

**Medical Directors**

Marc Fishman, MD
 Graeme Bolger, MD
 William Early, MD
 Darshan Gandhi, MD
 Sanjay Jain, MD
 Jurgen Kogler, MD
 Anna Schorer, MD
 Richard Wilder, MD

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Name: Sapna Parmar, PharmD, BCOP
 Company/Organization: Oncology Analytics, Inc.
 Address: 8751 W. Broward Blvd., Suite 500
 Plantation, Florida 33324
 Phone: 1-888-916-2616
 Email: sparmar@oncologyanalytics.com
 Date of request: 9/18/19
 NCCN Guidelines Panel: Esophageal and Esophagogastric Junction Cancers

Academic Advisors

James O. Armitage, MD
 Stephen Caplan, MD
 David Cohn, MD
 Deborah Dillon, MD
 Marc Lippman, MD
 John Lister, MD
 David Raben, MD
 John C. Ruckdeschel, MD
 Chaim Shustik, MD

Request:

On behalf of Oncology Analytics, Inc., I respectfully request the NCCN® Esophageal and Esophagogastric Junction Cancers (EGJ) Panel to review the submission below to change NCCN's recommendation on pembrolizumab as second-line therapy for esophageal cancer with PD-L1 expression by CPS of scores ≥ 10 . Specifically, revise the recommendation to remove adenocarcinoma and EGJ adenocarcinoma histologies, leaving only squamous cell carcinoma (SCC). To include all histologies in this specific setting is currently a category 2B recommendation from the NCCN.

FDA:

The FDA-approved prescribing information for pembrolizumab (Keytruda®) states the following for esophageal cancer:

“Treatment of recurrent locally advanced or metastatic SCC of the esophagus in patients whose tumors express PD-L1 (CPS ≥ 10) as determined by an approved test, with disease progression after one or more prior lines of systemic therapy.”¹

Rationale:

The Esophageal and Esophagogastric Junction Cancers NCCN guidelines currently supports pembrolizumab as second-line therapy for esophageal SCC, esophageal adenocarcinoma, and EGJ adenocarcinoma with PD-L1 expression by CPS scores ≥ 10 as a category 2B recommendation.² This differs from the FDA labeling for pembrolizumab in the treatment of recurrent locally advanced/metastatic esophageal cancer which includes only SCC histology.¹ FDA approval in this setting was based off of the KEYNOTE-181 trial which exists currently in preliminary abstract form.³

KEYNOTE-181 was a phase III, randomized, open-label study of single agent pembrolizumab versus physicians' choice of single agent docetaxel, paclitaxel, or irinotecan in patients with advanced/metastatic adenocarcinoma and SCC of the esophagus that have progressed after first-line standard therapy. Eligible patients were

Clinical Pharmacists

Laura Bobolts, PharmD, BCOP
 Irvin Molina, PharmD, BCOP, BCPS, CSP, AAHIVP
 Sapna Parmar, PharmD, BCOP
 Adam Peele, PharmD, MHA, BCPS, BCOP
 Barry Peterson, PharmD, MS
 Melissa Pozotrigio, PharmD, BCOP
 Rebecca Tombleson, PharmD, BCOP
 Marjorie Velasquez, PharmD



randomized 1:1 to pembrolizumab 200 mg every three weeks for up to 2 years or investigator's choice of paclitaxel, docetaxel, or irinotecan. Randomization was stratified by histology (SCC versus adenocarcinoma) and region (Asia versus rest of the world). Primary endpoints were overall survival (OS) in three different subgroups: 1) PD-L1 CPS ≥ 10 , any histology 2) SCC histology, any CPS score and 3) intention-to-treat (ITT) population.

A total of 628 patients were randomized (SCC: N=401; CPS ≥ 10 : N= 222). Results were reported as follows³⁻⁴:

Table 1:

Subgroup	Results	Notes
PD-L1 CPS ≥ 10 (both SCC + adenocarcinoma)	<ul style="list-style-type: none"> Pembrolizumab was superior to chemotherapy with respect to median OS: 9.3 months versus 6.7 months, respectively, P=0.0074. This was statistically significant as the pre-specified boundary was P\leq0.0085. 	Statistical significance was <u>not reported</u> for median OS benefit, when broken down by histology: <ul style="list-style-type: none"> CPS ≥ 10 SCC: 10.3 months (pembrolizumab) versus 6.7 months (chemotherapy). CPS ≥ 10 adenocarcinoma: 6.3 months (pembrolizumab) versus 6.9 months (chemotherapy).
SCC histology, any CPS score	There was a clinically meaningful improvement in OS with pembrolizumab versus chemotherapy, but this was not statistically significant per prespecified boundaries (8.2 months versus 7.1 months, respectively, P=0.0095).	Pre-specified boundary: P \leq 0.0077.
ITT group	Difference in OS was not statistically significant between pembrolizumab versus chemotherapy (7.1 months versus 7.1 months, respectively, P=0.0560)	Pre-specified boundary: P \leq 0.0077.

As outlined in Table 1, although pembrolizumab was superior to chemotherapy in the PD-L1 CPS ≥ 10 (both SCC + adenocarcinoma) subgroup, upon reviewing the breakdown of histologies, those with adenocarcinoma had a numerically worse OS with pembrolizumab compared to chemotherapy (6.3 versus 6.9 months, respectively) and statistical significance was not reported for these patients. Until the results of KEYNOTE-181 are fully published, it is difficult to assume a benefit incurred with pembrolizumab for patients with adenocarcinoma and PD-L1 CPS ≥ 10 .

In conclusion, to align with recommendations from the FDA and the published clinical trial abstract data (KEYNOTE-181), we respectfully request the NCCN® Esophageal and Esophagogastric Junction Cancers Panel



revise the recommendation on second-line therapy with pembrolizumab for esophageal cancer with PD-L1 expression by CPS \geq 10. Specifically, please change the recommendation to remove adenocarcinoma and EGJ adenocarcinoma histologies, leaving only squamous cell carcinoma in this setting.

References:

1. Pembrolizumab [package insert]. Merck & Co., Inc. Whitehouse Station, NJ. Revised 07/2019. Available at: https://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf (Accessed September 18, 2019).
2. Esophageal and Esophagogastric Junction Cancers. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Version 2.2019 – May 29, 2019. Available at: https://www.nccn.org/professionals/physician_gls/pdf/esophageal.pdf (Accessed September 18, 2019).
3. Kojima T, Muro K, Francois E, et al. Pembrolizumab versus chemotherapy as second-line therapy for advanced esophageal cancer: Phase III KEYNOTE-181 study. Journal of Clinical Oncology 2019 (abstract): https://ascopubs.org/doi/abs/10.1200/JCO.2019.37.4_suppl.2.
4. Helwick C. KEYNOTE-181: Pembrolizumab vs Chemotherapy in Second-Line Treatment of Advanced Esophageal Cancer. The ASCO Post February 10, 2019: <https://www.ascopost.com/issues/february-10-2019/keynote-181-pembrolizumab-vs-chemotherapy-in-advanced-esophageal-cancer/>.

Thank you for your time and consideration of our request. Please do not hesitate to contact me should the panel have any questions.

Sincerely,

DocuSigned by:

Sapna Parmar

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Sapna Parmar, PharmD, BCOP
Senior Clinical Oncology Pharmacist
Oncology Analytics, Inc.

DocuSigned by:

Marc Fishman

55ADD83E21934CB...

Marc Fishman, MD
Executive Chairman
Oncology Analytics, Inc.

DocuSigned by:

Sanjay Jain

7C46043A36F7401...

Sanjay Jain, MD
Medical Director
Oncology Analytics, Inc.