EPOCH is a level 1, phase III randomized controlled trial using transarterial radiation therapy for mCRC liver metastases that demonstrated statistically significant improvements in both Progression-Free Survival (PFS) and Hepatic Progression-Free Survival (hPFS) in patients who progressed on first-line chemotherapy.

Mulcahy, M. et al, Radioembolization With Chemotherapy for Colorectal Liver Metastases: A Randomized, Open-Label, International, Multicenter, Phase III Trial (EPOCH). Journal of Clinical Oncology, 20 Sept 2021.

TRIAL OBJECTIVE

To evaluate the safety and efficacy of TheraSphere Y-90 Glass Microspheres combined with second-line therapy (oxaliplatin- or irinotecan-based chemotherapy) in patients with mCRC of the liver.

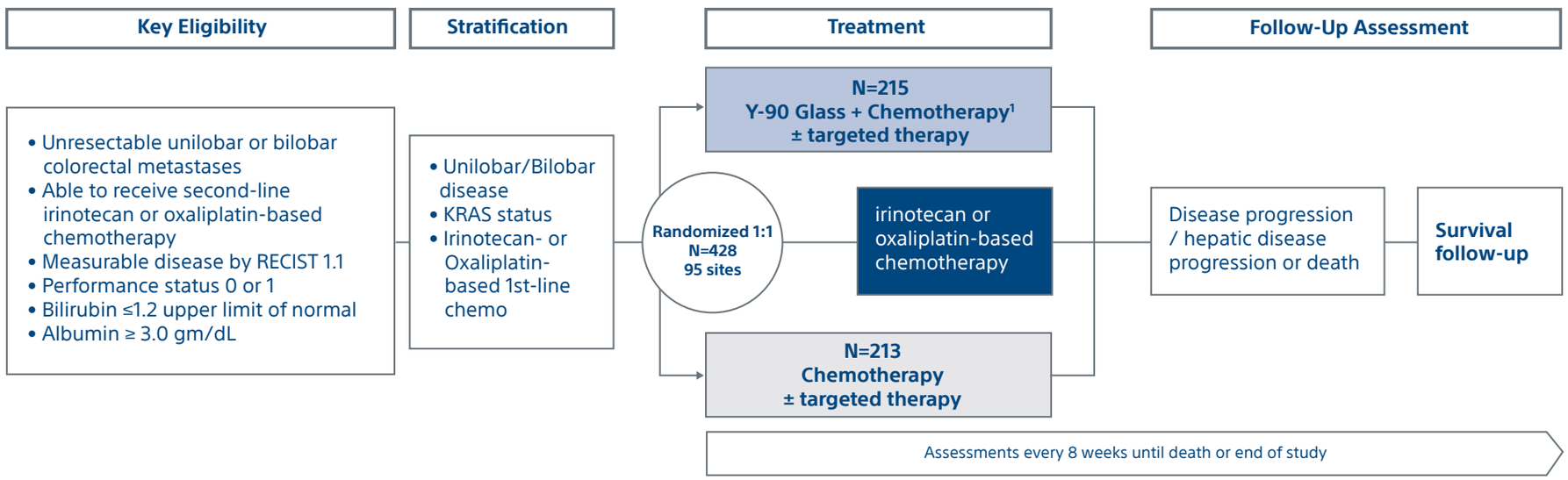
TRIAL DESIGN

An open-label, prospective, multicenter, phase III trial of 428 patients randomized 1:1 to treatment arm (TheraSphere + second-line chemotherapy) vs. control arm (second-line chemotherapy alone) across 95 centers in 12 countries, including North America, Europe and Asia.

PRIMARY ENDPOINTS

Progression-free survival (PFS) and hepatic PFS (hPFS)

- Time from randomization to progression by RECIST 1.1 or death
- Blinded independent central review (BICR)



1. TARE with Y-90 glass microspheres (TheraSphere™, Boston Scientific Corporation). Cycle 1= chemotherapy, Y-90 TARE replaces Cycle 2, Cycle 3 resume chemotherapy ± targeted therapy. ClinicalTrials.gov Identifier: NCT01483027. Chauhan N, Mulcahy MF, Salem R, et al. JMIR Res Protoc. 2019;8(1):e11545. doi: 10.2196/11545.

EPOCH TRIAL CONCLUSIONS

- Both primary endpoints were successfully met. Patients receiving TheraSphere Y-90 with second-line chemo were:
  - 31% less likely to experience disease progression or death (due to any cause) vs. chemo alone
  - 41% less likely to experience hepatic disease progression or death (due to any cause) vs. chemo alone
- The addition of TheraSphere Y-90 to second-line chemotherapy increased median Time to Progression (TTP) by 2.1 months* and increased median Hepatic Time to Progression (hTTP) by 4.9 months*
- Patients receiving TheraSphere Y-90 with second-line chemotherapy showed an Objective Response Rate (ORR) of 34.0% vs. 21.1% for the control arm*
- The addition of TheraSphere Y-90 to second-line chemotherapy:
  - Extended median Time to Subsequent Therapy by 10.9 months*
  - Did not compromise patients' ability to receive chemotherapy ± biologics
  - Did not compromise Quality of Life
  - Did not increase chemotherapy-related adverse events and no new safety signals were identified
- Subgroups receiving TheraSphere Y-90 with second-line chemo showed improved benefit in PFS, hPFS, and additional time to deterioration of QoL vs. chemo alone, and also showed greater magnitude in benefit compared to the overall ITT population (Subgroup A: excludes ECOG 1 and CEA ≥35 ng/mL. Subgroup B: excludes ECOG 1, CEA ≥35 ng/mL, and KRAS-m)
- Post-hoc safety analyses of overall ITT population showed patients with <10% tumor volume replacement and/or >10 lesions treated with TheraSphere Y-90 + second-line chemo experienced more liver-related TEAEs. Sequential lobar treatment, as opposed to same day whole liver treatment, may mitigate liver-related TEAEs.

*Indicates improvement in the treatment arm (TheraSphere + chemotherapy) compared to the control arm (chemotherapy alone) corresponding to 1-sided p <0.025

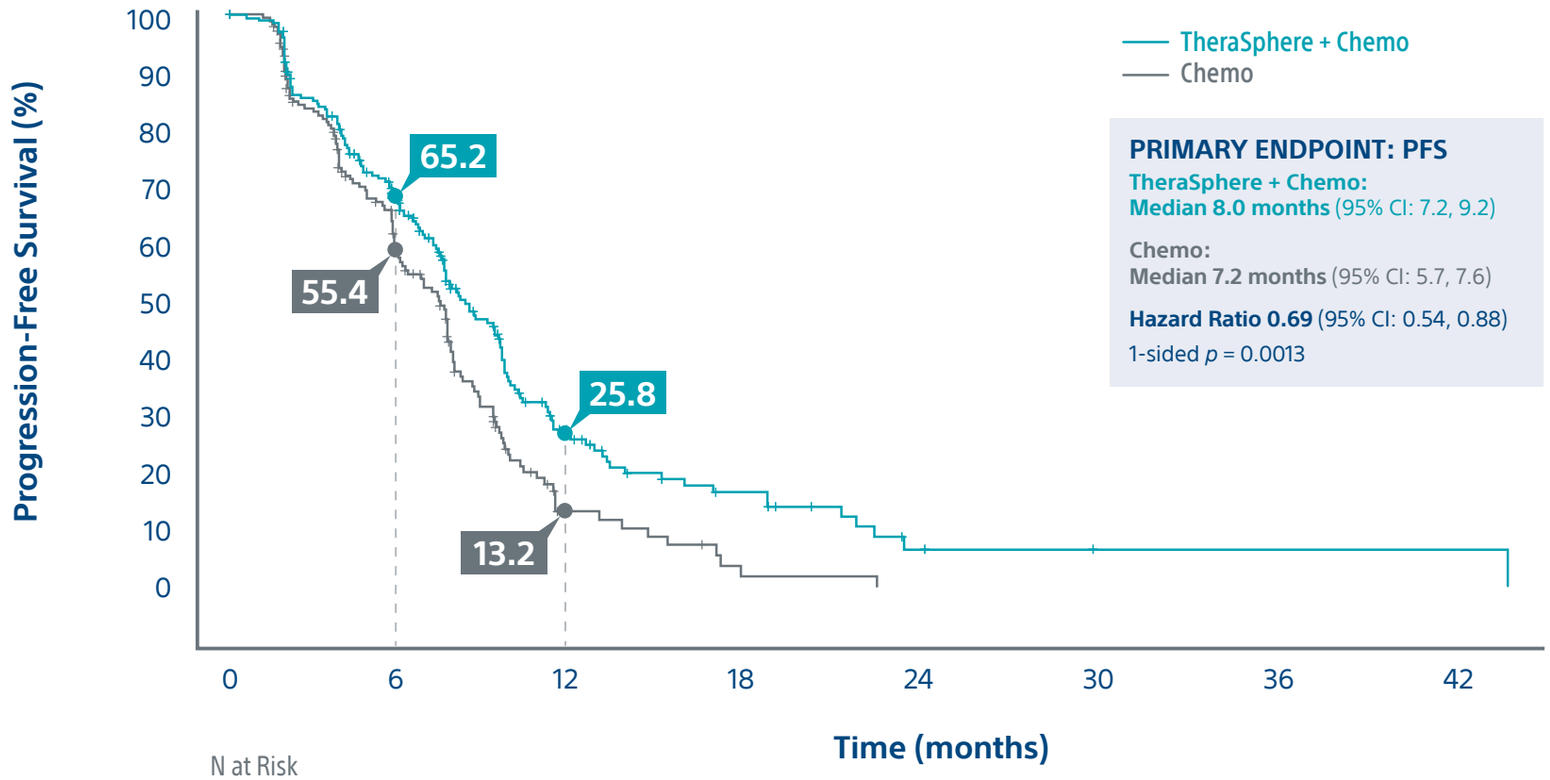
PRIMARY ENDPOINTS[1]

EPOCH demonstrated statistically significant improvements in both primary endpoints of PFS and hPFS in patients with colorectal liver metastases.

Progression Free Survival

31%

Patients receiving TheraSphere with second-line chemo were **31% less likely** to experience disease progression or death (due to any cause) vs. chemo alone.



PRIMARY ENDPOINT: PFS

TheraSphere + Chemo:
Median 8.0 months (95% CI: 7.2, 9.2)

Chemo:
Median 7.2 months (95% CI: 5.7, 7.6)

Hazard Ratio 0.69 (95% CI: 0.54, 0.88)
1-sided $p = 0.0013$

N at Risk

TheraSphere + Chemo	215	111	29	13	2	1	1	1
Chemo	213	76	9	1	0	0	0	0

1. Time from randomization to progression according to RECIST 1.1 by Blinded Independent Central Review (BICR) or death (due to any cause), whichever occurred first.

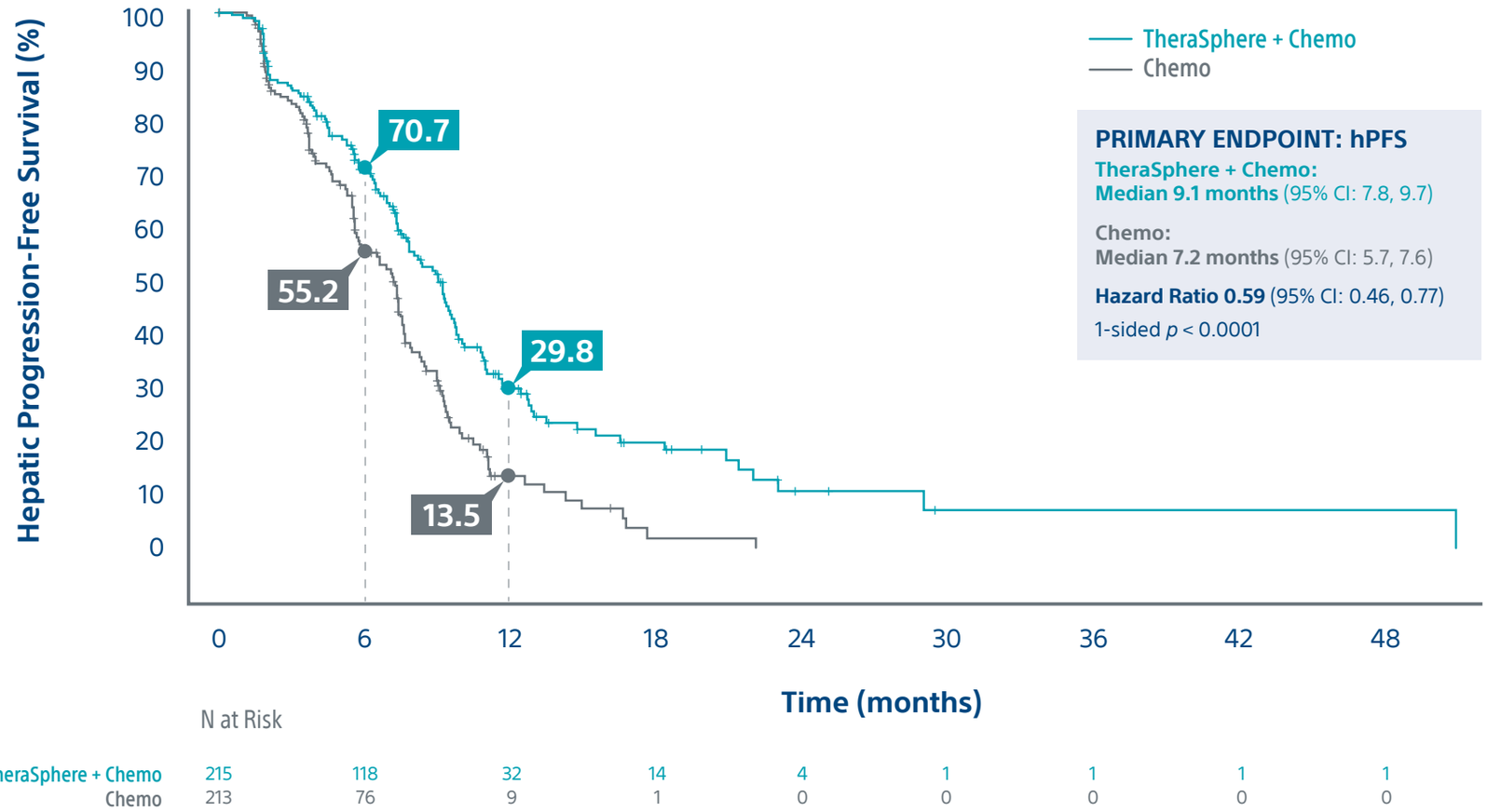
PRIMARY ENDPOINTS[1]

EPOCH demonstrated statistically significant improvements in both primary endpoints of PFS and hPFS in patients with colorectal liver metastases.

Hepatic Progression Free Survival

41%

Patients receiving TheraSphere with second-line chemo were **41% less likely** to experience hepatic disease progression or death (due to any cause) vs. chemo alone.



PRIMARY ENDPOINT: hPFS

TheraSphere + Chemo:
Median 9.1 months (95% CI: 7.8, 9.7)

Chemo:
Median 7.2 months (95% CI: 5.7, 7.6)

Hazard Ratio 0.59 (95% CI: 0.46, 0.77)

1-sided $p < 0.0001$

1. Time from randomization to hepatic progression according to RECIST 1.1 by Blinded Independent Central Review (BICR) or death (due to any cause), whichever occurred first.

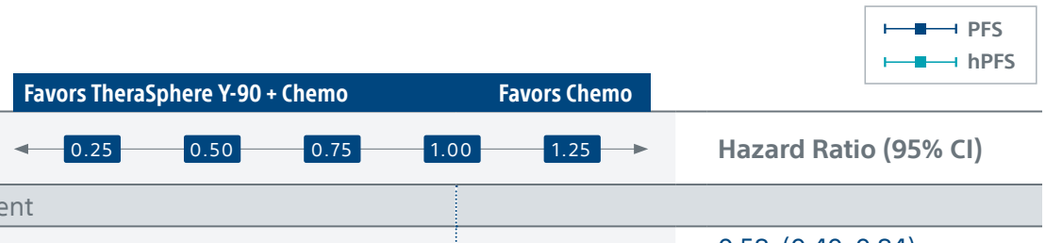
SUBGROUP ANALYSES FOR PFS & hPFS[1]

Subgroup	TheraSphere + Chemo	Chemo	Favors TheraSphere Y-90 + Chemo / Favors Chemo (0.25, 0.50, 0.75, 1.00, 1.25)	Hazard Ratio (95% CI)
Overall	215	213		0.69 (0.54, 0.88) 0.59 (0.46, 0.77)
Age				
Age ≥18 to ≤65 years	126	132		0.65 (0.47, 0.90) 0.56 (0.41, 0.78)
Gender				
Males	135	138		0.66 (0.49, 0.90) 0.58 (0.43, 0.80)
Females	80	75		0.74 (0.48, 1.12) 0.59 (0.38, 0.92)
Unilobar or Bilobar Disease at baseline				
Bilobar	176	173		0.71 (0.54, 0.93) 0.61 (0.46, 0.80)
Unilobar	39	40		0.59 (0.32, 1.09) 0.55 (0.29, 1.03)
KRAS				
KRAS mutation	100	101		0.57 (0.40, 0.80) 0.50 (0.35, 0.72)
KRAS wild type	115	112		0.79 (0.55, 1.12) 0.68 (0.47, 0.97)
Location of primary tumors at time of first diagnosis of primary CRC				
Right Side	49	61		0.74 (0.46, 1.20) 0.60 (0.36, 0.98)
Left Side	150	136		0.65 (0.48, 0.88) 0.59 (0.44, 0.81)

Continued

1. According to RECIST 1.1 by Blinded Independent Central Review (BICR).

SUBGROUP ANALYSES FOR PFS & hPFS[1]

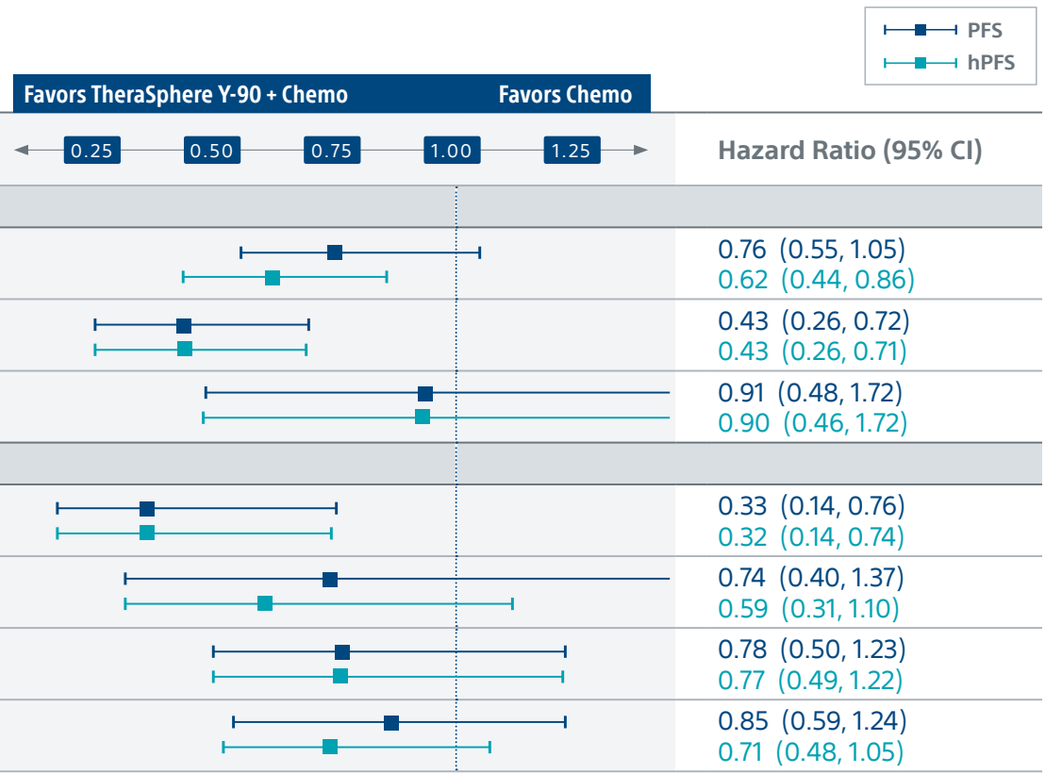


Subgroup	TheraSphere + Chemo	Chemo	Hazard Ratio (95% CI)
Biological agent received as part of second-line treatment			
Addition of biological agent	88	93	0.58 (0.40, 0.84) 0.48 (0.33, 0.71)
No addition of biological agent	127	120	0.76 (0.55, 1.06) 0.67 (0.48, 0.94)
Maximum liver lesion size at baseline			
< 4 cm	40	41	0.92 (0.51, 1.67) 0.69 (0.37, 1.28)
≥ 4 cm	162	142	0.62 (0.47, 0.81) 0.55 (0.42, 0.73)
Albumin at baseline			
< site LLN[2]	28	30	1.31 (0.71, 2.42) 1.28 (0.70, 2.35)
≥ site LLN[2]	182	177	0.65 (0.49, 0.85) 0.55 (0.41, 0.72)
Baseline CEA[3]			
Baseline CEA < 35 ng/mL	91	100	0.74 (0.50, 1.08) 0.61 (0.41, 0.91)
Baseline CEA ≥ 35 ng/mL	116	105	0.65 (0.46, 0.91) 0.57 (0.41, 0.81)

Previous Continued

1. According to RECIST 1.1 by Blinded Independent Central Review (BICR).
2. LLN = lower limit of normal.
3. CEA = carcinoembryonic antigen.

SUBGROUP ANALYSES FOR PFS & hPFS[1]



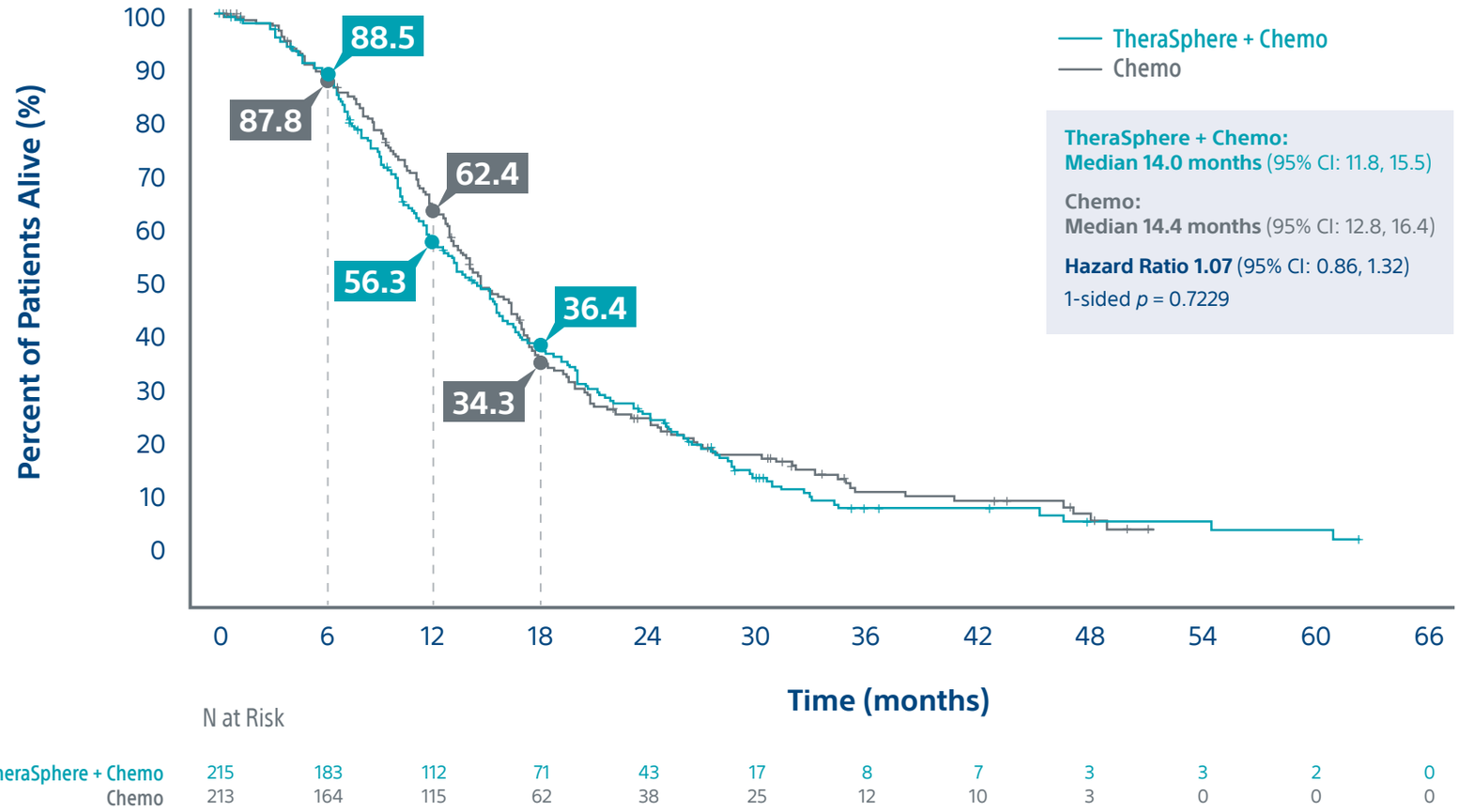
Subgroup	TheraSphere + Chemo	Chemo	Hazard Ratio (95% CI)
Liver tumor burden at baseline by BICR			
< 10%	124	121	0.76 (0.55, 1.05) 0.62 (0.44, 0.86)
≥ 10 to < 25%	54	47	0.43 (0.26, 0.72) 0.43 (0.26, 0.71)
≥ 25%	29	28	0.91 (0.48, 1.72) 0.90 (0.46, 1.72)
Number of lesions at baseline by BICR			
< 3 lesions	25	21	0.33 (0.14, 0.76) 0.32 (0.14, 0.74)
3-5 lesions	40	38	0.74 (0.40, 1.37) 0.59 (0.31, 1.10)
6-10 lesions	54	60	0.78 (0.50, 1.23) 0.77 (0.49, 1.22)
> 10 lesions	88	77	0.85 (0.59, 1.24) 0.71 (0.48, 1.05)

Previous

1. According to RECIST 1.1 by Blinded Independent Central Review (BICR).

OVERALL SURVIVAL (INTENT TO TREAT)[1]

There was no statistically significant difference in OS between the treatment and control arms in the intent to treat (ITT) population.



TheraSphere + Chemo:
Median 14.0 months (95% CI: 11.8, 15.5)

Chemo:
Median 14.4 months (95% CI: 12.8, 16.4)

Hazard Ratio 1.07 (95% CI: 0.86, 1.32)
1-sided $p = 0.7229$

N at Risk

TheraSphere + Chemo	215	183	112	71	43	17	8	7	3	3	2	0
Chemo	213	164	115	62	38	25	12	10	3	0	0	0

OVERALL SURVIVAL (PER PROTOCOL)[1,2]

TheraSphere + Chemo:
Median 15.2 months (95% CI: 12.7, 17.7)

Chemo:
Median 14.3 months (95% CI: 12.6, 16.4)

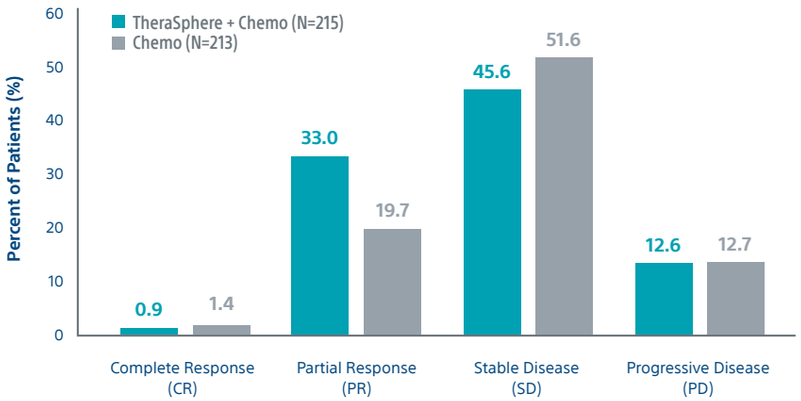
Hazard Ratio 0.96 (95% CI: 0.74, 1.24)
1-sided $p = 0.3841$

1. Time from randomization to death or last date known alive in absence of death.
2. OS Per Protocol: TheraSphere + Chemo (N=100) and Chemo (N=40) patients excluded from Per Protocol analysis due to major deviations.

TUMOR RESPONSE[1]

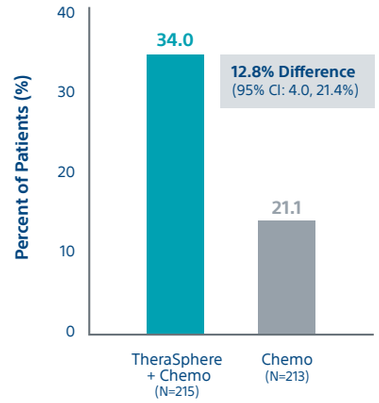
Patients receiving TheraSphere Y-90 with second-line chemotherapy showed an Objective Response Rate (ORR) of 34.0% vs. 21.1% for the control arm; a difference of 12.8%.

BEST OVERALL RESPONSE



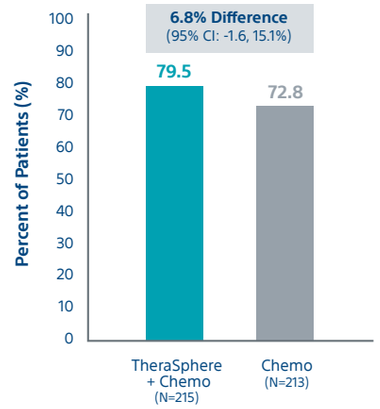
OBJECTIVE RESPONSE RATE (CR+PR)

1-sided $p = 0.0019$

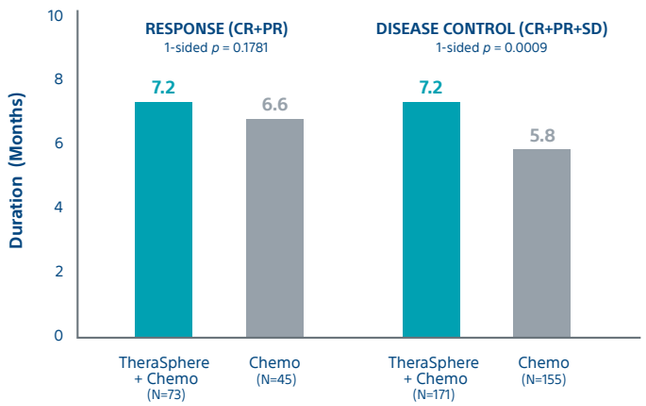


DISEASE CONTROL RATE (CR+PR+SD)

1-sided $p = 0.0626$



MEDIAN DURATION OF OBJECTIVE RESPONSE OR DISEASE CONTROL*

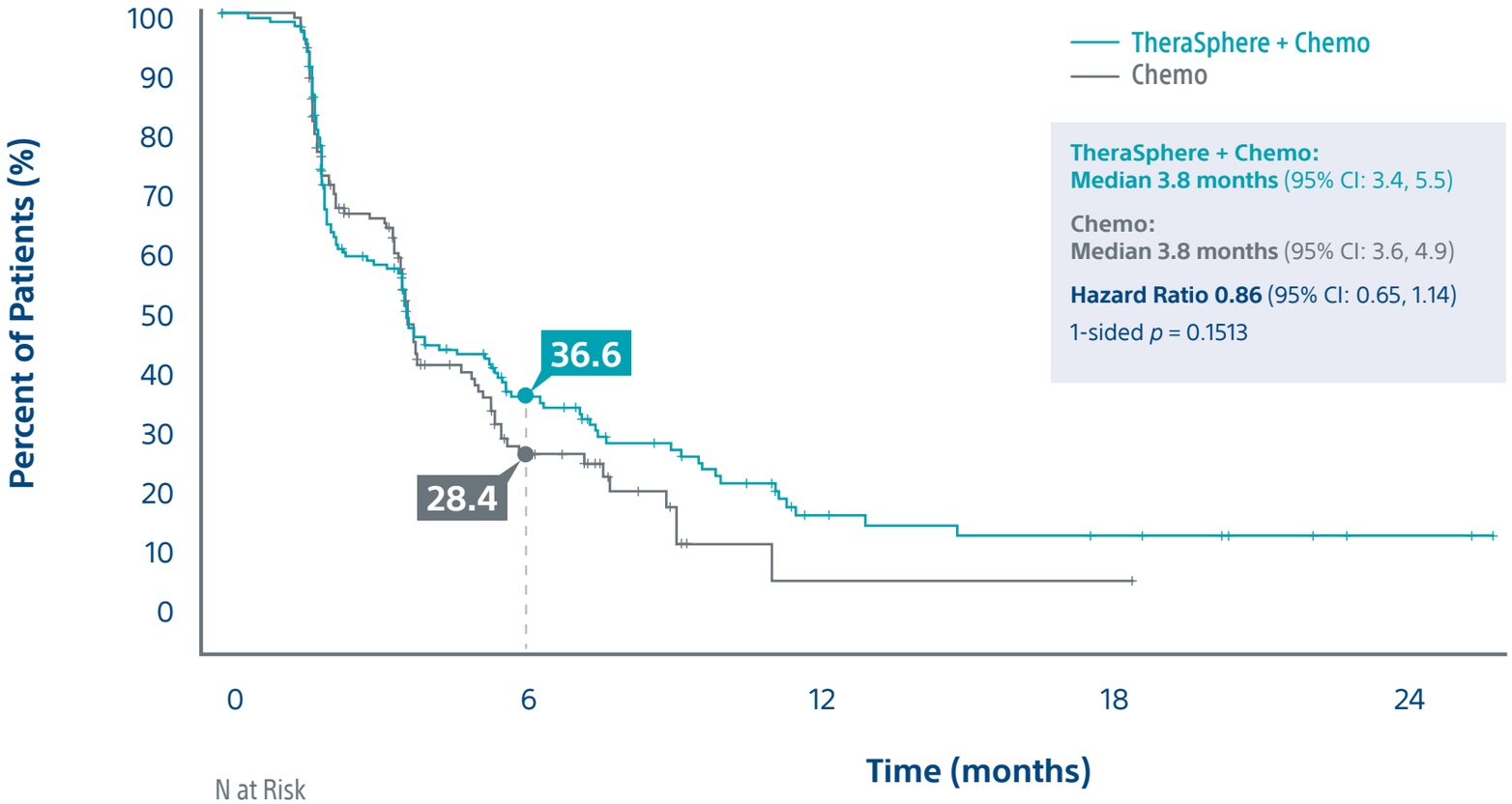


Duration of Disease Control was longer in the TheraSphere + Chemo group; however, Duration of Response in responders was not different between the two groups.

1. According to RECIST 1.1 by Blinded Independent Central Review (BICR).
2. By Kaplan-Meier analysis.
3. Time from first date of overall response of CR or PR by BICR until date of PD by BICR or death, whichever occurred first.
4. Time from first date of overall response of CR, PR, or SD by BICR until date of PD by BICR or death, whichever occurred first.

TIME TO DETERIORATION OF QUALITY OF LIFE (TTDQoL)[1]

The addition of TheraSphere Y-90 to second-line chemotherapy did not compromise quality of life.



TheraSphere + Chemo:
Median 3.8 months (95% CI: 3.4, 5.5)

Chemo:
Median 3.8 months (95% CI: 3.6, 4.9)

Hazard Ratio 0.86 (95% CI: 0.65, 1.14)

1-sided $p = 0.1513$

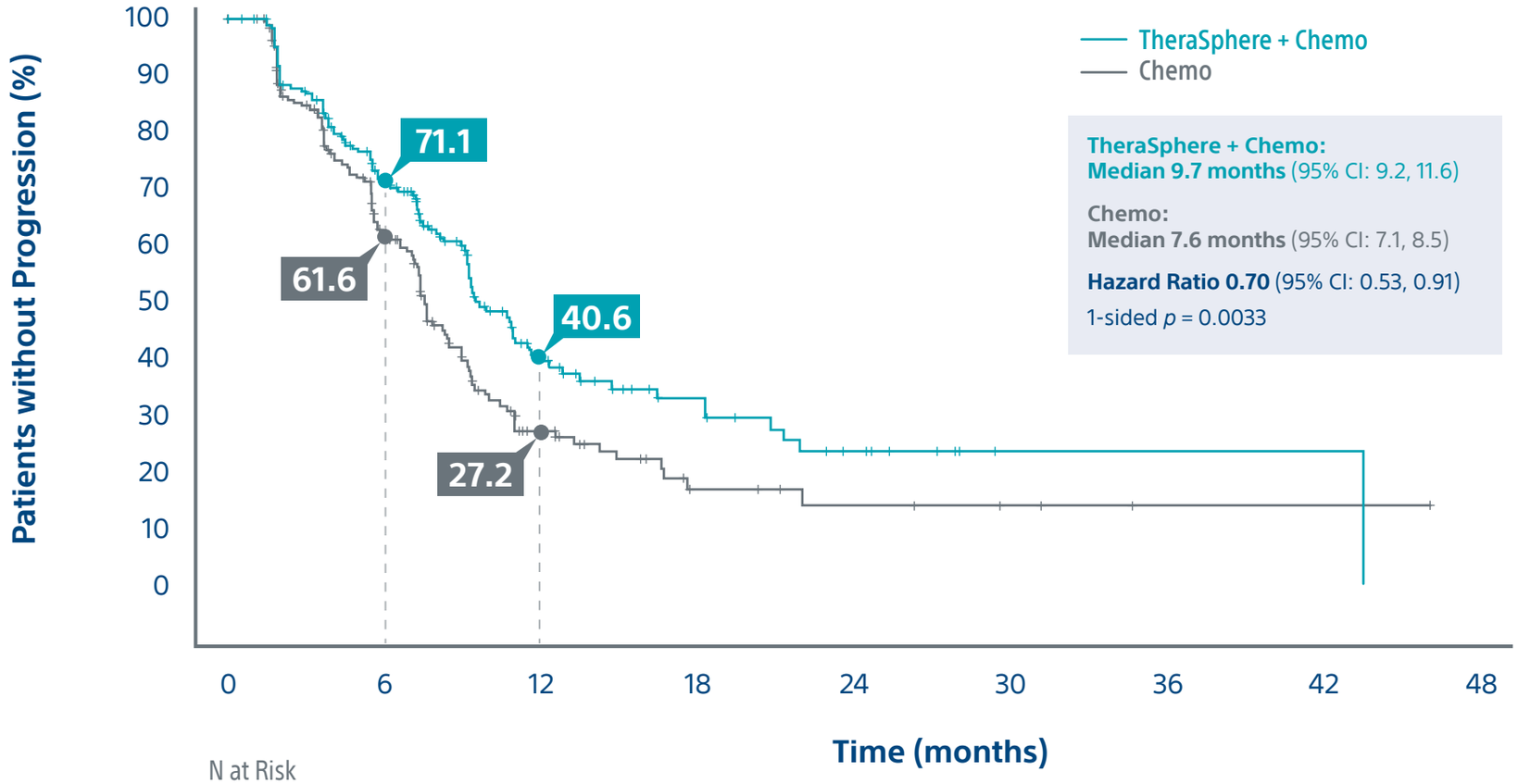
N at Risk

	0	6	12	18	24
TheraSphere + Chemo	215	43	11	7	2
Chemo	213	22	1	1	0

1. Time from randomization to the change from baseline in FACT-c total score ≤ -7 points or death, whichever occured first.

TIME TO PROGRESSION (TTP)[1]

The addition of TheraSphere Y-90 to second-line chemotherapy increased median TTP by 2.1 months.



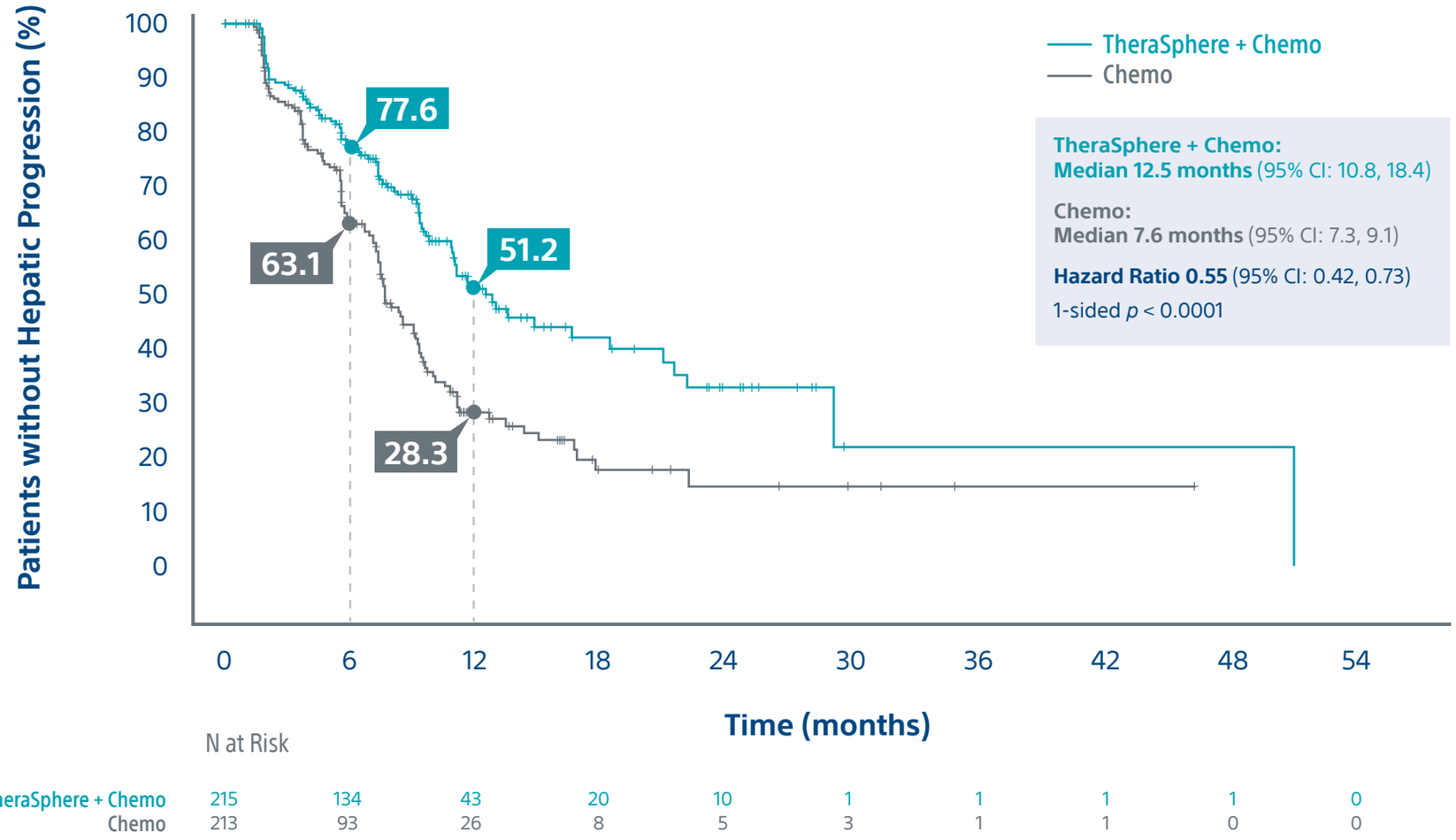
N at Risk

TheraSphere + Chemo	215	126	39	19	8	1	1	1	0
Chemo	213	93	26	8	5	3	1	1	0

1. Time from randomization to progression according to RECIST 1.1 by Blinded Independent Central Review (BICR) or death (due to any cause), whichever occurred first.

HEPATIC TIME TO PROGRESSION (hTTP)[1]

The addition of TheraSphere Y-90 to second-line chemotherapy increased median hTTP by 4.9 months.



TheraSphere + Chemo:
Median 12.5 months (95% CI: 10.8, 18.4)

Chemo:
Median 7.6 months (95% CI: 7.3, 9.1)

Hazard Ratio 0.55 (95% CI: 0.42, 0.73)
1-sided $p < 0.0001$

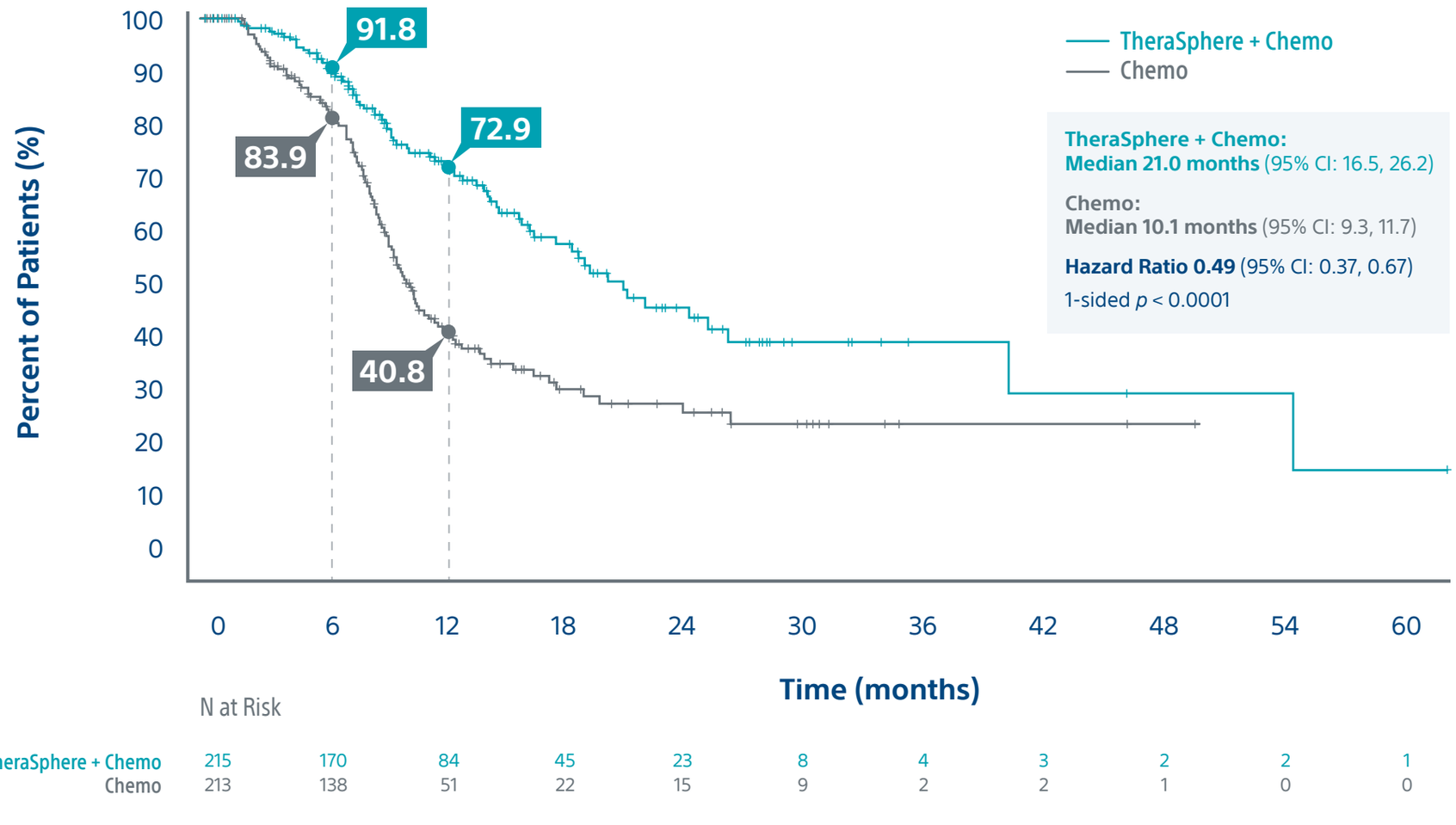
N at Risk

TheraSphere + Chemo	215	134	43	20	10	1	1	1	1	0
Chemo	213	93	26	8	5	3	1	1	0	0

1. Time from randomization to hepatic progression according to RECIST 1.1 by Blinded Independent Central Review (BICR) or death (due to any cause), whichever occurred first.

TIME TO START OF SUBSEQUENT THERAPY[1]

The addition of TheraSphere Y-90 to second-line chemotherapy extended median time to subsequent therapy by 10.9 months.



N at Risk

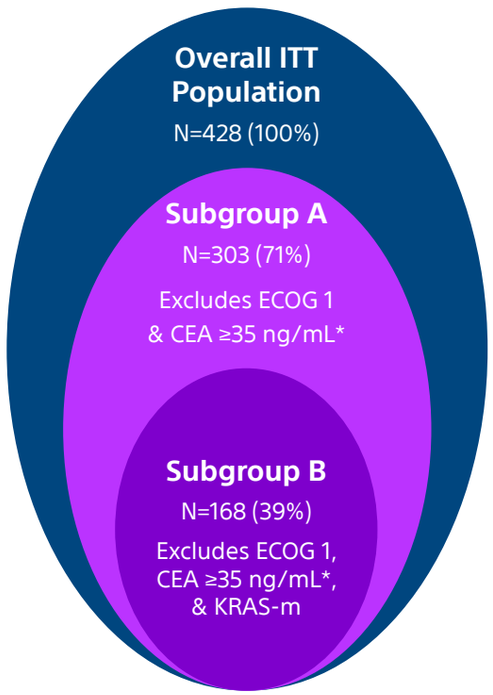
TheraSphere + Chemo	215	170	84	45	23	8	4	3	2	2	1
Chemo	213	138	51	22	15	9	2	2	1	0	0

1. Time from randomization to start of the subsequent mCRC therapy (i.e. a complete change in the treatment regimen or addition of another locoregional therapy, including ablation or resection).

POST-HOC SUBGROUP ANALYSES: PFS, hPFS, TTDQoL, & OS

Patients receiving TheraSphere Y-90 with second-line chemotherapy showed improved PFS and hPFS benefit, and additional time to deterioration of qualify of life (TTDQoL) in subgroups vs. chemo alone, and a greater magnitude in benefit compared to the overall intent to treat (ITT) population.

Two subgroup populations were identified based on three prognostic factors that impact TTDQoL



*35 ng/mL baseline CEA cutoff represents the median for the Overall ITT population in the study

Outcome (median, months)	Overall ITT Population[1]		Subgroup A[2]		Subgroup B[2]	
	TheraSphere + Chemo N=215	Chemo N=213	TheraSphere + Chemo N=143	Chemo N=160	TheraSphere + Chemo N=77	Chemo N=91
PFS	8.0	7.2	9.4	7.6	11.6	8.5
	Difference: +0.8 months **HR: 0.69** (95% CI: 0.54, 0.88) 1-sided p = 0.0013		**Difference: +1.8 months** **HR: 0.64** (95% CI: 0.47, 0.87) 1-sided p = 0.0020		**Difference: +3.1 months** **HR: 0.60** (95% CI: 0.39, 0.92) 1-sided p = 0.0089	
hPFS	9.1	7.2	10.8	7.6	12.5	8.5
	Difference: +1.9 months **HR: 0.59** (95% CI: 0.46, 0.77) 1-sided p < 0.0001		**Difference: +3.2 months** **HR: 0.53** (95% CI: 0.39, 0.73) 1-sided p < 0.0001		**Difference: +4.0 months** **HR: 0.51** (95% CI: 0.33, 0.79) 1-sided p = 0.0011	
TTDQoL	3.8	3.8	5.7	3.9	7.8	3.9
	Difference: +0.0 months **HR: 0.86** (95% CI: 0.65, 1.14) 1-sided p = 0.1513		**Difference: +1.8 months** **HR: 0.65** (95% CI: 0.46, 0.91) 1-sided p = 0.0063		**Difference: +3.9 months** **HR: 0.48** (95% CI: 0.30, 0.76) 1-sided p = 0.0008	

Overall Survival: No statistically significant difference in OS across Overall ITT Population or either Subgroups.

1. Mulcahy, M. et al, Radioembolization With Chemotherapy for Colorectal Liver Metastases: A Randomized, Open-Label, International, Multicenter, Phase III Trial (EPOCH). Journal of Clinical Oncology, 20 Sept 2021.
2. Harris, W. The EPOCH Trial: Identifying Key Patient Subgroups to Optimize Treatment Planning. Poster presented at: ASCO-GI; January 21, 2023; San Francisco, CA.

KEY PATIENT & DISEASE CHARACTERISTICS

Patient and disease characteristics were well-balanced between the treatment and control arms.

	TheraSphere + Chemo (N = 215)	Chemo (N = 213)
Median Age (y)	63.0	60.0
Male	135 (62.8%)	138 (64.8%)
Region		
North America	63 (29.3%)	56 (26.3%)
Europe	131 (60.9%)	145 (68.1%)
Asia	21 (9.8%)	12 (5.6%)
ECOG 0	119 (55.3%)	133 (62.4%)
Albumin ≥ Site LLN[1]	182 (84.7%)	177 (83.1%)
CEA[2] ≥ 35 ng/mL	116 (54.0%)	105 (49.3%)
KRAS Status		
Mutant	100 (46.5%)	101 (47.4%)
Wild Type	115 (53.5%)	112 (52.6%)
Bilobar disease	176 (81.9%)	173 (81.2%)
Liver tumor burden at baseline by BICR		
< 10%	124 (57.7%)	121 (56.8%)
≥ 10% to < 25%	54 (25.1%)	47 (22.1%)
≥ 25%	29 (13.5%)	28 (13.1%)
Missing	8 (3.7%)	17 (8.0%)
Maximum liver lesion size ≥ 4 cm	162 (75.3%)	142 (66.7%)
Primary tumor in situ	83 (38.6%)	69 (32.4%)
Left side primary tumor location	150 (69.8%)	136 (63.8%)
Extrahepatic metastases at baseline	113 (52.6%)	95 (44.6%)

1. LLN = lower limit of normal.
2. CEA = carcinoembryonic antigen.

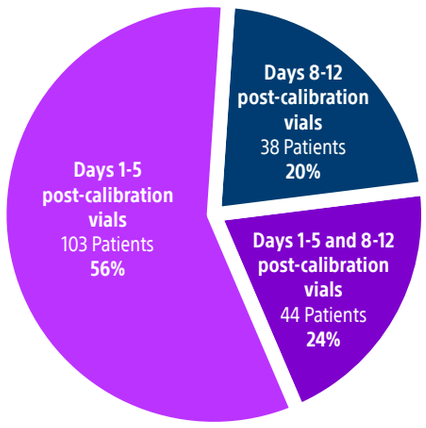
TREATMENT CHARACTERISTICS

Treatment characteristics were well-balanced between the treatment and control arms.

	TheraSphere + Chemo (N = 215)	Chemo (N = 213)
Received Assigned Therapy	187 (87.0%)	191 (89.7%)
2nd Line Chemo Administered	203 (94.4%)	191 (89.7%)
Irinotecan-based / Mean Number of Cycles	130 (60.5%) / 9.0	123 (57.7%) / 9.5
Oxaliplatin-based / Mean Number of Cycles	73 (34.0%) / 8.5	68 (31.9%) / 8.8
Biological Agent	88 (40.9%)	93 (43.7%)
TheraSphere Y-90 Glass Microspheres Treatment		
Median time to TheraSphere Y-90 treatment, days (range)	25 (12, 90)	NA

DOSIMETRY APPROACH

In the 185 patients treated with TheraSphere Y-90 prior to progression[1]:



Treatment Median: **Day 4** post-calibration

Median Specific Activity: **1,400 Bq** (single sphere)

Median dose absorbed by perfused volume: **117.0 Gy** (range: 61.7-156)

SAFETY

The addition of TheraSphere Y-90 to second-line chemotherapy did not increase chemo-related adverse events and no new safety signals were identified.[2]

Post-Hoc Analyses:
Liver-related treatment emergent adverse events (TEAEs) occurred more frequently in patients with <10% liver volume replaced by tumor and/or in patients with >10 lesions, likely due to increased proportion of irradiated normal liver tissue. Sequential lobar treatment, as opposed to same day whole liver treatment (as required by EPOCH protocol), may mitigate liver-related TEAEs.[3]

1. As assessed by investigator. 2. Mulcahy, M. et al, Radioembolization With Chemotherapy for Colorectal Liver Metastases: A Randomized, Open-Label, International, Multicenter, Phase III Trial (EPOCH). Journal of Clinical Oncology, 20 Sept 2021.
3. Salem, R. Optimizing patient selection for treating colorectal liver metastases with glass radioembolization plus chemotherapy: The EPOCH study. Lecture presented at: Society of Interventional Oncology; January 22, 2023; Washington, DC.

TheraSphere™ Y-90 Glass Microspheres Indications, Safety, and Warnings

https://www.bostonscientific.com/therasphere-indications

CAUTION: TheraSphere is under an investigational device exemption for treatment of patients with metastatic colorectal cancer. The safety and effectiveness for this treatment has not been established. For full adverse event rates and complete data set, reference Journal of Clinical Oncology manuscript.

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