Esophageal Squamous Cell Carcinoma

US Food & Drug Administration
Oncologic Drugs Advisory Committee
September 26, 2024

Bristol Myers Squibb®

Ian Waxman, MD

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BMS

Introduction

Opdivo® (nivolumab) Fully Approved for Esophageal Squamous Cell Carcinoma on May 30, 2022

First-line treatment of adult patients with unresectable advanced or metastatic esophageal squamous cell carcinoma

- In combination with fluoropyrimidine and platinum-containing chemotherapy
- In combination with ipilimumab

No restriction based on PD-L1 status

Opdivo USPI.

Current US Prescribing Information Includes Data by PD-L1 Expression Level in Section 14.12

Table 74: Efficacy Results - CHECKMATE-648

	OPDIVO with Cisplatin and Fluorouracil (n=321)	OPDIVO and Ipilimumab (n=325)	Cisplatin and Fluorouracil (n=324)	OPDIVO with Cisplatin and Fluorouracil (n=158)	OPDIVO and Ipilimumab (n=158)	Cisplatin and Fluorouracil (n=157)
	All Patients			TC PD-L1 expression ≥1%		
Overall Survival						
Deaths (%)	209 (65)	216 (66)	232 (72)	98 (62)	106 (67)	121 (77)
Median (months) (95% CI)	13.2 (11.1, 15.7)	12.8 (11.3, 15.5)	10.7 (9.4, 11.9)	15.4 (11.9, 19.5)	13.7 (11.2, 17.0)	9.1 (7.7, 10)
Hazard ratio (95% CI)[b]	0.74 (0.61, 0.90)	0.78 (0.65, 0.95)	-	0.54 (0.41, 0.71)	0.64 (0.49, 0.84)	-
p-value[c]	0.0021[S1]	0.0110[S2]	-	<0.0001[S3]	0.0010[S4]	-

Exploratory subgroup analyses of patients with TC PD-L1 expression <1% (N=492)

- OPDIVO with Chemotherapy (n = 163) vs. Chemotherapy (n = 165): unstratified OS HR was 0.99 (95% CI: 0.76, 1.29) with median OS of 12 months (95% CI: 9.9, 15.5) on the OPDIVO with Chemotherapy arm and 12.2 months (95% CI: 10.7, 14) on the Chemotherapy arm.
- OPDIVO with Ipilimumab (n = 164) vs. Chemotherapy (n = 165): unstratified OS HR was 0.97 (95% CI: 0.74, 1.26) with median OS of 12 months (95% CI: 10.1, 16.0) on the OPDIVO with Ipilimumab arm and 12.2 months (95% CI: 10.7, 14) on the Chemotherapy arm.

Exploratory subgroup analyses were also conducted by PD-L1 status per CPS (≥1 and <1)

- OPDIVO with Chemotherapy vs. Chemotherapy: unstratified OS HR was 0.69 (95% CI: 0.56, 0.84) for PD-L1 CPS ≥1 subgroup and 0.98 (95% CI: 0.50, 1.95) for PD-L1 CPS <1 subgroup.
- OPDIVO with Ipilimumab vs. Chemotherapy: unstratified OS HR was 0.76 (95% CI: 0.62, 0.93) for PD-L1 CPS ≥1 subgroup and 1.0 (95% CI: 0.52, 1.94) for PD-L1 CPS <1 subgroup.

TPS and CPS subgroup data, based on Agilent/Dako PD-L1 IHC 28-8 pharmDx test, provided in the clinical trial section.

NCCN Guidelines Complement Information Included in Opdivo Label

		Recommended Population to Treat	
Tumor Type	**Recommended First-line Regimen**	**USPI[1]**	**NCCN[2]**
Esophageal Squamous Cell Carcinoma	**Nivolumab** + fluoropyrimidine, and platinum-containing chemotherapy	No restriction	No restriction[Cat 1]
	Nivolumab + ipilimumab	No restriction	No restriction[Cat 2A]
	Pembrolizumab + fluoropyrimidine, and platinum-containing chemotherapy	No restriction	CPS ≥10[Cat 1/2A] CPS <10[Cat 2B]
	Tislelizumab + chemotherapy	TBD	TBD

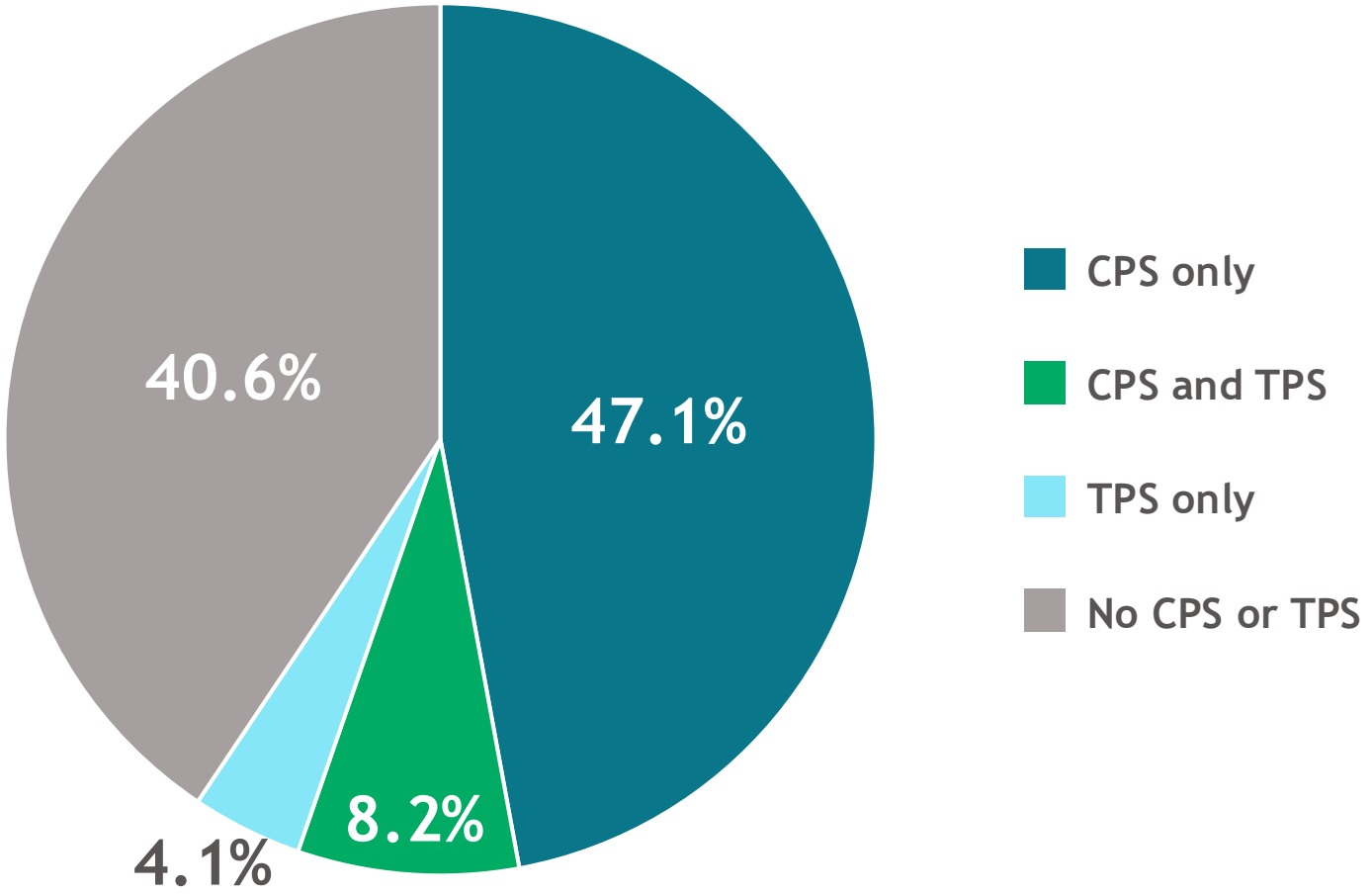
[1]Opdivo USPI.
[2]NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Esophageal Cancer. Version 4.2024 — July 30, 2024.

PD-L1 Testing Patterns — US Flatiron Analysis (N=170)

Esophageal Squamous Cell Carcinoma

~60%

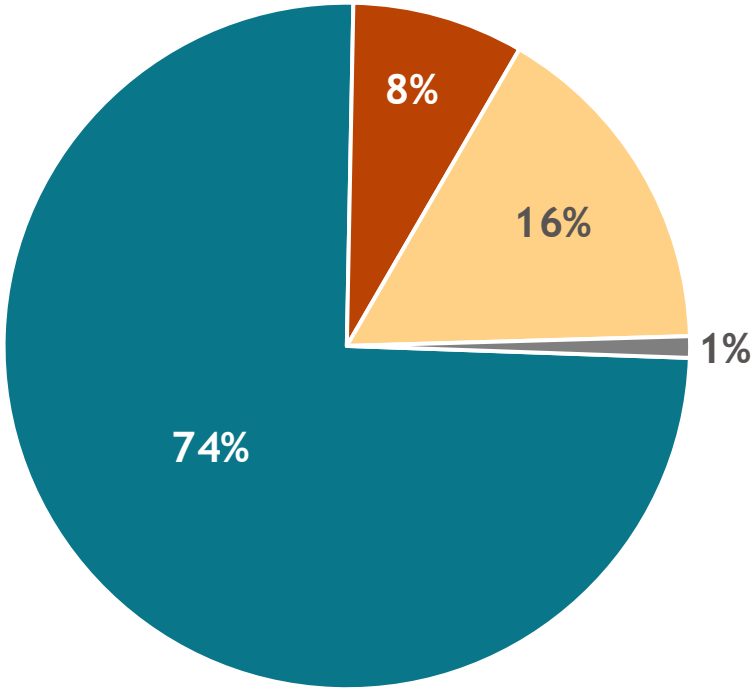
of ESCC patients are tested for PD-L1 expression



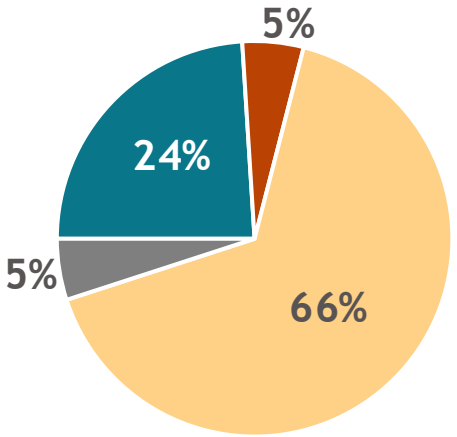
Flatiron analysis of PD-L1 CPS and TPS testing patterns of advanced ESCC patients who received 1L treatment from May 2022 to June 2024. PubD 00065623. Princeton, NJ: Bristol-Myers Squibb Company; 2024.

First-Line Treatment Patterns — Physician Survey (N=219)

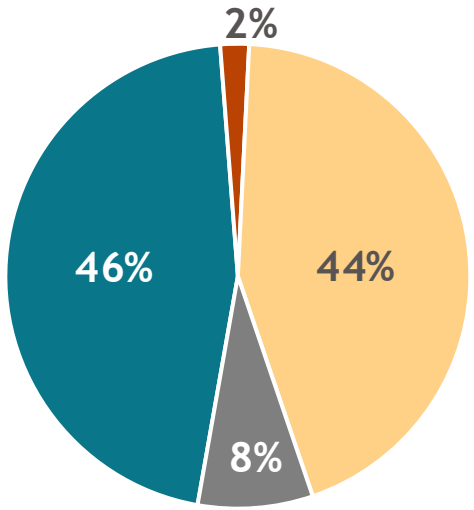
Esophageal Squamous Cell Carcinoma



PD-L1 Positive
n=116 (53%)



PD-L1 Negative
n=40 (18%)



Unknown or Untested
n=63 (29%)

IO + Chemo Nivo + Ipi Chemo alone Other

BMS Monthly Chart Audit, New patients, Weighted by Patient volume, Setting type and LOT size. PubD 00066034. Princeton, NJ: Bristol-Myers Squibb Company; 2024.

What We're Here to Discuss

1 ∞

Potential changes to the product label based on PD-L1 expression

2

We desire to do what's right for patients and ensure that information provided to physicians and patients is clear

3

Important challenges in seeking harmonization

Potential Labeling Options

Modify the indication to PD-L1 positive (by any FDA-approved test)

Benefit:

- Limits treatment to patients most likely to benefit based on clinical trial data
- Use of any FDA-approved test would minimize the need for clinicians to change their current testing practice

Considerations:

- PD-L1 is a dynamic biomarker and expression is heterogeneous leading to limitations in test interpretation
- Some patients may have inadequate tumor tissue for biomarker testing and endoscopy may be contraindicated

Keep current indication

Benefit:

- Provides physicians/patients an opportunity to make informed decisions on an individual patient basis
- USPI and practice guidelines are aligned
- High prevalence of PD-L1 expression limits risk of overtreatment

Considerations:

- Raises concerns about exposing patients who are less likely to benefit to additional toxicity

Agenda

Benefit Risk Profile in PD-L1 Subgroups

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Clinical Perspective

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Conclusion

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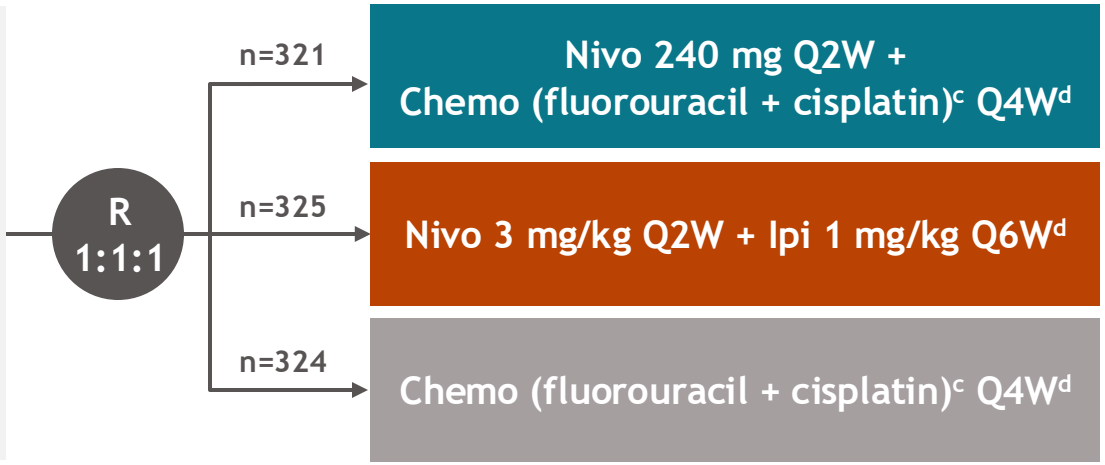
Benefit Risk Profile in PD-L1 Subgroups

Bristol Myers Squibb®

CheckMate 648 Study Design

Global, randomized, open-label, phase 3 study[1]

Key eligibility criteria
- Unresectable advanced, recurrent or metastatic ESCC
- ECOG PS 0-1
- No prior systemic treatment for advanced disease
- Measurable disease



N = 970

Primary endpoint:
- OS and PFS[e] (tumor cell PD-L1 ≥1%)

Secondary endpoints:
- OS and PFS[e] (all randomized)
- ORR[e] (tumor cell PD-L1 ≥1% and all randomized)

Stratification factors
- **Tumor cell PD-L1 expression (≥1% vs <1%[a])**
- Region (East Asia[b] vs rest of Asia vs ROW)
- ECOG PS (0 vs 1)
- Number of organs with metastases (≤1 vs ≥2)

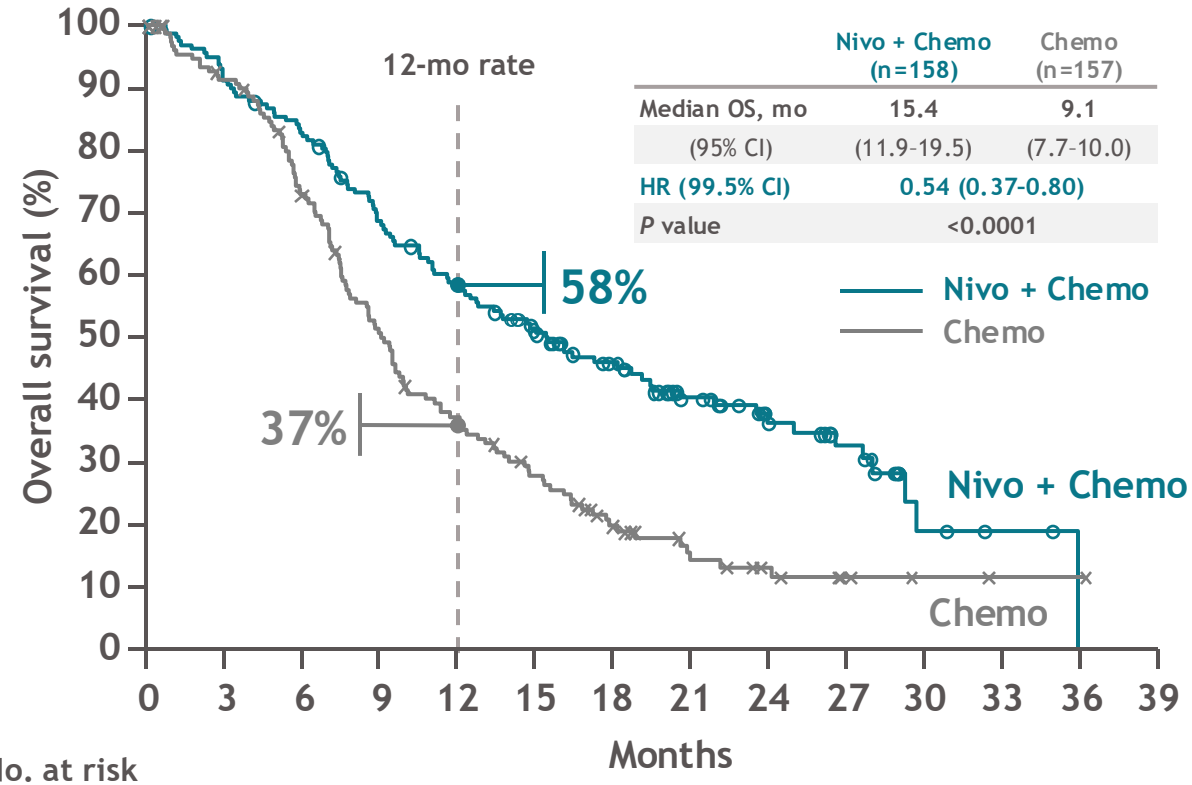
At data cutoff (January 18, 2021), minimum follow-up was 12.9 months[f]

[1]Doki Y, et al. *N Engl J Med* 2022;386:449-462. [a]<1% includes indeterminate tumor cell PD-L1 expression; determined by PD-L1 IHC 28-8 pharmDx assay (Dako). [b]East Asia includes patients from Japan, Korea, and Taiwan. [c]Fluorouracil 800 mg/m^2 IV daily (days 1-5) and cisplatin 80 mg/m^2 IV (day 1). [d]Until documented disease progression (unless consented to treatment beyond progression for Nivo + Ipi or Nivo + Chemo), discontinuation due to toxicity, withdrawal of consent, or study end. Nivo is given alone or in combination with Ipi for a maximum of 2 years. [e]Per BICR. [f]Time from last patient randomized to clinical data cutoff.

Statistically Significant and Clinically Meaningful OS Benefit

CheckMate 648, Nivo + Chemo

Primary endpoint (tumor cell PD-L1 ≥1%)[a]

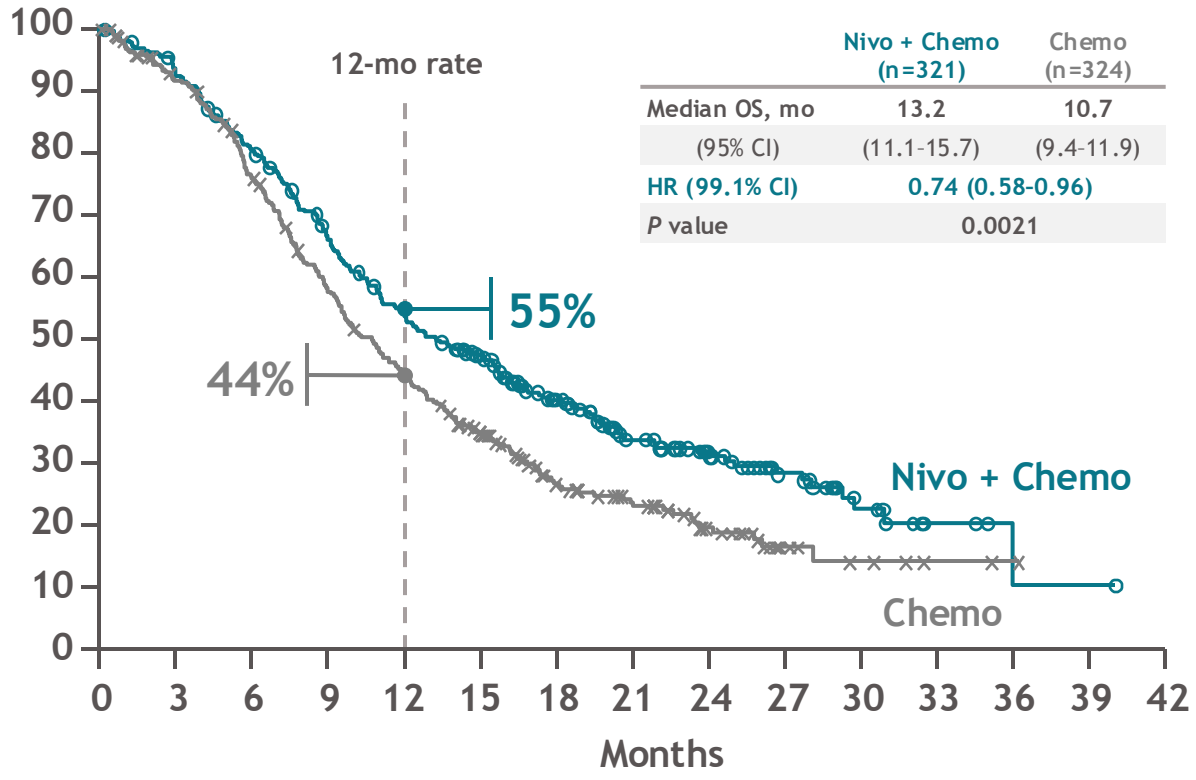


	Nivo + Chemo (n=158)	Chemo (n=157)
Median OS, mo	15.4	9.1
(95% CI)	(11.9-19.5)	(7.7-10.0)
HR (99.5% CI)	0.54 (0.37-0.80)	
P value	<0.0001	

No. at risk

Nivo + Chemo	158	143	129	105	88	70	53	36	22	16	4	2	0	0
Chemo	157	135	105	72	52	36	21	12	8	4	2	1	1	0

All randomized[a]



	Nivo + Chemo (n=321)	Chemo (n=324)
Median OS, mo	13.2	10.7
(95% CI)	(11.1-15.7)	(9.4-11.9)
HR (99.1% CI)	0.74 (0.58-0.96)	
P value	0.0021	

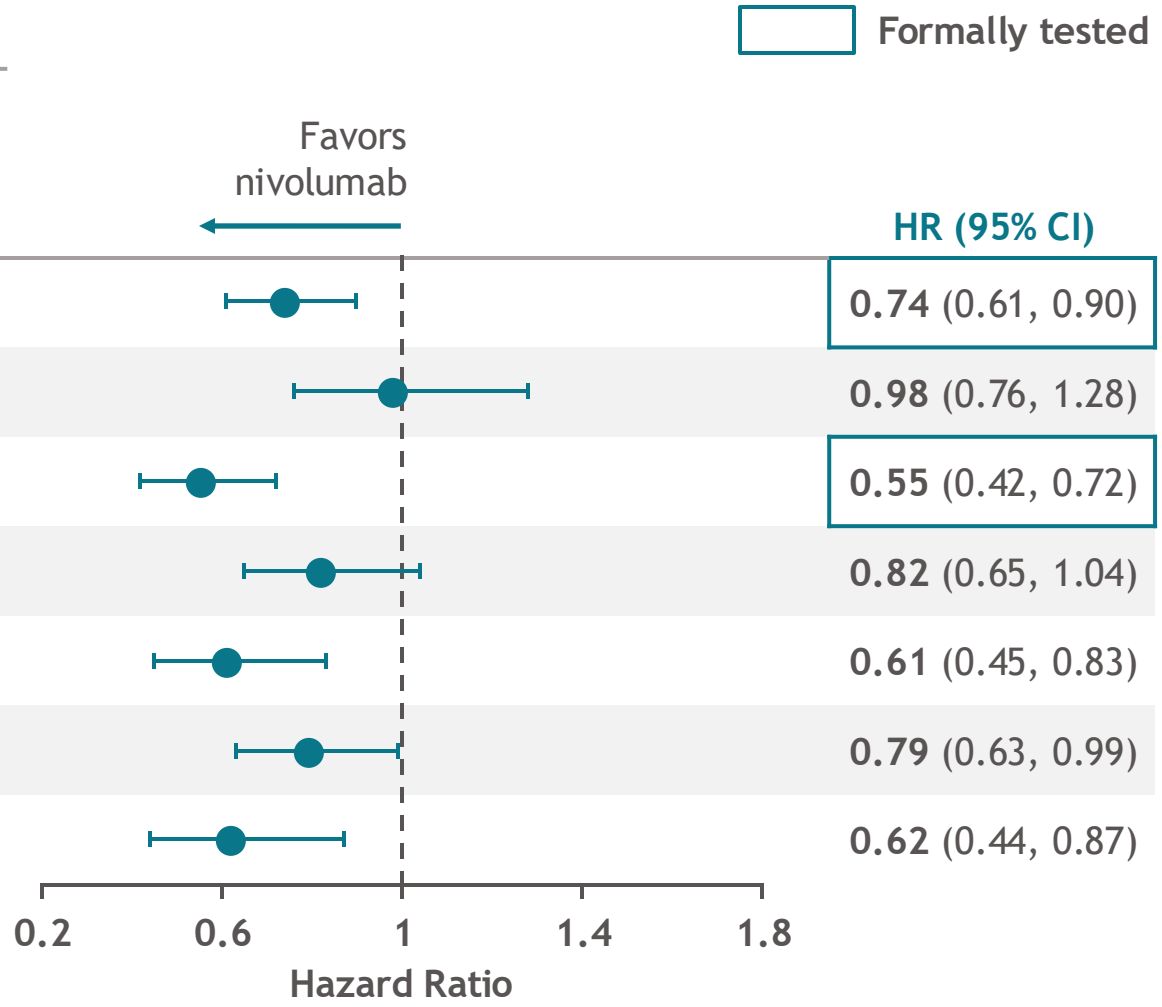
Nivo + Chemo	321	293	253	203	163	133	92	60	40	26	12	4	1	1	0
Chemo	324	281	229	171	131	93	56	41	23	9	5	2	1	0	0

[a]Minimum follow-up 12.9 months. Stratified hazard ratio. Doki Y, et al. *N Engl J Med* 2022;386:449-462.

OS in PD-L1 TPS Subgroups

CheckMate 648, Nivo + Chemo

	Nivo + Chemo			Chemo			
PD-L1	N	Events	Median, months	N	Events	Median, months	HR (95% CI)
All randomized	321	209	13.21	324	232	10.71	**0.74** (0.61, 0.90)
TPS <1%	163	111	11.96	166	111	12.16	**0.98** (0.76, 1.28)
TPS ≥1%	158	98	15.44	156	120	9.20	**0.55** (0.42, 0.72)
TPS <5%	201	131	12.81	207	146	11.14	**0.82** (0.65, 1.04)
TPS ≥5%	120	78	13.67	115	85	9.49	**0.61** (0.45, 0.83)
TPS <10%	219	143	12.29	225	161	10.84	**0.79** (0.63, 0.99)
TPS ≥10%	102	66	14.69	97	70	9.49	**0.62** (0.44, 0.87)

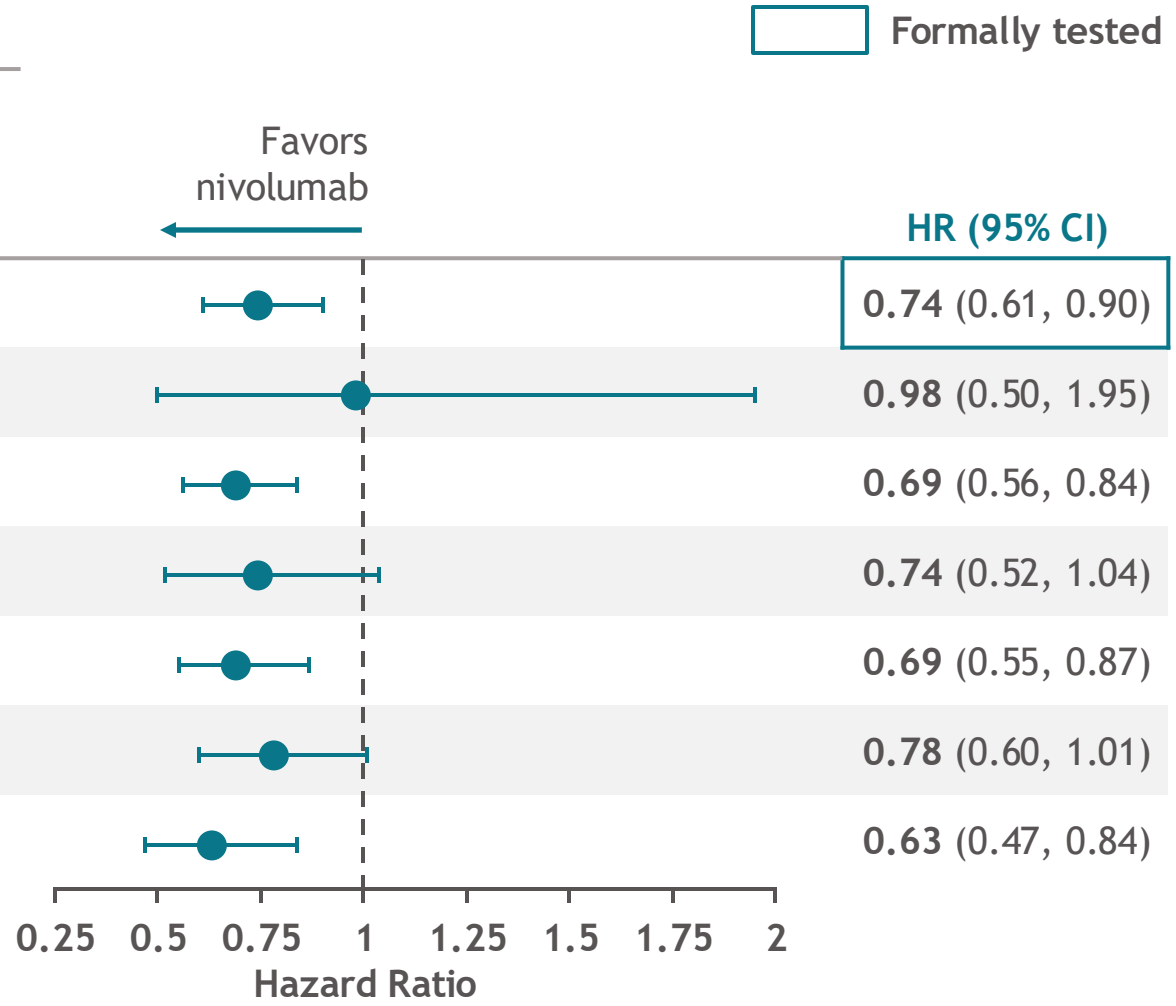


Unstratified hazard ratio. Doki Y, et al. *N Engl J Med* 2022;386:449-462.

OS in Exploratory PD-L1 CPS Subgroups

CheckMate 648, Nivo + Chemo

	Nivo + Chemo			Chemo			
PD-L1	N	Events	Median, months	N	Events	Median, months	HR (95% CI)
All randomized	321	209	13.21	324	232	10.71	**0.74** (0.61, 0.90)
CPS <1	27	19	9.86	24	16	12.09	**0.98** (0.50, 1.95)
CPS ≥1	278	177	13.77	280	205	9.76	**0.69** (0.56, 0.84)
CPS <5	97	62	11.96	91	66	9.40	**0.74** (0.52, 1.04)
CPS ≥5	208	134	15.18	213	155	11.14	**0.69** (0.55, 0.87)
CPS <10	170	115	12.06	159	118	9.69	**0.78** (0.60, 1.01)
CPS ≥10	135	81	16.13	145	103	11.63	**0.63** (0.47, 0.84)

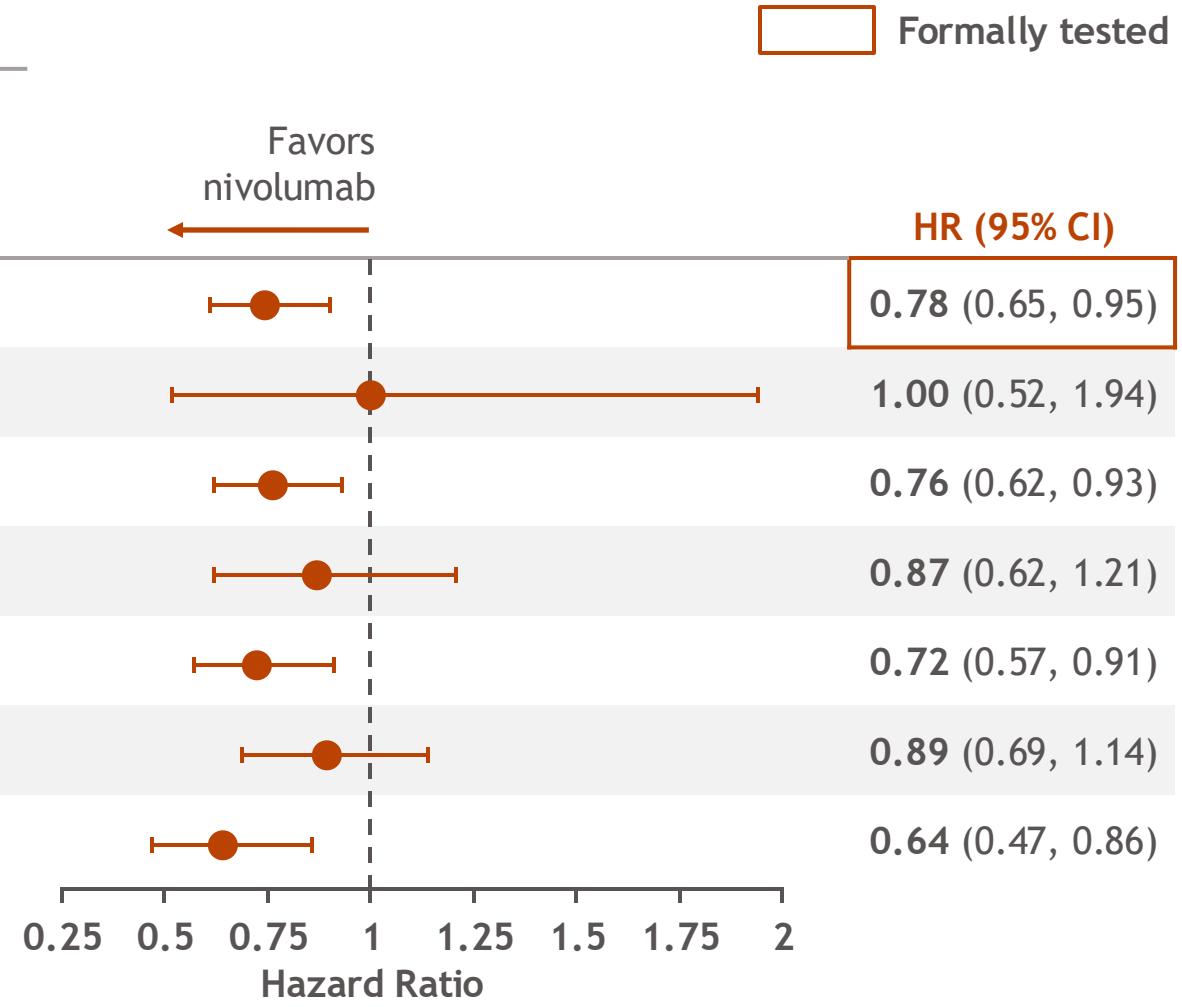


Unstratified hazard ratio. Doki Y, et al. *N Engl J Med* 2022;386:449-462.

OS in Exploratory PD-L1 CPS Subgroups

CheckMate 648, Nivo + Ipi

	Nivo + Ipi			Chemo			
PD-L1	N	Events	Median, months	N	Events	Median, months	HR (95% CI)
All randomized	325	216	12.75	324	232	10.71	**0.78** (0.65, 0.95)
CPS <1	31	21	11.47	24	16	12.09	**1.00** (0.52, 1.94)
CPS ≥1	266	179	12.75	280	205	9.76	**0.76** (0.62, 0.93)
CPS <5	106	73	11.43	91	66	9.40	**0.87** (0.62, 1.21)
CPS ≥5	191	127	14.52	213	155	11.14	**0.72** (0.57, 0.91)
CPS <10	171	121	11.24	159	118	9.69	**0.89** (0.69, 1.14)
CPS ≥10	126	79	16.69	145	103	11.63	**0.64** (0.47, 0.86)



Unstratified hazard ratio. Doki Y, et al. *N Engl J Med* 2022;386:449-462.

Overall Safety
CheckMate 648

	Patients, n (%)[1,2]		
	Nivo + Chemo (N=310)	Nivo + Ipi (N=322)	Chemo (N=304)
All grade, all causality AEs	308 (99.4)	316 (98.1)	301 (99.0)
All grade, TRAEs	297 (95.8)	256 (79.5)	275 (90.5)
Grade 3/4	147 (47.4)	102 (31.7)	108 (35.5)
All grade, TRAEs leading to DC[a]	106 (34.2)	57 (17.7)	59 (19.4)
Grade 3/4	29 (9.4)	41 (12.7)	14 (4.6)
Treatment-related deaths	5 (1.6)	5 (1.6)	4 (1.3)

No difference in safety profile based on PD-L1 status

[1]Data on file. BMS-REF-NIVO-0303. Princeton, NJ: Bristol-Myers Squibb Company; 2024. [2]Doki Y, et al. *N Engl J Med* 2022;386:449-462. [a]Reflects discontinuation (DC) of any component of a regimen.

Summary — First-Line Treatment of Advanced/Metastatic Esophageal Squamous Cell Carcinoma

- CM-648 demonstrated statistically significant and clinically meaningful OS benefit in the TPS ≥1% and all randomized populations
  - Exploratory analyses suggest similar OS benefit across all levels of PD-L1 positivity
  - Long-term follow-up data are consistent with the data available at the time of approval
- The safety profile of Nivo + Chemo and Nivo + Ipi was consistent with the known safety profile of the individual drug components
  - Consistent safety profile regardless of PD-L1 status
- Positive benefit risk profile in all PD-L1 positive subgroups

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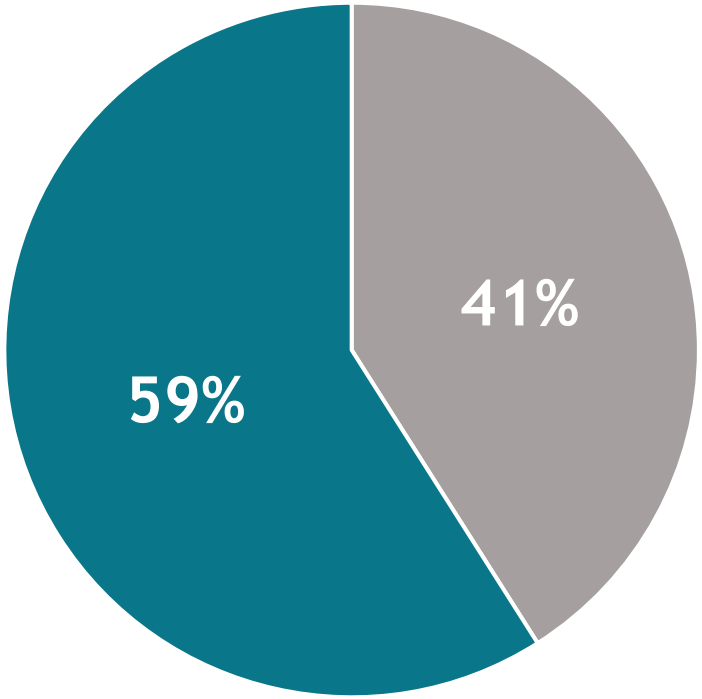
Clinical Perspective

Bristol Myers Squibb®

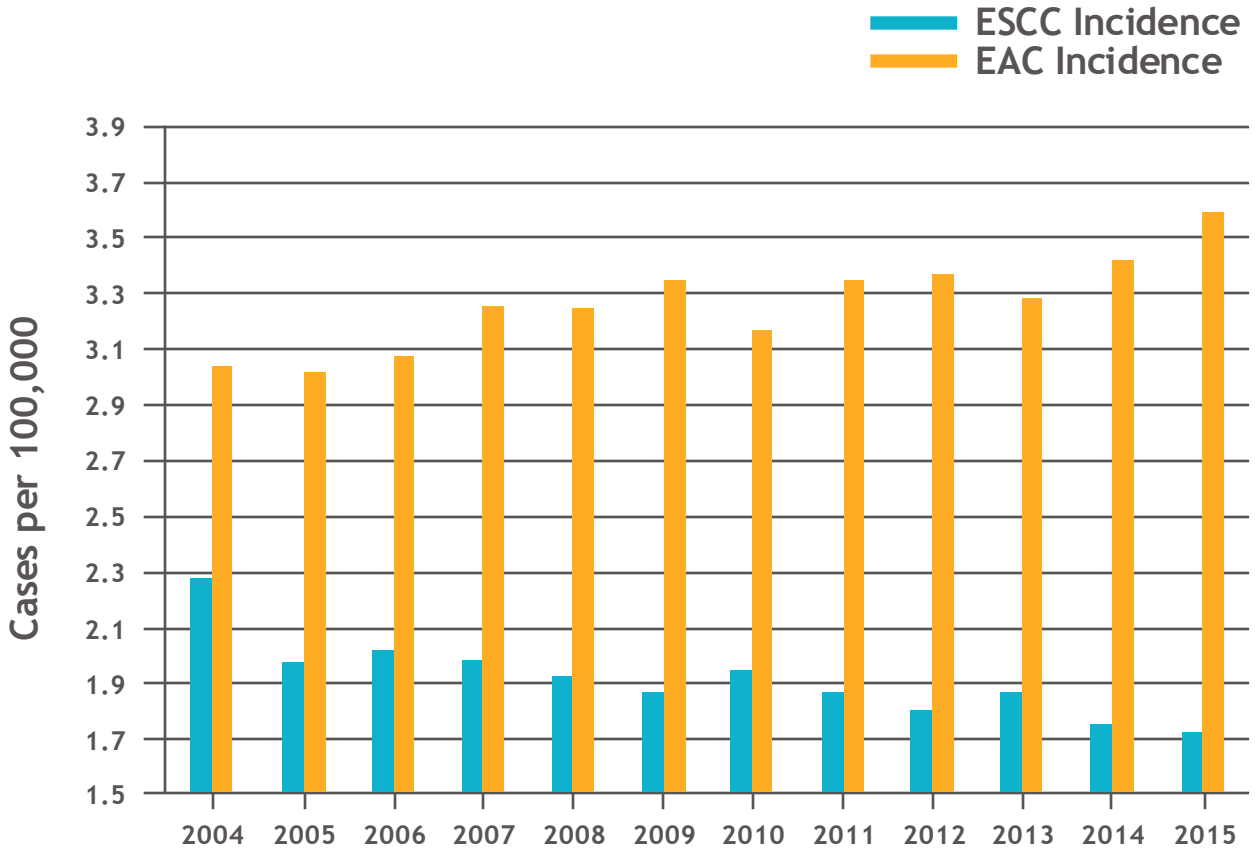
ESCC is an Orphan Disease in the United States

ESCC: SEER Database Analysis[a] 2004-2015



13,919
total patients diagnosed

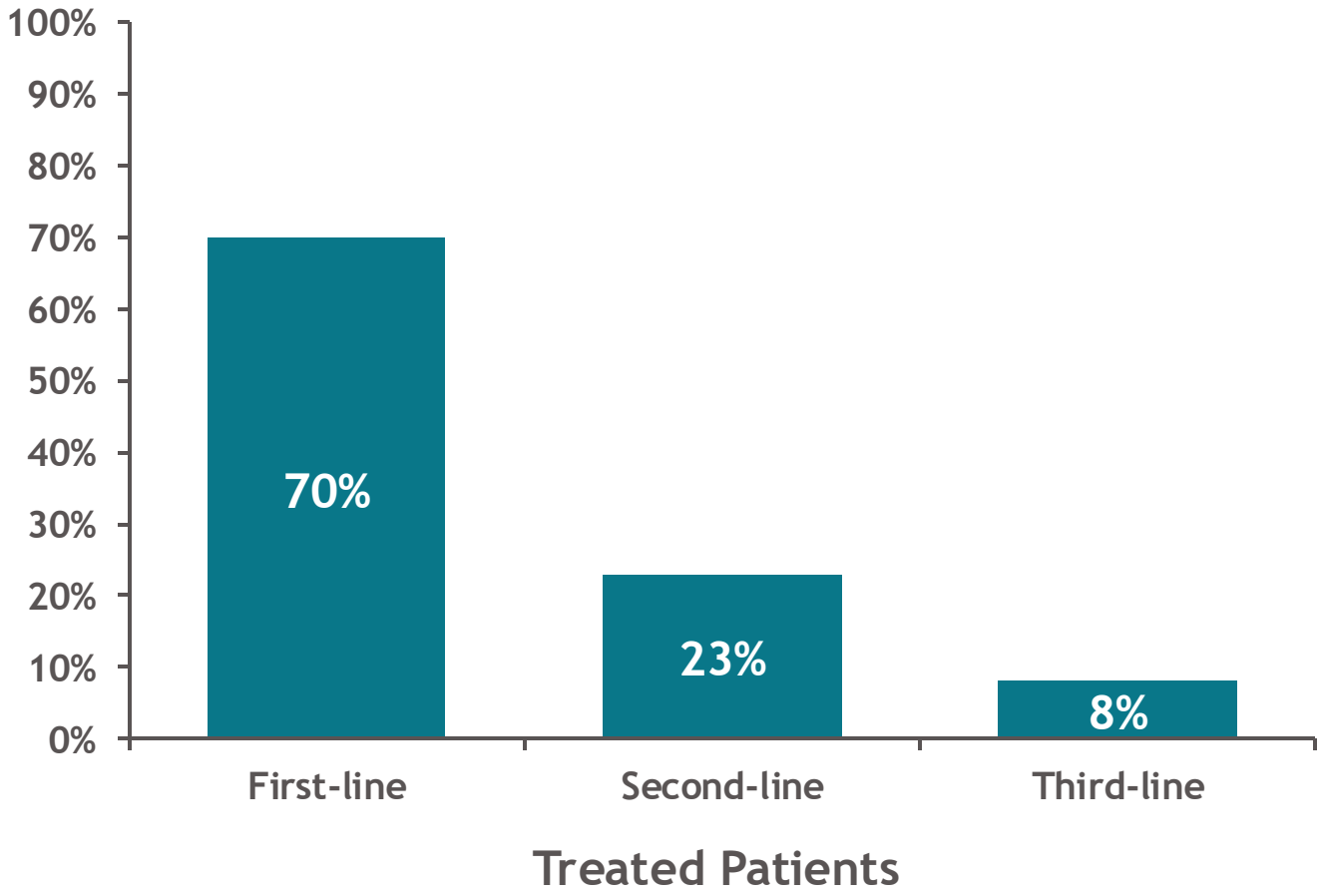
Early Stage (I/II) Later Stage (III/IV)



[a]Patients with known stage at diagnosis = 11,558. Then EO, et al. *World J Oncol*. 2020;11(2):55-64.

Few Patients With ESCC Go Beyond First-Line

Real-World Treatment Patterns[1]



<50% of patients in CM-648 received subsequent therapy[2]

Limited effective 2L treatment options and outcomes are poor

[1]Abraham P, et al. *Adv Ther*. 2020;37:3392-3403.
[2]Doki Y, et al. *N Engl J Med* 2022;386:449-462.

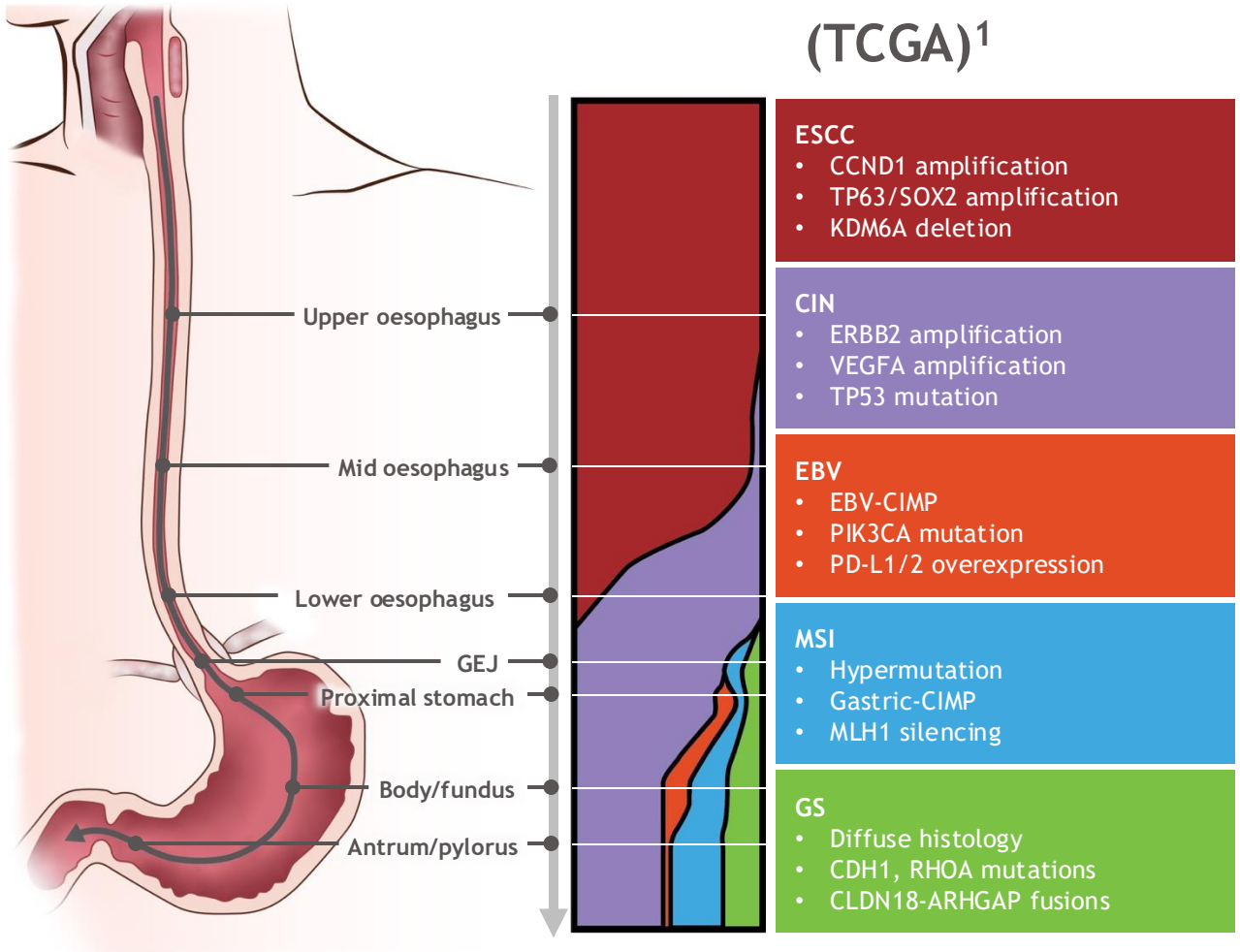
ESCC Is Biologically Different From Gastroesophageal Adenocarcinomas

Anatomic location of ESCC and genomic similarity to HNSCC

- Squamous esophageal cancer is more similar to squamous head and neck cancers than gastric cancer

Need to begin treatment quickly and palliate symptoms with radiotherapy

- Radiotherapy upregulates PD-L1[2]



[1]Cancer Genomic Atlas Research Network, Analysis Working Group, et al. *Nature*. 2017;541(7636):169-175. https://creativecommons.org/licenses/by/4.0/. [2]Kelly R, et al. ESMO GI 2023.

Reality of PD-L1 Testing in Clinical Practice

~60%

of ESCC patients are tested

- 47.1% CPS alone
- 8.2% CPS + TPS
- 4.1% TPS alone
- 40.6% Untested

- Heterogeneity of tumors
- Dynamic biomarker
- High interobserver variability
- Different assays and antibodies
- Different scoring systems (TPS vs CPS)

Flatiron analysis of PD-L1 CPS and TPS testing patterns of advanced ESCC patients who received 1L treatment from May 2022 to June 2024. PubD 00065623. Princeton, NJ: Bristol-Myers Squibb Company; 2024.

Conclusions and Recommendation

- Maintaining the current indication in ESCC is appropriate
  - The biology of ESCC is different from gastroesophageal adenocarcinomas
  - Only about 25% of patients make it to second-line treatment
  - Labeling is consistent with NCCN recommendations
- If a PD-L1 restriction is chosen, PD-L1 positivity by any FDA-approved test is easier for oncologists

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Late Development Oncology

BMS

Conclusion

Challenging Situation Without a Clear-Cut Answer

Modify indications based on PD-L1 positivity by any FDA-approved test

- Rational approach that would ensure only patients most likely to benefit receive treatment without requiring a major shift in current clinical testing practice
- However, this would also leave some patients without a potentially important treatment option
  - Risk could be minimized by choosing any measure of PD-L1 positivity

Keep current indication

- Leaves decision-making in the hands of the treating physician and maximizes the chance for patients to benefit, given the high prevalence of PD-L1 expression in ESCC and the shortcomings of available testing

Back Up Slides Shown

US Food & Drug Administration
Oncologic Drugs Advisory Committee
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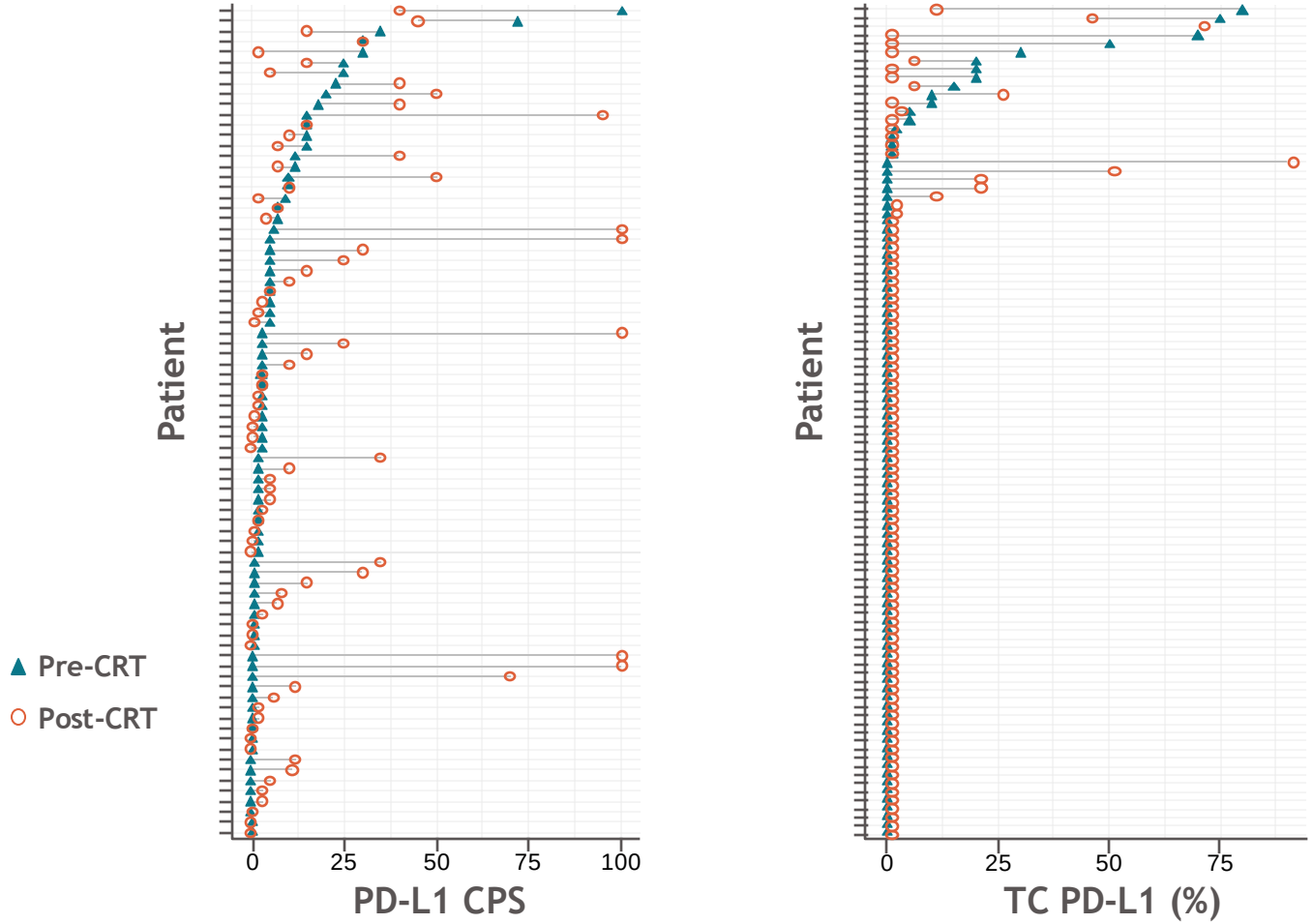
Post-CRT Changes in PD-L1 Expression

CheckMate 577

- <u>Increases</u> in PD-L1 expression after neoadjuvant CRT (prior to study treatment) were observed in 51% of CPS-evaluable patients[a]
- Expression remained <u>unchanged</u> in 76% of TC PD-L1-evaluable patients[b]



[a]CPS-evaluable patients defined as patients with paired pre-CRT and post-CRT tumor tissue that was evaluable for PD-L1 CPS (n = 80).
[b]TC PD-L1–evaluable patients defined as patients with paired pre-CRT and post-CRT tumor tissue that was evaluable for TC PD-L1 (n = 98).
Kelly R, et al. ESMO GI 2023.

DFS Based on Post-CRT Changes in PD-L1 Expression

CheckMate 577

The magnitude of DFS benefit appeared to be greater with nivolumab vs placebo in patients with an increase in PD-L1 CPS post-CRT (HR, 0.30 [95% CI, 0.11–0.78]) compared with the overall PD-L1 CPS-evaluable population[b] (HR, 0.64 [95% CI, 0.36–1.15])

	Nivolumab	Placebo	Total
PD-L1 CPS[a] evaluable,[b] n	**51**	**29**	**80**
Median DFS (95% CI), mo	25.1 (14.5-NE)	9.3 (5.6-26.3)	-
HR (95% CI)	**0.64 (0.36-1.15)**		-
PD-L1 CPS change > 0, n (%)	23 (45)	18 (62)	41 (51)
Median DFS (95% CI), mo	NR (27.1-NE)	8.9 (5.6-NE)	-
HR (95% CI)	**0.30 (0.11-0.78)**		-
PD-L1 CPS change = 0, n (%)	7 (14)	4 (14)	11 (14)
Median DFS (95% CI), mo	16.0 (1.9-NE)	5.5 (5.4-22.8)	-
HR (95% CI)	NA[c]		-
PD-L1 CPS change < 0, n (%)	21 (41)	7 (24)	28 (35)
Median DFS (95% CI), mo	8.3 (2.8-19.4)	15.1 (2.8-NE)	-
HR (95% CI)	NA[c]		-
TC PD-L1[d] evaluable,[e] n	**65**	**33**	**98**
Median DFS (95% CI), mo	25.1 (14.5-NE)	7.1 (5.6-15.1)	-
HR (95% CI)	**0.56 (0.33-0.96)**		-
TC PD-L1 change > 0, n (%)	6 (9)	2 (6)	8 (8)
Median DFS (95% CI), mo	19.8 (2.8-NE)	NA	-
HR (95% CI)	NA[c]		-
TC PD-L1 change = 0, n (%)	49 (75)	25 (76)	74 (76)
Median DFS (95% CI), mo	23.4 (9.8-NE)	5.6 (5.4-15.1)	-
HR (95% CI)	**0.51 (0.28-0.91)**		-
TC PD-L1 change < 0, n (%)	10 (15)	6 (18)	16 (16)
Median DFS (95% CI), mo	39.2 (3.6-NE)	NR (2.9-NE)	-
HR (95% CI)	NA[c]		-

[a]Defined as the number of PD-L1–positive tumor cells, lymphocytes, and macrophages divided by the total number of viable tumor cells multiplied by 100.
[b]PD-L1 CPS–evaluable patients were defined as patients with paired pre-CRT and post-CRT tumor tissue that was evaluable for PD-L1 CPS (n = 80).
[c]HR was not computed for subsets with fewer than 10 patients per treatment group.
[d]Defined as the number of positive tumor cells divided by the total number of viable tumor cells multiplied by 100.
[e]TC PD-L1–evaluable patients were defined as patients with paired pre-CRT and post-CRT tumor tissue that was evaluable for TC PD-L1 (n = 98).