progression-free survival. Objective response rates were also significantly lower. PD-L1 independently predicted benefit across all patients. Conclusion: Liver metastases were associated with worse outcomes irrespective of PD-L1 status, but PD-L1 status predicted benefit from durvalumab irrespective of LMs.

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Keywords: Immunotherapy, PD-L1, Prognosis, Response rate, Survival

Introduction

Liver metastasis at the time of diagnosis or before starting chemotherapy is associated with a poor prognosis in various tumor types, including lung cancer.1-3 In a large retrospective analysis, single-site metastasis to the brain or bone was associated with a median overall survival (OS) of 5 to 7 months compared with 3 months for liver metastasis (P < .001) in patients with adenocarcinoma or squamous cell carcinoma.1 For multiple metastases, those in the liver have been associated with shorter median OS than those in other organs or tissues in patients with adenocarcinoma or small-cell lung cancer.1 In a separate analysis of 1542 patients with metastatic non–small-cell lung cancer (NSCLC), 13% had liver metastases (LMs), and a Cox proportional hazards model showed that liver and adrenal gland metastases were unfavorable prognostic factors for survival. Median OS was 3.8 months in patients with LMs (LM+) and 8.7 months in patients without (P < .001).3
Liver Metastasis in Durvalumab-Treated Lung Cancer

Immune checkpoint inhibitors that disrupt the programmed cell death 1 (PD-1)/programmed cell death ligand 1 (PD-L1) signaling pathway via blockade of PD-1 (eg, nivolumab, pembrolizumab) or PD-L1 (eg, atezolizumab) have been shown to improve OS compared with conventional chemotherapy in patients with advanced lung cancer. However, benefit from these therapies is not universal. Baseline expression of PD-L1 on tumor, stromal, or immune cells within the tumor microenvironment might be an important biomarker to predict outcome with these agents. In addition, other immune, genomic, and clinical factors might contribute determinants of their efficacy. Several reports have shown that LMs are associated with poor clinical outcomes in patients with melanoma, lung cancer, and bladder cancer who are receiving anti–PD-1/PD-1 therapies.

Durvalumab is a selective, high-affinity, engineered human immunoglobulin G1 kappa monoclonal antibody that blocks PD-L1 binding to PD-1 and CD80. Durvalumab monotherapy has shown encouraging antitumor activity in NSCLC. In advanced NSCLC, patients with higher tumor PD-L1 expression had a higher objective response rate (ORR) and longer OS compared with patients with lower or negative PD-L1 expression. Durvalumab has been approved in the United States by the Food and Drug Administration for post-platinum treatment locally advanced or metastatic urothelial carcinoma and unresectable, stage III NSCLC.

A recent analysis of several studies showed that liver metastasis was associated with a reduced response rate and shortened progression-free survival (PFS) in patients with advanced NSCLC or melanoma who are receiving pembrolizumab. In the melanoma patients, PD-L1 expression at the invasive tumor margin did not differ significantly between patients with and without LMs (not reported in the NSCLC patients). Herein we report a retrospective analysis of 2 clinical studies of durvalumab in NSCLC (Study 1108 [NCT01693562] and ATLANTIC [NCT02087423]) to evaluate the effect of LMs on clinical outcomes, and the association of this effect with tumor PD-L1 expression status.

Patients and Methods

Patients and Study Design

The analyses were based on data from 2 independent clinical studies. All patients received durvalumab 10 mg/kg every 2 weeks for up to 12 months or until unacceptable toxicity or disease progression.

Study 1108 was a phase I/II, multicenter, open-label, dose-escalation and dose-expansion study in patients with advanced solid tumors, including NSCLC. Eligible patients with NSCLC had confirmed stage IIIb/IV disease and had progressed during, been ineligible for, or refused any number of previous therapies. Patients had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1, adequate organ and hematologic functions, and fresh tumor biopsy and/or archival tumor tissue available for PD-L1 testing. Initially, NSCLC patients were enrolled regardless of PD-L1 status. Subsequent enrollment was enriched for patients with PD-L1 ≥ 25% expression in tumor cells (TCs) assessed using immunohistochemistry using the VENTANA PD-L1 (SP263) Assay (Ventana Medical Systems, Tucson, AZ). Key exclusion criteria were active autoimmune disease or inflammatory bowel disease, previous severe or persistent immune-related adverse events, previous exposure to anti–PD-1/PD-L1 therapy, requirement for > 10 mg/d of prednisone or equivalent, and untreated central nervous system metastases. Tumor tissue from Study 1108 was prospectively tested for epidermal growth factor receptor (EGFR) mutations (EGFR+) and anaplastic lymphoma kinase (ALK) rearrangements (ALK+), however, patients harboring mutations in EGFR or ALK were not excluded from this analysis. Approximately 9% of patients from this study (26/301) harbored EGFR mutations, whereas < 1% (3/301) harbored ALK rearrangements.

The ATLANTIC trial was a phase II, noncomparative, open-label, multicenter study in patients with locally advanced/metastatic NSCLC (stage IIIb/IV) who had received ≥ 2 previous systemic treatment regimens, including 1 platinum-based chemotherapy regimen. Eligible patients had a World Health Organization (WHO) PS of 0 or 1, adequate organ and hematologic functions, and fresh tumor biopsy and/or archival tumor tissue available for PD-L1 testing. Patients were originally included regardless of tumor PD-L1 expression status. Subsequently, a protocol amendment was implemented to include only patients with PD-L1 ≥ 25% TC expression. Key exclusion criteria were previous exposure to any anti–PD-1/PD-L1 antibody, active or previous documented autoimmune disease, any previous Grade ≥ 3 immune-related adverse events, brain metastases, or spinal cord compression, and current or previous use of immunosuppressive medication within 28 days of durvalumab dosing (except for intranasal and inhaled corticosteroids or systemic corticosteroids at physiological doses, which were not to exceed 10 mg/d of prednisone, or an equivalent corticosteroid). Tumor tissue was prospectively tested for EGFR+ and ALK+. Only ATLANTIC patients with EGFR/ALK wild type or unknown tumor status were included in the current analysis.

All patients provided written informed consent, and studies were conducted in accordance with the principles of the Declaration of Helsinki. The institutional review board of each participating institution reviewed the study protocols before implementation.

Statistical Analysis

Survival analysis was performed to determine differences in OS and PFS between patients with and without LMs, further stratified according to PD-L1 TC expression (≥ 25% or < 25% of cells immunostaining for PD-L1 at any intensity). Statistically significant differences in Kaplan–Meier curves for OS and PFS in patients with/without LMs were determined using a log rank test. Median OS and PFS were determined for all patient subgroups (defined on the basis of LMs and PD-L1 status). Multivariate Cox proportional hazards analysis was conducted for PFS and OS (first among patients with/without LMs, then among patients with/without LMs and with PD-L1 ≥ 25% or < 25% TC expression) to determine the association of LMs, PD-L1 status, and other clinical factors with outcomes. Hazards analysis included ECOG/WHO PS, lung tumor stage, histology, sex, age, smoking status, and PD-L1 status as covariates. Binomial tests were used to compare ORR across patient groups.

Data underlying the findings described in this article may be obtained in accordance with AstraZeneca’s data-sharing policy.
Results

Patient Characteristics

As of the data cutoff dates (October 24, 2016 for Study 1108 and June 3, 2016 for ATLANTIC), 304 NSCLC patients were enrolled in Study 1108, most of whom were previously treated, and 265 previously treated NSCLC patients were enrolled in ATLANTIC, of whom 263 were assessed for the presence of LMs. Median duration of follow-up was 27 months in Study 1108 and 17 months in ATLANTIC. LMs were present at baseline in 96/304 patients (31.6%) in Study 1108 and 47/263 patients (17.9%) in ATLANTIC (LMs were not assessed in 2 patients). Baseline characteristics were well balanced between patients with/without LMs and between patients from Study 1108 and ATLANTIC, with the exception of lung histology (Table 1). Study 1108 enrolled a nearly equal proportion of patients with nonsquamous and squamous cell carcinoma, whereas ATLANTIC enrolled more patients with nonsquamous cell carcinoma. Most lung cancer patients in both studies had an ECOG/WHO PS of 1, although more LM+ patients had a PS of 1 in Study 1108 than in ATLANTIC (84.4% [81/304] vs. 61.7% [204/330]). Most patients in both studies had stage IV disease, were current or former smokers, and had known PD-L1 status (a slight majority of patients with PD-L1 ≥ 25% TC expression).

Efficacy Outcomes

The presence of LMs (unadjusted for other prognostic factors) was associated with significantly shorter survival (Figure 1A and B), irrespective of PD-L1 expression status (Figure 1C and D). In Study 1108, median OS was 5.5 months in LM+ patients compared with 16.7 months in patients without LMs (LM−), with an unadjusted hazard ratio (HR) of 2.13 (95% confidence interval [CI], 1.56-2.90; \( P < .0001 \); Figure 1A). In ATLANTIC, median OS in patients with and without LMs was 5.0 and 10.2 months, respectively (unadjusted HR, 1.83; 95% CI, 1.28-2.62; \( P < .005 \); Figure 1B).

A Cox proportional hazards model showed that the presence of LMs was an independent negative prognostic factor for OS and PFS in both studies after adjustment for other baseline prognostic factors and PD-L1 expression (Table 2, Figures 2 and 3). In Study 1108, LM+ patients had a 91% increased relative risk of death (\( P = .0001 \)) and a 52% increased relative risk of disease progression or death (\( P = .004 \)) compared with LM− patients. Increases in the relative risk of death (adjusted HR, 2.2; \( P < .0001 \)) and disease

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Study 1108 Patients, n (%)</th>
<th>ATLANTIC Patients, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥70</td>
<td>31 (32.3)</td>
<td>10 (21.3)</td>
</tr>
<tr>
<td>&lt;70</td>
<td>65 (67.7)</td>
<td>143 (68.8)</td>
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<tr>
<td>Sex</td>
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<td></td>
</tr>
<tr>
<td>Male</td>
<td>54 (56.3)</td>
<td>28 (69.6)</td>
</tr>
<tr>
<td>Female</td>
<td>42 (43.8)</td>
<td>19 (40.4)</td>
</tr>
<tr>
<td>ECOG/WHO PS</td>
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<td></td>
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<tr>
<td>0</td>
<td>15 (15.6)</td>
<td>18 (38.3)</td>
</tr>
<tr>
<td>1</td>
<td>81 (84.4)</td>
<td>148 (71.2)</td>
</tr>
<tr>
<td>NR</td>
<td>0</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Lung Tumor Type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonsquamous</td>
<td>47 (49.0)</td>
<td>36 (76.6)</td>
</tr>
<tr>
<td>Squamous</td>
<td>49 (51.0)</td>
<td>11 (23.4)</td>
</tr>
<tr>
<td>Tumor Stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤III</td>
<td>5 (5.2)</td>
<td>3 (6.4)</td>
</tr>
<tr>
<td>IV</td>
<td>91 (94.8)</td>
<td>182 (87.5)</td>
</tr>
<tr>
<td>NR</td>
<td>0</td>
<td>5 (10.6)</td>
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<tr>
<td>Smoking Status</td>
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<tr>
<td>Ever (smoker)</td>
<td>82 (85.4)</td>
<td>176 (84.6)</td>
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<tr>
<td>Never (non-smoker)</td>
<td>14 (14.6)</td>
<td>32 (15.4)</td>
</tr>
<tr>
<td>PD-L1 Status</td>
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<td></td>
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<tr>
<td>&lt;25% TC</td>
<td>39 (40.6)</td>
<td>16 (16.0)</td>
</tr>
<tr>
<td>≥25% TC</td>
<td>53 (55.2)</td>
<td>29 (61.7)</td>
</tr>
<tr>
<td>NR</td>
<td>4 (4.2)</td>
<td>2 (4.3)</td>
</tr>
</tbody>
</table>

Abbreviations: ECOG = Eastern Cooperative Oncology Group; LM+ = liver metastases present; LM− = liver metastases absent; NR = not reported; PD-L1 = programmed cell death ligand 1; PS = performance status; TC = tumor cell; WHO = World Health Organization.

Table 1 Baseline Characteristics Stratified According to the Presence or Absence of Liver Metastases
progression or death (adjusted HR, 1.92; \( P = .0005 \)) were also observed in LM+ patients in ATLANTIC. In both studies, the adverse prognostic significance of LMs was similar to that of ECOG/WHO PS (Figure 2).

In Study 1108 and ATLANTIC, LM+ patients had worse OS and PFS regardless of PD-L1 status (Table 2, Figures 2 and 3). However, PD-L1 expression \( \geq 25\% \) in TCs remained associated with a better outcome for OS in Study 1108 (adjusted HR, 0.63; \( P < .01 \)) and ATLANTIC (adjusted HR, 0.60; \( P < .01 \)) independent of LMs (Figure 2). Therefore, even after adjusting for the presence of LMs, PD-L1 expression \( \geq 25\% \) in TCs remained an independent predictor of improved survival in patients treated with durvalumab. No correlation was observed between higher PD-L1 expression and LMs in either Study 1108 (\( P = .986 \)) or ATLANTIC (\( P = .788 \)).

The ORR was significantly lower in LM+ patients than in LM− patients (Table 2). In Study 1108, the respective ORRs were 11.5% (11/96; 95% CI, 5.9-19.6) and 20.2% (42/208; 95% CI, 15.0-26.1; \( P < .001 \)). In ATLANTIC, 35 patients did not have a response evaluation and 2 patients did not have the presence of LMs assessed; hence, the analysis included 228 patients. The respective ORRs in the LM+ and LM− patients were 10.0% (4/40; 95% CI, 2.8-23.7) and 14.9% (28/188; 95% CI, 10.1-20.8; \( P < .001 \)). In both studies, ORR was highest in the PD-L1 \( \geq 25\% \) expression in TCs/LM− and PD-L1 \( \geq 25\% \) expression in TCs/LM+ patients (Table 2).

**Discussion**

In this retrospective analysis of Study 1108 and ATLANTIC, LMs were associated with shorter OS and PFS and lower ORR irrespective of PD-L1 status in NSCLC patients treated with durvalumab. The adverse prognostic significance of LMs was similar to that of ECOG/WHO PS in both studies. Other covariates had less consistent effects in the Cox proportional hazards model. However, PD-L1 expression remained a significant independent factor predicting benefit from durvalumab across all patients in both cohorts. Patients with PD-L1 \( \geq 25\% \) expression in TCs had significantly improved outcomes, consistent with reports of other anti-PD-1/PD-L1 agents.
Despite the adverse prognostic effect of LMs, durvalumab had promising activity in the subgroup of LM+ patients and PD-L1 ≥ 25% expression in TCs. Strikingly similar outcomes were observed between the 2 studies with respect to the effect of LMs on treatment outcomes in patients with NSCLC.

To our knowledge, this is the largest reported series on the effect of PD-1/PD-L1 blockade in patients with and without LMs from lung cancer. Data are consistent with recent reports showing that LMs are associated with poor outcomes in patients with melanoma,12,13 lung cancer,11,13 and bladder cancer14 treated with anti–PD-1/PD-L1 therapies. Our study adds to the body of evidence, focused on PD-L1 inhibition, with confirmatory OS data and a unique analysis stratified according to PD-L1 expression.

Anti–PD-1/PD-L1 agents have improved OS compared with standard chemotherapy in patients with NSCLC,4,5 but OS remains poor in LM+ patients. Median OS with durvalumab ranges from 4 to 5 months in such patients, which is consistent with the OS reported in lung cancer LM+ patients treated with other anti–PD-1/PD-L1 agents11 and with standard therapy. In contrast, median OS in LM− patients treated with durvalumab (median, 10-17 months) appears to be longer than that typically achieved with chemotherapy, on the basis of historical comparisons.1,17 A recent study also confirmed this finding, by showing that in LM+ patients, OS benefit was greater with nivolumab than with docetaxel treatment.21 Although a similar OS benefit was observed in LM− patients, the investigators noted that LM+ patients tended to have worse prognosis than the overall study population.

These data suggest that the presence of LMs has notable effects on PFS, OS, and ORR in clinical studies of anti–PD-1/PD-L1 therapies, and this should be a consideration when designing randomized trials. For example, in a recent phase III trial of nivolumab in patients with previously untreated advanced NSCLC with PD-L1 expression ≥ 5% (CheckMate 026), nivolumab was not associated with significantly longer PFS than chemotherapy. The authors suggested that imbalances in the baseline characteristics of the patients, including a smaller proportion of LM+ patients in the chemotherapy arm (13% vs. 20% in the nivolumab arm), could potentially have contributed to this outcome.22

### Table 2  Adjusted Overall Survival and Progression-Free Survival, and ORR According to Liver Metastases and PD-L1 Status/Liver Metastases

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Study 1108</th>
<th>ATLANTIC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n for Survival</td>
<td>OS, Adjusted HR; P Value</td>
</tr>
<tr>
<td>LM−</td>
<td>208</td>
<td>vs. LM−</td>
</tr>
<tr>
<td>LM+</td>
<td>96</td>
<td>1.91; .0001</td>
</tr>
<tr>
<td>PD-L1 &lt;25% TC/LM−</td>
<td>39</td>
<td>n3</td>
</tr>
<tr>
<td>PD-L1 ≥25% TC/LM−</td>
<td>53</td>
<td>0.69; .16</td>
</tr>
<tr>
<td>PD-L1 &lt;25% TC/LM−</td>
<td>81</td>
<td>0.56; .014</td>
</tr>
<tr>
<td>PD-L1 ≥25% TC/LM−</td>
<td>112</td>
<td>0.34; &lt;.0001</td>
</tr>
</tbody>
</table>

Abbreviations: HR = hazard ratio; IHC = immunohistochemistry; LM = liver metastases; LM+ = liver metastases present; LM− = liver metastases absent; OS = overall survival; PD-L1 = programmed cell death ligand 1; PFS = progression-free survival; TC = tumor cell.

*PD-L1 status (determined from IHC) was unavailable for 19 patients in Study 1108; hence, the PD-L1/LM analysis included 285 patients for survival and ORR.

*P values are from binomial test measuring difference from random chance.

*Thirty-five patients did not have a response evaluation and 2 patients did not have the presence of liver metastases assessed in ATLANTIC; hence, the LM analysis included 228 patients for ORR.

*PD-L1 status (determined from IHC) was unavailable for 21 patients in ATLANTIC; hence, the PD-L1/LM analysis included 242 patients for survival.

The PD-L1/LM analysis included 206 patients for ORR, who had PD-L1 status, LM, and response measured.
In a recent multistudy analysis it was reported that the limited activity of pembrolizumab in melanoma LMþ patients might be related to reduced CD8(+) T-cell density at the invasive tumor margin, potentially as a result of liver-induced systemic immune tolerance, suggesting a possible mechanism for why LMþ patients do not respond as well to anti-PD-1/PD-L1 therapies. Additional studies support this concept of liver-induced immune tolerance and the immunosuppressive environment of the liver. For example, a small pilot clinical study reported minimal toxicity after the infusion of T cells stimulated with interleukin-2 and autologous TCs into the liver through the hepatic artery. In addition, eicosanoid-deficient mice with implanted Lewis lung carcinoma cells have been shown to have increased LMs alongside decreased numbers of CD8 T cells compared with wild type controls. An older study profiled dendritic cells (DCs) from the liver and peripheral blood of surgical specimens. When both sets of DCs were stimulated with toll-like receptor 4, the peripheral blood DCs secreted proinflammatory cytokines whereas liver DCs secreted interleukin-10. This suggests that the difference in cytotoxic T-cell content in the liver might be directed by DCs.

The current analysis provides important insights but must be interpreted cautiously. Although it is on the basis of a large number of patients, it is retrospective; the 2 studies were noncomparative, and visceral metastasis was not a selection criterion in either study, which led to a small number of LM+ patients. Other potential limitations include imbalances between the 2 studies such as the
higher proportion of patients with nonsquamous disease in ATLANTIC, and the higher proportion of LM+ patients (and the higher proportion of patients with an ECOG/WHO PS of 1) in Study 1108. Although this analysis revealed a link between presence of LMs and poor outcomes, it is unclear whether burden of LMs, either quantified according to size or number of metastatic lesions, would affect the association with patient outcomes. Additional information on burden of LMs in prospective studies can be used to assess this. One of the strengths of our analysis is that the Cox proportional hazards model adjusted for other baseline prognostic factors such as PS, age, and tumor stage/histology, in addition to PD-L1 expression.

Conclusion

Our observations are consistent with previous reports indicating poor outcomes with anti–PD-1/PD-L1 therapy in patients with LMs secondary to lung cancer. Patient stratification on the basis of LMs might be warranted in clinical trials evaluating novel treatments, including anti–PD-1/PD-L1 agents. These findings require confirmation in a prospective, randomized trial.

Clinical Practice Points

- Liver metastases at baseline were associated with shorter survival in 2 studies of patients with advanced/metastatic NSCLC receiving the anti–PD-L1 antibody durvalumab, irrespective of tumoral PD-L1 expression.
- Patients with LMs in both studies also had significantly lower ORRs compared with LM− patients. These findings are consistent with previous observations with anti-PD-1/PD-L1 therapies.
- Tumoral PD-L1 expression was a significant independent factor in predicting benefit from durvalumab treatment in patients across both trials.
- Patient stratification on the basis of LMs might be warranted in clinical trials evaluating novel treatments, including anti–PD-1/PD-L1 agents.

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Disclosure

S. Sridhar, C. Morehouse, Y. Zheng, R. Narwal, B.W. Higgs, P.A. Dennis, J. Ye, and P. Mukhopadhyay are employees of AstraZeneca and stockholders of AstraZeneca. L. Paz-Ares has
Liver Metastasis in Durvalumab-Treated Lung Cancer

participated in advisory boards for Lilly, Roche, Merck Sharp & Dohme, Bristol-Myers Squibb, Celgene, Pfizer, Boehringer-Ingelheim, and Bayer. K. Shen, H. Liu, and K. Ranade are former employees of AstraZeneca. N. Rizvi has served in a leadership role and owned stock in Gritstone Oncology, has received research funding from Roche/Genentech, Merck, AstraZeneca, and Bristol-Myers Squibb, and has acted as a consultant for Bristol-Myers Squibb, Roche/Genentech, AstraZeneca, Merck, and Pfizer. X. Jin is a former employee and stockholder of AstraZeneca. A. Gupta is an employee of AstraZeneca and stockholder of AstraZeneca and Bristol-Myers Squibb.

References