Orally Administered MOMA-341 as Monotherapy or Combination Therapy in Participants With Advanced or Metastatic Solid Tumors: Phase 1 Study Design

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STUDY OBJECTIVES

- The primary objective is to characterize the safety and tolerability of MOMA-341 as monotherapy or in combination with chemotherapy or immunotherapy.
- Key secondary objectives include the following for MOMA-341 monotherapy and in combination with chemotherapy (irinotecan) or immunotherapy:
  - To identify the recommended phase 2 dose(s) and/or recommended optimization doses
  - To characterize the pharmacokinetic (PK) profile
  - To investigate the effects of food on PK parameters (in select participants only)
  - To assess preliminary evidence of antitumor activity
  - To characterize the pharmacodynamics (PDx)

SUMMARY

- MOMA-341 is a potent and selective inhibitor of WRN helicase in dMMR/MSI-H cancers.
- Characterizing the properties of MOMA-341 will support its potential utility to treat dMMR/MSI-H cancers as monotherapy and in combination with standard of care chemotherapy and immunotherapy.
- The results from this phase 1 study will help determine the MOMA-341 optimal biologic dose for future studies and will enable further understanding of the patient selection biomarker through analysis of the relationship between TA repeat expansions and response.

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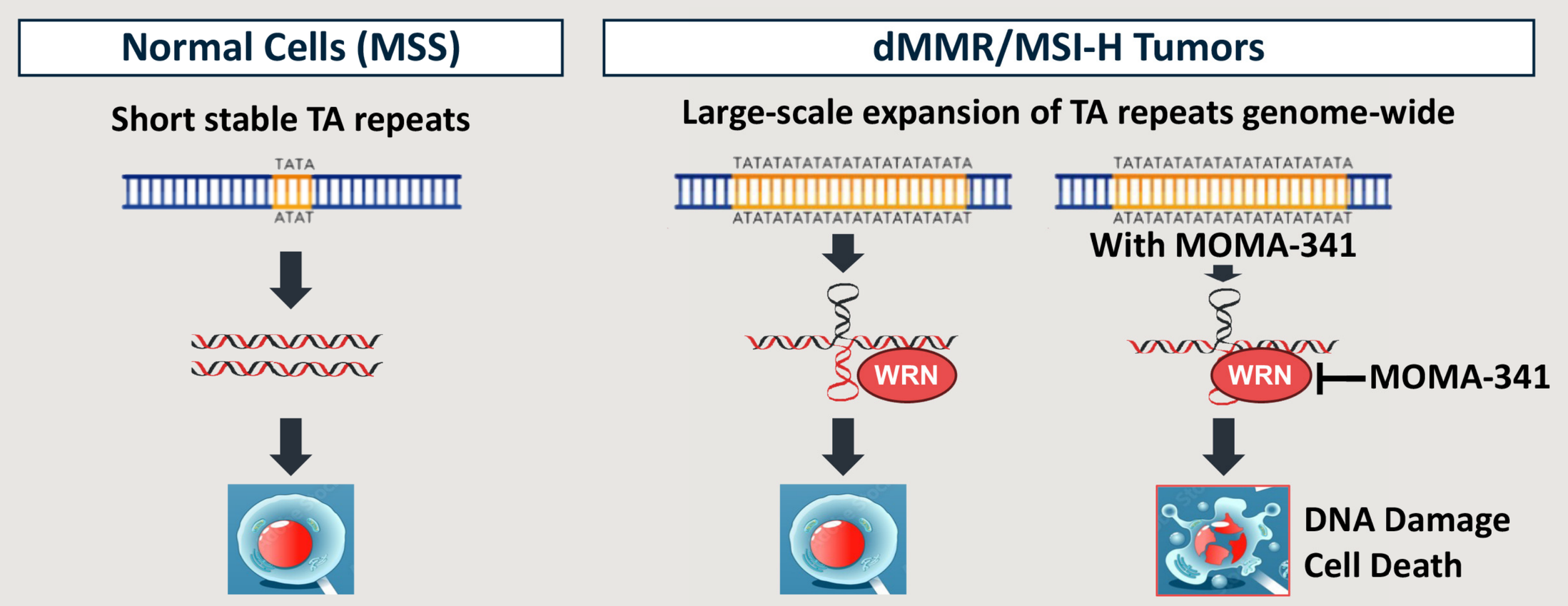
BACKGROUND

- Patients with advanced or metastatic solid tumors harboring microsatellite instability high (MSI-H) or DNA mismatch repair deficiency (dMMR) alterations have benefited from immune checkpoint inhibitors (ICIs).
- However, many patients cannot tolerate ICIs or show innate or acquired resistance to these agents. Additionally, in some regions access to ICIs is limited. Therefore, additional therapies with rapid response rates and longer durations of response are needed.
- Tumors with MSI-H or dMMR alterations have a specific dependence on Werner RecQ like helicase (WRN), whose role in DNA replication and repair is required in this context.
- WRN activity is required for successful DNA replication at expanded thymine and adenine (TA) dinucleotide repeats occurring from dMMR. Loss of WRN leads to DNA damage at TA repeat sites, resulting in cell death and tumor regression. Sensitivity to WRN loss or inhibition is proportional to the extent of TA repeat expansion.
- MOMA-341 is a potent and selective oral inhibitor of the WRN helicase domain that covalently ligates its target cysteine, WRN-C727, and induces DNA damage and cell death in tumor cells harboring MSI-H or dMMR, but not in normal microsatellite-stable cells (**Figure 1**).

Figure 1. MOMA-341 inhibition of WRN results in cell death in dMMR/MSI-H tumors



dMMR, DNA mismatch repair deficiency; MSI-H, microsatellite instability high; MSS, microsatellite stable; TA, thymine and adenine; WRN, Werner RecQ-like

MOMA-341 monotherapy preclinical data

- MOMA-341 treatment results in dose-dependent antitumor activity and tumor regression in a SW48 MSI-H colorectal cancer (CRC) xenograft model (**Figure 2A**)
- MOMA-341 monotherapy demonstrated dose-dependent target engagement (**Figure 2B**) and induction of DNA damage and WRN degradation (**Figure 2C**).

Figure 2A. Tumor Regressions in SW48 MSI-H CRC Xenograft Model

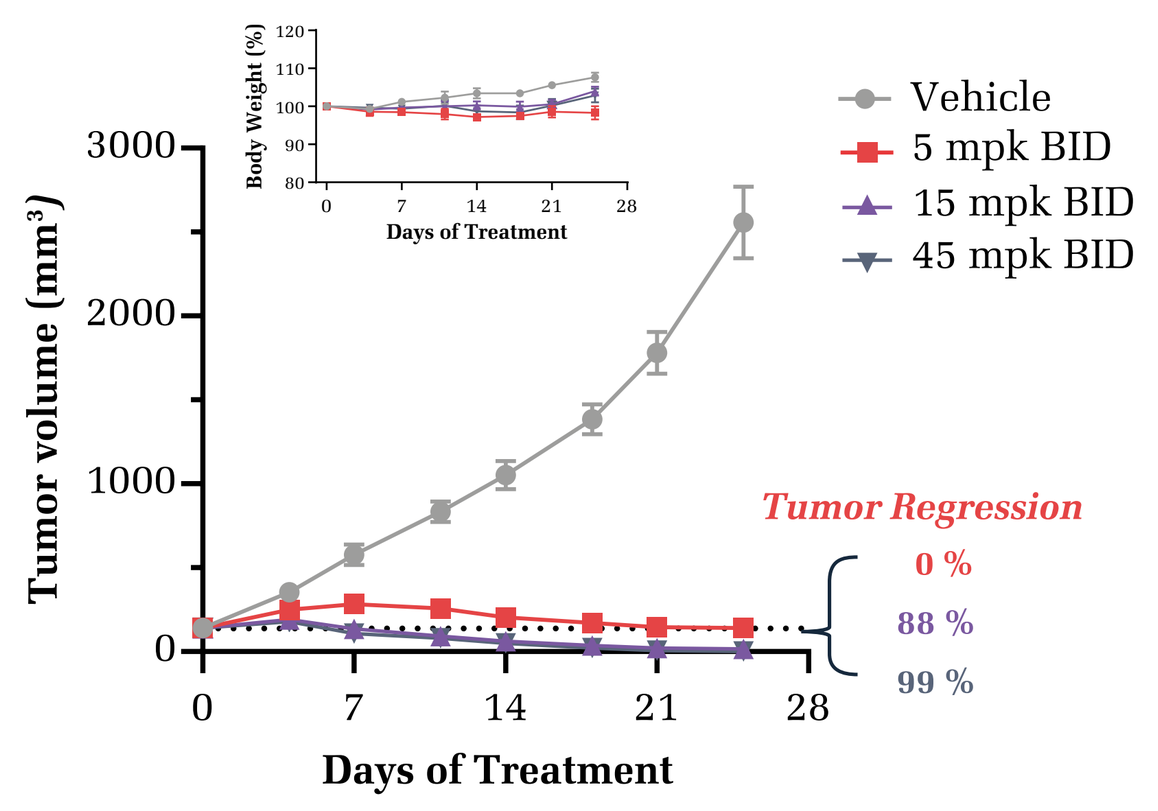


Figure 2B. Dose-Dependent Occupancy *in vivo* (C_{trough})

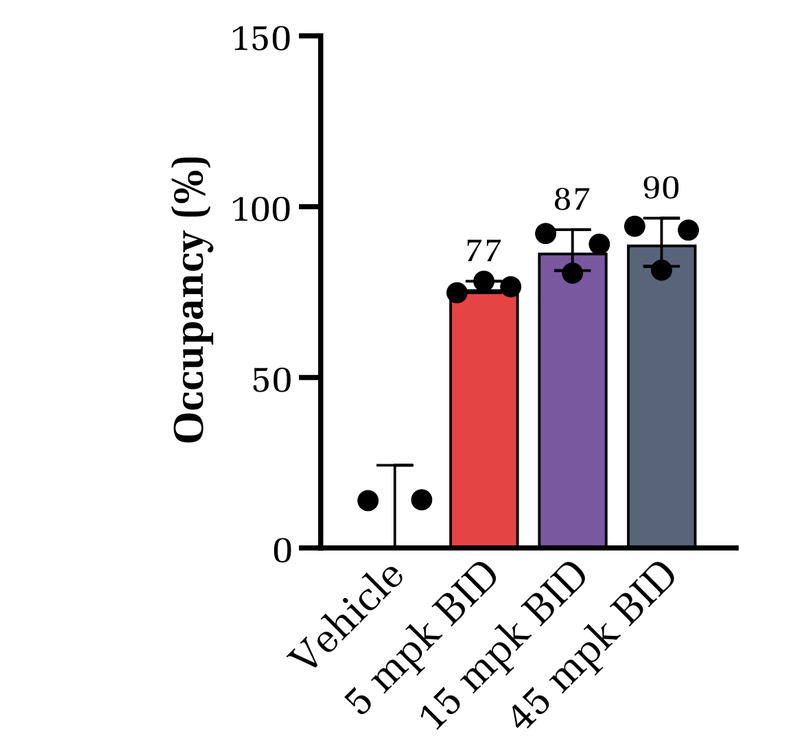
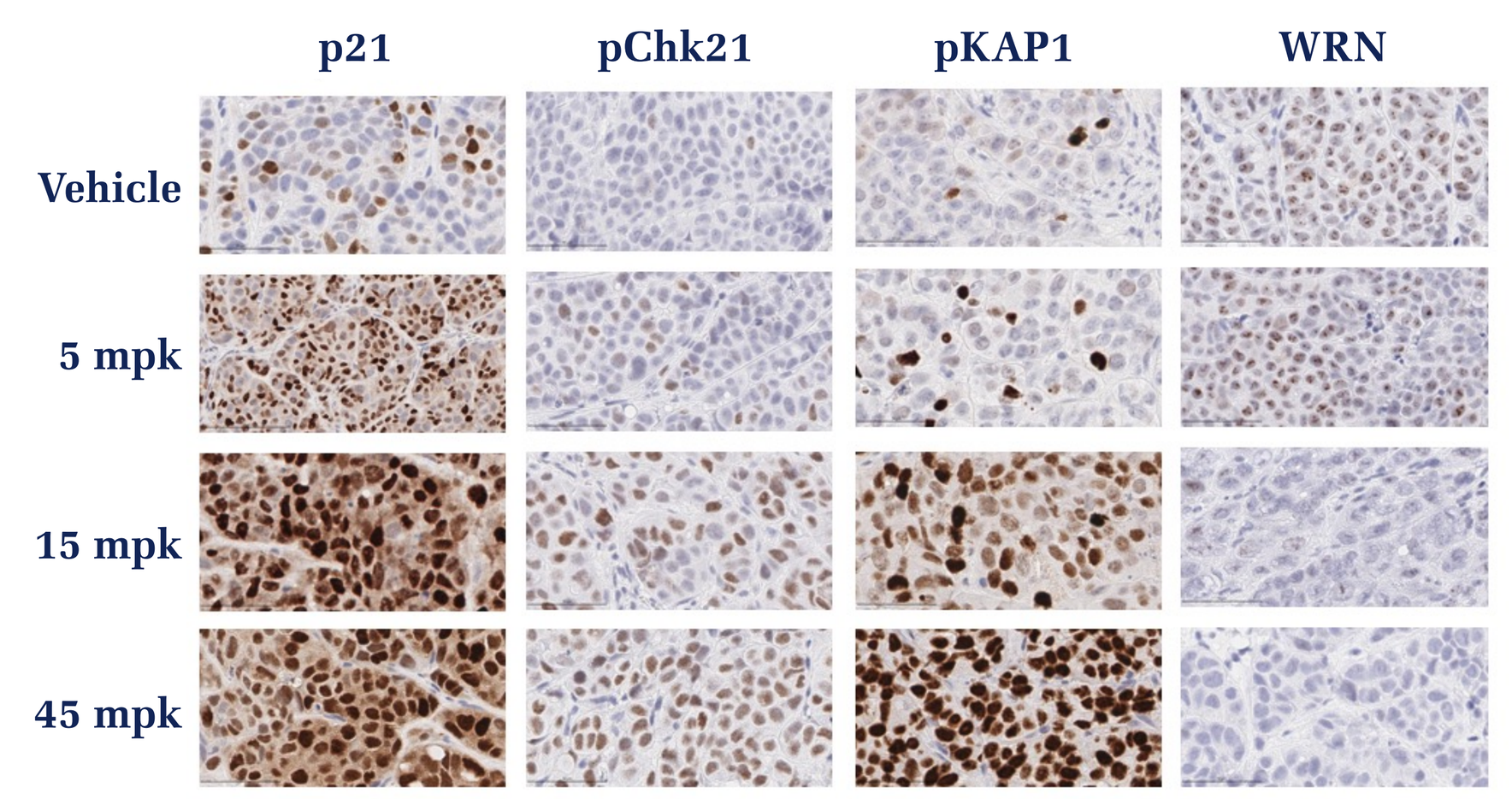


Figure 2C. Dose-Dependent Induction of DNA Damage Response and WRN Degradation



BID, twice daily; CRC, colorectal cancer; C_{trough}, trough concentration; mpk, milligrams per kilogram; MSI-H, microsatellite instability high; WRN, Werner RecQ-like

MOMA-341 chemotherapy combination preclinical data

- Combination of MOMA-341 with chemotherapy results in enhanced antitumor activity due to the additive induction of the DNA damage response by both agents (**Figure 3A, B**).
- In tumors with moderate TA expansions, higher doses of MOMA-341 or combination with standard chemotherapy, such as irinotecan, enhance DNA damage and antitumor activity (**Figure 3C**).

Figure 3A. MOMA-341 + Irinotecan Combination Enhances Antiproliferative Effect and p21 Induction

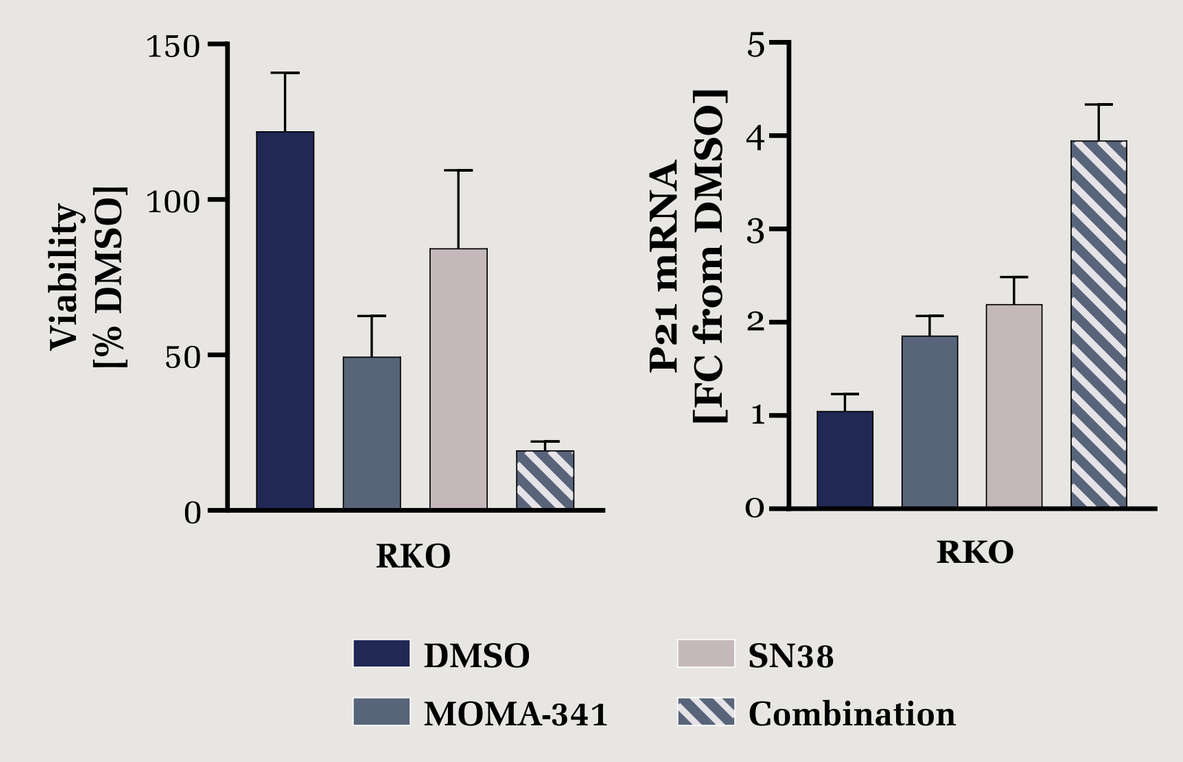


Figure 3B. MOMA-341 + Paclitaxel Combination Enhances Antiproliferative Effect

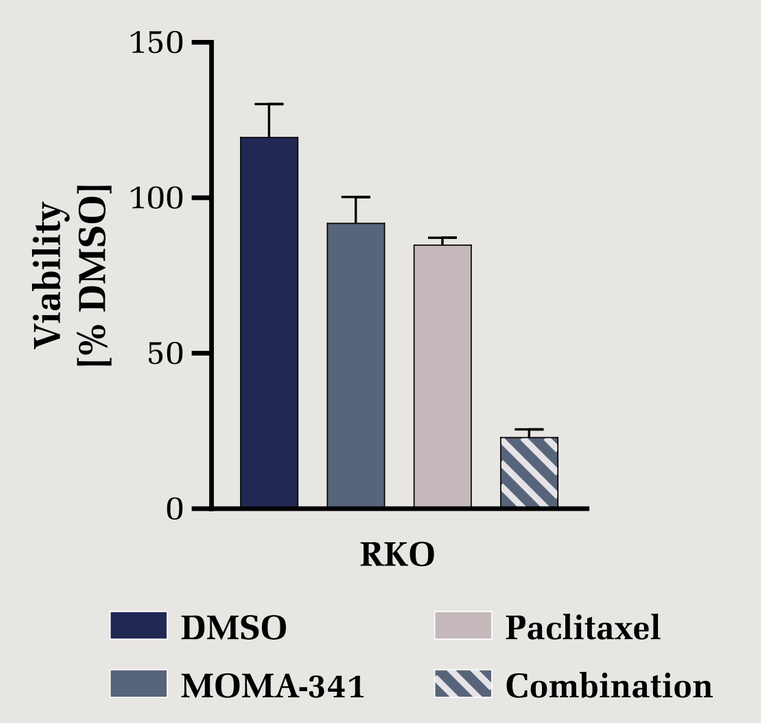
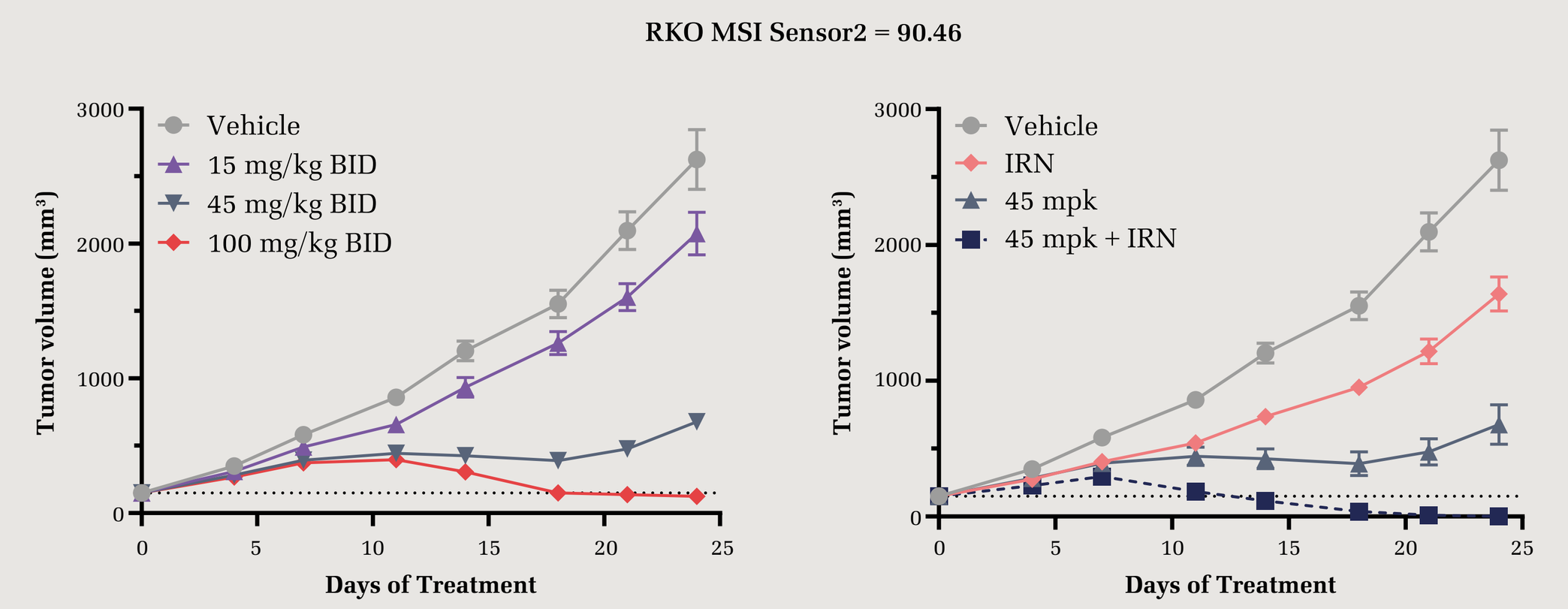


Figure 3C. CDX Model With Moderate TA Score (RKO) Benefits From Higher Dose MOMA-341 or Combination With Irinotecan



DSMO, dimethyl sulfoxide; mRNA, messenger RNA

BID, twice daily; IRN, irinotecan; MSI, microsatellite instability

- Combinations of MOMA-341 and standard of care agents including chemotherapy and immunotherapy are expected to provide additional benefit to patients.
- MOMA-341 was well-tolerated in nonclinical repeat-dose toxicology studies in rats and dogs at doses projected to be pharmacologically active.
- The selective activity of MOMA-341 and nonclinical data support its development as monotherapy or combination therapy for treatment of dMMR or MSI-H solid tumors in the clinical setting.

STUDY DESIGN AND METHODS

- This is a phase 1, first-in-human, multi-center, open-label dose escalation and dose optimization study designed to assess the safety, tolerability, PK, PDx, and preliminary clinical activity of MOMA-341 (NCT06974110).
- MOMA-341 will be administered orally as monotherapy or in combination with either chemotherapy or immunotherapy in participants with advanced or metastatic solid tumors harboring MSI-H/dMMR alterations.
- Key study inclusion and exclusion criteria are presented in **Table 1**.

Table 1. Key Study Entry Criteria

Inclusion criteria
≥18 years of age
Histologically confirmed disease with a known MSI-H or dMMR alteration and unresectable advanced (including locally) or metastatic solid tumors
Must have previously received and progressed on an anti-PD-(L) 1-based regimen unless ineligible or in a region without access to anti-PD(L)-1 therapies
Presence of ≥1 lesion at baseline (measurable or nonmeasurable) suitable for repeated imaging evaluation by RECIST v1.1 and, for participants with prostate cancer, identifiable disease by PCWG-3 criteria
ECOG PS ≤2
Fully recovered from the effects of prior therapy
Exclusion criteria
Known Werner Syndrome
History of condition, therapy, or laboratory abnormality that might confound the results of the study or prohibit participation
Known active infection
Severe or uncontrolled systemic disease(s)
Current active liver disease
Known positive HIV antibody results or AIDS-related illness
Active prior or concurrent malignancy
Clinically relevant cardiovascular disease
CNS metastases with progressive neurological symptoms, including leptomeningeal disease
Recently received or currently receiving anticancer therapy or radiotherapy
Systemic immunosuppressive treatment
Concomitant use of certain medications as defined in the study protocol

CNS, central nervous system; dMMR, DNA mismatch repair deficient; ECOG, Eastern Cooperative Oncology Group; MSI-H, microsatellite instability-high; PCWG-3, Prostate Cancer Working Group 3; PD-(L)1, programmed cell death (ligand) 1

Figure 4. Key Study Endpoints

Primary endpoints
- Adverse events
- Dose-limiting toxicities
- Serious AEs
- AEs leading to discontinuation
- Changes in safety laboratory tests, physical examination

Secondary endpoints
- Relationships between dose, exposure, PDx, antitumor and additional safety endpoints to identify the RP2D(s)

Plasma Pharmacokinetic Assessments
- Single and multiple day dosage PK parameters of MOMA-341 and irinotecan including AUC, C_{max}, T_{max}
- Half-life
- PK parameters of MOMA-341 under fed and fasted conditions

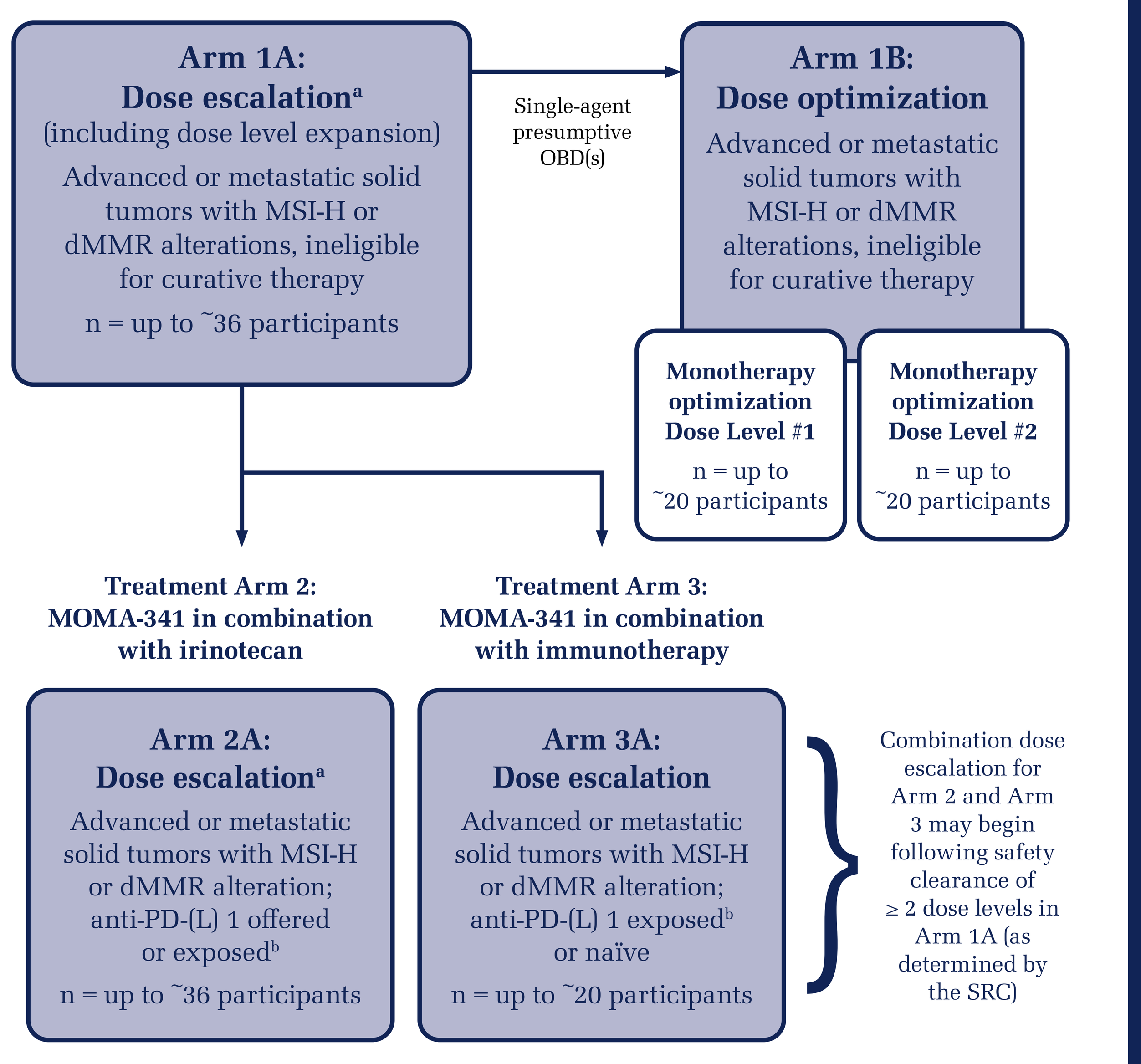
Clinical activity endpoints:
- Objective response rate
- Duration of response and time to response
- Progression free survival and overall survival
- Disease control rate

Exploratory endpoints
- Changes in circulating ctDNA abundance, DNA damage markers and/or WRN protein, and MOMA-341-WRN ligation from baseline, relationship between genomic parameters including dMMR alterations, MSI score, and TA repeat expansions with response

AE, adverse events; AUC, area under the curve; C_{max}, maximum concentration; ctDNA, circulating tumor deoxyribonucleic acid; PDx, pharmacodynamics; PK, pharmacokinetics; RP2D, recommended phase 2 dose; T_{max}, time to maximum concentration; WRN, Werner RecQ-like

- Enrollment began in July 2025 and is ongoing in Australia and the United States with an estimated target enrollment of 132 participants.

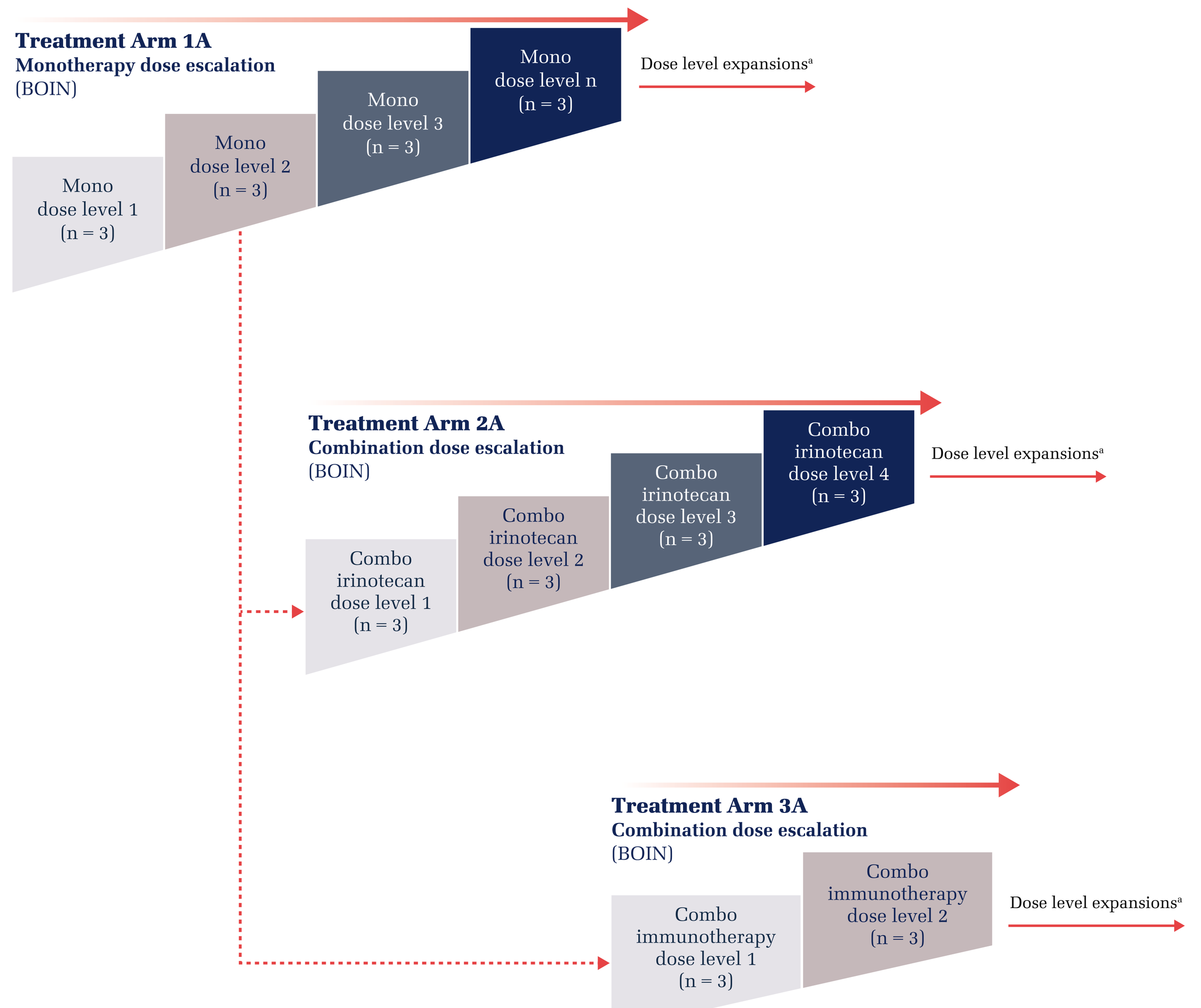
Figure 5. Study Design



Treatment Arm 1: MOMA-341 monotherapy
Arm 1A:
Dose escalationᵃ
(including dose level expansion)
Advanced or metastatic solid tumors with MSI-H or dMMR alterations, ineligible for curative therapy
n = up to ~36 participants
Single-agent presumptive OBD(s)
Arm 1B:
Dose optimization
Advanced or metastatic solid tumors with MSI-H or dMMR alterations, ineligible for curative therapy
Monotherapy optimization Dose Level #1
n = up to ~20 participants
Monotherapy optimization Dose Level #2
n = up to ~20 participants
Treatment Arm 2: MOMA-341 in combination with irinotecan
Treatment Arm 3: MOMA-341 in combination with immunotherapy
Arm 2A:
Dose escalationᵃ
Advanced or metastatic solid tumors with MSI-H or dMMR alteration; anti-PD-(L) 1 offered or exposedᵇ
n = up to ~36 participants
Arm 3A:
Dose escalation
Advanced or metastatic solid tumors with MSI-H or dMMR alteration; anti-PD-(L) 1 exposedᵇ or naïve
n = up to ~20 participants
Combination dose escalation for Arm 2 and Arm 3 may begin following safety clearance of ≥ 2 dose levels in Arm 1A (as determined by the SRC)

anti-PD-(L) 1, anti-programmed cell death/programmed death ligand-1; dMMR, DNA mismatch repair deficiency; MSI-H, microsatellite instability high; OBD, optimal biologic dose; SRC, Safety Review Committee
[a] Treatment Arm 1A includes a food effect evaluation substudy. [b] Participants living in certain regions may not have access to anti-PD(L) 1 therapy.
Note: One cycle of therapy is defined as 21 days for Treatment Arm 1, 28 days for Treatment Arm 2, and 21 days for Treatment Arm 3.

Figure 6. Dose Escalation Scheme



Treatment Arm 1A
Monotherapy dose escalation
(BOIN)
Mono dose level 1 (n = 3)
Mono dose level 2 (n = 3)
Mono dose level 3 (n = 3)
Mono dose level n (n = 3)
Dose level expansionsᵃ
Treatment Arm 2A
Combination dose escalation
(BOIN)
Combo irinotecan dose level 1 (n = 3)
Combo irinotecan dose level 2 (n = 3)
Combo irinotecan dose level 3 (n = 3)
Combo irinotecan dose level 4 (n = 3)
Dose level expansionsᵃ
Treatment Arm 3A
Combination dose escalation
(BOIN)
Combo immunotherapy dose level 1 (n = 3)
Combo immunotherapy dose level 2 (n = 3)
Dose level expansionsᵃ

BOIN, Bayesian optimal interval; combo, combination; mono, monotherapy; n, number; SRC, Safety Review Committee
[a] The expansion of a dose level may be initiated once a dose level in dose escalation has been determined safe (or "cleared") by the SRC. For Treatment Arms 1 and 2, ≥2 dose levels will be expanded with up to ~12 additional participants evaluated in each dose level. For Treatment Arm 3, dose levels will be expanded with ≤7 additional participants evaluated in each dose level.

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DISCLOSURES

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