Applications for Community Oncology

ASCO Data Review

July 14, 2022

2022 ASCO Key Studies

Breast Cancer
Presented by Dr. Perez

- DESTINY-Breast04*
- TROPiCS-02
- MAINTAIN
- ABCSG-18
- PALOMA-2
- LUMINA

GI Cancer

- DYNAMIC
- PARADIGM*
- CAIRO5
- TRIPLETE
- PD-1 blockade in MMRd RC

Other Notable Studies

- DETERMINATION*
- ATLAS
- rEECur*
- ECHELON-1
- RELATIVITY-047
- SKYSCRAPER-02

* Plenary Session

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FDA APPROVAL

DESTINY-Breast03

<u>On May 4, 2022</u>, the FDA approved fam-trastuzumab deruxtecan-nxki (Enhertu®) for adult patients with unresectable or metastatic HER2+ breast cancer who have received a prior anti-HER2-based regimen either in the metastatic setting, or in the neoadjuvant or adjuvant setting and have developed disease recurrence during or within 6 months of completing therapy.

- Approval was based on positive results from the DESTINY-Breast03 Phase III trial
  - Enhertu® reduced the risk of disease progression or death by 72% vs. trastuzumab emtansine (T-DM1) (HR 0.28; 95% CI: 0.22-0.37; p<0.0001) in patients with HER2+ unresectable and/or metastatic breast cancer previously treated with trastuzumab and a taxane ---- safety data updated at ASCO 2022
- NCCN guidelines: Enhertu® is a preferred category 1 treatment in the 2nd line setting for HER2-positive BC
  - Fam-trastuzumab deruxtecan-nxki may be considered in the first-line setting as an option for select patients (i.e., those with rapid progression within 6 months of neoadjuvant or adjuvant therapy [12 months for pertuzumab-containing regimens]).

SUMMARY

DESTINY-Breast03

Updated safety data presented at ASCO 2022

- Most TEAEs were grade 1 or 2 with exposure-adjusted incidence rates of grade ≥3 TEAEs and serious TEAEs were lower with T-DXd than T-DM1
- Risk of nausea, vomiting, fatigue and alopecia was higher for T-DXd
- There were no additional grade 3 adjudicated ILD/pneumonitis events with T-DXd and no grade 4 or 5 events overall
  - Median time to 1st onset: 6 months
  - Continue to monitor for ILD/pneumonitis

Drug-Related TEAEs Reported in ≥20% of Patients in Either Treatment Arm

	T-DXd n = 257		T-DM1 n = 261	
n (%)	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Nausea	189 (73.5)	17 (6.6)	72 (27.6)	1 (0.4)
Fatigue	118 (45.9)	16 (6.2)	76 (29.1)	2 (0.8)
Vomiting	114 (44.4)	4 (1.6)	15 (5.7)	1 (0.4)
Neutropenia	111 (43.2)	51 (19.8)	30 (11.5)	8 (3.1)
Alopecia	97 (37.7)	1 (0.4)	7 (2.7)	0
Anemia	82 (31.9)	16 (6.2)	37 (14.2)	11 (4.2)
Leukopenia	79 (30.7)	17 (6.6)	21 (8.0)	2 (0.8)
Decreased appetite	68 (26.5)	3 (1.2)	34 (13.0)	0
Thrombocytopenia	65 (25.3)	19 (7.4)	137 (52.5)	65 (24.9)
Diarrhea	61 (23.7)	1 (0.4)	11 (4.2)	2 (0.8)
Constipation	60 (23.3)	0	25 (9.6)	0

Adjudicated Drug-Related ILD/Pneumonitis	T-DXd n = 257	T-DM1 n = 261
Any grade, n (%)	28 (10.9)	5 (1.9)
Grade 1	7 (2.7)	4 (1.5)
Grade 2	19 (7.4)	1 (0.4)
Grade 3	2 (0.8)	0
Grade 4	0	0
Grade 5	0	0
Time to first onset, median (range), days	181 (33-507)	289 (80-499)
Outcome of worst event, n (%)		
Fatal	0	1 (20.0)[a]
Not recovered/not resolved	8 (28.6)	0
Ongoing	0	0
Recovering/resolving	2 (7.1)	0
Recovered/resolved with sequelae	2 (7.1)	0
Recovered/resolved	16 (57.1)	4 (80.0)

[a]Patient had an event of pulmonary embolism that the investigator considered to be grade 5. This was initially reported as respiratory failure but subsequently updated to pulmonary embolism. The ILD adjudication committee adjudicated this event as drug –related grade 1 ILD/pneumonitis. The death was not evaluable for adjudication. The investigator recorded disease progression as the primary cause of death.

ASCO 2022. Abstr 1000.

CLINICAL QUESTION

DESTINY-Breast04

Does fam-trastuzumab deruxtecan (T-DXd) provide benefit to patients with previously treated HER2-low mBC?

CLINICAL QUESTION

DESTINY-Breast04

How is HER2-low defined?

Current Classification and Treatment based on HER2 testing

Traditional definition

HER2+
(IHC 3+ or ISH+)

Daichii Sankyo definition

HER2+
(IHC 3+ or 2+/ISH+)

HER2- (IHC 0, 1+, 2+/ISH-)

HER2-/HR+ → **Endocrine therapy**
ET combinations
CDK 4/6 inhibitors
PARP inhibitors

HER2-/HR- (TNBC) → **Chemotherapy**
PD-1 inhibitor
PARP inhibitors
Sacituzumab govitecan

New Classification after DESTINY-Breast 04?

Daichii Sankyo definition

HER2+
(IHC 3+ or 2+/ISH+)

HER2-low
(IHC 1+, 2+/ISH-)

HER2-
(IHC 0)
(TNBC)

Missing on this definition is IHC 0-1, but ISH+

KEY DATA

DESTINY-Breast04

Study Design: Multicenter, randomized, open-label phase III trial

Stratified by HER2-low status (IHC1+ vs IHC2+ and ISH-), # of prior lines of chemotherapy (1 vs 2), HR status (HR+ [with vs without previous CDK4/6 inhibitor] vs HR-)

- HER2-low (IHC 1+ or IHC 2+/ISH-) unresectable or metastatic BC
- 1-2 lines of chemotherapy in the metastatic setting or recurrence ≤6 mo after adjuvant CT
- ≥1 ET if HR+
- Treated, stable brain metastases eligible

(N = 557)

R 2:1

T-DXd 5.4 mg/kg q3w
(n = 373)

HR+ ≈ 480 HR- ≈ 60

Treatment of physician's choice (TPC)
(capecitabine, eribulin, gemcitabine, paclitaxel, or nab-paclitaxel)
(n = 184)

Primary endpoints: PFS by BICR (HR+)
Key secondary endpoints: PFS by BICR (all patients); OS (HR+ and all patients)

Data cutoff: January 11, 2022

KEY DATA

DESTINY-Breast04

Baseline Characteristics

Characteristic	HR+ Patients		All Patients	
	T-DXd (n = 331)	TPC (n = 163)	T-DXd (n = 373)	TPC (n = 184)
Median age, yr (range)	57 (32-80)	56 (28-80)	58 (32-80)	56 (28-80)
Female, n (%)	329 (99)	163 (100)	371 (99)	184 (100)
Region, n (%)				
• Europe + Israel	149 (45)	73 (45)	166 (45)	85 (46)
• Asia	128 (39)	60 (37)	147 (39)	66 (36)
• North America	54 (16)	30 (18)	60 (16)	33 (18)
HER2 status (IHC), n (%)				
• 1+	193 (58)	95 (58)	215 (58)	106 (58)
• 2+/ISH-	138 (42)	68 (42)	158 (42)	78 (42)
ECOG PS, n (%)				
• 0	187 (57)	95 (58)	200 (54)	105 (57)
• 1	144 (44)	68 (42)	173 (46)	79 (43)
HR, n (%)				
• Positive	328 (99)	162 (99)	333 (89)	166 (90)
• Negative	3 (1)	1 (1)	40 (11)	18 (10)
Brain metastases, n (%)	18 (5)	7 (4)	24 (6)	8 (4)
Liver metastases, n (%)	247 (75)	116 (71)	266 (71)	123 (67)
Lung metastases, n (%)	98 (30)	58 (36)	120 (32)	63 (34)

KEY DATA

DESTINY-Breast04

Prior Therapies

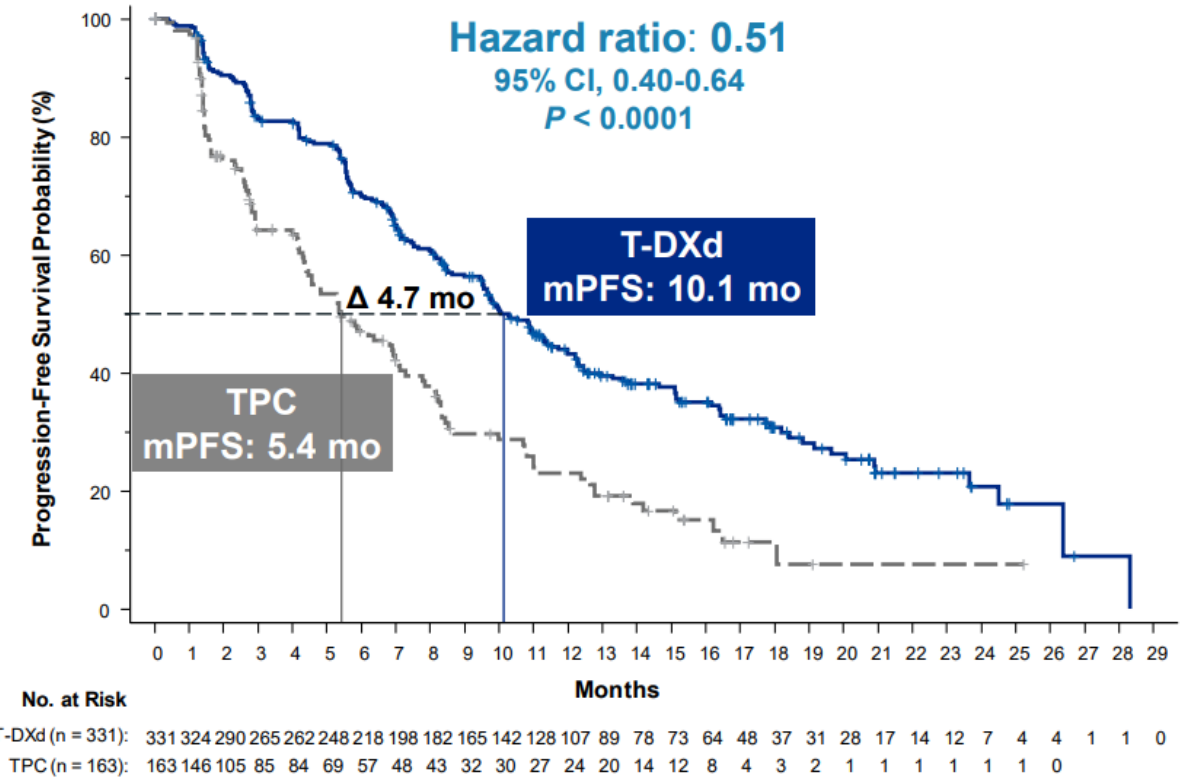
Prior Therapy	HR+ Patients		All Patients	
	T-DXd (n = 331)	TPC (n = 163)	T-DXd (n = 373)	TPC (n = 184)
Median lines of systemic therapy,* n (range)	3 (1-9)	3 (1-8)	3 (1-9)	3 (1-8)
# of prior lines of systemic therapy*, n (%)				
• 1	23 (7)	14 (9)	39 (10)	19 (10)
• 2	85 (26)	41 (25)	100 (27)	53 (29)
• ≥3	223 (67)	108 (66)	234 (63)	112 (61)
Median lines of chemotherapy,* n (range)	1 (0-3)	1 (0-2)	1 (0-3)	1 (0-2)
# of prior lines of chemotherapy*, n (%)				
• 0	1 (0.3)	1 (0.6)	1 (0-3)	1 (0.5)
• 1	203 (61.3)	93 (57.1)	221 (59.2)	100 (54.3)
• 2	124 (37.5)	69 (42.3)	145 (38.9)	83 (45.1)
• ≥3	3 (0.9)	0	6 (1.6)	0
Median lines of ET,* n (range)	2 (0-7)	2 (0-6)	2 (0-7)	2 (0-6)
# of prior lines of ET,* n (%)				
• 0	28 (8)	17 (10)	60 (16)	34 (18)
• 1	105 (32)	49 (30)	108 (29)	51 (28)
• 2	110 (33)	53 (33)	115 (31)	54 (29)
• ≥3	88 (37)	44 (27)	90 (24)	45 (24)
Prior targeted cancer therapy, n (%)	259 (78)	132 (81)	279 (75)	140 (76)
• CDK4/6 inhibitor	233 (70)	115 (71)	239 (64)	119 (65)

KEY DATA

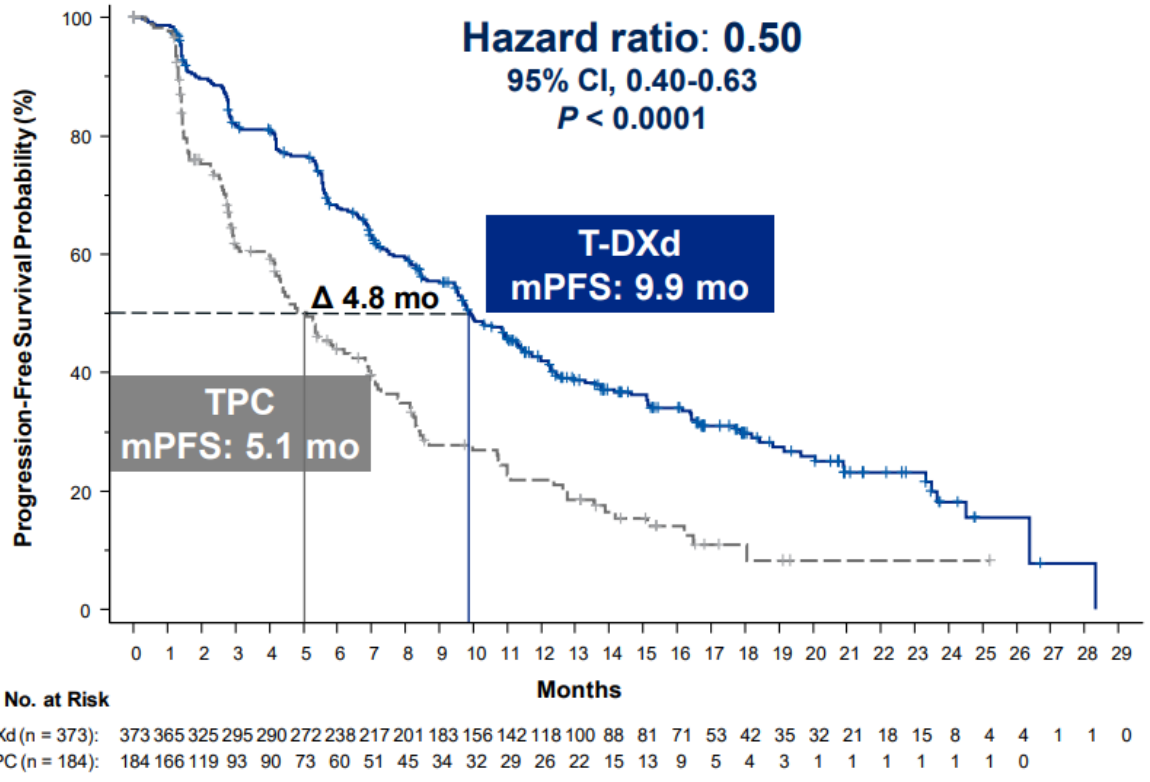
DESTINY-Breast04

Progression-Free Survival

HR+ Patients (1ary endpoint)



All Patients



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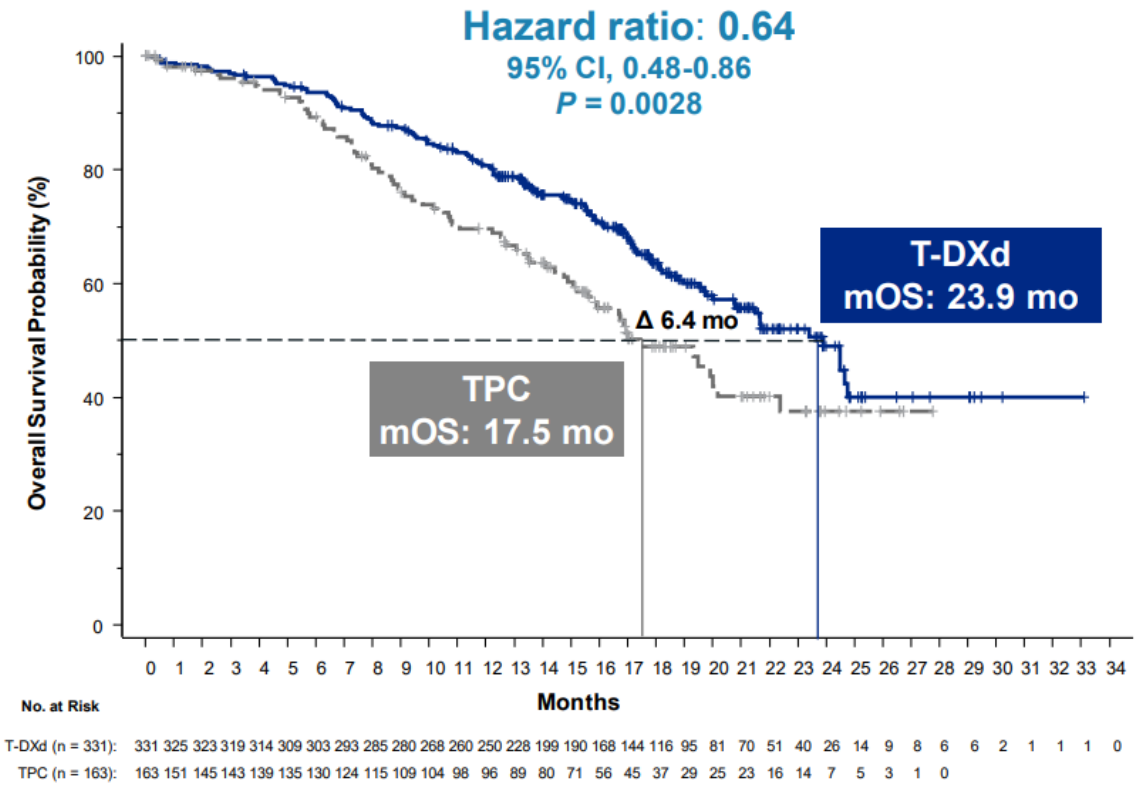
KEY DATA

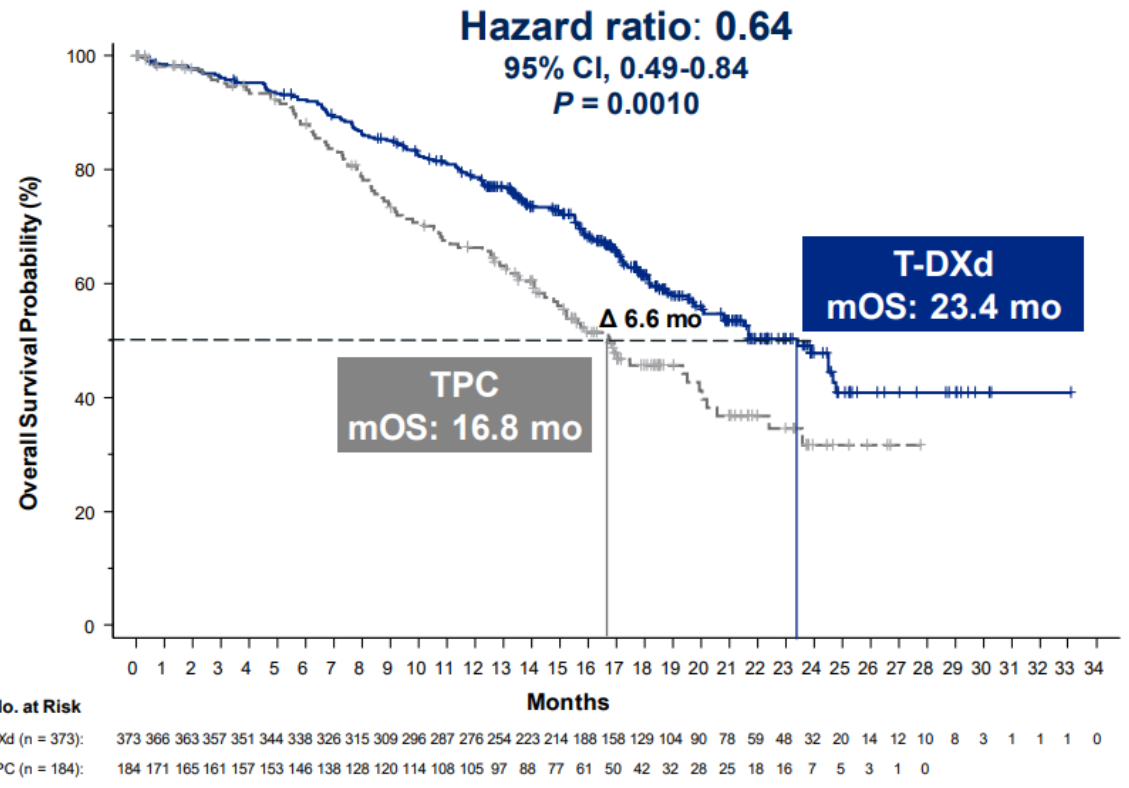
DESTINY-Breast04

Overall Survival

HR+ Patients



All Patients



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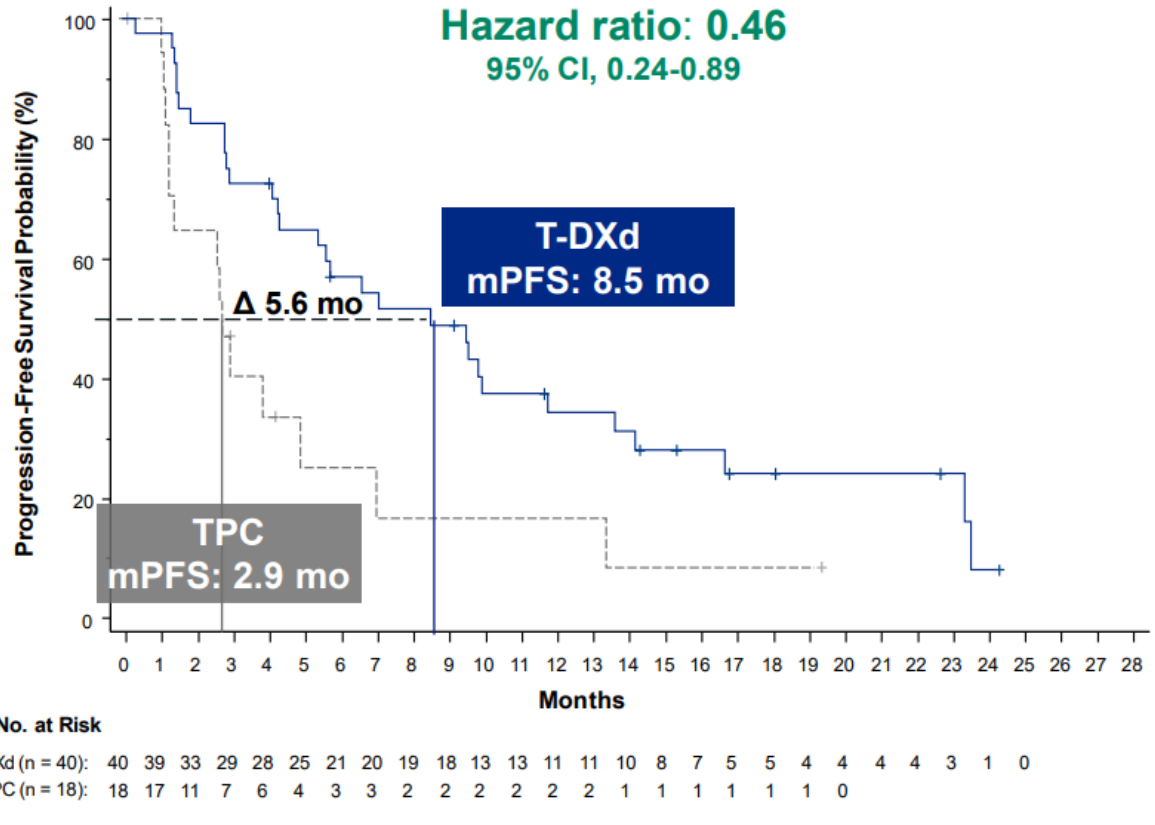
KEY DATA

DESTINY-Breast04

PFS and OS in 58 patients with HR- Breast Cancer – traditionally defined based on IHC 0-1 or 2/ISH neg, and ER/PR neg) TNBC ---- Exploratory Endpoints

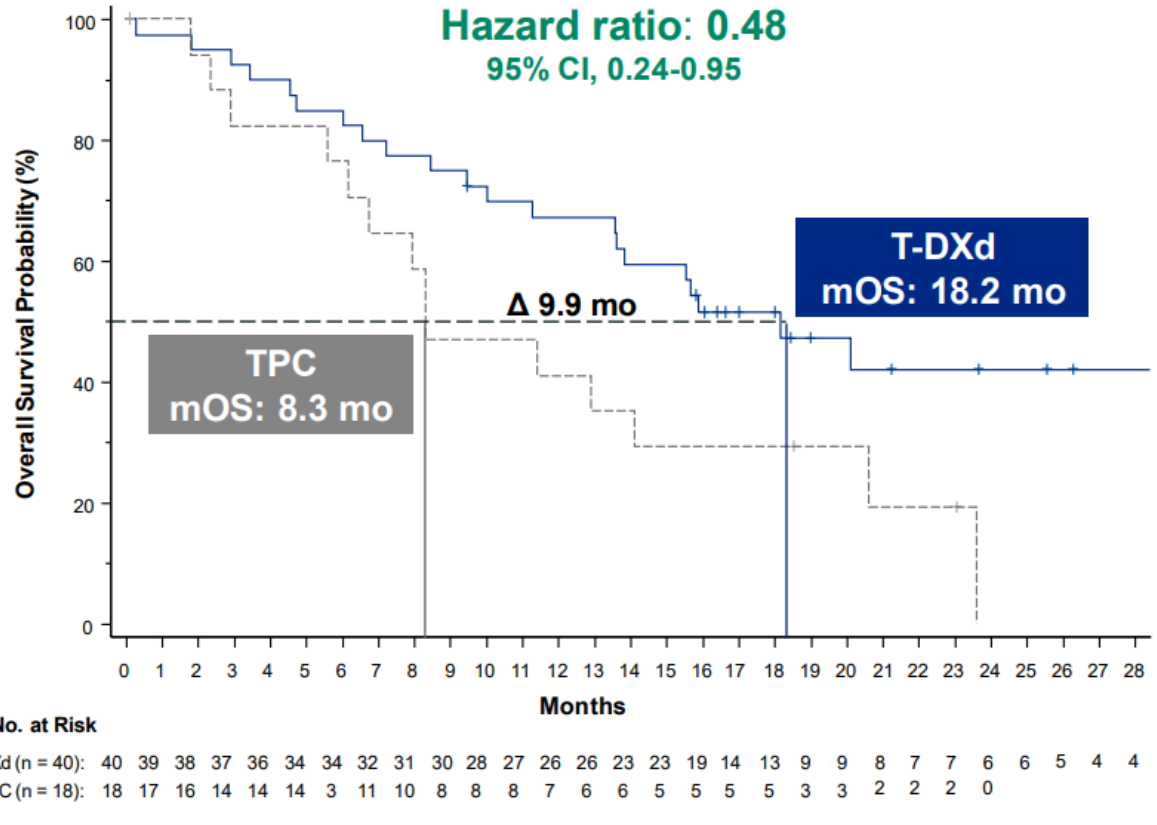
PFS HR- Patients



No. at Risk

T-DXd (n = 40):	40	39	33	29	28	25	21	20	19	18	13	13	11	11	10	8	7	5	5	4	4	4	4	3	1	0
TPC (n = 18):	18	17	11	7	6	4	3	3	2	2	2	2	2	2	1	1	1	1	1	1	0					

OS HR- Patients



No. at Risk

T-DXd (n = 40):	40	39	38	37	36	34	34	32	31	30	28	27	26	26	23	23	19	14	13	9	9	8	7	7	6	6	5	4	4
TPC (n = 18):	18	17	16	14	14	14	3	11	10	8	8	8	7	6	6	5	5	5	5	3	3	2	2	2	0				

These data challenge previous approaches for "TNBC". In other words, the "new TNBCs" will be a smaller % of pts

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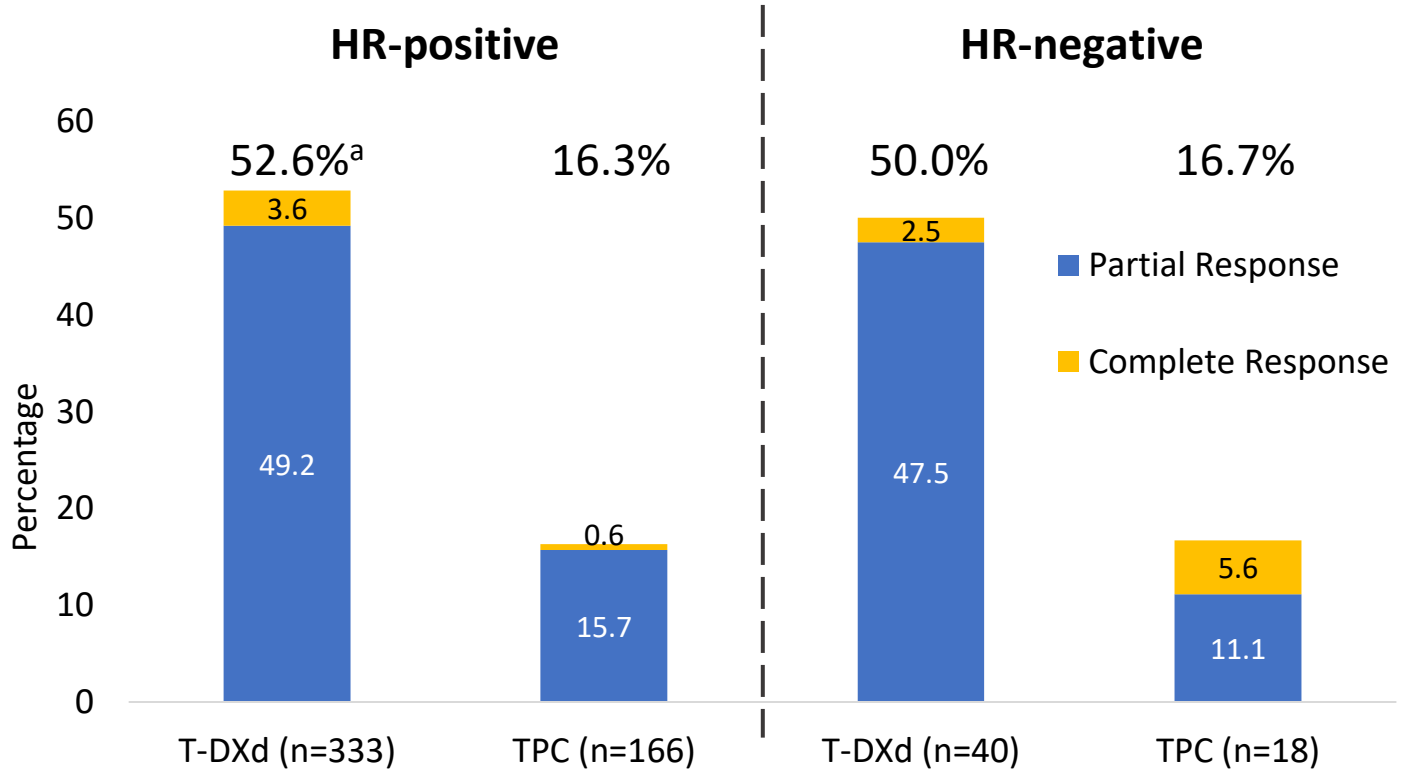
KEY DATA

DESTINY-Breast04

Confirmed ORR



	T-DXd (n=333)	TPC (n=166)	T-DXd (n=40)	TPC (n=18)
Progressive disease, %	7.8	21.1	12.5	33.3
Not evaluable, %	4.2	12.7	7.5	5.6
Clinical benefit rate,[b] %	71.2	34.3	62.5	27.8
Duration of response, months	10.7	6.8	8.6	4.9

Hormone receptor status is based on data from the electronic data capture corrected for misstratification.
ORR, objective response rate; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
[a]The response of 1 patient was not confirmed. [b]Clinical benefit rate is defined as the sum of complete response rate, partial response rate, and more than 6 months' stable disease rate, based on blinded independent central review.

DESTINY-Breast04

Overall Safety

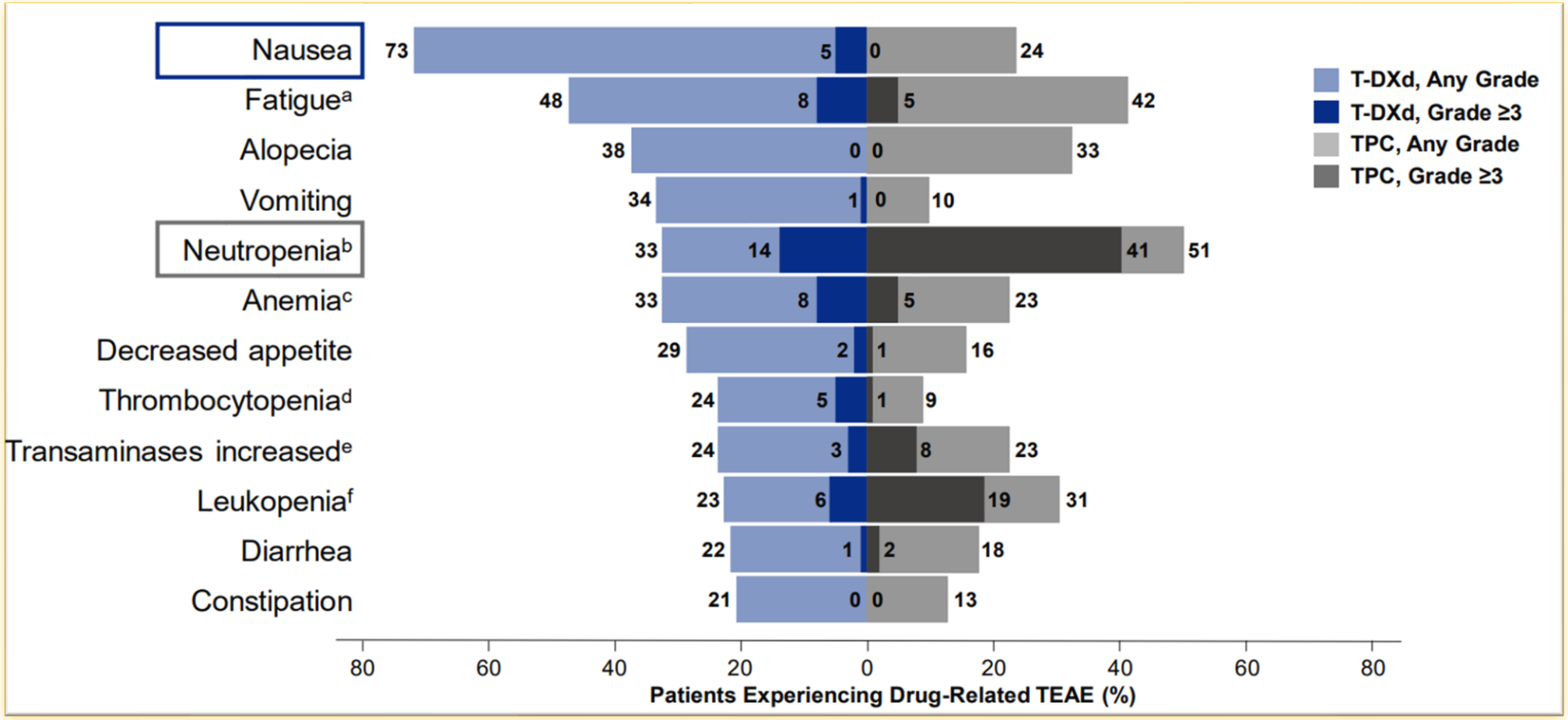
	Safety analysis set[a]	
n (%)	T-DXd (n = 371)	TPC (n = 172)
Total patient-years of exposure, years[b]	283.55	63.59
TEAEs	369 (99)	169 (98)
Grade ≥3	195 (53)	116 (67)
Serious TEAEs	103 (28)	43 (25)
TEAEs associated with dose discontinuations	60 (16)	14 (8)
TEAEs associated with dose interruptions	143 (39)	72 (42)
TEAEs associated with dose reductions	84 (23)	66 (38)
TEAEs associated with deaths	14 (4)	5 (3)

- **Median treatment duration**
  - **T-DXd: 8.2 months** (range: 0.2 – 33.3)
  - **TPC: 3.5 months** (range: 0.3 – 17.6)
- Most common TEAE associated with treatment discontinuation
  - T-DXd: 8.2%, ILD/pneumonitis[c]
  - TPC: 2.3%, peripheral sensory neuropathy
- Most common TEAE associated with dose reduction
  - T-DXd: 4.6%, nausea and fatigue[d]
  - TPC: 14.0%, neutropenia[d]
- Total on-treatment deaths[e]
  - T-DXd: 3.8%
  - TPC: 4.7%

ILD, interstitial lung disease; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event; TPC, treatment of physician's choice.
[a]Safety analyses were performed in patients who received ≥1 dose of a study regimen. [b]Patient-years of exposure are the treatment duration with year as unit. [c]Grouped term. [d]Fatigue includes the preferred terms fatigue, malaise, and asthenia; neutropenia included the preferred terms of neutropenia and neutrophil count decreased. [e]On-treatment death was defined as any death that occurred from the date of the first dose to 47 days after the last dose of study drug irrespective of the cause; the TEAEs associated with deaths represent a subset of on-treatment deaths reported by the investigators as adverse events.

DESTINY-Breast04

Drug-Related TEAEs in ≥20% of Patients



T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event; TPC, treatment of physician's choice.
[a]This category includes the preferred terms fatigue, asthenia, and malaise. [b]This category includes the preferred terms neutrophil count decreased and neutropenia. [c]This category includes the preferred terms hemoglobin decreased, red-cell count decreased, anemia, and hematocrit decreased. [d]This category includes the preferred terms platelet count decreased and thrombocytopenia. [e]This category includes the preferred terms transaminases increased, aspartate aminotransferase increased, alanine aminotransferase increased, gamma-glutamyltransferase increased, liver function test abnormal, hepatic function abnormal. [f]This category includes the preferred terms white-cell count decreased and leukopenia.

DESTINY-Breast04

Adverse Events of Special Interest

Adjudicated as drug-related ILD/pneumonitis[a]

n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
T-DXd (n = 371)	13 (3.5)	24 (6.5)	5 (1.3)	0	3 (0.8)	45 (12.1)
TPC (n = 172)	1 (0.6)	0	0	0	0	1 (0.6)

Left ventricular dysfunction[b]

n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
Ejection fraction decreased						
T-DXd (n = 371)	1 (0.3)	14 (3.8)	1 (0.3)	0	0	16 (4.3)
TPC (n = 172)	0	0	0	0	0	0
Cardiac failure[c]						
T-DXd (n = 371)	0	1 (0.3)	1 (0.3)	0	0	2 (0.5)
TPC (n = 172)	0	0	0	0	0	0

ILD, interstitial lung disease; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
[a]Median time to onset of ILD/pneumonitis for patients with T-DXd was 129.0 days (range, 26-710). [b]Left ventricular dysfunction was reported in a total of 17 (4.6%) patients in the T-DXd arm. One patient initially experienced ejection fraction decrease, then later developed cardiac failure. [c]Both patients with cardiac failure were reported to have recovered.

SUMMARY

DESTINY-Breast04

- T-DXd is the *first* HER2-targeted therapy to demonstrate benefit to pts with HER2-low advanced breast cancer
  - PFS: 9.9 months T-DXd vs 5.1 months TPC; HR 0.50, $P < 0.0001$
  - OS : 23.4 months T-DXd vs 16.8 months TPC; HR 0.64, $P = 0.001$
- T-DXd benefit observed across all patient subgroups
  - Including IHC 1+, IHC 2+/ISH-, HR+ or HR-, and prior treatments
- Continue to monitor for nausea, alopecia, and ILD

ASCO 2022. Abstr LBA03.

DESTINY-Breast04

Updated June 21, 2022

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2022
Invasive Breast Cancer

NCCN Guidelines Index
Table of Contents
Discussion

SYSTEMIC THERAPY REGIMENS FOR RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE[a,b,c]

HER2-Negative

Preferred Regimens		Other Recommended Regimens[i]	Useful in Certain Circumstances[i]
• Anthracyclines ▸ Doxorubicin ▸ Liposomal doxorubicin • Taxanes ▸ Paclitaxel • Anti-metabolites ▸ Capecitabine ▸ Gemcitabine • Microtubule inhibitors ▸ Vinorelbine ▸ Eribulin • Sacituzumab govitecan-hziy (for TNBC [category 1] or HR+/HER2-)[d]	• For HER2 IHC 1+ or 2+/ISH negative: ▸ Fam-trastuzumab deruxtecan-nxki[e,f] (category 1) • For germline *BRCA1/2* mutations[g] see additional targeted therapy options (BINV-R)[h] • Platinum (for TNBC and germline *BRCA1/2* mutation)[g] ▸ Carboplatin ▸ Cisplatin • For PD-L1–positive TNBC see additional targeted therapy options (BINV-R)[h]	• Cyclophosphamide • Docetaxel • Albumin-bound paclitaxel • Epirubicin • Ixabepilone	• AC (doxorubicin/cyclophosphamide) • EC (epirubicin/cyclophosphamide) • CMF (cyclophosphamide/ methotrexate/fluorouracil) • Docetaxel/capecitabine • GT (gemcitabine/paclitaxel) • Gemcitabine/carboplatin • Carboplatin + paclitaxel or albumin-bound paclitaxel

[e] For patients with tumors that are HER2 IHC 1+ or 2+ and ISH negative, who have received at least 1 prior line of chemotherapy for metastatic disease and, if tumor is HR+, are refractory to endocrine therapy.

[f] Fam-trastuzumab deruxtecan-nxki is contraindicated for patients with pneumonitis or interstitial lung disease (ILD).

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DESTINY-Breast04

Fam-trastuzumab deruxtecan (T-DXd) establishes a new classification and an anti-HER2 targetable population of patients with HER2-low BC demonstrating significant benefit with the potential to impact a large proportion of patients with mBC

Careful (re)examination of IHC status is warranted:

Inter-pathologist concordance, use of IHC or new quantitative methodologies for protein or mRNA analyses

2022 ASCO Key Studies

Breast Cancer

- DESTINY-Breast04*
- TROPiCS-02
- MAINTAIN
- ABCSG-18
- PALOMA-2
- LUMINA

GI Cancer

- DYNAMIC
- PARADIGM*
- CAIRO5
- TRIPLETE
- PD-1 blockade in MMRd RC

Other Notable Studies

- DETERMINATION*
- ATLAS
- rEECur*
- ECHELON-1
- CHECKMATE-816 or RELATIVITY-047
- SKYSCRAPER-02

* Plenary Session

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CLINICAL QUESTION

TROPiCS-02

Does sacituzumab govitecan provide benefit to previously treated patients with *HR+/HER2-* mBC?

On April 7, 2021, the Food and Drug Administration granted regular approval to sacituzumab govitecan (Trodelvy, Immunomedics Inc.) for patients with unresectable locally advanced or metastatic triple-negative breast cancer (mTNBC) who have received two or more prior systemic therapies, at least one of them for metastatic disease

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KEY DATA

TROPiCS-02

Study Design: Randomized, multicenter, open-label phase III study

Stratification by visceral metastases (yes vs no), ET in metastatic setting ≥6 mo (yes vs no), prior lines of chemotherapy (2 vs 3/4)

- Metastatic or locally recurrent, inoperable HR+/HER2- breast cancer with disease progression
- At least 1 ET, taxane, and CDK4/6 inhibitor in any setting
- 2-4 previous lines of CT for metastatic disease (neo/adjuvant therapy qualified as a prior line of CT if disease recurred within 12 mo)
- Measurable disease by RECIST v1.1

(N = 543)

R 1:1

Sacituzumab Govitecan
10 mg/kg IV Days 1 and 8, every 21 days
(n = 272)

Physician's Choice of Treatment*
(*Capecitabine, vinorelbine, gemcitabine, or eribulin)
(n = 271)

Until PD or unacceptable toxicity

Primary endpoint: PFS (BICR)
Secondary endpoints: OS, ORR, DoR, CBR (by LIR and BICR), PRO, safety

KEY DATA

TROPiCS-02

Prior Therapies

Setting of prior anticancer regimens, n (%)	Sacituzumab Govitecan (n = 272)	Physician's Choice (n = 271)
Neoadjuvant	67 (25)	62 (23)
Adjuvant	186 (68)	206 (76)
Advanced/Metastatic	272 (100)	271 (100)
Other/unknown	12 (4)	9 (3)

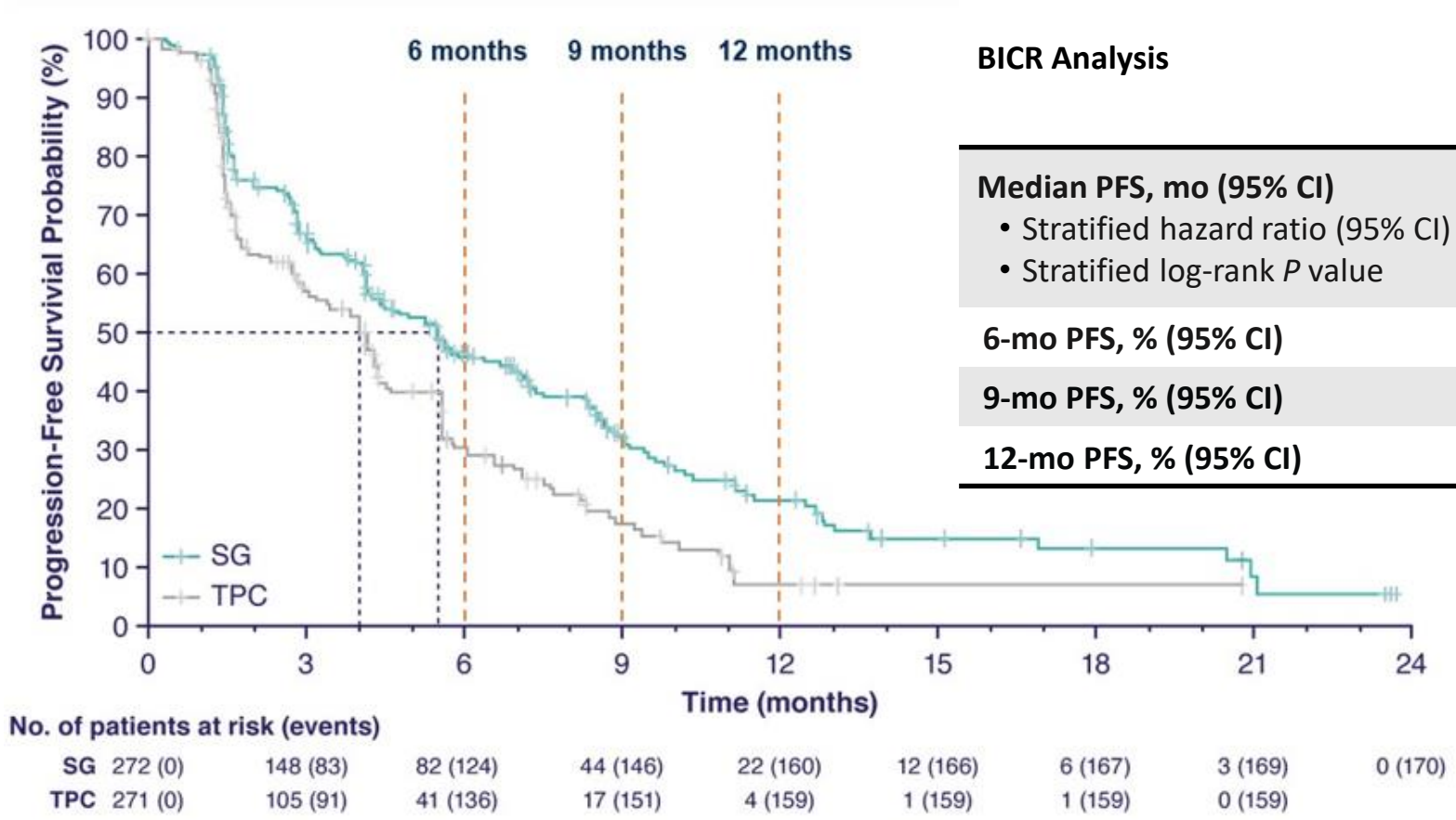
Most common prior anticancer therapy in the metastatic setting[1], n (%)	Sacituzumab Govitecan (n = 272)	Physician's Choice (n = 271)
Endocrine therapy[2]	268 (99)	269 (99)
CDK4/6 inhibitor[2]	267 (98)	270 (>99)
Targeted agent[3]	181 (67)	172 (63)
Immunotherapy	21 (8)	15 (6)
Chemotherapy	271 (>99)	271 (100)
• Capecitabine	221 (81)	232 (86)
• Paclitaxel	174 (64)	147 (54)
• Eribulin	95 (35)	88 (33)

[1]Includes any treatment used either as a single agent or in combination.
[2]The remaining patient were treated with these agents in early-stage disease.
[3]Targeted agents include PARP, mTOR, PI#K, BET, AKT, AAK and other kinase inhibitors.

KEY DATA

TROPiCS-02; Sacituzumab govitecan vs chemo for HR+, HER2 “neg”

PFS in the ITT Population



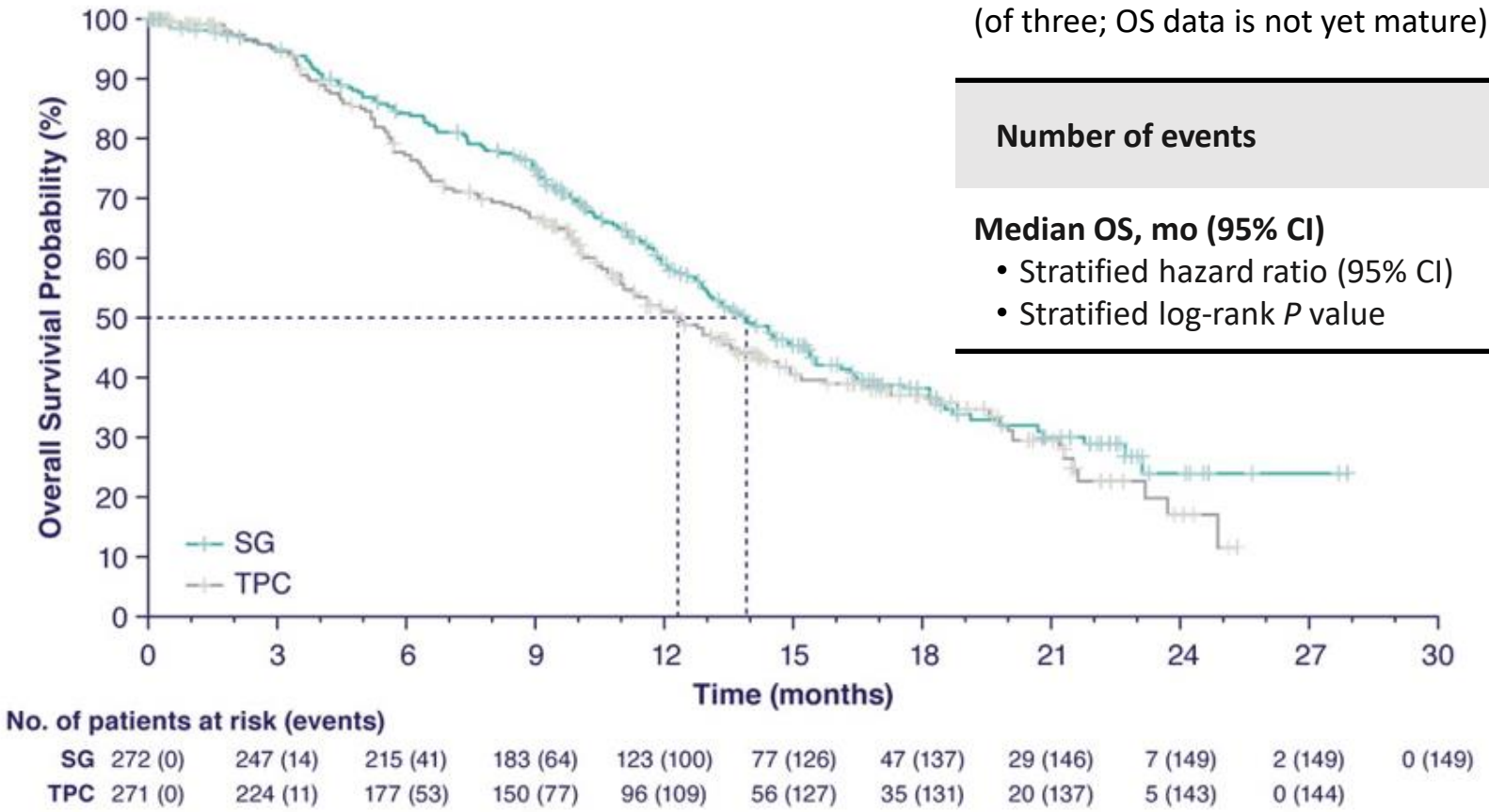
BICR Analysis	Sacituzumab Govitecan (n = 272)	Physician’s Choice (n = 271)
Median PFS, mo (95% CI)	**5.5 (4.2-7.0)**	**4.0 (3.1-4.4)**
• Stratified hazard ratio (95% CI)	**0.66 (0.53-0.83)**	
• Stratified log-rank *P* value	**0.0003**	
6-mo PFS, % (95% CI)	46.1 (39.4-52.6)	30.3 (23.6-37.3)
9-mo PFS, % (95% CI)	32.5 (25.9-39.2)	17.3 (11.5-24.2)
12-mo PFS, % (95% CI)	21.3 (15.2-28.1)	7.1 (2.8-13.9)

1.5 month difference in PFS…

ASCO 2022. Abstr LBA1001.

TROPiCS-02

OS in the ITT Population



First planned interim analysis (of three; OS data is not yet mature)	**Sacituzumab Govitecan (n = 272)**	**Physician's Choice (n = 271)**
Number of events	**149**	**144**
Median OS, mo (95% CI)	**13.9 (12.7 – 15.4)**	**12.3 (10.8 – 14.2)**
• Stratified hazard ratio (95% CI)	**0.84 (0.67-1.06)**	
• Stratified log-rank *P* value	**≈0.14**	

ASCO 2022. Abstr LBA1001.

TROPiCS-02

Response Rates

BICR Analysis	Sacituzumab Govitecan (n = 272)		Physician's Choice (n = 271)
ORR, n (%)	**57 (21)**		**38 (14)**
• OR (nominal *P* value)		**1.63 (*P* = 0.03)**	
Best overall response, n (%)			
• CR	2 (1)		0
• PR	55 (20)		38 (14)
• SD	142 (52)		106 (39)
• SD ≥6 mo	35 (13)		21 (8)
• PD	58 (21)		76 (28)
• NE	15 (6)		51 (19)
CBR*, n (%)	**92 (34)**		**59 (22)**
• OR (nominal *P* value)		**1.84 (*P* = 0.002)**	
Median DoR, mo (95% CI)	7.4 (6.5-8.6)		5.6 (3.8-7.9)

**CBR: clinical benefit rate*

TROPiCS-02

Safety: Treatment-related AEs – All Grade and Grade ≥3

TRAEs, n (%)	Sacituzumab Govitecan (n = 268)		Physician's Choice (n = 249)	
	All Grade	Grade ≥3	All Grade	Grade ≥3
Hematologic				
• Neutropenia	188 (70)	136 (51)	134 (54)	94 (38)
• Anemia	91 (34)	17 (6)	62 (25)	8 (3)
• Leukopenia	37 (14)	23 (9)	23 (9)	13 (5)
• Lymphopenia	31 (12)	10 (4)	25 (10)	8 (3)
• Febrile neutropenia	14 (5)	14 (5)	11 (4)	11 (4)
Gastrointestinal				
• Diarrhea	152 (57)	25 (9)	41 (16)	3 (1)
• Nausea	148 (55)	3 (1)	77 (31)	7 (3)
• Vomiting	50 (19)	1 (<1)	30 (12)	4 (2)
• Constipation	49 (18)	0	36 (14)	0
• Abdominal pain	34 (13)	2 (1)	17 (7)	0
Other				
• Alopecia	123 (46)	0	41 (16)	0
• Fatigue	100 (37)	15 (6)	73 (29)	6 (2)
• Asthenia	53 (20)	5 (2)	37 (15)	2 (1)
• Decreased appetite	41 (15)	1 (<1)	34 (14)	1 (<1)
• Neuropathy	23 (9)	3 (1)	38 (15)	6 (2)

Note: No ILD events in the SG arm vs 1% in the TPC arm; no TRAEs of cardiac failure or LV dysfunction in either arm

SUMMARY

TROPiCS-02

- Sacituzumab govitecan provided a statistically significant PFS benefit over TPC in pts with HR+/HER2- mBC previously treated with ET, CDK4/6 inhibitors, and ≥2 CT regimens for mets
  - Median PFS by BICR: 5.5 vs 4.0 mo (hazard ratio: 0.66; 95% CI: 0.53-0.83; *P*=0.0003)
    - Clinical significance?
  - OS data not yet mature
- GI and hematologic toxicities noted

ASCO 2022. Abstr LBA1001.

TROPiCS

Sacituzumab govitecan demonstrated statistically significant but modest clinical benefit to previously treated patients with HR+ disease

COMPARISON

DESTINY-Breast04 vs TROPiCS-02: Cross-study comparisons

HR+/ HER2-	DESTINY-Breast04		TROPiCS-02	
NCCN guideline or FDA approval in HR+ HER2- mBC	*NCCN Guideline: Category 1* *Preferred option for IHC 1-2+/ISH neg*		*Unresectable locally advanced or metastatic triple-negative breast cancer (mTNBC) who have received two or more prior systemic therapies, at least one of them for metastatic disease* *Preferred treatment option*	
Study Design	**T-DXd vs TPC**		**Sacituzumab Govitecan vs TPC**	
Inclusion Criteria	• HER2-low (IHC 1+ or IHC 2+/ISH-) unresectable or metastatic BC • ≥1 ET if HR+ • **1-2 lines of chemotherapy** in the metastatic setting or recurrence ≤6 mo after adjuvant CT • Treated, stable brain metastases eligible		• Metastatic or locally recurrent, inoperable HR+/HER2- breast cancer with disease progression • At least 1 ET, taxane, and CDK4/6 inhibitor in any setting • **2-4 previous lines of CT** for metastatic disease (neo/adjuvant therapy qualified as a prior line of CT if disease recurred within 12 mo)	
N of HR+ pts	331	163	272	271
Median PFS, months	**10.1**	5.4	**5.5**	4.0
	HR **0.51** (0.40-0.64) *P* < 0.0001		HR **0.66** (0.53-0.83) *P* = 0.0003	
Median OS, months	**23.9**	17.5	**13.9**	12.3
	HR **0.64** (0.48-0.86) *P* = 0.0028		HR **0.84** (0.67-1.06) *P* ≈0.14	(*OS immature*)
ORR, %	**52.6**	16.3	**21**	14
Median DoR, months	**10.7**	6.8	**7.4**	5.6

2022 ASCO Key Studies

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- TROPiCS-02
- MAINTAIN
- ABCSG-18
- PALOMA-2
- LUMINA

GI Cancer

- DYNAMIC
- PARADIGM*
- CAIRO5
- TRIPLETE
- PD-1 blockade in MMRd RC

Other Notable Studies

- DETERMINATION*
- ATLAS
- rEECur*
- ECHELON-1
- CHECKMATE-816 or RELATIVITY-047
- SKYSCRAPER-02

* Plenary Session

cornerstone specialty network™

CLINICAL QUESTION

MAINTAIN: switching CDK4/6 after tumor progression

Does switching to ET ± ribociclib after progression on ET ± CDK4/6 inhibitor benefit pts with *HR+/HER2-* mBC?

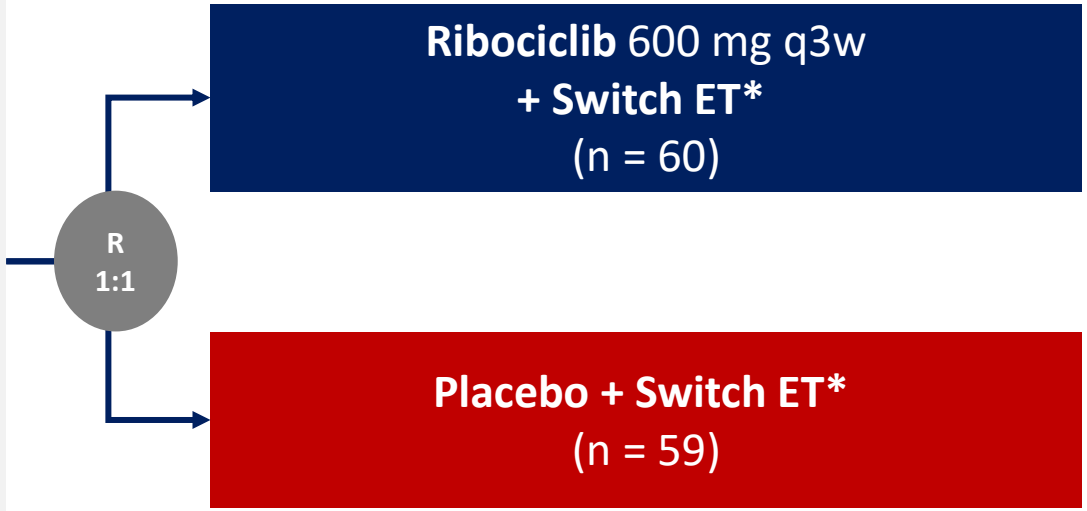
KEY DATA

MAINTAIN: switching CDK4/6 after tumor progression

Study Design: Randomized, multicenter, placebo-controlled phase II study

- ER and/or PR ≥1%
- HER2- MBC and progression on ET and CDK4/6 inhibitor
- ≤1 CT line for mBC
- ECOG PS 0 or 1
- Postmenopausal (or premenopausal with GnRH agonist)
- Stable brain metastases allowed

(N = 120)



Until PD or death

*Patients with progression on AI for MBC and no prior fulvestrant received fulvestrant.
After protocol amendment, patients who progressed on prior fulvestrant received exemestane.

Primary endpoint: PFS (locally assessed per RECIST v1.1)
Secondary endpoints: ORR, CBR, safety, tumor and blood markers (ctDNA)

Data Cutoff: January 4, 2022, median follow up 18.2 months

KEY DATA

MAINTAIN: switching CDK4/6 after tumor progression

Baseline Characteristics

Characteristics	Ribociclib + ET (n = 60)	Placebo + ET (n = 59)
Female, n (%)	60 (100)	58 (99)
Median age, yr (IQR)	55 (48-67)	59 (52-65)
Race/ethnicity, n (%)		
• White	46 (77)	42 (71)
• Black	5 (8)	8 (14)
• Asian	5 (8)	2 (3)
• Other	4 (7)	7 (12)
ECOG PS, n (%)		
• 0	40 (67)	38 (64)
• 1	20 (33)	21 (36)
De novo metastasis at diagnosis, n (%) * **	21 (35)	32 (54)
Visceral metastases, n (%)	36 (60)	35 (59)
Bone disease only, n (%)	13 (22)	9 (15)

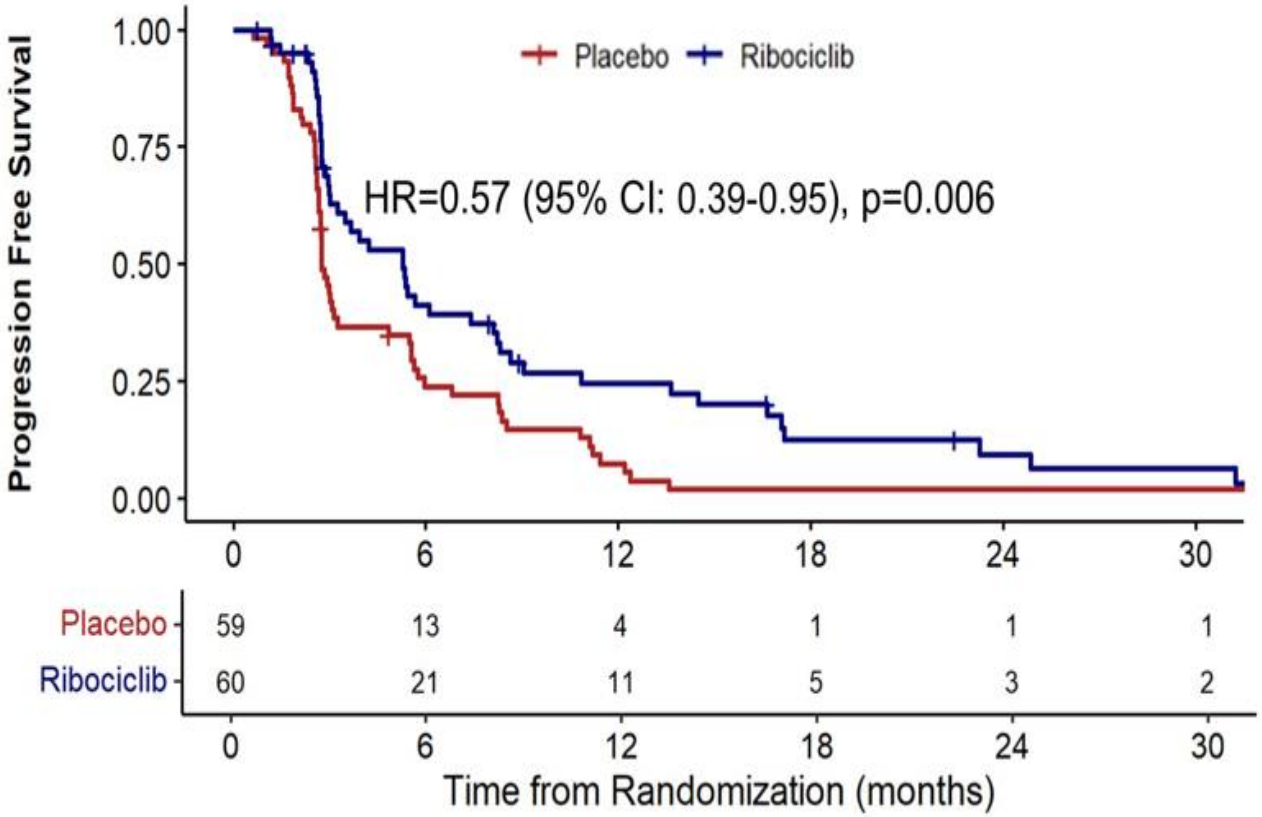
Prior Treatment	Ribociclib + ET (n = 60)	Placebo + ET (n = 59)
≥2 prior ET for mBC, n (%)	11 (18)	11 (19)
Chemotherapy for mBC, n (%)	4 (7)	7 (12)
Prior CDK4/6 inhibitor, n (%)		
• **Palbociclib***	**52 (87)**	**51 (88)**
• Ribociclib**	6 (10)	8 (14)
• Abemaciclib	2 (3)	0 (0)
Median duration of prior CDK4/6 inhibitor, mo (IQR)	15.5 (12-21)	17 (11-23.5)
Prior CDK4/6 inhibitor duration, n (%)**		
• ≤12 mo	18 (30)	21 (36)
• >12 mo	42 (70)	38 (64)
Prior CDK4/6 inhibitor in metastatic setting, n (%)	60 (100)	59 (100)
Subsequent therapy after progression on CDK4/6 inhibitor, n (%)	1 (2)	6 (10)

*Includes 1 pt who did not tolerate prior abemaciclib and 2 pts with insurance issues with ribociclib
** Includes 1 pt who did not tolerate prior palbociclib
*** p=0.035
**** 10 pts (17%) in placebo arm and 7 pts (12%) in ribociclib arm on prior CDK4/6 inhibitor ≤ 6 months

KEY DATA

MAINTAIN: switching CDK4/6 after tumor progression

PFS



	Placebo + ET (n=59)	Ribociclib + ET (n=60)
Median: 95% CI (months)	**2.76** (2.66-3.25)	**5.29** (3.02-8.12)

	Placebo + ET (n=59)	Ribociclib + ET (n=60)
PFS rate at 6 months (95% CI)	**23.9%** (12.8%-35%)	**41.2%** (27.8%-54.6%)
PFS rate at 12 months (95% CI)	**7.4%** (0.4%-14.3%)	**24.6%** (12.5%-36.7%)

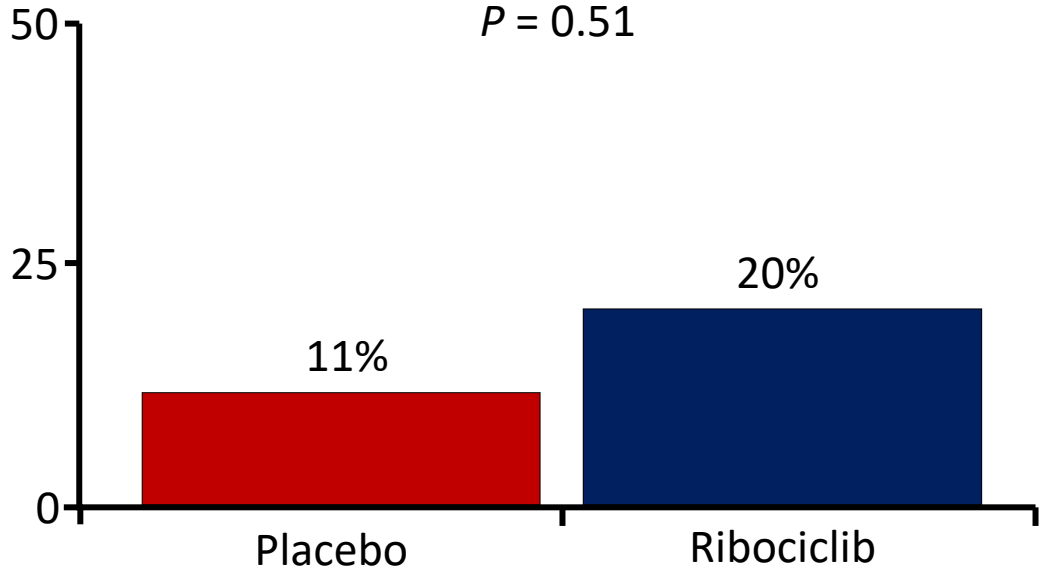
ASCO 2022. Abstr LBA1004.

KEY DATA

MAINTAIN: switching CDK4/6 after tumor progression

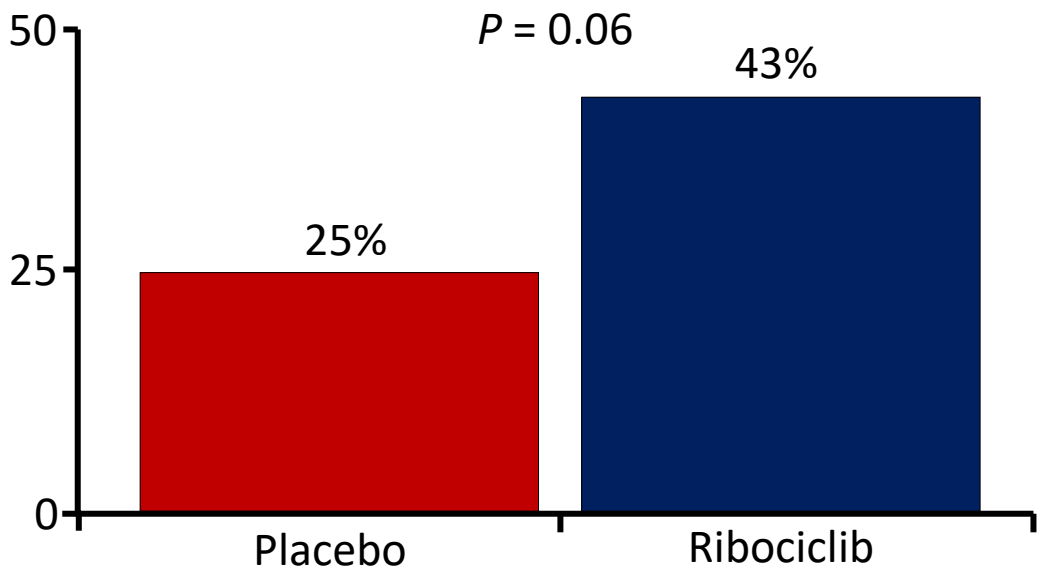
Response

Overall Response Rate (n = 70)



Characteristic	Placebo + ET (n = 35)	Ribociclib + ET (n = 35)
CR, n (%)	0 (0)	2 (6)
PR, n (%)	4 (11)	5 (14)
Median DoR, mo (IQR)	14.8 (6.7-21.3)	18.8 (11.4-50.2)

Clinical Benefit Rate (n = 105)



Characteristic	Placebo + ET (n = 57)	Ribociclib + ET (n = 49)
CR, PR, or SD ≥24 wk, n (%)	14 (25)	21 (43)

SUMMARY

MAINTAIN: switching CDK4/6 after tumor progression

- Small, but interesting study
- Switching to ribociclib + ET after progression provided a statistically significant PFS benefit over placebo + ET in patients with HR+/HER2- metastatic breast cancer previously treated with an ET + CDK4/6 inhibitor
  - 43% risk reduction of progression or death
  - Improved PFS (at 6 months and 12 months) and clinical benefit rate
  - Benefit observed in fulvestrant subgroup and for patients with *ESR1* WT
- No new safety concerns

ASCO 2022. Abstr LBA1004.

MAINTAIN: switching CDK4/6 after tumor progression

Switching of ET + CDK4/6 inhibitor treatments for previously treated patients with HR+, HER2- breast cancer continues to provide benefit

Optimal sequencing of treatments for HR+, HER2- patients to be determined

2022 ASCO Key Studies

Breast Cancer

- DESTINY-Breast04*
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- MAINTAIN
- ABCSG-18
- PALOMA-2
- LUMINA

GI Cancer

- DYNAMIC
- PARADIGM*
- CAIRO5
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- PD-1 blockade in MMRd RC

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- ATLAS
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- SKYSCRAPER-02

* Plenary Session

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CLINICAL QUESTION

ABCSG-18

Does adjuvant denosumab reduce fracture, and improve PFS and OS in postmenopausal patients with HR+ early stage breast cancer?

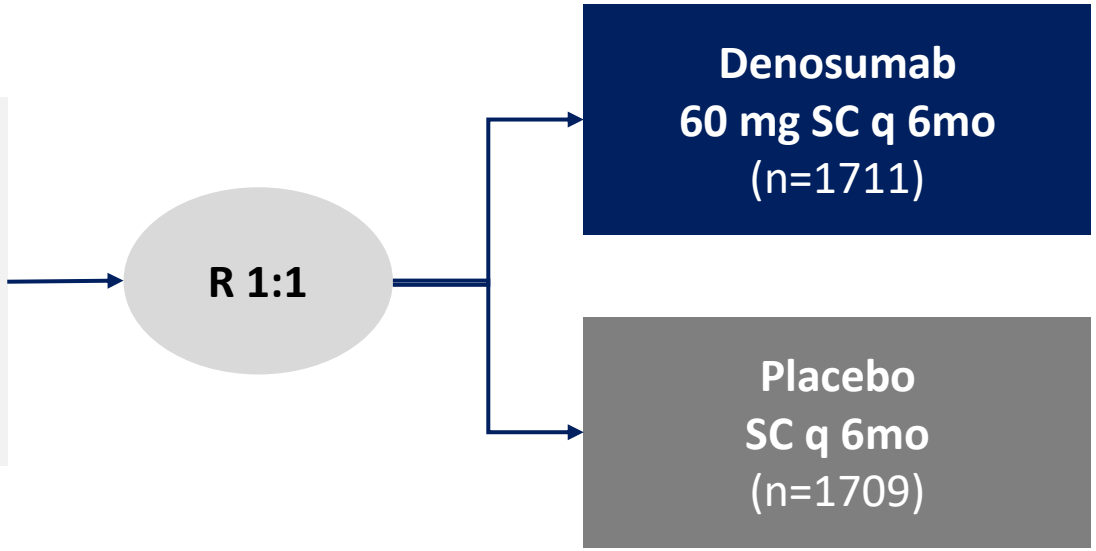
KEY DATA

ABCSG-18

Study Design: Prospective, randomized, placebo-controlled, double-blind multicenter phase III trial

- Postmenopausal women with early breast cancer
- ER+ and or PR+
- Adjuvant non-steroidal aromatase inhibitor therapy

N=3420



Exclusion criteria:
- Prior or concurrent treatment with SERMs
- Current or prior IV bisphosphonate administration
- Recent use of oral bisphosphonates
- Known history of: Pagel's disease, Cushing's disease, hyperprolactinamia, hypercalcemia or hypocalcemia, other active metabolic bone disease

Primary endpoint: time to first clinical fracture
Secondary endpoints: % change in BMD; Vertebral fractures; DFS, BMFS*, OS

*Bone metastasis-free survival (BMFS)

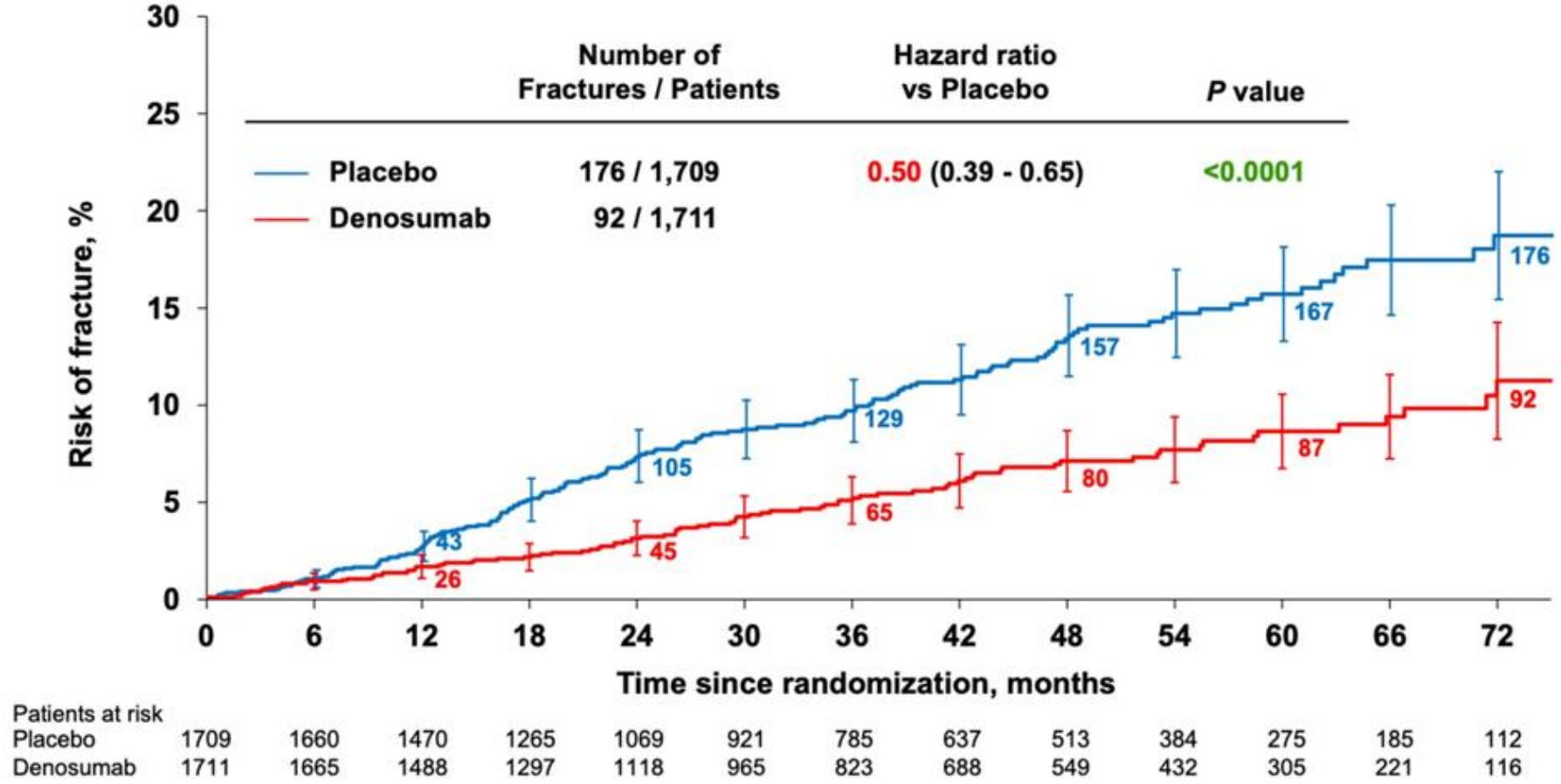
Trial Status 2022:
- 554 (16.2%) of patients chose to be unblinded
  - 252 of the placebo group received Denosumab (median duration 3 years)
- Median follow-up 8 years (Q1,3: 6.0 - 9.6 years)
- DFF events: 677 (19.8%)
- Deaths: 285 (8.3%)

ASCO 2022. Abstr 507. Gnant M. et al., Lancet 2015; 386: 433-443

KEY DATA

ABCSG-18

Primary endpoint: Time to first clinical fracture

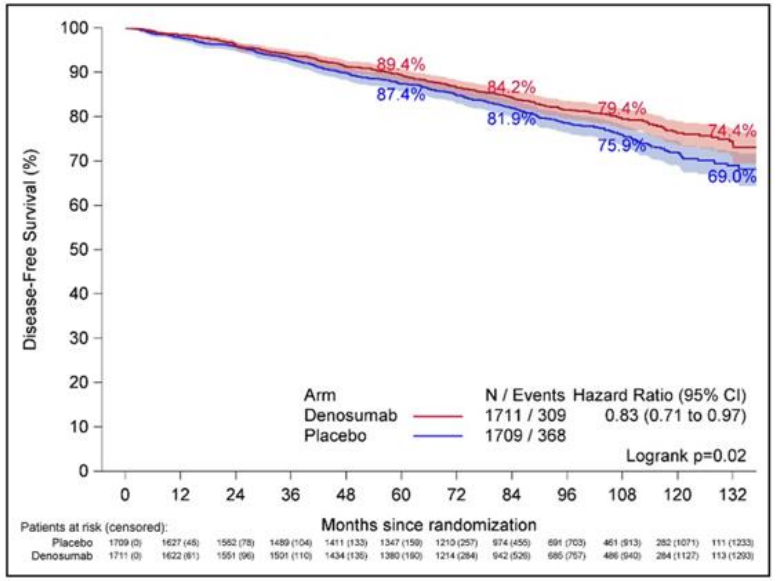


ASCO 2022. Abstr 507. Gnant M. et al., Lancet 2015; 386: 433-443

KEY DATA

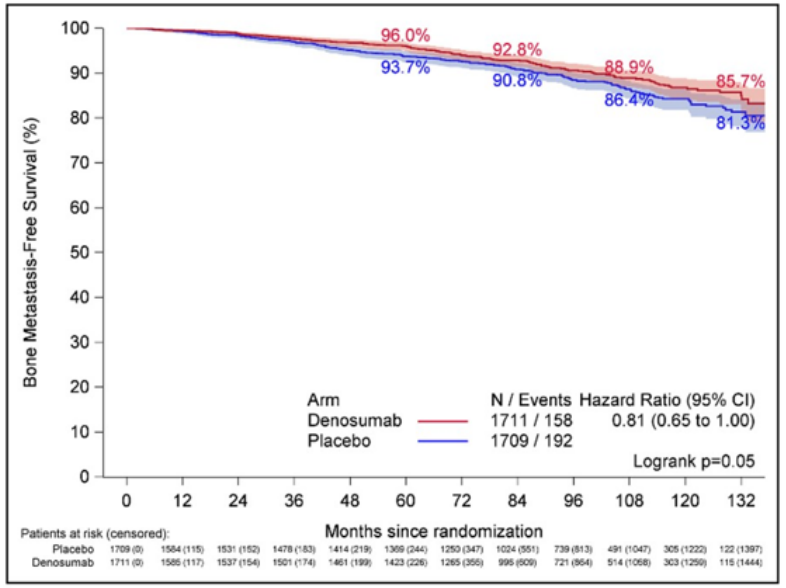
ABCSG-18

Disease-free Survival



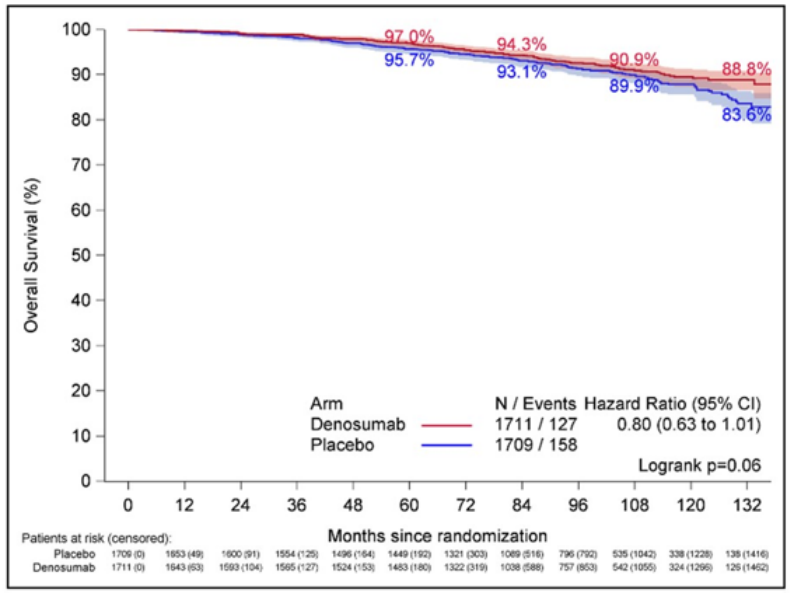
DFS improved in the Dmab group vs the placebo group (309 versus 368 DFS events, (HR 0.83, 95% CI 0.71-0.97, p = 0.016), absolute 9-year DFS difference of 3.5% (79.4% vs 75.9%, respectively)

Bone metastasis-free Survival



BMFS improved by 19% (158 versus 192 BMFS events, HR 0.81, 95% CI 0.65-1.00, p = 0.047) in the Dmab group

Overall Survival



OS improved by 20% in the uncensored analysis (127 versus 158 OS events, HR 0.80, 95% CI 0.64-1.01, p = 0.065), and 26% after censoring (HR 0.74, 95% CI 0.58-0.94, p = 0.013)

ASCO 2022. Abstr 507.

SUMMARY

ABCSG-18

- Addition of adjuvant denosumab reduces AI treatment-related clinical fractures
  - DFS, BMFS, and OS improved with the addition of denosumab to AI treatment
- At the final analysis, the median follow-up was 8 years. All patients had been off study treatment for a median of 5 years but the reduction in fracture risk persisted in the denosumab arm
- No new toxicities: 3 treatment-emergent (but not treatment related) deaths in the denosumab group
  - No osteonecrosis of the jaw was reported

ASCO 2022. Abstr 507.

ABCSG-18

The addition of adjuvant denosumab every 6 months during AI treatment provides durable QoL and clinical benefit for postmenopausal patients with HR+ breast cancer and should be considered standard of care

2022 ASCO Key Studies

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* Plenary Session

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PALOMA-2

Does first-line palbociclib with letrozole provide benefit for patients with *HR+/HER2-* mBC?

Final OS analysis

KEY DATA

PALOMA-2

Study Design: Multicenter, international, double-blind, randomized phase III trial

Stratified by disease site (visceral vs nonvisceral),
disease-free interval (de novo metastatic; ≤ 12 mo vs > 12 mo),
prior neoadjuvant or adjuvant hormonal therapy (yes vs no)

- Postmenopausal women with ER+/HER2- advanced breast cancer
- No prior treatment for advanced disease
- ECOG PS 0-2

(N = 666)

R 2:1

Palbociclib 125 mg QD (3 wk on, 1 wk off)
+ Letrozole 2.5 mg QD
(n = 444)

Placebo QD (3 wk on, 1 wk off)
+ Letrozole 2.5 mg QD
(n = 222)

Primary endpoint: PFS (by investigator)
Secondary endpoints: OS, ORR, CBR, safety, biomarkers, patient reported outcomes

PFS: Study powered to detect ~44% increase in median PFS from 9 mo (placebo) to 13 mo (palbociclib), assuming HR 0.69 favoring Palbociclib (90% power to detect 1-sided α = 0.025)
OS: Assuming median OS 34-46 mo (placebo ~ 35% improvement), 390 events needed to detect HR ≤0.74 (80% power to detect 1-sided α = 0.025)

ASCO 2022. Abstr LBA1003.

KEY DATA

PALOMA-2

Overall Survival - ITT

Outcome	Palbociclib + Letrozole (n = 444)	Placebo + Letrozole (n = 222)	HR (95% CI)
Planned ITT Analysis* Median OS in ITT population, mo (95% CI)	53.9 (49.8-60.8)	51.2 (43.7-58.9)	0.956 (0.777-1.777); P = .3378
Post Hoc Sensitivity Analysis Median OS (excluding patients with missing survival data†), mo (95% CI)	51.6 (46.9-57.1)	44.6 (37.0-52.3)	0.869 (0.706-1.069)
Median duration of treatment, mo	22.0	13.8	--
Discontinued study treatment, n (%)	399 (90)	217 (98)	--
Median time to chemotherapy, mo (95% CI)	38.1 (34.1-42.2)	29.8 (24.7-34.8)	0.730 (0.607-0.879)

*Median follow-up: 90 mo.
†Survival data missing in 13% of patients in palbociclib arm vs 21% in placebo arm.

PALOMA-1 and PALOMA-2 Combined OS Analysis	Palbociclib + Letrozole (n = 528)	Placebo + Letrozole (n = 303)	HR (95% CI)
ITT Analysis: Median OS, mo (95% CI)	51.8 (47.8-56.9)	46.8 (38.8-52.3)	0.934 (0.780-1.120)
Subgroup With DFI >12 Mo: Median OS, mo (95% CI)	64.0 (49.2-73.4)	44.6 (37.0-53.2)	0.736 (0.551-0.982)

SUMMARY

PALOMA-2

- Overall OS was not significantly increased among patients randomized to receive palbociclib (final OS analysis)
  - Interpretation of OS data in this trial potentially limited by a high number of patients with missing survival data
- In postmenopausal patients with ER+/HER2- advanced breast cancer, the addition of palbociclib to frontline letrozole significantly extended PFS
  - PALOMA-1: median 10-mo PFS increase with palbociclib + letrozole vs letrozole alone (HR: 0.49; *P* = 0.0004)
  - PALOMA-2: median PFS of 24.8 mo with palbociclib + letrozole vs 14.5 mo with placebo + letrozole (HR: 0.58; *P* <0.001)
- No new safety concerns

ASCO 2022. Abstr LBA1003.

PALOMA-2

The addition of palbociclib to letrozole did not provide statistically significant OS benefit to patients with HR+/HER2- mBC

Head-to-head study of CDK4/6 inhibitors needed to determine best practice

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- SKYSCRAPER-02

* Plenary Session

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CLINICAL QUESTION

LUMINA

Can adjuvant breast radiotherapy be omitted in very low risk patients after breast conserving surgery in T1N0 luminal A breast cancer?

Prospective trial

KEY DATA

LUMINA

Study Design: Retrospective analysis

- Age ≥55 yrs
- Invasive ductal T1N0 luminal A breast cancer post BCS and SLNB
- ER ≥1%, PgR >20%, HER2 negative
- ET* alone for ≥5 yr
- Margins ≥1 mm
- Grade 1/2, without multifocal/ multicentric tumor >25% DCIS, or lymphatic vascular invasion

N=500

*Aromatase inhibitor (anastrozole, letrozole, or exemestane) or tamoxifen for ≥5 yr.

Central Ki67 testing

3 labs (Hamilton, Toronto, Vancouver) International Ki67 Working Group methods

Central Ki67 ≤13.25%

Enrolled on trial

No RT

Follow-up:
- Every 6 months for first 2 years then yearly
- Yearly mammogram

Central Ki67 >13.25%
Rx off study

- Patients accrued from August 2013 to July 2017
- 26 centers across Canada participated
- Median follow-up of 5 years

Primary Outcome: Local recurrence (LR): any invasive or non-invasive event
Secondary Outcomes: Contralateral breast cancer, any recurrence, disease-free survival, overall survival

Statistical considerations: Sample size based on precision of estimate of 5-year LR; Assuming LR of 3.5% and an upper bound of 2-sided 90% (one sided 95%) CI to be <5%, required 500 patients; Probability of LR estimated using cumulative incidence function with death as a competing risk; Intention to treat analysis planned at a median follow-up of 5 year

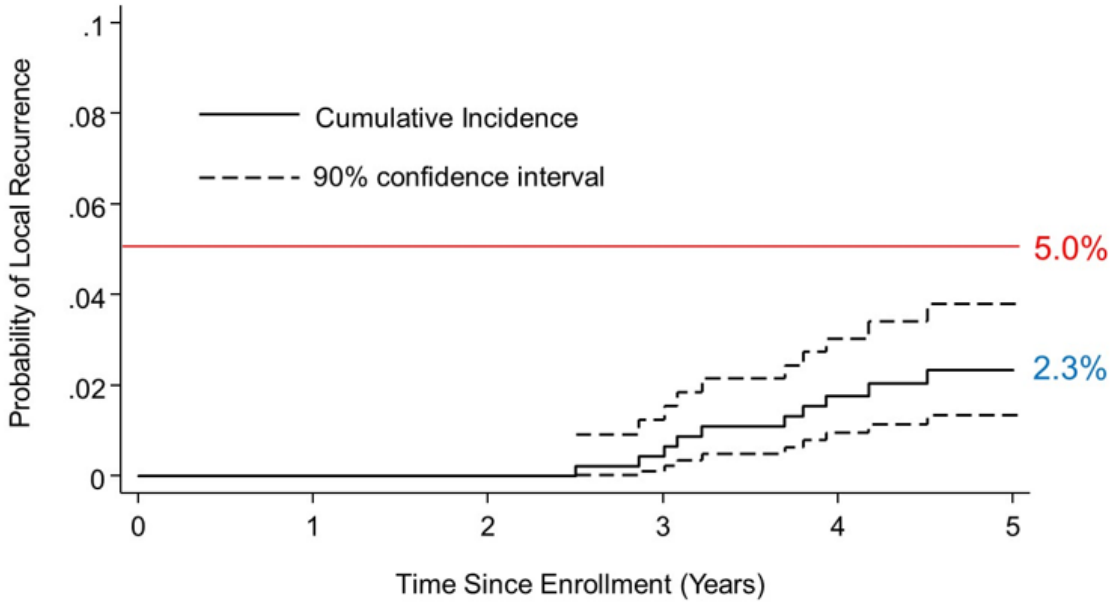
LUMINA

Baseline Characteristics

Characteristic	All Patients (N = 500)
Mean age, yr	**67**
• 55 to <65, n (%)	200 (40)
• 65 to <75, n (%)	242 (48)
• ≥75, n (%)	58 (12)
Mean tumor size, cm	**1.1**
• <0.5, n (%)	40 (8)
• 0.51-1.0, n (%)	216 (43)
• 1.1-2.0, n (%)	244 (49)
Tumor grade, n (%)	
• 1	330 (66)
• 2	170 (34)
Endocrine therapy, n (%)	
• Tamoxifen	200 (41)
• Aromatase inhibitor	292 (59)

LUMINA

Local Recurrence Events



Outcome	Total Events at 5 Yr	5-Yr Rate (90% CI)
Local recurrence	**10¥**	**2.3 (1.3-3.8)**
Contralateral breast cancer	8	1.9 (1.1-3.2)
Any recurrence	12	2.7 (1.6-4.1)
DFS	47*	89.9 (87.5-92.2)
OS	13†	97.2 (95.9-98.4)

¥ All were invasive
*23 second primary non-breast cancer
†1 death from breast cancer

SUMMARY

LUMINA

- Women age ≥55 yr with T1N0, Grade 1/2 luminal A breast cancer following BCS and treated with endocrine therapy alone had a low 5-yr local recurrence rate of 2.3%

ASCO 2022. Abstr LBA501.

LUMINA

Carefully selected low risk patients may be able to avoid adjuvant radiation reducing toxicity as well as minimizing cost and inconvenience for the patient

2022 ASCO Key Studies

Breast Cancer

- DESTINY-Breast04*
- TROPiCS-02
- MAINTAIN
- ABCSG-18
- PALOMA-2
- LUMINA

GI Cancer
Presented by Dr. Kalmadi

- DYNAMIC
- PARADIGM*
- TRIPLETE
- CAIRO5
- PD-1 blockade in MMRd RC

Other Notable Studies

- DETERMINATION*
- ATLAS
- rEECur*
- ECHELON-1
- RELATIVITY-047
- SKYSCRAPER-02

* Plenary Session

cornerstone specialty network™

CLINICAL QUESTION

DYNAMIC

Does a ctDNA-guided approach for patients with stage II colon cancer reduce the use of adjuvant chemotherapy without compromising recurrence risk?

DYNAMIC

Study Design: Randomized, multicenter, phase II trial

- R0 resection
- ECOG 0-2
- Staging CT within 8 weeks
- Provision of adequate tumor tissue within 4 weeks post-op
- No synchronous colorectal cnacer

N = 455

(23 institutions, Aug 2015 – Aug 2019)

Stratified by T stage (T3 or T4); type of participating center (metropolitan vs regional)

R 2:1

Plasma collections at week 4 and week 7 post-op

ctDNA-guided management

IF ctDNA-positive at week 4 or 7 → adjuvant chemo*
IF ctDNA-negative → observation
N=294¥

*oxaliplatin-based or single agent FP

Standard management

Adjuvant treatment decisions based on conventional clinic-pathologic criteria
N=147 ¥ ¥

Surveillance:
CEA: 3-monthly for 24 months, then 6-monthly for 36 months
CT C/A/P: 6-monthly for 24 months, then at 36 months

¥ctDNA-guided management ITT population N=294: 8 excluded from ITT and additional 5 did not receive ctDNA-guided management
¥ ¥standard management ITT population N=147: 6 excluded from ITT

Primary endpoints: RFS rate at 2 years
Key secondary endpoints: proportion receiving adjuvant chemo; RFS by ctDNA status for ctDNA-guided arm; TTR; OS

DYNAMIC

Baseline Characteristics

Characteristics	ctDNA-guided management N=247, n (%)	Standard management N=147, n (%)
Age median (range), years	65 (30 – 94)	62 (28 – 84)
Sex, male	154 (52)	81 (55)
ECOG, 0	226 (77)	124 (84)
Center type, metropolitan	240 (82)	121 (82)
Primary tumor site, left-sided	126 (43)	78 (53)
Tumor stage, T3	250 (85)	127 (86)
Tumor differentiation, poor	43 (15)	17 (12)
Lymph node yield, < 12	13 (4)	7 (5)
Lymphovascular invasion, present	82 (28)	38 (26)
MMR, deficient	59 (20)	27 (18)
Clinical risk group, high*	116 (40)	60 (41)

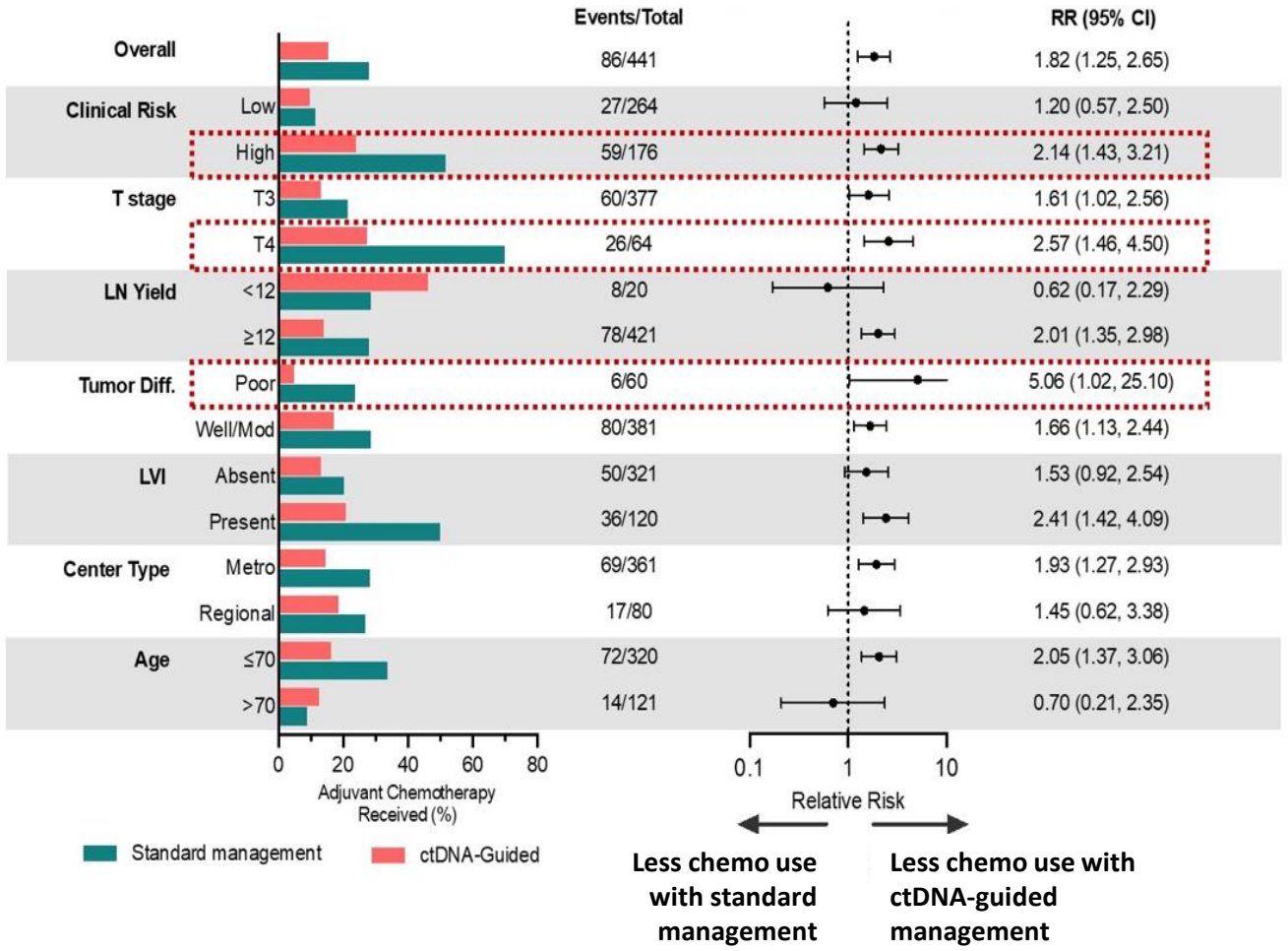
* High clinical risk: proficient MMR + ≥1 high-risk feature (T4, poor tumor differentiation, < 12 lymph node yield, LVI, tumor perforation and or bowel obstruction

DYNAMIC

Adjuvant Treatment

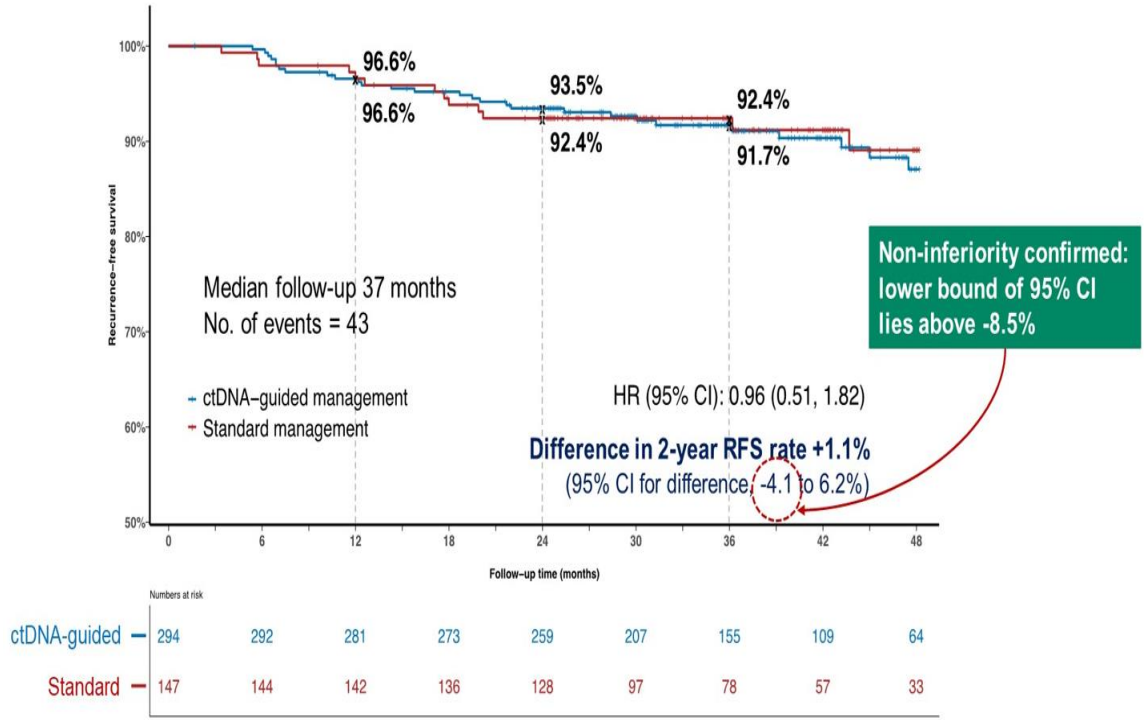
Treatment	ctDNA-Guided Management N=247, n (%)	Standard Management N=147, n (%)	
Adjuvant chemotherapy received, n	**45 (15%)**	**41 (28%)**	***P* = 0.0017**
Chemotherapy regimen received, n			
• Oxaliplatin-based doublet	**28/45 (62%)**	**4/41 (10%)**	***P* < 0.0001**
• Single agent fluoropyrimidine	17/45 (38%)	27/41 (90%)	
Time from surgery to commencing chemotherapy, median (IQR), days	**83 (76 – 89)**	**53 (49 – 61)**	***P* < 0.0001**
Treatment duration, median (IQR), weeks	24 (19 – 24)	24 (21 – 24)	*P* = 0.9318
Completed planned treatment, n	38 (85%)	32 (78%)	*P* = 0. 7036
Percentage of full dose delivered, median (IQR)	78 (56 – 100)	84 (64 – 100)	*P* = 0.6194

Adjuvant Treatment in Key Subgroups

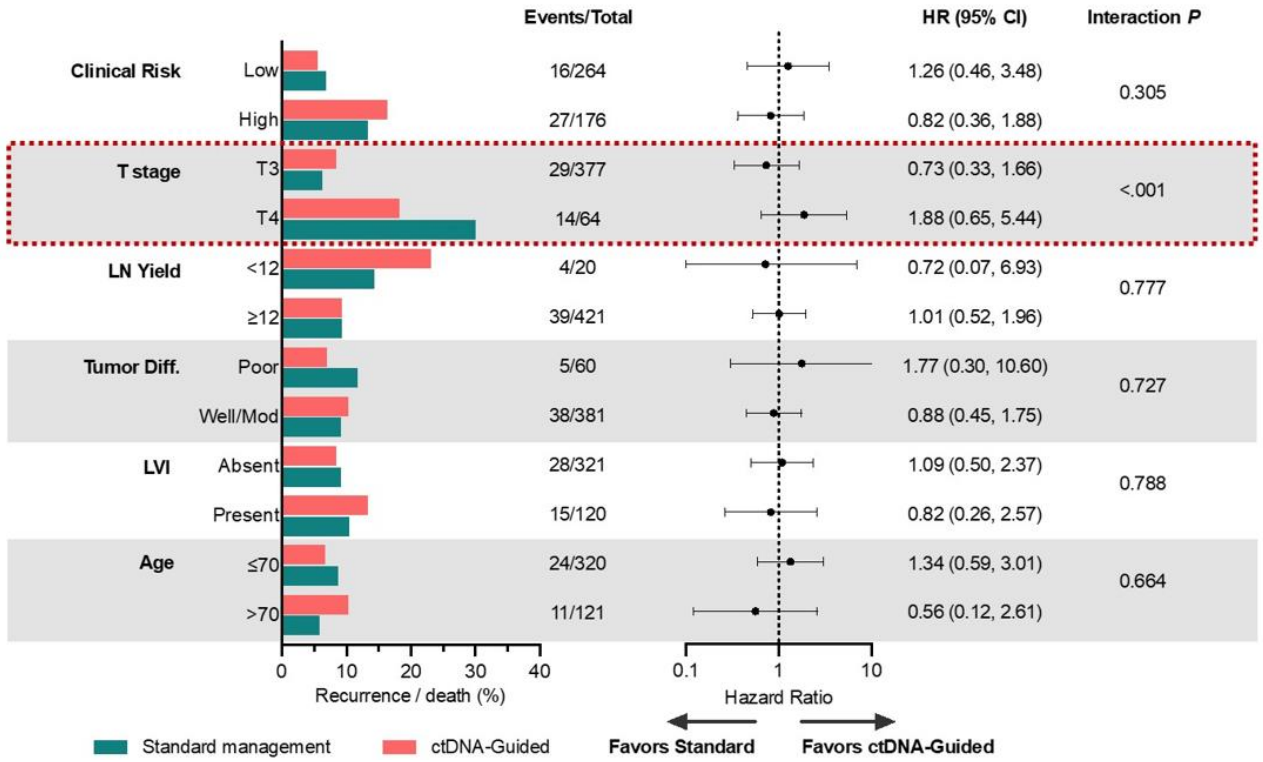


DYNAMIC

Recurrence-Free Survival



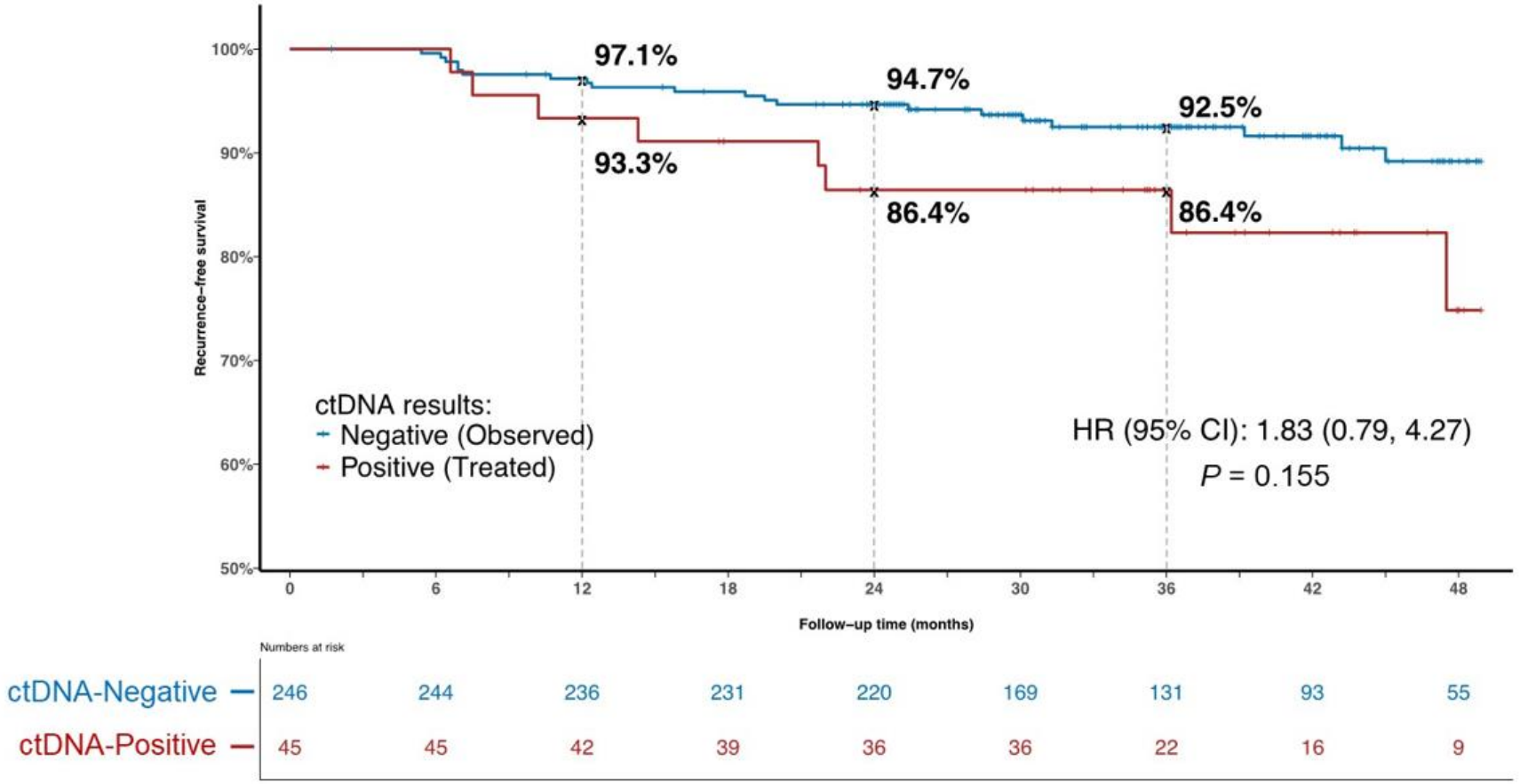
Recurrence-Free Survival in Key Subgroups



DYNAMIC

Recurrence-Free Survival in ctDNA-Guided Management

- ctDNA-Negative vs ctDNA-Positive



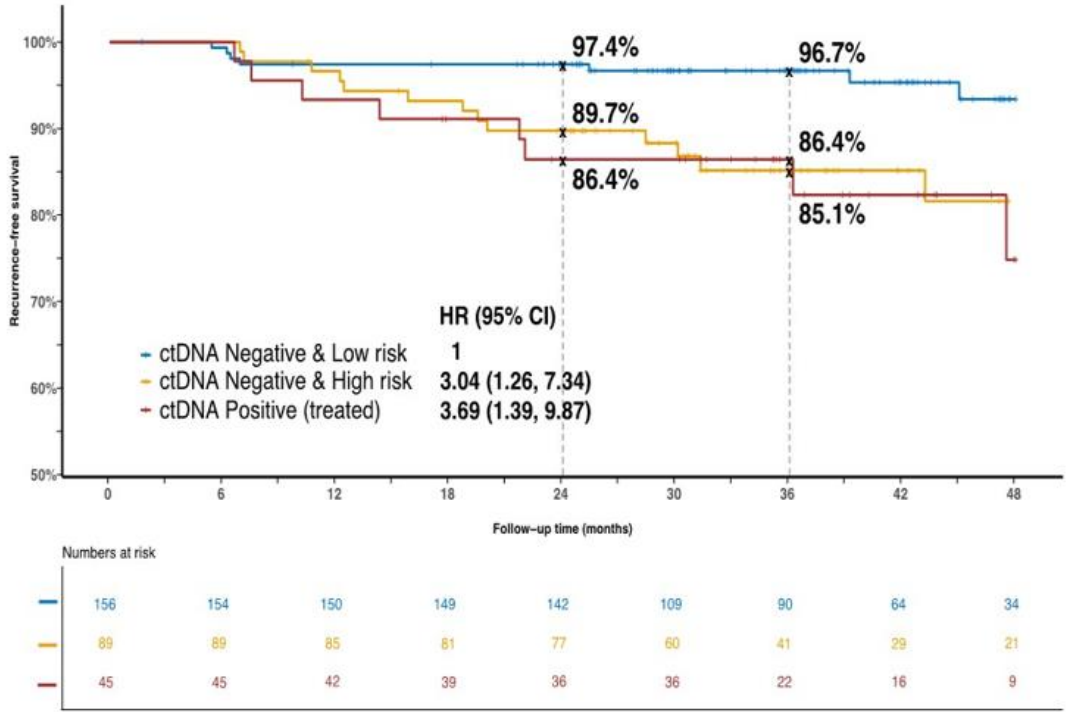
ASCO 2022. Abstr LBA100.

DYNAMIC

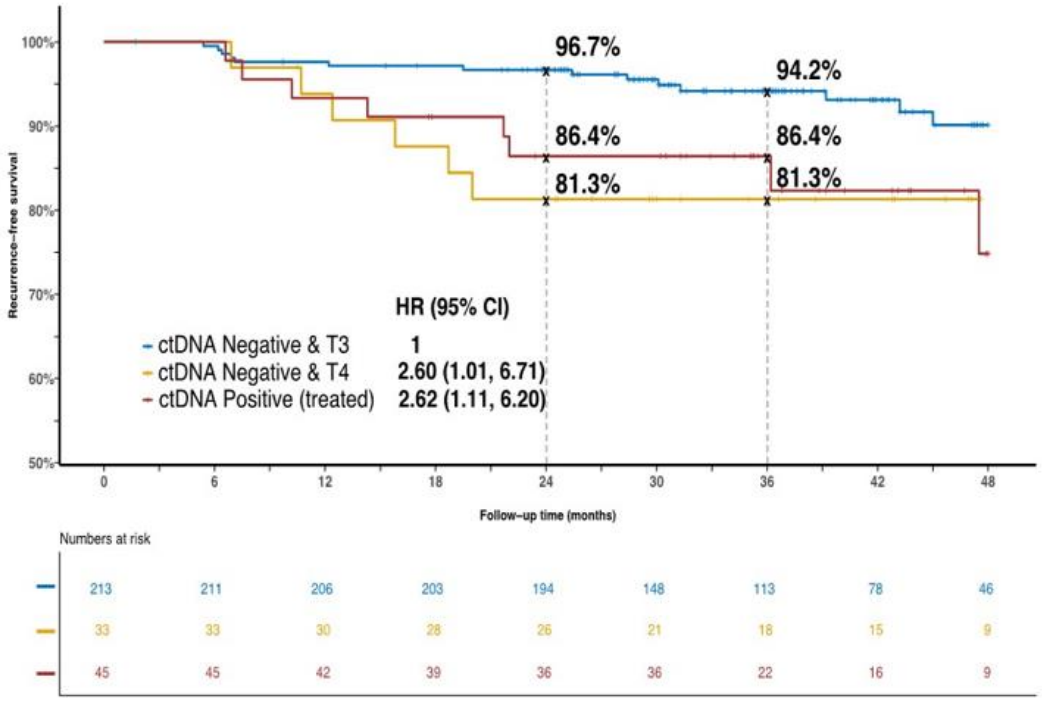
Recurrence-Free Survival in ctDNA-Guided Management

- ctDNA, clinical risk and T stage

ctDNA and Clinical Risk



ctDNA and T Stage



ASCO 2022. Abstr LBA100.

SUMMARY

DYNAMIC

- ctDNA-guided management vs standard management of stage II colon cancer can reduce the number of patients receiving adjuvant chemotherapy
  - Adjuvant chemotherapy received decreased: 28% to 15%
  - Recurrence-free survival at 2 years was consistent: 93.5% vs 92.4%

- Identification of patients with a positive ctDNA after surgery may benefit from adjuvant chemotherapy
  - Recurrence-free survival at 3 years: 86.4%

- Identification of patients with a negative ctDNA after surgery can avoid adjuvant chemotherapy
  - Recurrence-free survival at 3 years: 92.5%

ASCO 2022. Abstr LBA100.

DYNAMIC

ctDNA can be used to identify patients with stage II colon cancer that may benefit from adjuvant chemotherapy as well as identifying patients that do not require chemotherapy while maintaining outcomes

Liquid biopsies can be a useful tool for guiding treatment decisions

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- MAINTAIN
- ABCSG-18
- PALOMA-2
- LUMINA

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- DYNAMIC
- PARADIGM*
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- PD-1 blockade in MMRd RC

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- rEECur*
- ECHELON-1
- RELATIVITY-047
- SKYSCRAPER-02

* Plenary Session

cornerstone specialty network™

PARADIGM

Does panitumumab or bevacizumab, in combination with mFOLFOX6, provide benefit for patients with unresectable metastatic colorectal cancer (mCRC) without *RAS* mutations in the first line setting?

KEY DATA

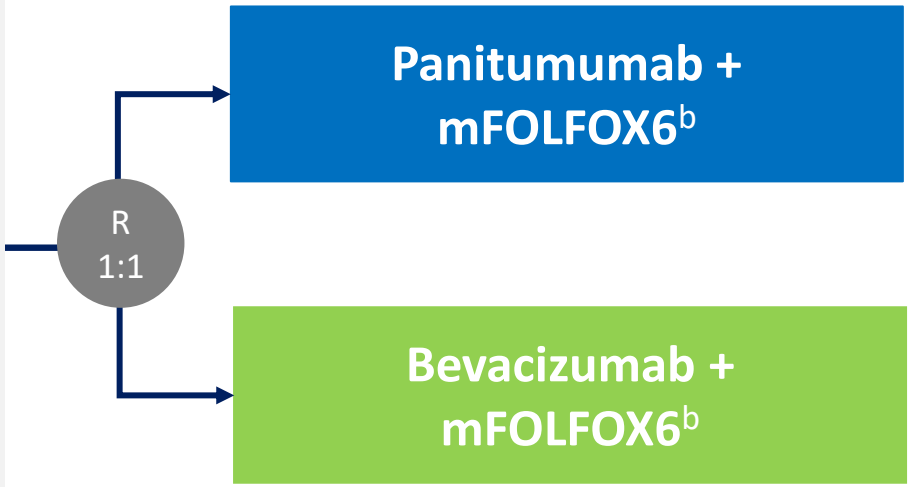
PARADIGM

Study Design: Multicenter, randomized, open-label phase III trial

Stratified by institution, age (20-64 vs 65-79 yr), liver metastases (present vs absent)

- Patients with WT RAS mCR
- Age 20-79 years
- Unresectable disease
- No prior chemotherapy[a]
- ECOG PS 0 – 1
- At least 1 evaluable lesion
- Adequate organ function
- Life expectancy ≥ 3 months

(N = 823)



Until PD, unacceptable toxicity, withdrawal of consent, investigator's judgement, or curative intent resection

Primary endpoints: OS in left-sided[c] population; if significant (P < 0.04202), then OS in overall population (P <0.05)
Secondary endpoints: PFS, RR, DoR, R0 resection (left-sided[c] and overall populations), safety
Exploratory endpoints: ETS, depth of response, DCR: left-sided[c] and overall population

Data cutoff date: Jan 14, 2022
Median follow-up: 61 months

DCR, disease control rate; DOR; duration of response; ECOG, Eastern Cooperative Oncology Group; ETS, early tumor shrinkage; mCRC, metastatic colorectal cancer; OS, overall survival; PFS, progression free survival; RR, response rate; R0, curative resection; WT, wild type.
[a]Adjuvant fluoropyrimidine monotherapy allowed if completed > 6 months before enrollment. [b]Until disease progression, unacceptable toxicity, withdrawal of consent or investigator's judgement or curative intent resection.
[c]Primary tumor in descending colon, sigmoid colon, rectosigmoid, and rectum.

ASCO 2022. Abstr LBA1.

PARADIGM

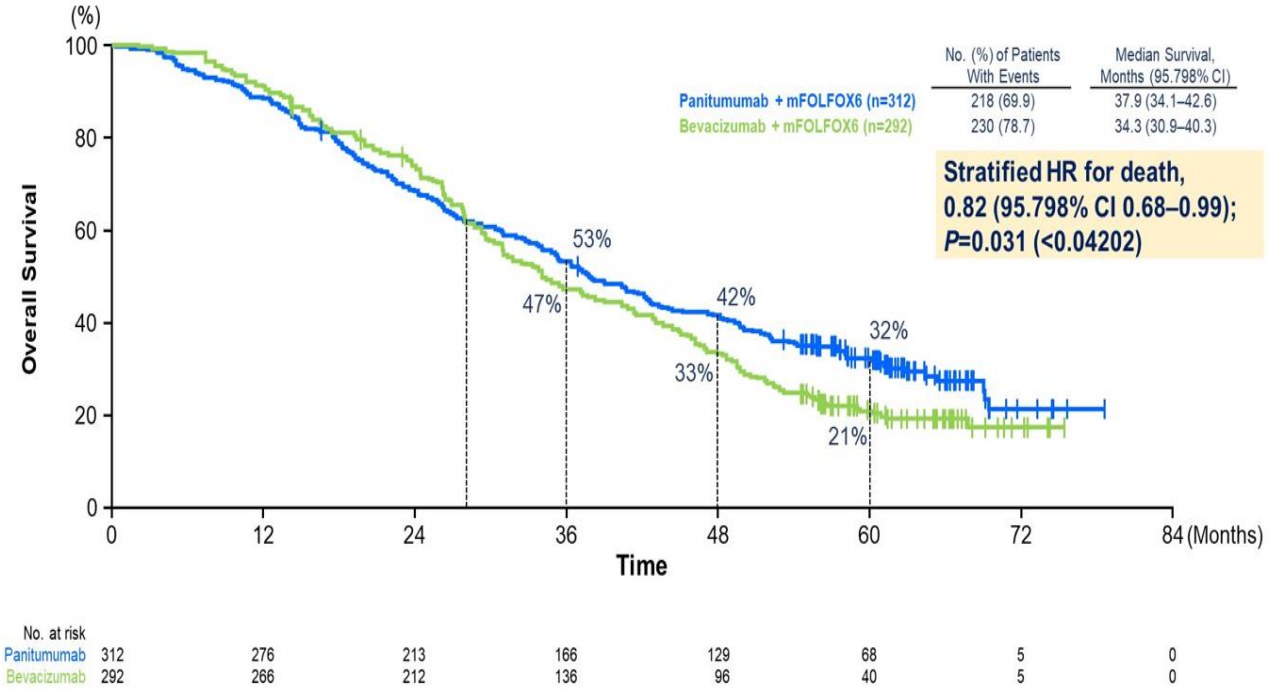
Baseline Characteristics

Characteristic, %		Left-Sided Population		Overall Population	
		Panitumumab + mFOLFOX6 (n = 312)	Bevacizumab + mFOLFOX6 (n = 292)	Panitumumab + mFOLFOX6 (n = 400)	Bevacizumab + mFOLFOX6 (n = 402)
Age	20-64 yr	44.2	43.5	41.0	41.8
	65-79 yr	55.8	56.5	59.0	58.2
Female		33.3	31.2	37.0	33.3
ECOG PS	0	83.7	79.1	82.0	79.4
	1	16.3	20.9	17.8	20.6
Primary tumor location*	Left sided	100	100	78.0	72.6
	Right sided	0	0	21.0	25.6
No. of metastatic organs	1	49.7	50.3	49.0	48.3
	≥2	50.3	49.7	51.0	51.7
Metastatic site					
	Liver	72.1	70.5	68.8	69.2
	Liver as only site of metastasis	28.8	30.5	26.3	28.1
Prior treatment					
	Primary tumor resection	59.3	66.1	59.8	67.7
	Radiotherapy	0.6	0.7	0.5	0.7
	Adjuvant chemotherapy	5.4	5.5	5.5	5.0

*4 patients receiving panitumumab and 7 patients receiving bevacizumab had multiple primary lesions in both the left-sided and right-sided

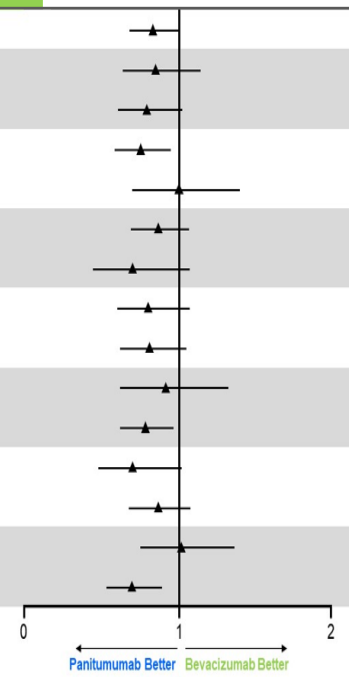
PARADIGM

Overall Survival in left-sided population



OS subgroup analyses in left-sided population

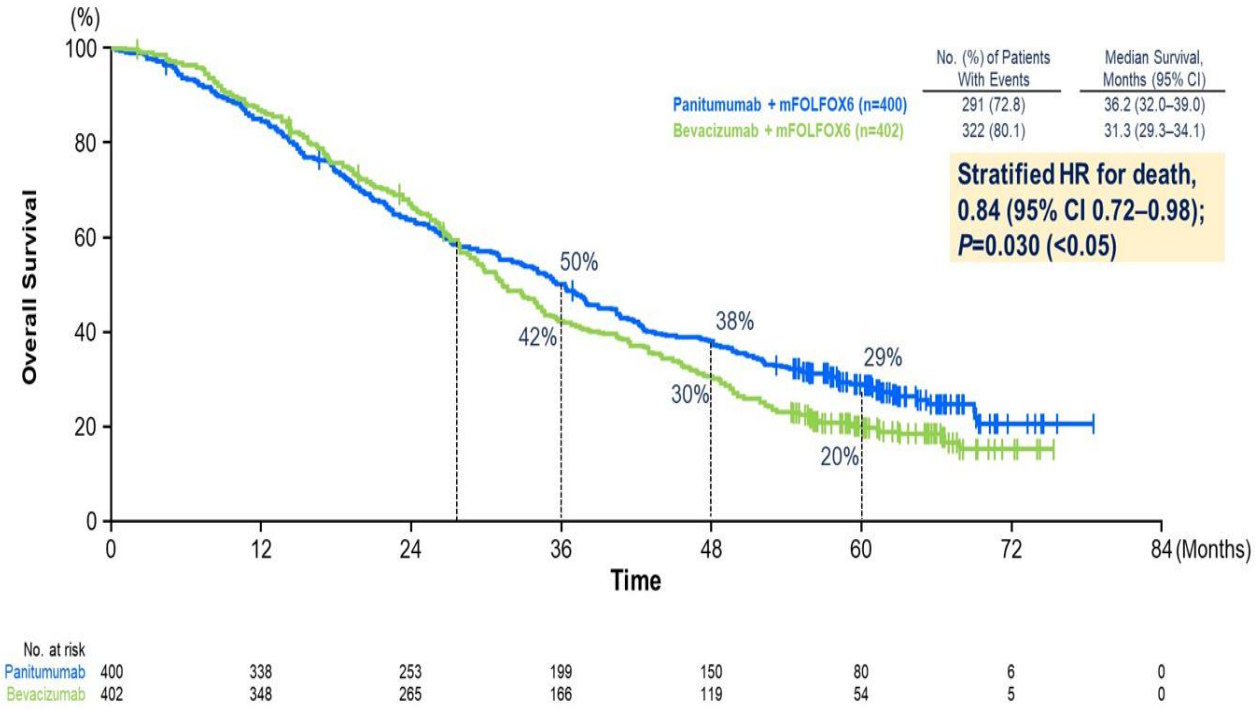
Subgroup		Events/Patients: Panitumumab + mFOLFOX6	Events/Patients: Bevacizumab + mFOLFOX6	Hazard Ratio 95% CI)
	Overall*	218/312	230/292	0.82 (0.68–0.99)
Age	20-64 yr	95/138	95/127	0.86 (0.65–1.15)
	65-79 yr	123/174	135/165	0.80 (0.63–1.02)
Sex	Male	147/208	164/201	0.76 (0.61–0.95)
	Female	71/104	66/91	1.00 (0.71–1.40)
ECOG PS	0	182/261	179/231	0.87 (0.70–1.07)
	1	36/51	51/61	0.70 (0.46–1.08)
No. of organs with metastasis	0-1	91/155	100/147	0.81 (0.61–1.08)
	≥2	127/157	130/145	0.81 (0.64–1.04)
Liver metastasis	No	56/87	59/86	0.91 (0.63–1.32)
	Yes	162/225	171/206	0.79 (0.63–0.97)
Organs with metastasis	Liver only	52/90	65/89	0.71 (0.49–1.02)
	Other	166/222	165/203	0.87 (0.70–1.07)
Primary tumor resection	No	101/127	81/99	1.02 (0.76–1.37)
	Yes	117/185	149/193	0.69 (0.54–0.89)



* Stratified HR shown with 95% CI

PARADIGM

Overall Survival in overall population



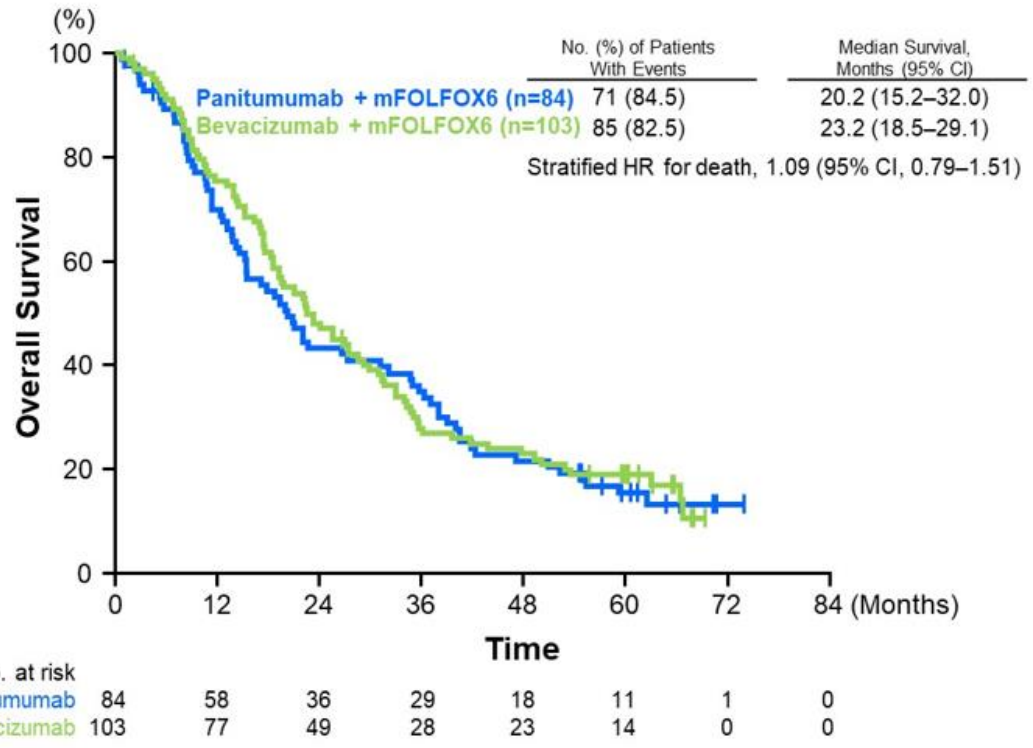
OS subgroup analyses in overall population

Subgroup		Events/Patients: Panitumumab + mFOLFOX6	Events/Patients: Bevacizumab + mFOLFOX6	Hazard Ratio 95% CI)
	Overall*	291/400	322/402	0.84 (0.72–0.98)
Primary tumor location	Left-sided	218/312	230/292	0.83 (0.69–1.00)
	Right-sided	71/84	85/103	1.06 (0.77–1.45)
Age	20-64 yr	117/164	129/168	0.89 (0.69–1.14)
	65-79 yr	174/236	193/234	0.81 (0.66–1.00)
Sex	Male	185/252	221/268	0.77 (0.63–0.93)
	Female	106/148	101/134	1.00 (0.76–1.31)
ECOG PS	0	237/328	253/319	0.85 (0.71–1.02)
	1	53/71	69/83	0.79 (0.56–1.14)
No. of organs with metastasis	0-1	123/196	133/194	0.88 (0.69–1.13)
	≥2	168/204	189/208	0.79 (0.64–0.98)
Liver metastasis	No	83/125	89/124	0.88 (0.65–1.19)
	Yes	208/275	233/278	0.83 (0.68–1.00)
Organs with metastasis	Liver only	66/105	83/113	0.78 (0.56–1.08)
	Other	225/295	239/289	0.85 (0.71–1.02)
Primary tumor resection	No	132/161	110/130	0.97 (0.75–1.25)
	Yes	159/239	212/272	0.74 (0.60–0.91)

* Stratified HR shown with 95% CI

PARADIGM

Exploratory: Overall Survival in right-sided population



OS subgroup analyses in right-sided population

Subgroup		Events/Patients: Panitumumab + mFOLFOX6	Events/Patients: Panitumumab + mFOLFOX6	Hazard Ratio (95% CI)
	Overall*	71/84	85/103	1.09 (0.79-1.51)
Age	20-64 yr	22/26	32/39	1.26 (0.73-2.17)
	65-79 yr	49/58	53/64	0.97 (0.66-1.44)
Sex	Male	37/41	51/61	1.04 (0.68-1.60)
	Female	34/43	34/42	1.08 (0.67-1.74)
ECOG PS	0	54/65	68/82	0.96 (0.67-1.37)
	1	16/18	17/21	1.33 (0.66-2.67)
No. of organs with metastasis	0-1	31/40	30/44	1.27 (0.77-2.10)
	≥2	40/44	55/59	0.94 (0.63-1.42)
Liver metastasis	No	26/35	29/37	0.87 (0.51-1.49)
	Yes	45/49	56/66	1.23 (0.83-1.83)
Organs with metastasis	Liver only	13/14	15/21	1.66 (0.79-3.50)
	Other	58/70	70/82	0.93 (0.66-1.32)
Primary tumor resection	No	30/33	28/30	0.87 (0.51-1.45)
	Yes	41/51	57/73	1.09 (0.73-1.63)

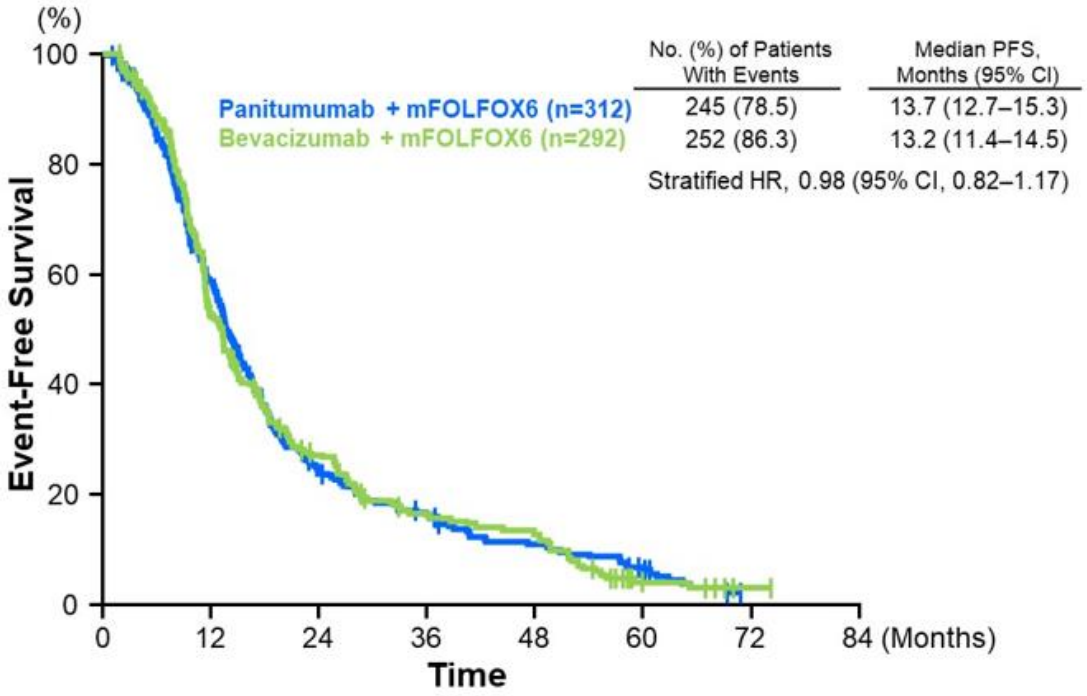
* Stratified HR shown with 95% CI

KEY DATA

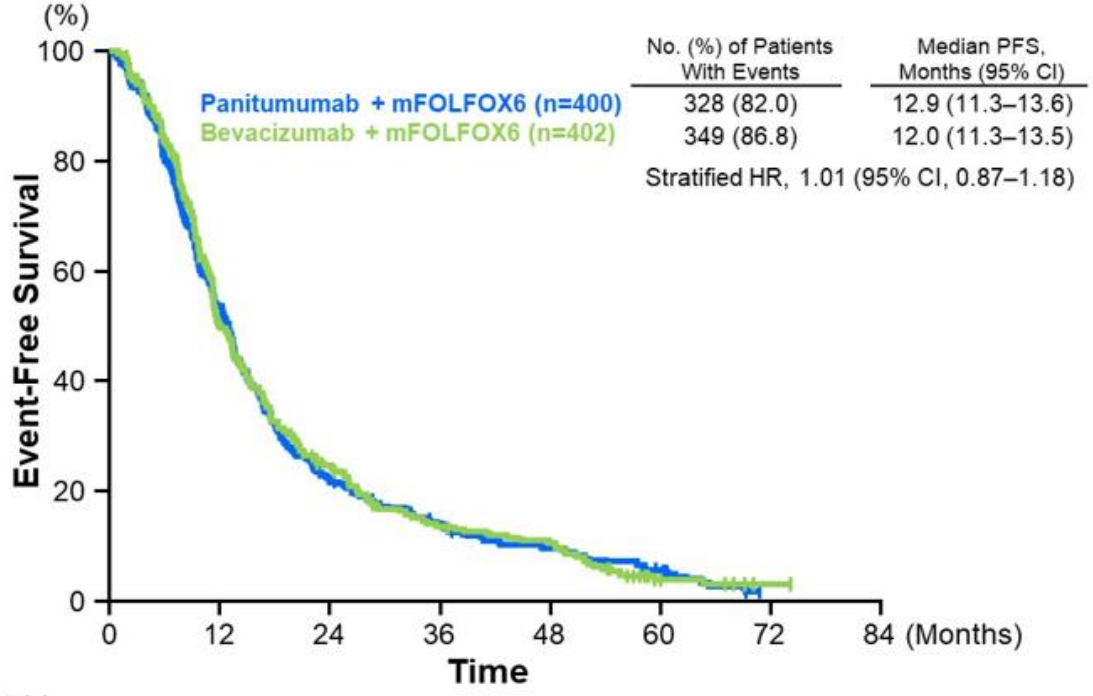
PARADIGM

Progression-free Survival

PFS in left-sided population



PFS in overall population



[a]Patients who underwent curative-intent resection were censored at the last tumor evaluable assessment date before the resection.

ASCO 2022. Abstr LBA1.

PARADIGM

Response Rates

Parameter	Left-Sided Population		Overall Population	
	Panitumumab + mFOLFOX6 (n = 308)	Bevacizumab + mFOLFOX6 (n = 287)	Panitumumab + mFOLFOX6 (n = 394)	Bevacizumab + mFOLFOX6 (n = 397)
Response rate, % (95% CI)	**80.2** (75.3-84.5)	**68.6** (62.9-74.0)	**74.9** (70.3-79.1)	**67.3** (62.4-71.9)
DCR, % (95% CI)	97.4 (94.9-98.9)	96.5 (93.7-98.3)	94.9 (92.3-96.9)	95.5 (92.9-97.3)
Median DoR,* mo (95% CI)	13.1 (11.1-14.8)	11.2 (9.6-13.1)	11.9 (10.5-13.4)	10.7 (9.5-12.2)
R0 rate,† % (95% CI)	**18.3** (14.1-23.0)	**11.6** (8.2-15.9)	**16.5** (13.0-20.5)	**10.9** (8.1-17.1)

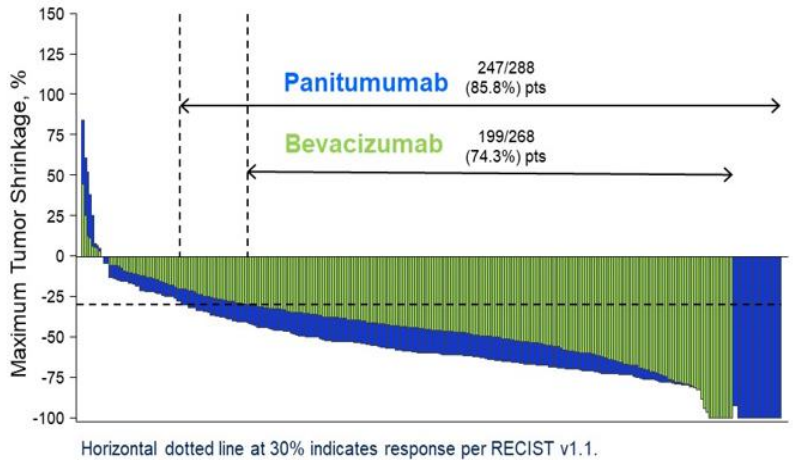
*DoR evaluated in patients with CR or PR. †R0 rate evaluated in all patients of efficacy analysis population.

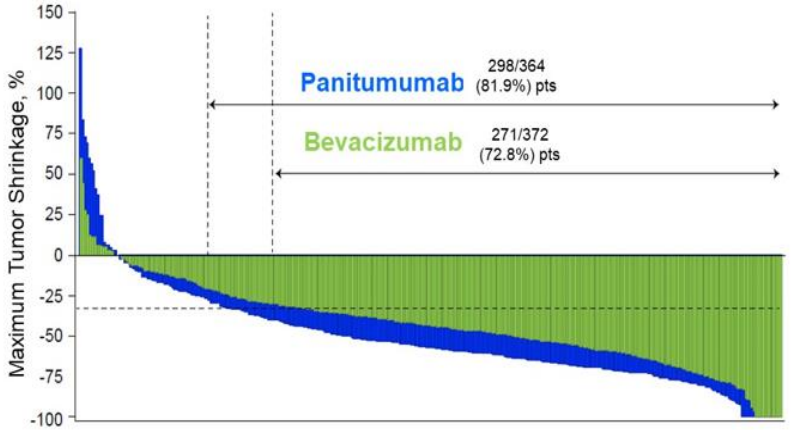
ASCO 2022. Abstr LBA1.

PARADIGM

Depth of Response

Parameter	Left-Sided Population		Overall Population	
	Panitumumab + mFOLFOX6 (n = 288)	Bevacizumab + mFOLFOX6 (n = 268)	Panitumumab + mFOLFOX6 (n = 364)	Bevacizumab + mFOLFOX6 (n = 372)
Depth of response				
≥30% tumor shrinkage, %	85.8	74.3	81.9	72.8
Median maximum tumor shrinkage, %	-59.4	-43.6	-57.3	-43.6





PARADIGM

Safety

AE, n (%)	Panitumumab + mFOLFOX6 (n = 404)	Bevacizumab + mFOLFOX6 (n = 407)
Any AE	402 (99.5)	399 (98.0)
Grade ≥3 AE	**290 (71.8)**	**264 (64.9)**
Serious AE related to treatment	72 (17.8)	44 (10.8)
AE leading to treatment discontinuation	**96 (23.8)**	**75 (18.4)**

AE reported in ≥ 20% of patients, %	Panitumumab + mFOLFOX6 (n = 404)		Bevacizumab + mFOLFOX6 (n = 407)	
	Grade 1/2	Grade ≥3	Grade 1/2	Grade ≥3
Acne-like dermatitis	**58**	**17**	**3**	**0**
Peripheral sensory neuropathy	62	9	64	10
Stomatitis	55	7	39	2
Decreased appetite	48	8	46	4
Paronychia	**43**	**9**	**5**	**<1**
Decreased neutrophil count	18	32	20	35
Dry skin	**38**	**8**	**9**	**<1**
Nausea	38	2	37	3
Fatigue	35	5	36	4
Diarrhea	31	6	30	3
Dysgeusia	31	0	23	0
Hypomagnesemia	**22**	**8**	**2**	**0**
Constipation	23	0	26	1
Decreased platelet count	20	2	19	1

ASCO 2022. Abstr LBA1.

SUMMARY

PARADIGM

- Panitumumab in combination with mFOLFOX6 compared to bevacizumab in combination with mFOLFOX6 provides significant improvement in OS in left-sided and overall mCRC populations in the 1L setting
- PFS was comparable for both arms
- Response and R0 resection rates were higher in the panitumumab arm vs bevacizumab for both the left-sided and overall mCRC populations
- No new safety concerns in either arms

ASCO 2022. Abstr LBA1.

PARADIGM

Panitumumab in combination with mFOLFOX6 provides benefit to patients with WT RAS and left-sided mCRC, and supports consideration as standard of care in the first-line setting for this patient population

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- ABCSG-18
- PALOMA-2
- LUMINA

GI Cancer

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- SKYSCRAPER-02

* Plenary Session

cornerstone specialty network™

CLINICAL QUESTION

TRIPLETE

Does triplet chemotherapy (FOLFOXIRI) vs doublet chemotherapy (FOLFOX/FOLFIRI) with panitumumab provide benefit to patients with unresectable mCRC without *RAS or BRAF* mutations in the first line setting?

KEY DATA

TRIPLETE

Study Design: Randomized, open-label phase III trial

Stratification by ECOG PS (0-1 vs 2), primary tumor location (right vs left), metastatic spread (liver only vs not liver only

- Aged 18-75 yr
- Histologically proven adenocarcinoma
- Unresectable RAS and BRAF WT mCRC
- No previous treatment for metastatic disease*
- Measurable disease (by RECIST 1.1)
- Adequate bone marrow, liver, and renal functions
- ECOG PS 0-2

(N = 435)

*Adjuvant oxaliplatin-containing chemotherapy not allowed; adjuvant fluoropyrimidine monotherapy allowed if >6 months between end of therapy and first relapse.

R 1:1

mFOLFOXIRI + Panitumumab
for up to 12 cycles
(n = 218)

mFOLFOXIRI dosing: LV 200 mg/m2, 5-FU 2400 mg/m2, oxaliplatin 85 mg/m2, irinotecan 150 mg/m2. Panitumumab dosed at 6 mg/kg.

mFOLFOX6 + Panitumumab
for up to 12 cycles
(n = 217)

5-FU/LV + Panitumumab until PD

Primary endpoints: ORR (by RECIST 1.1)
Key secondary endpoints: depth of response, early tumor shrinkage, R0 resection rate, PFS, OS

57 participating centers from Sept 2017 – Sept 2021

TRIPLETE

Baseline Characteristics

Characteristic	mFOLFOXIRI + Panitumumab (n = 218)	mFOLFOX6 + Panitumumab (n = 217)
Median age, yr (IQR)	59 (51-64)	59 (51-65)
Male, %	62	64
ECOG PS 0, %	84	80
Synchronous metastases, %	87	88
Prior adjuvant chemotherapy, %	6	2
Resected primary tumor, %	51	43
>1 metastatic site, %	53	52
Liver-only disease, %	39	37
Left-sided disease, %	88	88
MMR proficient/deficient/NE, %	74/3/23	67/1/32

ASCO 2022. Abstr LBA3505.

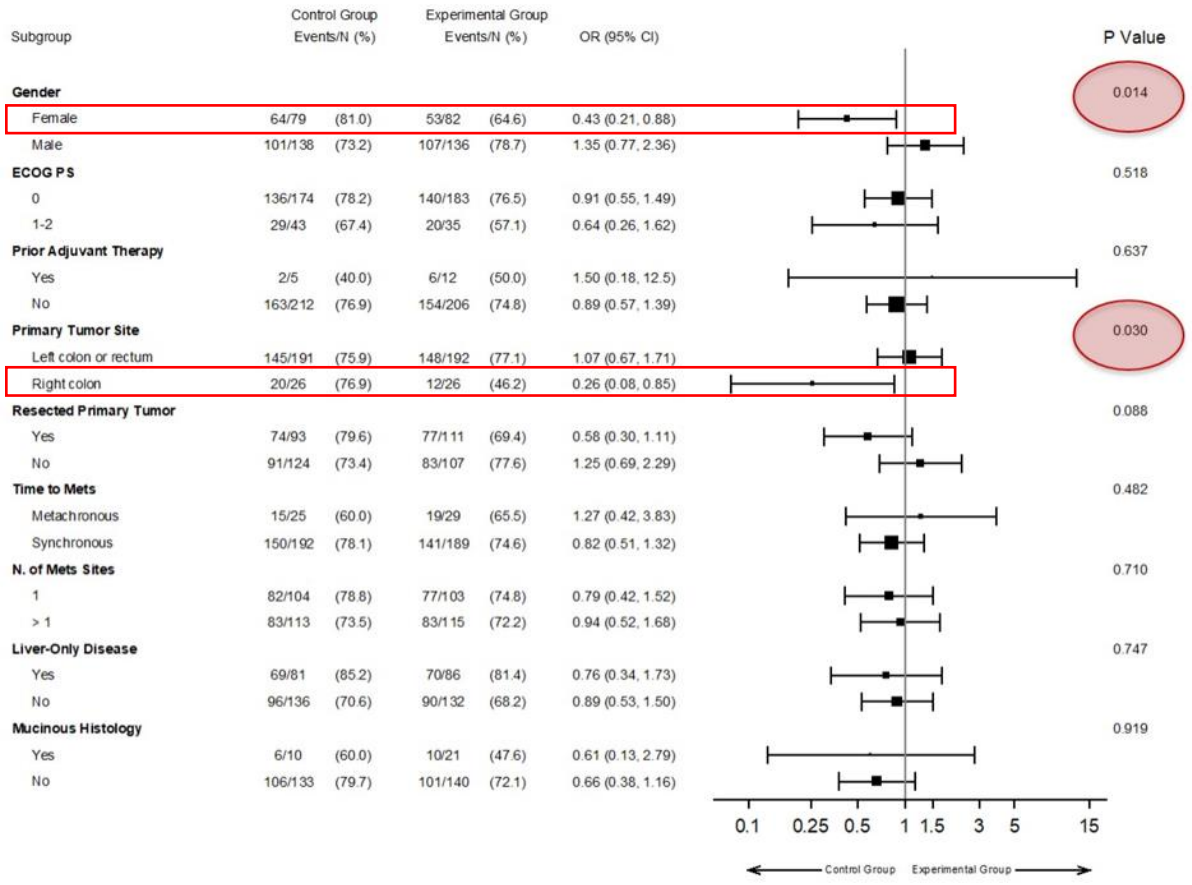
TRIPLETE

Primary Endpoint: Response Rate

Efficacy Outcome	mFOLFOXIRI + Panitumumab (n = 218)	mFOLFOX6 + Panitumumab (n = 217)	OR (95% CI)	P Value
ORR, %	73	76	0.87 (0.56-1.34)	0.526
Best response, %				
• CR	7	7		
• PR	66	69		
• SD	18	17		
• PD	5	5		
• Not assessed	4	2		
Median depth of response,* %	48	47		0.845
Early tumor shrinkage,† %	57	58	0.97 (0.66-1.42)	0.878
R0 resection, %	25	29	0.81 (0.53-1.23)	0.317

*Relative change in the sum of the longest diameters of target lesions at the nadir in the absence of new lesions or progression of non-target lesions.
†≥20% decrease in the sum of the diameters of RECIST target lesions after 8 wk.

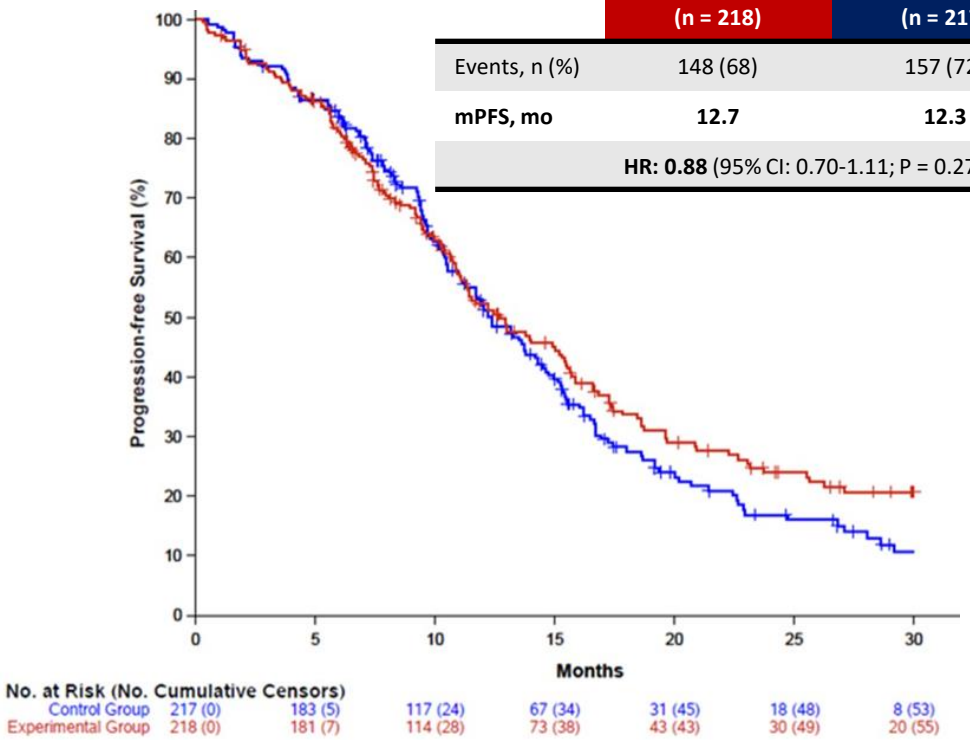
Subgroup analyses: ORR



TRIPLETE

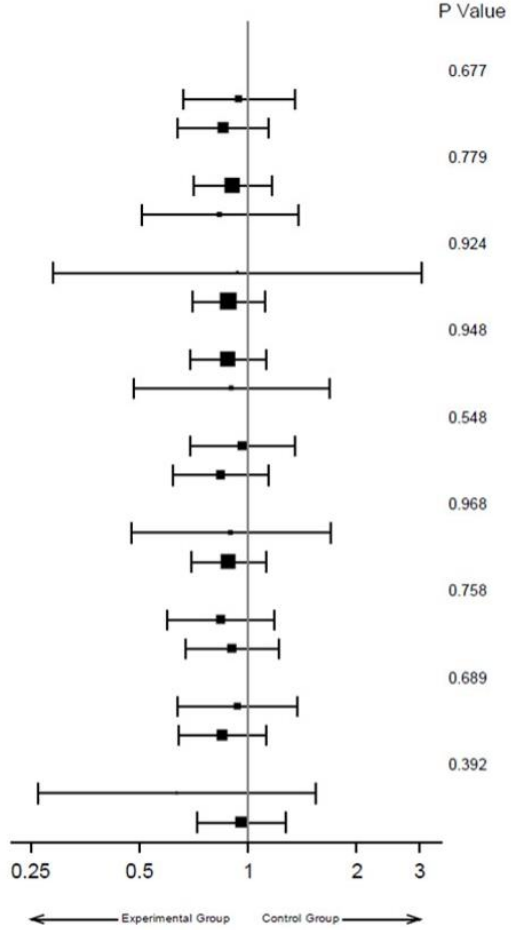
Progression-Free Survival

	mFOLFOXIRI + Pan (n = 218)	mFOLFOX6 + Pan (n = 217)
Events, n (%)	148 (68)	157 (72)
mPFS, mo	**12.7**	**12.3**
	HR: 0.88 (95% CI: 0.70-1.11; P = 0.277)	



Subgroup analyses: PFS

Subgroup	Control Group Events/N (%)		Experimental Group Events/N (%)		HR (95% CI)	P Value
Gender						0.677
Female	64/79	(81.0)	58/82	(70.7)	0.94 (0.66, 1.35)	
Male	93/138	(67.4)	90/136	(66.2)	0.85 (0.64, 1.14)	
ECOG PS						0.779
0	122/174	(70.1)	121/183	(66.1)	0.91 (0.70, 1.17)	
1-2	35/43	(81.4)	27/35	(77.1)	0.84 (0.51, 1.38)	
Prior Adjuvant Therapy						0.924
Yes	4/5	(80.0)	9/12	(75.0)	0.94 (0.29, 3.04)	
No	153/212	(72.2)	139/206	(67.5)	0.88 (0.70, 1.11)	
Primary Tumor Site						0.948
Left colon or rectum	137/191	(71.7)	129/192	(67.2)	0.88 (0.69, 1.12)	
Right colon	20/26	(76.9)	19/26	(73.1)	0.90 (0.48, 1.69)	
Resected Primary Tumor						0.548
Yes	64/93	(68.8)	73/111	(65.8)	0.97 (0.69, 1.35)	
No	93/124	(75.0)	75/107	(70.1)	0.84 (0.62, 1.14)	
Time to Mets						0.968
Metachronous	18/25	(72.0)	20/29	(69.0)	0.90 (0.47, 1.69)	
Synchronous	139/192	(72.4)	128/189	(67.7)	0.88 (0.69, 1.12)	
N. of Mets Sites						0.758
1	70/104	(67.3)	62/103	(60.2)	0.84 (0.60, 1.19)	
> 1	87/113	(77.0)	86/115	(74.8)	0.90 (0.67, 1.22)	
Liver-Only Disease						0.689
Yes	53/81	(65.4)	52/86	(60.5)	0.94 (0.64, 1.37)	
No	104/136	(76.5)	96/132	(72.7)	0.85 (0.64, 1.12)	
Mucinous Histology						0.392
Yes	8/10	(80.0)	13/21	(61.9)	0.63 (0.26, 1.54)	
No	94/133	(70.7)	96/140	(68.6)	0.96 (0.72, 1.27)	



TRIPLETE

Safety

Grade 3/4 AEs, %	mFOLFOXIRI + Panitumumab (n = 218)	mFOLFOX6 + Panitumumab (n = 213)
Neutropenia	32	20
Diarrhea	23	7
Skin rash	19	29
Stomatitis	7	7
Fatigue	7	2
Febrile neutropenia	5	3
Nausea	5	2
Neurotoxicity	2	4
Vomiting	2	1
Hypomagnesemia	1	1

ASCO 2022. Abstr LBA3505.

SUMMARY

TRIPLETE

- Triplet chemotherapy in combination with panitumumab did not provide benefit compared to doublet chemotherapy in combination with panitumumab in patients with mCRC without *RAS* or *BRAF* mutations

- OS results are immature

- Higher rates of Grade 3 and Grade 4 toxicities in the triplet regimen (as expected)

ASCO 2022. Abstr LBA3505.

TRIPLETE

Intensification of chemotherapy in combination with panitumumab in the front line setting does not provide benefit and should not be recommended to patients with RAS and BRAF WT mCRC

2022 ASCO Key Studies

Breast Cancer

- DESTINY-Breast04*
- TROPiCS-02
- MAINTAIN
- ABCSG-18
- PALOMA-2
- LUMINA

GI Cancer

- DYNAMIC
- PARADIGM*
- TRIPLETE
- CAIRO5
- PD-1 blockade in MMRd RC

Other Notable Studies

- DETERMINATION*
- ATLAS
- rEECur*
- ECHELON-1
- RELATIVITY-047
- SKYSCRAPER-02

* Plenary Session

cornerstone specialty network™

CLINICAL QUESTION

CAIRO5

Does triplet chemotherapy (FOLFOXIRI) vs doublet chemotherapy (FOLFOX/FOLFIRI) plus bevacizumab provide benefit in patients with unresectable colorectal cancer liver metastases (CRLM) and right-sided and/or *RAS/BRAF*^{V600E}-mutated primary tumors?

KEY DATA

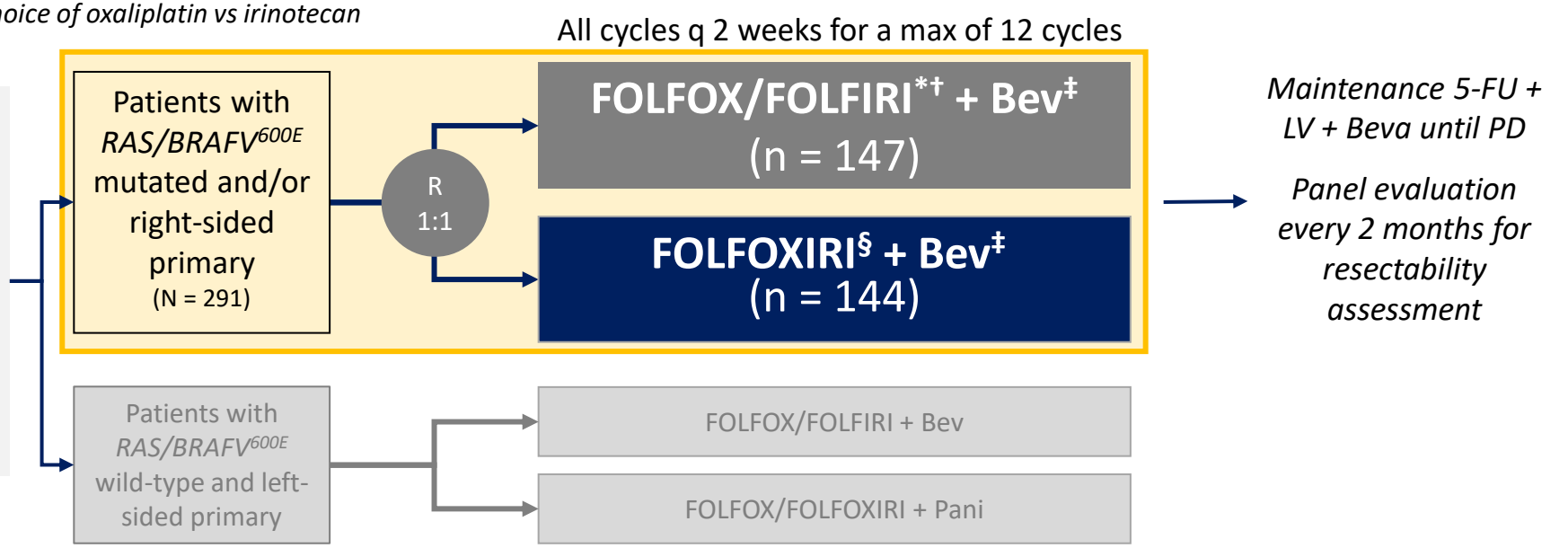
CAIRO5

Study Design: Prospective, randomized phase III trial

Stratified by potentially vs permanently unresectable, serum LDH (normal vs abnormal), BRAF^{V600E} mutation status, choice of oxaliplatin vs irinotecan

- Aged ≥18 yr
- mCRC with previously untreated liver-only mets
- Initial unresectable CRLM confirmed by a liver expert panel
- WHO PS 0-1
- Primary tumor, resectable if in situ

(N = 564)



Liver expert panel

- 15 liver surgeons and 3 abdominal radiologists
- CT scans (and MRI if available) evaluated at baseline and follow-up
- If no consensus reached with CT scan evaluation among 3 liver surgeons, 2 additional liver surgeons evaluated the scan and decision made by majority vote

*FOLFOX or FOLFIRI by patient preference; all patients could receive local treatments (ablation, 2-stage surgery, portal vein embolization) and up to 12 cycles of systemic tx without bev after local tx.
†Oxaliplatin 85 mg/m^2 or irinotecan 180 mg/m^2 with LV 400 mg/m^2 in 120 min; bolus 5-FU 400 mg/m^2, infusional 5-FU 2400 mg/m^2 in 46h Q2W.
‡5 mg/kg IV in 15-30 min.
§Oxaliplatin 85 mg/m^2, irinotecan 165 mg/m^2 with LV 400 mg/m^2 in 120 min; infusional 5-FU 3200 mg/m^2 in 46h.

Primary endpoints: PFS

Secondary endpoints: OS, ORR, toxicity, rates of R0/1 resection rates, postoperative morbidity

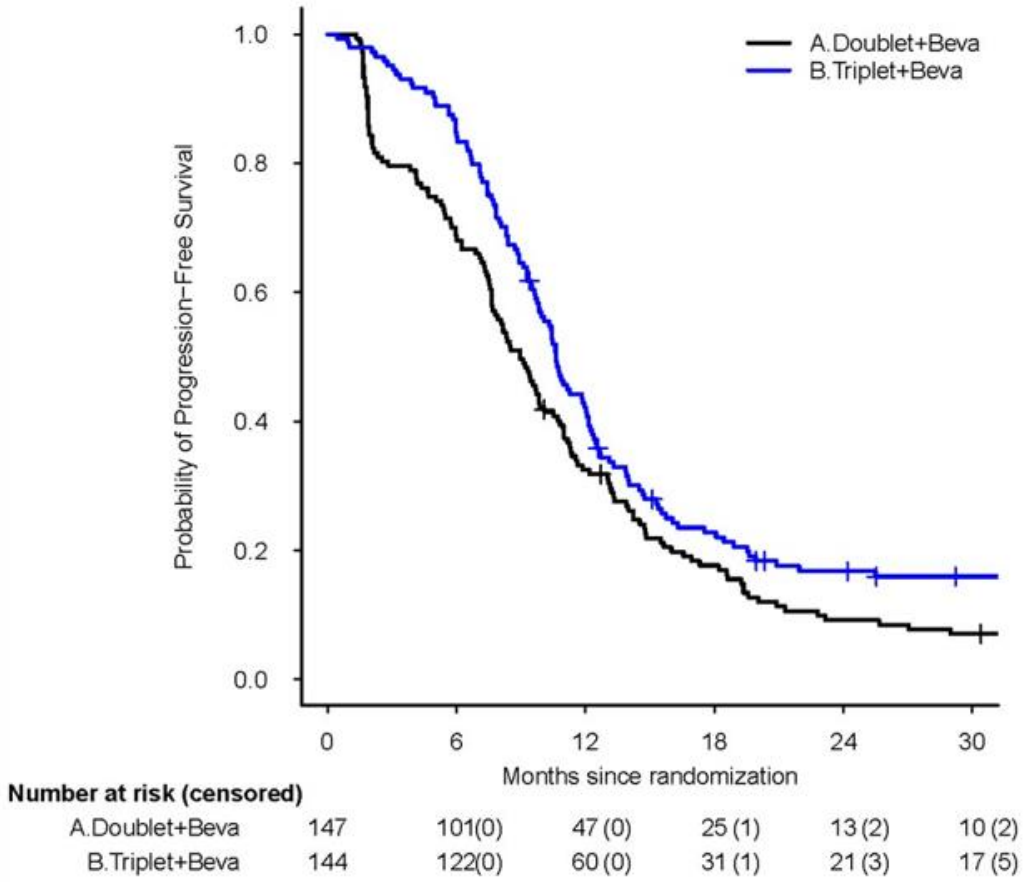
CAIRO5

Baseline Characteristics

Characteristic	FOLFOX/FOLFIRI + Bevacizumab (n = 147)	FOLFOXIRI + Bevacizumab (n = 144)
Median age, yr (range)	61 (39-79)	65 (35-81)
Male, %	64	60
WHO PS 0, %	64	69
Right-sided primary, %	41	42
RAS mutation, %	86	86
$BRAF^{V600E}$ mutation, %	7	8
Synchronous metastases, %	86	90
Prior adjuvant chemotherapy, %	5	5
Median # CRC liver metastases, n (range)	12 (7-24)	12 (7-22)
Normal serum LDH, %	52	52
Preference for oxaliplatin, %	93	94
Potentially resectable CRLM (panel), %	88	86

CAIRO5

Progression-Free Survival



Parameter	FOLFOX/FOLFIRI + Bevacizumab (n = 147)	FOLFOXIRI + Bevacizumab (n = 144)	HR (95% CI)	P Value
Median PFS, mo	**9.0**	**10.6**	**0.77** (0.60-0.99)	**0.038**
Median no. of cycles,* n (range)	8 (1-16)	8 (1-15)	--	
ORR, %	**33.3**	**53.5**	**--**	**<0.001**

*Excluding maintenance cycles and any adjuvant chemotherapy.

- PFS subgroup analyses showed no significant interaction between baseline unresectability or mutation status (*RAS*, *BRAF*^{V600E}, WT, and right-sided) and PFS
- At a median follow-up of 41 months, OS data not yet mature

CAIRO5

Safety

Key Grade ≥3 AEs, %	FOLFOX/FOLFIRI + Bevacizumab (n = 147)	FOLFOXIRI + Bevacizumab (n = 144)	P Value
Any	**59.2**	**75.7**	**0.003**
Neutropenia	12.9	38.2	<0.001
Diarrhea	3.4	19.4	<0.001
Death	0	1.4 (n=2)	

ASCO 2022. Abstr LBA3506.

KEY DATA

CAIRO5

Local Treatment

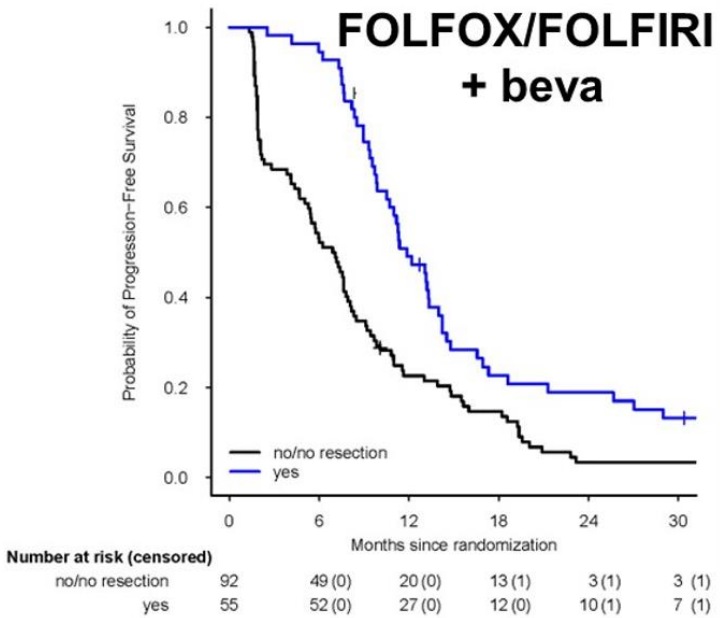
Parameter	FOLFOX/FOLFIRI + Bevacizumab (n = 147)	FOLFOXIRI + Bevacizumab (n = 144)	P Value
Resection with or without ablation, %	46	57	0.08
Postoperative complications, %			
• Any	40	51	0.19
• Grade ≥3 Clavien-Dindo	15	27	0.08
• Death	0	2*	
Median no. of induction cycles, n (range)	7 (4-12)	6 (2-12)	--
Adjuvant chemotherapy, %	38	45	--
Median no. of adjuvant cycles, n (range)	6 (1-8)	4 (1-8)	--
Rate of R0/1 resection ± ablation, %			
• Any	37	51	0.02
• 2-stage surgery ± PVE	16	32	0.04

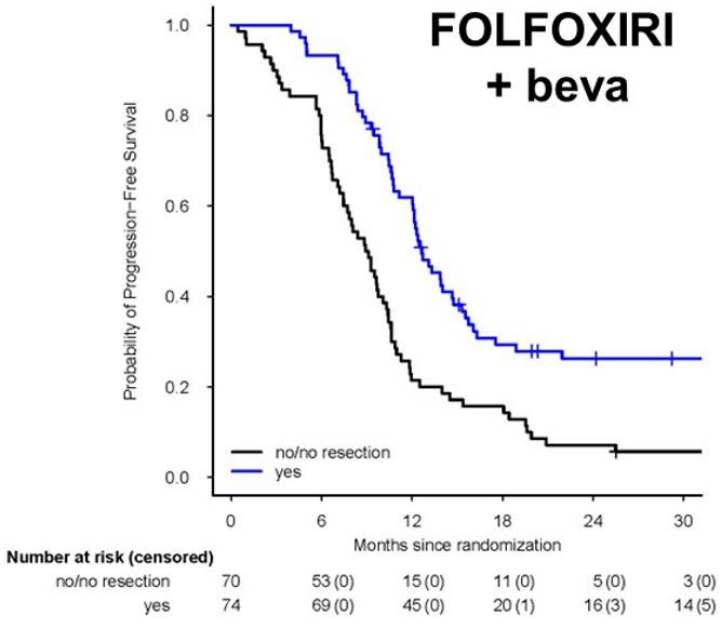
*Total of n=3 patients

CAIRO5

Outcomes of R0/1 resections with or without ablation

Parameter	FOLFOX/FOLFIRI + Bevacizumab			FOLFOXIRI + Bevacizumab		
	Without Successful Local Tx (n = 92)	***With*** Successful Local Tx (n = 55)	HR; P Value	***Without*** Successful Local Tx (n = 70)	***With*** Successful Local Tx (n = 74)	HR; P Value
Median PFS, mo	7.0	11.9	0.49; <0.0001	9.0	12.7	0.43; <0.0001





SUMMARY

CAIRO5

- For patients with initially unresectable colorectal liver metastases and right-sided and/or *RAS/BRAF*^{V600E}-mutated primary tumors triplet versus doublet chemotherapy (plus bevacizumab) significantly improves PFS, ORR, and R0/1 resection with or without ablation rate

- OS data was immature at the time of data cutoff

- Increased toxicity with triplet regimen but manageable

- The utilization of a liver expert panel allows for the selection of an increased number of patients who are eligible for local treatment with curative intent

Liver Expert Panel Outcomes

- 676 CT scans evaluated
- Median turnaround time on CT scans: 6 days (IQR: 4-9)
- 66% rate of consensus on (un)resectability at baseline evaluations
- 41% rate of consensus on (un)resectability at follow-up evaluations

ASCO 2022. Abstr LBA3506.

CAIRO5

Intensification of chemotherapy in combination with bevacizumab provides benefits for patients with unresectable colorectal liver metastases and right-sided and/or RAS/BRAF^{V600E}-mutated primary tumors and should be considered as a treatment option in the front line setting

2022 ASCO Key Studies

Breast Cancer

- DESTINY-Breast04*
- TROPiCS-02
- MAINTAIN
- ABCSG-18
- PALOMA-2
- LUMINA

GI Cancer

- DYNAMIC
- PARADIGM*
- TRIPLETE
- CAIRO5
- PD-1 blockade in MMRd RC

Other Notable Studies

- DETERMINATION*
- ATLAS
- rEECur*
- ECHELON-1
- RELATIVITY-047
- SKYSCRAPER-02

* Plenary Session

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CLINICAL QUESTION

PD-1 blockade in MMRd RC

Does a checkpoint inhibitor provide benefit to patients with mismatch repair deficient locally advanced rectal cancer?

KEY DATA

PD-1 blockade in MMRd RC

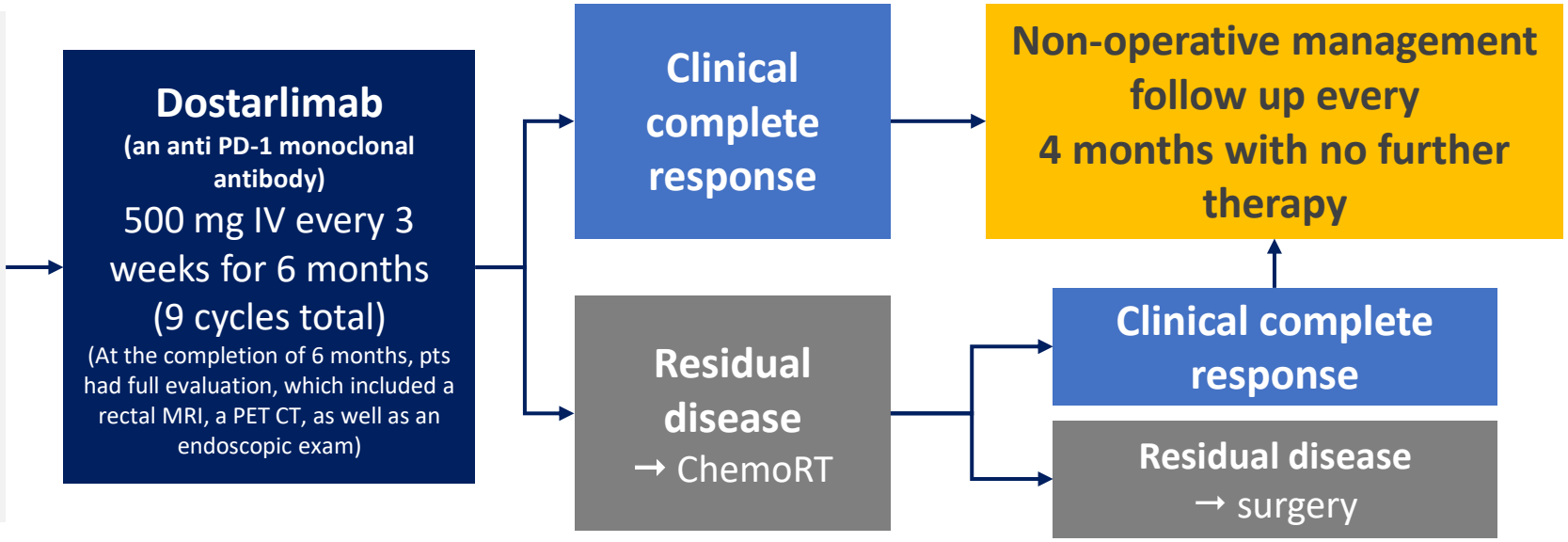
Study Design: Non-randomized, open-label Phase II trial

Simon's two stage minimax design

- Mismatch repair* deficient rectal cancer
- Adenocarcinoma
- Stage II (T3-4, N-) or Stage III (Any T, N+)
- No evidence of distant metastases
- ≥ 18 years old
- ECOG 0-1

(N = 30)

*Immunohistochemistry or microsatellite instability as demonstrated by NGS or PCR



Primary endpoints: ORR* (with or without chemoradiation); pathological complete response (pCR) or clinical complete response** (cCR) at 12 months with or without chemoradiation

Secondary endpoints: safety and tolerability

*Overall response: Rectal MRI and endoscopic exam graded as SD, PR, nCR, and CR

**Clinical complete response (cCR): Endoscopic exam (visual disappearance of the rectal primary, normal digital rectal exam); Rectal MRI, lack of signal at DWI with scar on T2WI (DWI vol=0); each target lymph node must have decreased short axis to <0.5 cm

Statistical considerations:

- The null hypothesis was an ORR less than 25%, which is based on the response to chemo in mismatch repair deficient colon cancer of 7%
- Rejection of the null hypothesis required a response in 11 or more patients

ASCO 2022. Abstr LBA5.

PD-1 blockade in MMRd RC

Baseline Characteristics

Characteristic	n (%)
Age, median (range)	54 (26 – 78)
Sex: male / female	6 (33) / 12 (67)
Race/Ethnicity	
• White non Hispanic	11 (61)
• Hispanic	1 (6)
• Black or African American	3 (17)
• Asian-Far East / Indian Subcontinent	3 (17)
Tumor Staging	
• T1/2	4 (22)
• T3, T4	14 (78)
Nodal Staging	
• Node-positive	17 (94)
• Node-negative	1 (6)
Germline mutation status (n=17)	
• MSH2, MLH1, MSH6, PMS2	10 (59)
• Negative	7 (41)
$BRAF^{V600E}$ WT	18 (100)
Tumor Mutational Burden (mut/Mb, mean (range)	67 (36 – 106)

ASCO 2022. Abstr LBA5.

KEY DATA

PD-1 blockade in MMRd RC

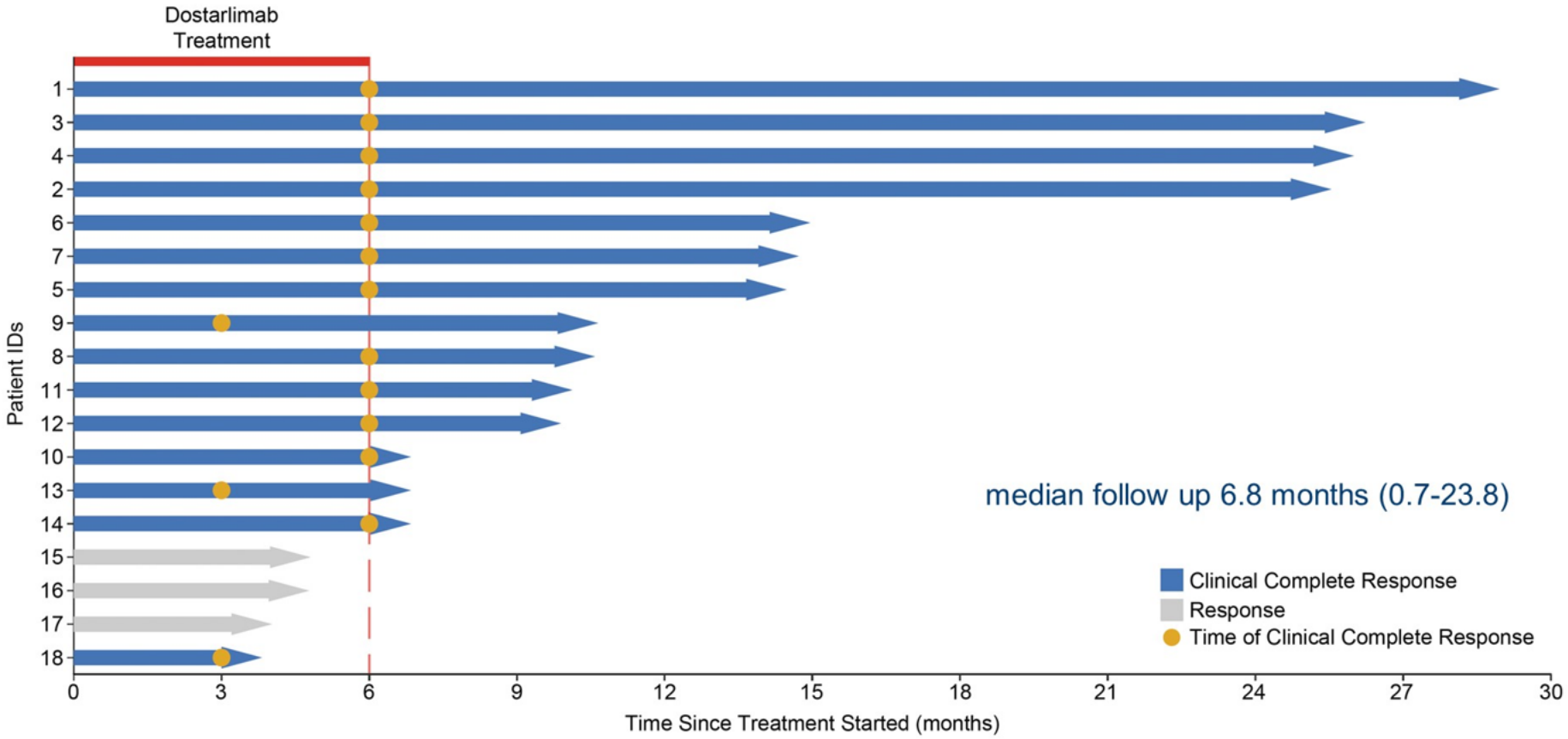
Individual responses to PD-1 blockade with dostarlimab

ID	Age	Stage T	Stage N	Follow up (months)	Digital rectal exam response	Endoscopic best response	Rectal MRI best response	Overall response
1	38	T4	N+	23.8	CR	CR	CR	**cCR**
2	30	T3	N+	20.5	CR	CR	CR	**cCR**
3	61	T1/2	N+	20.6	CR	CR	CR	**cCR**
4	28	T4	N+	20.5	CR	CR	CR	**cCR**
5	53	T1/2	N+	9.1	CR	CR	CR	**cCR**
6	77	T1/2	N+	11.0	CR	CR	CR	**cCR**
7	77	T1/2	N+	8.7	CR	CR	CR	**cCR**
8	55	T3	N+	5.0	CR	CR	CR	**cCR**
9	68	T3	N+	4.9	CR	CR	CR	**cCR**
10	78	T3	N+	1.7	CR	CR	CR	**cCR**
11	5	T3	N+	4.7	CR	CR	CR	**cCR**
12	27	T3	N+	4.4	CR	CR	CR	**cCR**
13	26	T3	N+	0.8	CR	CR	CR	**cCR**
14	43	T3	N+	0.7	CR	CR	CR	**cCR**

ASCO 2022. Abstr LBA5.

PD-1 blockade in MMRd RC

Duration of Response



ASCO 2022. Abstr LBA5.

SUMMARY

PD-1 blockade in MMRd RC

- 100% clinical complete response was achieved in 14 patients
- No patients have required chemotherapy, radiation, or surgery
- No disease recurrence observed during the follow-up period
- No grade 3 or 4 adverse events observed

ASCO 2022. Abstr LBA5.

PD-1 blockade in MMRd RC

Dostarlimab in the front line setting provides a potential curative option for patients with mismatch repair deficient locally advanced rectal cancer without the need for chemotherapy, radiation, or surgery

Small study, more to come…

2022 ASCO Key Studies

Breast Cancer

- DESTINY-Breast04*
- TROPiCS-02
- MAINTAIN
- ABCSG-18
- PALOMA-2
- LUMINA

GI Cancer

- DYNAMIC
- PARADIGM*
- TRIPLETE
- CAIRO5
- PD-1 blockade in MMRd RC

Other Notable Studies
Presented by Dr. Schaefer

- DETERMINATION*
- ATLAS
- rEECur*
- ECHELON-1
- RELATIVITY-047
- SKYSCRAPER-02

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CLINICAL QUESTION

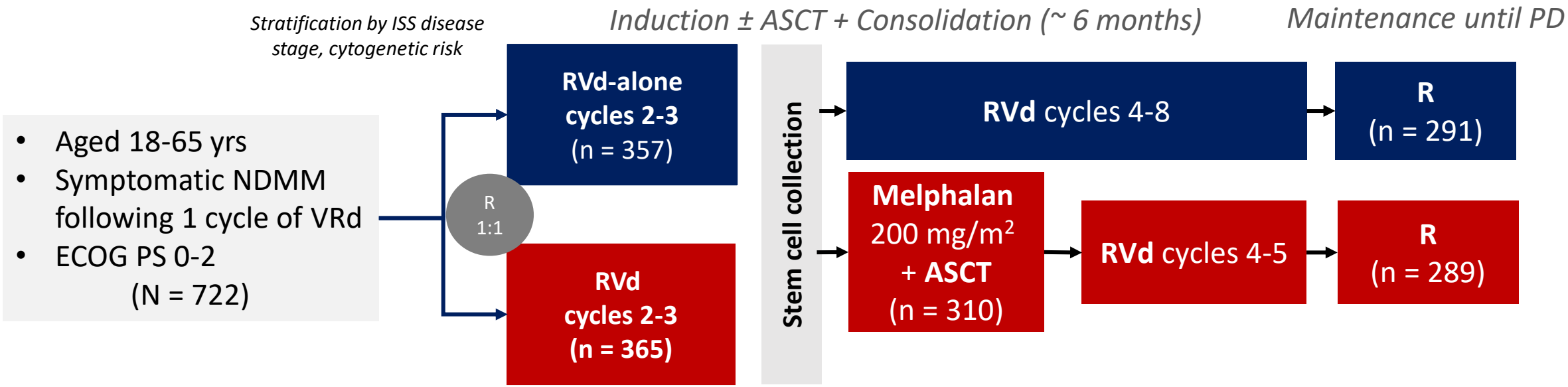
DETERMINATION

Does early ASCT provide benefit for newly diagnosed multiple myeloma patients receiving RVd and lenalidomide maintenance until disease progression?

KEY DATA

DETERMINATION

Study Design: Multicenter, randomized, open-label phase III trial conducted in 56 sites within the United States



RVd in 21-day cycles: R 25 mg/day PO Days 1-14; V 1.3 mg/m2 IV/SC Days 1, 4, 8, 11; Dex 20/10 mg PO Days 1, 2, 4, 5, 8, 9, 11, 12. Lenalidomide (R) maintenance: 10 mg/day during months 1-3, 15 mg/day from months 4 onward.

Primary endpoints: PFS
Key secondary endpoints: OS, response rates, DoR, TTP, QoL, safety

Pts registered between Oct 1, 2010 and Jan 30, 2018
Data cutoff: 12/10/21

DETERMINATION

Baseline Characteristics

Characteristic	RVd Alone (n = 357)	RVd + ASCT (n = 365)
Median age, yr (IQR)	57 (25-66)	55 (30-65)
Male, %	56.6	58.9
Race White/Black/other, %	76.4/18.8/4.8	75.8/18.4/5.8
ECOG PS 0/1/2, %	42.9/49.6/7.6	45.1/44.2/10.7
BMI <25/25 to <30/≥30, %	22.4/39.5/38.1	22.2/34.8/43.0
MM disease type: IgG/IgA/light chain only/other, %	66.7/21.8/10.3/1.2	59.3/28.2/12.2/0.3
ISS disease stage: I/II/III, %	49.9/36.4/13.7	50.4/36.7/12.9
Elevated LDH (≥225 U/L), %	27.0	25.4
Cytogenetics: high risk*/standard risk, %	19.8/80.2	19.4/80.6
Cytogenetics: t(4;14)/t(14;16)/del 17p, %	9.6/3.0/11.4	8.2/4.4/10.0
Revised ISS disease stage†: I/II/III, %	30.9/60.7/8.4	31.2/62.6/6.2

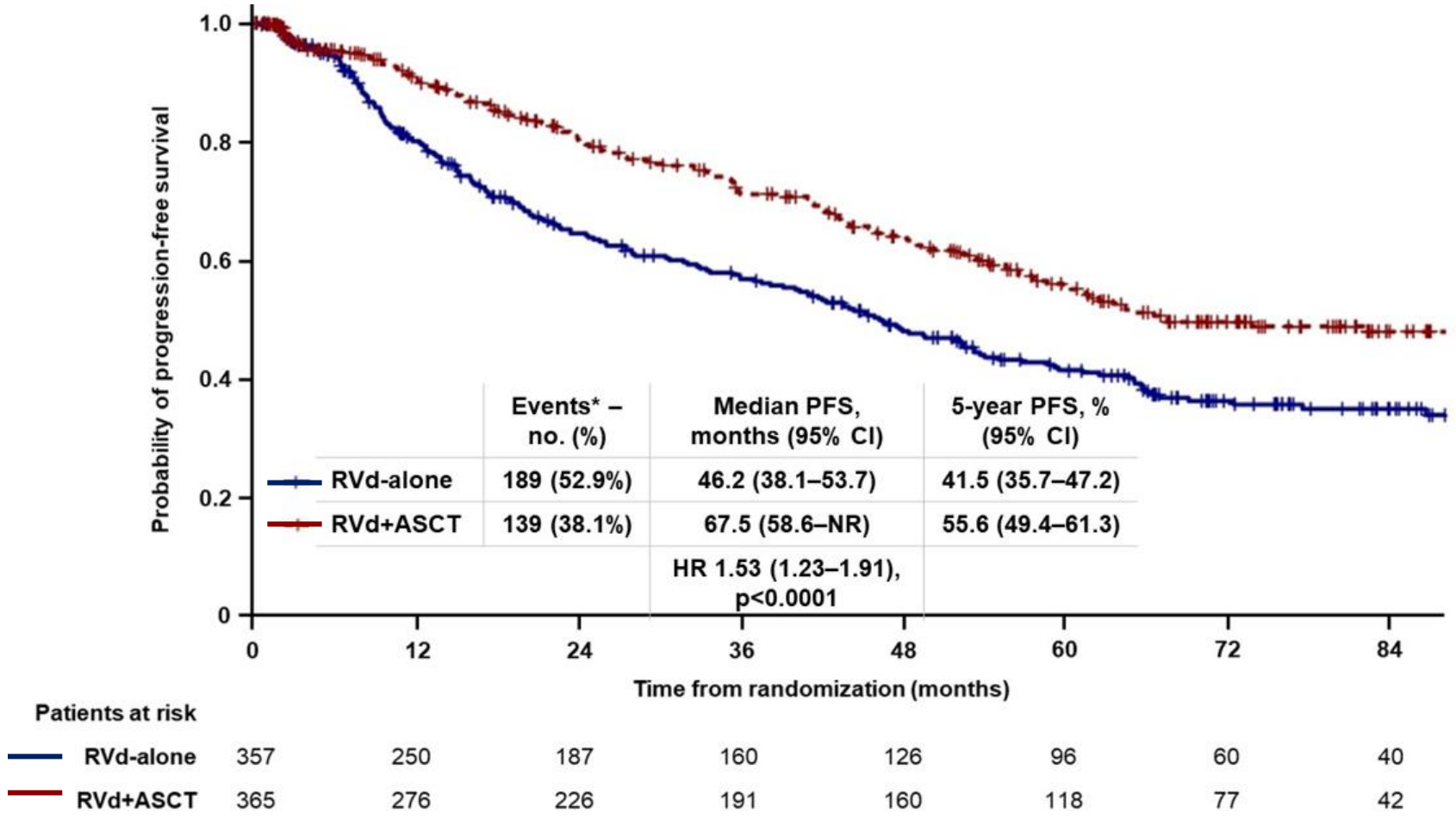
*Includes t(4;14), t(14;16), and del 17p.

†Classified using ≥225 U/L cutoff for elevated LDH.

KEY DATA

DETERMINATION

Primary Endpoint: PFS

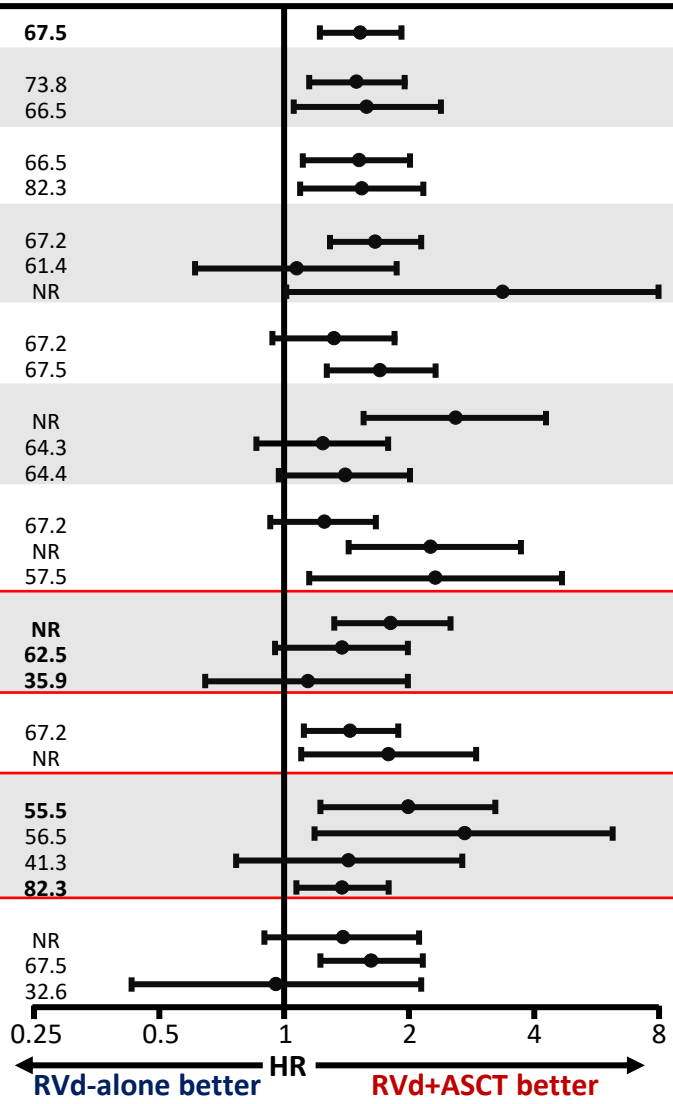


Median follow-up: 76 mo

KEY DATA

DETERMINATION

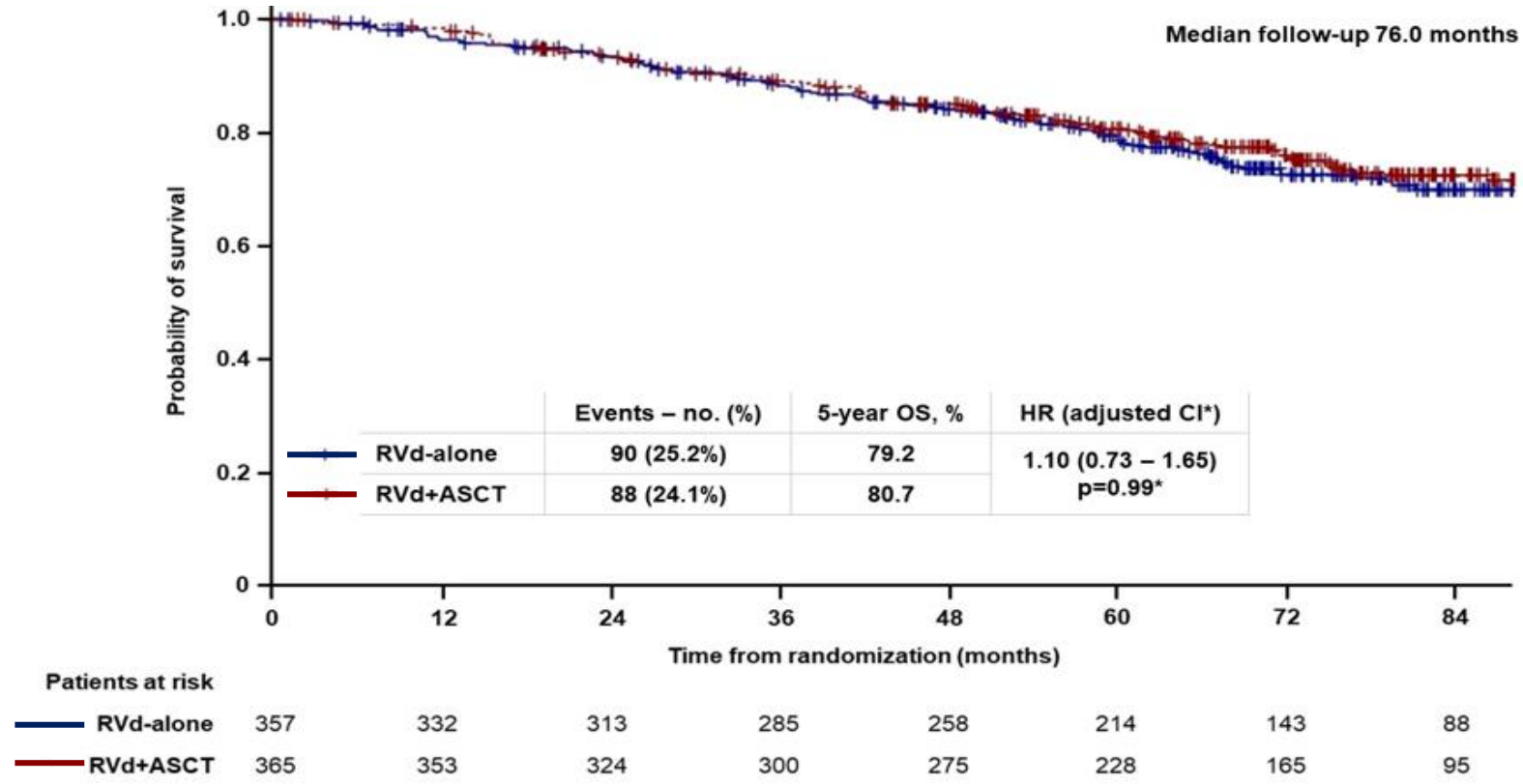
Subgroup analysis for progression-free survival	Median, months				HR	
	RVd-alone	RVd-ASCT	RVd-alone	RVd-ASCT		
All patients, ITT analysis	189/357	139/365	**46.2**	**67.5**	**1.53**	**(1.23-1.91)**
Age						
< 60 years	122/235	100/283	46.2	73.8	1.49	(1.14-1.95)
≥ 60 years	67/122	39/102	46.5	66.5	1.59	(1.05-2.40)
Sex						
Male	107/202	81/215	47.4	66.5	1.50	(1.11-2.02)
Female	82/155	58/150	45.3	82.3	1.54	(1.09-2.17)
Race						
White/Caucasian	150/268	104/272	44.3	67.2	1.67	(1.29-2.15)
Black/African American	24/66	24/66	NR	61.4	1.07	(0.61-1.89)
Other	12/17	5/21	38.1	NR	3.40	(1.00-11.5)
ECOG performance status						
0	75/153	54/164	56.7	67.2	1.32	(0.94-1.85)
1-2	113/204	75/200	37.5	67.5	1.72	(1.28-2.32)
Body mass index						
< 25	49/80	25/81	33.6	NR	2.60	(1.56-4.31)
25 to < 30	71/141	54/127	52.3	64.3	1.24	(0.86-1.80)
≥ 30	69/136	61/157	45.8	64.4	1.41	(0.98-2.02)
Myeloma type						
IgG	108/220	80/200	53.3	67.2	1.25	(0.93-1.67)
IgA	43/72	33/95	46.5	NR	2.31	(1.43-3.74)
Light chain	21/34	16/41	23.3	57.5	2.33	(1.14-4.74)
ISS stage						
I	**89/178**	**62/184**	**52.0**	**NR**	**1.83**	**(1.32-2.54)**
II	**69/130**	**56/134**	**46.2**	**62.5**	**1.38**	**(0.96-1.96)**
III	**31/49**	**21/47**	**40.3**	**35.9**	**1.14**	**(0.64-2.01)**
Lactate dehydrogenase level						
Not elevated (< 225 U/L)	132/260	106/270	47.7	67.2	1.45	(1.12-1.88)
Elevated (≥ 225 U/L)	58/96	31/92	41.1	NR	1.77	(1.09-2.88)
FISH cytogenetics						
High risk	**37/66**	**28/68**	**17.1**	**55.5**	**1.99**	**(1.21-3.26)**
b (4, 14)	18/32	11/28	19.8	56.5	2.72	(1.19-6.24)
Del (17p)	22/38	18/34	16.3	41.3	1.44	(0.79-2.73)
Standard risk	**135/268**	**103/274**	**53.2**	**82.3**	**1.38**	**(1.07-1.79)**
Revised-ISS stage						
I	45/103	39/105	59.1	NR	1.38	(0.90-2.12)
II	109/202	78/211	40.9	67.5	1.63	(1.22-2.19)
III	17/28	11/21	22.2	32.6	0.96	(0.43-2.13)



Indicates stratification factors

DETERMINATION

Overall Survival



*CI and P value adjusted using Bonferroni correction to control for overall family-wise error rate for secondary outcomes.

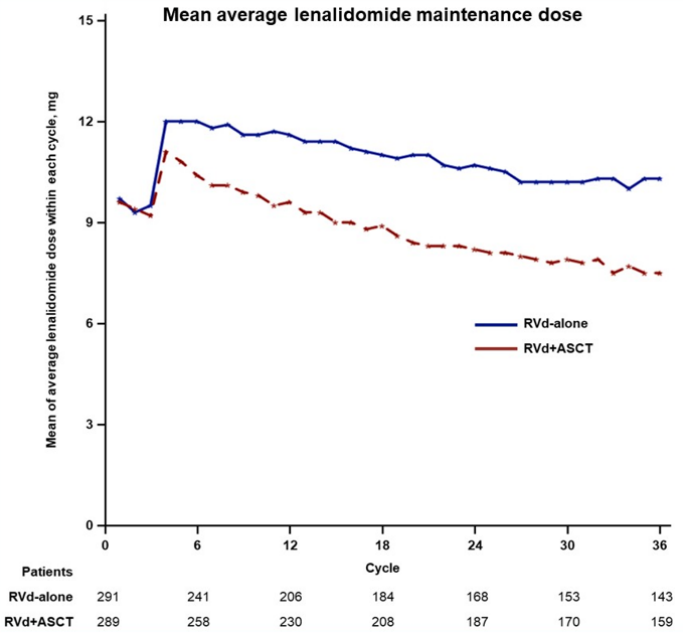
DETERMINATION

Response and Duration of Response

Efficacy Endpoint	VRd Alone (n = 357)	VRd + ASCT (n = 365)	HR (95% CI)	P Value
Best overall response, %				
• ≥ CR	42.0	46.8	--	0.99*
• ≥ VGPR	79.6	82.7	--	0.99*
• ≥ PR	95.0	97.5	--	0.55*
Median duration of ≥ PR, mo	**38.9**	**56.4**	**1.45 (1.09-1.93)**	**0.003**
5-year duration of ≥ CR, %	52.9	60.6	1.35 (0.83-2.22)	0.7

*Calculated with Fisher exact test.

- Median duration of treatment with RVd alone vs RVd + ASCT
  - All treatment: 28.2 vs 36.1 months
  - Lenalidomide maintenance: 36.4 vs 41.5 months
- Median proportion of maintenance cycles with average lenalidomide dose ≥ 10 mg
  - 87% vs 60%



DETERMINATION

Safety

Grade ≥3 TRAEs (All Treatment), %	RVd Alone (n = 357)	RVd + ASCT (n = 365)
Any	78.2	94.2
• Any hematologic	60.5	89.9
• **Any grade 5***	**0.3**	**1.6**
Neutropenia	42.6	86.3
Thrombocytopenia	**19.9**	**82.7**
Leukopenia	19.6	39.7
Anemia	18.2	29.6
Lymphopenia	9.0	10.1
Febrile neutropenia	4.2	9.0
Diarrhea	3.9	4.9
Nausea	0.6	6.6
Mucositis oral	0	5.2
Fatigue	2.8	6.0
Fever	2.0	5.2
Pneumonia	5.0	9.0
Hypophosphatemia	9.5	8.2
Neuropathy	5.6	7.1

- All grade ≥3 TRAEs, and hematologic grade ≥3 TRAEs, significantly more frequent with RVd + ASCT vs RVd alone (both *P* <.001)
- Rates of hematologic grade ≥3 TRAEs during maintenance:
  - 26.1% with RVd alone vs 41.9% RVd + ASCT
- Rates of related SAEs with RVd alone vs RVd + ASCT
  - Prior to maintenance: 40.3% vs 47.1%
  - During maintenance: 11.3% vs 16.6%

*Treatment-related grade 5 events: 1 in RVd alone (CV collapse) and 5 in RVd + ASCT (stroke, endocarditis, necrotizing fasciitis, sepsis, respiratory failure).

DETERMINATION

Secondary Primary Malignancies

SPMs, %	RVd Alone (n = 357)		RVd + ASCT (n = 365)
Overall incidence			
• Any	10.4		10.7
• Any invasive	5.3		6.8
• Any hematologic	2.5		3.6
• ALL, n	7		3
• **AML/MDS, n**	**0**	***P*= 0.002**	**10**
• CLL/CML, n	2		0
• Any solid tumor	3.4		3.3
• Any non-invasive solid tumor	0		0.5
• Any non-melanoma skin cancer	5.9		4.1
5-yr cumulative incidence			
• Any	9.7		10.8
• Invasive	4.9		6.5
• **Hematologic**	**1.6**	***P*= 0.316**	**3.5**

SUMMARY

DETERMINATION

- RVd in combination with ASCT provides significantly greater PFS compared to RVd alone demonstrating tolerability and clinical benefit of long term lenalidomide maintenance
  - 67.5 vs 46.2 months
- No OS benefit observed after median follow-up of > 6 years
  - 5-yr OS rate: 80.7% vs 79.2%
- Similar ORR and rates of ≥VGPR and ≥CR observed
- Addition of ASCT to RVd was tolerable but higher incidence of AEs observed

ASCO 2022. Abstr LBA4.

DETERMINATION

The addition of early ASCT provides PFS benefit in the first line setting and can be considered a treatment option for these patients

Heightened toxicity with the addition of ASCT should be considered during patient selection

2022 ASCO Key Studies

Breast Cancer

- DESTINY-Breast04*
- TROPiCS-02
- MAINTAIN
- ABCSG-18
- PALOMA-2
- LUMINA

GI Cancer

- DYNAMIC
- PARADIGM*
- TRIPLETE
- CAIRO5
- PD-1 blockade in MMRd RC

Other Notable Studies

- DETERMINATION*
- ATLAS
- rEECur*
- ECHELON-1
- RELATIVITY-047
- SKYSCRAPER-02

* Plenary Session

cornerstone specialty network™

ATLAS

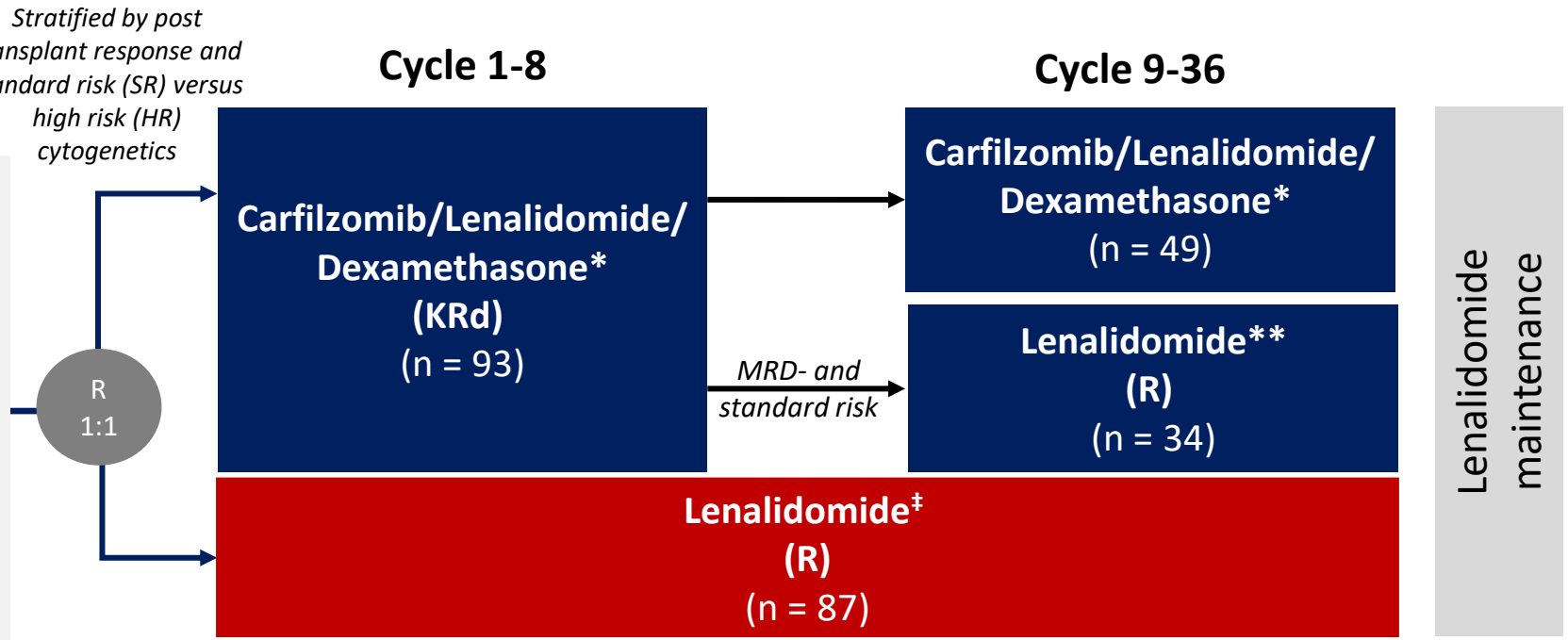
Does carfilzomib, lenalidomide, and dexamethasone compared to lenalidomide alone as maintenance after ASCT benefit patients with newly diagnosed multiple myeloma?

ATLAS

Study Design: Multicenter, randomized, open-label phase III trial

- Patients with NDMM who received induction therapy for ≤12 months
- Achieved at least SD within 100 days ASCT
- ≤ 2 induction regimens
- ≤2 months post diagnosis

(N = 180)



*Carfilzomib 36 mg/m2 Days 1,2,8,9,15,16 (cycles 1-4), then Days 1,2,15,16 (cycle 5+); lenalidomide 25 mg Days 1-21; dexamethasone 20 mg Days 1,8,15,22. ‡Lenalidomide 10 mg in cycle s1-3, 15 mg cycle 4+ if tolerated, on Days 1-28

**KRd patients with SR cytogenetics having reached IMWG MRD, (International Myeloma Working Group Measurable Residual Disease) negativity after cycle 6 converted to R alone after cycle 8

Primary endpoint: PFS from randomization

Secondary endpoints: MRD at cycles 6 and 12, ORR, VGPR, CR, sCR, safety

ASCO 2022. Abstr 8001.

ATLAS

Baseline Characteristics

Characteristic	KRd (n = 92)	Lenalidomide (n = 86)
Median age, yr (range)	57 (32-70)	59 (34-71)
Female, n (%)	46 (50)	35 (41)
ECOG PS 1, n (%)	47 (52)	54 (63)
ISS at diagnosis, n (%) • 1 | 2 | 3	39 (42) | 38 (41) | 15 (16)	28 (32) | 41 (48) | 17 (20)
≥VGPR at study entry, n (%)	**81 (88)**	**79 (92)**
High-risk cytogenetics, n (%)	**21 (23)**	**18 (21)**
Median time from HSCT, days	92	94.5
Induction regimen, n (%) • **VTD** • VCD • Other*	 **63 (68)** 14 (15) 15 (16)	 **52 (60)** 17 (20) 17 (20)
Previous lenalidomide, n (%)	10 (11)	11 (13)
Previous carfilzomib, n (%)	4 (4)	5 (6)
2 induction regimens, n (%)	7 (8)	5 (6)

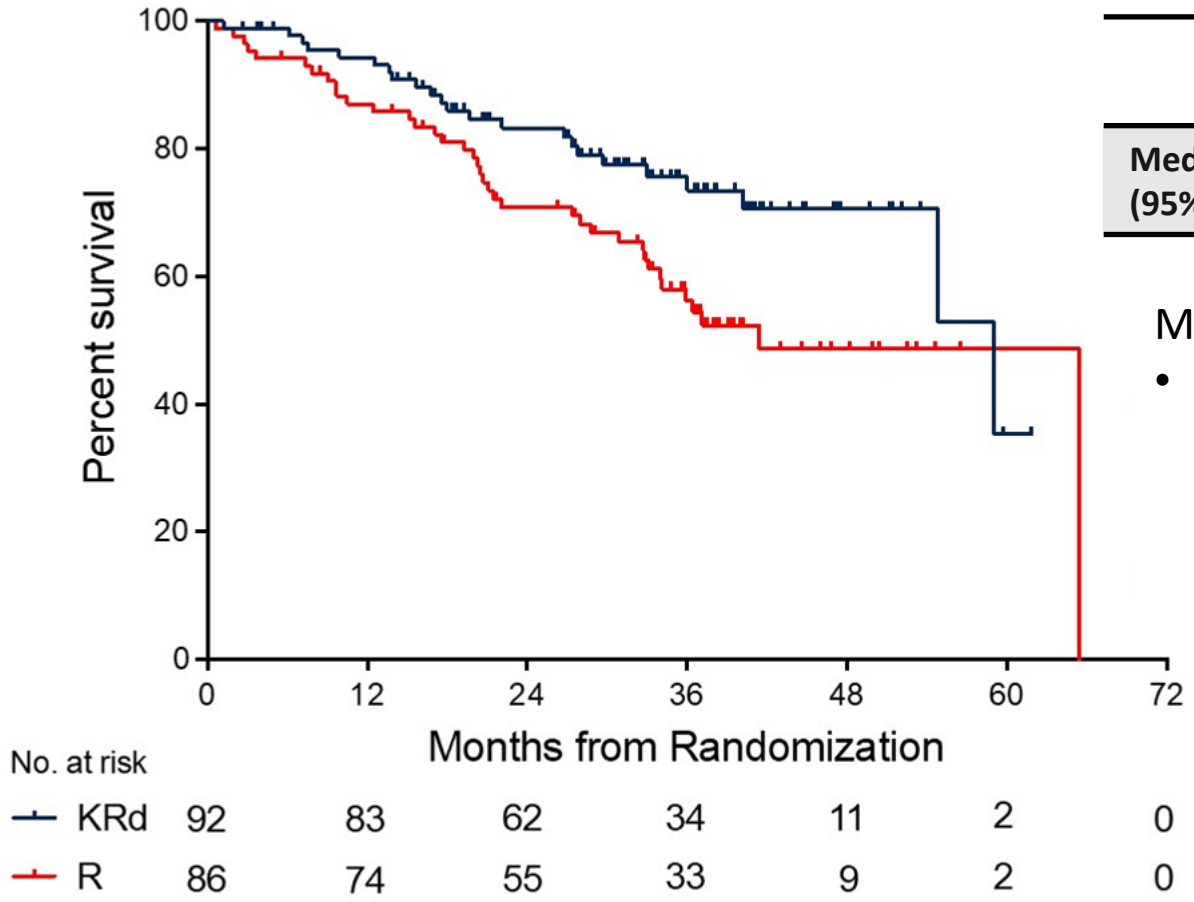
*del13, t(4:14), t(14:16), del17p, hypodiploidy, #KRd, Vd, VTD-PACE, PAD, VRd

VCD, bortezomib/cyclophosphamide/dexamethasone; VTD, bortezomib/thalidomide/dexamethasone.

ASCO 2022. Abstr 8001.

ATLAS

Progression-Free Survival



	KRd (n = 92)	Lenalidomide (n = 86)	HR (95% CI)	P Value
Median PFS, mo (95% CI)	**59.0** (52.5-NR)	**41.1** (33.4-65.4)	**0.56** (0.34-0.93)	**0.026**

Median follow-up: 33.8 months

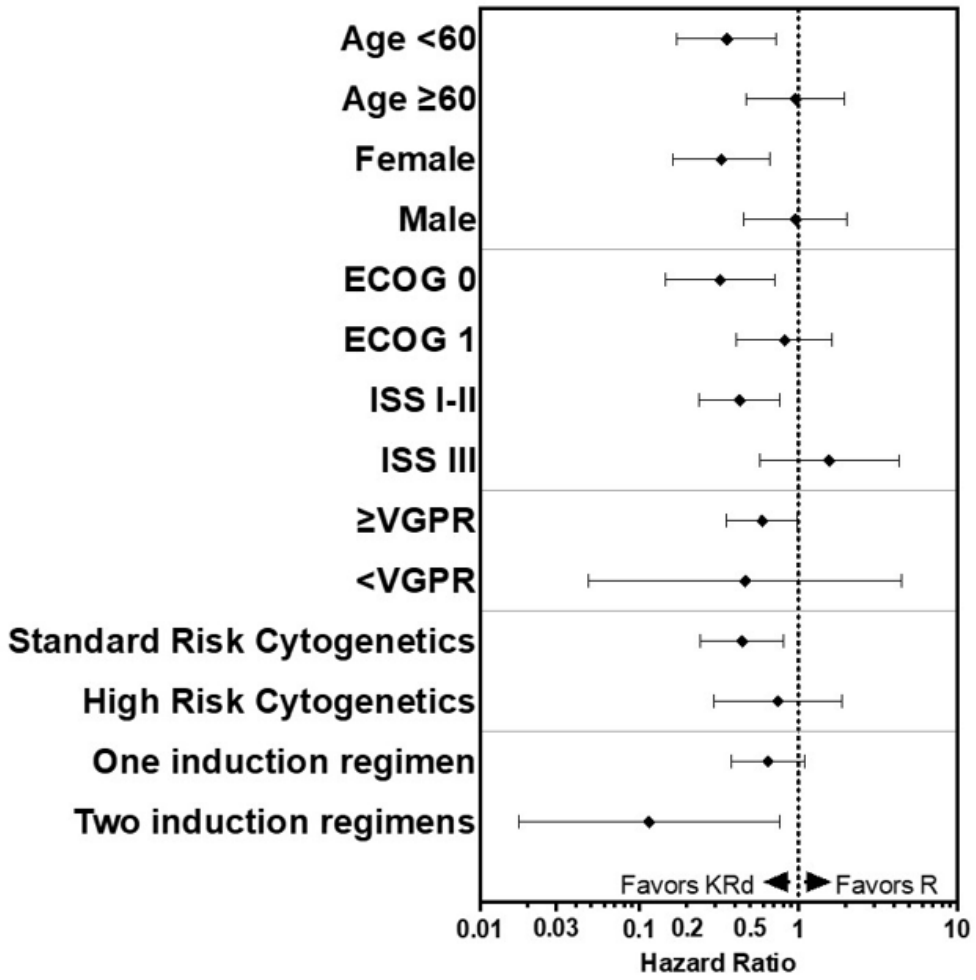
- 61 PFS events
  - 23 in the KRd arm
  - 38 in the R arm

Interim analysis, conducted at 60% of PFS events for primary analysis, for which the p-value criterion for significance (P=0.05) was not adjusted for the interim nature of the comparison. Patients will be followed up until the primary analysis which will be adjusted accordingly.

ASCO 2022. Abstr 8001.

ATLAS

Progression-Free Survival: subgroup analysis



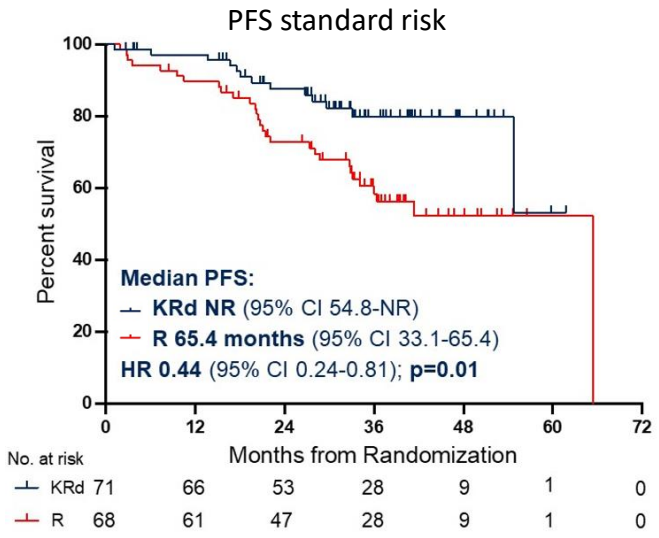
	KRd		R		HR
	Events	n=	Events	n=	(KRd/R)
Age <60	9	55	21	46	0.36 (0.17-0.73)
Age ≥60	14	37	17	40	0.96 (0.47-1.95)
Female	11	49	22	35	0.33 (0.17-0.66)
Male	12	43	16	51	0.96 (0.46-2.03)
ECOG 0	11	44	17	32	0.32 (0.15-0.71)
ECOG 1	12	48	21	54	0.82 (0.41-1.64)
ISS I-II	13	74	27	64	0.41 (0.22-0.76)
ISS III	8	13	8	17	1.95 (0.69-5.49)
≥VGPR	22	81	36	79	0.59 (0.35-0.99)
<VGPR	1	11	2	7	0.46 (0.05-4.46)
Standard Risk Cytogenetics	13	71	29	68	0.44 (0.24-0.81)
High Risk Cytogenetics	10	21	9	18	0.74 (0.30-1.86)
One induction regimen	19	72	27	66	0.72 (0.40-1.28)
Two induction regimens	4	20	11	20	0.26 (0.09-0.74)

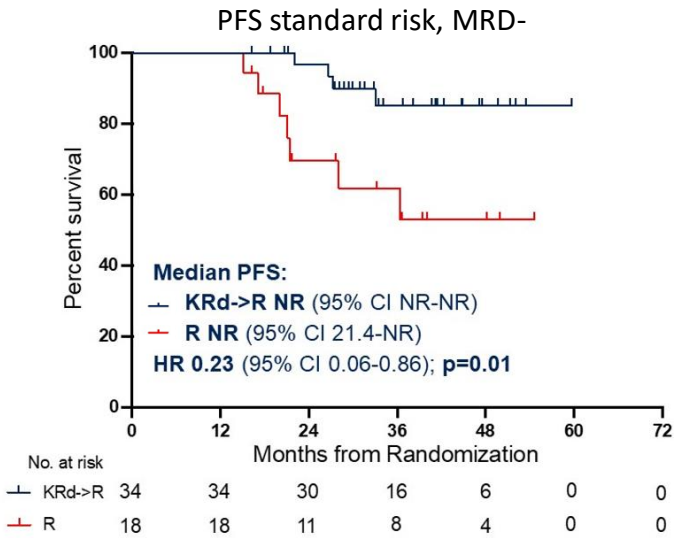
In some subsets # of events remains low

Efficacy with MRD-directed risk adapted maintenance

	Patients With Standard-Risk Cytogenetics (n = 139)			
	KRd (n = 71)	Lenalidomide (n = 68)	HR (95% CI)	P Value
MRD at cycle 6*				
• By IMWG	44	27		0.027
• By NGS (10^{-5})	50	33		0.07
• By NGS (10^{-6})	33	24		0.25
MRD by IMWG at cycle 6 in standard risk, %	**44**	**26**		**0.05**
Median PFS, mo (95% CI)				
• Standard risk	NR (54.8-NR)	65.4 (33.1-65.4)	**0.44** (0.24-0.81)	0.01
• MRD negative and standard risk**	NR (NR-NR)	NR (21.4-NR)	**0.23** (0.06-0.86)	0.01

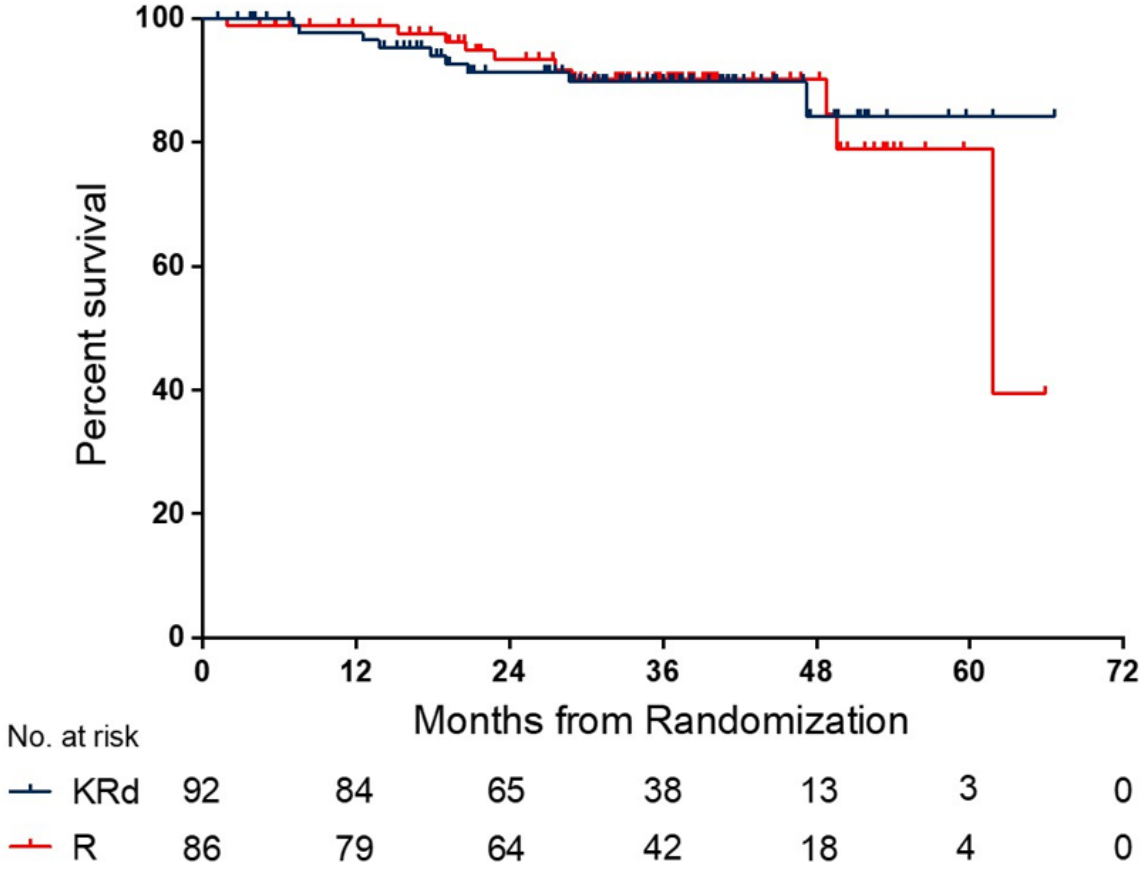
- *MRD by IMWG: minimum sensitivity ≥10^{-5} by NGS and if not available by multiparametric flow cytometry (MFC), ≥ CR (n = 90 for KRd, n = 84 for lenalidomide).
  MRD by NGS: using clonoSEQ, LoD 6.8 x 10^{-7} with input of 20 µg DNA (n = 66 for KRd, n = 63 for lenalidomide)
- **KRd followed by lenalidomide: n = 34; lenalidomide: n = 18.





ATLAS

Overall Survival



	KRd (N = 92)	Lenalidomide (N = 86)	HR (95% CI)	P Value
Median OS, mo (95% CI)	**NR (NR-NR)**	**61.8 (61.8-NR)**	**0.92 (0.37-2.26)**	**0.86**
Deaths, n/N (%)	9/92 (9.8)	11/86 (12.8)		

ASCO 2022. Abstr 8001.

ATLAS

Safety

Grade ≥3 Hematologic AEs, n (%)	KRd (n = 92)	Lenalidomide (n = 86)
Neutropenia	**44 (48)**	**51 (59)**
Febrile neutropenia	4 (4)	5 (6)
Thrombocytopenia	12 (13)	6 (7)
Lymphopenia	7 (8)	2 (2)
Anemia	4 (4)	0 (0)
Grade ≥3 AEs of Interest, n (%)		
Cardiovascular	4 (4)	5 (6)
Infection	**14 (15)**	**5 (6)**
Secondary malignancy	2 (2)	2 (2)
Treatment related death	1 (1)	0 (0)

Grade ≥3 Other AEs, n (%)	KRd (n = 92)	Lenalidomide (n = 86)
Elevated liver enzymes	5 (5)	0 (0)
Hyperglycemia	2 (2)	0 (0)
Diarrhea	1 (1)	2 (2)
Neurological	1 (1)	2 (2)
Rash	1 (1)	2 (2)
Dental	1 (1)	1 (1)
Flu-like symptoms	1 (1)	1 (1)
Hypokalemia	1 (1)	1 (1)
Cataract	1 (1)	1 (1)

ASCO 2022. Abstr 8001.

SUMMARY

ATLAS

- Interim analysis of KRd post ASCT results in significantly greater improvement in PFS compared to lenalidomide maintenance alone with a 44% reduction in risk of death or progression
  - Median PFS: 59.0 vs 41.1 months; HR: 0.56 (95% CI: 0.34-0.93); *P* = 0.026
- MRD-directed, risk-adapted KRd maintenance may a be more effective alternative to lenalidomide maintenance
- All-grade toxicities experienced in each arm were comparable with no new safety concerns

ASCO 2022. Abstr 8001.

ATLAS

Extended use of KRd therapy post ASCT provides benefit to patients with newly diagnosed multiple myeloma

MRD-directed risk adapted maintenance may represent a new standard of care

2022 ASCO Key Studies

Breast Cancer

- DESTINY-Breast04*
- TROPiCS-02
- MAINTAIN
- ABCSG-18
- PALOMA-2
- LUMINA

GI Cancer

- DYNAMIC
- PARADIGM*
- TRIPLETE
- CAIRO5
- PD-1 blockade in MMRd RC

Other Notable Studies

- DETERMINATION*
- ATLAS
- rEECur*
- ECHELON-1
- RELATIVITY-047
- SKYSCRAPER-02

* Plenary Session

cornerstone specialty network™

rEECur

Does topotecan and cyclophosphamide or high-dose ifosfamide provide benefit for patients with recurrent and primary refractory Ewing sarcoma (RR-ES)?

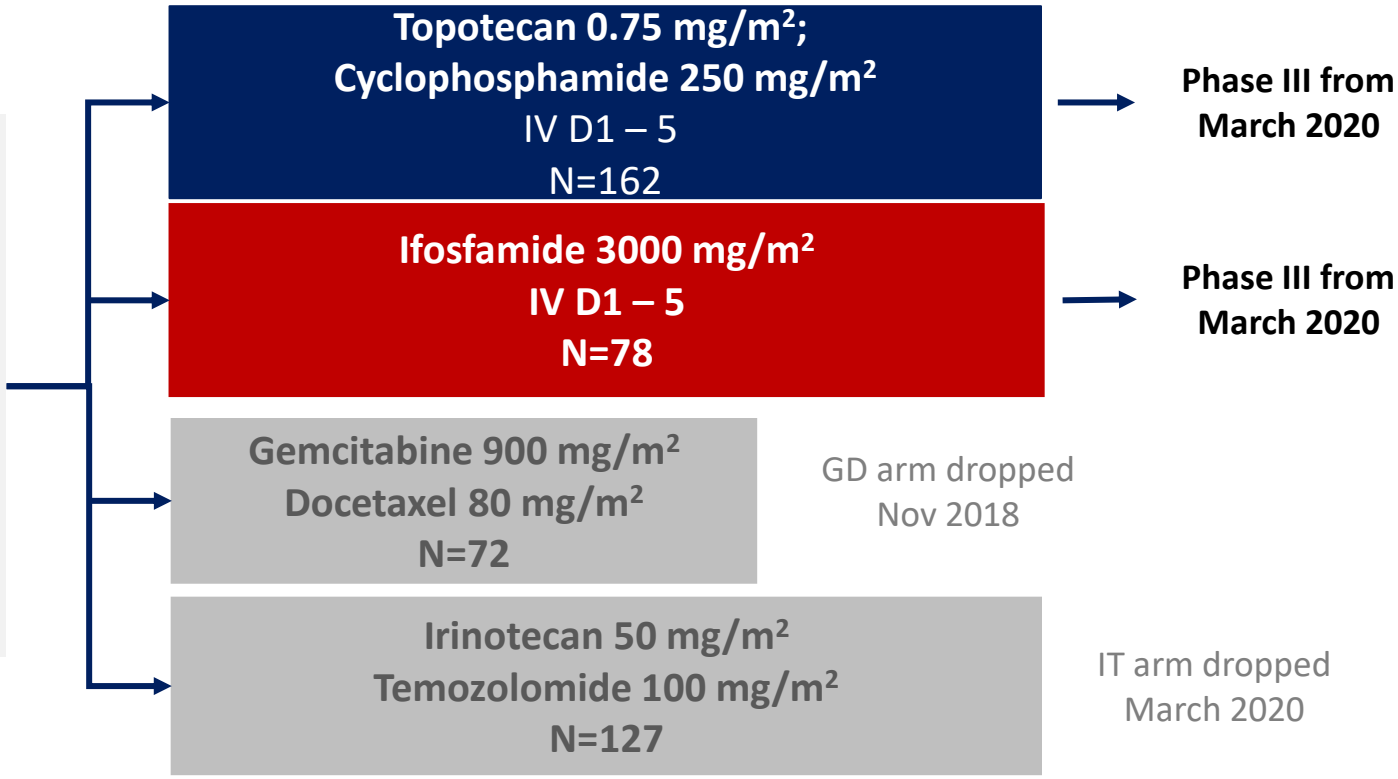
KEY DATA

rEECur

Study Design: Multi-arm, multi-stage (MAMS) phase II / III *"drop-a-loser"* randomized trial

- Aged 4 – 50 yrs
- Histologically proven Ewing sarcoma at initial diagnosis or recurrence
- Progression during or after 1L treatment
- Medically fit to receive trial treatment
- No RT to target lesion within 6 weeks
- No cytotoxic chemo within 2 weeks
- Myeloablative therapy within 8 weeks

(N = 439)



Primary endpoints: EFS

Key secondary endpoints: RECIST 1.1 response C 2, 4, 6, EoT; toxicity per CTCAE v4; PFS; OS; QoL; Days in hospital; PETCT response after cycle 4

ASCO 2022. Abstr LBA2.

rEECur

Baseline Characteristics

Whole cohort*		TC (N=162)	IFOS (N=78)	OVERALL (N=439)
Sex	Male	64%	63%	284 (65%)
	Female	36%	37%	155 (35%)
Age	Median (range)	20 (4 – 49)	19 (6 – 48)	19 (4 – 49)
	Pre-pubertal	12%	10%	49 (11%)
Pubertal stage	Peri-pubertal	12%	21%	65 (15%)
	Post-pubertal	69%	65%	301 (69%)
Prior Ofosfamide		94%	91%	92%
Prior Cyclophosphamide		58%	59%	58%
PS 0/1 (WHO) or ≥ 70% (Lansky)		85%	77%	79%

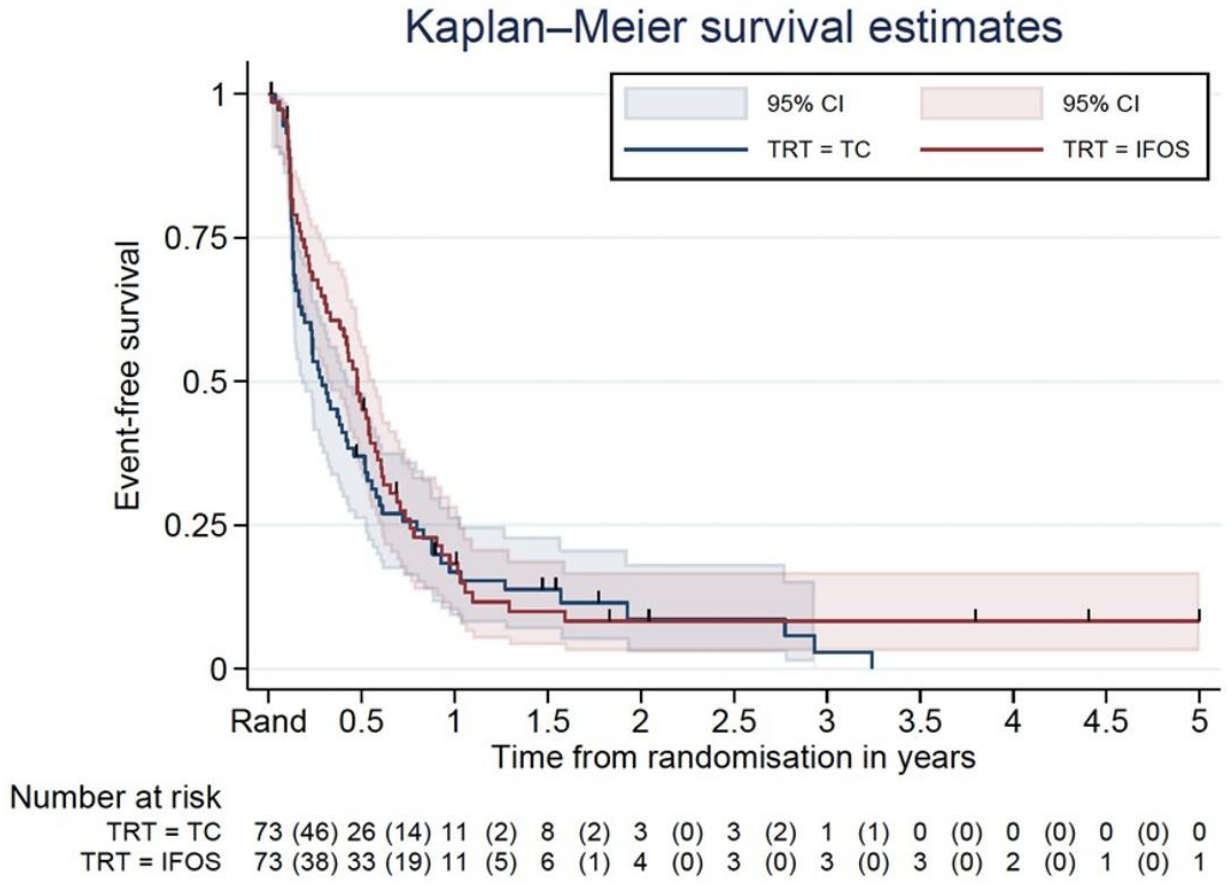
*Not shown, GD arm: N=72; IT arm: N=127

Phase III cohort only		TC (N=73)	IFOS (N=73)	OVERALL (N=146)
Disease Type	• Primary refractory	19%	15%	69 (17%)
	• 1st recurrence less than 2 yrs	51%	53%	180 (52%)
	• 1st recurrence ≥ 2yrs	14%	15%	55 (14%)
	• 2nd or subsequent recurrence	16%	16%	51 (16%)
Disease Sites	• Local progression only	12%	14%	56 (13%)
	• Pleuropulmonary metastases	34%	36%	114 (35%)
	• Other metastatic disease	53%	51%	185 (52%)
Measurable Disease	• Yes	86%	84%	310 (85%)
	• No	14%	16%	45 (15%)

83% in first progression

rEECur

Primary Endpoint: EFS by treatment group



Note: Small n's beyond ~6 months

1st Event	TC	IFOS	Overall
No Events	6 (8%)	10 (14%)	16 (11%)
Events	67 (92%)	63 (86%)	130 (89%)
Total	73	73	146

Median survival

- TC: **3.5** months (95% CI 2.1-5.1)
- IFOS: **5.7** months (95% CI 3.8-6.9)

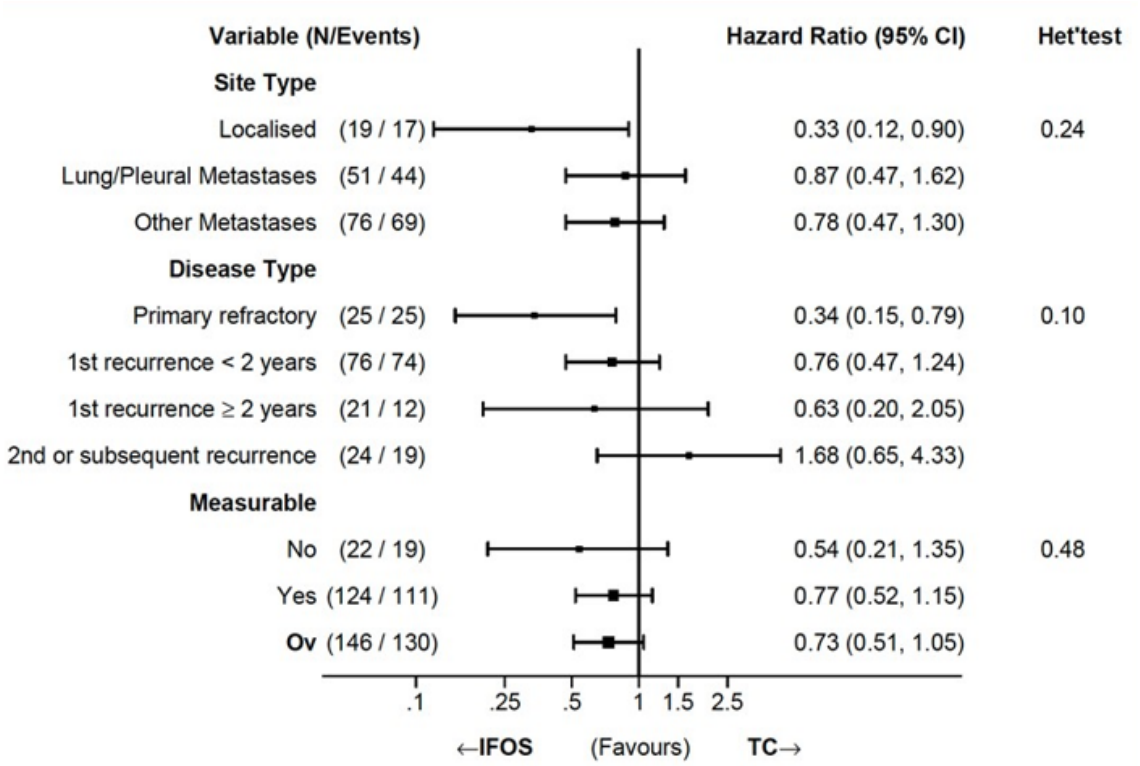
HR 0.73 (95% CrI: 0.51-1.05)

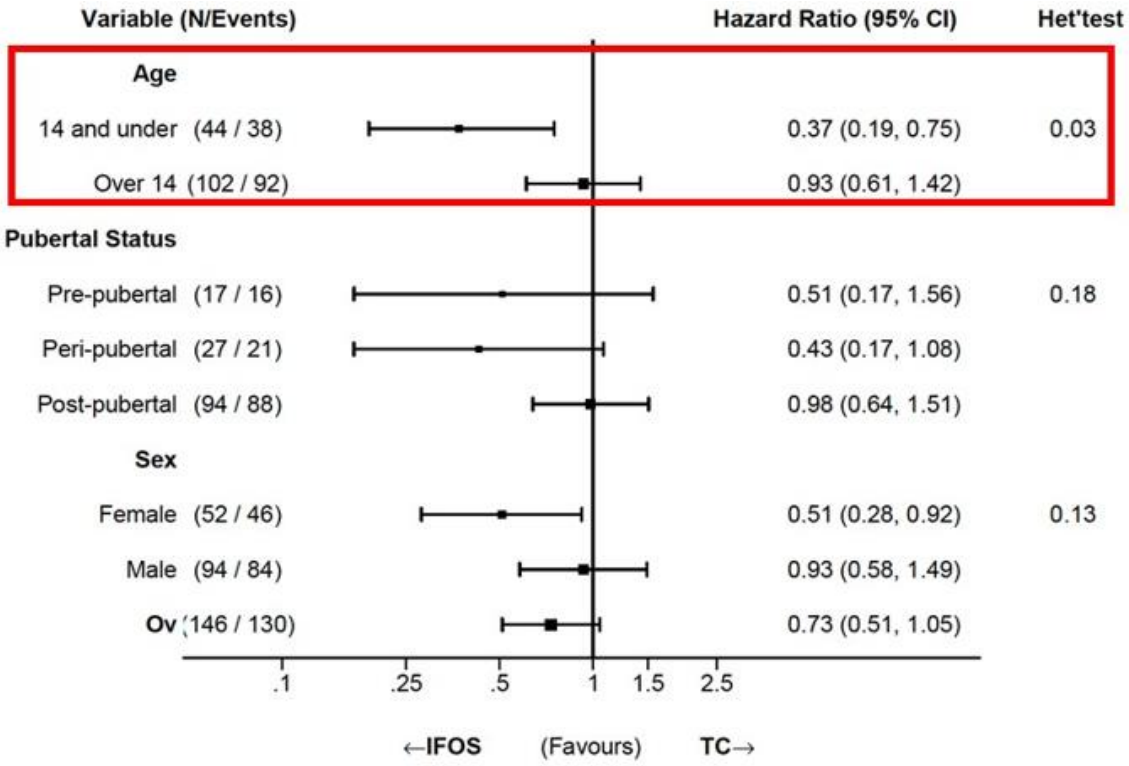
6-month survival

- TC: 37% (95% CI 26%-48%)
- IFOS: 47% (95% CI 35%-58%)

rEECur

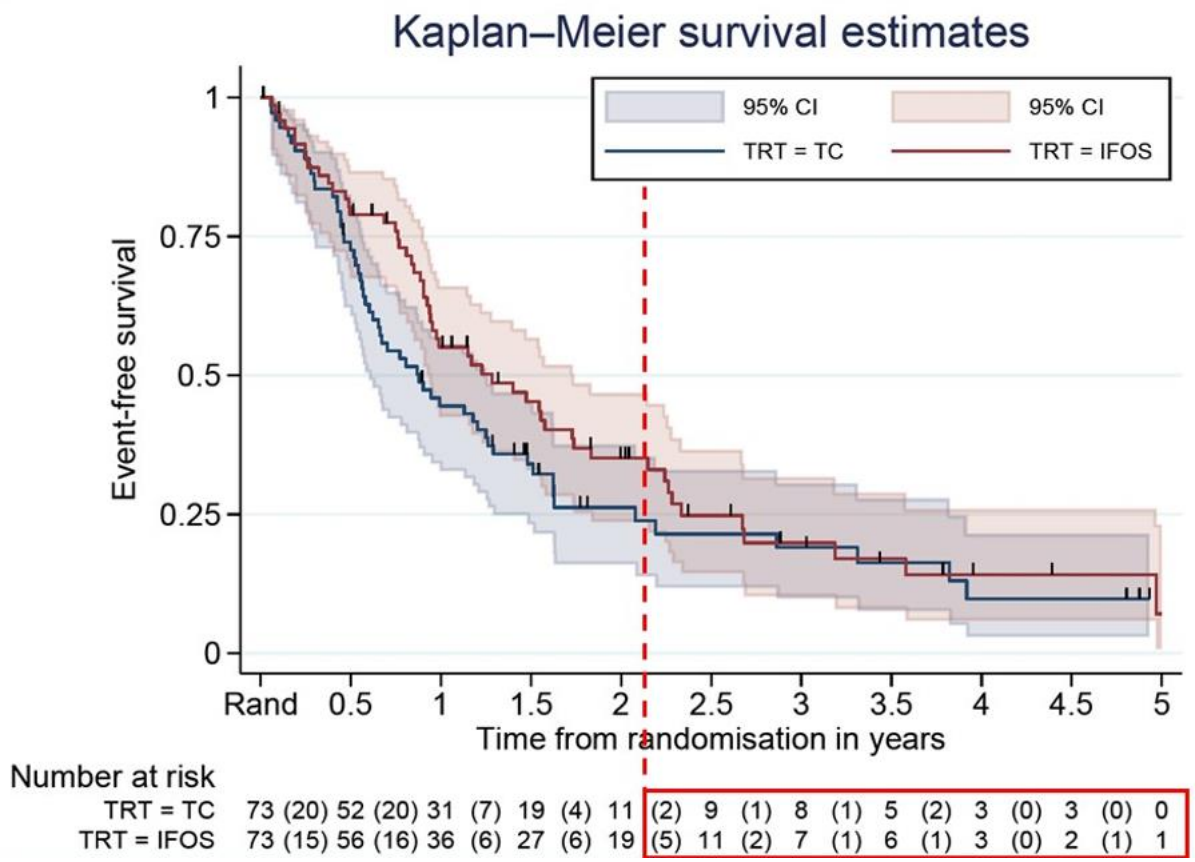
Primary Endpoint: EFS by treatment group





rEECur

OS by treatment group



Note: Small n's beyond ~2 years

Vital Status	TC	IFOS	Overall
Alive	16 (22%)	20 (27%)	36 (25%)
Dead	57 (78%)	53 (73%)	110 (75%)
Total	73	73	146

Median survival

- TC: 10.5 months (95% CI: 7.2-15.0)
- IFOS: 15.4 months (95% CI: 11.3-20.9)

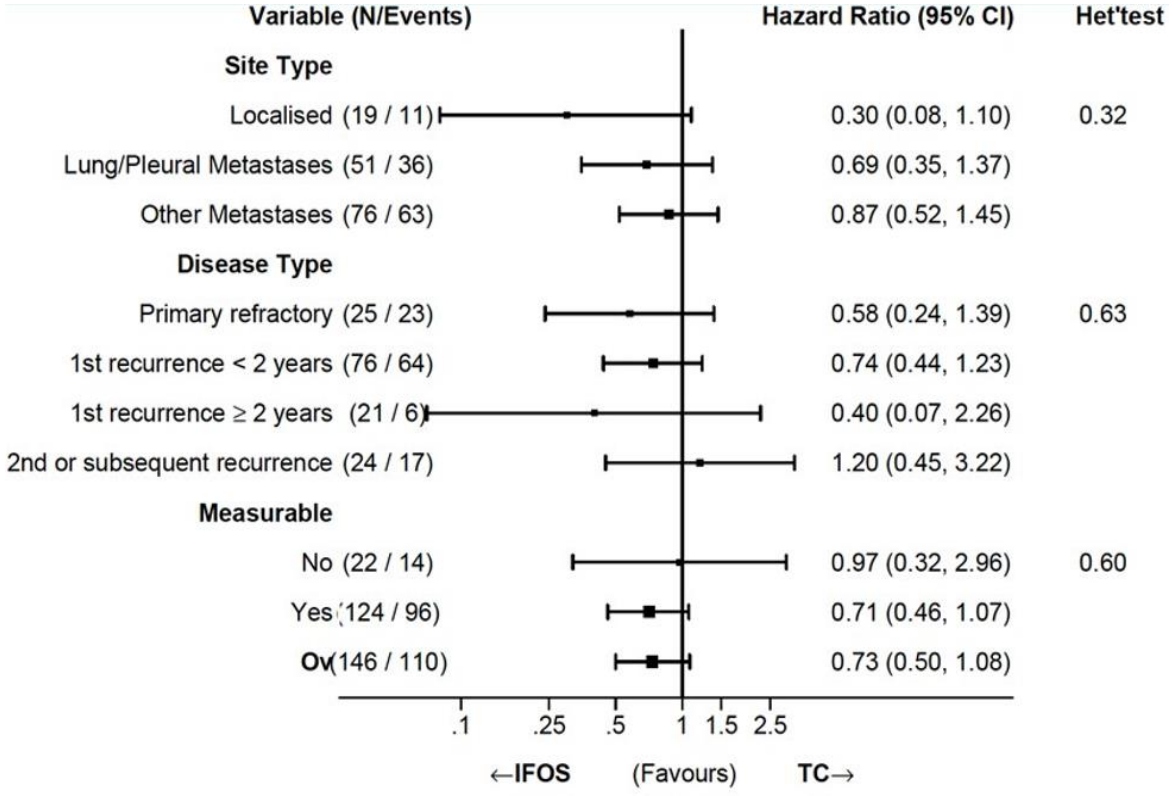
HR 0.73 (95% CrI: 0.50-1.08)

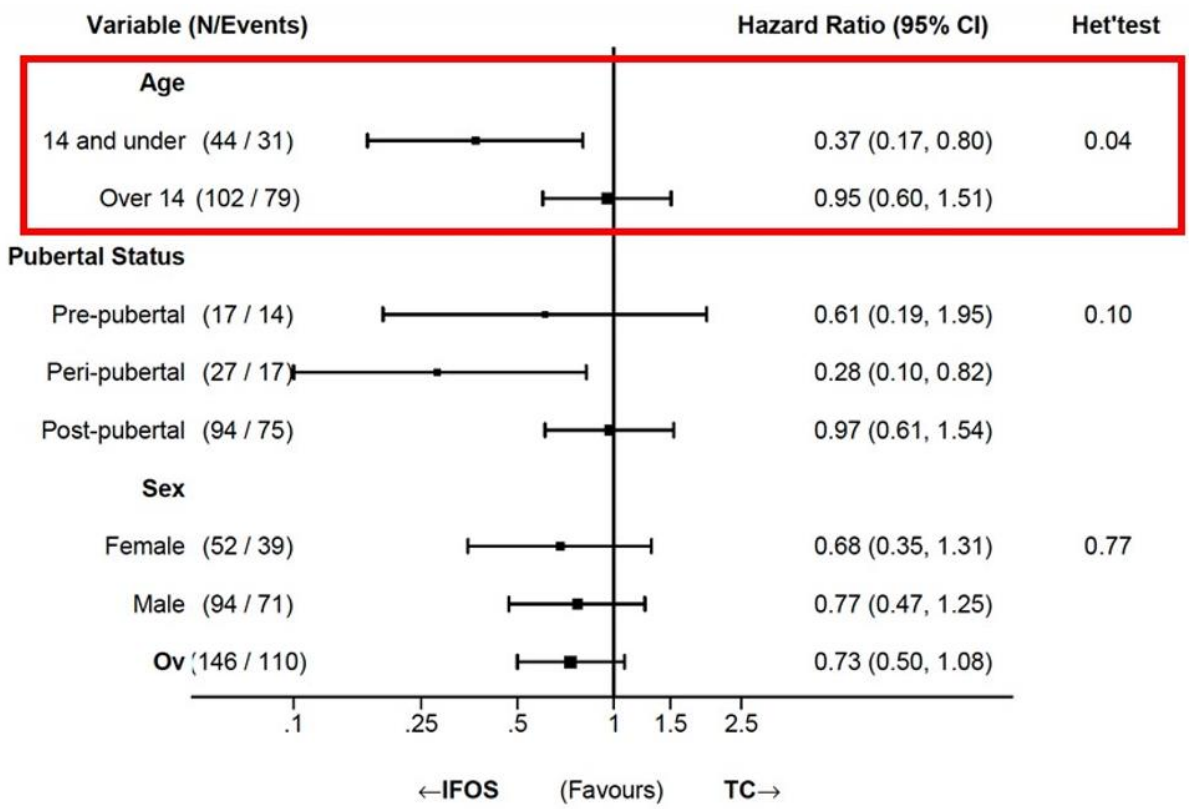
1-year OS

- TC: 45% (95% CI: 33%-56%)
- IFOS: 55% (95% CI: 43%-66%)

rEECur

OS by subgroup analysis





rEECur

Safety: Phase III comparison

	TC	IFOS
Missing data	1%	2%
At least one grade 3+	44%	57%
Febrile neutropenia	26%	25%
Infections & infestations	8%	14%
Nervous system disorders	3%	8%
• Encephalopathy	-	7%
• Neuropathy (sensory)	3%	1%
Fatigue	1%	5%
Renal and urinary disorders	-	8%
• Acute kidney injury	-	3%
• Raised creatinine	-	1%
• Haematuria	-	1%
• Proteinuria	-	1%
• Other renal	-	3%
Gastrointestinal disorders	3%	5%
• Diarrhoea	1%	1%
• Nausea	0%	3%
• Vomiting	1%	1%
Respiratory	4%	3%

	TC	IFOS
Treatment discontinuation due to progression	39 (53%)	16 (22%)
Treatment discontinuation due to toxicity		19 (26%)
• CNS toxicity	-	7
• Myelosuppression	-	5
• Febrile neutropenia	-	3
• Renal or tubular toxicity	-	3
• Other	-	3

ASCO 2022. Abstr LBA2.

SUMMARY

rEECur

- This is the first randomized trial to compare different chemotherapy regimens in recurrent and primary refractory Ewing sarcoma
- IFOS was more effective at extending median EFS and OS compared to TC
  - Median EFS was 5.7 months for ifosfamide vs. to 3.7 months for topotecan plus cyclophosphamide
  - Median OS was 15.4 months for ifosfamide vs. 10.4 months for topotecan plus cyclophosphamide
- The benefit of IFOS may be greater in children
- There were more discontinuations with IFOS due to toxicity compared to TC

ASCO 2022. Abstr LBA2.

rEECur

Ifosfamide provides benefit for patients with recurrent and primary refractory Ewing sarcoma compared to three other standard-of-care treatments

2022 ASCO Key Studies

Breast Cancer

- DESTINY-Breast04*
- TROPiCS-02
- MAINTAIN
- ABCSG-18
- PALOMA-2
- LUMINA

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- RELATIVITY-047
- SKYSCRAPER-02

* Plenary Session

cornerstone specialty network™

ECHELON-1

Does first line brentuximab vedotin plus chemotherapy improve overall survival in patients with stage III/IV classical Hodgkin lymphoma?

An updated analysis

KEY DATA

ECHELON-1

Study Design: phase III trial

- Adult with newly diagnosed Ann Arbor stage III/IV cHL
- Measurable disease
- ECOG PS 0-2

(N = 1334)

A+AVD x 6 cycles (n=664)
Brentuximab vedotin 1.2 mg/kg
IV infusion days 1 and 15

ABVD x 6 cycles (n=670)
IV infusion days 1 and 15

EOT
CT/PET scan

Follow-up
Every 3 months for 36 months, then every 6 months until study closure

End-of-cycle-2 PET scan by IRF per Deauville 5-point scale
- PET–: 1–3
- PET+: 4–5

Primary endpoint: modified PFS per IRF (previously reported[1])

Key secondary endpoint: alpha-controlled, event-driven analysis of OS

Long-term follow-up assessments:
- Exploratory analysis of OS among patients who were PET2-positive and PET2-negative
- PFS per investigator
- Subsequent treatment use
- Safety outcomes including:
  - PN resolution and improvement rates
  - Second malignancies
  - Outcomes of pregnancy among patients and their partners

Data cut-off for current analysis, June 1, 2021.
CT, computerized tomography; EOT, end of treatment; IRF, independent review facility; ITT, intention to treat; IV, intravenous; PET2, PET status at the end of cycle 2.
1. Connors JM, et al. N Engl J Med 2018;378:331–44.

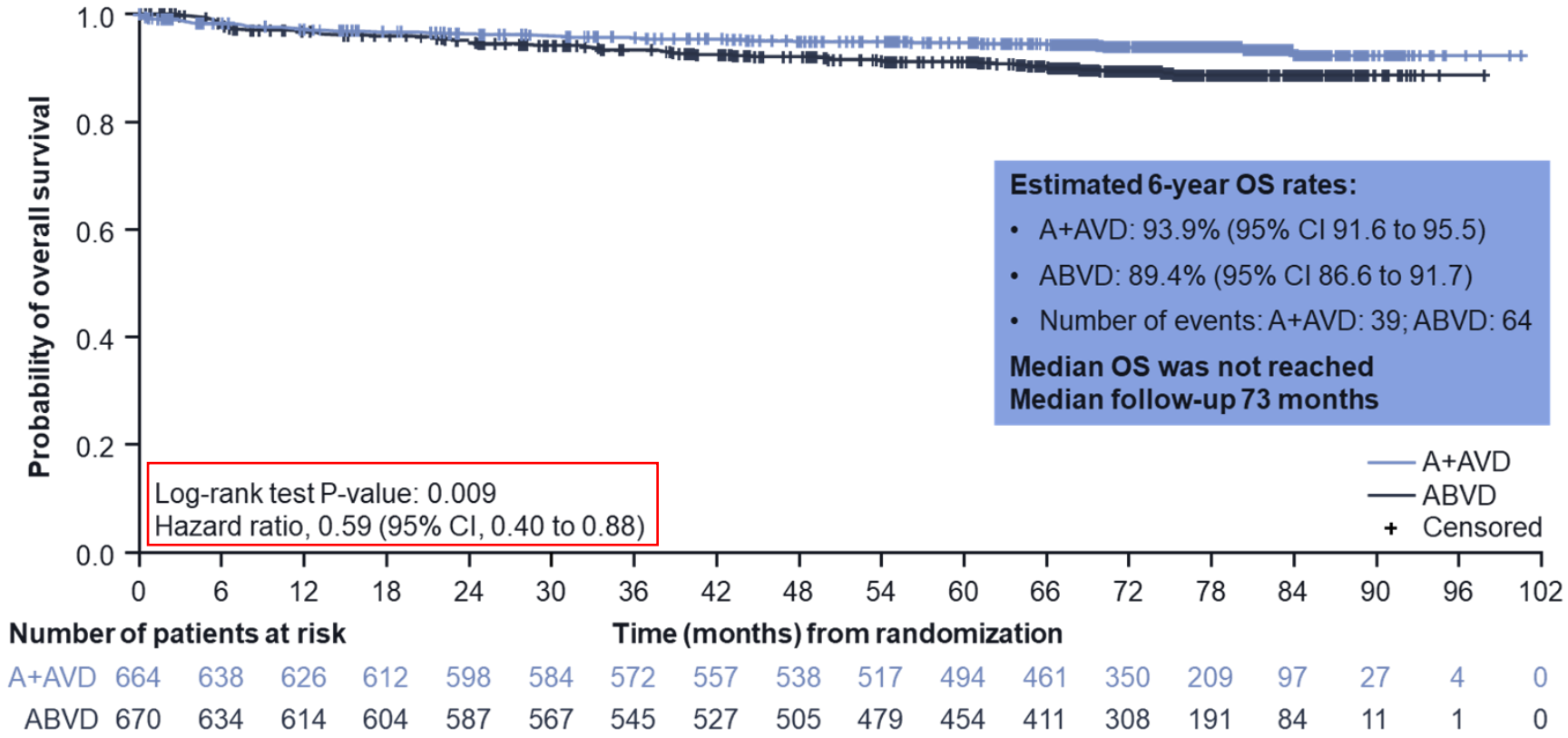
ECHELON-1

Baseline Characteristics

Characteristic	A+AVD (n=664)	ABVD (n=670)	Total (N=1,334)
Male sex, n (%)	378 (57)	398 (59)	776 (58)
Median age, years (interquartile range)	35 (26 to 51)	37 (27 to 53)	36 (26 to 52)
Aged <60 years, n (%)	580 (87)	568 (85)	1148 (86)
Aged ≥60 years, n (%)	84 (13)	102 (15)	186 (14)
Ann Arbor stage at initial diagnosis — n (%)*			
Stage II†	1 (<1)	0	1 (<1)
Stage III	237 (36)	246 (37)	483 (36)
Stage IV	425 (64)	421 (63)	846 (64)
Not applicable/unknown/missing	1 (<1)	3 (<1)	4 (<1)
IPS‡, n (%)			
0–1	142 (21)	141 (21)	283 (21)
2–3	355 (53)	357 (53)	712 (53)
4–7	167 (25)	172 (26)	339 (25)
PET2 status#, n (%)			
Positive	47 (7)	58 (9)	105 (8)
Negative	588 (89)	578 (86)	1166 (87)
Unknown/unavailable	29 (4)	34 (5)	63 (5)

ECHELON-1

Overall Survival



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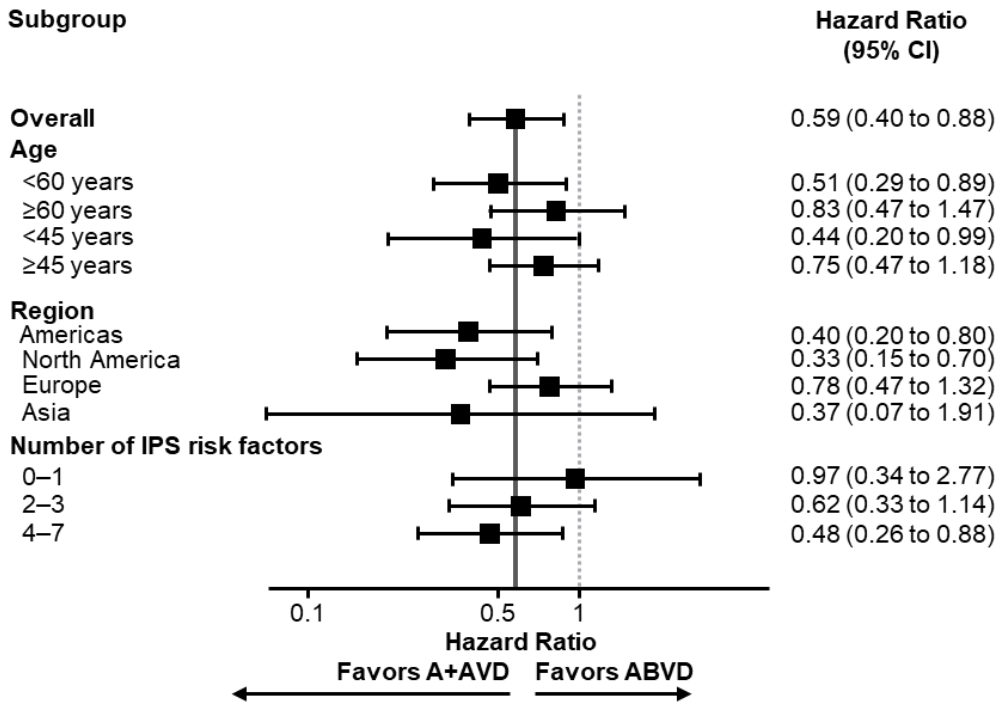
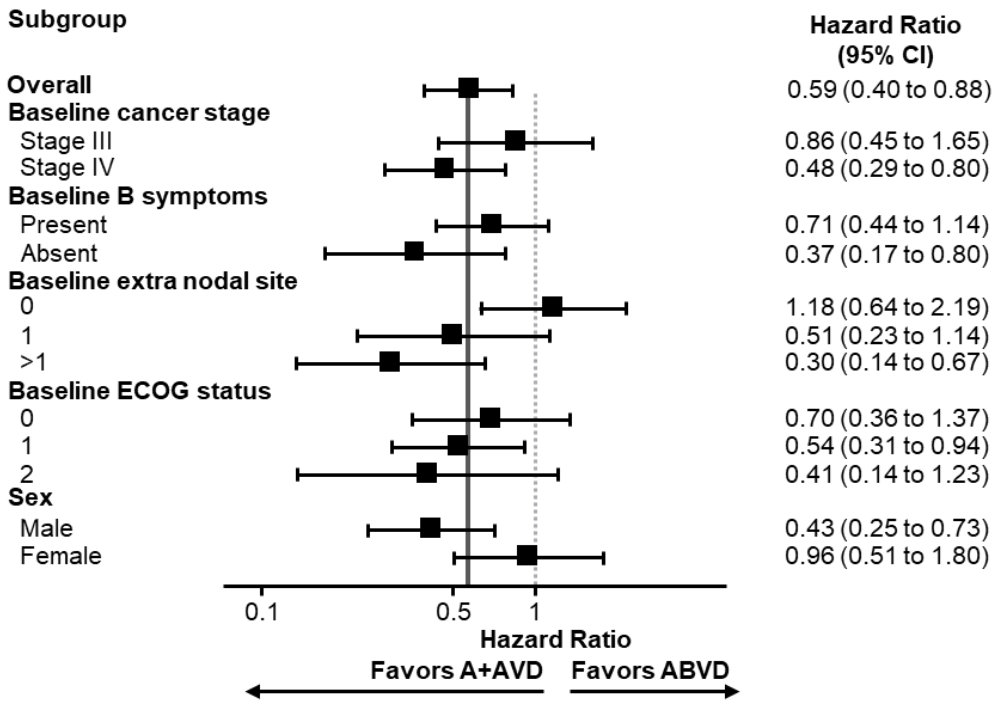
ECHELON-1

Overall Survival

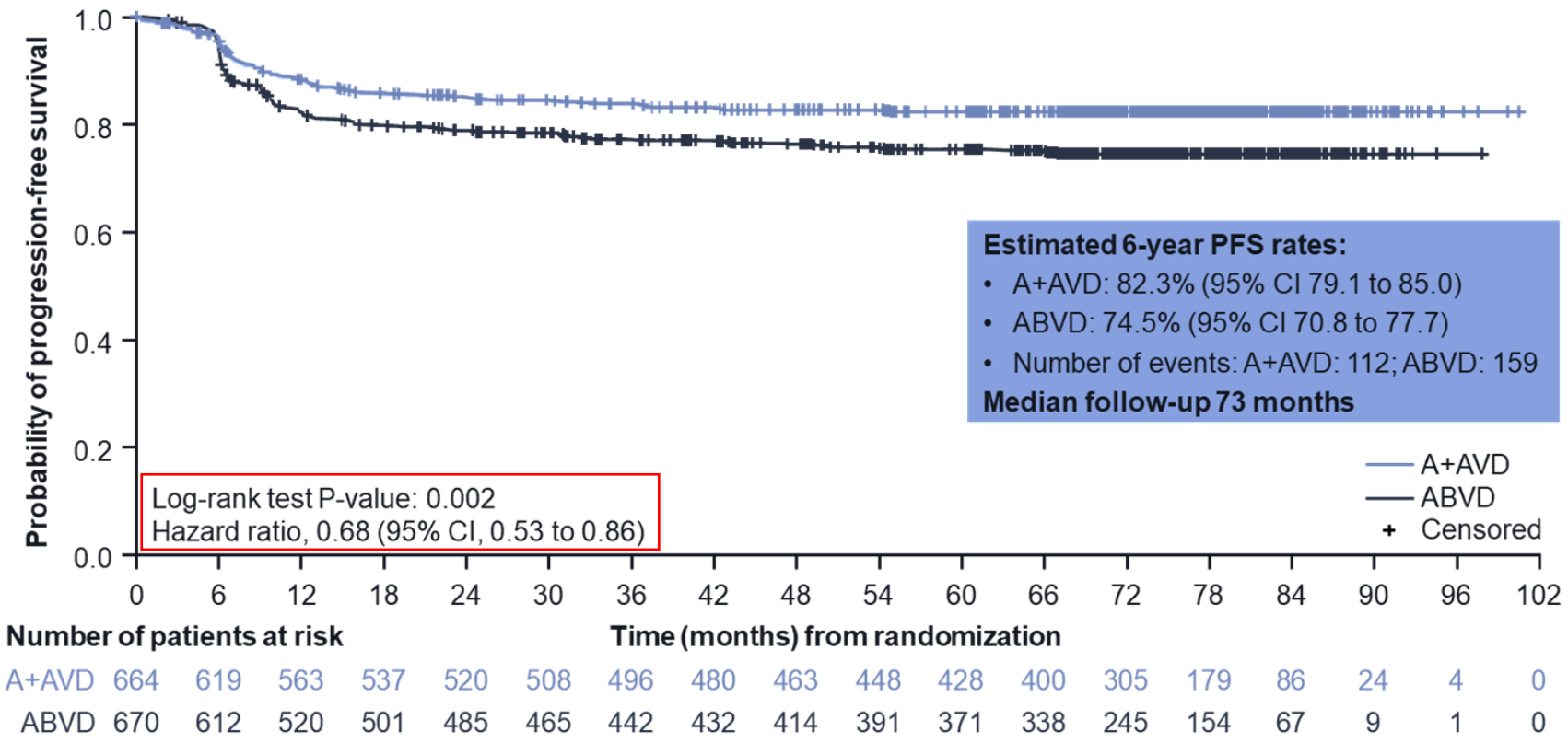




- The OS benefit with A+AVD was preserved in a multivariable analysis when simultaneously adjusting for baseline demographic and disease factors (HR 0.53; 95% CI, 0.34 to 0.83)
- Age, non-white race, ECOG performance status score, and PET2 status were identified as the covariates with greatest evidence of association with overall survival

ECHELON-1

Progression-Free Survival



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ECHELON-1

Safety

Cause of death per investigator	A+AVD (n=662)	ABVD (n=659)
Total Deaths	**39 (5.9%)**	**64 (9.7%)**
Hodgkin lymphoma or complications	32	45
Second malignancies	1	11
Other causes	**6**	**8**
Unknown cause	1	5*
Accident or suicide	3	0
COVID-19	0	1
Heart failure	1	1
Intracranial hemorrhage	1	0
Lower respiratory tract infection	0	1

*In 2 patients in the ABVD arm, death was reported to be of indeterminate cause, but the event occurred following investigator-documented disease progression.

Among those who died:

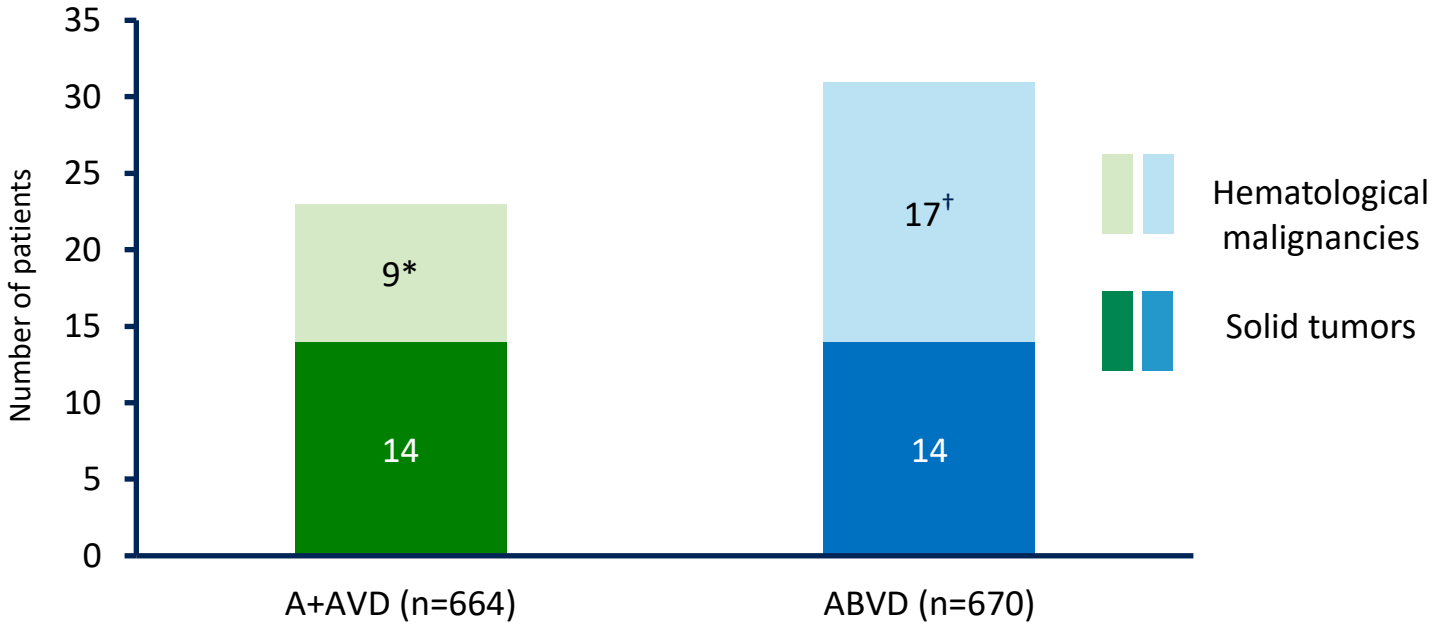
- A+AVD: 19 patients had prior disease progression (not always the cause of death); 18 received subsequent therapy
- ABVD: 28 patients had prior disease progression, 25 received a subsequent therapy (13 received brentuximab vedotin)

	A+AVD (n=662)	ABVD (n=659)	Total (N=1,321)
Patients with ≥1 subsequent anticancer therapy, n (%)	135 (20)	157 (24)	292 (22)
Type of therapy, n (%)			
Chemotherapy regimens	78 (12)	108 (16)	186 (14)
Brentuximab vedotin monotherapy	8 (1)	49 (7)	57 (4)
Brentuximab vedotin + chemotherapy	2 (<1)	20 (3)	22 (2)
Radiation	54 (8)	54 (8)	108 (8)
Chemotherapy + radiation	1 (<1)	4 (<1)	5 (<1)
High-dose chemotherapy + transplant	44 (7)	59 (9)	103 (8)
Allogeneic transplant	4 (<1)	12 (2)	16 (1)
Immunotherapy*	18 (3)	24 (4)	42 (3)
Brentuximab vedotin + nivolumab	0 (0)	4 (<1)	4 (<1)
Nivolumab	15 (2)	18 (3)	33 (2)
Pembrolizumab	2 (<1)	6 (<1)	8 (<1)
Nivolumab combinations	1 (<1)	1 (<1)	2 (<1)

*Immunotherapy was based predominantly on anti-PD-1 agents.

ECHELON-1

Secondary malignancies



*Includes 2 cases of acute myeloid leukemia and 6 cases of B- or T-cell lymphomas.
†includes 1 case each of acute myeloid leukemia, acute promyelocytic leukemia, and myelodysplastic syndrome, and 13 cases of B- or T-cell lymphomas.
‡Includes 1 unknown malignancy.

Among patients with second malignancies:

- Two patients on each arm received transplant
- Three patients on the ABVD arm received prior radiation (none with A+AVD)

ECHELON-1

Pregnancy and peripheral neuropathy data consistent with prior reports

Pregnancies

- Fertility was not formally assessed
- A total of 191 pregnancies were reported among patients and their partners (A+AVD: 113; ABVD: 78)
  - Among female patients with A+AVD and ABVD:
    - Pregnancies: 49 and 28
    - Live births*: 56 and 23
  - Among partners of male patients with A+AVD and ABVD:
    - Pregnancies: 33 and 33
    - Live births*: 40 and 36
- No still births were reported in either arm

Peripheral neuropathy

- Incidence of PN at 2 years of follow-up was greater with A+AVD (67%) vs ABVD (43%)[1]
- In patients with PN in the A+AVD and ABVD arms, after 6 years follow-up:
  - Treatment-emergent PN either resolved or continued to improve† in 86% and 87%
  - Median time to resolution was 16 and 10 weeks

Safety population	A+AVD (n=662)	ABVD (n=659)
Patients with ongoing PN at last follow-up, n (%)	125 (19)	59 (9)
Grade 1	71 (11)	39 (6)
Grade 2	38 (6)	16 (2)
Grade 3‡	15 (2)	4 (<1)
Grade 4‡	1 (<1)	0

*Some female patients (13 on the A+AVD arm and 3 on the ABVD arm)/partners of male patients (8 on the A+AVD arm and 7 on the ABVD arm) recorded more than one live birth; †Resolution was defined as resolved/recovered with or without sequelae or return to baseline or lower severity as of the latest assessment for pre-existing events. Improvement was defined as resolution or a decrease by at least 1 grade from the worst grade with no higher grade thereafter; ‡Patients who were lost to follow-up or died prior to resolution or improvement were not censored (11/16 patients [including the 1 patient with Grade 4 PN] on the A+AVD arm; 4/4 on the ABVD arm).

ASCO 2022. Abstr 7503.

SUMMARY

ECHELON-1

- With approximately 6 years of follow-up, the addition of brentuximab vedotin to AVD significantly improved overall survival vs ABVD in patients with previously untreated advanced cHL
  - HR: 0.59; 95% CI: 0.40-0.88; log-rank *P* = .009
  - OS improved despite high rate of subsequent therapy use in ABVD arm (24% vs 20% with BV + AVD)

- Brentuximab vedotin plus AVD resulted in fewer second malignancies compared to ABVD

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ECHELON-1

The addition of brentuximab vedotin to AVD provided benefit for patients with previously untreated advanced cHL and should be considered as a first-line treatment option for patients with untreated stage III or IV cHL

2022 ASCO Key Studies

Breast Cancer

- DESTINY-Breast04*
- TROPiCS-02
- MAINTAIN
- PALOMA-2
- LUMINA
- ABCSG-18

GI Cancer

- DYNAMIC
- PARADIGM*
- TRIPLETE
- CAIRO5
- PD-1 blockade in MMRd RC

Other Notable Studies

- DETERMINATION*
- ATLAS
- rEECur*
- ECHELON-1
- RELATIVITY-047
- SKYSCRAPER-02

* Plenary Session

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RELATIVITY-047

Does relatlimab plus nivolumab versus nivolumab alone in the first-line setting provide benefit for patients with advanced melanoma?

On March 18, 2022, the FDA approved nivolumab and relatlimab-rmbw (Opdualag) for adult and pediatric patients 12 years of age or older with unresectable or metastatic melanoma

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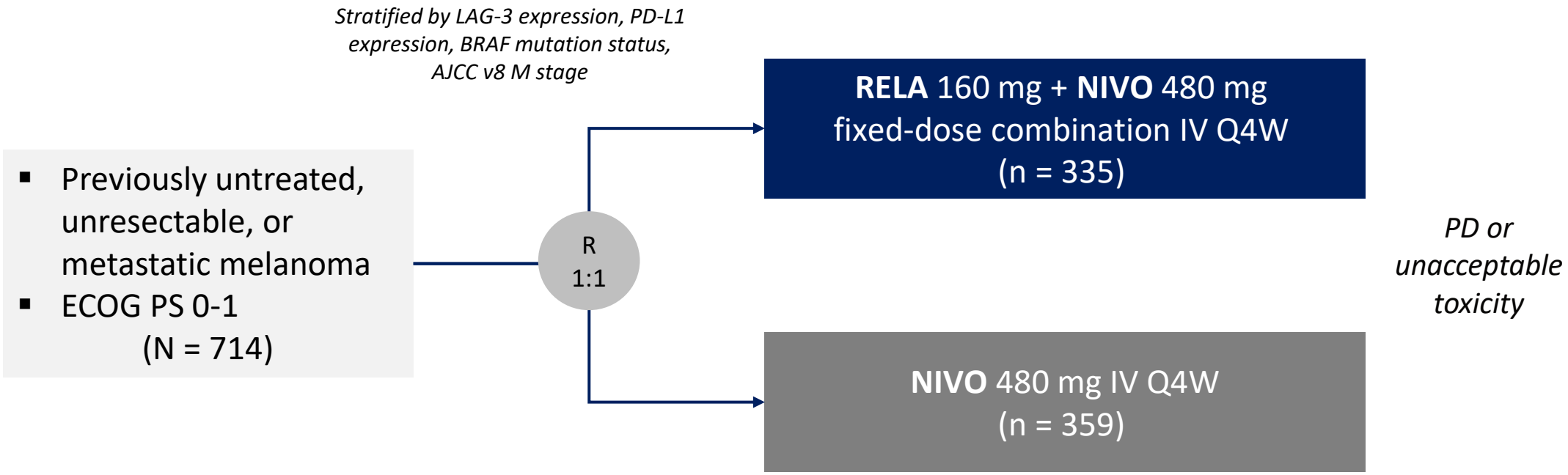
KEY DATA

RELATIVITY-047

Study Design: Global, randomized, double-blind phase II/III trial



Primary endpoint: PFS by BICR

Key secondary endpoints: OS, ORR by BICR

Hierarchical statistical testing: PFS, then OS, then ORR

ASCO 2022. Abstr 9505.

KEY DATA

RELATIVITY-047

Baseline Characteristics

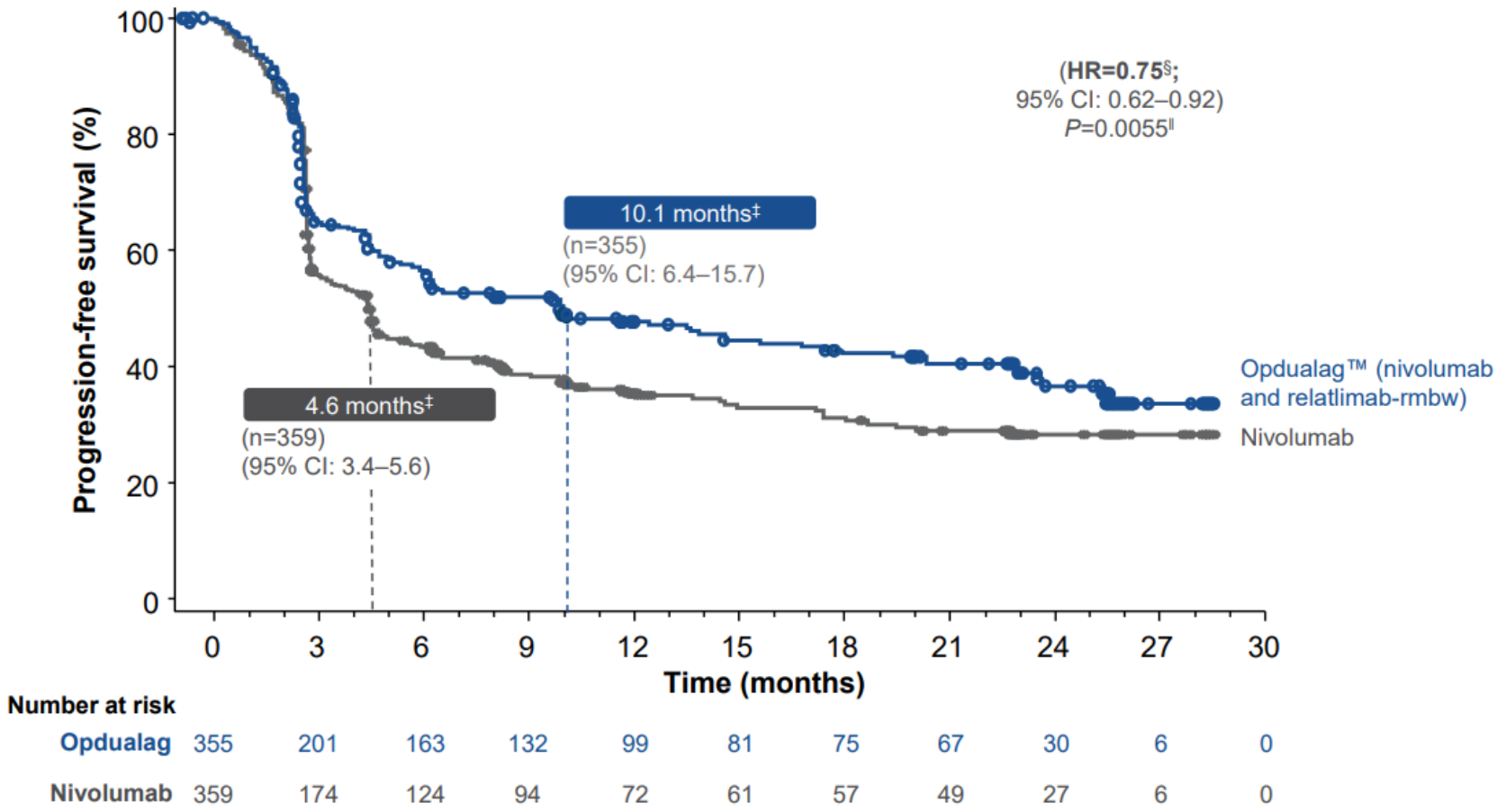
Characteristic	RELA + NIVO (n = 355)	NIVO (n = 359)
Median age, yr	63	62
Female, n (%)	145 (40.8)	153 (42.6)
AJCC v8 M stage, n (%)		
• M1a	77 (21.7)	107 (29.8)
• M1b	85 (23.9)	88 (24.5)
• M1c	151 (42.5)	127 (35.4)
• M1d	6 (1.7)	11 (3.1)
ECOG PS 1, n (%)	119 (33.5)	117 (32.6)
Serum LDH, n (%)		
• > ULN	130 (36.6)	128 (35.7)
• >2x ULN	32 (9.0)	31 (8.6)
Prior (neo)adjuvant treatment, n (%)*	33 (9.3)	27 (7.5)
Median tumor burden, mm† (min-max)	59.0 (10-317)	54.5 (10-548)

Characteristic	RELA + NIVO (n = 355)	NIVO (n = 359)
Melanoma subtype, n (%)		
• Cutaneous nonacral	249 (70.1)	254 (70.8)
• Acral	41 (11.5)	41 (11.4)
• Mucosal	23 (6.5)	28 (7.8)
Stratification factor, n (%)		
• LAG-3 expression		
– ≥1%	268 (75.5)	269 (74.9)
– <1%	87 (24.5)	90 (25.1)
• PD-L1 expression		
– ≥1%	146 (41.1)	147 (40.9)
– <1%	209 (58.9)	212 (59.1)
• BRAF mutation status		
– Mutant	136 (38.3)	139 (38.7)
– Wild-type	219 (61.7)	220 (61.3)
• AJCC M stage		
– M0/M1any[0]	232 (65.4)	237 (66.0)
– M1any[1]§	123 (34.6)	122 (34.0)

*Interferon was the most common therapy. †Sum of reference diameters. ‡LDH not elevated. §LDH elevated.

RELATIVITY-047

Primary endpoint: PFS by BICR



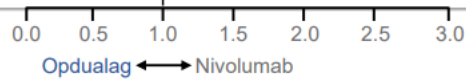
Median follow-up was 13.2 months.

KEY DATA

RELATIVITY-047

PFS Subgroup Analysis

Subgroup		RELA + NIVO	NIVO	Unstratified HR (95% CI)
		Events (no. of patients)		
Overall		180 (355)	211 (359)	0.76 (0.62–0.92)
Age categorization	≥18 and <65 years	99 (187)	117 (196)	0.83 (0.64–1.09)
	≥65 and <75 years	50 (102)	60 (103)	0.69 (0.47–1.00)
	≥65 years	81 (168)	94 (163)	0.69 (0.51–0.93)
	≥75 years	31 (66)	34 (60)	0.69 (0.42–1.13)
Sex	Male	98 (210)	123 (206)	0.68 (0.52–0.89)
	Female	82 (145)	88 (153)	0.88 (0.65–1.19)
LDH	≤ULN	100 (224)	127 (231)	0.70 (0.54–0.91)
	>ULN	79 (130)	84 (128)	0.80 (0.59–1.09)
	≤2× ULN	158 (322)	186 (328)	0.75 (0.60–0.92)
	>2× ULN	21 (32)	25 (31)	0.75 (0.42–1.35)
ECOG PS	0	108 (236)	136 (242)	0.74 (0.57–0.95)
	1	72 (119)	75 (117)	0.78 (0.56–1.07)
Tumor burden per BICR	<Q1	26 (74)	37 (83)	0.62 (0.37–1.03)
	Q1 to <Q3	84 (161)	96 (153)	0.80 (0.60–1.07)
	≥Q3	53 (84)	53 (75)	0.72 (0.49–1.06)
***BRAF* mutation status**	Mutant	67 (136)	83 (139)	0.74 (0.54–1.03)
	Wild type	113 (219)	128 (220)	0.76 (0.59–0.98)
AJCC v8 M stage	M0/M1 any [0] LDH not elevated	104 (232)	130 (237)	0.71 (0.55–0.92)
	M1 any [1] elevated LDH level	76 (123)	81 (122)	0.79 (0.58–1.09)
PD-L1	≥1%	68 (146)	67 (147)	0.95 (0.68–1.33)
	<1%/nonquantifiable	112 (209)	144 (212)	0.66 (0.51–0.84)
	≥5%	33 (88)	36 (86)	0.86 (0.54–1.38)
	<5%/nonquantifiable	147 (267)	175 (273)	0.73 (0.58–0.90)
LAG-3	≥1%	131 (268)	151 (269)	0.75 (0.59–0.95)
	<1%	49 (87)	60 (90)	0.78 (0.54–1.15)
Melanoma subtype classification	Cutaneous acral	31 (41)	29 (41)	0.84 (0.50–1.39)
	Cutaneous non-acral	111 (249)	139 (254)	0.73 (0.57–0.93)
	Mucosal	14 (23)	19 (28)	0.72 (0.36–1.45)
	Other	24 (42)	24 (36)	0.77 (0.44–1.36)



Median follow-up was 13.2 months.[1,2]

ASCO 2022. Abstr 9505.

RELATIVITY-047

Safety

AEs, n (%)	RELA + NIVO (n = 355)		NIVO (n = 359)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Any AE	**352 (99.2)**	**154 (43.4)**	**344 (95.8)**	**126 (35.1)**
Any TRAE	**297 (83.7)**	**75 (21.1)**	**260 (72.4)**	**40 (11.1)**
TRAEs leading to discontinuation	54 (15.2)	32 (9.0)	26 (7.2)	13 (3.6)
TRAEs ≥10%				
Pruritus	87 (24.5)	0	59 (16.4)	2 (0.6)
Fatigue	83 (23.4)	5 (1.4)	47 (13.1)	1 (0.3)
Rash	59 (16.6)	3 (0.8)	48 (13.4)	2 (0.6)
Hypothyroidism	55 (15.5)	0	46 (12.8)	0
Arthralgia	53 (14.9)	3 (0.8)	29 (8.1)	1 (0.3)
Diarrhea	53 (14.9)	4 (1.1)	36 (10.0)	2 (0.6)
Vitiligo	45 (12.7)	0	42 (11.7)	0
Treatment-related deaths*	4 (1.1)	0	2 (0.6)	0

*4 deaths in RELA + NIVO arm due to hemophagocytic lymphohistiocytosis, acute lung edema, pneumonitis, and multiorgan failure (n = 1 each); 2 deaths in NIVO arm due to sepsis and myocarditis and worsening pneumonia.

RELATIVITY-047

Safety

Immune-Mediated AEs, n (%)	RELA + NIVO (n = 355)		NIVO (n = 359)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Hypothyroidism/thyroiditis	66 (18.6)	0	53 (14.8)	0
Rash	39 (11.0)	3 (0.8)	28 (7.8)	5 (1.4)
Diarrhea/colitis	25 (7.0)	5 (1.4)	12 (3.3)	5 (1.4)
Hyperthyroidism	23 (6.5)	0	25 (7.0)	0
Hepatitis	21 (5.9)	15 (4.2)	11 (3.1)	6 (1.7)
Adrenal insufficiency	19 (5.4)	6 (1.7)	4 (1.1)	0
Pneumonitis	14 (3.9)	2 (0.6)	7 (1.9)	2 (0.6)
Hypophysitis	10 (2.8)	2 (0.6)	4 (1.1)	1 (0.3)
Nephritis and renal dysfunction	7 (2.0)	4 (1.1)	5 (1.4)	4 (1.1)
Hypersensitivity	5 (1.4)	0	5 (1.4)	0

Other AEs of interest: Any-grade myocarditis occurred in 6 (1.7%) patients with RELA + NIVO and 2 (0.6%) patients with NIVO; per specified protocol, troponin monitoring performed for first 2 months of treatment

SUMMARY

RELATIVITY-047

- Relatlimab + nivolumab significantly improved PFS by BICR compared with nivolumab alone in previously untreated patients with advanced melanoma with longer follow-up

- Efficacy outcomes of PFS, OS, and ORR favored relatlimab + nivolumab vs nivolumab alone across key subgroups regardless of prognostic factors and biomarkers (PD-L1, LAG-3, or BRAF)
  - Median OS has not yet been reached for RELA + NIVO vs 34.1 months for NIVO monotherapy

- Relatlimab + nivolumab showed manageable safety profile compared with nivolumab alone, and no unexpected safety signals were observed
  - Grade 3/4 TRAEs: 21.1% relatlimab + nivolumab vs 11.1% nivolumab alone

ASCO 2022. Abstr 9505.

COMPARISON

CheckMate-067 vs Relativity-047

	CheckMate-067		Relativity-047	
FDA approval NCCN Guideline	• For patients with unresectable or metastatic melanoma, as a single agent or in combination with ipilimumab • NCCN Guideline: Category 1 Preferred regimen		• OPDUALAG is a combination of nivolumab, a programmed death receptor-1 (PD-1) blocking antibody, and relatlimab, a lymphocyte activation gene-3 (LAG-3) blocking antibody, indicated for the treatment of adult and pediatric patients 12 years of age or older with unresectable or metastatic melanoma. • NCCN Guideline: Category 2A preferred regimen	
Study Design	**NIVO + IPI vs NIVO** Phase 3 study in the first-line treatment of metastatic melanoma		**NIVO + RELA vs NIVO** Phase 3 study in the first-line treatment of metastatic melanoma	
Minimum follow-up	6.5 years		8.7 months	
N	314	316	335	359
Median PFS, months	11.5 (HR=0.79; 95% CI: 0.65–0.97)	6.9	10.1 (HR=0.78; 95% CI: 0.64–0.94)	4.6
Median OS, months	72.1 (HR=0.84; 95% CI: 0.67–1.04)	36.9	*Not reached* (HR=0.80; 95% CI: 0.64–1.01)	34.1
ORR, %	58	45	43	33
Grade 3-4 TRAEs	59%	24%	21	11

RELATIVITY-047

Dual checkpoint inhibition with RELA + NIVO provided added benefit over NIVO monotherapy in patients with advanced melanoma and should be considered as a first-line treatment option

Who should receive NIVO + IPI or RELA + NIVO? Monotherapy vs combination therapy?

2022 ASCO Key Studies

Breast Cancer

- DESTINY-Breast04*
- TROPiCS-02
- MAINTAIN
- PALOMA-2
- LUMINA
- ABCSG-18

GI Cancer

- DYNAMIC
- PARADIGM*
- TRIPLETE
- CAIRO5
- PD-1 blockade in MMRd RC

Other Notable Studies

- DETERMINATION*
- ATLAS
- rEECur*
- ECHELON-1
- RELATIVITY-047
- SKYSCRAPER-02

* Plenary Session

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CLINICAL QUESTION

SKYSCRAPER-02

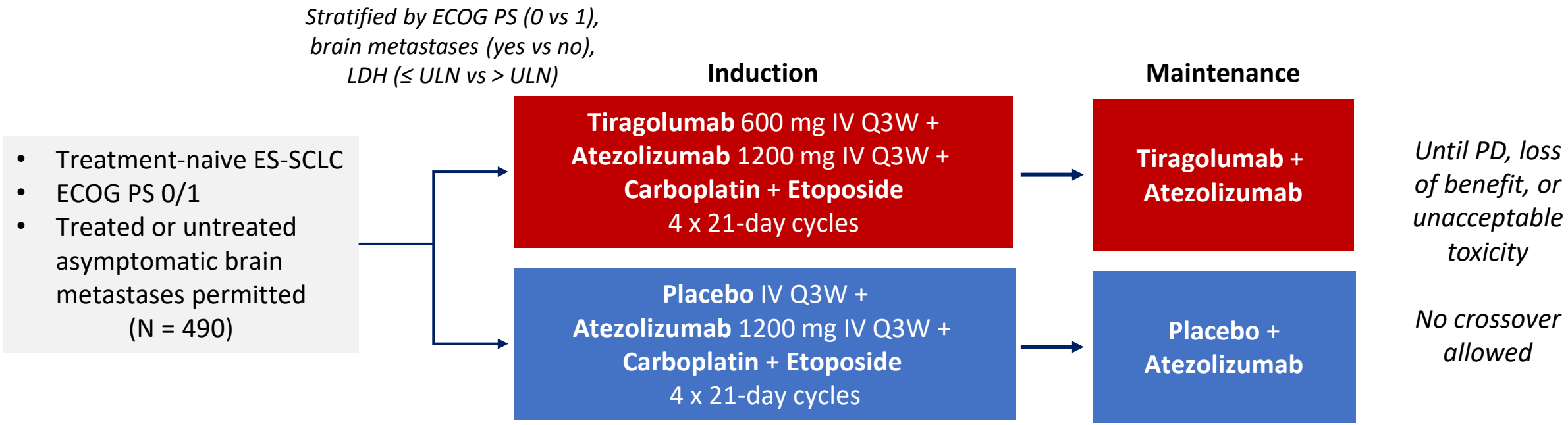
Does the addition of tiragolumab (an anti-TIGIT antibody) to atezolizumab in combination with carboplatin/etoposide in the first line setting benefit patients with ES-SCLC?

Based on IMpower133 atezolizumab combined with carboplatin/etoposide is a current first-line SoC for ES-SCLC

KEY DATA

SKYSCRAPER-02

Study Design: Randomized, double-blind, placebo-controlled phase III study



- **Coprimary endpoints:** OS and investigator-assessed PFS in primary analysis set*
- **Secondary endpoints:** PFS and OS in full analysis set (all randomized patients), ORR, DoR, safety, PK

*All randomized patients without presence or history of brain metastases at baseline (n = 397).

Cutoff date: Feb 6, 2022
Median follow-up: 14.3 months

SKYSCRAPER-02

Primary endpoint: Efficacy

Primary analysis set		Tira + Atezo + CE (n =196)	Placebo + Atezo + CE (n = 201)
PFS	Patients with events, n (%)	170 (86.7%)	170 (84.6%)
	Median, months (95% CI)	5.4 (4.7 – 5.5)	5.6 (5.4 – 5.9)
	Stratified HR (95% CI); p-value	**1.11 (0.89 – 1.38); p=0.3504**	
OS	Patients with events, n (%)	107 (54.6%)	105 (52.2%)
	Median, months (95% CI)	13.6 (10.8 – 14.9)	13.6 (12.3 – 15.2)
	Stratified HR (95% CI); p-value	**1.04 (0.79 – 1.36); p=0.7963**	

*1 patient (0.4%) in tiragolumab arm and 2 patients (0.8%) in placebo arm had a CR.

SKYSCRAPER-02

Secondary endpoints: Efficacy

Full analysis set		Tira + Atezo + CE (n = 243)	Placebo + Atezo + CE (n = 247)
PFS	Patients with events, n (%)	213 (87.7%)	215 (87%)
	Median, months (95% CI)	5.1 (4.4 – 5.4)	5.4 (4.5 – 5.7)
	Stratified HR (95% CI)	**1.08** (0.89 – 1.31)	
OS	Patients with events, n (%)	132 (54.3%)	132 (53.4%)
	Median, months (95% CI)	13.1 (10.9 – 14.4)	12.9 (12.1 – 14.5)
	Stratified HR (95% CI)	**1.02** (0.80 – 1.30)	
ORR*, % (95% CI)		**70.8** (64.6 – 76.3)	**65.6** (59.3 – 71.4)
Duration of Response	Median, months (95% CI)	**4.2** (4.1 – 4.4)	**5.1** (4.4 – 5.8)
	Responders, n	172	162
	With subsequent event, n (%)	147 (85.5)	135 (83.3)

*1 patient (0.4%) in tiragolumab arm and 2 patients (0.8%) in placebo arm had a CR.

SUMMARY

SKYSCRAPER-02

- The addition of tiragolumab (an anti-TIGIT antibody) to atezolizumab in combination with carboplatin/etoposide in the first line setting does not provide further benefit to patients with ES-SCLC
  - No difference in PFS or OS between the treatment arms
  - There were no safety concerns associated with the addition of tiragolumab

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SKYSCRAPER-02

These data support the results from IMpower133 and confirm atezolizumab with carboplatin/etoposide as a standard of care first-line treatment for ES-SCLC