Tislelizumab Versus Chemotherapy as Second-Line Treatment for Advanced or Metastatic Esophageal Squamous Cell Carcinoma (RATIONALE-302): A Randomized Phase III Study

Lin Shen, MD, PhD; Ken Kato, MD, PhD; Sung-Bae Kim, MD, PhD; Jaffer A. Ajani, MD, PhD; Kuaile Zhao, MD; Zhiyong He, MD; Xinmin Yu, MD; Yongqian Shu, MD; Qi Luo, MD; Jufeng Wang, MD, PhD; Zhedong Chen, MD; Zuoxing Niu, MD; Longzhen Zhang, MD; Tienan Yi, MD; Jing-Mu Sun, MD, PhD; Jianhua Chen, MD, PhD; Guohua Yu, MD; Chen-Yuan Lin, MD, PhD; Hiroki Hara, MD; Bing Li, MD; Taroh Satoh, MD; Roberto Pazo-Cid, MD; Hendrick-Tobias Arkenau, MD, PhD; Christophe Borg, MD, PhD; Florian Lordick, MD, PhD; Liyun Li, MD; Ningning Ding, MD; Aiyang Tao, PhD; Jingwen Shi, PhD; and Eric Van Cutsem, MD, PhD; for the RATIONALE-302 Investigators

abstract

PURPOSE Patients with advanced or metastatic esophageal squamous cell carcinoma (ESCC) have poor prognosis. For these patients, treatment options are limited after first-line systemic therapy.

PATIENTS AND METHODS In this open-label phase III clinical study, patients with advanced or metastatic ESCC, whose tumor progressed after first-line systemic treatment, were randomly assigned (1:1) to receive intravenous tislelizumab, an anti–programmed cell death protein 1 antibody, 200 mg every 3 weeks or chemotherapy (investigator’s choice of paclitaxel, docetaxel, or irinotecan). The primary end point was overall survival (OS) in all patients. The key secondary end point was OS in patients with programmed death-ligand 1 tumor area positivity (TAP) score $\geq 10\%$.

RESULTS In total, 512 patients across 11 countries/regions were randomly assigned. At final analysis, conducted after 410 death events occurred, OS was significantly longer with tislelizumab versus chemotherapy in all patients (median, 8.6 v 6.3 months; hazard ratio [HR], 0.70 [95% CI, 0.57 to 0.85]; one-sided $P = .0001$), and in patients with TAP $\geq 10\%$ (median, 10.3 months v 6.8 months; HR, 0.54 [95% CI, 0.36 to 0.79]; one-sided $P = .0006$). Survival benefit was consistently observed across all predefined subgroups, including those defined by baseline TAP score, region, and race. Treatment with tislelizumab was associated with higher objective response rate (20.3% v 9.8%) and a more durable antitumor response (median, 7.1 months v 4.0 months) versus chemotherapy in all patients. Fewer patients experienced grade 3 treatment-related adverse events (18.8% v 55.8%) with tislelizumab versus chemotherapy.

CONCLUSION Tislelizumab significantly improved OS compared with chemotherapy as second-line therapy in patients with advanced or metastatic ESCC, with a tolerable safety profile. Patients with programmed death-ligand 1 TAP $\geq 10\%$ also demonstrated statistically significant survival benefit with tislelizumab versus chemotherapy.

J Clin Oncol 40:3065-3076. © 2022 by American Society of Clinical Oncology

INTRODUCTION

In 2020, esophageal cancer (EC) was ranked the seventh most common cancer worldwide and sixth most common cause of cancer-related deaths.1 Esophageal squamous cell carcinoma (ESCC) is the most common histologic subtype, accounting for more than 85% of ECs worldwide.2,3 Reports from the SEER Program show that between 2011 and 2017, the prognosis of metastatic ESCC was poor, with a 5-year survival rate of 5.2%.4 First-line systemic therapy for advanced or metastatic ESCC typically consists of a fluoropyrimidine- and platinum-based regimen.5-7 In the second-line setting, single-agent taxane or irinotecan is typically used; however, these are associated with significant toxicities and marginal antitumor activity with poor long-term survival.8-12 Recently, trials studying the programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) pathway have demonstrated prolonged survival and safety benefits with anti–PD-1 antibodies versus...
**CONTEXT**

**Key Objective**
Esophageal squamous cell carcinoma (ESCC) is an aggressive cancer associated with a 5-year survival rate of 5%. The phase III RATIONALE-302 study that enrolled a global population of 512 patients with advanced or metastatic ESCC evaluated whether tislelizumab monotherapy improved overall survival versus chemotherapy when used as second-line treatment for patients with advanced or metastatic ESCC.

**Knowledge Generated**
Tislelizumab demonstrated statistically significant and clinically meaningful improvement in overall survival versus chemotherapy, with a tolerable safety profile, in patients with advanced or metastatic ESCC in a global population in second-line treatment. In patients with programmed death-ligand 1 tumor area positivity ≥ 10%, tislelizumab also demonstrated statistically significant survival benefit. Survival benefit of tislelizumab over chemotherapy was observed across subgroups of region, race, and programmed death-ligand 1 expression level.

**Relevance**
The results of RATIONALE-302 suggest that tislelizumab is an appropriate treatment option for patients with advanced or metastatic ESCC in second-line treatment setting.

chemotherapy in patients with advanced or metastatic ESCC whose disease progressed after first-line systemic therapy.10-13 These studies demonstrated survival benefit specifically in patients with high PD-L1 expression, or in Asian or Chinese patients irrespective of PD-L1 expression level.10-12

Tislelizumab is an investigational humanized immunoglobulin G4 monoclonal antibody with high affinity for PD-1, designed to minimize binding to FcγR on macrophages to limit antibody-dependent phagocytosis, a potential mechanism of resistance to anti–PD-1 therapy.14 In early-phase clinical studies, tislelizumab monotherapy or in combination with chemotherapy demonstrated antitumor activity in patients with solid tumors, including ECs, and showed a safety profile similar to other anti–PD-1 antibodies.15-17

Here, we report the efficacy and safety results from the global, randomized phase III RATIONALE-302 study (ClinicalTrials.gov identifier: NCT03430843) of tislelizumab versus chemotherapy as second-line treatment for advanced or metastatic ESCC.

**PATIENTS AND METHODS**

**Patients**
Eligible patients were adults (age ≥ 18 years) with histologically confirmed ESCC who had advanced or metastatic disease that progressed after first-line systemic treatment. Patients who had tumor progression within 6 months after definitive chemoradiotherapy, neoadjuvant, or adjuvant therapy were also eligible. Patients were required to have an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1, at least one measurable/evaluable lesion by RECIST v1.1, and adequate hematologic, hepatic, renal, and coagulation function. Exclusion criteria included patients who had received prior therapies targeting PD-1 or PD-L1, active brain or leptomeningeal metastasis, active autoimmune disease, or other prior malignancies active within 2 years before random assignment. Full eligibility criteria are provided in the Data Supplement (online only).

The Protocol (online only) was approved by the relevant Institutional Review Board/Independent Ethics Committee for each study site. The full Protocol is available with the Data Supplement. The study was carried out in accordance with the International Conference on Harmonisation Good Clinical Practice Guideline, the principles of the Declaration of Helsinki, and local laws and regulations. All patients provided written informed consent before participation.

**Trial Design and Treatment**
This open-label, randomized, active-controlled, multicenter, phase III clinical study recruited patients across 11 countries/regions (Belgium, mainland China, France, Germany, Italy, Japan, Republic of Korea, Spain, Taiwan, the United Kingdom, and the United States). Eligible patients were randomly assigned (1:1) to receive tislelizumab or investigator’s choice of the following single-agent chemotherapies: paclitaxel, docetaxel, or irinotecan. Tislelizumab was administered intravenously (IV) 200 mg once every three weeks. Paclitaxel was administered as 135-175 mg/m² IV once every 3 weeks, or in doses of 80-100 mg/m² once weekly as per regional guidelines. In Japan, paclitaxel was administered as 100 mg/m² IV in cycles consisting of once weekly dosing for 6 weeks, followed by one week of rest. Docetaxel was administered as 75 mg/m² IV once every 3 weeks (70 mg/m² IV once every 3 weeks in Japan). Irinotecan 125 mg/m² IV was administered on days 1 and 8, every 21 days. Stratified randomization was used and was stratified by region (Asia [excluding Japan] v Japan v Europe/North America), ECOG PS (0 v 1), and investigator-chosen chemotherapy (paclitaxel v...
docetaxel v irinotecan). Patients were treated until disease progression, unacceptable toxicity, or withdrawal for other reasons. At the discretion of the investigator, patients receiving tislelizumab could continue to receive treatment after progression if the patient was likely to benefit from continued treatment, provided that the patient provided written informed consent. Details of random assignment and tumor response assessment methods are described in the Data Supplement.

Assessments

PD-L1 expression was centrally assessed using the analytically validated VENTANA PD-L1 (SP263) assay with tumor area positivity (TAP) score, which is defined as the total percentage of the tumor area covered by tumor cells with any membrane staining above background and tumor-associated immune cells with any staining above background. Patients with PD-L1-positive expression were defined as having a TAP score of $\geq 10\%$. Tumor responses were assessed using computed tomography or magnetic resonance imaging, every 6 weeks for 6 months, and then every 9 weeks, by the investigator per RECIST v1.1. Adverse events (AEs) were assessed throughout the study and up to 30 days after the last dose of study drug or initiation of a new anticancer therapy, whichever occurred first, according to National Cancer Institute Common Terminology Criteria for Adverse Events v4.03. Immune-related AEs were recorded up to 90 days after the last dose of study drug.
regardless of whether the patient started a new anticancer therapy. All suspected study-drug–related serious AEs continued to be recorded by the investigators after treatment discontinuation.

### End Points

The primary end point of this study was overall survival (OS) in all randomly assigned patients (the intent-to-treat [ITT] population). The key secondary end point was OS in patients with PD-L1 TAP ≥ 10%. Other secondary end points included progression-free survival (PFS), objective response rate (ORR), and duration of response (DoR), assessed by the investigator per RECIST v1.1 in the ITT population and in patients with PD-L1 TAP ≥ 10%, and safety and tolerability. A complete list of study end points is provided in the Data Supplement.

### Statistical Analyses

The OS hazard ratio (HR) of interest for tislelizumab versus chemotherapy was assumed to be 0.75 with a median OS of 8 versus 6 months, respectively. Approximately 400 death events were required to provide a power of 82% at a one-sided significance level of 0.025 to detect superiority of tislelizumab over chemotherapy. Assuming a 26-month period to observe the target number of death events and a dropout rate of 5% per year, approximately 500 patients were to be enrolled. The target number of death events was estimated to occur approximately 30.2 months after the first patient enrolled.

For OS analysis, \( P \) values for the comparison between treatment arms were estimated from a one-sided log-rank test stratified by ECOG PS and investigator-chosen chemotherapy. HRs and associated two-sided 95% CIs were estimated from a stratified Cox regression model including treatment arm as a covariate and with chemotherapy option and ECOG PS as strata. Median OS and 95% CI were calculated using a generalized Brookmeyer and Crowley method, and the cumulative probability of OS at 6 and 12 months was calculated (with two-sided 95% CI) using Greenwood’s formula. Kaplan-Meier survival curves were also presented for each arm. When superiority in OS in the ITT population was determined, a hierarchical hypothesis testing approach for the key secondary end point of OS in patients with PD-L1 TAP ≥ 10% was used to preserve a study-wise type I error rate at 5%. The subgroup analysis of OS in the ITT population was prespecified in the Statistical Analysis Plan provided in the Data Supplement.

Median PFS and median DoR with 95% CI were calculated using a generalized Brookmeyer and Crowley method. For ORR, a stratified Cochran-Mantel-Haenszel test was used to calculate common odds ratios and associated two-sided 95% CIs. ORR, difference in ORR, and Clopper-Pearson 95% CI were also calculated.

Safety was evaluated in all randomly assigned patients who received at least one dose of study drug and analyzed using descriptive statistics. All calculations and analyses were conducted using SAS version 9.4 or higher. Full statistical methods are provided in the Statistical Analysis Plan provided in the Data Supplement.

### Table 1: Patient Demographics and Baseline Characteristics in the Intent-to-Treat Population

| Characteristic                        | Tislelizumab (n = 256) | Chemotherapy (n = 256) |
|---------------------------------------|------------------------|------------------------|
| Age, years, median (range)            | 62.0 (40-86)           | 63.0 (35-81)           |
| < 65, No. (%)                         | 157 (61.3)             | 161 (62.9)             |
| ≥ 65, No. (%)                         | 99 (38.7)              | 95 (37.1)              |
| Sex, No. (%)                          |                        |                        |
| Male                                  | 217 (84.8)             | 215 (84.0)             |
| Female                                | 39 (15.2)              | 41 (16.0)              |
| Race, No. (%)                         |                        |                        |
| Asian                                 | 201 (78.5)             | 207 (80.9)             |
| White or Caucasian                    | 53 (20.7)              | 44 (17.2)              |
| Black or African American             | 0 (0.0)                | 2 (0.8)                |
| Other                                 | 0 (0.0)                | 1 (0.4)                |
| Not reported/unknown                  | 2 (0.8)                | 2 (0.8)                |
| Geographic region, No. (%)            |                        |                        |
| Asia*                                 | 201 (78.5)             | 203 (79.3)             |
| Europe/North America                  | 55 (21.5)              | 53 (20.7)              |
| ECOG PS, No. (%)                      |                        |                        |
| 0                                     | 66 (25.8)              | 60 (23.4)              |
| 1                                     | 190 (74.2)             | 196 (76.6)             |
| PD-L1 expression, No. (%)             |                        |                        |
| TAP ≥ 10%                             | 89 (34.8)              | 68 (26.6)              |
| TAP < 10%                             | 116 (45.3)             | 140 (54.7)             |
| Unknown                               | 51 (19.9)              | 48 (18.8)              |
| Smoking status, No. (%)               |                        |                        |
| Never                                 | 68 (26.6)              | 63 (24.6)              |
| Former/current                        | 188 (73.4)             | 192 (75.0)             |
| Missing                               | 0 (0.0)                | 1 (0.4)                |
| Previous therapies, No. (%)           |                        |                        |
| Surgery                               | 94 (36.7)              | 99 (38.7)              |
| Radiotherapy                          | 169 (66.0)             | 163 (63.7)             |
| Platinum-based chemotherapy           | 249 (97.3)             | 252 (98.4)             |

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; PD-L1, programmed death-ligand 1; TAP, tumor area positivity.

*There were 50 patients from Japan: 25 patients in the tislelizumab arm and 25 patients in the chemotherapy arm.
RESULTS

Patients and Treatment

Between January 2018 and March 2020, 512 patients in Asia (404 patients [78.9%]) and Europe and North America (108 patients [21.1%]) were randomly assigned to receive tislelizumab (n = 256) or chemotherapy (n = 256) and were included in the ITT population (Fig 1). Of these, 255 patients in the tislelizumab arm and 240 patients in the chemotherapy arm received at least one dose of assigned treatment (Fig 1). Patient characteristics and demographics were generally balanced between treatment arms (Table 1). The median age of patients was 62 years, 79.7% of patients were Asian, and 84.4% of patients were male. A total of 487 (95.1%) patients had metastatic disease at study entry, and 157 (30.7%) patients had PD-L1 TAP $10\%$ tumors. More patients in the Tislelizumab (n = 256) arm had PD-L1 TAP $10\%$ tumors than in the Chemotherapy (n = 256) arm (77.0% vs 83.2%). The median OS in the Tislelizumab arm was 10.3 (95% CI, 8.5 to 16.1) months, and in the Chemotherapy arm, it was 6.8 (95% CI, 4.1 to 8.3) months. The HR for OS in the Tislelizumab arm was 0.54 (95% CI, 0.36 to 0.79). The one-sided P value was estimated from a log-rank test stratified by ECOG PS and chemotherapy option. HR was based on a Cox regression model including treatment as a covariate and ECOG PS and chemotherapy option as strata.

FIG 2. Kaplan-Meier plot of OS in the (A) intent-to-treat population, (B) PD-L1 TAP $\geq 10\%$, (C) PD-L1 TAP $< 10\%$, and (D) TAP unknown populations. One-sided P value was estimated from a log-rank test stratified by ECOG PS and chemotherapy option. HR was based on a Cox regression model including treatment as a covariate and ECOG PS and chemotherapy option as strata. ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; OS, overall survival; PD-L1, programmed death-ligand 1; TAP, tumor area positivity. (continued on following page)
tislelizumab arm had PD-L1 TAP $\geq$ 10% versus patients in the chemotherapy arm (34.8% vs 26.6%).

At the time of data cutoff (December 1, 2020), median follow-up from random assignment to data cutoff or death, whichever came first, was 8.5 months (0.2 to 31.7 months) for tislelizumab and 5.8 months (0.0 to 30.8 months) for chemotherapy. The median duration of exposure was 84.0 days (7-862 days) to tislelizumab and 45.5 days (7-584 days) to chemotherapy. More patients in the tislelizumab arm received $\geq$ 6 months of study treatment versus patients in the chemotherapy arm (25.5% vs 8.7%).

**Efficacy**

At final analysis, a total of 197 (77.0%) versus 213 (83.2%) deaths occurred in the tislelizumab and chemotherapy arms, respectively. OS was significantly improved in the tislelizumab arm versus the chemotherapy arm (median 8.6 months [95% CI, 7.5 to 10.4] vs 6.3 months [95% CI, 5.3 to 7.0]; HR for death 0.70, 95% CI, 0.57 to 0.85; one-sided $P = .0001$; Fig 2). The 12-month OS rate was 37.4% (95% CI, 31.4 to 43.4) versus 23.7% (95% CI, 18.5 to 29.3) in the tislelizumab and chemotherapy arms, respectively. In total, 11 patients...
(4.3%) versus 55 patients (21.5%) in the tislelizumab and chemotherapy arms, respectively, had received anti–PD-1 or anti–PD-L1 therapy after discontinuation of study treatment (Data Supplement). Post hoc adjustment analyses for baseline PD-L1 expression status confirmed that the imbalance between treatment arms in baseline PD-L1 expression status had little impact on the estimate of the treatment effect on OS results (Data Supplement). Survival benefit of tislelizumab versus chemotherapy was observed in all predefined subgroups, including those defined by baseline PD-L1 expression status, region, and race (Fig 3; Data Supplement).

In patients with TAP ≥ 10%, tislelizumab significantly improved OS versus chemotherapy (median 10.3 months; 95% CI, 8.5 to 16.1 v 6.8 months; 95% CI, 4.1 to 8.3; HR 0.54; 95% CI, 0.36 to 0.79; one-sided \( P = .0006; \) Fig 2, Data Supplement). Survival benefits with tislelizumab versus chemotherapy were also observed in patients with TAP < 10% (HR, 0.82; 95% CI, 0.62 to 1.09) and TAP unknown (HR, 0.67; 95% CI, 0.41 to 1.12; Fig 2, Data Supplement). The post hoc interaction analysis between treatment group and baseline PD-L1 expression status showed the \( P \) value was .21, indicating no significant interaction of treatment effect by PD-L1 status (\( P \) value ≥ .15).

A total of 223 (87.1%) versus 180 (70.3%) patients had disease progression or died at data cutoff in the tislelizumab and chemotherapy arms, respectively. Median PFS was 1.6 months (95% CI, 1.4 to 2.7) versus 2.1 months (95% CI, 1.5 to 2.7) in the tislelizumab and chemotherapy arms, respectively (HR, 0.83; 95% CI, 0.67 to 1.01; Fig 4). The PFS Kaplan-Meier curves began to separate at approximately 3 months in favor of tislelizumab versus chemotherapy. The estimated PFS rates in the tislelizumab versus chemotherapy arms were 21.7% versus 14.9% at 6 months and 12.7% versus 1.9% at 12 months (Fig 4). PFS results in patients with TAP ≥ 10% are shown in the Data Supplement.
Safety and Tolerability

Fewer patients experienced treatment-related AEs (TRAEs) with tislelizumab versus chemotherapy (73.3% vs 93.8%; Table 3). The most common TRAEs with tislelizumab were increased aspartate aminotransferase (11.4%), anemia (11.0%), and hypothyroidism (10.2%). The most common TRAEs with chemotherapy were decreased white blood cell count (40.8%), decreased neutrophil count (39.2%), and anemia (34.6%). Fewer patients had grade 3 TRAEs with tislelizumab versus chemotherapy (18.8% vs 55.8%). The incidence of serious TRAEs was 14.1% versus 19.6% with tislelizumab versus chemotherapy, respectively. Fewer patients discontinued tislelizumab versus chemotherapy (6.7% vs 13.8%) because of a TRAE (Table 3).

In both treatment arms, the primary cause of death was disease progression, which occurred at a lower frequency.
TABLE 2. Summary of Antitumor Activity

| Antitumor Response | Tislelizumab (n = 256) | Chemotherapy (n = 256) |
|--------------------|------------------------|------------------------|
| ORR, No. (%) [95% CI]* | 52 (20.3) [15.6 to 25.8] | 25 (9.8) [6.4 to 14.1] |
| Odds ratio for ORR (95% CI) | 2.39 (1.42 to 4.01) |
| Best overall response, No. (%) |
| Complete response | 5 (2.0) | 1 (0.4) |
| Partial response | 47 (18.4) | 24 (9.4) |
| Stable disease | 68 (26.6) | 82 (32.0) |
| Progressive disease | 116 (45.3) | 86 (33.6) |
| Not evaluableb | 1 (0.4) | 3 (1.2) |
| Not assessablec | 19 (7.4) | 60 (23.4) |
| DoR, months, median (95% CI)a | 7.1 (4.1 to 11.3) | 4.0 (2.1 to 8.2) |
| Patients with ongoing response, No./n (%) | 10/52 (19.2) | 0/25 (0.0) |

Abbreviations: DoR, duration of response; ORR, overall response rate.

*ORR and DoR results were based on unconfirmed tumor responses.

bNot evaluable on the basis of RECIST v1.1.

cPatients with no postbaseline tumor assessment by data cutoff, including those who discontinued study for any reason or died without having any postbaseline tumor assessment.

with tislelizumab versus chemotherapy (59.8% vs 66.0%). Deaths attributed to TRAEs were reported for 5 (2.0%) patients in the tislelizumab arm versus 7 (2.9%) patients in the chemotherapy arm.

**DISCUSSION**

The RATIONALE-302 phase III study was designed to detect the superiority of tislelizumab versus chemotherapy in improving survival in all randomly assigned patients and met this primary end point at final analysis. Treatment with tislelizumab showed a statistically significant and clinically meaningful improvement in OS versus chemotherapy in patients with advanced or metastatic ESCC whose disease progressed during or after first-line therapy. Survival benefit was observed across all prespecified subgroups, including region, race, and PD-L1 expression level.

RATIONALE-302 was, to our knowledge, the first study that demonstrated significant survival benefit with an anti–PD-1 antibody in a global ESCC population from Asia and Europe/North America. The OS improvement (30% reduction in the risk of death and 2.3-month extension in median OS) was similar to other studies investigating anti–PD-1 antibodies as second-line treatment for ESCC.10,12 In ATTRACTION-3, which mainly enrolled Asian patients (96%), OS was significantly improved with nivolumab versus chemotherapy (paclitaxel or docetaxel): 10.9 months versus 8.4 months, HR = 0.77, P = .019.10 In ESCORT, a study conducted in solely in China, significant improvement in OS was seen with camrelizumab versus chemotherapy (docetaxel or irinotecan): 8.3 months versus 6.2 months, HR = 0.71, P = .001.14 KEYNOTE-181 was a global study that enrolled patients with ESCC and esophageal adenocarcinoma. However, its favorable improvement in OS with pembrolizumab versus chemotherapy (paclitaxel, docetaxel, or irinotecan) in patients with ESCC (8.2 months vs 7.1 months, HR = 0.78, P = .0095) failed to meet the prespecified boundary for statistical significance.11 Notably, the magnitude of OS benefit with tislelizumab in the RATIONALE-302 study was observed in the context of a much higher rate of subsequent anti–PD-1/PD-L1 treatment after discontinuing from study treatment in the chemotherapy arm (21.5%) versus the tislelizumab arm (4.3%), whereas in other studies, 6%-9% of patients in the chemotherapy arm received subsequent anti–PD-1/PD-L1 antibodies.10,12

RATIONALE-302 enrolled 79% of patients from Asia and 21% of patients from Europe/North America, which reflected the global distribution of patients with ESCC. The survival benefit of tislelizumab versus chemotherapy was observed in both Asian (HR, 0.73) and non-Asian patients (HR, 0.55). Although Asian patients with ESCC in KEYNOTE-181 (58% from Asia) appeared to have enhanced benefit with pembrolizumab versus chemotherapy, this was not observed with other anti–PD-1 antibodies, including tislelizumab in RATIONALE-302 and nivolumab in two other large global phase III studies investigating nivolumab versus placebo in the adjuvant treatment of EC (Checkmate-577) and nivolumab plus chemotherapy versus chemotherapy in first-line treatment of EC (Checkmate-648).16,19 RATIONALE-302 enrolled patients regardless of PD-L1 expression status. The TAP score (SP263) used to assess PD-L1 expression demonstrated comparable efficacy association in gastric cancer to CPS (22C3).20 According to the hierarchical testing, OS was significantly improved with tislelizumab over chemotherapy in patients with PD-L1 TAP ≥ 10% (HR, 0.54), and in the prespecified exploratory analysis, tislelizumab also showed a favorable trend of
Improvement in OS versus chemotherapy in patients with PD-L1 TAP $\geq 10\%$ (HR, 0.82). Although the OS benefit appeared to be enriched in patients with PD-L1 TAP $\geq 10\%$ in RATIONALE-302, post hoc analysis of OS with the adjustment for PD-L1 expression status confirmed the OS benefit in all randomly assigned patients (HR, 0.70; 95% CI, 0.57 to 0.87), and post hoc interaction analysis between treatment and baseline PD-L1 expression status showed that OS benefit was observed regardless of PD-L1 expression level. Similarly, consistent survival benefit was also observed across patients with different PD-L1 expression levels with nivolumab and camrelizumab over chemotherapy in ATTRACTION-3 and ESCORT studies, which measured PD-L1 expression status using alternative assays. Consistent with OS findings, tislelizumab showed a greater and more durable antitumor response than chemotherapy. ORR was twice as high with tislelizumab versus chemotherapy. Median DoR was 3.1 months longer with tislelizumab versus chemotherapy, with more responders exhibiting ongoing responses at data cutoff. Although median PFS was shorter with tislelizumab versus chemotherapy, the numerically favorable HR of PFS and increasing separation of the Kaplan-Meier curves after 3 months suggested a potential benefit in PFS. Similar separation of Kaplan-Meier curves of PFS in favor of anti–PD-1 antibodies was also observed in other studies conducted in this setting.

### TABLE 3. Summary of Adverse Events

| Adverse Event               | Tislelizumab (n = 255) | Chemotherapy (n = 240) |
|-----------------------------|------------------------|------------------------|
| Patients with at least one TEAE, No. (%) | 244 (95.7) | 236 (98.3) |
| ≥ Grade 3 TEAE             | 118 (46.3) | 163 (67.9) |
| Serious TEAE               | 105 (41.2) | 105 (43.8) |
| TEAE leading to treatment discontinuation | 49 (19.2) | 64 (26.7) |
| TEAE leading to death       | 35 (13.7) | 28 (11.7) |
| Patients with at least one TRAE, No. (%) | 187 (73.3) | 225 (93.8) |
| ≥ Grade 3 TRAE             | 48 (18.8) | 134 (55.8) |
| Serious TRAE               | 36 (14.1) | 47 (19.6) |
| TRAE leading to treatment discontinuation | 17 (6.7) | 33 (13.8) |
| TRAE leading to death       | 7 (2.7) | 8 (3.3) |
| TRAEs occurring in ≥ 10% of patients, No. (%)| | |
| AST increased              | 29 (11.4) | 9 (3.8) |
| Anemia                     | 28 (11.0) | 83 (34.6) |
| Hypothyroidism             | 26 (10.2) | 0 (0.0) |
| Fatigue                    | 19 (7.5)  | 33 (13.8) |
| Decreased appetite         | 16 (6.3)  | 75 (31.3) |
| Diarrhea                   | 14 (5.5)  | 66 (27.5) |
| Asthenia                   | 12 (4.7)  | 28 (11.7) |
| Malaise                    | 10 (3.9)  | 35 (14.6) |
| Weight decreased           | 8 (3.1)   | 25 (10.4) |
| Nausea                     | 7 (2.7)   | 66 (27.5) |
| Leukopenia                 | 7 (2.7)   | 30 (12.5) |
| WBC count decreased        | 5 (2.0)   | 98 (40.8) |
| Vomiting                   | 4 (1.6)   | 43 (17.9) |
| Constipation               | 4 (1.6)   | 25 (10.4) |
| Neutrophil count decreased | 3 (1.2)   | 94 (39.2) |
| Neutropenia                | 2 (0.8)   | 31 (12.9) |
| Alopecia                   | 0 (0.0)   | 42 (17.5) |

Abbreviations: TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

*Death events because of disease progression were excluded. Deaths attributed to TRAEs included one each of hemoptysis, pulmonary arterial hypertension, upper gastrointestinal hemorrhage, pneumonia, and decreased platelet count in the tislelizumab arm, and three of septic shock, and one each of pneumonia, febrile neutropenia, death, and multiple organ dysfunction syndrome in the chemotherapy arm.

*By system organ class and preferred term.
antitumor effect seen with immunotherapies versus cytotoxic drugs.\textsuperscript{21} Despite longer drug exposure with tislelizumab, fewer TRAEs were observed versus chemotherapy. The incidence of $\geq$ grade 3 TRAEs, serious TRAEs, and TRAEs leading to treatment discontinuation was also lower in the tislelizumab arm versus the chemotherapy arm. Overall, the safety profile of tislelizumab was favorable over chemotherapy.

Limitations of this study include the open-label study design, which may have affected compliance, and a lack of blinded review of response data by an independent committee, which may have affected response data (ORR, PFS, and DoR). In addition, future studies are needed to explore the analytical concordance of the assays and the predictiveness of PD-L1 TAP expression in ESCC.

In conclusion, tislelizumab provided a statistically significant and clinically meaningful improvement in OS versus chemotherapy in patients with advanced or metastatic ESCC who had disease progression after first-line systemic therapy, with a tolerable safety profile. Patients with PD-L1 TAP $\geq$ 10\% also demonstrated statistically significant survival benefit with tislelizumab versus chemotherapy.

**AFFILIATIONS**
\textsuperscript{1}Department of Gastrointestinal Oncology, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Peking University Cancer Hospital & Institute, Beijing, China
\textsuperscript{2}Department of Head and Neck Esophageal Medical Oncology, National Cancer Center Hospital, Tokyo, Japan
\textsuperscript{3}Department of Oncology, Ansan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea
\textsuperscript{4}Department of Gastrointestinal Medical Oncology, University of Texas MD Anderson Cancer Center, Houston, TX
\textsuperscript{5}Department of Radiation Oncology, Fudan University Shanghai Cancer Center, Shanghai, China
\textsuperscript{6}Fujian Cancer Hospital, Fujian Medical University Cancer Hospital, Fuzhou, China
\textsuperscript{7}Department of Medical Oncology, Zhejiang Cancer Hospital, Hangzhou, China
\textsuperscript{8}Department of Oncology, Jiangsu Province Hospital, Jiangsu, China
\textsuperscript{9}Department of Gastrointestinal Tumor Surgery, The First Affiliated Hospital of Xiamen University, Fujian, China
\textsuperscript{10}Department of Medical Oncology, The Affiliated Cancer Hospital of Zhengzhou University, Henan Cancer Hospital, Henan, China
\textsuperscript{11}Oncology Department, 2nd Hospital of Anhui Medical University, Anhui, China
\textsuperscript{12}Department of Medical Oncology, Shandong Cancer Hospital, Shandong Academy of Medical Sciences, Jinan, China
\textsuperscript{13}Cancer Institute of Xuzhou Medical University, Affiliated Hospital of Xuzhou Medical University, Xuzhou, China
\textsuperscript{14}Xiangyang Central Hospital, Hubei, China
\textsuperscript{15}Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea
\textsuperscript{16}Department of Medical Oncology, Hunan Cancer Hospital, Changsha, China
\textsuperscript{17}Clinical Oncology Department, WeiFang People’s Hospital, WeiFang, China
\textsuperscript{18}Department of Medical Oncology, China Medical University Hospital, and China Medical University, Taichung, Taiwan
\textsuperscript{19}Department of Gastroenterology, Saitama Cancer Center, Saitama, Japan
\textsuperscript{20}Yunnan Cancer Hospital, Yunnan, China
\textsuperscript{21}Osaka University Hospital, Suita, Japan
\textsuperscript{22}Medical Oncology Department, Hospital Universitario Miguel Servet, Zaragoza, Spain
\textsuperscript{23}Sarah Cannon Research Institute UK and University College London, Cancer Institute, London, United Kingdom
\textsuperscript{24}Department of Medical Oncology, University Hospital of Besançon, CIC-1431 INSERM, Besançon, France
\textsuperscript{25}Department of Oncology, Gastroenterology, Hepatology, Pneumology, and Infectious Diseases, University Cancer Center Leipzig (UCLL), Leipzig University Medical Center, Leipzig, Germany

**CORRESPONDING AUTHOR**
Lin Shen, MD, PhD, Department of Gastrointestinal Oncology, Beijing Cancer Hospital, 52 Fucheng Rd, Haidian District, Beijing, China, 100142; e-mail: linshenpku@163.com.

**DATA SHARING STATEMENT**
On request, and subject to certain criteria, conditions, and exceptions, BeiGene, Ltd, will provide access to individual deidentified participant data from BeiGene-sponsored global interventional clinical studies conducted for medicines (1) for indications that have been approved or (2) in programs that have been terminated. BeiGene will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data requests may be submitted to DataDisclosure@beigene.com.

**AUTHOR CONTRIBUTIONS**
Conception and design: Lin Shen, Ken Kato, Sung-Bae Kim, Jaffer A. Ajani, Kuaile Zhao, Zhiyong He, Qi Luo, Jufeng Wang, Zhendong Chen, Zuoxing Niu, Longzhen Zhang, Tienan Yi, Jianhua Chen, Guohua Yu, Lin Shen, Ken Kato, Sung-Bae Kim, Jaffer A. Ajani, Kuaile Zhao, Zhiyong He, Qi Luo, Jufeng Wang, Zhendong Chen, Zuoxing Niu, Longzhen Zhang, Tienan Yi, Jianhua Chen, Guohua Yu,
REFERENCES

1. Sung H, Ferlay J, Siegel RL, et al: Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 71:209-249, 2021
2. Wang QL, Xie SH, Wahlin K, et al: Global time trends in the incidence of esophageal squamous cell carcinoma. Clin Epidemiol 10:717-728, 2018
3. Huang FL, Yu SJ: Esophageal cancer: Risk factors, genetic association, and treatment. Asian J Surg 41:210-215, 2018
4. SEER: Cancer Stat Facts: Esophageal Cancer. 2021. https://seer.cancer.gov/statfacts/html/esoph.html
5. Shah MA, Kennedy EB, Catenacci DV, et al: Treatment of locally advanced esophageal carcinoma: ASCO Guideline. J Clin Oncol 38:2677-2694, 2020
6. Lordick F, Mariette C, Haustermans K, et al: Esophageal cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 27: v50-v57, 2016
7. Muro K, Lordick F, Tsushima T, et al: Pan-Asian adapted ESMO clinical practice guidelines for the management of patients with metastatic oesophageal cancer: A JSMO-ESMO initiative endorsed by CSO, KSMO, MOS, SSO and TOS. Ann Oncol 30:34-43, 2019
8. Assensohn L, Brown G, Cunningham D, et al: Phase II study of irinotecan and 5-fluorouracil/leucovorin in patients with primary refractory or relapsed advanced oesophageal and gastric carcinoma. Ann Oncol 15:64-69, 2004
9. Ford HE, Marshall A, Bridgewater JA, et al: Docetaxel versus active symptom control for refractory oesophagogastric adenocarcinoma (COUGAR-02): An open-label, phase 3 randomised controlled trial. Lancet Oncol 15:78-86, 2014
10. Kato K, Cho BC, Takahashi M, et al: Nivolumab versus chemotherapy in patients with advanced oesophageal squamous cell carcinoma refractory or intolerant to previous chemotherapy (ATTRACTION-3): A multicentre, randomised, open-label, phase 3 trial. Lancet Oncol 20:1506-1517, 2019
11. Kojima T, Shah MA, Muro K, et al: Randomized phase III KEYNOTE-181 study of pembrolizumab versus chemotherapy in advanced esophageal cancer, J Clin Oncol 38:4138-4148, 2020
12. Huang J, Xu J, Chen Y, et al: Camrelizumab versus investigator’s choice of chemotherapy as second-line therapy for advanced or metastatic oesophageal squamous cell carcinoma (ESCORt): A multicentre, randomised, open-label, phase 3 study. Lancet Oncol 21:832-842, 2020
13. Lu Z, Peng Z, Liu C, et al: Current status and future perspective of immunotherapy in gastro-intestinal cancers. Innovation (N Y) 1:100041, 2020
14. Zhang T, Song X, Xu L, et al: The binding of an anti-PD-1 antibody to Fc RI has a profound impact on its biological functions. Cancer Immunol Immunother 67: 1079-1090, 2018
15. Desai J, Deva S, Lee JS, et al: Phase Ib/B study of single-agent tislelizumab, an investigational anti-PD-1 antibody, in solid tumors. J Immunother Cancer 8: e000452, 2020
16. Xu J, Bai Y, Xu N, et al: Tislelizumab plus chemotherapy as first-line treatment for advanced esophageal squamous cell carcinoma and gastric/gastroesophageal junction adenocarcinoma. Clin Cancer Res 26:4542-4550, 2020
17. Shen L, Guo J, Zhang Q, et al: Tislelizumab in Chinese patients with advanced solid tumors: An open-label, non-comparative, phase 1/2 study. J Immunother Cancer 8:e000437, 2020
18. Chau I, Doki Y, Ajani JA, et al: Nivolumab (NIVO) plus ipilimumab (IPI) or NIVO plus chemotherapy (chemo) versus chemo as first-line (1L) treatment for advanced esophageal squamous cell carcinoma (ESCC): First results of the CheckMate 648 study. J Clin Oncol 39, 2021 (abstr LBA4001)
19. Kelly RJ, Ajani JA, Kudzdzal J, et al: Adjuvant nivolumab in resected esophageal or gastroesophageal junction cancer. N Engl J Med 384:1191-1203, 2021
20. Chao Y, Yang S, Zhang Y, et al: IS4P Investigation of PD-L1 expression and tislelizumab efficacy in gastroesophageal adenocarcinoma using a novel tumor and immune cell score with VENTANA PD-L1 (SP263) assay and Combined Positive Score (CPS). Ann Oncol 31:S300, 2020
21. Boland P, Pavlick AC, Weber J, et al: Immunotherapy to treat malignancy in patients with pre-existing autoimmunity. J Immunother Cancer 8:e000356, 2020
AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Tislelizumab Versus Chemotherapy as Second-Line Treatment for Advanced or Metastatic Esophageal Squamous Cell Carcinoma (RATIONALE-302): A Randomized Phase III Study

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO’s conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/authors/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

Lin Shen
Consulting or Advisory Role: MSD, Bristol-Myers Squibb, AstraZeneca, Daiichi Sankyo, Roche, Mingli Biopharmaceutical, Harbour BioMed, Merck
Research Funding: Nanjing Yaojianankang Biotechnology (Inst), Baiji Shenzhou (Beijing) Biotechnology Co Ltd (Inst), Beijing Xiantong Biomedical Technology Co Ltd (Inst), QiLu Pharmaceutical (Inst), Zaiding Pharmaceutical (Inst)

Ken Kato
Honoraria: Lilly, BMS, Ono Pharmaceutical
Consulting or Advisory Role: Ono Pharmaceutical, BeiGene, MSD, Oncolys BioPharma, Bayer
Speakers’ Bureau: Ono Pharmaceutical, Bristol Myers Squibb Japan, MSD
Research Funding: Ono Pharmaceutical (Inst), Shionogi (Inst), MSD Oncology (Inst), Beigene (Inst), Chugai Pharma (Inst), Bayer (Inst), AstraZeneca (Inst), Taiho Pharmaceutical (Inst)

Jafger A. Ajani
Honoraria: Lilly, Bristol Myers Squibb, Merck, Aduro Biotech, DAVA Pharmaceuticals, AstraZeneca, Acrotech Biopharma, Zymeworks, Astellas Pharma, Aragen, OncoTherics, Daiichi Sankyo, Novartis, Servier, Gilead Sciences, Beigene, Fresenius Kabi, Boehringer Ingelheim, GRAIL

Sung-Bae Kim
Stock and Other Ownership Interests: Neogene TC Corp, Genopeak
Honoraria: DAEHWA Pharmaceutical, ISU Abex
Consulting or Advisory Role: Lilly (Inst), AstraZeneca, DAEHWA Pharmaceutical, ISU Abex, Beigene, Daiichi Sankyo/AstraZeneca
Research Funding: Novartis (Inst), Dongkook Pharma (Inst), Genzyme (Inst)

Xinmin Yu
Research Funding: Beigene, Innovent Biologics, BMS, MSD, Hansoh

Jianhua Chen
Consulting or Advisory Role: Hansoh Pharma
Research Funding: Hansoh Pharma

Hiroki Hara
Honoraria: Chugai Pharma, Taiho Pharmaceutical, Merck Serono, Yakult Honsha, Lilly, Ono Pharmaceutical, Takeda, Bristol Myers Squibb, Sanofi, MSD, Daiichi Sankyo, Kyowa Hakko Kirin, Bayer, Asahi Kasei
Consulting or Advisory Role: Ono Pharmaceutical, MSD, Boehringer Ingelheim, Daewoong Sumitomo, Bristol Myers Squibb Japan, Daiichi Sankyo/UCB Japan
Research Funding: AstraZeneca (Inst), Merck Serono (Inst), MSD (Inst), Ono Pharmaceutical (Inst), Taiho Pharmaceutical (Inst), BoehringerIngelheim (Inst), Daiwen Sumitomo Pharma (Inst), Daiichi Sankyo (Inst), Eisai (Inst), Incyte (Inst), Beigene (Inst), Astellas Pharma (Inst), Bayer (Inst), Amgen (Inst), Chugai Pharma (Inst), Janssen Oncology (Inst)

Taroh Satoh
Honoraria: Chugai Pharma, Merck Serono, Bristol Myers Squibb, Takeda, Yakult Honsha, Lilly, Bayer Yakuhin, Ono Pharmaceutical, Merck, Astellas Pharma, Taiho Pharmaceutical, Nihonkayaku, Daiichi-Sankyo
Consulting or Advisory Role: Bayer Yakuhin, Lilly, Ono Pharmaceutical, Takara Bio, Merck Serono, Nihonkayaku
Research Funding: Yakult Honsha (Inst), Chugai Pharma (Inst), Ono Pharmaceutical (Inst), Sanofi (Inst), Lilly (Inst), Daiichi Sankyo (Inst), Merck (Inst), Merck Serono (Inst), Gilead Sciences (Inst), Daiwen Sumitomo Pharma (Inst), IQVIA (Inst)

Roberto Paz-Cid
Consulting or Advisory Role: Baxalta/Shine, Celgene, Lilly, Roche, Bristol Myers Squibb/Celgene, Servier
Travel, Accommodations, Expenses: Celgene, Lilly

Hendrik-Tobias Arkenau
Employment: Hospital Corporation of America
Honoraria: Roche, Guardant Health, Bicycle Therapeutics, Servier, Merck KGaA, Beigene, Bayer
Consulting or Advisory Role: Onoctura, Engtix
Research Funding: Sarah Cannon Research Institute

Christophe Borg
Consulting or Advisory Role: Roche/Genentech, MSD Oncology, Bayer, Pierre Fabre
Research Funding: Roche/Genentech (Inst)

Florian Lordick
Honoraria: Lilly, Merck Sharp & Dohme, Bristol Myers Squibb, AstraZeneca, Elsevier, BioNTech, Servier, Merck KGaA, Roche, Medscape, Incyte, Art Tempi, Medupdate, Streamedup!
Research Funding: Lilly, Merck Sharp & Dohme, Bristol Myers Squibb, Astellas Pharma, Servier, Zymeworks, Amgen, Daiichi Sankyo, Novartis, Beigene
Travel, Accommodations, Expenses: Bristol Myers Squibb (Inst), MSD (Inst)

Liyun Li
Research Funding: Bristol Myers Squibb, Lilly

Jingwen Shi
Employment: Beigene
Travel, Accommodations, Expenses: Beigene, Johnson & Johnson/Janssen

Eric Van Cutsem
Consulting or Advisory Role: Bayer, Lilly, Roche, Servier, Bristol Myers Squibb, Celgene, Merck Sharp & Dohme, Merck KGaA, Novartis, AstraZeneca, Halozyme, Arrow BioPharma, Boxcart, GiacoSmithKline, Daiichi Sankyo, Pierre Fabre, Sirtex Medical, Taiho Pharmaceutical, Incyte, Astellas Pharma
Research Funding: Amgen (Inst), Bayer (Inst), Boehringer Ingelheim (Inst), Lilly (Inst), Novartis (Inst), Roche (Inst), Celgene (Inst), Ipsen (Inst), Merck (Inst), Merck KGaA (Inst), Servier (Inst), Bristol Myers Squibb (Inst)

No other potential conflicts of interest were reported.
### Table A1. List of RATIONALE-302 Investigators

| Country | Principal Investigator          |
|---------|---------------------------------|
| China   | Kuaile Zhao                     |
| China   | Lin Shen (SC chair)             |
| China   | Zhiyong He                      |
| China   | Xinmin Yu                       |
| China   | Yongqian Shu                    |
| China   | Wang Jufeng                     |
| China   | Longzhen Zhang                  |
| China   | Qi Luo                          |
| Korea   | Jong-Mu Sun                     |
| China   | Zhendong Chen                   |
| China   | Tienna Yi                       |
| China   | Zuoxing Niu                     |
| Korea   | Sung-Bae Kim (SC member)        |
| Belgium | Eric Van Cutsem (SC member)     |
| Japan   | Hiroki Hara                     |
| China   | Guohua Yu                       |
| China   | Jianhua Chen                    |
| China   | Sheng Hu                        |
| Taiwan  | Chih-Hung Hsu                   |
| Taiwan  | Chen-Yuan Lin                   |
| France  | Jean-Philippe Metges            |
| China   | Qing Bi                         |
| China   | Wang Feng                       |
| China   | Jun Wu                          |
| France  | Christophe Borg                 |
| Japan   | Ken Kato (SC member)            |
| China   | Wei Ren                         |
| China   | Lu Ping                         |
| China   | Jianhua Shi                     |
| China   | Honglin Hu                      |
| China   | Xiaoyan Lin                     |
| Taiwan  | Yee Chao                        |
| Spain   | Roberto Pazo                    |
| United Kingdom | Won-Ho Edward Park |
| Japan   | Taro Satoh                      |
| Japan   | Takashi Kojima                  |
| Japan   | Satoru Motoyama                 |
| France  | Judith Raimbourg                |
| France  | Farid El Hajbi                  |
| Spain   | Tamara Sauri                    |
| Spain   | Maria Alsina                    |

(continued in next column)
### TABLE A1. List of RATIONALE-302 Investigators (continued)

| Country   | Principal Investigator          |
|-----------|---------------------------------|
| China     | Zhao Lin                        |
| China     | Yulong Zheng                    |
| China     | Yanhong Deng                    |
| China     | Shuqun Zhang                    |
| Taiwan    | Chien-Liang Lin                 |
| United States | Igor Rybkin                |
| United States | Rex Mowat               |
| Belgium   | Pieter-Jan Cuyle                |
| France    | Eric Terrebonne                 |
| France    | David Tougeron                  |
| France    | Francois Ghiringhelli           |
| France    | Pascal Artru                   |
| Spain     | Laura Visa                      |
| Spain     | Carlos Gomez                    |
| Italy     | Luca Frassineti                 |
| Japan     | Manabu Muto                     |
| Japan     | Masaru Morita                   |
| Japan     | Ryu Ishihara                    |
| Japan     | Yuichi Shibuya                  |
| Japan     | Masahiro Goto                   |
| Japan     | Keisho Chin                     |
| China     | Zhiping Li                      |
| United States | David Park               |
| United States | Syma Iqbal                |
| United States | Jason Burris                |
| United States | Dragana Tomic             |
| United States | Anirudha Dasgupta            |
| Belgium   | Joelle Collignon                |
| France    | Louis Marie Dourthe             |
| Spain     | Montserrat Blanco               |
| Spain     | Miguel Marin                    |
| Italy     | Ferdinando De Vita              |
| Italy     | Luigi Cavanna                   |
| Italy     | Roberto Bordonaro               |
| United Kingdom | Anna Mary Young         |
| United Kingdom | David Cunningham          |
| United Kingdom | Mano Joseph            |
| Germany   | Matthias Ebert                  |
| Germany   | Volker Heinemann                |
| Germany   | Gunnar Folprecht                |
| Germany   | Eray Gokkurt                    |
| Germany   | Dirk Arnold                     |
| Germany   | Thomas Zander                   |
| China     | Da Jiang                        |
| China     | Jing Huang                      |
| China     | Bing Xia                        |
| Taiwan    | Chuan-Cheng Wang                |
| Taiwan    | Wei-Yu Chen                      |

(continued in next column)