Phase 1b trial of NG-350A, a CD40 agonist antibody expressing adenoviral vector, in combination with chemoradiotherapy (CRT), in patients with mismatch repair-proficient (pMMR) locally advanced rectal cancer (LARC): initial results from the FORTRESS study

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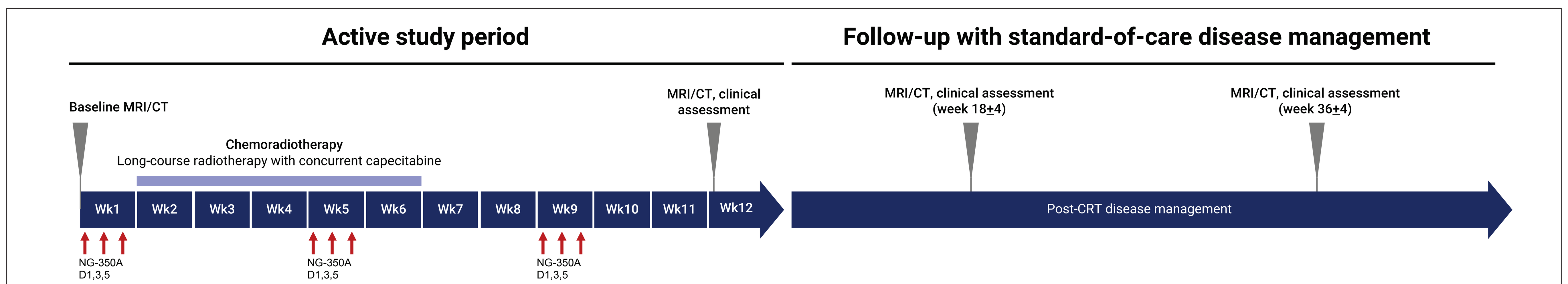
Introduction

- Locally advanced rectal cancer (LARC) is defined by the spread of rectal cancer to nearby tissues or lymph nodes. Patients with mismatch repair–proficient (pMMR) tumors account for approximately 95% of all LARC cases (~30,000 new cases annually in the US).
- The rising incidence of young-onset LARC highlights the need to improve the standard of care with treatments aimed at eradicating a patient's tumor while also potentially enabling that patient to avoid surgery to remove portions of the rectum where cancerous tissue was initially detected.
- NG-350A is an intravenously delivered Tumor-Specific Immuno-Gene (T-SIGn®) therapeutic that can directly kill cancer cells via oncolysis, releasing tumor-associated antigens into the draining lymph nodes of the tumor. In addition, NG-350A drives intratumoral expression of a CD40 agonist transgene which activates antigen-presenting cells (APCs) to trigger a systemic anti-tumor immune response.
- The ongoing Phase 1b FORTRESS study (NCT06459869) aims to demonstrate improved composite response rates (near clinical complete response [ncCR] + clinical complete response [cCR]) at week 12 for NG-350A in combination with chemoradiotherapy (CRT) in adult patients with pMMR LARC relative to expected composite response rates for CRT alone.
- Achievement of a ncCR has been predictive of subsequent achievement of a cCR, with a substantial proportion of ncCRs (up to 90%) converting to cCRs after the initial ncCR assessment (Hupkens 2018).
- Historical efficacy benchmarks in LARC report complete response rates (cCR/pCR) of 10–15% with CRT alone (Bosset 2005; Conroy 2021; Temmink 2023). A recent study investigating non-operative management approaches for pMMR LARC patients utilized a composite response rate (cCR + ncCR) of 25% at 12 weeks as a benchmark to define superiority to CRT alone (de Gooyer 2024).
- The delivery of improved composite response rates with CRT in combination with NG-350A could support both a non-operative management approach, while also eliminating the need for post-CRT chemotherapy (i.e., consolidation chemotherapy – an approach utilized in the context of total neoadjuvant treatment to increase composite response rates beyond what is achievable by CRT alone [Fokas 2019; Garcia-Aguilar 2022]).
- The CEDAR study, an investigator-initiated trial of EnAd (a predecessor to NG-350A with no transgene) plus CRT in patients with LARC, demonstrated an ncCR + cCR composite response rate of 50% (O'Cathail 2023).
- Demonstrating composite response rates in the FORTRESS study comparable to that observed in CEDAR would provide confirmation that NG-350A is clearly enhancing the potency of CRT in the neoadjuvant setting in pMMR LARC.

Methods

- Multicenter, open-label, non-randomized, Phase 1b trial of NG-350A in combination with long course chemoradiotherapy (LC-CRT); response rate assessment is based on MRI-based imaging, endoscopy and digital rectal exam (DRE).
- Enrollment target is 30 patients
- The primary endpoint is the composite response rate defined as the proportion of patients achieving a near clinical complete response (ncCR) or a clinical complete response (cCR) at 12 weeks after initiating NG-350A in combination with CRT.
- Secondary endpoints include safety/tolerability, characterization of the anti-tumor effects according to magnetic resonance tumor regression grade (mrTRG) and rectoscopic assessments.

Figure 1. Study schema with active treatment period of 12 weeks and follow up phase



Conclusions

- NG-350A plus LC-CRT has achieved a composite response rate of 50% among the first 10 pMMR LARC patients in FORTRESS, consistent with the 50% composite response rate observed in the CEDAR study and significantly exceeding the expected composite response rate for CRT alone.
- No serious adverse events or new safety signals related to NG-350A have been identified, supporting its favorable tolerability as an oncolytic immunotherapy.
- While these are early results, the 50% composite response rate achieved via the addition of NG-350A to LC-CRT may expand the population who could consider a non-operative management approach to treatment.
- Continued investigation of NG-350A in combination with CRT for pMMR LARC may enable more patients to pursue a watch-and-wait protocol with the goal of colorectal organ preservation.

Table 1. Summary of clinical assessment: 50% composite response rate (cCR + ncCR) at week 12 (primary endpoint)*

Patient	Screening					Week 12		
	Stage	cT	cN	Distance to Anal Verge	Risk Factors	mrTRG	DRE/ Rectoscopy	Composite Response Assessment
#1	IIIB	T3a	N1a	9.4 cm	MRF+; EMVI+	1	ncCR	✓ ncCR
#2	IIA	T3b	N0	3.8 cm	MRF+	3	Incomplete response	Incomplete response
#3	IIIB	T3b	N1b	6.8 cm	MRF+	2	ncCR	✓ ncCR
#4	IIIB	T3b	N1b	3.8 cm	MRF+	2	Not done	✓ ncCR
#5	IIIB	T3c	N2a	2.9 cm	MRF+; EMVI+	3	Incomplete response	Incomplete response
#6	IIIB	T3b	N1b	10.8 cm	MRF+	1	ncCR	✓ cCR
#7	IIIC	T3b	N2b	10.4 cm	MRF+; EMVI+	4	Not done	Incomplete response
#8	IIIB	T3a	N1	4.5 cm	MRF+	1	ncCR	✓ ncCR
#9	IIIB	T3b	N1	8 cm	MRF+; EMVI+	3	Not done	Incomplete response
#10	IIIB	T4a	N0	9.1 cm	MRF+	3	Incomplete response	Incomplete response

*Not all data verified

Table 2. pMMR LARC patient characteristics*

Characteristic	N=10
Median age, year (IQR)	52 (49 – 62)
Female, No (%)	2 (20)
Stage, No (%)	
IIA	1 (10)
IIIB	8 (80)
IIIC	1 (10)
cT classification, No (%)	
cT3	9 (90)
cT3a-b	*8 (80)*
cT3c-d	*1 (10)*
cT4	1 (10)
Location of tumor	
Low	4
Middle	6
cN classification, No (%)	
cN0	2 (20)
cN1	6 (60)
cN2	2 (20)
Median tumor distance from anal verge, cm (IQR)	7.4 (3.8 – 9.4)
Median tumor length, cm (IQR)	4.5 (2.9 – 5.1)
Number of risk factors, median	2
MRF involved, No (%)	10 (100)
EMVI positive, No (%	4 (40)

*As of 08-Apr-2026

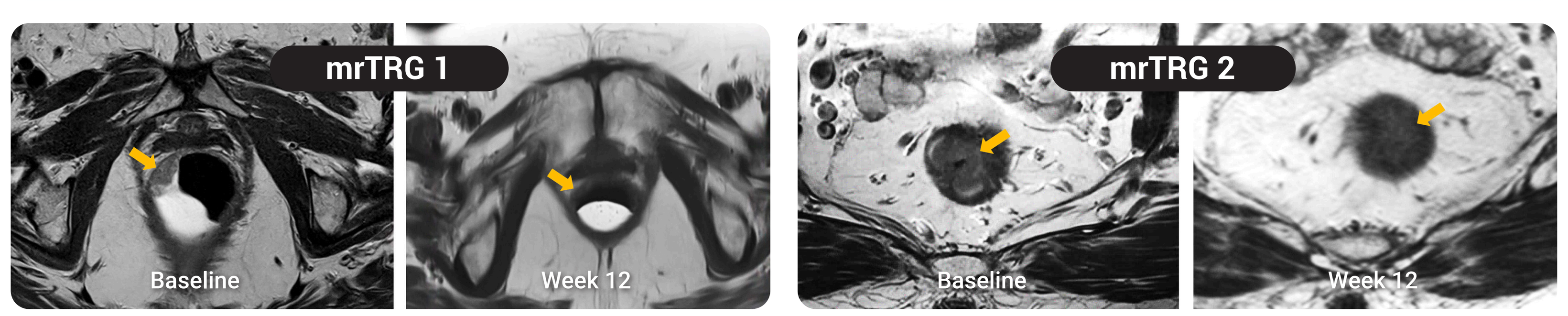
Median age 52; all tumors located in the lower two-thirds of the rectum with MRF involvement (≤1 mm).

Table 3. Treatment-emergent adverse events: well-tolerated; no SAE or Grade 3+ events

Row Labels	Overall (N=10), n (%)	Grade 1, n (%)	Grade 2, n (%)
Any TEAE	**9 (90%)**	**6 (60%)**	**3 (30%)**
Chills	4 (40%)	40 (40%)	-
Fatigue	4 (40%)	2 (20%)	2 (20%)
Proteinuria	3 (30%)	1 (10%)	2 (20%)
Vomiting	2 (20%)	2 (20%)	-
Nausea	2 (20%)	2 (20%)	-
Influenza like illness	2 (20%)	2 (20%)	-
Pyrexia	2 (20%)	2 (20%)	-
White blood cell count decreased	2 (20%)	1 (10%)	1 (10%)
Neutrophil count decreased	2 (20%)	-	2 (20%)
Diarrhoea	1 (10%)	1 (10%)	-
Sinus tachycardia	1 (10%)	1 (10%)	-
Night sweats	1 (10%)	1 (10%)	-
Platelet count decreased	1 (10%)	1 (10%)	-
Sneezing	1 (10%)	1 (10%)	-
Pollakiuria	1 (10%)	1 (10%)	-
Decreased appetite	1 (10%)	1 (10%)	-
Hyperuricaemia	1 (10%)	1 (10%)	-
Dermatitis acneiform	1 (10%)	1 (10%)	-

AEs limited to transient systemic viremia and no typical immune therapy or CD40-related AEs observed

Figure 2. Imaging results of patients with a mrTRG 1 and 2 at week 12



The distinction between mrTRG 1 and mrTRG 2 lies in the extent of fibrotic scarring (low signal intensity), in the absence of any macroscopic tumor signal. The impact of potential local inflammation induced by oncolytic immunotherapy on MRI imaging remains unknown.

Acknowledgement
We would like to thank the patients, their families, and the site staff of the FORTRESS trial.

References:
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