ASCO Update 2020

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Disclosure

- BMS supported research grant evaluating inflammation and immunotherapy

Objectives

- At the end of this presentation participants will be able to:

1. Identify recently presented efficacy data that may impact patient treatment
2. Determine which patient populations should be considered for these new treatment approaches
3. Recognize the potential toxicity associated with these new treatments

A Great Year for Promising New Therapies

Outline and trials discussed

1. Lung Cancer: Destiny-Lung01, CheckMate 9LA and ADAURA
2. Breast Cancer: HER2CLIMB and Keynote-355
3. Bladder Cancer: JAVELIN Bladder 100
4. Colorectal Cancer: DESTINY-CRC01, and Keynote-177

To many trials to present so they were filtered by cancer frequency and potential impact

Trastuzumab Deruxtecan (T-DXd; DS-8201) in Patients With HER2-Mutated Metastatic Non-Small Cell Lung Cancer: Interim Results of DESTINY-Lung01

Smit, EF, et al. ASCO Abstract #9504

DESTINY-Lung01

OPEN Label Phase II trial w/ 2 cohorts

All Patients Received Fam-Trastuzumab Deruxtecan (T-DXd) dose 6.4 mg/kg IV q3week

- Recurrent metastatic nonsquamous NSCLC (PS 0 or 1)
- Failed Prior Standard Therapy
- HER2-expressing or HER2- activating mutation
- No prior HER2-targeted therapy, except pan-HER TKIs

Endpoints

- ORR, disease control, PFS, and DOR

Cohort 1 (n = 42)
HER2 expressing (IHC 3+ or IHC 2+)

Cohort 2 (n = 42)
HER2 mutated

Demographics:

- Median age 63
- CNS mets – 45%
- Prior treatment: median 2 (range 1-6)
  - 91% platinum based
  - 54% ICI
  - 19% Docetaxel

Egbert F. Smit, ASCO Abstract #9504

Efficacy in the HER2 Mutated Population

	Patients (N = 42)
Confirmed ORR by ICR	**61.9% (n = 26)** (95% CI, 45.6%-76.4%)
CR	2.4% (n = 1)
PR	59.5% (n = 25)
SD	28.6% (n = 12)
PD	4.8% (n = 2)
Not evaluable	4.8% (n = 2)
Disease control rate	**90.5%** (95% CI, 77.4%-97.3%)
Duration of response, median	Not reached (95% CI, 5.3 months-NE)
PFS, median	**14.0 mo (**95% CI, 6.4-14.0 months)

Egbert F. Smit, ASCO Abstract #9504

T-DXd is an Antibody Directed Cytotoxin that is Approved for Breast Cancer

- Noteworthy Efficacy Measures for 3rd line mNSCLC
  - Benefit limited to HER2 mutated patients, but significant
- Drug is available for Breast Ca
- Dose in this study was slightly higher than approved dose (6.4 mg/kg vs 5.4 mg/kg)
- Toxicity is characterized and acceptable in this population:
- Boxed warning – Interstitial Lung Disease, Embryofetal toxicity
- Common Toxicity – Nausea and Vomiting, myelosuppression, fatigue, alopecia, constipation,, diarrhea, and cough

Egbert F. Smit, ASCO Abstract #9504 and ENHERTU Prescribing Information

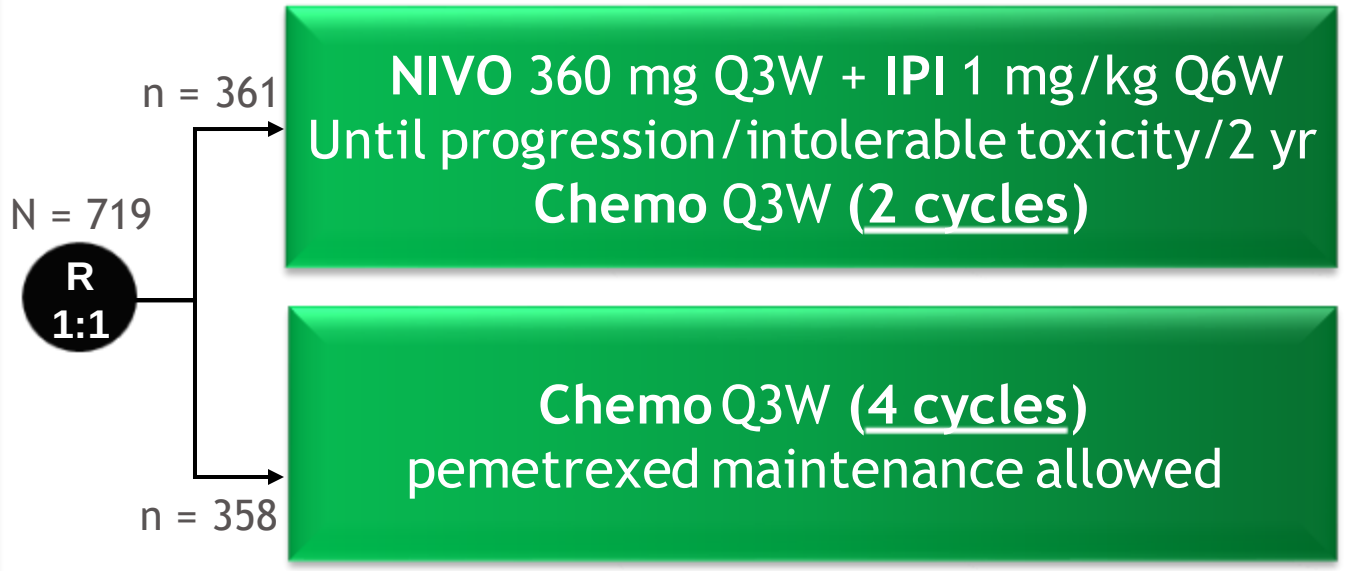
Nivolumab + ipilimumab + 2 cycles of platinum-doublet chemotherapy vs 4 cycles chemotherapy as first-line treatment for stage IV/recurrent NSCLC: CheckMate 9LA

Reck, M, et al. ASCO *Abstract Number 9501*

CheckMate 9LA

Randomized Phase III
- Stage IV or recurrent NSCLC
- No prior systemic therapy
- No sensitizing *EGFR* mutations or known *ALK* alterations
- ECOG PS 0–1

Stratified by PD-L1[b] (< 1%[c] vs ≥ 1%), sex, and histology (SQ vs NSQ)



Primary endpoint
- OS

Secondary endpoints
- PFS by BICR
- ORR by BICR
- Efficacy by tumor PD-L1 expression

Demographics:
- Median age 65
- Never Smoker – 13-14%
- PD-L1 expression:
  - <1% = 40%
  - 1-49% = 38%
  - ≥50% = 22%

Reck, M, et al. ASCO *Abstract Number 9501*

Overall survival subgroup analysis (minimum f/u 12.7 mo)

Overall and Subgroup	Median OS, mo		Unstratified HR	Unstratified HR (95% CI)
	NIVO + IPI + chemo n = 361	Chemo n = 358		
All randomized (N = 719)	**15.6**	**10.9**	**0.66**	**(0.55-0.8)**
Never smoker (n = 98)	14.1	17.8	1.14	(0.66 – 1.97)
Smoker (n = 621)	15.6	10.4	0.62	(0.5-0.75)
Squamous (n = 227)	14.5	9.1	0.62	(0.45-0.86)
Non-squamous (n = 492)	17.0	11.9	0.69	(0.55-0.87)
Liver metastases (n = 154)	10.2	8.1	0.83	(0.57-1.2)
No liver metastases (n = 565)	19.4	12.4	0.64	(0.51-0.8)
Bone metastases (n = 207)	11.9	8.3	0.74	(0.53-1.01)
No bone metastases (n = 512)	20.5	12.4	0.65	(0.51-0.82)
PD-L1 < 1% (n = 264)	16.8	9.8	0.62	(0.45-0.85)
PD-L1 ≥ 1% (n = 407)	15.8	10.9	0.64	(0.5-0.82)
PD-L1 1–49% (n = 233)	15.4	10.4	0.61	(0.44-0.84)
PD-L1 ≥ 50% (n = 174)	18.0	12.6	0.66	(0.44-0.99)

Reck, M, et al. ASCO *Abstract Number 9501*

NIVO + IPI + chemo in first-line NSCLC

- Nivolumab + IPI + limited chemotherapy is clearly better than just chemotherapy
  - Better across all subgroups, except never smokers
  - Relevant, likely could lead to FDA approval – however a couple of key questions remain
    - How would Nivo/Ipi + 2 or 4 cycles of chemotherapy compare?
    - How will it compare to Pembrolizumab + 4 cycles of chemotherapy?
    - The OS curves separated early – will they continue to be separate long term (e.g. 5 years)
- No new safety signals were observed for NIVO + IPI + 2 cycles of chemo

Reck, M, et al. ASCO *Abstract Number 9501*

Osimertinib as adjuvant therapy in patients with stage IB–IIIA EGFR mutation positive NSCLC after complete tumor resection: ADAURA

Roy S. Herbst, RS, et al. Abstract #LBA5

ADAURA

Randomized Placebo Control Phase III

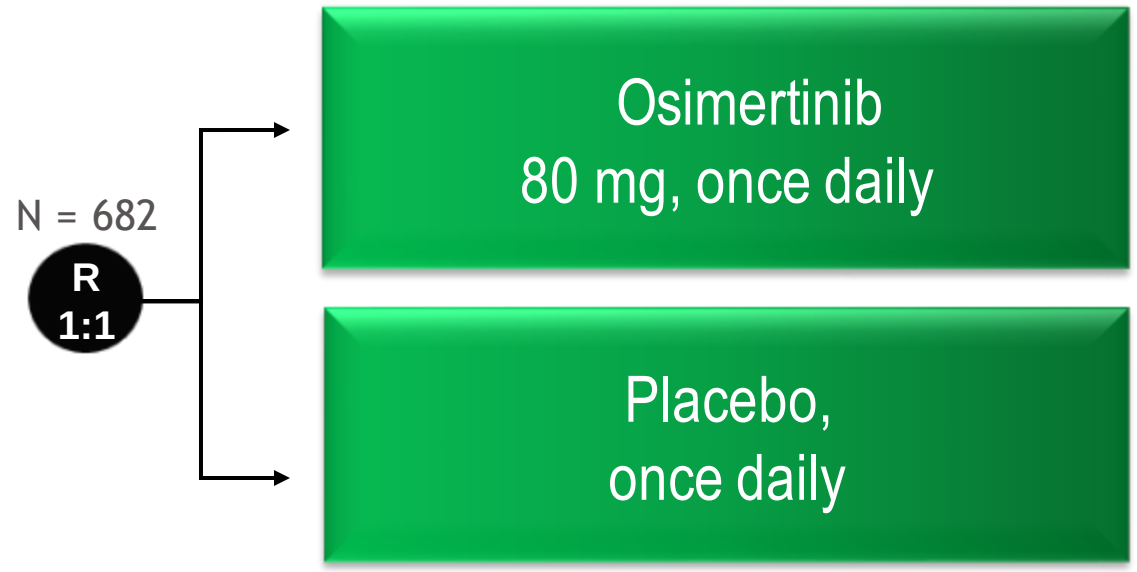
Completely resected stage IB, II, IIIA NSCLC

- Non-Squamous histology
- Ex19del / L858R *EGFR* mutations
- ECOG PS 0–1

Max. interval between surgery and randomization:

- 10 weeks without adjuvant chemotherapy
- 26 weeks with adjuvant chemotherapy

Stratified by stage, mutation, and race



Primary endpoint

- DFS for stage II/IIIa

Secondary endpoints

- DFS for all patient
- DFS at 2, 3, 4, and 5 years
- OS, Safety, and QOL

Note the Study was unblinded early due to efficacy in the treatment arm.

Roy S. Herbst, RS, et al. ASCO Abstract #LBA5

Baseline characteristics in the overall population (stage IB/II/IIIA)

Characteristic	Osimertinib % (n=339)	Placebo % (n=343)
Sex: male / female	32 / 68	28 / 72
Age, median (range), years	64 (30–86)	62 (31–82)
Smoking status: smoker / non-smoker	32 / 68	25 / 75
Race: Asian / non-Asian	64 / 36	64 / 36
AJCC staging at diagnosis (7th edition): IB / II / IIIA	31 / 35 / 34	31 / 34 / 35
EGFR mutation at randomization‡: Ex19del / L858R	55 / 45	56 / 44
Adjuvant chemotherapy: yes / no	55 / 45	56 / 44

Roy S. Herbst, RS, et al. ASCO Abstract #LBA5

ADAURA Efficacy - DFS in Stage II/IIIA @ 24 mo 90% vs 44%

Overall Population	Group	HR	95% CI
Overall (N=682)	Stratified log-rank	0.21	0.16, 0.28
	Unadjusted Cox PH	0.20	0.14, 0.29
Sex	Male (n=204)	0.21	0.11, 0.36
	Female (n=478)	0.20	0.12, 0.30
Smoking status	Smoker (n=194)	0.14	0.06, 0.27
	Non-smoker (n=488)	0.23	0.15, 0.34
Race	Asian (n=434)	0.22	0.14, 0.33
	Non-Asian (n=248)	0.17	0.08, 0.31
Stage	Stage IB (n=212)	0.50	0.25, 0.96
	Stage II (n=236)	0.17	0.08, 0.31
	Stage IIIA (n=234)	0.12	0.07, 0.20
EGFRm	Ex19del (n=378)	0.12	0.07, 0.20
	L858R (n=304)	0.35	0.21, 0.55
Adjuvant chemotherapy	Yes (n=378)	0.18	0.11, 0.29
	No (n=304)	0.23	0.13, 0.38

Roy S. Herbst, RS, et al. ASCO Abstract #LBA5

Adjuvant Osimertinib in NSCLC

- Osimertinib is clearly superior to placebo after complete resection regardless of stage or adjuvant chemotherapy
  - Better across all subgroups (NOTE only EGFR mutated patients included)
  - New Standard of Care – should lead to FDA approval
    - Unclear if adjuvant chemotherapy is of value?
- No new safety signals were observed for Osimertinib

Roy S. Herbst, RS, et al. ASCO Abstract #LBA5

NSCLC Summary

- Adjuvant osimertinib is a new standard for patients with completely resected stage Ib/II/IIIa NSCLC that harbors an EGFR mutation
- Nivolumab + Ipilimumab + blunted (2 cycles) chemotherapy is superior to chemotherapy
  - it is unclear how this will compare to other chemo-immunotherapy regimens first line, but it should be a new option available to the majority of patients
  - Note the Nivolumab/Ipilimumab dosing is different that what has been used in early combination studies
- Fam-Trastuzumab deruxtecan appears to be highly active as 3rd line therapy for metastatic NSCLC patients whose tumor harbors a HER2 mutation

Intracranial Efficacy and Survival With Tucatinib Plus Trastuzumab and Capecitabine for Previously Treated HER2-Positive Breast Cancer With Brain Metastases in the HER2CLIMB Trial

Lin, NU et al. J Clin Oncol 38:2610-2619

HER2CLIMB, Phase III Trial
Trastuzumab/Capecitabine +/- Tucatinib

Randomized, double-blind, placebo controlled, phase III trial

- HER2+ advanced breast cancer
- Prior trastuzumab, pertuzumab, and T-DM1
- ECOG PS 0–1
- Brain mets allowed

N=612

n=410

- **Tucatinib 300 mg PO BID**
- Trastuzumab 6 mg/kg IV Q3W (loading dose: 8 mg/kg C1D1)
- Capecitabine 1000 mg/m^2 PO BID, D1-14

n=202

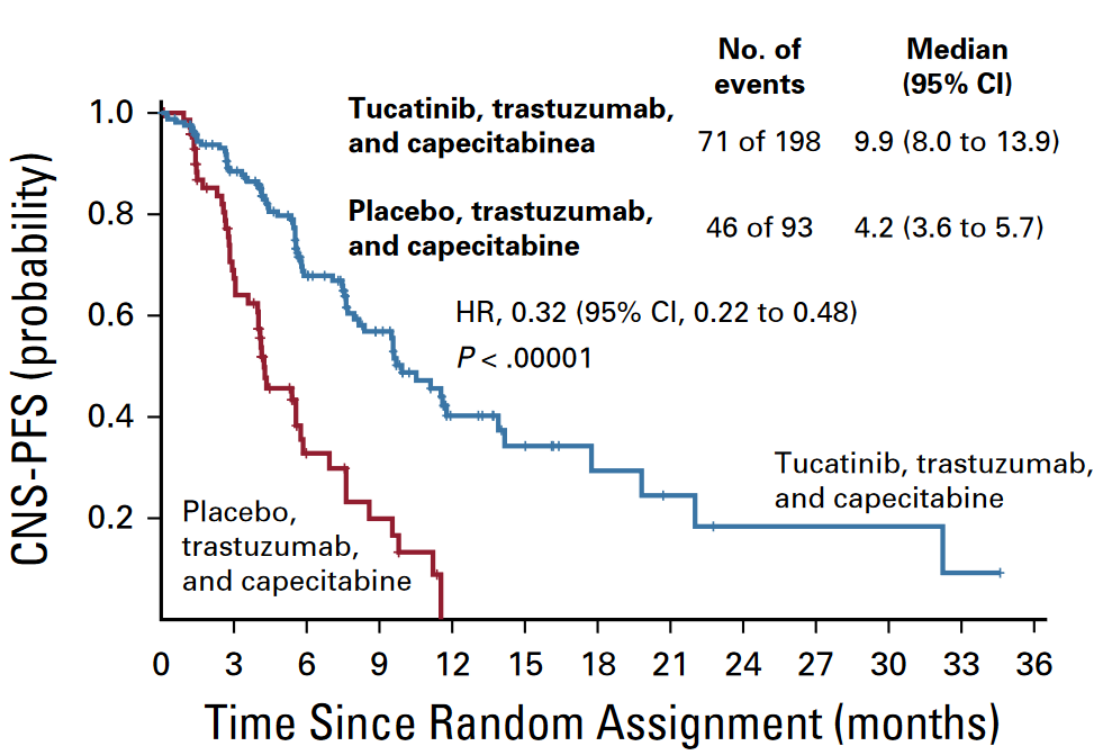
- Placebo PO BID
- Trastuzumab 6 mg/kg Q3W IV (loading dose: 8 mg/kg C1D1)
- Capecitabine 1000 mg/m^2 PO BID, D1-140

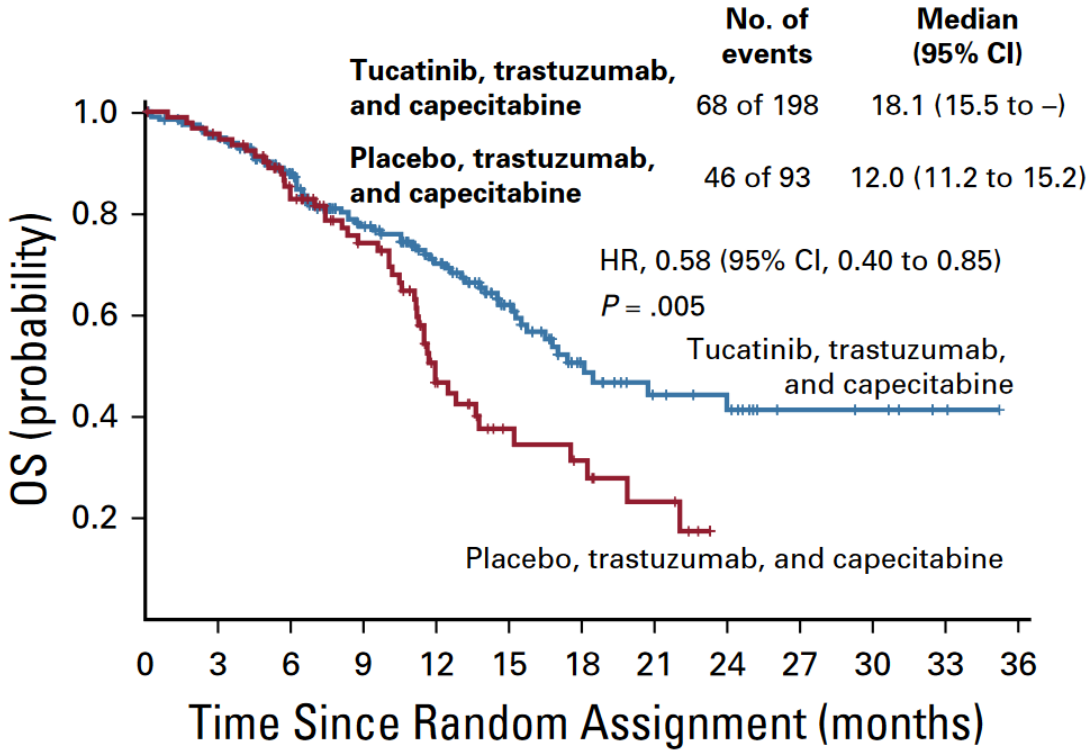
Study Presented at SABC meeting and published in NEJM 2/2020

291 Patients had Brain Metastasis – Analysis presented at ASCO and recently published in J Clin Oncol 2020;38:2610-19

Murthy RK, et al. *N Engl J Med*. 2020.

HER2CLIMB, CNS – PFS and OS Outcomes





No. at risk:

Tucatinib, trastuzumab, and capecitabine	198	132	74	45	18	11	6	4	2	2	2	1	0
Placebo, trastuzumab, and capecitabine	93	41	11	6	0	0	0	0	0	0	0	0	0

No. at risk:

Tucatinib, trastuzumab, and capecitabine	198	184	146	108	79	49	26	17	14	7	6	2	0
Placebo, trastuzumab, and capecitabine	93	87	67	49	23	12	9	5	0	0	0	0	0

9.9 mo vs 4.2 mo HR 0.32 (0.22-0.48)

18.1 mo vs 12 mo HR 0.58 (0.4-0.85)

Tucatinib for HER2+ mBreast Cancer

- This is a significant new drug in a busy space – It clearly shines and should be used in patients with Brain metastasis. This includes those that are active as well as those that are stable.
- Tucatinib was recently approved for HER2+ breast cancer who have been previously treated with a HER2 therapy.
- MOA it is a TKI that inhibits phosporylation of HER2 and HER3
- **Common Toxicity** include: diarrhea, palmar-plantar erythrodysesthesia, nausea, fatigue, hepatotoxicity, vomiting, stomatitis, decreased appetite, abdominal pain, headache, anemia, and rash

J Clin Oncol 2020;38:2610-19 and TUKYSA prescribing information

KEYNOTE-355: Randomized, double-blind, phase III study of pembrolizumab + chemotherapy versus placebo + chemotherapy for previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer

Cortez, J et al. ASCO Abstract 1000

KEYNOTE-355 – Adv/metastatic TN Breast Cancer

Randomized, double-blind, placebo controlled, phase III trial

Adult patients with previously untreated locally recurrent inoperable or metastatic TNBC; completed curative intent Tx ≥ 6 mos before first recurrence

Stratify by Chemotherapy, *PD-L1 (CPS > 1 vs < 1); Previous Tx for EBC*

N= 847

Pembrolizumab 200 mg IV Q3W + chemotherapy* (n = 566)

Placebo + chemotherapy* (n = 281)

*Investigator's choice of chemotherapy was permitted:

Nab-paclitaxel 100 mg/m^2 IV on Days 1, 8, 15 of 28-day cycle

Paclitaxel 90 mg/m^2 IV on Days 1, 8, 15 of 28-day cycle

Gem 1000 mg/m^2 + carbo AUC 2 on Days 1, 8 of 21-day cycle

Primary endpoints: PFS and OS (PD-L1 CPS ≥ 10, PD-L1 CPS ≥ 1, and ITT)

Secondary endpoints: ORR, DoR, DCR, safety

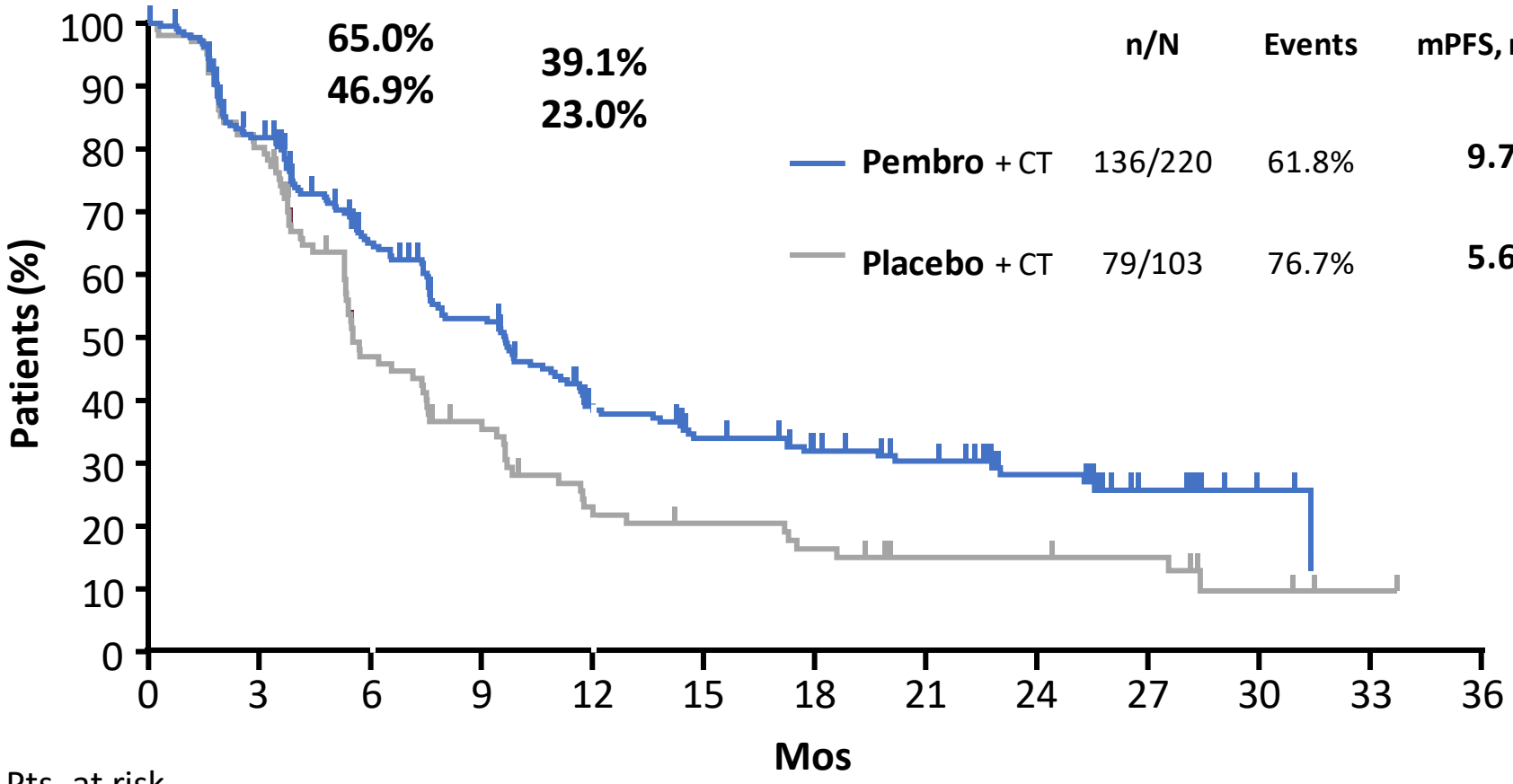
Cortez, J et al. ASCO Abstract 1000

KEYNOTE-355 : Baseline Characteristics

Characteristics, n (%)	Pembrolizumab + CT (N = 566)	Placebo + CT (N = 281)
ECOG PS 1	232 (41.0)	108 (38.4)
PD-L1–positive CPS ≥1	425 (75.1)	211 (75.1)
PD-L1–positive CPS ≥10	220 (38.9)	103 (36.7)
CT on study		
▪ Taxane	255 (45.1)	127 (45.2)
▪ Gem/carbo	311 (54.9)	154 (54.8)
Previous same-class CT		
▪ Yes	124 (21.9)	62 (22.1)
▪ No	442 (78.1)	219 (77.9)
Disease-free interval		
▪ De novo metastasis	167 (29.5)	84 (29.9)

Cortes. ASCO 2020. Abstr 1000.

KEYNOTE-355: PFS in PD-L1 CPS ≥ 10 Population



	n/N	Events	mPFS, mos	HR (95% CI)	*P* value (one-sided)
Pembro + CT	136/220	61.8%	**9.7**	0.65 (0.49-0.86)	0.0012
Placebo + CT	79/103	76.7%	**5.6**		

Pts. at risk

220	173	122	96	63	52	44	37	25	12	5	0	0
103	80	41	30	18	15	12	8	8	7	3	1	0

Cortes. ASCO 2020. Abstr 1000. Reproduced with permission.

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KEYNOTE-355: Conclusions

- Pembrolizumab + chemotherapy significantly improved PFS across all subsets compared with chemotherapy alone as first-line therapy in patients with mTNBC
- PFS at 12 months
  - PD-L1 CPS ≥ 10 = increased by 16%
  - PD-L1 CPS ≥ 1 = increased by 12%
  - ITT population = increased by 9%
- Improvement numerically appeared better when combined with a taxane as apposed to gemcitabine/carboplatin
- Safety outcomes were consistent with previous chemoimmunotherapy data

Cortes. ASCO 2020. Abstr 1000.

Maintenance avelumab + best supportive care (BSC) versus BSC alone after platinum-based first-line (1L) chemotherapy in advanced urothelial carcinoma (UC): JAVELIN Bladder 100 phase III interim analysis

Powles, T, et al. ASCO Abstract LBA1

JAVELIN Bladder 100

Randomized, open label, placebo controlled, phase III trial

Patients with unresectable locally advanced or metastatic UC who attained CR, PR, or SD with 4-6 cycles of standard first-line chemotherapy (cisplatin/gemcitabine or carboplatin/gemcitabine)
Stratified by best response and metastatic site (visceral vs nonvisceral)

Avelumab 10 mg/kg Q3W + BSC
(n = 350)

BSC
(n = 350)

Primary endpoint: OS in all randomized patients, PD-L1+ populations
Secondary endpoints: PFS (RECIST v1.1), ORR (RECIST v1.1), safety and tolerability, PROs

Powles, T, et al. ASCO Abstract LBA1

Baseline Characteristics

	Overall Population (N = 700)		PD-L1+ Population (n = 358)	
Characteristic	Avelumab + BSC (n = 350)	BSC (n = 350)	Avelumab + BSC (n = 189)	BSC (n = 169)
Tumor in upper tract (renal pelvis, ureter)/ lower tract (bladder, urethra, prostate), %	30/70	23/77	23/77	21/79
Visceral/nonvisceral* metastasis, %	55/45	55/45	47/53	47/53
PD-L1 status, % ▪ Positive ▪ Negative	 54 40	 48 38	 100 0	 100 0
First-line chemotherapy regimen, % ▪ Gemcitabine + cisplatin ▪ Gemcitabine + carboplatin ▪ Gemcitabine + cisplatin/carboplatin	 52 42 6	 59 35 6	 53 39 7	 58 32 9
CR or PR to first-line chemotherapy, %	72	72	74	76

Powles, T, et al. ASCO Abstract LBA1

JAVELIN Bladder 100: Survival

Overall Population	Avelumab + BSC (n = 350)	BSC (n = 350)	HR (95% CI)	P Value
Median OS, mos	21.4	14.3	0.69 (0.56-0.86)	< .001
▪ 12-mo OS, %	71	58	--	--
▪ 18-mo OS, %	61	44	--	--
Median PFS, mos	3.7	2.0	0.62 (0.52-0.75)	< .001
▪ 12-mo PFS, %	30	13	--	--

PD-L1+ Population	Avelumab + BSC (n = 189)	BSC (n = 169)	HR (95% CI)	P Value
Median OS, mos	Not estimable	17.1	0.56 (0.40-0.79)	< .001
▪ 12-mo OS, %	79	60	--	--
▪ 18-mo OS, %	70	48	--	--
Median PFS,[†] mos	5.7	2.1	0.56 (0.43-0.73)	< .001
▪ 12-mo PFS, %	36	15	--	--

Powles, T, et al. ASCO Abstract LBA1

JAVELIN Bladder 100: Summary

- The primary endpoint in overall population and PD-L1+ population, with maintenance avelumab significantly prolonging OS in patients with response or stable disease after prior first-line platinum chemotherapy
  - Median OS in overall population: 21.4 vs 14.3 mos (HR: 0.69; 95% CI: 0.56-0.86; *P* < .001)
  - Median OS in PD-L1+ population: NE vs 17.1 mos (HR: 0.56; 95% CI: 0.40-0.79; *P* < .001)
  - OS benefit observed across patient subgroups
- Avelumab safety profile deemed manageable, with relatively low rates of grade ≥ 3 AEs; consistent with previous reports
- Investigators conclude that avelumab maintenance in patients with advanced urothelial carcinoma whose disease did not progress after first-line, platinum-based chemotherapy represents a new standard-of-care therapy
  - On June 30, 2020, the FDA approved avelumab as maintenance therapy for patients with locally advanced/metastatic UC that has not progressed on first-line platinum-based chemotherapy

Powles, T, et al. ASCO Abstract LBA1

Slide credit: clinicaloptions.com

A phase II, multicenter, open-label study of trastuzumab deruxtecan (T-DXd; DS-8201) in patients (pts) with HER2-expressing metastatic colorectal cancer (mCRC): DESTINY-CRC01

Siena S, et al. ASCO Abstract 4000

DESTINY-CRC01

Phase II, open label multicohort trial

Unresectable/metastatic CRC that is HER2 expressing

RAS/BRAF wild type

≥ 2 previous regimens

previous anti-HER2 tx permitted

ECOG PS 0-1

(N = 78)

Cohort A: HER2 Positive (IHC 3+ or IHC 2+/ISH+)

T-DXd 6.4 mg/kg Q3W (n = 53)

Cohort B*: HER2 IHC2+/ISH-

T-DXd 6.4 mg/kg Q3W (n = 7)

Cohort C*: HER2 IHC 1+

T-DXd 6.4 mg/kg Q3W (n = 18)

Primary endpoint: confirmed ORR by ICR in Cohort A

Secondary endpoints: DoR, DCR, ORR, PFS, OS, PK

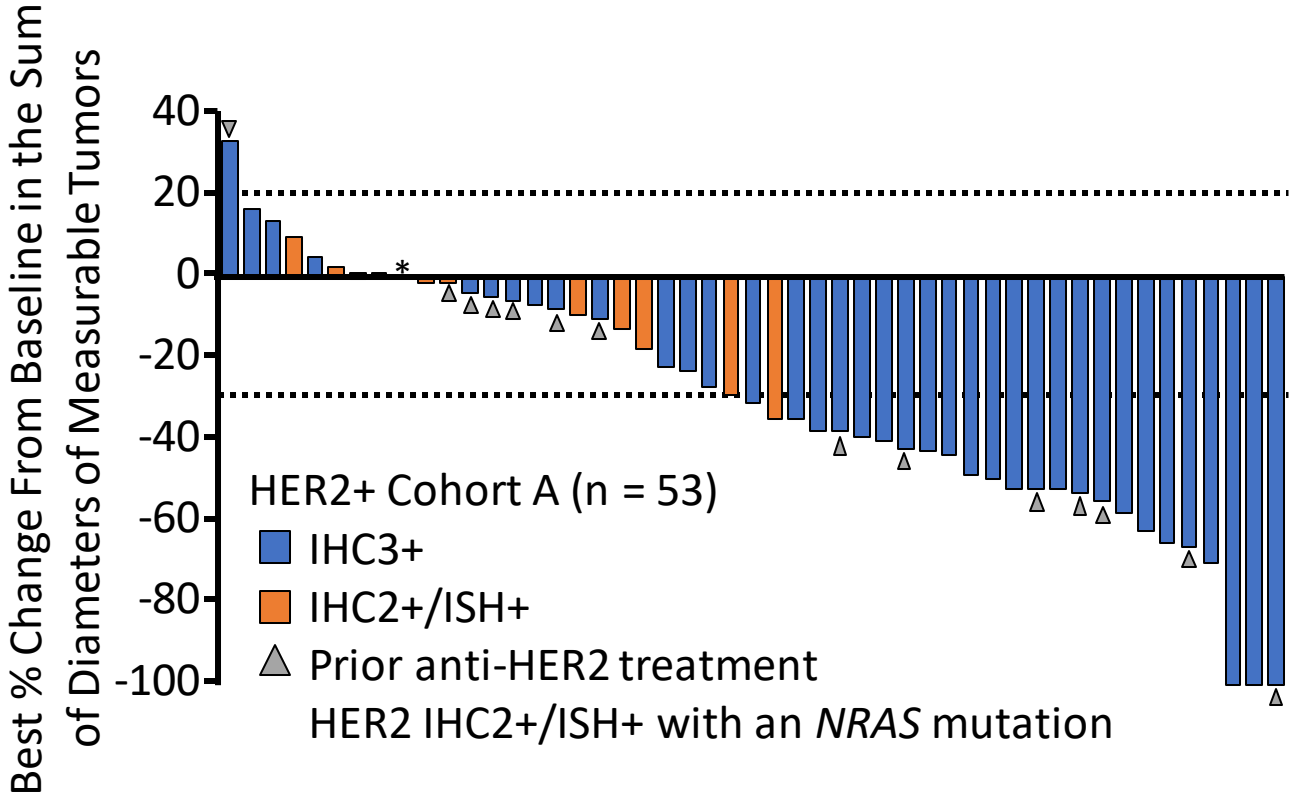
*Cohorts B and C opened when futility monitoring performed after ≥ 20 patients enrolled on Cohort A had 12 wks of follow-up.

Siena S, et al. ASCO Abstract 4000

DESTINY-CRC01: Baseline Characteristics

Characteristic	HER2+ Cohort A (n = 53)	All Patients (N = 78)
Median age, yrs (range)	57 (27-79)	58.5 (27-79)
▪ Europe ▪ Asia ▪ N. America	52.8 28.3 18.9	52.6 32.1 15.4
ECOG PS 0 / 1 / 2, %	69.8 / 30.2 / 0	62.8 / 35.9 / 1.3
Primary tumor site left / right, %	88.7 / 11.3	89.7 / 10.3
Median prior lines of treatment, n (range)	—	4 (2-11)
Previous treatment, % ▪ Irinotecan ▪ 5-FU / capecitabine ▪ Oxaliplatin ▪ Cetuximab or panitumumab ▪ Bevacizumab ▪ Anti-HER2 therapy	 100 100 / 54.7 100 100 75.5 30.2	 100 98.7 / 53.8 100 98.7 79.5 20.5

DESTINY-CRC01: Overall Response



Response, n (%)	HER2+ Cohort A (n = 53)
Confirmed ORR by ICR (1° endpoint)	24 (45.3)
▪ CR	1 (1.9)
▪ PR	23 (43.4)
▪ SD	20 (37.7)
▪ PD	5 (9.4)
▪ NE	4 (7.5)
DCR, %	83.0

- Tumor shrinkage generally detected by Mo 2 and sustained or deepened over time
- No confirmed responses in Cohorts B and C

Siena. ASCO 2020. Abstr 4000. Reproduced with permission.

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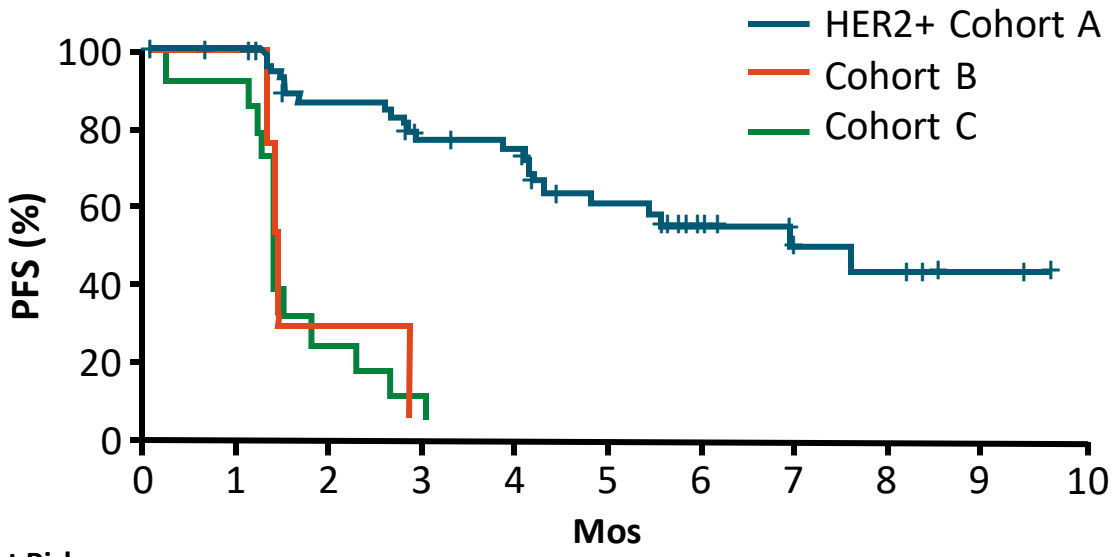
DESTINY-CRC01: PFS and OS by Cohort

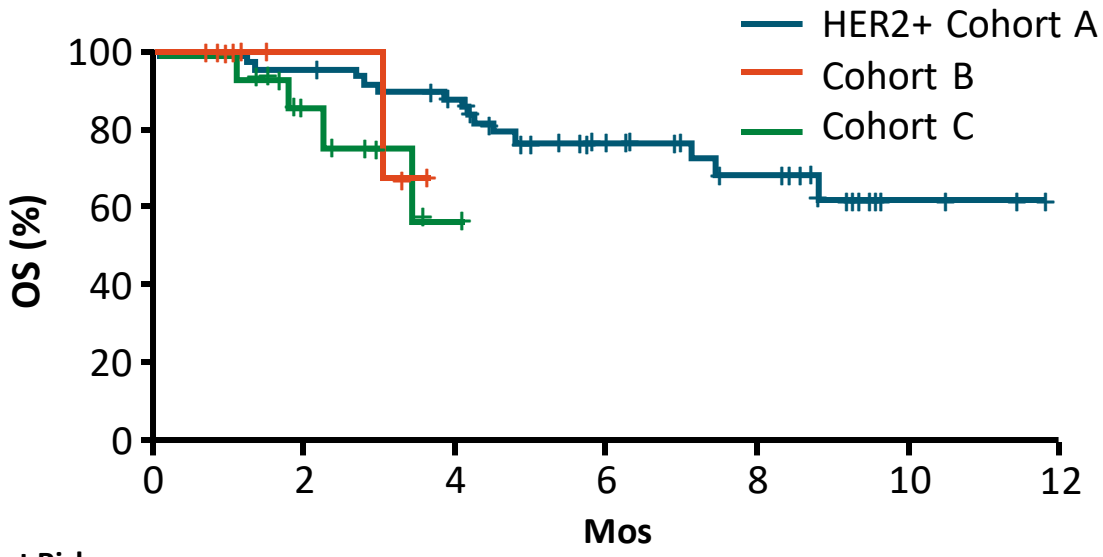
Progression-Free Survival
Median PFS in Cohort A: 6.9 mos



Patients at Risk, n

Cohort A	53	50	42	35	33	21	11	7	6	2	0
Cohort B	7	6	1	0	0	0	0	0	0	0	0
Cohort C	18	13	3	1	0	0	0	0	0	0	0

Overall Survival
Median OS in any Cohort: NR



Patients at Risk, n

Cohort A	53	49	42	23	14	4	0
Cohort B	7	3	0	0	0	0	0
Cohort C	18	9	1	0	0	0	0

- Less follow-up in Cohorts B and C due to opening for enrollment after Cohort A

Siena. ASCO 2020. Abstr 4000. Reproduced with permission.

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Fam-Trastuzumab Deruxtecan Summary

- Metastatic CRC patients who have HER2+ disease (Breast cancer definition) have a significant benefit with T-DXd. Those who have low HER2 expression do not appear to benefit.
  - 45% overall response rate that appears to be durable. Outcomes appeared durable across subgroups in the analysis
  - The median PFS in HER2+ patients (Cohort A), was 6.9 mos in the 3rd line setting, which is significant
- No new safety signals observed
  - Most common toxicities were gastrointestinal (any-grade nausea in ~ 60% of patients) and hematologic any-grade anemia and decreased neutrophil counts
  - The major concern is ILD, which was observed in 5 (6.4%) patients, including 2 (2.6%) deaths
- In this population the benefit appears to outweigh the risk, but treatment requires careful monitoring and rapid intervention needed to mitigate risk of ILD with T-DXd

KEYNOTE-177: Phase 3, open-label, randomized study of first-line pembrolizumab (Pembro) versus investigator-choice chemotherapy for mismatch repair-deficient (dMMR) or microsatellite instability-high (MSI-H) metastatic colorectal carcinoma (mCRC)

Diaz, LS et al. ASCO Abstract TPS877

KEYNOTE-177

Randomized, open-label phase III trial

Patients with treatment-naive MSI-H (PCR)/dMMR (IHC) stage IV CRC; ECOG PS 0/1; measurable disease (N = 307)

- Pembrolizumab 200 mg Q3W for up to 35 cycles (n = 153)
- Investigator-choice of chemotherapy* (n = 154)

*Chemotherapy options included mFOLFOX6 or FOLFIRI ± bevacizumab or cetuximab.
†Blinded independent central review per RECIST v1.1.

Dual primary endpoints: PFS,† OS

Trial positive if pembrolizumab superior to chemotherapy for either primary endpoint

Secondary endpoints: ORR,† safety

Data cutoff: February 29, 2020

Median follow-up: 28.4 mos in pembrolizumab arm, 27.2 mos in comparator arm

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KEYNOTE-177: Baseline Characteristics

Characteristic	Pembrolizumab (n = 153)	Chemotherapy (n = 154)
Median age, yrs (range)	63.0 (24-93)	62.5 (26-90)
Male, n (%)	71 (46)	82 (53)
ECOG PS 0, n (%)	75 (49)	84 (55)
Region, n (%) ▪ W. Europe/N. America ▪ Asia	 109 (71) 22 (14)	 113 (73) 26 (17)
Metachronous disease, n (%)	80 (52)	74 (48)
Hepatic metastases, n (%)	71 (46)	54 (35)
Right-sided / left-sided tumor, n (%)	102 (67) / 46 (30)	107 (70) / 42 (27)
Prior neoadjuvant/adjuvant therapy, n (%)	38 (25)	45 (29)
Mutation status, n (%) ▪ Wild-type BRAF, KRAS, and NRAS ▪ BRAF V600E mutant ▪ KRAS or NRAS mutant	 34 (22) 34 (22) 33 (22)	 35 (23) 43 (28) 41 (27)

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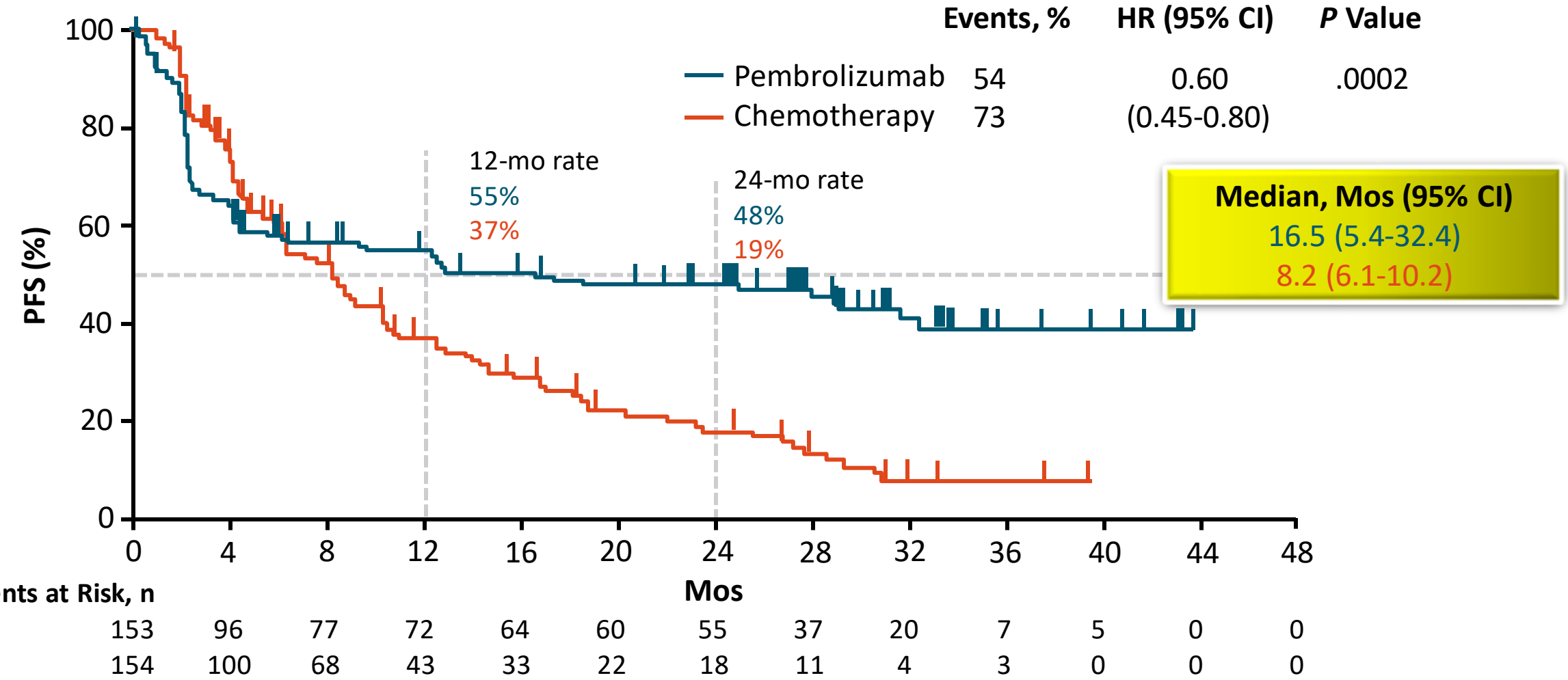
KEYNOTE-177: PFS (Primary Endpoint; ITT)



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KEYNOTE-177: Other Efficacy Endpoints

Efficacy Outcomes (ITT)	Pembrolizumab (n = 153)	Chemotherapy (n = 154)	P Value
ORR, %	43.8	33.1	.0275
DCR (CR + PR + SD), %	64.7	75.3	
Best overall response, % ▪ CR ▪ PR ▪ SD ▪ PD ▪ Not evaluable ▪ No assessment	 11.1 32.7 20.9 29.4 2.0 3.9	 3.9 29.2 42.2 12.3 1.3 11.0	
Median time to response, mos (range)	2.2 (1.8-18.8)	2.1 (1.7-24.9)	

- 36% of patients in chemotherapy arm crossed over to receive pembrolizumab; 23% received anti–PD-1/PD-L1 therapy outside of study
- OS analysis ongoing

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KEYNOTE 177 Summary

- Pembrolizumab produced significant and clinically meaningful improvements in outcomes vs standard therapy in treatment-naive patients with MSI-H mCRC
  - Median PFS: 16.5 vs 8.2 mos (HR: 0.60, 95% CI 0.45-0.80; *P* = .0002)
  - ORR: 43.8% vs 33.1% (*P* = .0275)
  - Median DoR: not reached vs 10.6 mos
- Pembrolizumab associated with favorable safety profile vs chemotherapy
  - Grade ≥ 3 treatment-related AEs: 22% vs 66%
- KEYNOTE-177 deemed a positive study based on PFS outcomes; OS outcomes still awaited
- Investigators concluded that single-agent pembrolizumab should be the new first-line standard of care for patients with MSI-H mCRC

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ASCO 2020 Summary

- New Standard of Care
  - Aduvant osimertinib for EGFR mutated NSCLC after complete resection +/- adjuvant chemotherapy
  - Maintenance avelumab in unresectable bladder cancer patients who respond to a platinum doublet
  - First line pembrolizumab monotherapy for mCRC patients with MSI-H/dMMR
- Should Have a Role in Therapy
  - Tucatinib plus trastuzumab and capecitabine for HER2+ metastatic breast cancer patients with brain metastasis after failing HER2 therapy
  - First line Nivolumab + Ipilimumab and 2 cycles of chemotherapy 1st line mNSCLC
  - First line Pembrolizumab + chemotherapy for metastatic triple negative breast CA
  - Third line and beyond trastuzumab deruxtecan for HER2 mutated NSCLC and HER2+ metastatic colorectal cancer (small but promising studies)