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Abstract #SESS-1642

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PHENOMENAL: Efficacy and safety of liposomal irinotecan in patients with HER2-negative breast cancer and brain metastases

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BACKGROUND

- Among all solid tumors, advanced breast cancer (ABC) is the second cause of brain metastases (BMs).[1]
- HER2[-] breast cancer (BC) patients (pts) with central nervous system (CNS) involvement progressing after prior local therapy have limited therapeutic options and very poor outcomes.[2-3]
- Liposomal irinotecan (nal-IRI) is a novel formulation of irinotecan, a topoisomerase 1 inhibitor encapsulated in a liposome drug delivery system that has shown promising activity in pts with BMs.[4]
- We hypothesized that nal-IRI could exhibit relevant clinical activity in HER2[-] ABC pts with BMs.[5]

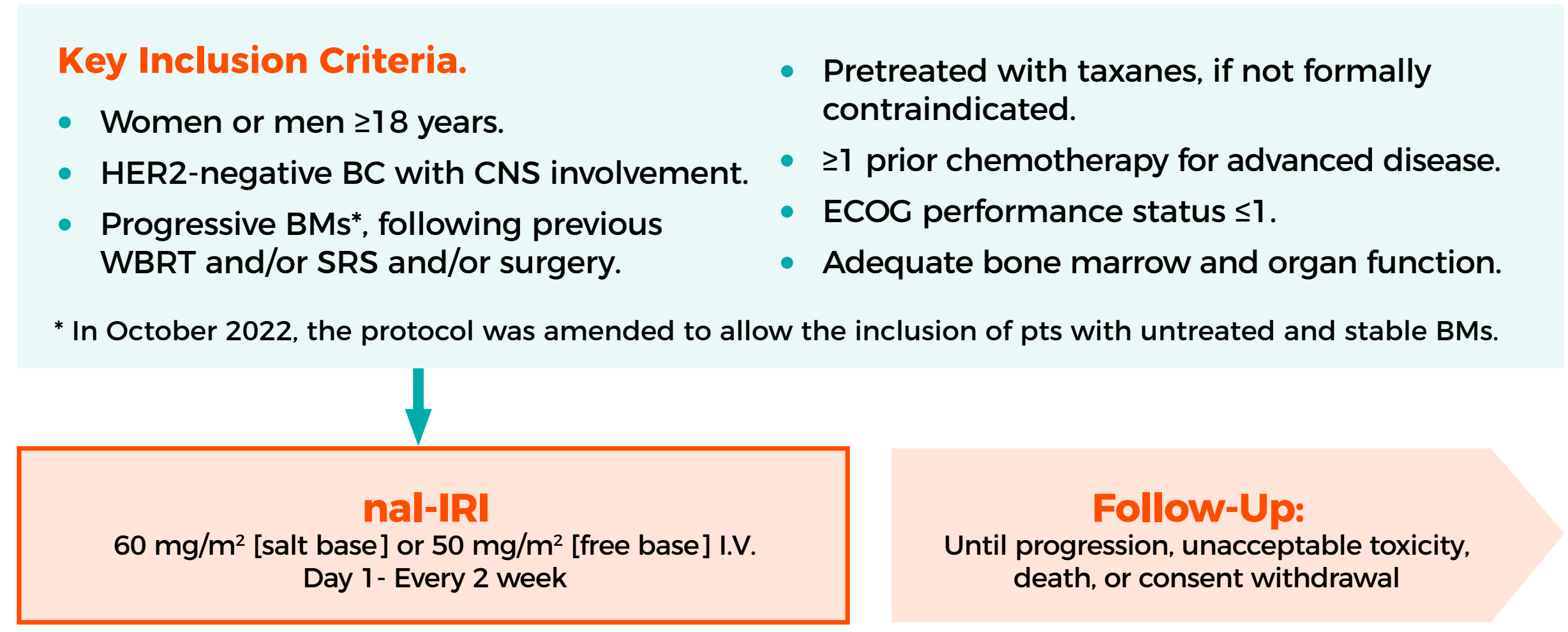
OBJECTIVE

- To assess the intracranial objective response rate (IC-ORR) according to Response Assessment in Neuro-oncology (RANO)-BM in pts with progressive BMs.

STUDY DESIGN

Figure 1. PHENOMENAL Study Design (NCT03328884)

- Open-label, single-arm, multicenter phase IIa clinical trial.
- Simon two-stage minimax design.
  - Stage 1: ≥ 2/23 responders to nal-IRI required to progress to stage 2.
  - Stage 1+2: ≥ 6/56 responders to nal-IRI to declare signal of efficacy.



Key Inclusion Criteria.

- Women or men ≥18 years.
- HER2-negative BC with CNS involvement.
- Progressive BMs*, following previous WBRT and/or SRS and/or surgery.
- Pretreated with taxanes, if not formally contraindicated.
- ≥1 prior chemotherapy for advanced disease.
- ECOG performance status ≤1.
- Adequate bone marrow and organ function.

* In October 2022, the protocol was amended to allow the inclusion of pts with untreated and stable BMs.

nal-IRI
60 mg/m² [salt base] or 50 mg/m² [free base] I.V.
Day 1- Every 2 week

Follow-Up:
Until progression, unacceptable toxicity, death, or consent withdrawal

- **Primary endpoint:** IC-ORR by RANO-BM in pts with progressive BMs.
- **Secondary endpoints:** IC, EC, and overall (IC + EC) ORR, CBR at 12 weeks per RECIST v.1.1, PFS, OS, duration of response, safety and tolerability as per NCI-CTCAE v.4.0.

METHODS

PRIMARY ENDPOINT

- IC-ORR in pts with progressive BMs as per a modified RANO-BM criteria with local confirmation until the next tumor assessment (after 6 weeks) or with a ≥65% volumetric reduction of IC lesions by blinded independent central review.

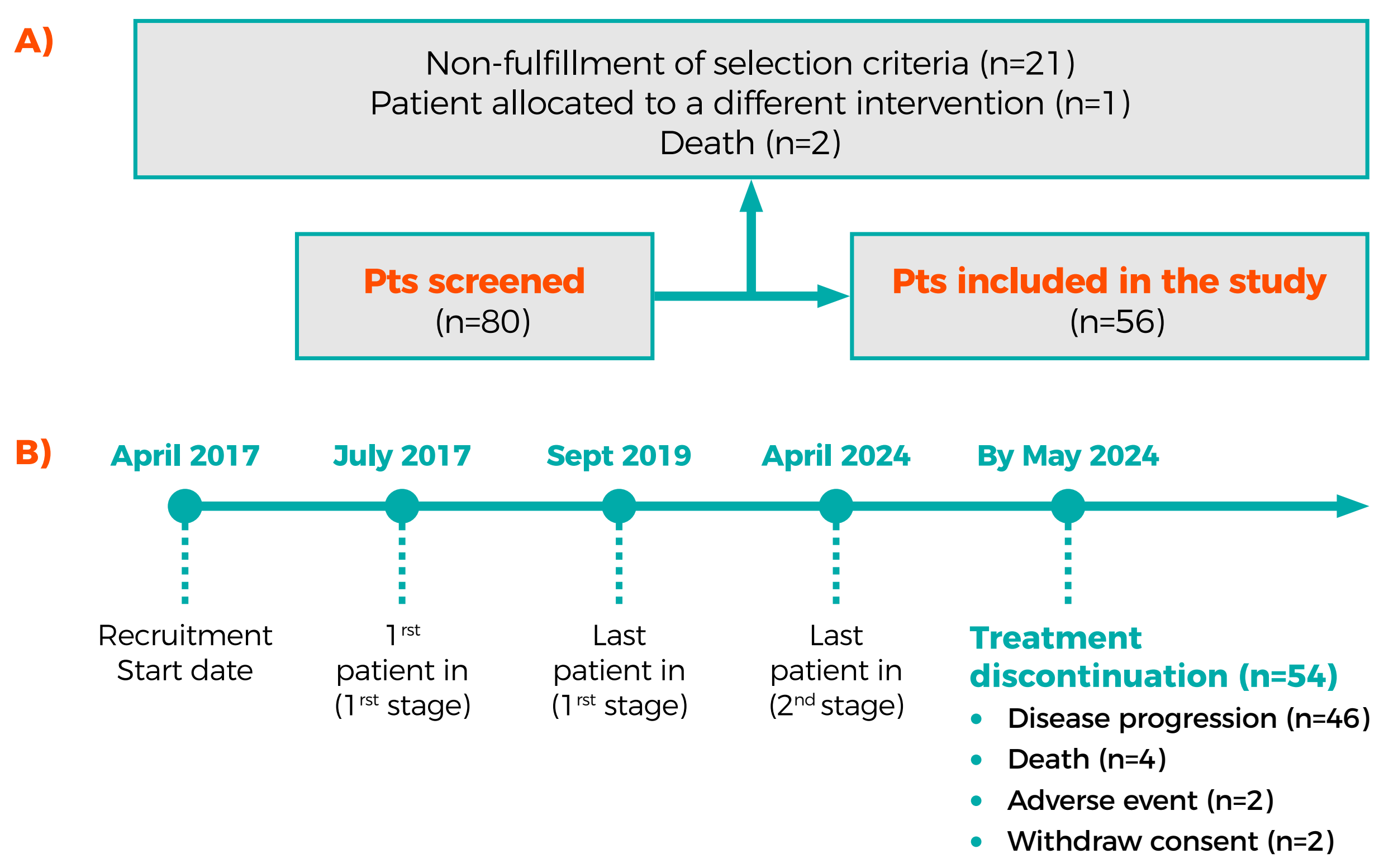
SECONDARY ENPOINTS

- ORR according to a CNS volumetric parameter, as per RANO-BM criteria for IC lesions, and as per RECIST v.1.1 for EC and overall (IC + EC) lesions.
- CBR ≥12 weeks determined locally by investigator per RECIST v1.1.
- PFS (time from the first dose of treatment until objective tumor progression or death by any cause).
- OS (time from the first dose of treatment until death by any cause).
- Duration of response.
- Safety and tolerability as per NCI-CTCAE v.4.0.

STATISTICS

- Primary analysis estimated the IC-ORR (H0≤5.0%; H1: IC-ORR ≥15.0%).
- 95%CI and p-value were calculated with the method of Jung and Koyama.
- Sample size was planned to attain an 80% power at a nominal a level of 0.05.

Figure 2. Recruitment **(A)** and study timeline **(B)**



A)

Non-fulfillment of selection criteria (n=21)
Patient allocated to a different intervention (n=1)
Death (n=2)

Pts screened (n=80)

Pts included in the study (n=56)

B)

April 2017 Recruitment Start date

July 2017 1rst patient in (1rst stage)

Sept 2019 Last patient in (1rst stage)

April 2024 Last patient in (2nd stage)

By May 2024 **Treatment discontinuation (n=54)**

- Disease progression (n=46)
- Death (n=4)
- Adverse event (n=2)
- Withdraw consent (n=2)

RESULTS

1. RECRUITMENT AND PATIENT DISPOSITION

- Between July 2017 and April 2024, 56 pts were enrolled across 16 hospitals in Spain.
- Fifty-one pts (91.1%) had progressive BMs. A total of two (3.6%) and three pts (5.3%) had stable and previously untreated BMs, respectively.
- Twenty-seven pts (48.2%) had HR[+]/HER2[-] tumors and 29 pts (51.8%) had triple-negative breast cancer.
- The median number of previous lines of therapy for advanced disease was 3 (range, 1-8).
- At data cutoff date (May 15, 2024), median follow-up was 5.7 months (range, 0.4-56.5 months) and two pts(3.6%) remained on therapy.

Table 1. Patient characteristics at Baseline

Baseline characteristics, n (%)	N=56
Age, Median (Min; Max), years	52 (32; 83)
ECOG	
0	17 (30.3%)
1	38 (67.9%)
2	1 (1.8%)
Tumor Subtype	
HR[+]/HER2[-]	27 (48.2%)
TNBC	29 (51.8%)
EC measurable disease	
No	19 (33.9%)
Yes	37 (66.1%)
Number of metastatic organs involved	
<3	24 (42.9%)
≥3	32 (57.1%)
Type of BMs	
Progressive	51 (91.1%)
Previously untreated	3 (5.3%)
Stable	2 (3.6%)
Prior local treatment for IC disease	
WBRT	38 (67.9%)
SRS	21 (37.5%)
Surgery	13 (23.2%)
Number of prior lines for advanced disease	
1	14 (25.0%)
2	12 (21.4%)
≥3	30 (53.6%)

2. EFFICACY ENDPOINTS

- The primary endpoint of the study was met with 10 out of 51 pts (19.6%; 95%CI 11.1-28.9) with progressive BMs achieving a confirmed IC-ORR (p<0.001).
- IC-ORR in all pts was 19.6% (11/56 pts; 95%CI, 10.2-32.4).
- EC-ORR in pts with measurable EC disease was 2.7% (1/37 pts; 95%CI, 0.0-14.2) and overall (IC + EC) ORR in all pts was 5.4% (3/56 pts; 95% CI, 1.1–14.9).
- Median PFS was 1.5 mo (95%CI, 1.4-2.8) (Figure 3).
- Median OS was 6.4 mo (95%CI, 4.3-10.8) (Figure 4).

Figure 3. Progression-Free Survival

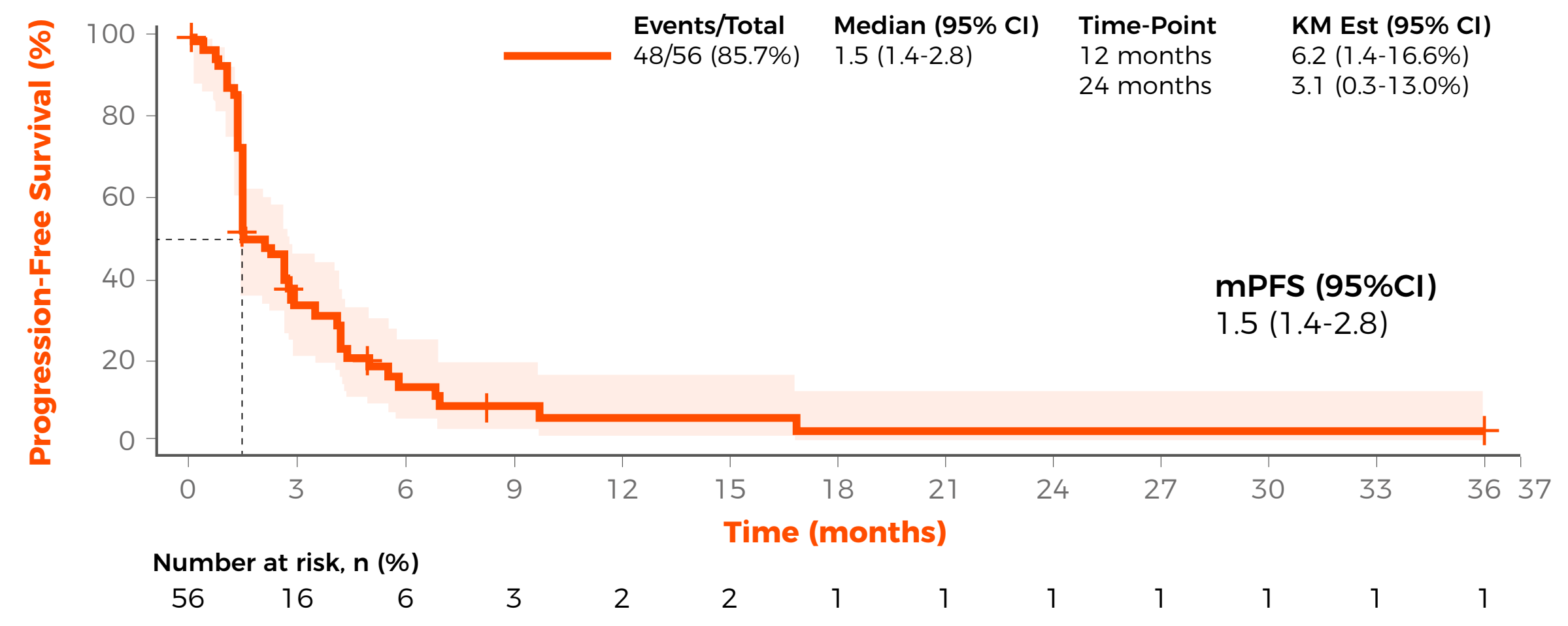
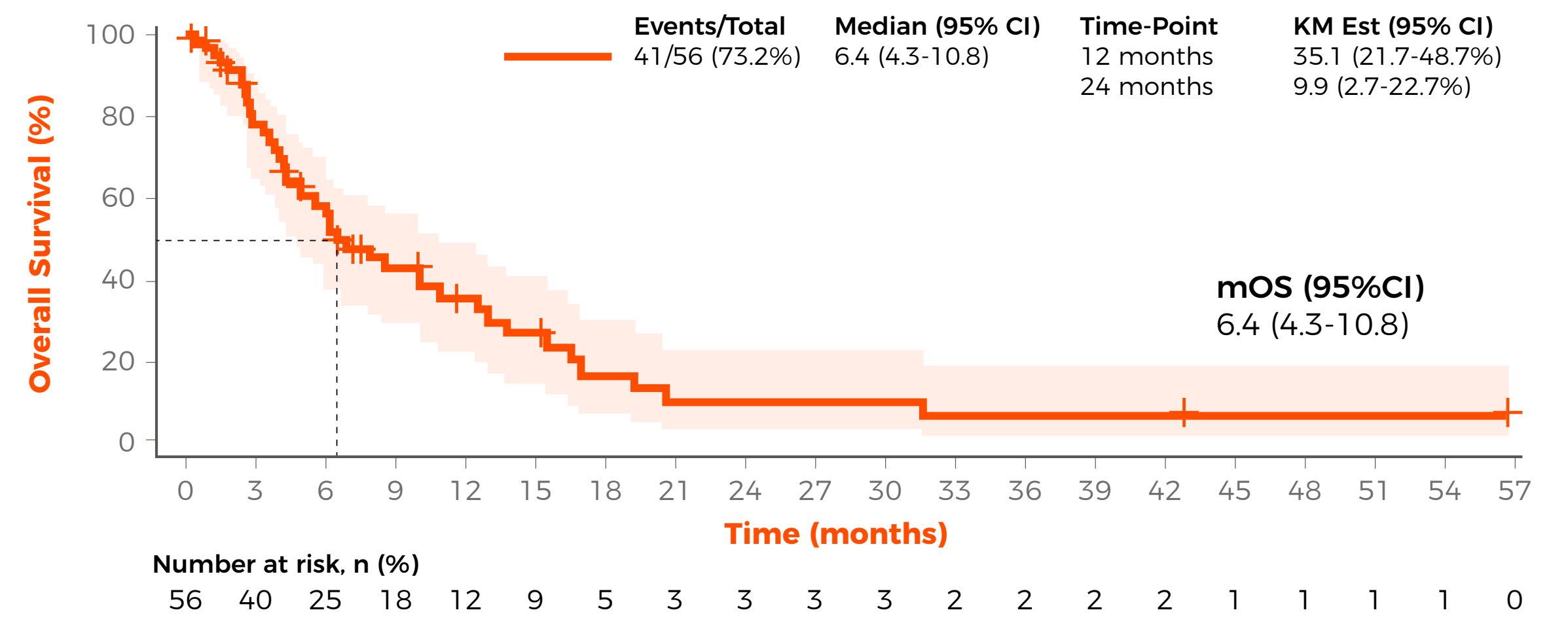


Figure 4. Overall Survival



3. SAFETY ENDPOINTS

- The most common treatment emergent adverse events (TEAEs) of any grade (G) were fatigue (55.4%; 7.1% G≥3) and headache (44.6%; 1.8% G≥3) (Table 2).
- There were no treatment-related deaths and no new safety issues were reported.

Table 2. Summary of TEAEs

TEAEs	Overall (n=56)	Treatment related
Any	49 (87.5%)	32 (57.1%)
Grade 3-5	17 (30.4%)	8 (14.3%)
Serious	9 (16.1%)	1 (1.8%)
Leading to discontinuation	4 (7.1%)	-

TEAEs occurring in more than 15% of pts, n (%)	Any grade	Grade ≥3
Non-hematologic		
Fatigue	31 (55.4%)	4 (7.1%)
Headache	25 (44.6%)	1 (1.8%)
Diarrhea	24 (42.9%)	0 (0.0%)
Nausea	14 (25.0%)	0 (0.0%)
Hematologic		
Neutropenia	11 (19.6%)	3 (5.4%)

CONCLUSIONS

- **PHENOMENAL met its primary endpoint of IC-ORR in patients with progressive BMs**
- **Although overall (IC + EC) ORR is low and median PFS is limited, OS results are clinically meaningful in a patient population with dismal prognosis**
- **nal-IRI had a manageable toxicity profile and no new safety concerns were identified**

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Presenter Author Conflict of Interest: None.

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Abbreviations: ABC: advanced breast cancer; **pts:** patients; **BM:** brain metastases; **CNS:** central nervous system; **IV:** Intravenous; **nal-IRI:** liposomal Irinotecan. **IC:** Intracranial; **EC:** Extracranial; **ORR:** Objective Response Rate; **RANO:** Response Assessment in Neuro-oncology; **RECIST:** Response Evaluation Criteria In Solid Tumors; **SRS:** Stereotactic radiosurgery; **WBRT:** whole-brain radiotherapy; **ECOG:** Eastern Cooperative Oncology Group; **NCI-CTCAE:** Common Terminology Criteria for Adverse Events; **PFS:** progression-free survival; **OS:** overall survival; **CBR:** Clinical benefit rate; **BOR:** Best Overal Response; **TEAEs:** Treatment emergent adverse events; **G:** grade.