#104

DKN-01 Plus Bevacizumab and Chemotherapy as Second-line (2L) Investigational Therapy in Advanced Microsatellite Stable (MSS) Colorectal Adenocarcinoma (CRC): DeFianCe Trial

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BACKGROUND

- Hyperactivation of the Wnt signaling pathway is a critical driver of colorectal cancer (CRC). Greater than 90% of CRC tumors contain at least one alteration in a Wnt-pathway gene such as Adenomatous Polyposis Coli (APC).[1,2]
- Zhao et al. 2021 previously reported that high DKK1 expression has been shown to correlate with 5-Fluorouracil (5-FU) resistance in CRC tumors, and knockdown of DKK1 in vitro sensitizes 5-FU-resistant cells to subsequent 5-FU treatment.[3]
- In two 5-FU-resistant models of CRC (HCT116 and SW480), 5-FU treatment failed to show inhibition of tumor growth. However, both DKN-01 and the combination of DKN-01 with 5-FU demonstrated significant reductions in these mouse models reflective of a second line CRC setting.[4]
- First-line metastatic CRC (mCRC), microsatellite stable (MSS) treatment commonly includes a fluoropyrimidine-based chemotherapy regimen in combination with oxaliplatin (FOLFOX) or irinotecan (FOLFIRI) and frequently a targeted biologic therapy such as an anti-VEGF antibody or an epidermal growth factor receptor inhibitor. Second line therapy includes switch chemotherapy, anti-VEGF therapy and if present actionable targeted agents.
- Patients requiring second-line therapy for mCRC represent a significant unmet medical need and novel therapies are necessary.
- DKN-01 is a novel IgG4 monoclonal antibody that potently neutralizes DKK1, a regulator of the Wnt signaling pathway.
- Clinically DKN-01 has previously been shown to synergize with 5-FU-based regimens in other indications including esophagogastric cancer.[5]

METHODS

DeFianCe Study: FOLFIRI/FOLFOX and Bevacizumab +/- DKN-01 as Second-line Treatment of Advanced Colorectal Cancer

Key eligibility criteria:

- One prior 5-FU-based therapy for advanced colorectal adenocarcinoma
- RECIST v1.1 measurable disease
- MSS and absence of BRAFV600 mutation

Outcomes Assessments

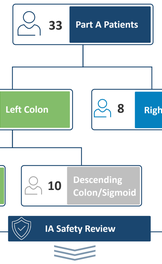
- Data cutoff: Dec. 6, 2023
- Response assessed per investigator by RECIST v1.1

Safety review

- Frequency of serious adverse events and Grade ≥3 treatment-related adverse events

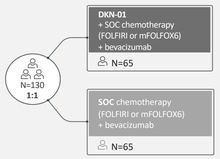
Part A – Safety Run-in Study (reported here)

DKN-01 + SOC chemotherapy (FOLFIRI or mFOLFOX6) + bevacizumab



Part B - Phase 2 Randomized Controlled Trial

N ≈ 130 | Enrolling



- Primary endpoint: PFS
- Secondary endpoints: ORR, DoR, OS

RESULTS of PART A

Baseline Characteristics

Characteristic	Part A Patients (N=33) n (%)
Male	20 (60.6)
Female	13 (39.4)
Age, median (min, max)	56.0 (35, 84)
Primary Tumor Location	
Right	8 (24.2)
Left	25 (75.8)
Rectal/Rectosigmoid	15 (45.5)
DKK1 ≥ 1 TPS	16/29 (55)
ECOG PS	
0	18 (54.5)
1	15 (45.5)
Liver Metastasis	23 (69.7)
Prior Systemic Therapy (5-FU based)	33 (100.0)
Oxaliplatin based	30 (90.9)
Irinotecan based	3 (9.1)
Bevacizumab/biosimilar	17 (51.5)
Cetuximab	1 (3.0)
Genetics*	24/33 (72.7)
KRAS mutations	18/24 (75.0)
APC mutations	22/24 (91.7)

*Genetics were performed on baseline plasma using the FoundationOne® Liquid CDx test (Foundation Medicine, Cambridge, MA)

Disposition and Exposure

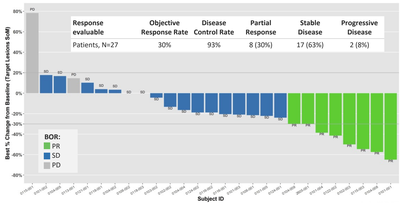
- 91% received FOLFIRI in combination with DKN-01 and bevacizumab
- 6 non-evaluable patients
  - 4 early discontinuations: 1 withdrew consent, 2 patient decision, 1 physician decision for non-compliance
  - 2 deaths prior to week 8 imaging

	Part A Patients (N=33)
Number of cycles, median (min, max)	10 (1, 22)
Duration on treatment (months), median (min, max)	5.68 (0.1, 12.0)
Duration on study (months), median (min, max)	8.31 (0.4, 13.6)
Treatment ongoing	9
Reasons for study drug discontinuation, n (%)	24
Patient request to withdraw	4
Objective disease progression	13
Investigator decision	2
Non-compliance with study protocol	1
Death	4
Reasons for study discontinuation, n (%)	10
Withdrawal of consent	2
Death	8

Second-line Therapy Efficacy Outcomes

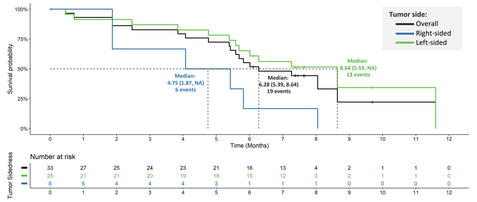
Best Overall Response (Response Evaluable Population)

- ORR = 30% (8/27)
- DCR = 93% (25/27)



PFS Overall and by Left and Right Colon (Intent to Treat Population)

- Preliminary median PFS in left-sided tumors is 8.6 months; 9 patients remain on therapy



Safety Summary

- Majority of DKN-01 related events are low grade (Grade 1/2)
- Overall, 21.2% of subjects reported a serious adverse event, only 1 (3%) related to DKN-01
- Only 1 subject discontinued DKN-01 due to a DKN-01 related adverse event

Adverse Events by Participant*	Part A Patients N = 33 n (%)
One or more adverse events	32 (97.0%)
Grade 1-2	32 (97.0%)
Grade ≥3	21 (63.6%)
Serious adverse events	7 (21.2%)
Deaths	3[#] (9.1%)
DKN-01 related adverse events	24 (72.7%)
Grade 1-2	24 (72.7%)
Grade ≥3	9 (27.3%)
Serious adverse events	1 (3.0%)
Deaths	1 (3.0%)
Led to DKN-01 dose reduction	2 (6.1%)
Led to DKN-01 discontinuation	1 (3.0%)

*Assessed by investigator
[#]One regimen–related death (sepsis), one large bowel hemorrhage and one bowel perforation (non-protocol population subject)

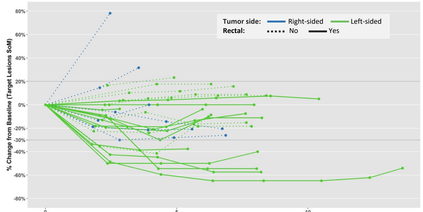
Enriched Responses in Left-sided Tumors, Particularly Rectal/Rectosigmoid Junction

Best Overall Response by Tumor Side/Location

- Superior ORR (33%) and DCR (100%) in left-sided patients, which is enriched by rectal/rectosigmoid patients with ORR (46%) and DCR (100%)

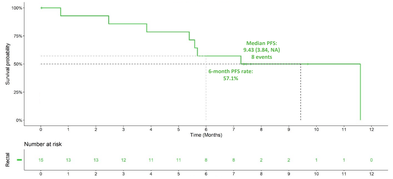
Tumor Percentage Change from Baseline

- Clinical benefit was largest and longest in rectal/rectosigmoid patients

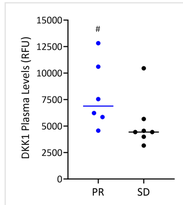


Preliminary PFS in Rectal Tumors

- Median PFS 9.4 months; 6 patients remain on therapy
- 6-month PFS rate was 57% in the rectal subgroup ITT population



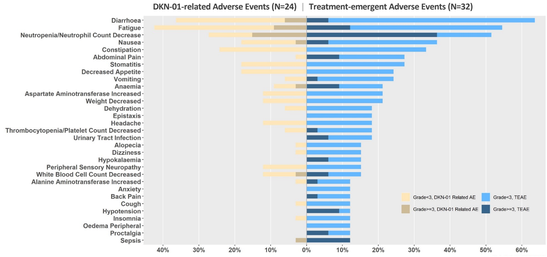
Baseline Circulating DKK1 in Rectal Tumors



- High DKK1 expression has been shown to correlate with response (PR, n=6) vs stable disease patients (SD, n=7)
- DKK1 plasma levels analyzed using the SomaScan platform (SomaLogic, Boulder, CO)

Data shown as median plasma values
[#] P < 0.05 (Mann-Whitney test)

Adverse Events Reported in ≥10% of Patients



CONCLUSIONS

- DKN-01 + SOC chemotherapy (FOLFIRI or mFOLFOX6) + bevacizumab was well tolerated
- Promising clinical activity in a heterogeneous 2L MSS population with poor prognosis
  - ORR 30%, DCR 93%
  - PFS was 6.3 months
    - 9 subjects remain on study therapy
- Subgroup analysis demonstrated the greatest benefit in rectal/rectosigmoid junction cancer patients
  - ORR 46%, DCR 100%
  - Preliminary median PFS 9.4 months with 6 patients ongoing
  - Elevated baseline plasma DKK1 levels correlate with greater clinical response
- Enrollment in the randomized controlled trial (Part B) is ongoing and expected to be completed in Q3 2024

Abbreviations: 2L: second-line; 5-FU: 5-Fluorouracil; AE: adverse event; CRC: colorectal adenocarcinoma; DKK1: Dickkopf-related protein 1; DoR: duration of response; MSS: microsatellite status; ORR: objective response rate; OS: overall survival; PFS: progression-free survival; PR: partial response; PD: progressive disease; RECIST: Response Evaluation Criteria in Solid Tumors; SOC: standard of care; SD: stable disease; TEAE: treatment-emergent adverse event

References: 1. Cancer Genome Atlas Network. *Nature*. 2012; 487(7407):330–7. 2. Giannakis M, et al. *Nat Genet*. 2014;46(12):1264-6. 3. Zhao Y, et al. *Carcinogenesis*. 2021;42(6):814-825. 4. Haas M, et al. *J ImmunoTherapy Cancer*. 2022;10 (Supplement 2): A1183. 5. Klempner SJ, et al. *J Clin Oncol*. 2023;41:16_suppl:4027.

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