Pr KEYTRUDA® (pembrolizumab)

A combination therapy option in the first-line setting of locally advanced unresectable or metastatic

ESOPHAGEAL CARCINOMA

- Patient Profiles →
- Safety Profile →
- Trial Design →
- Dosing →
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KEYTRUDA®, in combination with platinum and fluoropyrimidine based chemotherapy, is indicated for the first-line treatment of adult patients with locally advanced unresectable or metastatic carcinoma of the esophagus or HER2 negative adenocarcinoma of the esophagogastric junction (EGJ; tumour centre 1 to 5 centimetres above the gastric cardia)[1].

EGJ= esophagogastric junction; HER2= human epidermal growth factor receptor 2.

Consider KEYTRUDA® for your patients with esophageal cancer

Claire*, 60 years old

Meet Claire →

Richard*, 56 years old

Meet Richard →

Victor*, 72 years old

Meet Victor →

Sophie*, 35 years old

Meet Sophie →

* Fictitious patient profile. May not be representative of all patients.

Background

Age: 60 years old

History of gastroesophageal reflux disease, managed with medication

Imaging/biopsy results

Esophagogastroduodenoscopy showed a 150-mm type 1 tumor on the EGJ; histopathological examination of a biopsy specimen revealed well-differentiated adenocarcinoma; computed tomography revealed evidence of liver metastasis.

Clinical notes

ECOG PS: 0

Metastatic staging: M1

PD-L1 CPS: 11

HER2: Negative

Diagnosis: adenocarcinoma of the EGJ (1 to 5 cam above the gastric cardia)

CPS=combined positive score; ECOG PS=Eastern Cooperative Oncology Group performance status; EGJ=esophagogastric junction; HER2= human epidermal growth factor receptor 2; PD-L1=programmed death-ligand 1.

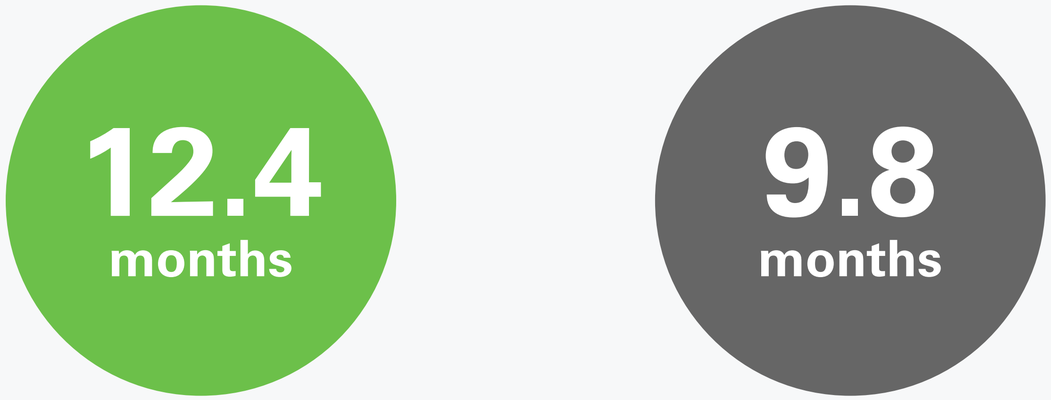
* Fictitious patient profile. May not be representative of all patients.

Results from trial KEYNOTE-590: ITT population

27% improvement in overall survival (interim analysis)
(HR: 0.73* [95% CI: 0.62, 0.86], $p<0.0001^{\dagger}$)

KEYTRUDA® + chemotherapy (262/373 with event) vs. placebo + chemotherapy (309/376 with event)

Median overall survival‡ (interim analysis)



KEYTRUDA® + chemotherapy
(95% CI: 10.5, 14.0)

Placebo + chemotherapy
(95% CI: 8.8, 10.8)

Exploratory analysis

Median overall survival in patients with esophageal adenocarcinoma (n=201) was **11.6 months** (95% CI: 9.7, 15.2) for KEYTRUDA® + chemotherapy, and **9.9 months** (95% CI: 7.8, 12.3) for placebo + chemotherapy.

HR: 0.74 (95% CI: 0.52, 1.02)

Chemotherapy=cisplatin + fluorouracil; CI=confidence interval; HR=hazard ratio; ITT=intent-to-treat.
* Based on stratified Cox proportional hazard model.
† The corresponding *p*-value bounds at the interim analysis was 0.01421.
‡ Based on Kaplan-Meier estimation.

Background

Age: 72 years old

Retired electrician

Imaging/biopsy results

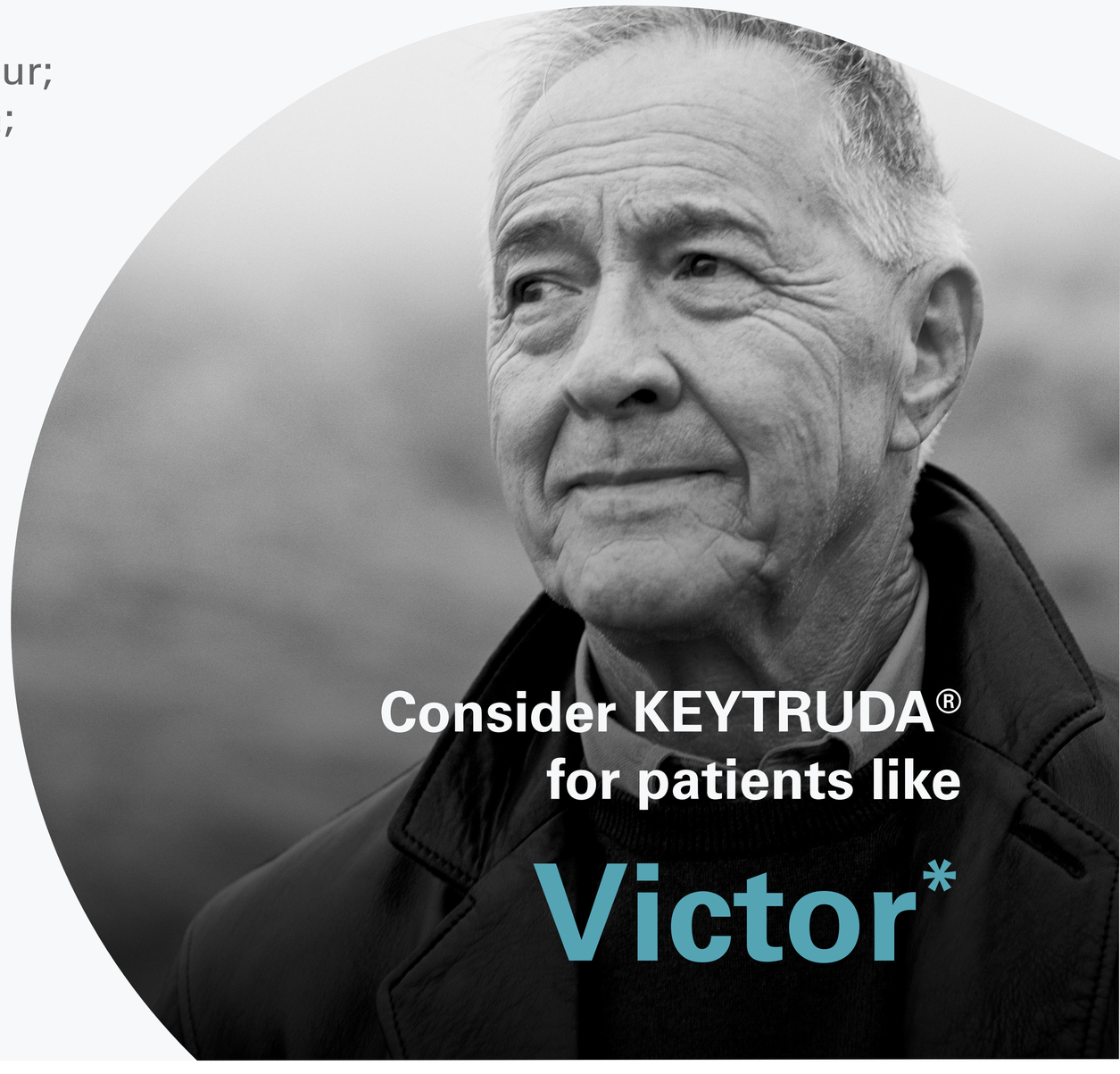
Esophagogastroduodenoscopy revealed a large tumour; pathology report confirmed squamous cell carcinoma; computed tomography examination demonstrated evidence of metastases.

Clinical notes

ECOG PS: 0

Metastatic staging: M1

Diagnosis: squamous cell carcinoma of the esophagus



ECOG PS=Eastern Cooperative Oncology Group performance status

* Fictitious patient profile. May not be representative of all patients.

Results from trial KEYNOTE-590 study publication: ESCC subgroup

28% improvement in overall survival (interim analysis)
(HR: 0.72* [95% CI: 0.60, 0.88], *p*=0.0006†‡)

KEYTRUDA® + chemotherapy (190/274 with event) vs. placebo + chemotherapy (222/274 with event)

Median overall survival§ (interim analysis)

KEYTRUDA® + chemotherapy
(95% CI: 10.2, 14.3)

Placebo + chemotherapy
(95% CI: 8.6, 11.1)

Exploratory analysis

Median overall survival in patients with squamous cell carcinoma and PD-L1 CPS <10 (n=247) was **10.5 months** (95% CI: 9.2, 13.5) for KEYTRUDA® + chemotherapy, and **11.1 months** (95% CI: 9.1, 12.4) for placebo + chemotherapy.

HR: 0.99 (95% CI: 0.74, 1.32)

Chemotherapy=cisplatin + flourouracil; CI=confidence interval; CPS=combined positive score;
ESCC=esophageal squamous cell carcinoma; PD-L1=programmed death-ligand 1; HR=hazard ratio.
* Based on stratified Cox proportional hazard model.
† Based on stratified log-rank test.
‡ The corresponding *p*-value bounds at the interim analysis in ESCC was 0.01003, following pre-specified multiplicity adjustment.
§ Based on Kaplan-Meier estimation.

Background

Age: 56 years old

Mechanic

Imaging/biopsy results

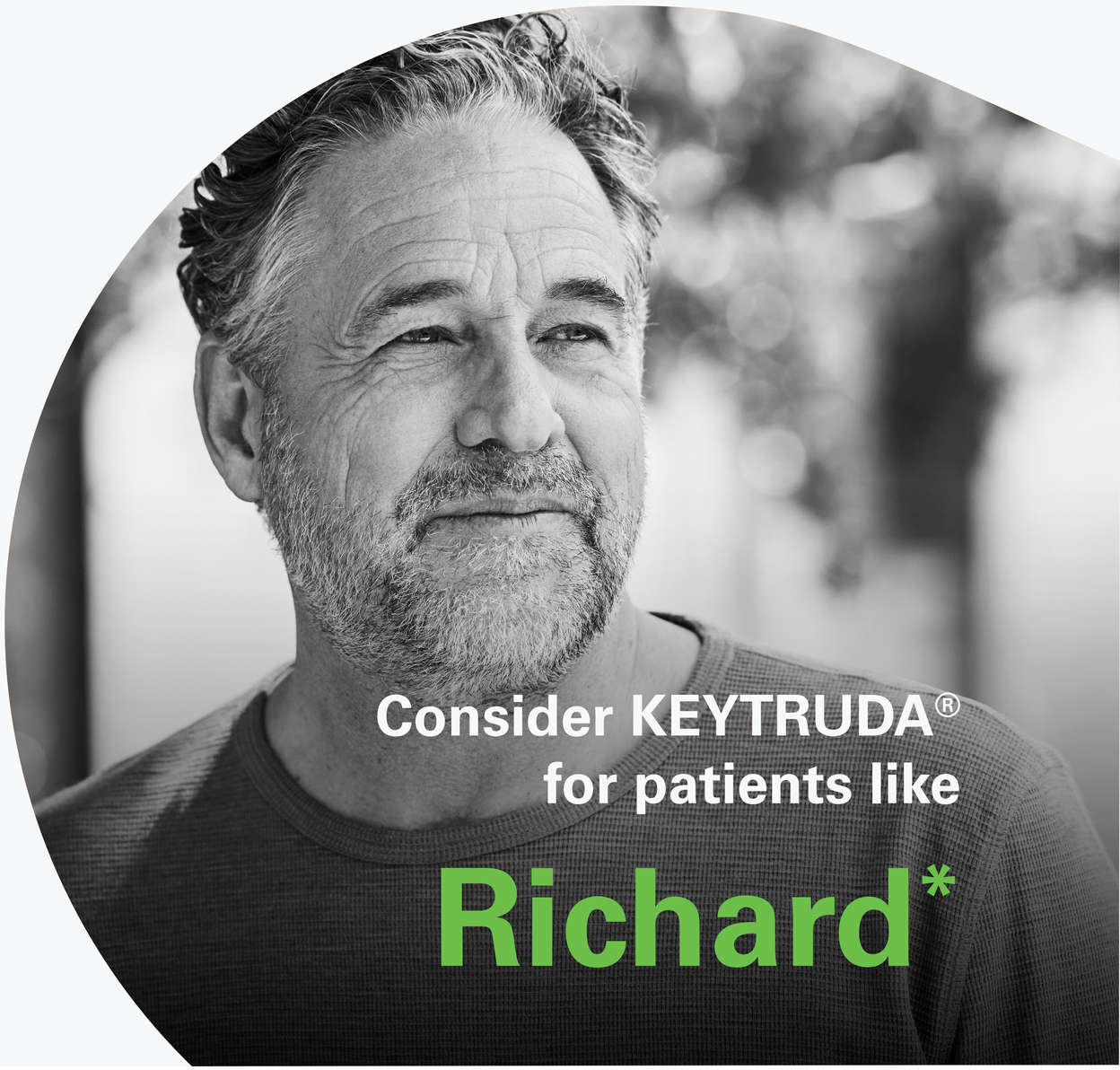
Primary tumour discovered during upper gastrointestinal endoscopy. Lung and liver metastases were not observed.

Clinical notes

ECOG PS: 1

Metastatic staging: M1

Diagnosis: adenocarcinoma of the EGJ (1 to 5 cm above the gastric cardia)



ECOG PS=Eastern Cooperative Oncology Group performance status; EGJ = esophagogastric junction.

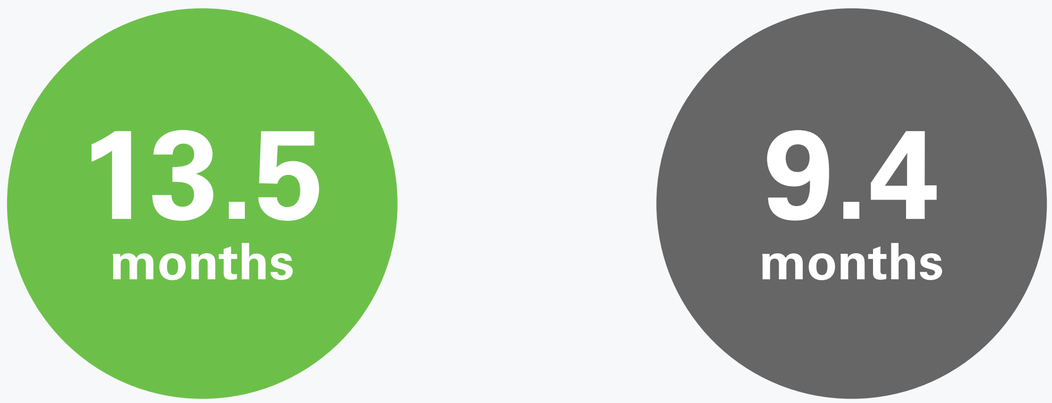
* Fictitious patient profile. May not be representative of all patients.

Results from trial KEYNOTE-590 study publication: PD-L1 CPS ≥10 subgroup

38% improvement in overall survival (interim analysis)
(HR: 0.62* [95% CI: 0.49, 0.78], $p<0.0001^{\dagger\ddagger}$)

KEYTRUDA® + chemotherapy (124/186 with event) vs. placebo + chemotherapy (165/197 with event)

Median overall survival§ (interim analysis)



KEYTRUDA® + chemotherapy
(95% CI: 11.1, 15.6)

Placebo + chemotherapy
(95% CI: 8.0, 10.7)

Exploratory analysis

Median overall survival in patients with PD-L1 CPS <10 (n=347) was **10.5 months** (95% CI: 9.7, 13.5) for KEYTRUDA® + chemotherapy, and **10.6 months** (95% CI: 8.8, 12.0) for placebo + chemotherapy.

HR: 0.86 (95% CI: 0.68, 1.10)

Chemotherapy=cisplatin + fluorouracil; CI=confidence interval; CPS=combined positive score; ESCC=esophageal squamous cell carcinoma; HR=hazard ratio; PD-L1=programmed death-ligand 1.
* Based on stratified Cox proportional hazard model.
† Based on stratified log-rank test.
‡ The corresponding *p*-value bound at the interim analysis in ESCC (esophageal squamous cell carcinoma) was 0.01414, following prespecified multiplicity adjustment.
§ Based on Kaplan-Meier estimation.

Background

Age: 35 years old

Grade school educator

Imaging/biopsy results

An upper endoscopy was performed;
biopsies taken from lesional tissue;
biopsy confirmed squamous cell carcinoma.

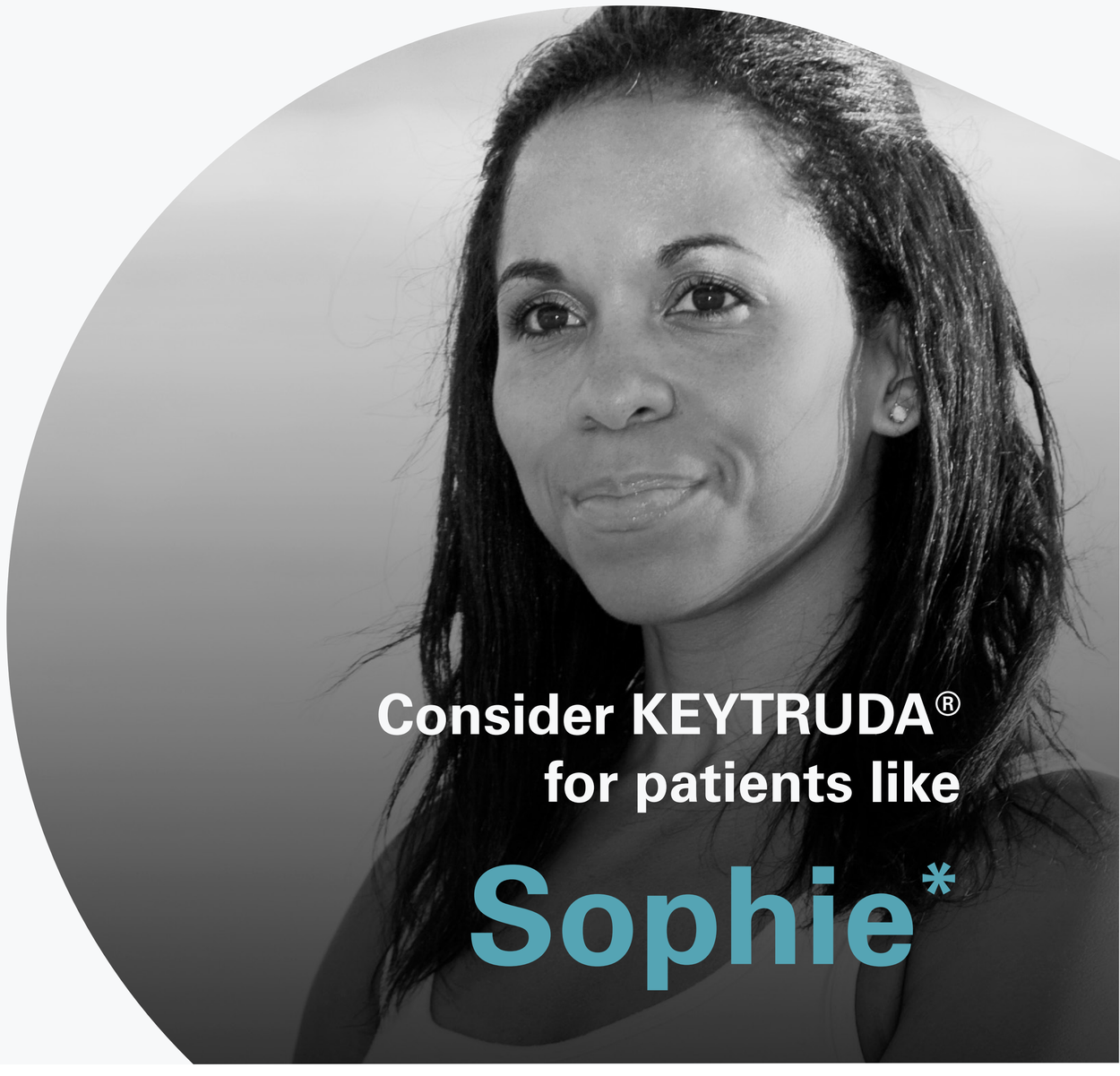
Clinical notes

ECOG PS: 1

Metastatic staging: M1

PD-L1 CPS: 15

Diagnosis: squamous cell carcinoma of the esophagus



CPS=combined positive score;
ECOG PS=Eastern Cooperative Oncology Group performance status;
PD-L1=programmed death-ligand 1.

* Fictitious patient profile. May not be representative of all patients.

Results from trial KEYNOTE-590 study publication: ESCC and PD-L1 CPS ≥10 subgroup

43% improvement in overall survival (interim analysis) (HR: 0.57* [95% CI: 0.43, 0.75], $p<0.0001^{\dagger\ddagger}$)

KEYTRUDA® + chemotherapy (94/143 with event) vs. placebo + chemotherapy (121/143 with event)

Median overall survival§ (interim analysis)

KEYTRUDA® + chemotherapy
(95% CI: 11.1, 17.7)

Placebo + chemotherapy
(95% CI: 7.8, 10.5)

Chemotherapy=cisplatin + fluorouracil; CI=confidence interval; CPS=combined positive score; ESCC=esophageal squamous cell carcinoma; HR=hazard ratio; PD-L1=programmed death-ligand 1.

* Based on stratified Cox proportional hazard model.

† Based on stratified log-rank test.

‡ The corresponding *p*-value bounds at the interim analysis in ESCC PD-L1 CPS≥10 was 0.0067, following pre-specified multiplicity adjustment.

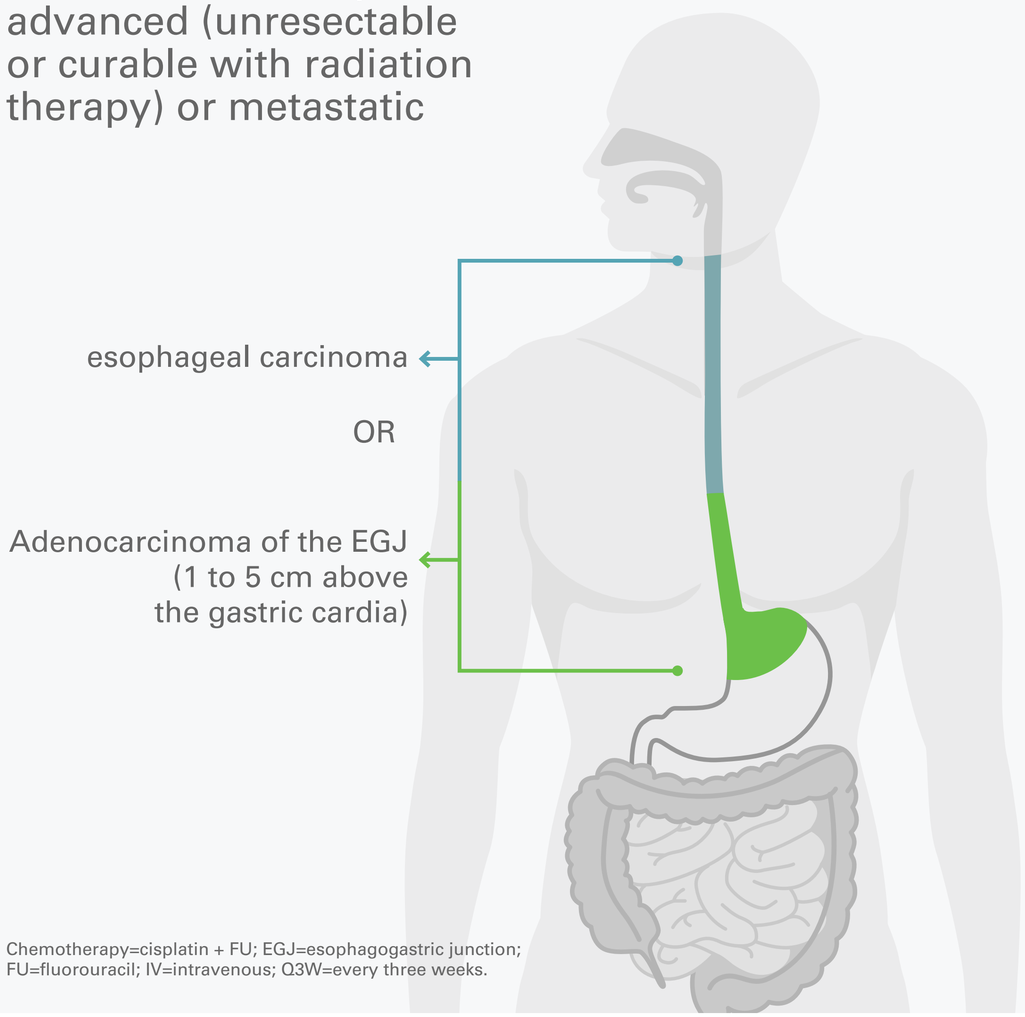
§ Based on Kaplan-Meier estimation.

Pivotal trial KEYNOTE-590 study publication: KEYTRUDA® in combination with chemotherapy (cisplatin and FU)

KEYNOTE-590 study design

Multicentre, randomized, placebo-controlled encompassing 749 treatment-naïve patients

Patients had locally advanced (unresectable or curable with radiation therapy) or metastatic



Chemotherapy=cisplatin + FU; EGJ=esophagogastric junction; FU=fluorouracil; IV=intravenous; Q3W=every three weeks.

Treatment arms

KEYTRUDA® + chemotherapy	Placebo + chemotherapy
200mg Q3W (n=373)	(cisplatin + FU, n=376)

Chemotherapy doses: cisplatin 80 mg/m^2 IV on Day 1 of each 3-week cycle for up to 6 cycles and FU 800 mg/m^2 IV per day on Days 1 to 5 of each 3-week cycle, or per standard for FU administration.

- Treatment continued until unacceptable toxicity or disease progression, or for up to 24 months

Endpoints[1]

Primary endpoints

- Overall survival, assessed by the investigator according to RECIST 1.1
- Progression-free survival, assessed by the investigator according to RECIST 1.1

In addition to the total population, prespecified analyses of the primary endpoints were:

Patients with **squamous cell** histology and patients with **PD-L1 CPS ≥10**

Secondary endpoints

- Objective response rate, assessed by the investigator per RECIST v1.1
- Duration of response, assessed by the investigator per RECIST v1.1

CPS=combined positive score; PD-L1=programmed death-ligand 1; RECIST=Response Evaluation Criteria in Solid Tumours.

Selected baseline demographics

		KEYTRUDA® + chemotherapy (n=373)	Placebo + chemotherapy (n=376)
Male		82%	85%
Age, median (range)		64 (28-94) years	62 (27-89) years
ECOG	**PS 0**	40%	40%
	PS 1	60%	60%
Metastatic staging	**M0**	8%	10%
	M1	92%	90%
Histology	**Adenocarcinoma**	27%	27%
Squamous cell carcinoma		74%	73%

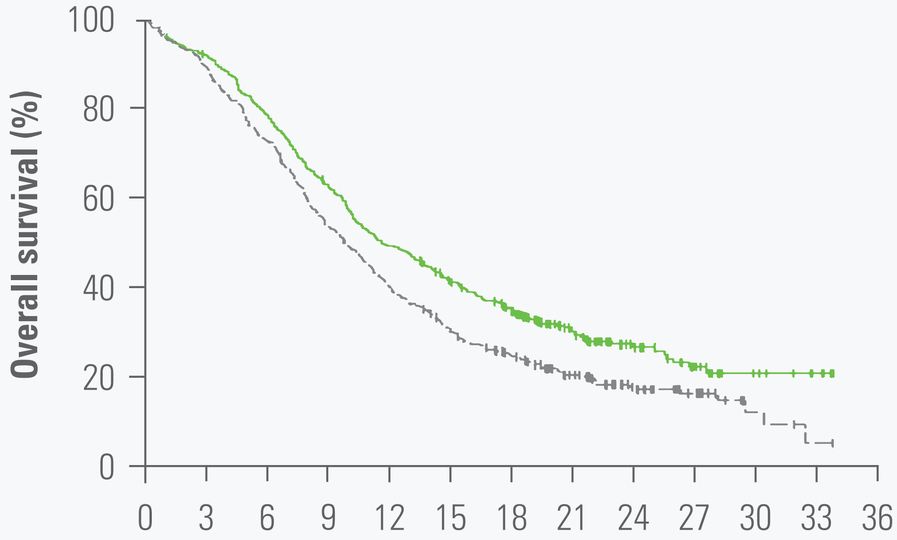
Chemotherapy=cisplatin + fluorouracil; ECOG=Eastern Cooperative Oncology Group; PS=performance status.

KEYTRUDA® + chemotherapy demonstrated powerful improvement in overall survival vs. placebo + chemotherapy (HR: 0.73 [95% CI: 0.62, 0.86], *p*<0.0001) in patients with locally advanced or metastatic esophageal and adenocarcinoma of the EGJ (1 to 5 cm above the gastric cardia) in the KEYNOTE-590 study publication (ITT population)

Number of patients with event:

70% (262/373) KEYTRUDA® + chemotherapy vs. **82%** (309/376) KEYTRUDA® + chemotherapy (*p*<0.0001)

Overall survival for KEYTRUDA® + chemotherapy vs. placebo + chemotherapy



Number at risk													
KEYTRUDA® + chemotherapy	373	348	295	235	187	151	118	68	36	17	7	2	0
Placebo + chemotherapy	376	338	274	200	147	108	82	51	28	15	4	1	0

Adapted from the KEYTRUDA® Product Monograph.

In locally advanced unresectable or metastatic esophageal carcinoma, CONSIDER KEYTRUDA®.

Chemotherapy=cisplatin + fluorouracil; CI=confidence interval; EGJ=esophagogastric junction; HR=hazard ratio; ITT=intent-to-treat.

Efficacy demonstrated among patient with a **range** of clinical characteristics

ITT population

27% improvement in overall survival (interim analysis)
(HR: 0.73* [95% CI: 0.62, 0.86], $p<0.0001^{\dagger}$)

KEYTRUDA® + chemotherapy (262/373 with event) vs. placebo + chemotherapy (309/376 with event)

Median overall survival[§] (interim analysis)

12.4 months
KEYTRUDA® + chemotherapy
(95% CI: 10.5, 14.0)

9.8 months
Placebo + chemotherapy
(95% CI: 8.8, 10.8)

ESCC subgroup

28% improvement in overall survival (interim analysis)
(HR: 0.72* [95% CI: 0.60, 0.88], $p=0.0006^{\ddagger}$)

KEYTRUDA® + chemotherapy (190/274 with event) vs. placebo + chemotherapy (222/274 with event)

Median overall survival[§] (interim analysis)

12.6 months
KEYTRUDA® + chemotherapy
(95% CI: 10.2, 14.3)

9.8 months
Placebo + chemotherapy
(95% CI: 8.6, 11.1)

PD-L1 CPS ≥10 subgroup

38% improvement in overall survival (interim analysis)
(HR: 0.62* [95% CI: 0.49, 0.78], $p<0.0001^{\ddagger}$)

KEYTRUDA® + chemotherapy (124/186 with event) vs. placebo + chemotherapy (165/197 with event)

Median overall survival[§] (interim analysis)

13.5 months
KEYTRUDA® + chemotherapy
(95% CI: 11.1, 15.6)

9.4 months
Placebo + chemotherapy
(95% CI: 8.0, 10.7)

ESCC and PD-L1 CPS ≥10 subgroup[‡]

43% improvement in overall survival (interim analysis)
(HR: 0.57* [95% CI: 0.43, 0.75], $p<0.0001^{\ddagger}$)

KEYTRUDA® + chemotherapy (94/143 with event) vs. placebo + chemotherapy (121/143 with event)

Median overall survival[§] (interim analysis)

13.9 months
KEYTRUDA® + chemotherapy
(95% CI: 11.1, 17.7)

8.8 months
Placebo + chemotherapy
(95% CI: 7.8, 10.5)

Chemotherapy=cisplatin + fluorouracil; CI=confidence interval; CPS=combined positive score; ESCC=esophageal squamous cell carcinoma; HR=hazard ratio; ITT=intent-to-treat; PD-L1=programmed death-ligand 1.

* Based on stratified Cox proportional hazard model.

† The corresponding *p*-value bounds at the interim analysis was 0.01421, following pre-specified multiplicity adjustment.

‡ The corresponding *p*-value bounds at the interim analysis in ESCC PD-L1 CPS≥10, ESCC and PD-L1 CPS≥10 was 0.0067, 0.01003 and 0.01414, respectively, following pre-specified multiplicity adjustment.

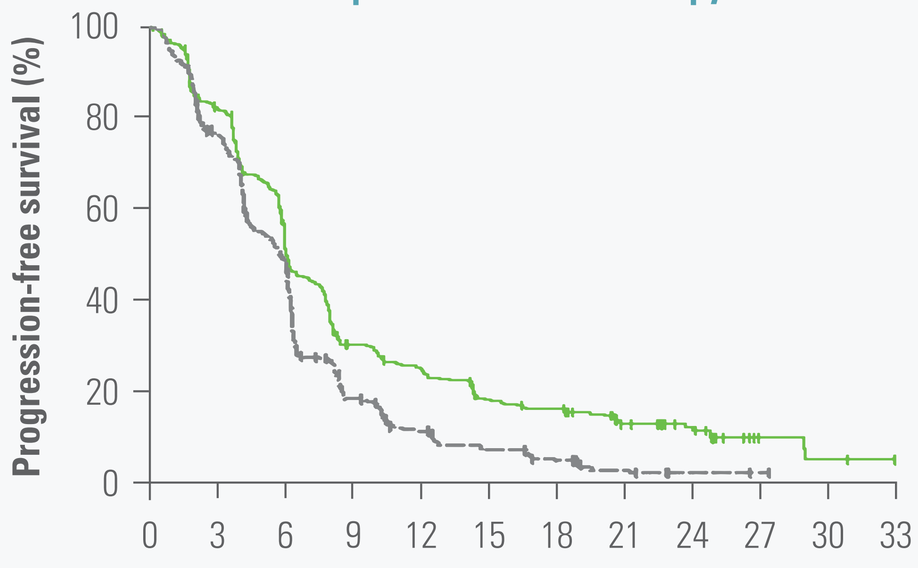
§ Based on Kaplan-Meier estimation.

KEYTRUDA® + chemotherapy demonstrated powerful improvement in progression-free survival vs. placebo + chemotherapy (HR: 0.65 [95% CI: 0.55, 0.76], p<0.0001) in patients with locally advanced or metastatic esophageal and adenocarcinoma of the EGJ (1 to 5 cm above the gastric cardia) in the KEYNOTE-590 study publication (ITT population)

Number of patients with event:

79.6% (297/373) KEYTRUDA® + chemotherapy vs. **88.6%** (333/376) placebo + chemotherapy (*p*<0.0001)

Progression-free survival for KEYTRUDA® + chemotherapy vs. placebo + chemotherapy



Number at risk

KEYTRUDA® + chemotherapy	373	289	210	96	79	55	45	25	17	4	2	0
Placebo + chemotherapy	376	278	172	62	36	22	14	6	2	1	0	0

Adapted from the KEYTRUDA® Product Monograph.

35% improvement in progression-free survival (interim analysis) (HR: 0.65* [95% CI: 0.55, 0.76], *p*<0.0001†)

Median progression-free survival (interim analysis)‡

KEYTRUDA® + chemotherapy (297/373 with event) vs. placebo + chemotherapy (333/376 with event)

6.3 months
KEYTRUDA® + chemotherapy
(95% CI: 6.2, 6.9)

5.8 months
Placebo + chemotherapy
(95% CI: 5.0, 6.0)

Chemotherapy=cisplatin + fluorouracil; CI=confidence interval; EGJ=esophagogastric junction; HR=hazard ratio; ITT=intent-to treat.* Based on stratified Cox proportional hazard model.

† The corresponding *p*-value bounds at the interim analysis was 0.02477, following pre-specified multiplicity adjustment.

‡ Based on Kaplan-Meier estimation.

Objective response rate (secondary endpoint)

KEYTRUDA® + chemotherapy

45% (95% CI: 39.9, 50.2)
p<0.0001*†

Complete response: 6.4%
Partial response: 38.6%

Placebo + chemotherapy

29.3% (95% CI: 24.7, 34.1)

Complete response: 2.4%
Partial response: 26.9%

Duration of response, median (secondary endpoint)

8.3 months

KEYTRUDA® + chemotherapy
(range: 1.2+, 31.0+)

6.0 months

Placebo + chemotherapy
(range: 1.5+, 25.0+)

Chemotherapy=cisplatin + fluorouracil; CI=confidence interval.
* Miettinen-Nurminen method.
† The *p*-value bound at the interim analysis was 0.025, following pre-specified multiplicity adjustment.

Established safety profile in locally advanced unresectable or metastatic esophageal carcinoma with KEYTRUDA® in combination with cisplatin and FU in KEYNOTE-590 study publication[1]

Most common treatment-related adverse events (trAEs, reported in ≥20% of patients) with either KEYTRUDA® + chemotherapy or placebo + chemotherapy

	KEYTRUDA® + chemotherapy (n=370)				Placebo + chemotherapy (n=370)			
	Any grade	Grade 3	Grade 4	Grade 5	Any grade	Grade 3	Grade 4	Grade 5
Nausea	63.0%	7%	0%	0%	59.5%	6.5%	0%	0%
Decreased appetite	39.2%	3.5%	0%	0%	32.2%	4.3%	0%	0%
Anemia	38.6%	12.2%	0.3%	0%	43.8%	14.6%	0%	0%
Fatigue	36.5%	5.9%	0.3%	0%	28.9%	5.4%	0%	0%
Decreased neutrophil count	36.5%	16.2%	6.5%	0%	29.5%	11.6%	5.1%	0%
Vomiting	29.7%	6.2%	0%	0%	26.8%	4.9%	0%	0%
Diarrhea	26.2%	2.7%	0.3%	0.3%	23.0%	1.9%	0%	0%
Neutropenia	25.9%	11.1%	3.2%	0%	23.8%	12.2%	4.1%	0%
Stomatitis	25.9%	5.7%	0%	0%	25.1%	3.8%	0%	0%
Decreased white blood cells	24.1%	7.3%	1.4%	0%	18.6%	3.2%	1.6%	0%

Adapted from the KEYTRUDA® Product Monograph.

- Fatal trAEs occurred in 2.4% of KEYTRUDA® + chemotherapy patients, including 1 case each of multiple organ dysfunction syndrome, pulmonary embolism, interstitial lung disease, pneumonitis, febrile neutropenia, pneumonia, acute kidney injury, diarrhea and hepatic failure.
- Serious trAEs occurred in 32% of KEYTRUDA® + chemotherapy patients. Serious AEs occurring in ≥2% of patients were pneumonia (3.5%), pneumonitis (3.2%), febrile neutropenia (2.4%), acute kidney injury (2.2%) and vomiting (2.2%).
- KEYTRUDA® was discontinued for trAEs in 7.3% of patients.

Chemotherapy=cisplatin + fluorouracil; FU=fluorouracil; AEs=adverse events; trAEs=treatment-related adverse events.

Flexible dosing with KEYTRUDA®[1]

Recommended dosing regimens in esophageal cancer:

Administered as an intravenous infusion over 30 minutes

Q3W= dosing every three weeks; Q6W= dosing every six weeks.

Continue until:

- Unacceptable toxicity
- Disease progression
- Up to 24 months

Administer KEYTRUDA® prior to chemotherapy when given on the same day.

Let patients know that they have two options for KEYTRUDA® dosing, and discuss which regimen is right for them

Atypical responses (i.e., an initial transient increase in tumour size or small new lesions within the first few months followed by tumour shrinkage) have been observed. Clinically stable patients with initial evidence of disease progression may remain on treatment until disease progression is confirmed.

Please see the Product Monograph for complete information on dosage, administration and dosage adjustments.

NCCN Clinical Practice Guidelines In Oncology (NCCN Guidelines®) for Esophageal and Esophagogastric Junction Cancers

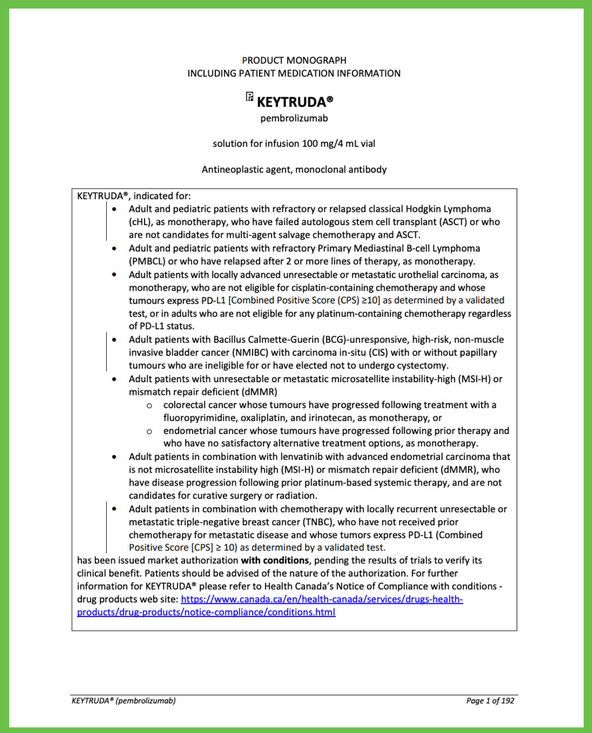
Systemic therapy recommendations for unresectable locally advanced or metastatic cancer (where local therapy is not indicated)[2]

- Pembrolizumab, fluorouracil, and cisplatin is a **preferred first-line therapy** regimen

Please see the 2022 NCCN Guidelines® for detailed recommendations, including other options.

NCCN=National Comprehensive Cancer Network® (NCCN®).

Resources



PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

Pr **KEYTRUDA®**
pembrolizumab

solution for infusion 100 mg/4 mL vial

Antineoplastic agent, monoclonal antibody

KEYTRUDA®, indicated for:

- Adult and pediatric patients with refractory or relapsed classical Hodgkin Lymphoma (cHL), as monotherapy, who have failed autologous stem cell transplant (ASCT) or who are not candidates for multi-agent salvage chemotherapy and ASCT.
- Adult and pediatric patients with refractory Primary Mediastinal B-cell Lymphoma (PMBCL) or who have relapsed after 2 or more lines of therapy, as monotherapy.
- Adult patients with locally advanced unresectable or metastatic urothelial carcinoma, as monotherapy, who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 [Combined Positive Score (CPS) ≥10] as determined by a validated test, or in adults who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status.
- Adult patients with Bacillus Calmette-Guerin (BCG)-unresponsive, high-risk, non-muscle invasive bladder cancer (NMIBC) with carcinoma in-situ (CIS) with or without papillary tumours who are ineligible for or have elected not to undergo cystectomy.
- Adult patients with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR)
  - colorectal cancer whose tumours have progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, as monotherapy, or
  - endometrial cancer whose tumours have progressed following prior therapy and who have no satisfactory alternative treatment options, as monotherapy.
- Adult patients in combination with lenvatinib with advanced endometrial carcinoma that is not microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR), who have disease progression following prior platinum-based systemic therapy, and are not candidates for curative surgery or radiation.
- Adult patients in combination with chemotherapy with locally recurrent unresectable or metastatic triple-negative breast cancer (TNBC), who have not received prior chemotherapy for metastatic disease and whose tumors express PD-L1 (Combined Positive Score [CPS] ≥ 10) as determined by a validated test.

has been issued market authorization **with conditions**, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization. For further information for KEYTRUDA® please refer to Health Canada's Notice of Compliance with conditions - drug products web site: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/notice-compliance/conditions.html

KEYTRUDA® (pembrolizumab) *Page 1 of 192*

**KEYTRUDA®
Product Monograph**

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THE LANCET

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Pembrolizumab plus chemotherapy versus chemotherapy alone for first-line treatment of advanced oesophageal cancer (KEYNOTE-590): a randomised, placebo-controlled, phase 3 study

Jong-Mu Sun, MD · Lin Shen, MD · Prof Manish A Shah, MD · Peter Enzinger, MD · Prof Antoine Adenis, MD · Toshihiko Doi, MD · et al. Show all authors · Show footnotes

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Summary

Background

First-line therapy for advanced oesophageal cancer is currently limited to fluoropyrimidine plus platinum-based chemotherapy. We aimed to evaluate the antitumour activity of pembrolizumab plus chemotherapy versus chemotherapy alone as first-line treatment in advanced oesophageal cancer and Siewert type 1 gastro-oesophageal junction cancer.

Methods

We did a randomised, placebo-controlled, double-blind, phase 3 study across 168 medical centres in 26 countries. Patients aged 18 years or older with previously untreated, histologically or cytologically confirmed, locally advanced, unresectable or metastatic oesophageal cancer or Siewert type 1 gastro-oesophageal junction cancer (regardless of PD-L1 status), measurable disease per Response Evaluation Criteria in Solid Tumors version 1.1, and Eastern Cooperative Oncology Group performance status of 0–1, were randomly assigned (1:1) to intravenous pembrolizumab 200 mg or placebo, plus 5-fluorouracil and cisplatin (chemotherapy), once every 3 weeks for up to 35 cycles. Randomisation was stratified by geographical region, histology, and performance status. Patients, investigators, and site staff were masked to group assignment and PD-L1 biomarker status. Primary endpoints were overall survival in patients with oesophageal squamous cell carcinoma and PD-L1 combined positive score (CPS) of 10 or more, and overall survival and progression-free survival in patients with oesophageal squamous cell carcinoma, PD-L1 CPS of 10 or more, and in all randomised patients. This trial is registered with ClinicalTrials.gov, NCT03189719, and is closed to recruitment.

Findings

Between July 25, 2017, and June 3, 2019, 1020 patients were screened and 749 were enrolled and randomly assigned to pembrolizumab plus chemotherapy (n=373 [50%]) or placebo plus chemotherapy (n=376 [50%]). At the first interim analysis (median follow-up of 22·6 months), pembrolizumab plus chemotherapy was superior to placebo plus chemotherapy for overall survival in patients with oesophageal squamous cell carcinoma and PD-L1 CPS of 10 or more (median 13·9 months *vs* 8·8 months; hazard ratio 0·57 [95% CI 0·43–0·75]; p<0·0001), oesophageal squamous cell carcinoma (12·6 months *vs* 9·8 months; 0·72 [0·60–0·88]; p=0·0006), PD-L1 CPS of 10 or more (13·5 months *vs* 9·4 months; 0·62 [0·49–0·78]; p<0·0001), and in all randomised patients (12·4 months *vs* 9·8 months; 0·73 [0·62–0·86]; p<0·0001). Pembrolizumab plus chemotherapy was superior to placebo plus chemotherapy for progression-free survival in patients with oesophageal squamous cell carcinoma (6·3 months *vs* 5·8 months; 0·65 [0·54–0·78]; p<0·0001), PD-L1 CPS of 10 or more (7·5 months *vs* 5·5 months; 0·51 [0·41–0·65]; p<0·0001), and in all randomised patients (6·3 months *vs* 5·8 months; 0·65 [0·55–0·76]; p<0·0001). Treatment-related adverse events of grade 3 or higher occurred in 266 (72%) patients in the pembrolizumab plus chemotherapy group versus 250 (68%) in the placebo plus chemotherapy group.

Interpretation

Compared with placebo plus chemotherapy, pembrolizumab plus chemotherapy improved overall survival in patients with previously untreated, advanced oesophageal squamous cell carcinoma and PD-L1 CPS of 10 or more, and overall survival and progression-free survival in patients with oesophageal squamous cell carcinoma, PD-L1 CPS of 10 or more, and in all randomised patients regardless of histology, and had a manageable safety profile in the total as-treated population.

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Important safety information

Clinical use:

Safety and efficacy of KEYTRUDA® in pediatric patients have not been established for esophageal cancer.

Pediatrics (<18 years of age): The safety and efficacy of KEYTRUDA® has not been established for pediatric patients.

Geriatrics (>65 years of age): No overall differences in safety or efficacy were reported between elderly patients (65 years and over) and younger patients (less than 65 years).

Relevant warnings and precautions:

- Immune-mediated adverse reactions, including severe and fatal cases:
  - Pneumonitis
  - Colitis
  - Hepatitis
  - Nephritis and renal dysfunction
  - Endocrinopathies including adrenal insufficiency, hypophysitis, type 1 diabetes mellitus, diabetic ketoacidosis, hypothyroidism, and hyperthyroidism
  - Severe skin reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis
- Other immune-mediated adverse events including uveitis, arthritis, myositis, encephalitis, sarcoidosis, myasthenic syndrome/myasthenia gravis, vasculitis, Guillain-Barré syndrome, hemolytic anemia, pancreatitis, myelitis, hypoparathyroidism, myocarditis, sclerosing cholangitis
- Solid organ transplant rejection
- Allogeneic hematopoietic stem cell transplant after and before treatment
- Severe infusion-related reactions
- Teratogenic toxicity
- Women of childbearing potential should use highly effective contraception and take active measure to avoid pregnancy during treatment with KEYTRUDA® and for at least 4 months after the last dose
- Patients with hepatic impairment
- Renal impairment
- Driving and operating machinery
- Monitoring requirements
- Pediatrics
- Geriatrics

For more information:

Please consult the Product Monograph at https://www.merck.ca/confirm-monograph.xhtml?file=KEYTRUDA-PM_E.pdf for important information regarding adverse reactions, drug interactions, and dosing information which have not been discussed in this piece. The Product Monograph is also available by calling us at 1-800-567-2594 or by email at medinfocanada@merck.com.

References

References: 1. KEYTRUDA® Product Monograph. Merck Canada Inc., January 25, 2023. **2.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Esophageal and Esophagogastric Junction Cancers V4.2022. © National Comprehensive Cancer Network, Inc. 2022. All rights reserved. Accessed October 27, 2022. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

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