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KEYTRUDA in First-Line HER2-Negative Gastric and Gastroesophageal Junction (GEJ) Cancer

M. Catherine Pietanza, MD

Vice President, Clinical Research

Global Clinical Development, Late-Stage Oncology

Merck Sharp & Dohme LLC

What You Will Hear Today

Overview of Pembrolizumab and PD-L1 22C3 PharmDx

M. Catherine Pietanza, MD
Vice President, Clinical Research
Global Clinical Development, Late-Stage Oncology
Merck Sharp & Dohme LLC

KEYNOTE-859 Results in HER2-Negative Gastric Cancer

Pooja Bhagia, MD
Executive Director
Global Clinical Development, Late-Stage Oncology
Merck Sharp & Dohme LLC

Clinical Management of Gastric Cancer

Yelena Y. Janjigian, MD
Chief Attending
Gastrointestinal Oncology
Memorial Sloan Kettering Cancer Center, NY

KEYTRUDA Helps Address an Unmet Need in Gastric Cancer

- Metastatic gastric cancer is a rare disease, and patients have a poor prognosis
- Current SOC of chemotherapy + IO in 1L HER2-negative gastric cancer addresses significant unmet need

KEYNOTE-859

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

→

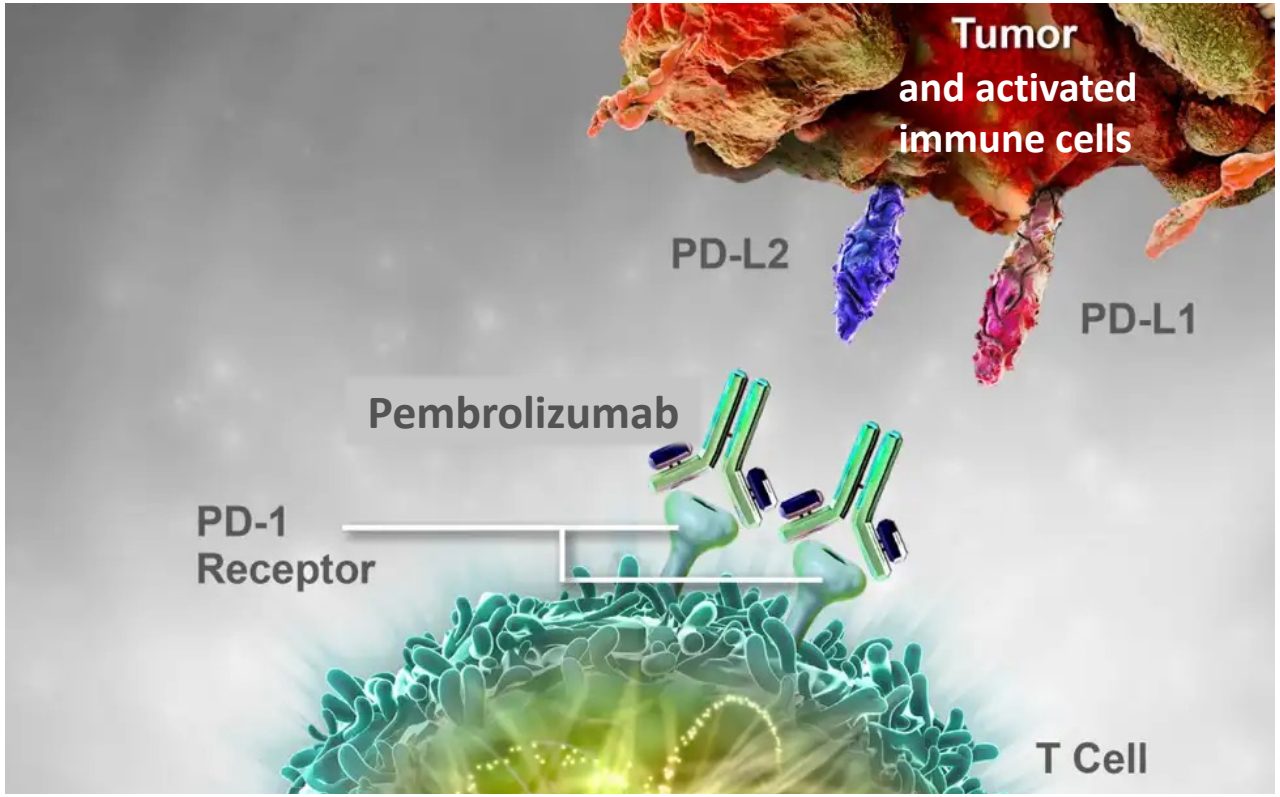
Key study data reflected in current label

→

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

Current indication for pembrolizumab should be retained

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.

Robust Sample Processing, Cut-point Determination, Scoring, and Validation Underlie 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: 0 to 100

2 Training sets

Merck clinical studies

CPS≥1:

- KN-012 (n=38)
- KN-059 (n=256)

CPS≥10:

- KN-061 (n=590)

3 Cut-point determination

Trial-specific CPS cut-points

4 Validation set

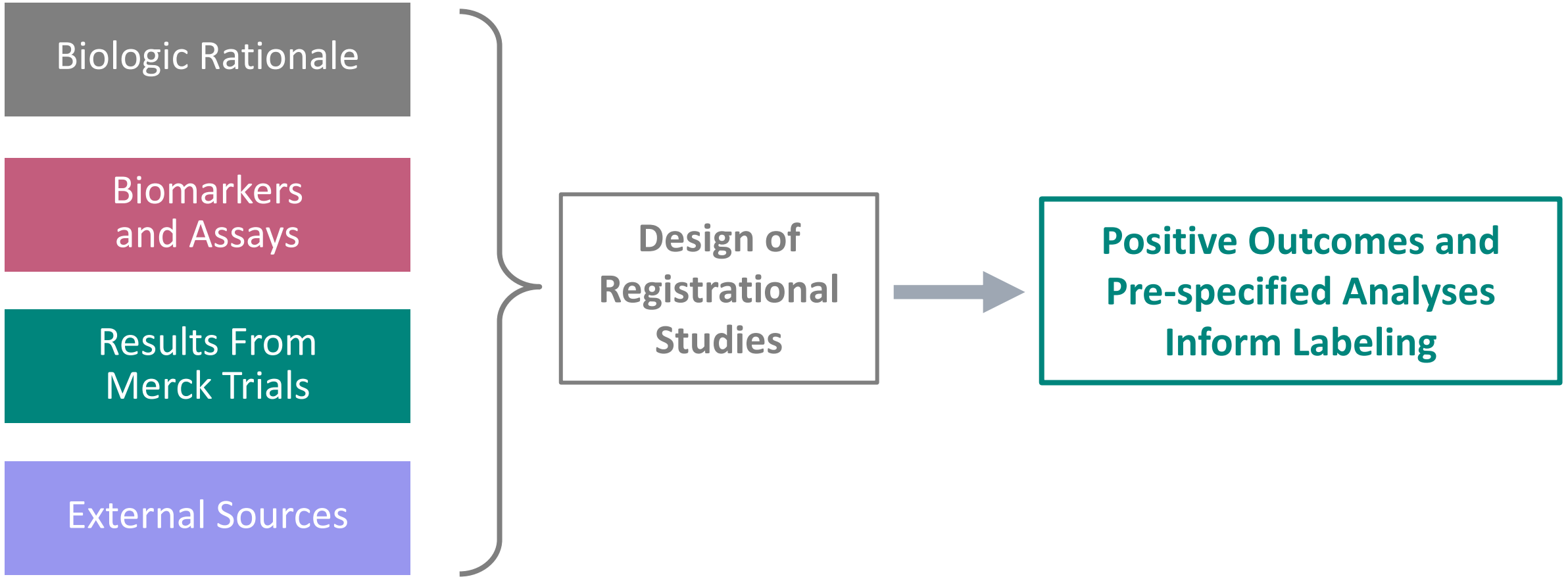
KEYNOTE-859

Cut-points were

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

Robust PD-L1 data in KEYNOTE-859 support the currently approved indication

Multifactorial, Rigorous Approach to Inform Study Design and Labeling



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 Gastric Cancer Based on PD-L1 Status

- KN-859 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-859 Results in HER2-Negative Gastric Cancer

Pooja Bhagia, MD

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1L HER2-Negative Gastric and GEJ Adenocarcinoma (KEYNOTE-859)

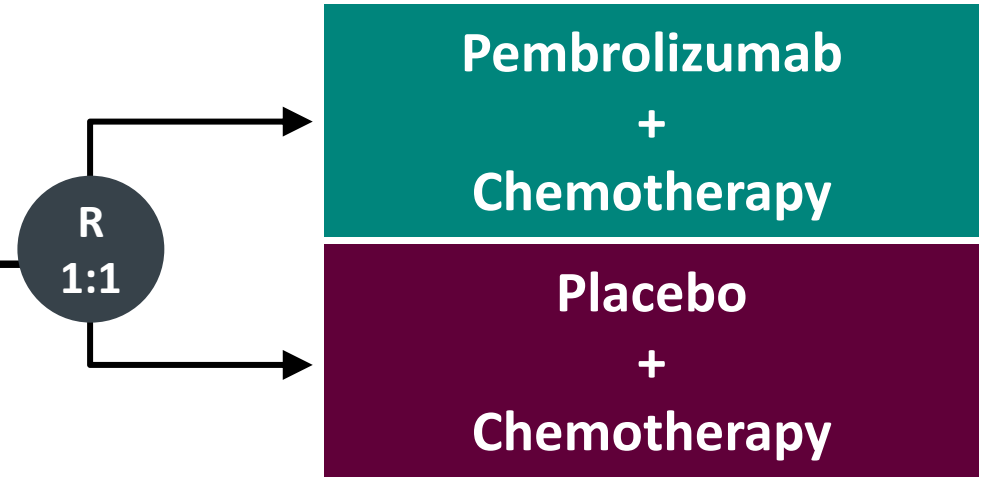
KEYTRUDA, in combination with fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the first-line treatment of adults with locally advanced unresectable or metastatic HER2-negative gastric or gastroesophageal junction (GEJ) adenocarcinoma.

Phase 3, 1L HER2-Negative Gastric and GEJ Adenocarcinoma Study

KN-859

Key Eligibility Criteria

- Adenocarcinoma of the stomach or GEJ
- Locally advanced unresectable or metastatic disease
- Known PD-L1 status



Primary Endpoint
- OS

Key Secondary Endpoints
- PFS
- ORR

Alpha Controlled
- Overall, PD-L1 CPS≥1, PD-L1 CPS≥10

Additional Secondary Endpoints:
- DOR
- Safety

Stratification Factors
- Choice of chemotherapy (FP vs CAPOX)
- Geographic region
- PD-L1 CPS (<1 vs ≥1)

Key Study Design Elements Based on PD-L1 Expression

KN-859

Central PD-L1 Testing

- Early monotherapy studies indicated potential for increased efficacy in CPS≥1 population
- Agilent PD-L1 IHC 22C3 pharmDx assay validated at CPS≥1

Initial Study Design

- Stratify by CPS≥1 versus <1
- Hypothesis testing in CPS≥1 and ITT

78% of ITT was CPS≥1

KN-062 Readout After KN-859 Initiation

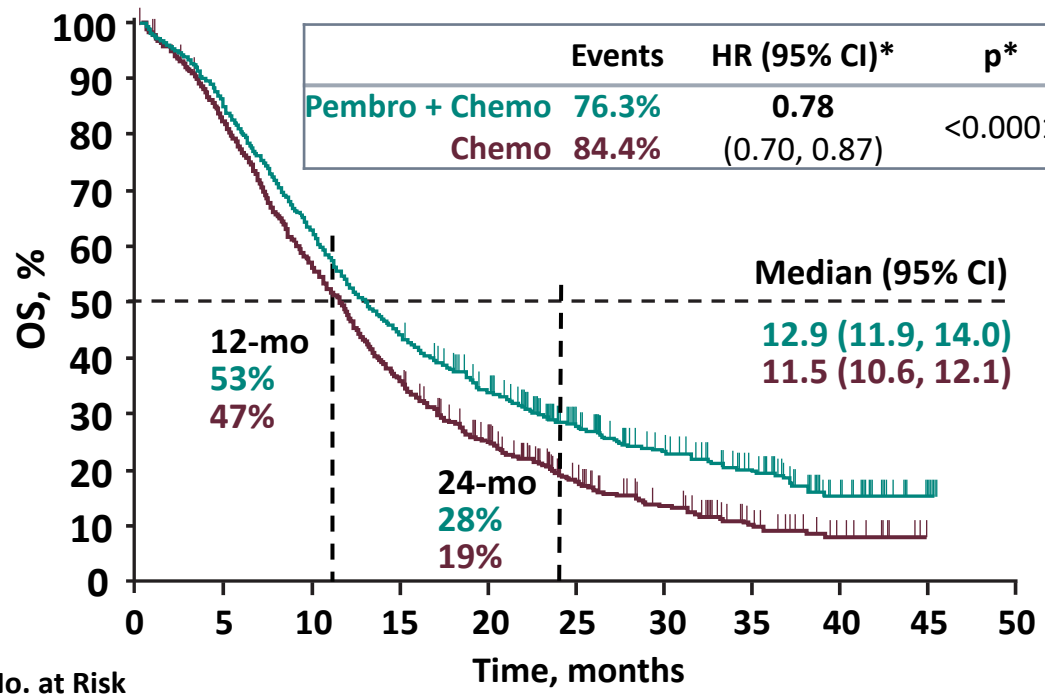
- Added hypothesis testing in CPS≥10

35% of ITT was CPS≥10

Statistically Significant Overall Survival and Progression-Free Survival

KN-859: ITT

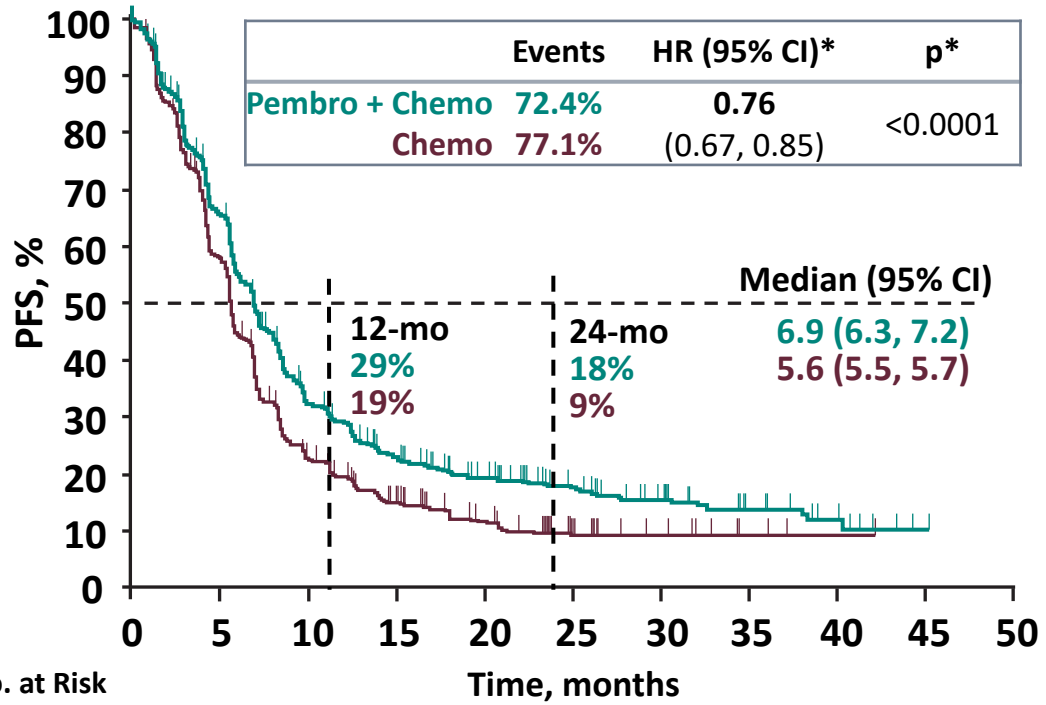
Overall Survival



No. at Risk

Pembro + Chemo	790	663	490	343	240	143	95	55	19	3	0
Chemo	789	636	434	274	169	95	58	26	10	0	0

Progression-Free Survival



No. at Risk

Pembro + Chemo	790	461	199	131	94	63	36	22	9	1	0
Chemo	789	407	130	71	41	19	11	3	1	0	0

Safety profile of pembrolizumab with chemotherapy is consistent with that of the individual agents

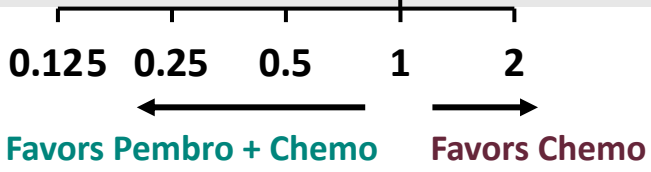
*Based on stratified analyses pre-specified in sSAP.

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

KN-859: ITT

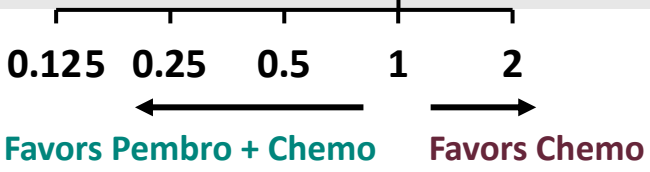
Overall Survival

CPS Subgroup	N/Events	HR (95% CI)[a]
ITT	1579/1269	**0.77** (0.69, 0.86)
<1	344/279	**0.92** (0.73, 1.17)
≥1	1235/990	**0.73** (0.65, 0.83)
≥1 to <5	452/384	**0.78** (0.64, 0.96)
≥5 to <10	232/192	**0.93** (0.70, 1.24)
≥1 to <10	684/576	**0.83** (0.70, 0.98)
≥10	551/414	**0.64** (0.52, 0.77)



Progression-Free Survival

CPS Subgroup	N/Events	HR (95% CI)[a]
ITT	1579/1180	**0.76** (0.67, 0.85)
<1	344/254	**0.90** (0.70, 1.15)
≥1	1235/926	**0.72** (0.63, 0.82)
≥1 to <5	452/352	**0.79** (0.64, 0.97)
≥5 to <10	232/174	**0.92** (0.68, 1.24)
≥1 to <10	684/526	**0.83** (0.70, 0.98)
≥10	551/400	**0.62** (0.51, 0.76)



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

[a] Based on unstratified Cox regression model.

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 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

Memorial Sloan Kettering Cancer Center

Clinical Management of Gastric Cancer

Yelena Y. Janjigian, MD

Chief Attending

Gastrointestinal Oncology

Memorial Sloan Kettering Cancer Center, NY

Disclosures

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- Merck Serono
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- Paradigm Medical Communications
- PeerView Institute
- Pfizer
- Physician's Education Resource, LLC
- Research to Practice
- Sanofi Genzyme
- Seagen
- Silverback Therapeutics
- Talem Health
- TotalCME
- Zymeworks Inc.

Other:

- Inspirna (stock options)

Optimizing First-Line Treatment in Gastric Cancer

- Assess patient functional status and disease burden
- Therapeutic urgency
  - Small window of time
  - Response in 1L important
- PD-L1 expression guides treatment continuation
- Maximize therapeutic options for patients unable to receive 2L therapy (>50%)
- IO has established safety profile and health-related QoL is generally maintained
- Long-term survival observed in some IO patients

Validated Biomarkers in Gastric Cancer

Biomarker	Prevalence in Metastatic Gastric Cancer
ERBB2/HER2[1]	20%
MSI-high[2]	5% in stage IV, 20% in stage I-III
PD-L1 CPS[3]	78% CPS≥1; 35% CPS≥10

Clinical need for patients with no other biomarker

1. Janjigian et al. *Ann Oncol.* 2012 Oct;23(10):2656-2662; 2. Le et al. *Science*. 2017 Jul 28;357(6349):409-413; 3. PD-L1 CPS prevalence from KN-859 trial.

Practical Limitations of PD-L1 Testing

Representative Sampling

- Difficulty obtaining sample sufficient for PD-L1 testing
- Tumor heterogeneity

Assay

- Variability in PD-L1 testing in clinical practice

Pathologist Interpretation

- Learning curve for interpretation of CPS
- Challenging to distinguish intermediate values between CPS 1-10

PD-L1 expression level helps guide management decisions while on treatment

Biomarker Testing and IO Use in the Real World

Based on Flatiron Health EHR database on HER2-negative gastric cancer patients treated in 1L after April 16, 2021 (US community setting)

- 77% had evidence of PD-L1 testing prior to 1L therapy start
- About 50% were treated with IO in 1L
- Restriction of label will limit access further

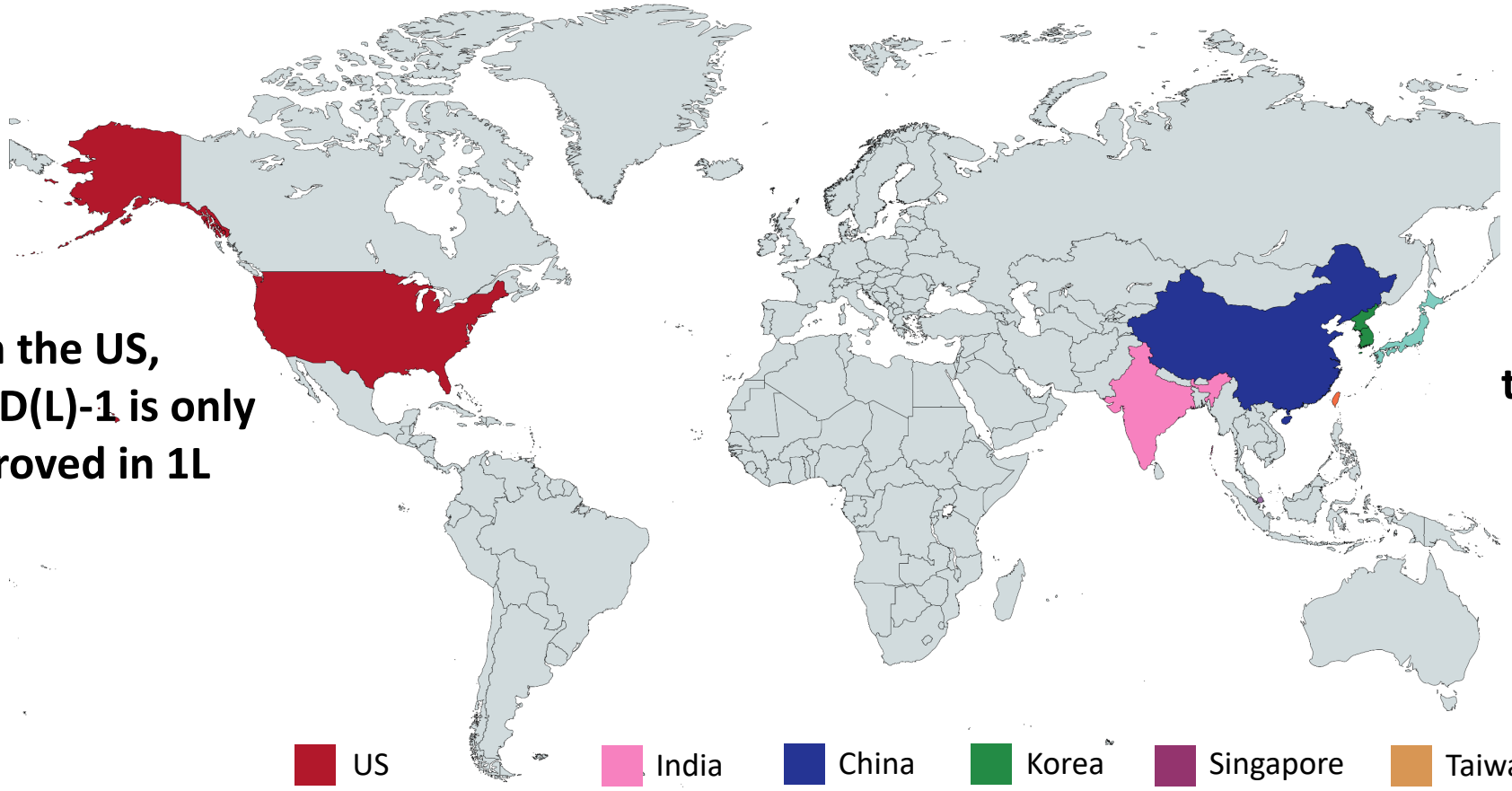
PD-L1 Assay at Index Date*	n (%)
Dako PD-L1 IHC 22C3 pharmDx	199 (47%)
Dako PD-L1 IHC 28-8 pharmDx	53 (13%)
Ventana PD-L1 (SP142 or SP263) Assay	5 (1.2%)
Lab-developed test	75 (18%)
Unknown/not documented	88 (21%)

*1L therapy start date.

Data from Flatiron Health electronic health record database between 4/16/2021 and 3/31/2024, data on file.

Immunotherapy is not an Option in 2L for Patients in the US

In the US, anti–PD(L)-1 is only approved in 1L



In Asia, anti–PD(L)-1 therapy is approved in later lines

A need for broad immunotherapy treatment options in the US

Clinical Perspective Conclusion

- Improved long-term survival and tumor response with IO has changed treatment landscape
- Choice of 1L therapy drives long term outcome; access to 2L therapy varies
- Patients with limited access to testing, sample limitations, and inherent issues with PD-L1 testing
- Clinical guidelines informed by scientific community shapes decision-making
- Physicians need options to personalize therapy decisions

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Concluding Remarks

M. Catherine Pietanza, MD

Vice President, Clinical Research

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Summary

KEYNOTE-859 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 are <1

First-line metastatic gastric 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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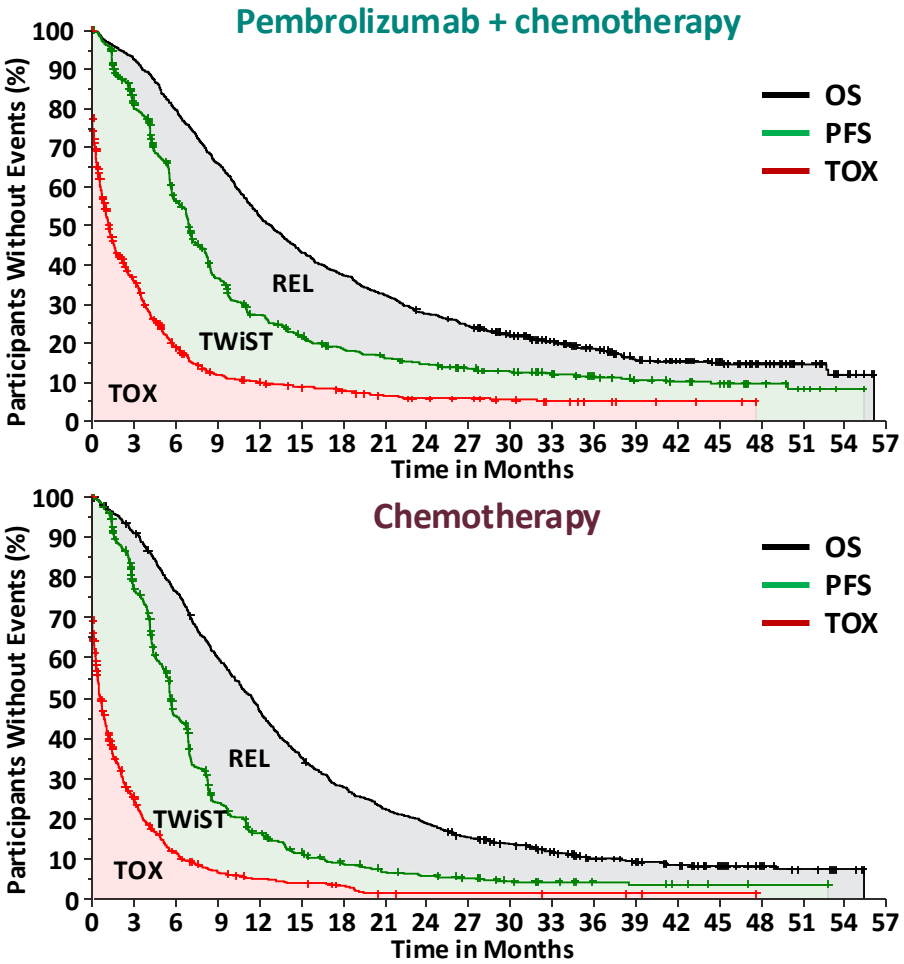
Back Up Slides Shown

For KEYNOTE-859, There was a Relative Q-TWiST Gain in all CPS Cut Points

Kaplan-Meier survival curves for the Q-TWiST health states in all randomly assigned patients[a]



Relative Q-TWiST gain for pembrolizumab + chemotherapy vs chemotherapy with US quality of life weights

KEYNOTE-859	Relative Q-TWiST Gain, % (CI)[b]
ITT	20.9 (12.49, 30.56)
CPS ≥ 1	25.34 (16.04, 36.26)
CPS ≥ 10	38.05 (23.21, 56.59)

[a]PFS is investigator assessed and toxicity represents Grade 3+ all-cause AEs; [b]Relative Q-TWiST gains of ≥ 10% are 'clinically important' and ≥ 15% are 'clearly clinically important'. August 2023 data cut off

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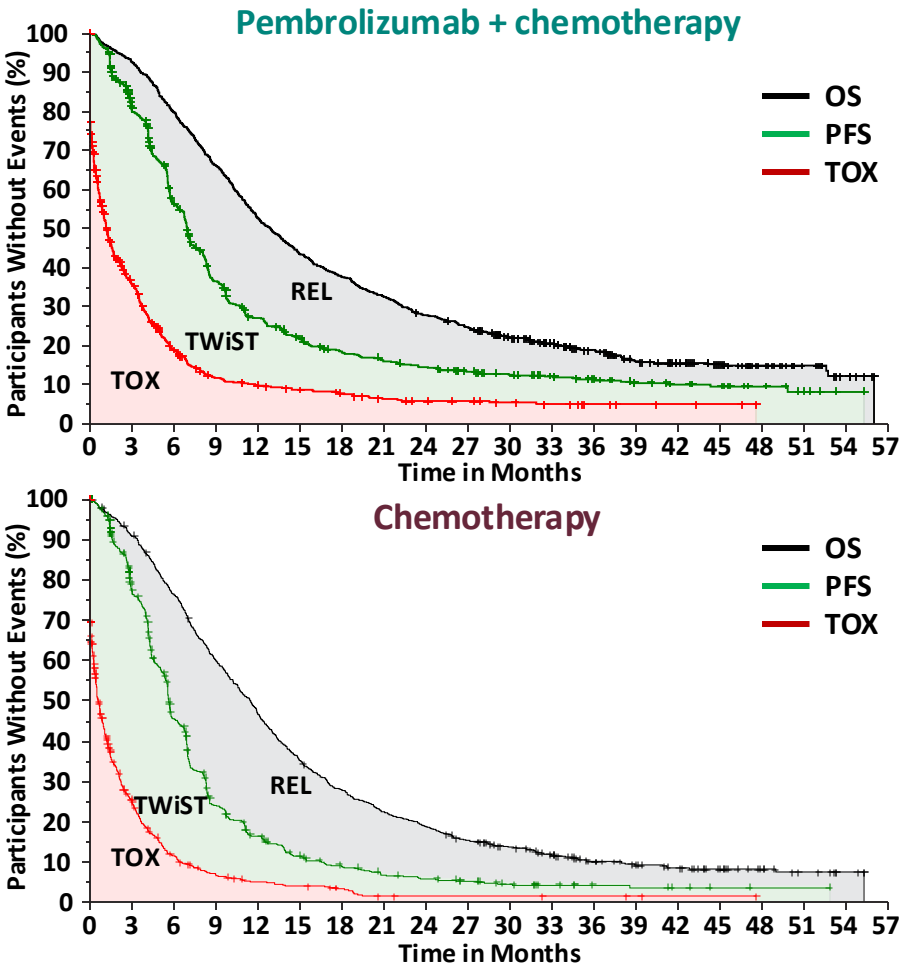
Kaplan-Meier survival curves for the Q-TWiST health states in all randomly assigned patients[a]



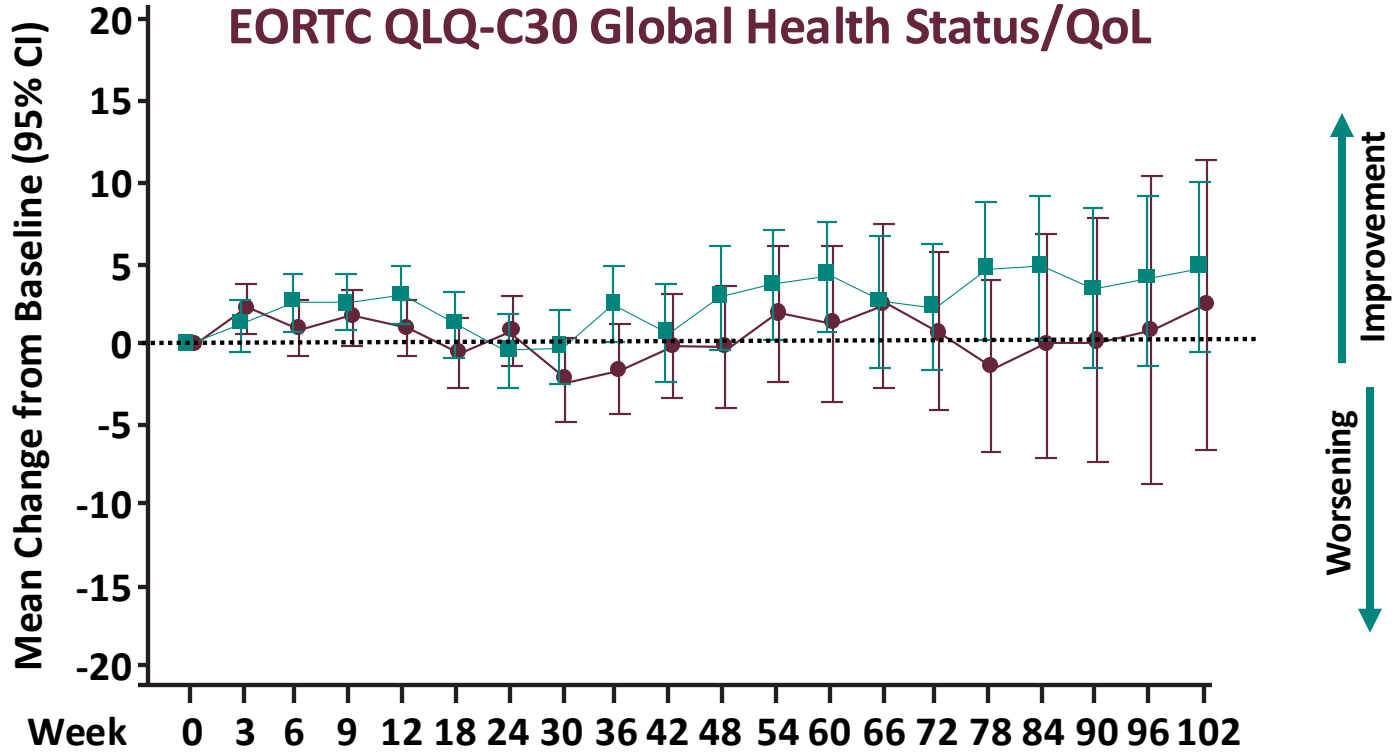
Relative Q-TWiST gain for pembrolizumab + chemotherapy vs chemotherapy with US quality of life weights

KEYNOTE-859	Relative Q-TWiST Gain, % (CI)[b]
ITTb	20.9 (12.49, 30.56)
CPS < 1	4.58 (-6.66, 19.87)
CPS ≥ 1	25.34 (16.04, 36.26)
CPS 1-9	14.02 (3.24, 26.91)
CPS ≥ 10	38.05 (23.21, 56.59)

[a]PFS is investigator assessed and toxicity represents Grade 3+ all-cause AEs; [b]Relative Q-TWiST gains of ≥ 10% are 'clinically important' and ≥ 15% are 'clearly clinically important'. August 2023 data cut off

Health-related QoL Was Maintained During Pembrolizumab + Chemotherapy Treatment*

KN-859: PRO Full Analysis Set



(Database Cutoff: 03Oct2022)

*Including an assessment at the safety follow-up visit 30 days post Last Dose. PRO FAS=Randomized subjects who received at least one dose of study medication and had at least one PRO assessment.

HRQoL results were generally similar across CPS subgroups.

OS, PFS, ORR and DOR
KN-859: ITT, CPS <1

Overall Survival

Subgroup	N/Events	OS HR (95% CI)
ITT	1579/ 1269	**0.77** (0.69, 0.86)
CPS <1	344/279	**0.92** (0.73, 1.17)

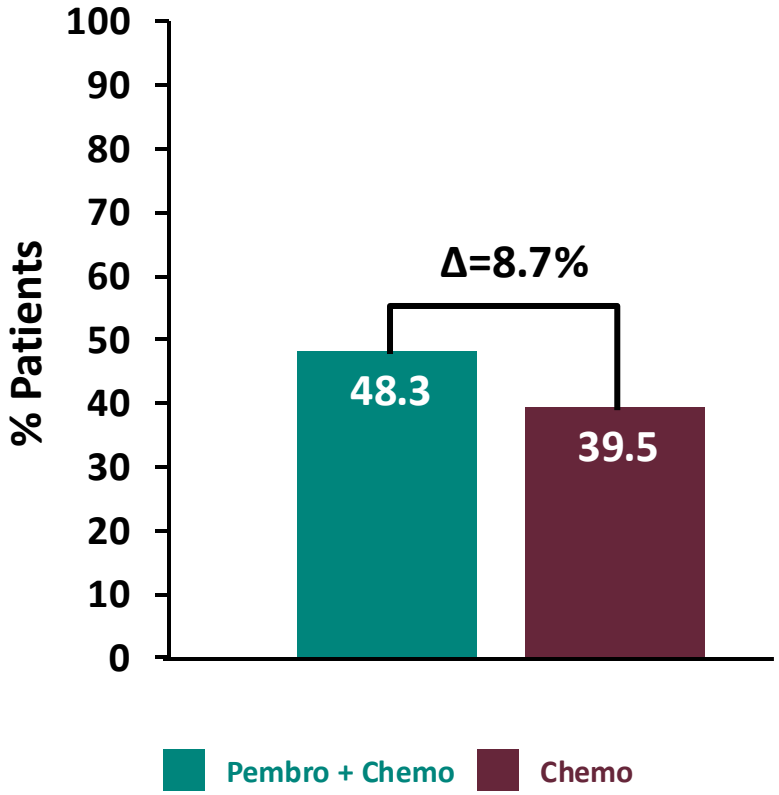
Progression-Free Survival

Subgroup	N/Events	OS HR (95% CI)
ITT	1579/1180	**0.76** (0.67, 0.85)
CPS <1	344/254	**0.90** (0.70, 1.15)

DOR

N/ responses	**172/83**	**172/68**
Median DOR (range), months	**7.0 (1.3+ - 39.8+)**	**5.7 (1.4+ - 34.7+)**

Overall Response Rate



Based on unstratified analysis
Database cutoff date: 03OCT2022

Safety was consistent across CPS subgroups, with no new safety signals.
QoL was maintained across CPS subgroups with the addition of pembrolizumab to chemotherapy.