New First-Line Systemic Treatment Options for Metastatic Esophageal Squamous Cell Carcinoma

Presented by Michael K. Gibson, MD, PhD

ABSTRACT

Esophageal squamous cell carcinoma is an aggressive malignancy with histologic variability depending on where in the world it is diagnosed, with most of these cancers occurring in China and other parts of Asia. Previous studies with cytotoxic chemotherapy combinations led to a plateau median overall survival of approximately 10 to 12 months, as well as a need for more effective treatment options. Cytotoxic chemotherapy served as the control arm in 3 studies that evaluated the safety and efficacy of immunotherapy + chemotherapy versus chemotherapy alone; in all 3 prospective randomized trials, the addition of immunotherapy resulted in a survival benefit in the first-line relapsed/metastatic setting. Data support these immunotherapy regimens as new standard-of-care systemic therapy options for unresectable, locally advanced, recurrent or metastatic esophageal cancers, and these regimens have now been incorporated into the NCCN Guidelines.

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For many years, treatment options for patients with metastatic esophageal squamous cell carcinoma (SCC) were few, and survival rates were low. Combination cytotoxic chemotherapy regimens afforded patients roughly another year of survival at most, creating a huge unmet need for better treatment options and increased survival in people with this malignancy, according to Michael K. Gibson, MD, PhD, Director of Translational Research for Esophago-Gastric Cancer; Associate Professor of Medicine, Vanderbilt-Ingram Cancer Center, Nashville, Tennessee, and member of the NCCN Guidelines Panel for Esophageal/Gastric Cancers. Now, the addition of immunotherapy to chemotherapy in the frontline setting has led to a survival benefit in 3 large randomized clinical trials and is considered the standard-of-care treatment option for patients with advanced esophageal SCC.

“Until immunotherapy came along, we had been stuck for a while with cytotoxic chemotherapy,” said Dr. Gibson. “But now, we have a new class of immune checkpoint inhibitors which, when added to cytotoxic drugs, will increase the survival of patients with recurrent metastatic SCC of the esophagus.”

At the NCCN 2023 Annual Conference, Dr. Gibson discussed the importance of developing additional treatment strategies for patients with advanced or metastatic esophageal SCC, and focused on the available evidence supporting the use of immune checkpoint inhibitors in this malignancy.

Esophageal Cancer Incidence and Survival

In 2020, esophageal cancer (including SCC and adenocarcinoma) represented 604,000 new cases and 544,000 deaths globally, making it the seventh most common cancer worldwide and the sixth most common cause of cancer-related death, accounting for 5.5% to 6% of cancer deaths.¹ “Even if it’s not the most common cancer worldwide, it is a very lethal disease,” said Dr. Gibson. “This is why we desperately need additional and better therapies.” Ninety percent of esophageal cancers across the world are SCC histology. Although most SCC diagnoses (~65%) occur in Asia, more than half (53%) of global esophageal SCC cases occur in China. Adenocarcinoma histology is more common in North America and Europe.²

Locally advanced SCC can be treated curatively with surgery or definitive chemoradiation, but patients with recurrent or metastatic disease should be treated with palliative intent, focused on prolonging survival while maintaining quality of life, he noted.

Approximately 50% of patients present with incurable disease, and 40% to 50% of those treated with curative intent will experience a recurrence and go on to receive palliative treatment. As such, the overall cure rate for those with esophageal cancer is low, at approximately 20%.³

Approach to Recurrent or Metastatic Disease

“Recurrent or metastatic incurable disease treated with palliative intent should focus on quality and quantity,” according to Dr. Gibson. “So, if you get both of those right, it’s a win for the patient.”
Median survival in patients with recurrent or metastatic incurable disease typically ranges from 10 to 12 months. Although adenocarcinoma is associated with a more “hopeful future”—because of the development of drugs that can target predictive markers such as HER2, FGFRb, and CLDN18.2—treatment of SCC had been “a bit stuck,” admitted Dr. Gibson. “That is, until we became aware of immunotherapy, which improves survival when added to cytotoxic chemotherapy,” he added.

Comparative trials are few and the choice of treatment is often individualized, but historically, fluoropyrimidine + platinum has been the optimal chemotherapy backbone for SCC of the esophagus, commented Dr. Gibson. Before immunotherapy, treatment of esophageal SCC with various combination cytotoxic chemotherapy regimens led to a median overall survival (OS) of approximately a year, at best.⁴ “The data suggest that we’ve reached the limit of our progress in cytotoxic chemotherapy for recurrent or metastatic esophageal SCC,” he said. “Based on that, we’ve generated the Principles of Systemic Therapy pages in the current version of the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Esophageal and Esophagogastric Junction Cancers” (Figure 1).⁵

Dr. Gibson discussed the first 4 bullet points, clarifying that interchangeable use of cytotoxic regimens is generally allowed for SCC and adenocarcinoma. He also touched on the fact that treatment with >2 cytotoxic chemotherapy drugs tends to lead to increased toxicity with limited additional survival benefit.

NCCN category 1 evidence also supports the notion that multidisciplinary care improves outcomes for patients with esophagogastric cancers. Therefore, a multidisciplinary team approach (which may include surgical oncology, medical oncology, gastroenterology, radiation oncology, radiology, and pathology) is necessary to optimize treatment.⁵

“It’s important to maintain the patient’s overall performance status,” Dr. Gibson noted. “This is not only for the patient’s well-being, but it also enables us to give the drugs more safely and effectively.”

**New First-Line Options: Addition of Immunotherapy**

High-level evidence demonstrates that adding immunotherapy to a chemotherapy backbone can improve survival in recurrent or metastatic esophageal SCC. Data from 3 large randomized clinical trials (KEYNOTE-590, CheckMate 648, and ESCORT-1st) have led to uniform NCCN consensus on the efficacy of these regimens and their recommendation in the NCCN Guidelines.

**KEYNOTE-590**
The phase III KEYNOTE-590 trial compared first-line pembrolizumab + chemotherapy versus chemotherapy alone in treatment-naive patients with advanced esophageal cancer.⁶ Two-thirds of patients had SCC histology, and approximately half had a PD-L1 combined positive score (CPS) of ≥10. The addition of immunotherapy to chemotherapy led to a statistically significant and clinically meaningful improvement in antitumor activity in all patients with locally advanced or metastatic esophageal or gastroesophageal junction carcinoma. After a median follow-up of 34.8 months, updated trial data continue to show OS and progression-free survival (PFS) benefits.⁷

In patients with esophageal SCC who received immunotherapy, the addition of pembrolizumab to chemotherapy led to a median OS of 12.6 versus 9.8 months with chemotherapy alone. In all patients, regardless of CPS score or histology, the addition of pembrolizumab to

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**Figure 1. Principles of systemic therapy.** NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Esophageal and Esophagogastric Junction Cancers, Version 1.2023 [ESOPH-F, 1 of 17]. © 2023 National Comprehensive Cancer Network, Inc. All rights reserved. These guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN®. To view the most recent and complete version of these NCCN Guidelines, go to www.nccn.org.

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**PRINCIPLES OF SYSTEMIC THERAPY**

- Systemic therapy regimens recommended for advanced esophageal and EGJ adenocarcinoma, SCC of the esophagus, and gastric adenocarcinoma may be used interchangeably (except as indicated).
- Regimens should be chosen in the context of performance status (PS), comorbidities, and toxicity profile.
- Trastuzumab¹ should be added to first-line chemotherapy for HER2 overexpression positive adenocarcinoma.
- Two-drug cytotoxic regimens are preferred for patients with advanced disease because of lower toxicity. The use of three cytotoxic drugs in a regimen should be reserved for medically fit patients with excellent PS and easy access to frequent toxicity evaluations.
- Modifications of category 1 regimen or use of category 2A or 2B regimens may be preferred (as indicated), with evidence supporting more favorable toxicity profile without compromising efficacy.⁷
- Doses and schedules for any regimen that is not derived from category 1 evidence is a suggestion, and subject to appropriate modifications depending on the circumstances.
- Alternate combinations and schedules of cytotoxics based on the availability of the agents, practice preferences, and contraindications are permitted.
- Preoperative chemoradiation is the preferred approach for localized adenocarcinoma of the thoracic esophagus or EGJ.² Perioperative chemoradiation is an alternative option for distal esophagus and EGJ.³⁴
- In the adjuvant setting, upon completion of chemotherapy or chemoradiation, patients should be monitored for any long-term treatment-related complications.
chemotherapy led to a statistically significant 27% reduction in the risk of death (hazard ratio [HR], 0.73). This was reflected in the PFS data, with median rates of 6.3 versus 5.8 months with chemotherapy (HR, 0.65). “For patients with a CPS ≥10, the HR dropped to 0.51, which you could argue is unprecedentedly low in this tumor type,” Dr. Gibson noted. “It’s heartening to see that.”

Immune-related adverse events aside (26.8% with pembrolizumab vs 13.8% with chemotherapy), the occurrence of adverse events was well matched between the study arms. “Importantly, patients’ quality of life was maintained, even when pembrolizumab was added to chemotherapy,” he said. “So, we achieved increased survival without a huge cost in terms of worse side effects.”

These longer-term data support the first-line use of pembrolizumab + chemotherapy as a new standard of care in patients with locally advanced and metastatic esophageal cancers.

CheckMate 648

The checkpoint inhibitor nivolumab has also demonstrated efficacy in the treatment of recurrent or metastatic esophageal SCC. In the phase III CheckMate 648 trial, patients with advanced, recurrent, or metastatic esophageal SCC were randomly assigned to first-line treatment in 1 of 3 arms: nivolumab + chemotherapy, nivolumab + ipilimumab, or chemotherapy alone. Approximately 70% of study participants were treated in Asia, half of the study participants had PD-L1 expression ≥1%, and half had PD-L1 expression <1%. The study’s primary endpoint was OS and PFS in patients with tumor cell PD-L1 expression ≥1%. Baseline characteristics were balanced across all treatment arms. “In this trial, the investigators were trying to see if immunotherapy alone could be equivalent to or better than cytotoxic chemotherapy,” Dr. Gibson said.

After a 29-month follow-up, nivolumab + chemotherapy and nivolumab + ipilimumab continued to demonstrate a clinically meaningful survival benefit and durable responses compared with chemotherapy alone. In patients with PD-L1 expression ≥1%, nivolumab + chemotherapy led to a median OS of 15 versus 9.1 months with chemotherapy alone (HR, 0.59). Combination immune checkpoint inhibitor therapy with nivolumab + ipilimumab was also superior to chemotherapy alone in these patients, with a median PFS of 13.1 months (HR, 0.62). OS favored nivolumab + chemotherapy and nivolumab + ipilimumab across most subgroups (less...
benefit was seen in women, who made up ~15% of study participants). A higher PFS benefit and higher overall response rate were seen with nivolumab + chemotherapy versus chemotherapy alone. Overall, patients treated with nivolumab had a longer duration of response.

Other than expected immune-related adverse events, no new safety signals were identified with nivolumab-containing regimens. These data further support nivolumab + chemotherapy and nivolumab + ipilimumab as new first-line standard-of-care treatment regimens for patients with advanced esophageal SCC.

ESCORT-1st
A third phase III randomized trial from China (ESCORT-1st) compared another checkpoint inhibitor, camrelizumab, in combination with chemotherapy versus chemotherapy alone in treatment-naïve patients with advanced or metastatic esophageal SCC.10 “China has the highest count of [having] squamous cell cancers, from which the mortality rate is very high,” stated Dr. Gibson. “So, they decided to investigate checkpoint inhibitors in their geographic region.”

After a maximum follow-up of 22 months, camrelizumab + chemotherapy provided superior median OS (15.3 vs 12.0 months) and median PFS (6.9 vs 5.6 months) versus chemotherapy alone, with a manageable safety profile. According to Dr. Gibson, these data demonstrate “another win for chemotherapy + immunotherapy in SCC of the esophagus.”

Preferred immunotherapy regimens from these trials are now incorporated into the NCCN Guidelines for the treatment of esophageal cancers (Figure 2).

References