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KEYTRUDA in First-Line Esophageal Cancer

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What You Will Hear

Overview of Pembrolizumab and PD-L1 22C3 PharmDx

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KEYNOTE-590 Results in Esophageal Cancer

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Clinical Management of Esophageal Cancer

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KEYTRUDA Helps Address an Unmet Need in Esophageal Cancer

- Metastatic esophageal cancer is a rare disease, and patients have a poor prognosis
- Current SOC of chemotherapy + IO in 1L esophageal cancer addresses a significant unmet need

KEYNOTE-590

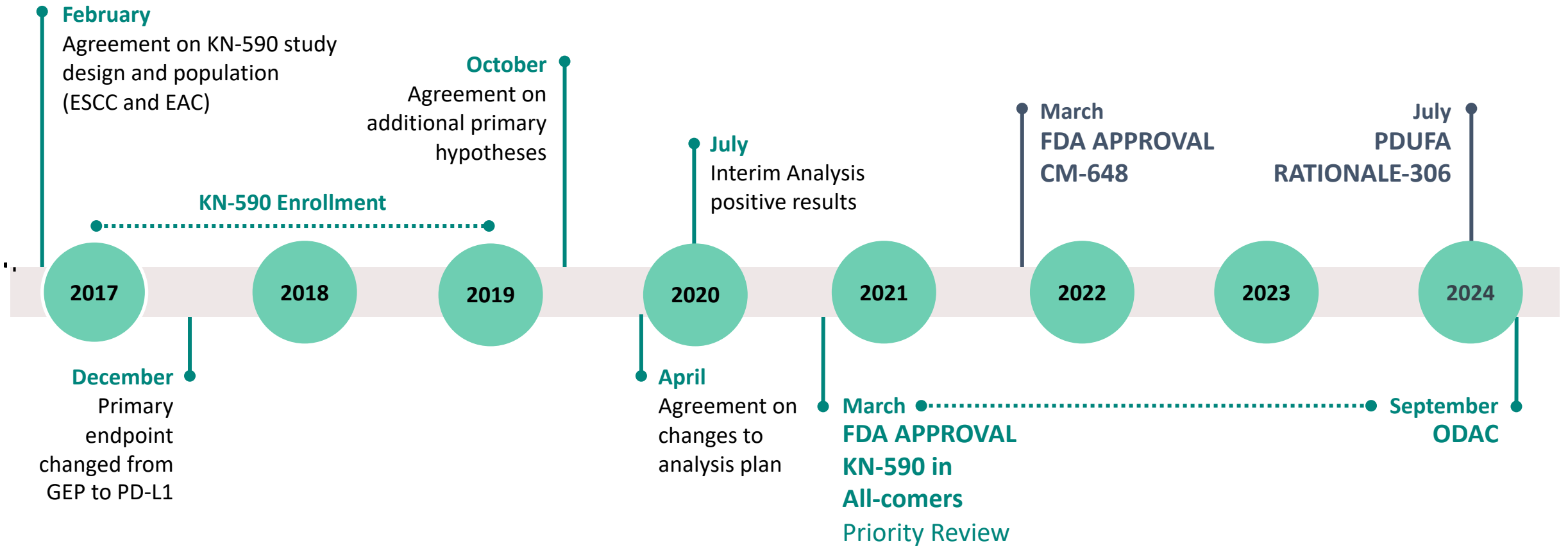
- Rigorous study design and conduct
- Success criteria met for all endpoints

→ Key study data reflected in current label →

- Guides physician-patient decision making
- All patients who may benefit retain access

Current indication for pembrolizumab should be retained

Development and Regulatory History for KEYNOTE-590



KN-590 is the first approval with IO in first-line treatment of metastatic esophageal cancer in the US

Robust Sample Processing, Cut-point Determination, Scoring, and Validation in Merck Randomized Trials

1 Sample processing, PD-L1 staining, and scoring

Assay kit: PD-L1 IHC 22C3 pharmDx by Agilent

Quantified using combined positive score (CPS):

- CPS captures PD-L1 expression on tumor cells, lymphocytes, and macrophages
- CPS scores range: 0 to 100

2 Training set

Merck clinical study

3 Cut-point determination

Trial-specific CPS cut-point

4 Validation set

KEYNOTE-590

Cut-point was

- Pre-specified in trials
- Scored by pathologists
- Analytically validated by Dx partner and testing lab

Robust PD-L1 data support all-comers indication for KEYNOTE-590

Rigorous Statistical Approaches in Phase 3 Trials and Limitations of Post hoc Subgroup and Pooled Analyses

- Statistically rigorous and accepted methodology for Phase 3 studies:
  - Strong type 1 error control and adequate sample size required to prospectively test a hypothesis
  - Subgroup analysis is considered exploratory to assess directional consistency of treatment effect
- Post hoc subgroup analysis at various cut-points not rigorously assessed or pre-specified may lead to spurious finding of randomly high or low treatment effect estimates
- Pooled analysis to inform product labeling has inherent limitations and does not replace well controlled individual studies
  - Assumes identical:
    - Efficacy for all ICIs
    - Patient population within the selected subgroup, despite trial, assay and cut-point differences

Key Considerations When Evaluating Benefit-Risk of Pembrolizumab in Esophageal Cancer Based on PD-L1 status

- KN-590 is a large Phase 3 study conducted with rigorous statistical design
  - No new data with pembrolizumab that changes benefit-risk
- The PD-L1 IHC 22C3 pharmDx assay is specifically studied for pembrolizumab in the approved indication
- There are key differences in considering a restriction of this indication by PD-L1 cut-point compared to those for cetuximab/panitumumab and olaparib

The practice of medicine is informed by clinical guidelines and individual benefit-risk assessment

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KEYNOTE-590 Results in Esophageal Cancer

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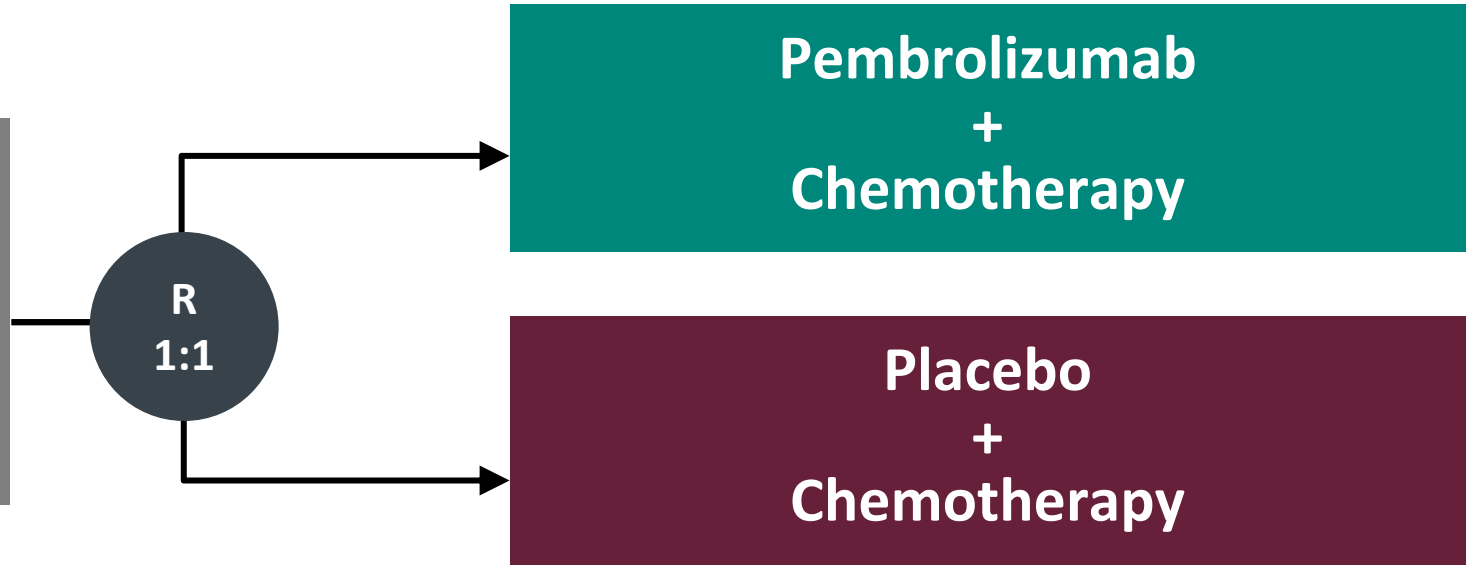
1L Esophageal Cancer (KEYNOTE-590)

Keytruda, for the treatment of patients with locally advanced or metastatic esophageal or gastroesophageal junction (GEJ) (tumors with epicenter 1 to 5 centimeters above the GEJ) carcinoma that is not amenable to surgical resection or definitive chemoradiation in combination with platinum- and fluoropyrimidine-based chemotherapy.

Phase 3, 1L Esophageal Cancer Study
KN-590

Key Eligibility Criteria

- Locally advanced unresectable or metastatic EAC or ESCC or EGJ Siewert type 1 adenocarcinoma
- Treatment naive
- ECOG PS 0 or 1
- Measurable disease (RECIST v1.1)



Dual Primary Endpoints: OS and PFS

- **OS** in ESCC PD-L1 CPS≥10
- **OS** in ESCC
- **OS** in PD-L1 CPS≥10
- **OS** in all patients
- **PFS** in ESCC
- **PFS** in PD-L1 CPS≥10
- **PFS** in all patients

Stratification Factors

- Asia vs Non-Asia region
- ESCC vs EAC
- ECOG PS 0 vs 1

EAC=esophageal adenocarcinoma; ECOG PS=Eastern Cooperative Oncology Group performance status; EGJ=esophagogastric junction, ESCC=esophageal squamous cell carcinoma.

Key Study Design Elements Based on PD-L1 Expression

KN-590

Central PD-L1 Testing

- Early pembrolizumab monotherapy study indicated antitumor response
- Agilent PD-L1 IHC 22C3 pharmDx assay validated at CPS≥10

Initial Study Design

- Hypothesis testing in ITT and GEP biomarker-positive

Protocol Amendment After KN-180 Readout

- Added hypothesis testing in CPS≥10

~51% of ITT was CPS≥10

GEP=gene expression profile.

Baseline Characteristics Were Balanced

KN-590: ITT

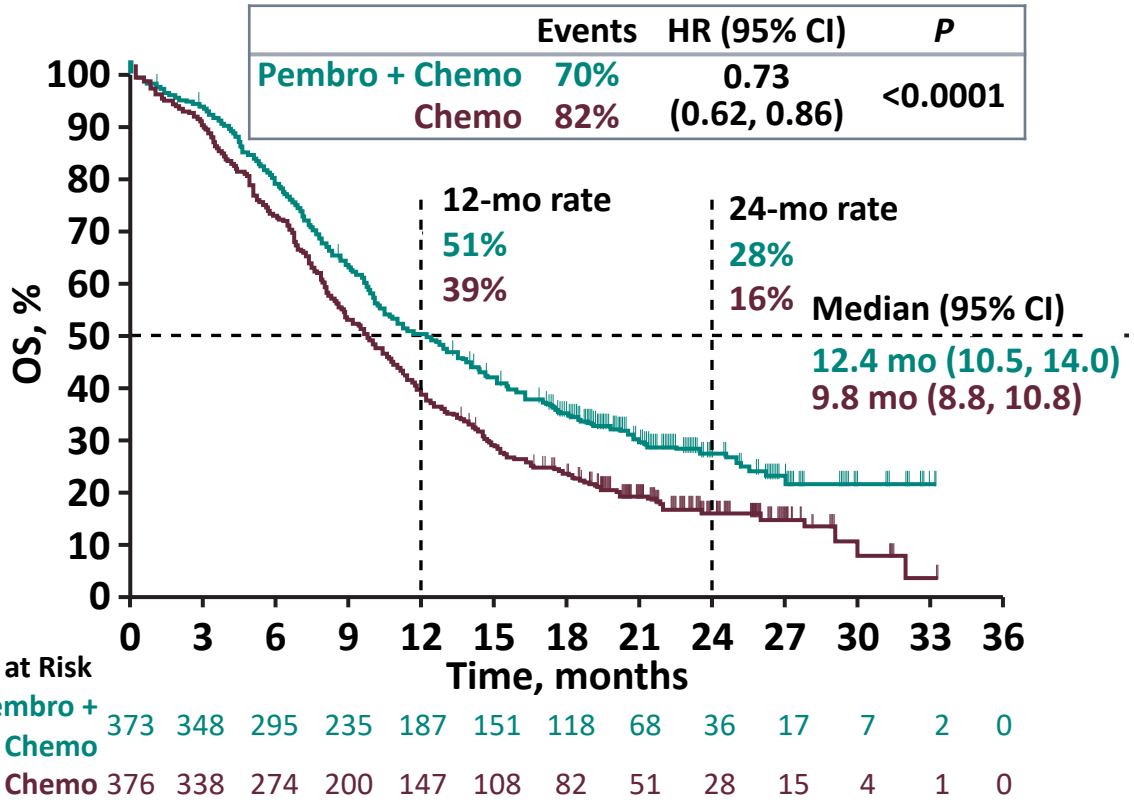
Characteristic	Pembro + Chemo (n=373)	Chemo (n=376)
Median age, years (range)	64.0 (28-94)	62.0 (27-89)
≥65 years	46%	40%
Male	82%	85%
Asia region	53%	52%
ECOG PS 1	60%	60%
Metastatic disease	92%	90%
Squamous cell carcinoma	74%	73%
Adenocarcinoma	27%	27%
PD-L1 CPS≥1[a,b]	86%	87%
PD-L1 CPS≥10[b]	50%	52%

[a]PD-L1 CPS≥1 subgroup was analyzed post hoc; [b]PD-L1 status was not evaluable or missing in 12 patients in the pembro + chemo group and 7 patients in the chemo group.
Cutoff date: 02JUL2020.

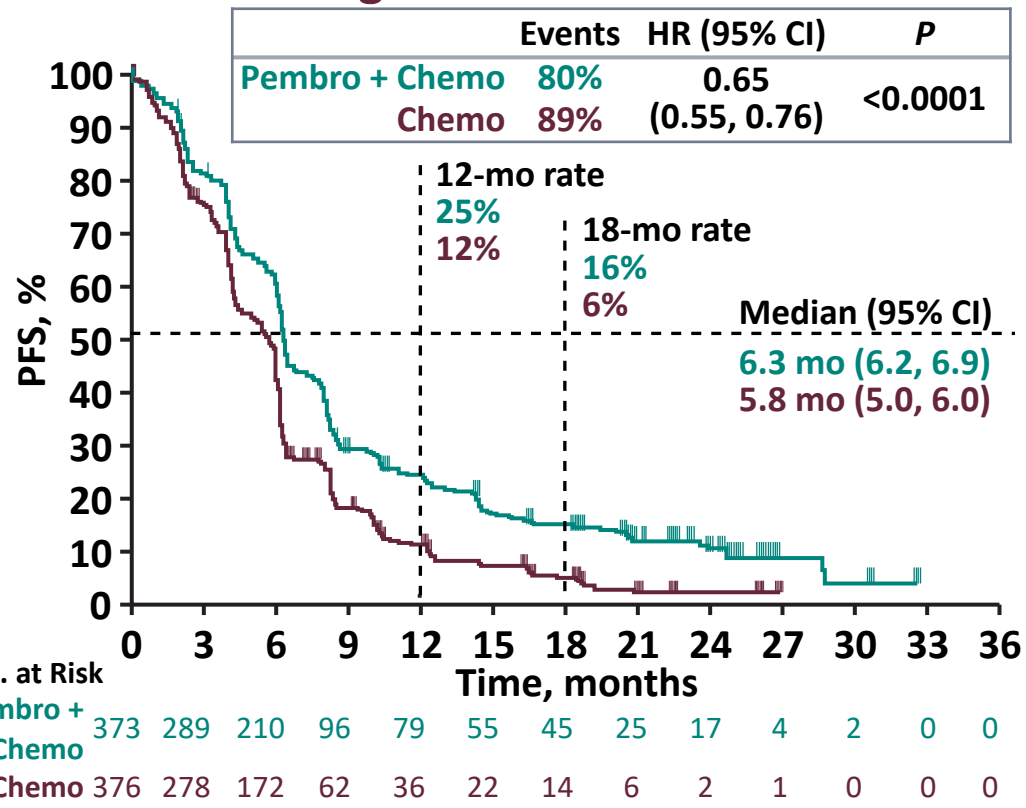
Statistically Significant and Clinically Meaningful OS and PFS Improvements

KN-590: ITT

Overall Survival



Progression-Free Survival



Safety profile of investigational arm is consistent with the individually established safety profiles of each agent

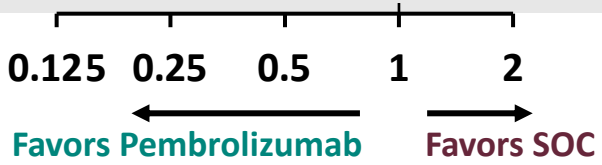
HR and p value are from protocol pre-specified stratified analysis.
Cutoff Date: 02JUL2020, Interim Analysis.

OS and PFS Are Directionally Consistent at All PD-L1 Cut-points

KN-590: ITT

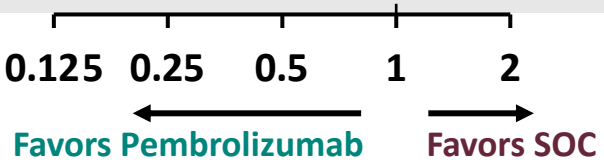
Overall Survival

CPS Subgroup	N/Events	HR (95% CI)[a]
ITT	749/571	**0.73** (0.61, 0.86)
<1	83/67	**0.96** (0.59, 1.55)
≥1	647/493	**0.70** (0.59, 0.84)
<5	231/182	**0.83** (0.62, 1.11)
≥5	499/378	**0.68** (0.55, 0.83)
≥1 to <5	148/115	**0.78** (0.54, 1.12)
≥5 to <10	116/89	**0.91** (0.59, 1.38)
≥1 to <10	264/204	**0.84** (0.63, 1.10)
≥10	383/289	**0.62** (0.49, 0.79)



Progression-Free Survival

CPS Subgroup	N/Events	HR (95% CI)[a]
ITT	749/630	**0.65** (0.56, 0.76)
<1	83/73	**0.88** (0.55, 1.39)
≥1	647/543	**0.63** (0.53, 0.74)
<5	231/202	**0.86** (0.65, 1.13)
≥5	499/414	**0.57** (0.47, 0.70)
≥1 to <5	148/129	**0.83** (0.59, 1.18)
≥5 to <10	116/100	**0.68** (0.45, 1.02)
≥1 to <10	264/229	**0.77** (0.59, 1.00)
≥10	383/314	**0.54** (0.43, 0.68)



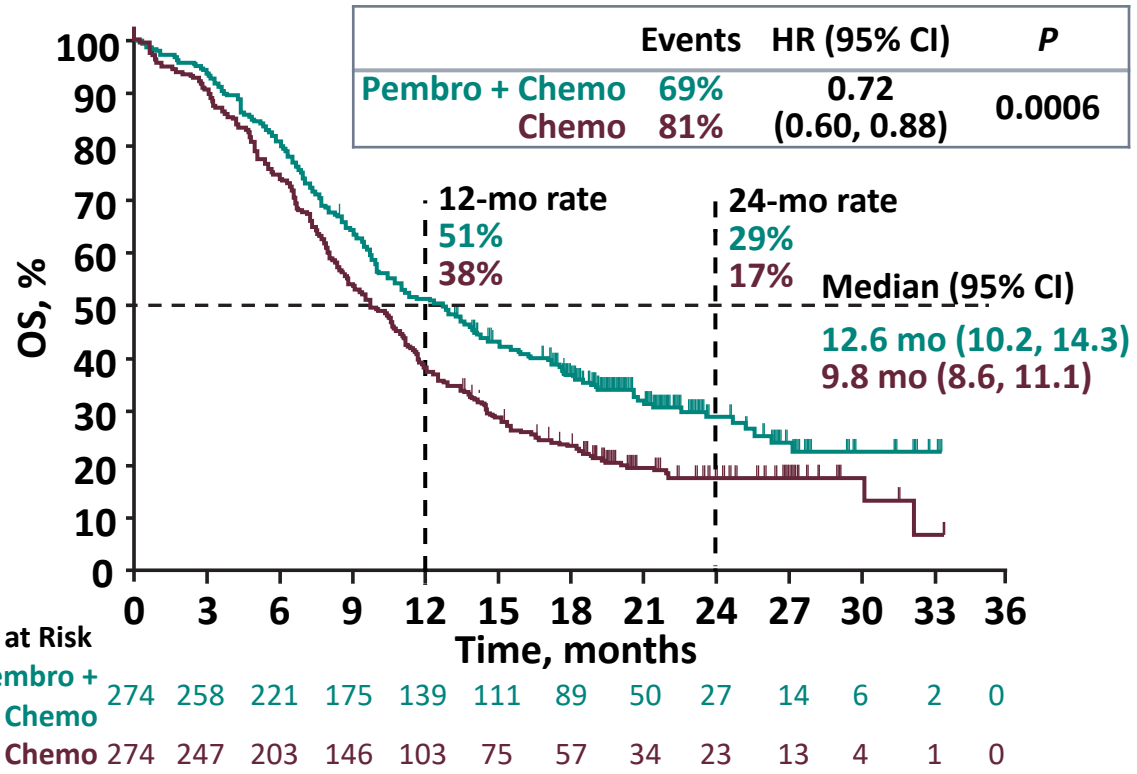
Safety profile of pembrolizumab and chemotherapy is generally similar across PD-L1 CPS subgroups

a. Based on unstratified analysis.
Database cutoff date: 02JUL2020.

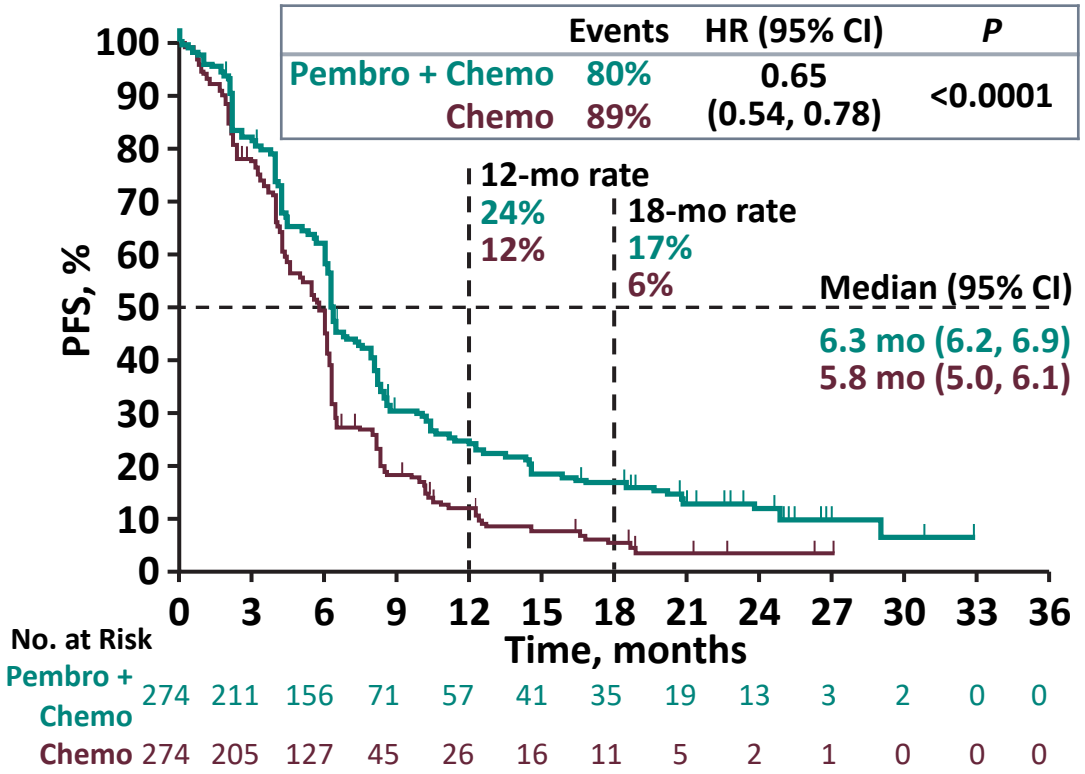
Statistically Significant and Clinically Meaningful OS and PFS Improvement

KN-590: ESCC

Overall Survival



Progression-Free Survival



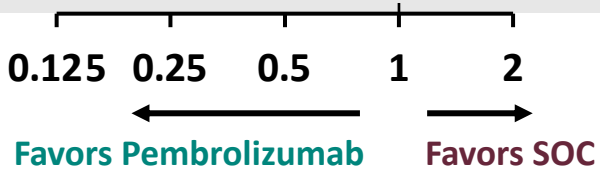
HR and p value are from protocol pre-specified stratified analysis.
Cutoff Date: 02JUL2020, Interim Analysis

OS and PFS Across PD-L1 CPS Subgroups in ESCC

KN-590: ESCC

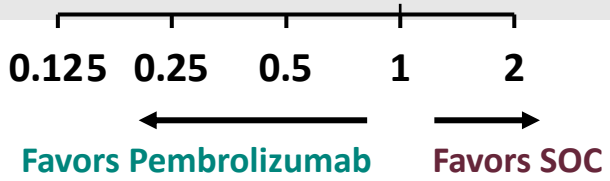
Overall Survival

CPS Subgroup	N/Events	HR (95% CI)[a]
ITT	548/412	**0.72** (0.59, 0.87)
<1	55/41	**1.00** (0.54, 1.85)
≥1	478/364	**0.69** (0.56, 0.85)
≥1 to <5	113/91	**0.82** (0.54, 1.24)
≥5 to <10	79/58	**1.03** (0.61, 1.75)
≥1 to <10	192/149	**0.94** (0.68, 1.29)
≥10	286/215	**0.57** (0.44, 0.75)



Progression-Free Survival

CPS Subgroup	N/Events	HR (95% CI)[a]
ITT	548/463	**0.66** (0.55, 0.79)
<1	55/47	**0.96** (0.54, 1.72)
≥1	478/406	**0.63** (0.52, 0.77)
≥1 to <5	113/100	**0.82** (0.55, 1.22)
≥5 to <10	79/70	**0.66** (0.40, 1.10)
≥1 to <10	192/170	**0.79** (0.58, 1.07)
≥10	286/236	**0.54** (0.42, 0.70)



[a]Based on unstratified analysis.
Cutoff Date: 02JUL2020, Interim Analysis

Pembrolizumab in Combination With Chemotherapy Addresses a Significant Unmet Need

- Statistically significant and clinically meaningful efficacy was demonstrated in the ITT population
  - Magnitude of benefit increases with higher levels of PD-L1 expression, with clear benefit seen in the CPS ≥1 subgroup
  - Efficacy trends in the CPS <1 subgroup of ITT favored the combination
- Health-related QoL remained stable during treatment, was generally similar between arms, and generally consistent across PD-L1 CPS subgroups
- Safety profile of the combination was manageable and similar across PD-L1 CPS subgroups
- The label for this indication delineates efficacy by PD-L1 expression level and supports a benefit-risk discussion between physicians and patients

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Clinical Management of Esophageal Cancer

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Gastrointestinal Oncologist

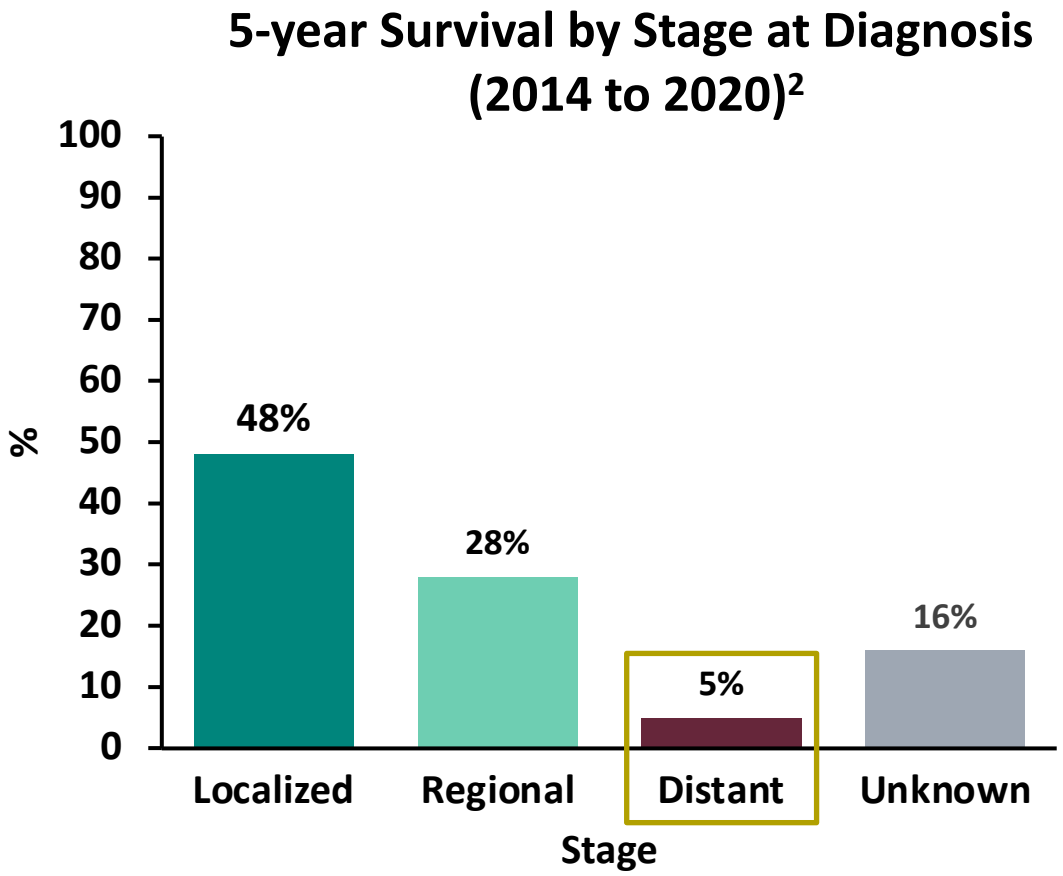
Dana-Farber Cancer Institute

In the past 2 years, Dr. Enzinger has been a consultant for:

Astellas Pharma
BeiGene USA, Inc.
Daiichi Sankyo
Eisai, Inc
Legend Biotech
Merck Sharp & Dohme LLC
Novartis
Oncolys
Regeneron
Sanofi-Aventis U.S. LLC
Servier Pharmaceuticals LLC

High Unmet Need Remains for US Patients With Metastatic Esophageal Cancer

- **Strong need for new treatment options**
  - Difficult-to-treat patient population
  - Only innovation in last 30 years is ICIs
  - Chemotherapy is the only other treatment option
  - ~40% of patents will receive 2L, underscoring the need for best treatment upfront[1]
- **Considerations for patients in need of 1L treatment**
  - Therapeutic urgency and timing of biomarker testing
  - Adverse event profile
  - Long-term survival
  - PD-L1 expression level to assist with patient management decision



1.Data from Flatiron Health electronic health record Database; data on file 2. National Cancer Institute. SEER Cancer Stat Facts: Esophageal Cancer. https://seer.cancer.gov/statfacts/html/esoph.html.

Challenges of PD-L1 Testing and Scoring in Real-World Clinical Practice

Technical Challenges

- Different assays and antibody clones may be used locally that are not FDA approved
- Staining variability
- Sample quality[1]

Interpretation

- Inconsistency in pathologist training and cut-point interpretation

[1]Jiang C et al. *Oncol Lett* 2019;17:1626-1634.

Real-World PD-L1 Testing and Treatment in Esophageal Cancer

- **Among patients with advanced/metastatic esophageal cancer treated in 1L:**
  - **66%** had evidence of PD-L1 expression testing[1]
  - **41%** received ICI-based regimens[1]

Many patients with advanced/ metastatic esophageal cancer do not receive ICI-based regimens in 1L, suggesting physicians and patients carefully weigh risks and benefits of available options

If indication is restricted, many patients with advanced/ metastatic esophageal cancer who have limited treatment options will be excluded from potentially life-saving therapy

*Based on PD-L1 CPS prevalence in KN-590 (N = 730): CPS≥1, 89%; CPS≥10, 52%

1. Data from Flatiron Health electronic health record database after 3/22/2021 to 3/31/2024, data on file.

Data source: SEER Cancer Stat Facts: Esophageal Cancer. National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/statfacts/html/stomach.html.

KEYNOTE-590 Patient With Esophageal Cancer

Female (Western) in 40s with esophageal cancer enrolled in KEYNOTE-590

- ☐ Histology-confirmed esophageal squamous cell carcinoma
- ☐ PD-L1 evaluation indicated CPS <1 as assessed by central lab
- ☐ Imaging confirmed stage IV disease with lung metastasis
- ☐ Achieved partial response at cycle 6 and complete response at cycle 15 with chemotherapy and pembrolizumab combination. DOR was ~50 months and patient was alive at 5-year follow-up

Clinical Perspective Conclusions

For patients with unresectable or metastatic esophageal cancer:

- Treatment options have been limited and consisted of platinum, fluoropyrimidine, and taxane chemotherapy
- The approval of checkpoint inhibitors has revolutionized care of these patients and has improved survival and maintained health-related quality of life
- The choice to add a checkpoint inhibitor must be individualized and depends on many factors
- Variability in real-world PD-L1 biomarker testing may complicate treatment decisions
- The scientific community further informs decision making through clinical guidelines

The all-comers indication allows patients to have immunotherapy as a first-line treatment option at the discretion of the patient and their treating physician

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Concluding Remarks

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Summary

KEYNOTE-590 was rigorously designed, executed, and success criteria for all endpoints were met

- Current approved indication in the US reflects a positive benefit-risk assessment
- OS and PFS hazard ratios for all PD-L1 subgroups in ITT population are <1

First-line metastatic esophageal cancer remains an unmet need with poor prognosis

- Pembrolizumab labeling is informative and helps guide the physician/patient decision-making process

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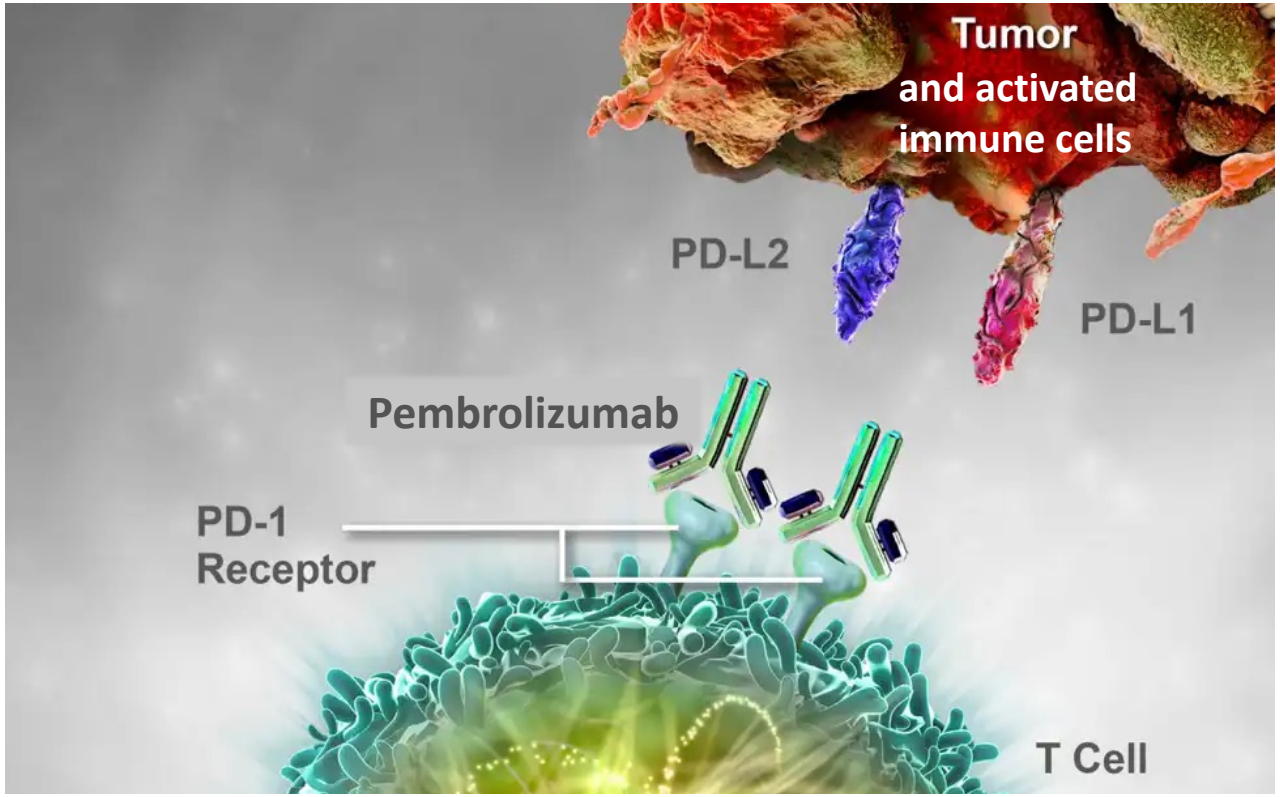
Appendix

Pembrolizumab Mechanism of Action Centers Around Tumor-Specific Expression of PD-L1



PD-1=programmed death receptor-1; PD-L1=programmed death ligand 1; PD-L2=programmed death ligand 2.

- Pembrolizumab restores immune response by binding PD-1 and blocking its interaction with PD-L1 and PD-L2
- Increased expression of PD-L1 enriches for response with pembrolizumab monotherapy

PD-L1 expression is tumor type specific and interpretation is dependent on the assay and scoring method used

Biological Evidence That Combining Pembrolizumab With Chemotherapy Modulates Antitumor Response

- Antigen shedding and presentation
- Altered immune regulatory receptors, ligands, and cytokines
- Activation of innate immunity
- Favorable effect on immune regulatory cells

- Post-chemotherapy induction of immune regulatory receptors, ligands, and cytokines
- Unfavorable effect on immune regulatory cells

Potential complementary effects between chemotherapy and pembrolizumab could benefit patients across a broad range of PD-L1 expression

Bracci L et al. *Cell Death Differ* 2014;21:15-25. Roselli M et al. *Oncoimmunology* 2013;2:e27025. Galluzzi L et al. *Cancer Cell* 2015;28:690-714. Medler TR et al. *Trends Cancer* 2015;1:66-75. van Meir H et al. *Oncoimmunology* 2017;6:e1267095. Peng J et al. *Cancer Res* 2015;75:5034-5045. Zhang P et al. *Cancer Sci* 2016;107:1563-1571. Novosiadly RD et al. 18th IASLC World Conference on Lung Cancer; Oct 15-18, 2017; abstract P3.07-006.