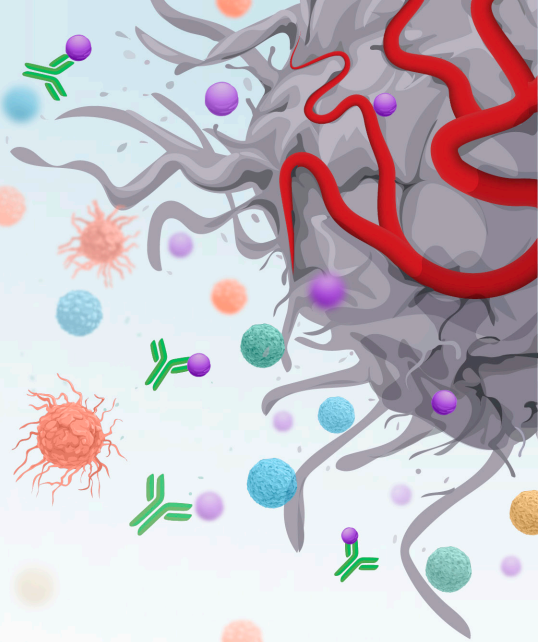
LEAP THERAPEUTICS
company presentation

DKN-01 in Patients with Colorectal Cancer

DeFianCe Study

January 23, 2024



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Agenda

Introduction	Cynthia Sirard, MD, Chief Medical Officer, Leap
Colorectal cancer background	Meredith Pelster, MD Assistant Director, Gastrointestinal Research Sarah Cannon Research Institute
	Zev Wainberg, MD Professor of Medicine and Co-Director of the GI Oncology Program UCLA
DKN-01 in colorectal cancer background	Jay Baum, PhD, Chief Scientific Officer, Leap
DeFianCe study Part A data	Dr. Pelster & Dr. Wainberg
Questions & Answers	

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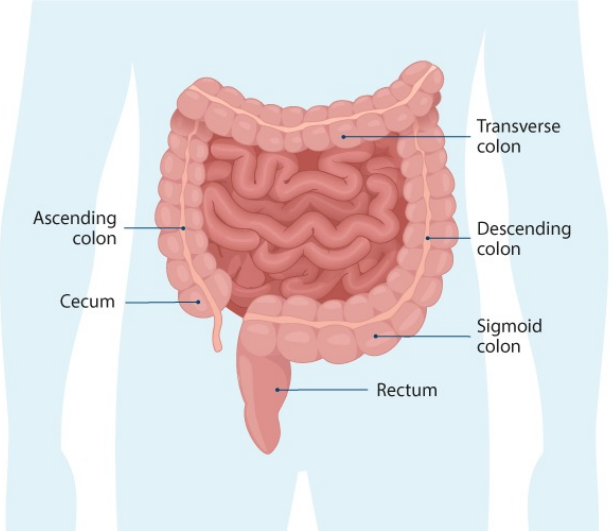
Colorectal cancer background



- Includes right colon (cecum, ascending and transverse colon) and left colon (descending colon, sigmoid, and rectum)
- When symptoms appear, such as rectal bleeding, anemia, or abdominal pain, most patients already have advanced stage disease where cancers are aggressive and incurable
- Third most frequent cancer globally and the second leading cause of cancer-related death
- Globally, nearly 2,000,000 new cases of CRC in 2020, with nearly 1,000,000 deaths.
- In the US, estimated that there will be approximately 150,000 cases of CRC each year, resulting in more than 50,000 deaths.

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What influences treatment choices in mCRC?

PATIENT CHARACTERISTICS

Age	Comorbidities	Prior adjuvant treatment	Performance status

TUMOR CHARACTERISTICS

Tumor burden	Resectability	Tumor location

MOLECULAR CHARACTERISTICS

RAS	*BRAF*	MSI-high	HER2

PATIENT PREFERENCE

Quality of life	Toxicity profile	Dosing schedule	Convenience

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Metastatic colorectal cancer treatment flow

1L Systemic

- **FOLFOX, FOLFIRI, CAPEOX, or FOLFIRINOX ± anti-VEGF/EGFR**
- **Nivolumab ± ipilimumab or pembrolizumab** (MSI-H/dMMR)

2L Systemic

- **Chemotherapy ± anti-VEGF/EGFR** (dependent on 1L tx)
- **Encorafenib + anti-EGFR** (*BRAF*^{V600E})
- **Trastuzumab + pertuzumab, lapatinib, or tucatinib; trastuzumab deruxtecan** (HER2-amplified)
- **Pembrolizumab, nivolumab ± ipilimumab, or dostarlimab** (MSI-H/dMMR)

3L+ Systemic

- **Pembrolizumab, nivolumab ± ipilimumab, or dostarlimab** (MSI-H/dMMR)
- **Chemotherapy ± anti-VEGF/EGFR**
- **Trifluridine/tipiracil ± Bevacizumab**
  Regorafenib
  Fruquitinib
- **Trastuzumab + tucatinib, pertuzumab, or lapatinib, or trastuzumab deruxtecan** (HER2-amplified)

NCCN Colon Cancer Guidelines

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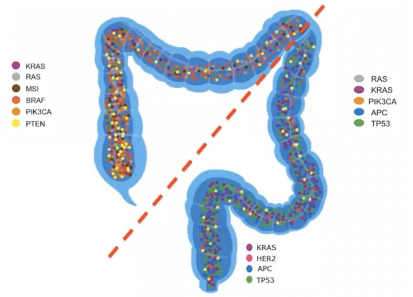
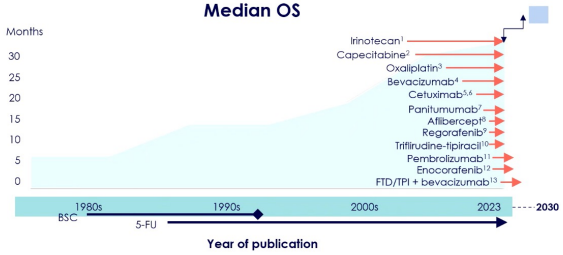
Evolution of second-line mCRC therapy

- Last 20 years have provided enhanced knowledge regarding the pathogenesis of colorectal cancer
- Understanding that colorectal cancer is not one disease but rather includes a wide heterogeneity of underlying biology
- Movement towards more personalized treatment approach, but most patients do not have actionable alterations
- Overall survival of patients with advanced disease at diagnosis has improved from ~ 6 months to ~ 30 months in the last 30 years with current available therapies and a continuum of care
- Microsatellite stable (MSS) patients are an unmet medical need without targeted therapies and no immunotherapeutic approach has improved clinical outcomes to date
- Growing incidence of young adult colorectal cancer
- Recent studies represent the disease heterogeneity and the treatment diversity and complexity





No direct comparison of the studies is intended.

FTD/TPI, trifluridine + tipiracil; **mCRC**, metastatic colorectal cancer; **5FU**, fluorouracil. Trifluridina/tipiracilo en combinación con bevacizumab no está registrado en España. Trifluridine/tipiracil in combination with bevacizumab is not registered in Spain.
1. Rougier P, Van Cutsem E, et al. Lancet. 1998 Oct 31;352(9138):1407-12. **2.** Van Cutsem E, et al. Br J Cancer. 2004 Mar 22;90(6):1190-7. **3.** Rothenberg ML, et al. J Clin Oncol. 2003 Jun 1;21(11):2059-69. **4.** Hurwitz H, et al. N Engl J Med. 2004 Jun 3;350(23):2335-42. **5.** Cunningham D, et al. N Engl J Med. 2004 Jul 22;351(4):337-45. **6.** Van Cutsem E,et al. N Engl J Med. 2009 Apr 2;360(14):1408-17. **7.** Van Cutsem E, et al. J Clin Oncol. 2007 May 1;25(13):1658-64. **8.** Van Cutsem E, et al. J Clin Oncol. 2012 Oct 1;30(28):3499-506. **9.** Grothey A, Van Cutsem E, et al. Lancet. 2013 Jan 26;381(9863):303-12. **10.** Mayer RJ, Van Cutsem E, et al. N Engl J Med. 2015 May 14;372(20):1909-19. **11.** Andre T, et al. N Engl J Med. 2020 Dec 3;383(23):2207-2218. **12.** Kopetz S, et al. N Engl J Med. 2019 Oct 24;381(17):1632-1643. **13.** Prager G, et al. N Engl J Med. 2023; 388:1657-1667.

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Second-line colorectal cancer is a heterogenous disease

- Patient characteristics and first-line therapy drive choice of second-line therapy and expected outcomes
  - Prior bevacizumab (induction and/or maintenance therapy)
  - Tumor characteristics
    - Genetic profile (BRAF, KRAS/NRAS, Her2, MSI-H/MSS)
    - Location of primary tumor (left vs right-sided)
    - Consensus Molecular Subtype (CMS 1, 2, 3, 4)
  - Prior chemotherapy used in first-line setting, including modifications of regimens over time (e.g., FOLFOX4 vs mFOLFOX6)
  - Sites of metastatic disease (liver and/or lung)
  - Rapid progressors
    - Progression within 6-12 months of completion of neoadjuvant/adjuvant or first-line therapy
- Historical clinical efficacy in Phase 3 controlled trials:
  - ORR range: 4 - 22%
  - DCR range: 62 - 78%
  - PFS range: 2.5 – 6.9 months
  - OS range: 11.2 – 15.5 months
- No treatment paradigm changing options in past decade beyond bevacizumab maintenance or in targeted patient populations

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DKN-01 IN CRC BACKGROUND

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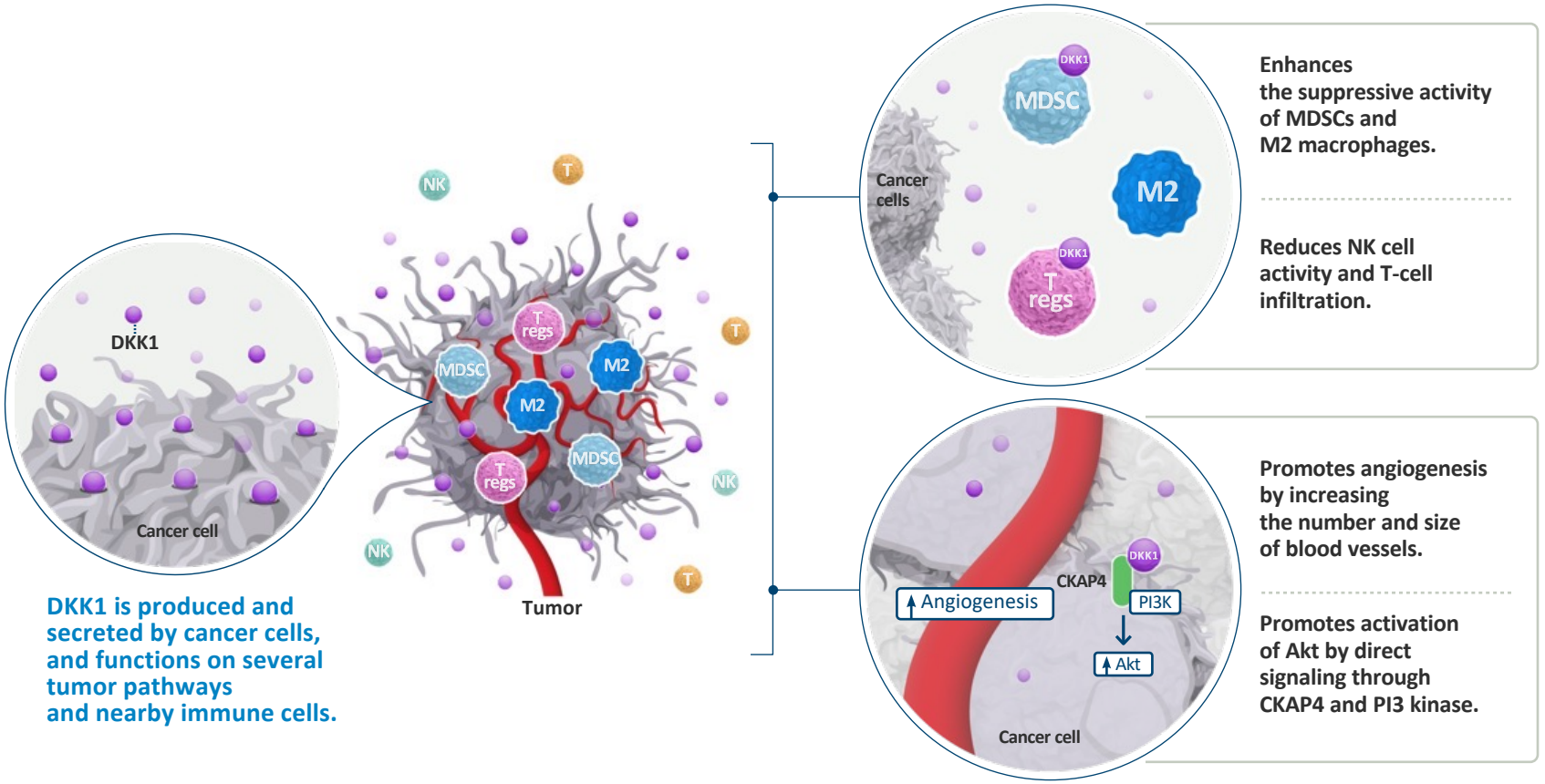
The role of DKK1 in cancer



DKK1 is produced and secreted by cancer cells, and functions on several tumor pathways and nearby immune cells.

Enhances the suppressive activity of MDSCs and M2 macrophages.

Reduces NK cell activity and T-cell infiltration.

Promotes angiogenesis by increasing the number and size of blood vessels.

Promotes activation of Akt by direct signaling through CKAP4 and PI3 kinase.

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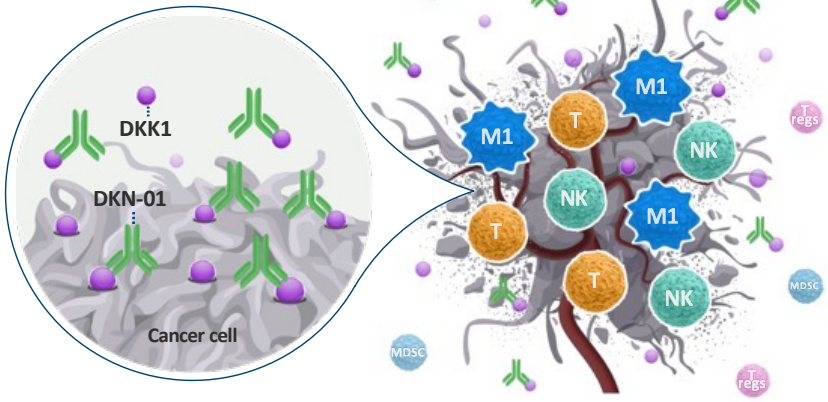
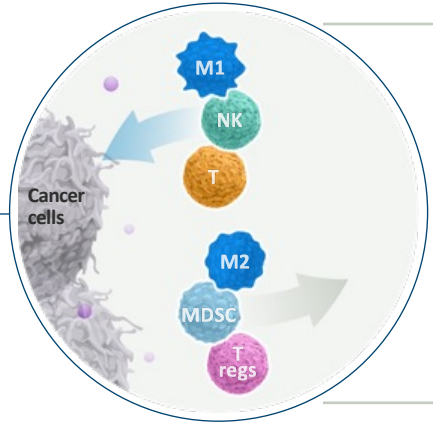
Activity of DKN-01 to treat cancer

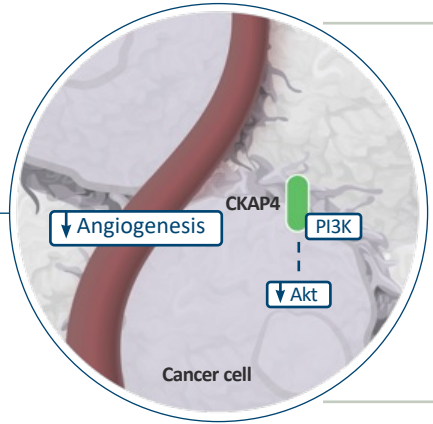


DKN-01 treatment neutralizes DKK1 and stimulates an immune mediated anti-tumor response.



DKN-01 activates NK cells, reprograms macrophages into the tumor-attacking M1 subtype and promotes T cell infiltration.

DKN-01 reduces MDSCs and tumor suppressive M2 macrophages in the TME.



DKN-01 reduces angiogenesis and inhibits pro-oncogenic PI3K/AKT signaling.

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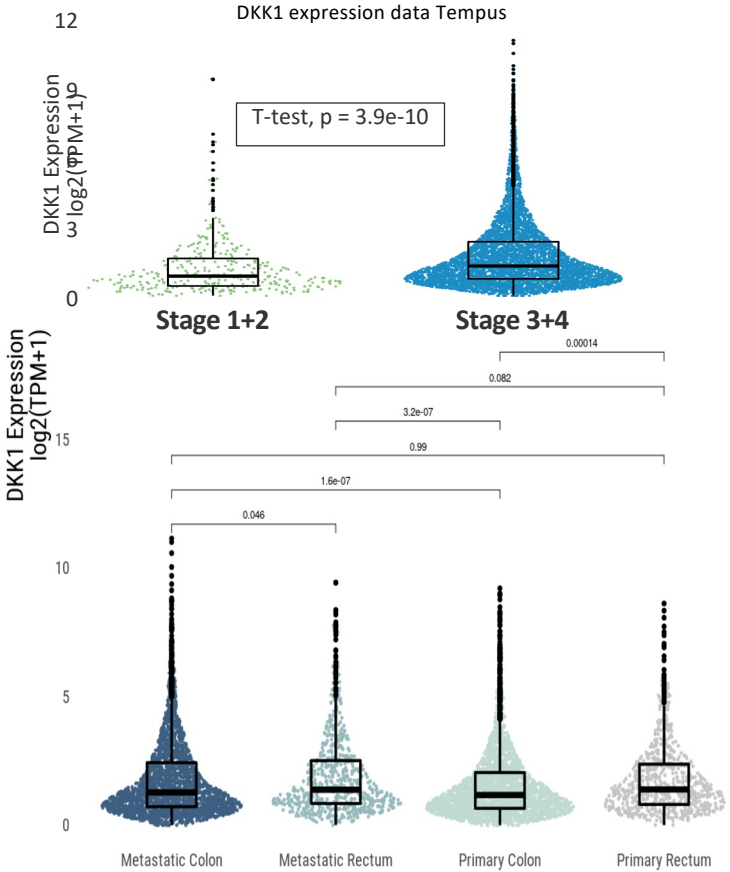
Rationale for targeting colorectal cancer with DKN-01
DKK1 expression is the highest in metastatic rectum



- CRC is characterized by hyperactivation of the Wnt pathway, often believed to be the initiating and driving event
  - CMS2 subtype more commonly found in left-sided tumors
- DKK1 highest in metastatic rectum
- DKK1 drives resistance to 5FU chemotherapy
- Preclinically DKN-01 treatment:
  - Shows additive activity with 5FU and is able to overcome 5FU-resistance
  - Has activity alone and with an anti-VEGF antibody

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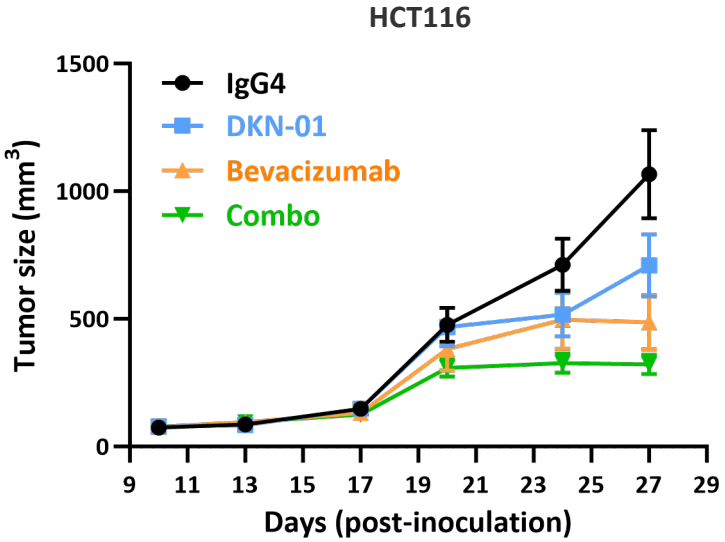
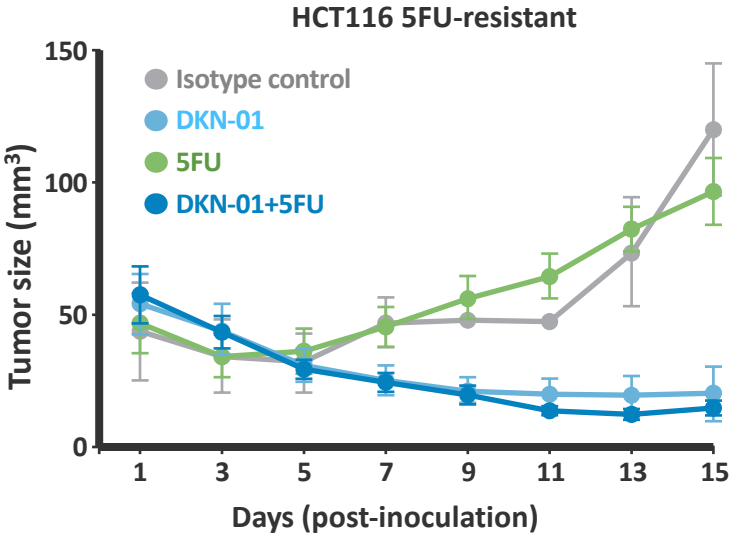
DKN-01 has activity in CRC models in combination with bevacizumab or 5FU

- DKN-01 has efficacy in CRC syngeneic models including HCT116
- Additive activity was seen with bevacizumab
- In a 5FU chemotherapy-resistant model, DKN-01 demonstrates significant inhibition of tumor growth alone and with 5FU





Data courtesy of Goel Lab at City of Hope Cancer Center

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DEFIANCE STUDY

Second-line CRC patients

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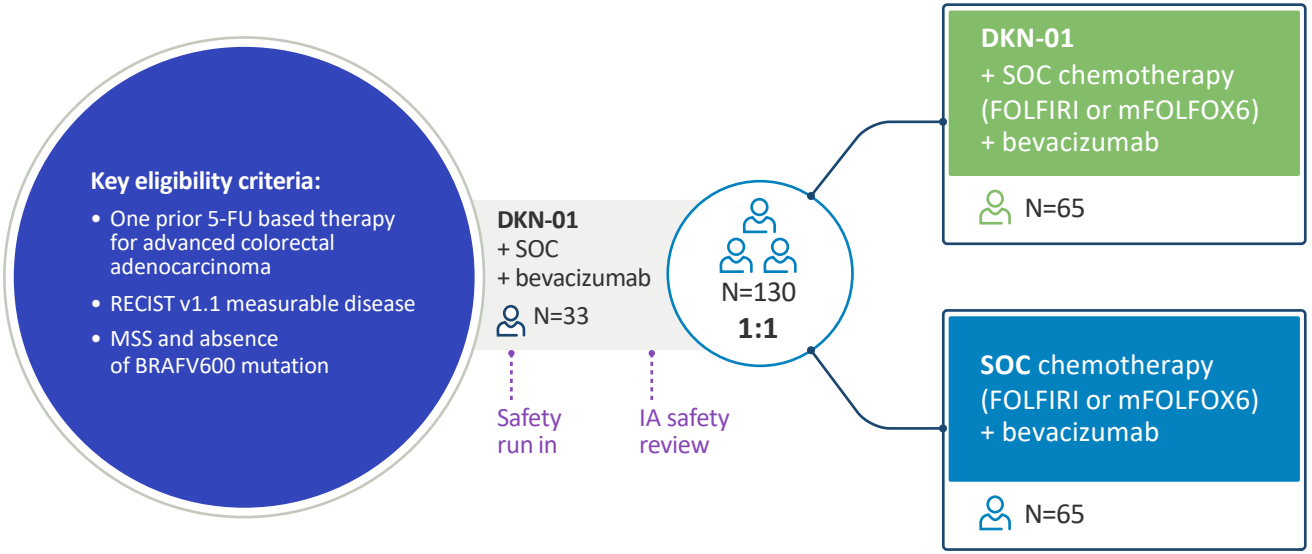
DeFianCe study design: advanced colorectal cancer

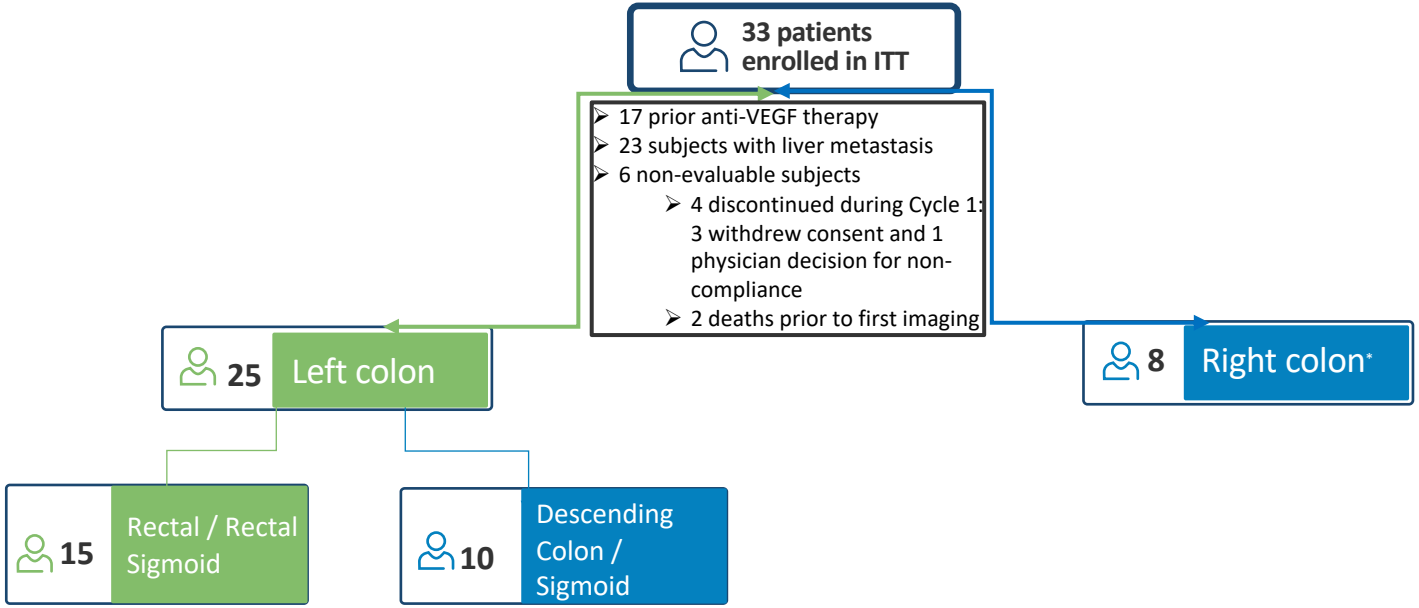
Randomized phase 2 study of FOLFIRI/FOLFOX and bevacizumab +/- DKN-01 as second-line treatment of advanced colorectal cancer

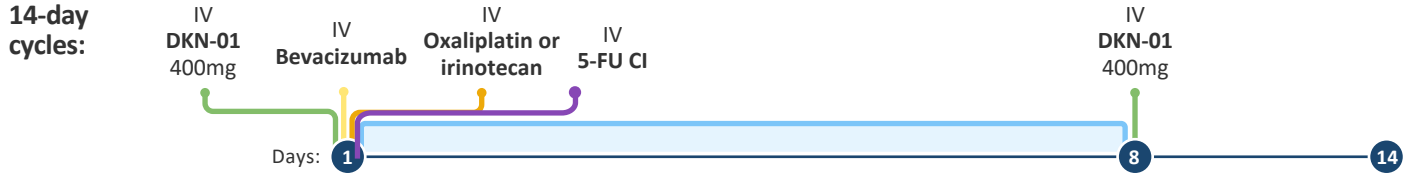


Primary objective:
PFS

Secondary objectives:
– ORR
– DoR
– OS

Part A consort diagram





*Right colon includes transverse colon

Part A population

N=33	n (%)
Male	20 (61)
Female	13 (39)
Age, median (min, max)	56.0 (35, 84)
Primary Tumor Location	
Right	8 (24)
Left	25 (76)
Rectal/Rectosigmoid	15 (45)
DKK1 ≥ 1 TPS (n=29)	16 (55)
ECOG PS	
0	18 (55)
1	15 (45)
Liver metastasis	23 (70)
Prior Systemic Therapy- 5FU based	33 (100)
Oxaliplatin based	30 (91)
Irinotecan based	3 (9)
Bevacizumab/biosimilar	17 (52)
Cetuximab	1 (3)
Genetics (n=24)*	(73)
KRAS mutations	18 (75)

*ctDNA collected at study baseline

- 76% left colon
  - 45% rectal / rectosigmoid
- 52% prior bevacizumab
- 75% KRAS mutations
- 70% with liver metastasis

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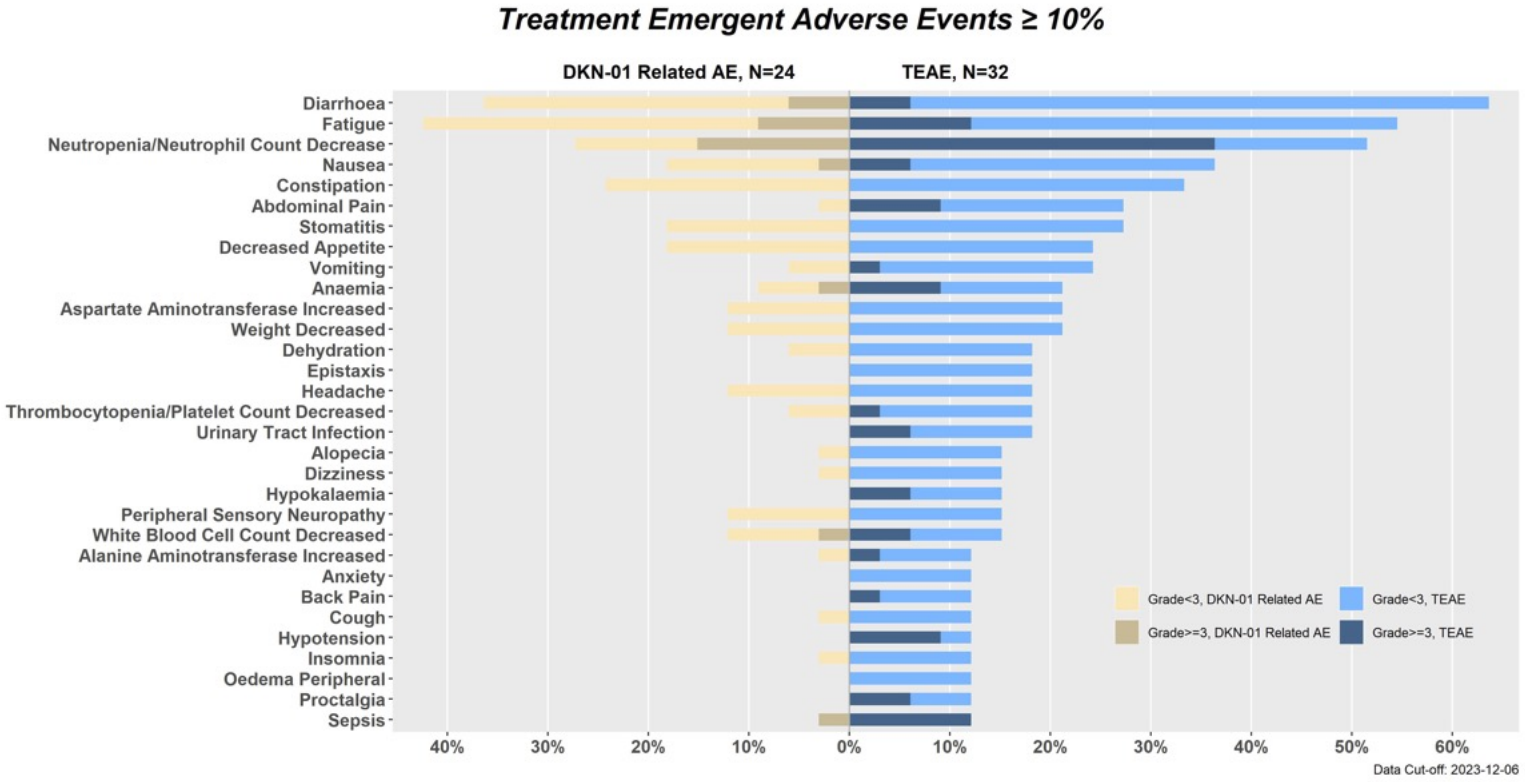
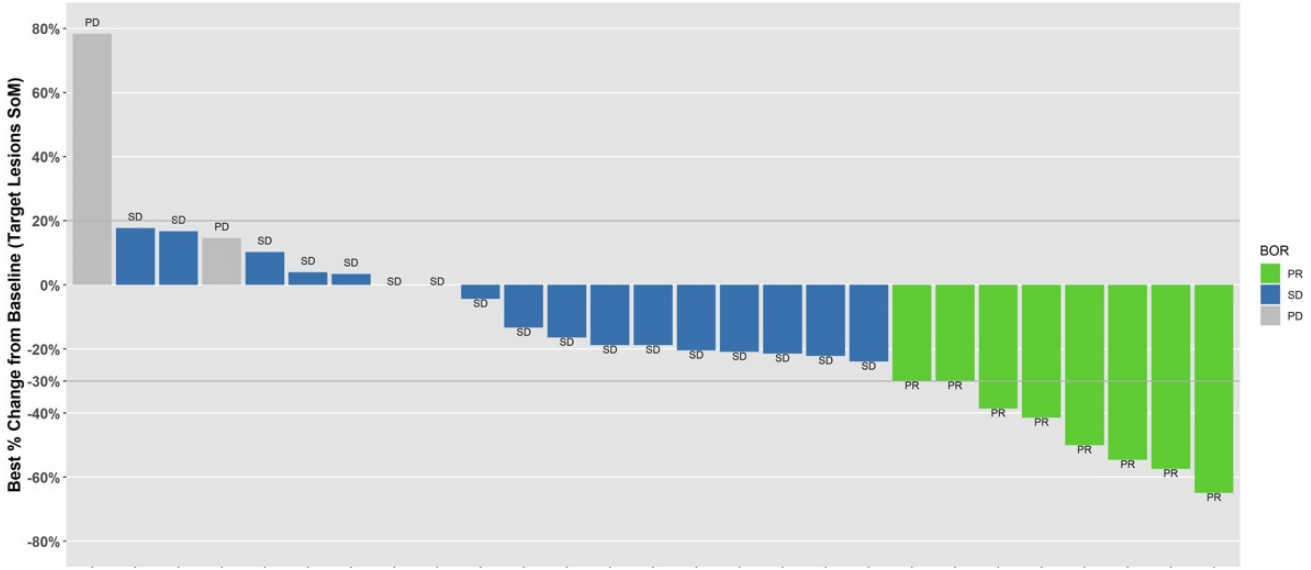
Part A safety summary



Overall response rate exceeded 20% target with high disease control rate



	Objective Response Rate (%)	Disease Control Rate (%)	Partial Response n (%)	Stable Disease n (%)	Progressive Disease n (%)
Overall, n=27	30	93	8 (30)	17 (63)	2 (8)

ORR in RE patients:
8/27 = 30%

DCR in RE patients:
25/27 = 93%

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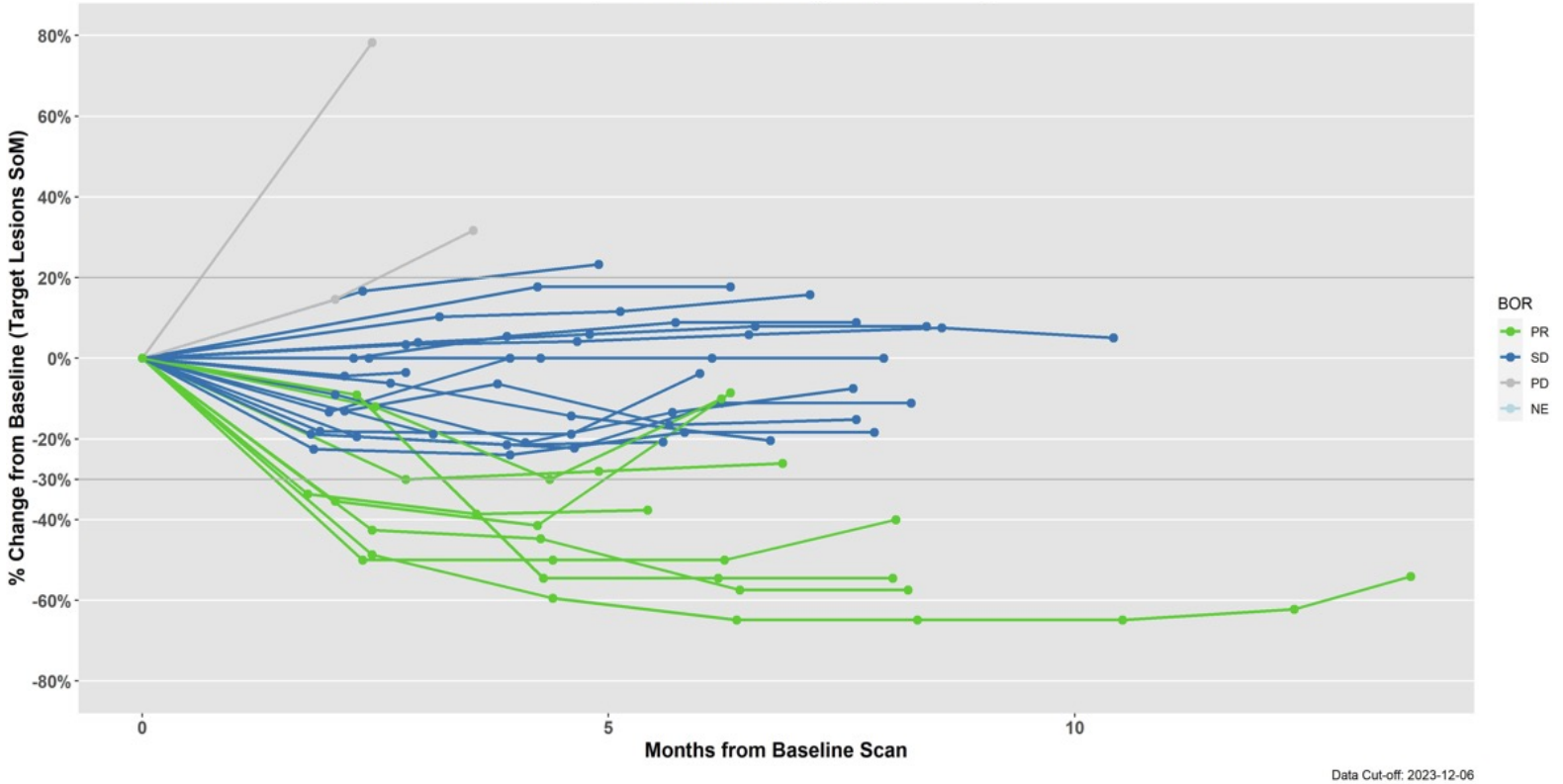
Duration of clinical benefit



Data Cut-off: 2023-12-06

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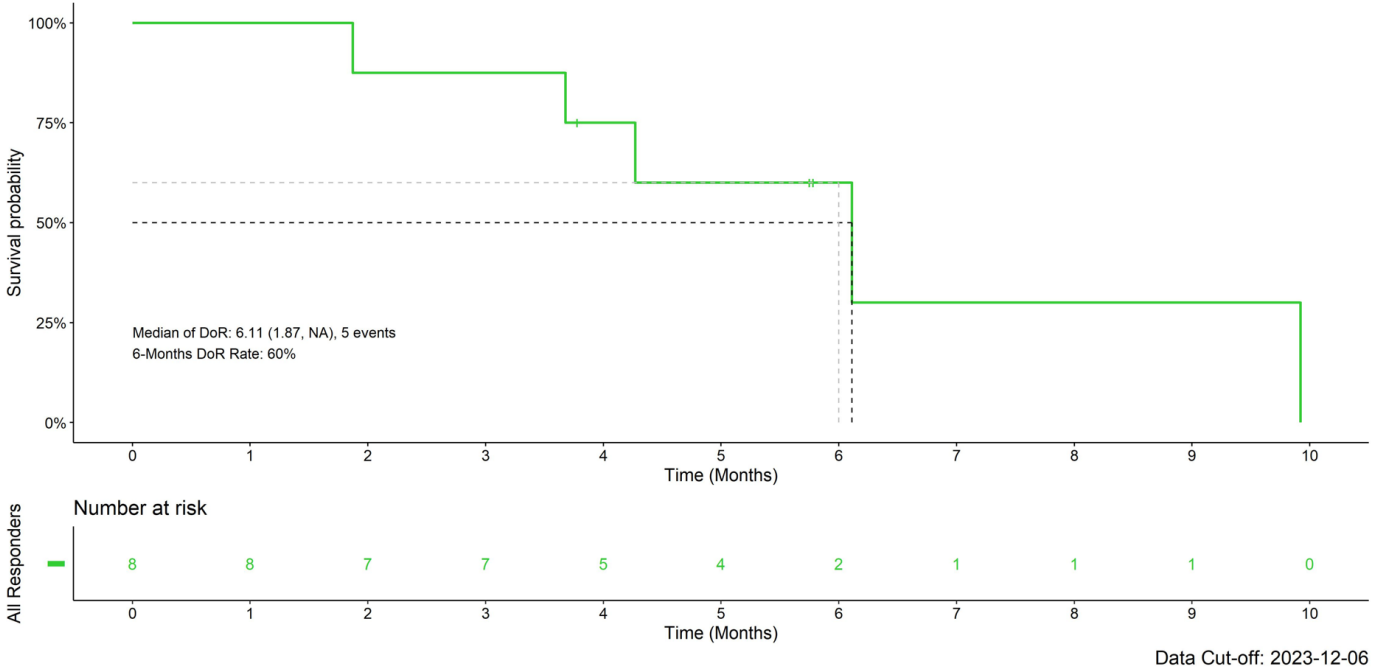
Duration of response

- Preliminary duration of response in responder population: 6.1 months
- 60% 6-month duration of response rate
- 3 ongoing responders



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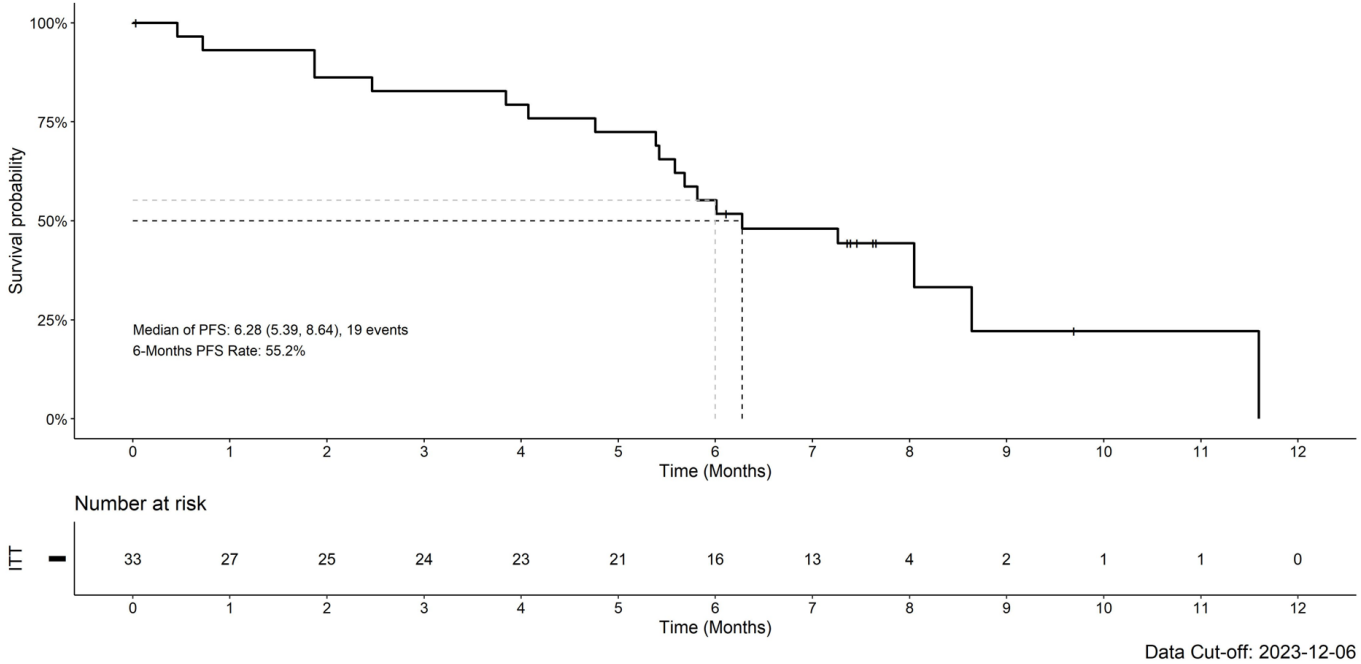
Progression-free survival

- Heterogeneous population included many unfavorable subgroups
- 9 patients remain on therapy at a minimum of 8.5 months on therapy



Median PFS:
6.3 months

6-month PFS rate:
55.2%

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SUBGROUP ANALYSES

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TUMOR SIDEDNESS

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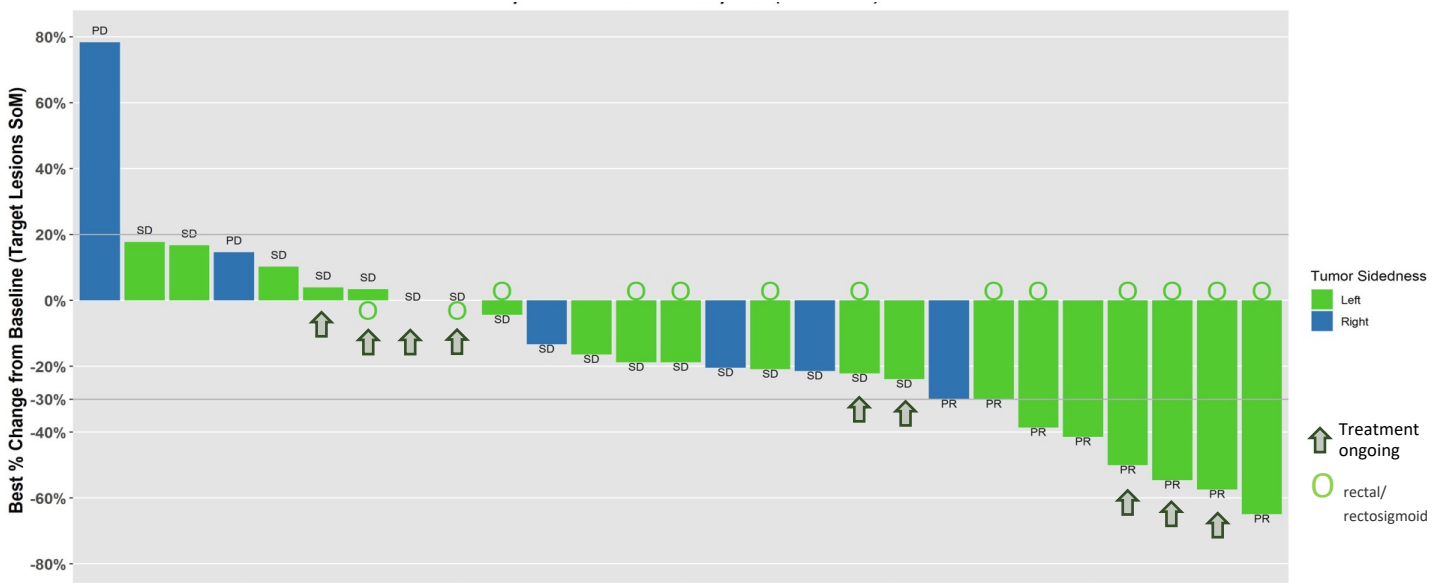
Greater activity in left-sided tumors subgroup

- 9 patients who remain on study therapy are left-sided, 6 of whom are rectal/rectosigmoid patients



Overall, n=27	Objective Response Rate (%)	Disease Control Rate (%)	Partial Response n (%)	Stable Disease n (%)	Progressive Disease n (%)
Left (n=21)	33	100	7 (33)	14 (67)	0 (0)
Right (n=6)	17	67	1 (17)	3 (50)	2 (33)

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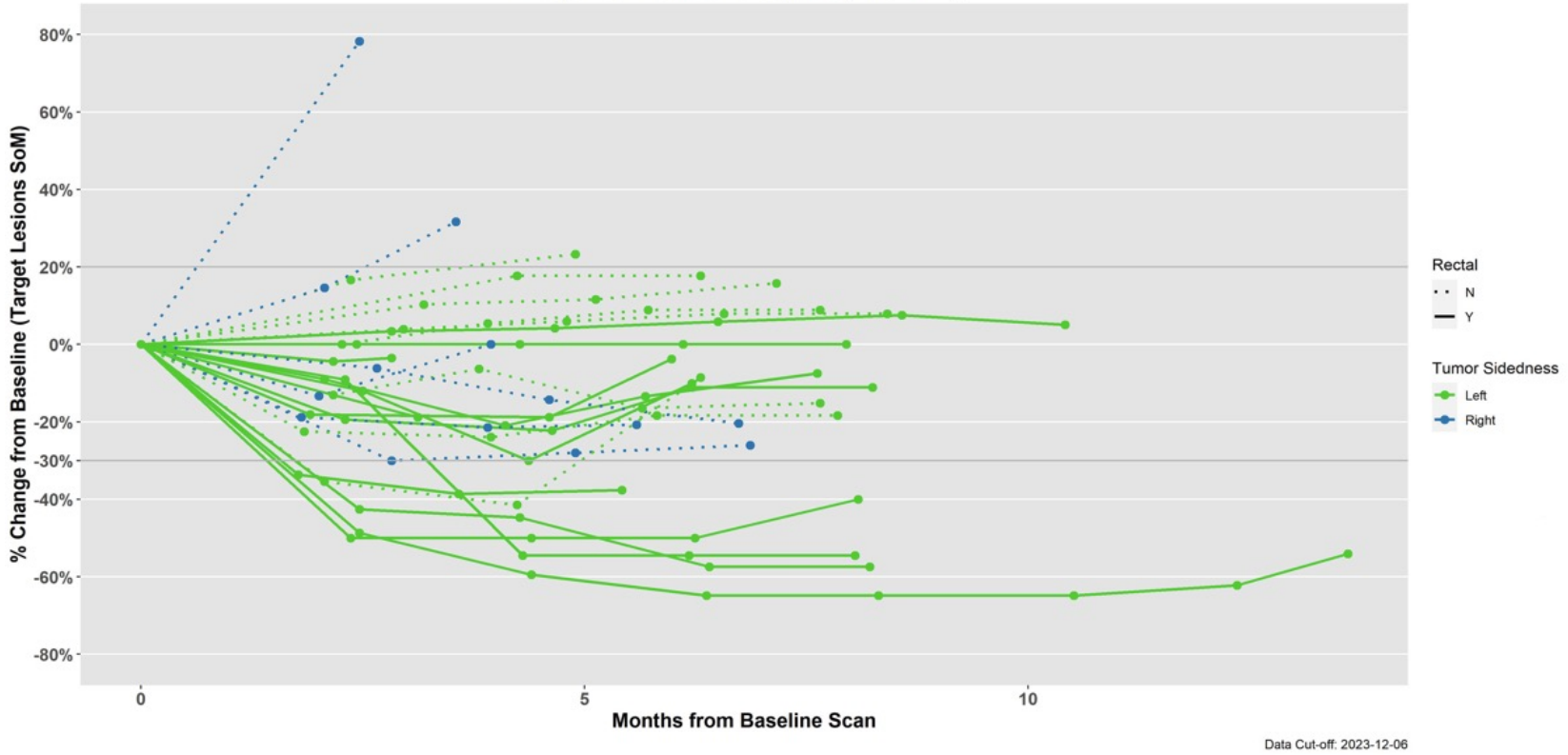
Duration of clinical benefit
Tumor sidedness subgroup



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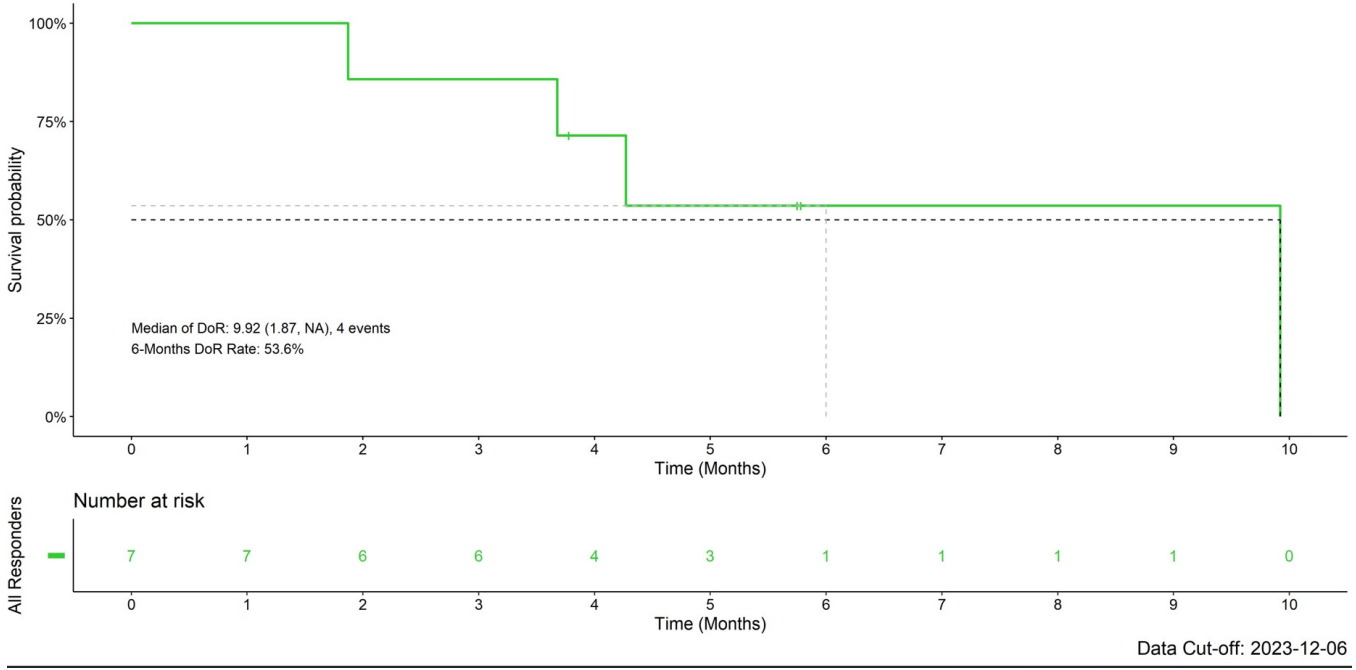
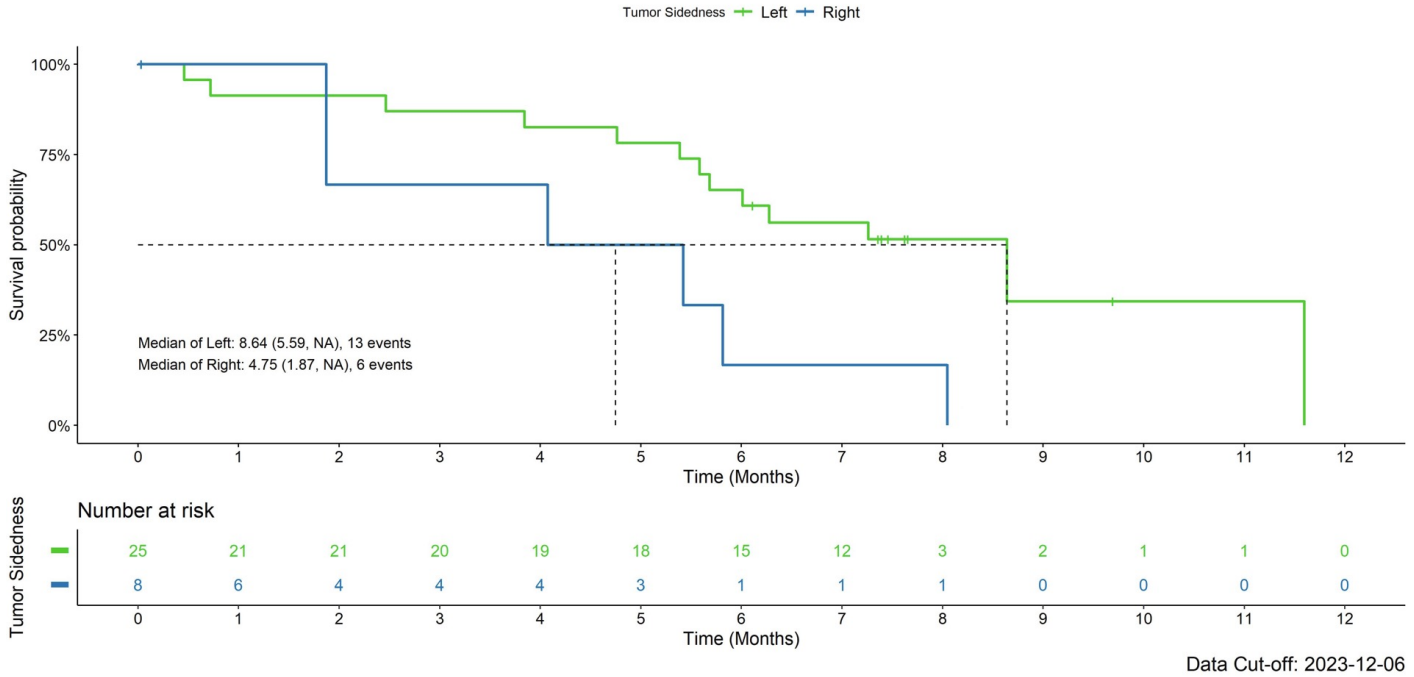
Duration of response
Tumor sidedness subgroup

- Preliminary duration of response in left-sided responder population: 9.9 months
- 3 ongoing partial responders



Longer progression-free survival in patients with left-sided tumors

- Preliminary median PFS in left-sided tumors: 8.6 months
- 9 left-sided tumor patients remain on therapy



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RECTAL/RECTOSIGMOID PRIMARIES

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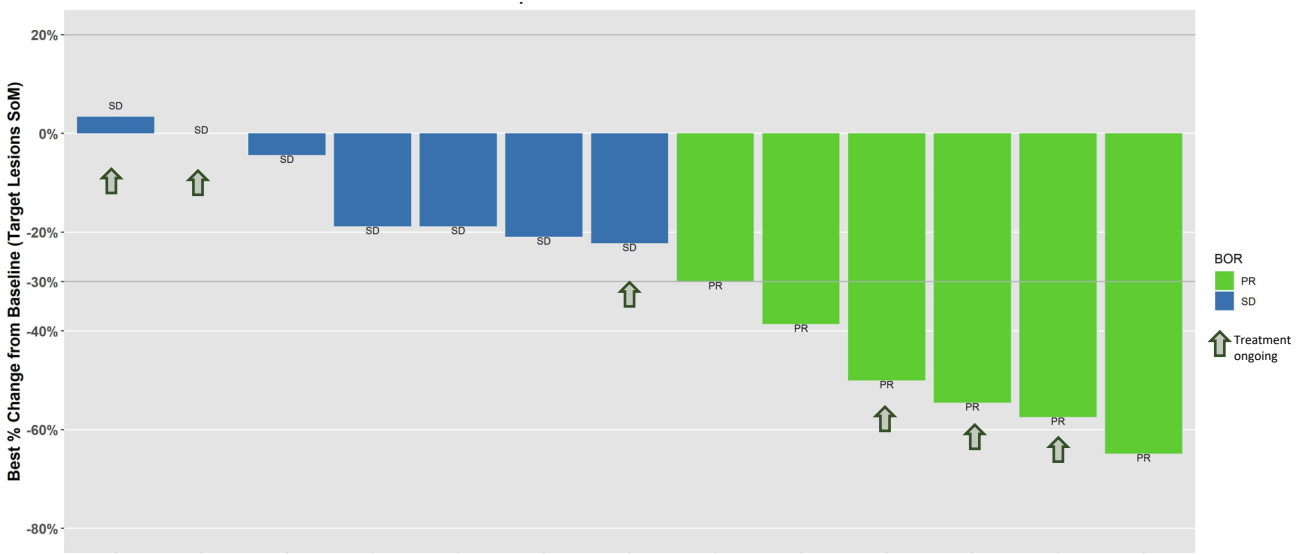
Enriched responses in rectal/rectosigmoid cancer patients



Overall, n=13	Objective Response Rate (%)	Disease Control Rate (%)	Partial Response n (%)	Stable Disease n (%)	Progressive Disease n (%)
Rectal	46	100	6 (46)	7 (54)	0 (0)

6 of the 8 responding patients were in the rectal/rectosigmoid subgroup

ORR RE: 46%

6 patients continue on therapy

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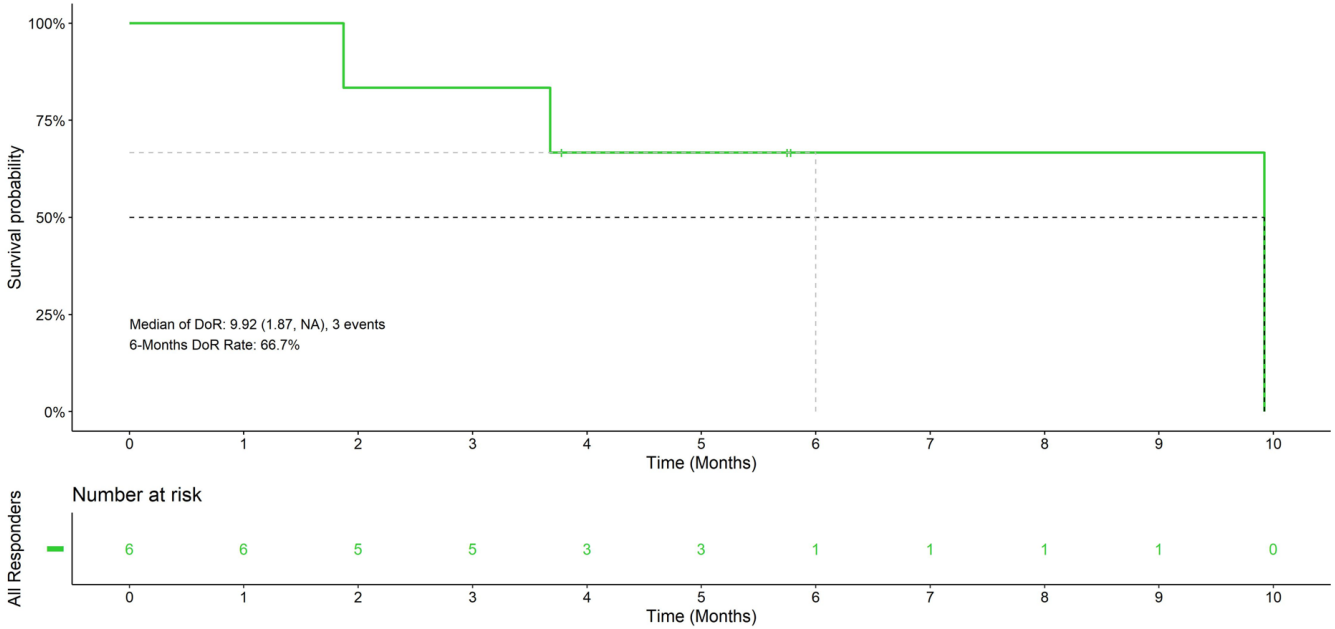
Duration of response
Rectal/rectosigmoid cancer subgroup

- Preliminary duration of response in rectal responder population: 9.9 months
- 67% 6-month duration of response
- 3 ongoing responders



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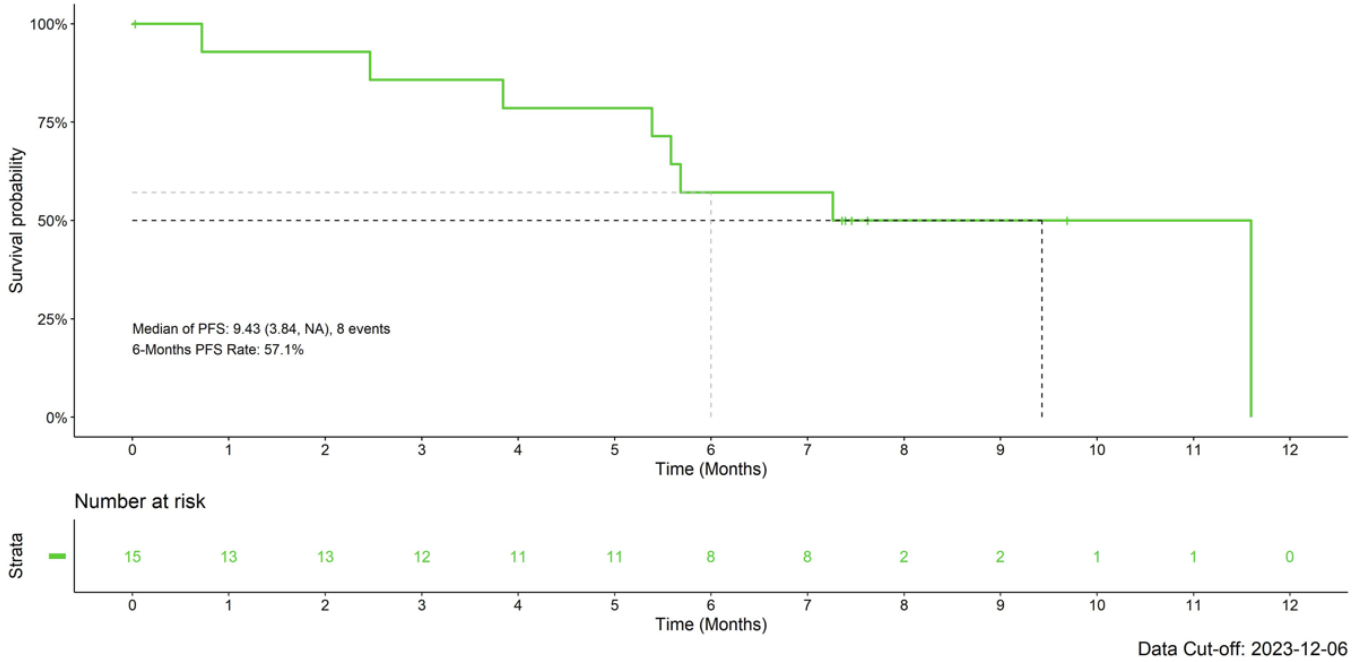
PFS still maturing with 6 patients continuing on therapy
Rectal/rectosigmoid cancer subgroup



Preliminary median PFS: 9.4 months

6-month PFS rate: 57.1%

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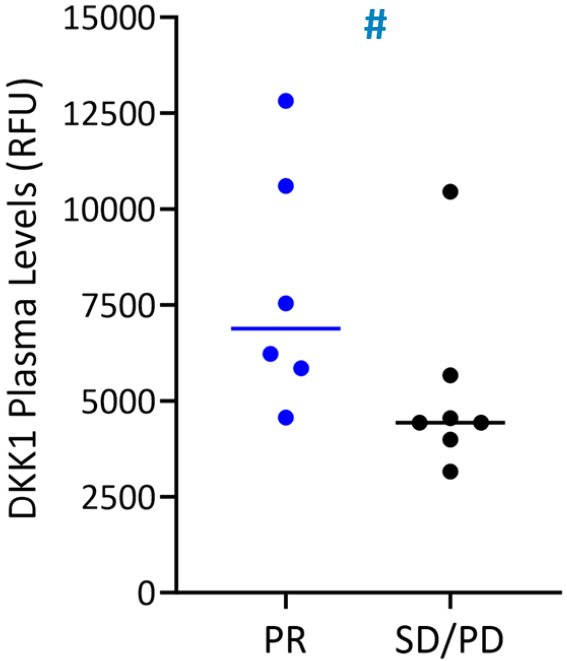
Higher baseline plasma DKK1 correlates with improved responses in rectal/rectosigmoid cancers



Baseline circulating DKK1 from rectal cancer patients demonstrates higher expression in partial responders (n=6) as compared to stable disease or progressive disease patients (n=7). DKK1 plasma levels were analyzed using the SomaScan platform (SomaLogic; Boulder, CO). Data shown as median plasma values. #, $P < 0.05$ (Mann-Whitney test).

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KRAS MUTATIONS

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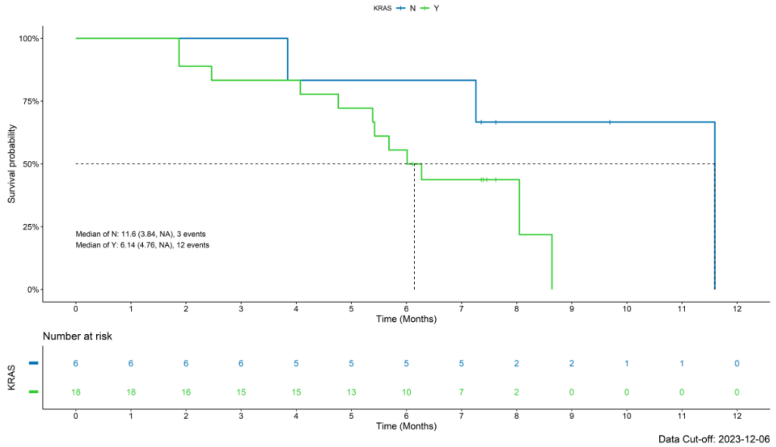
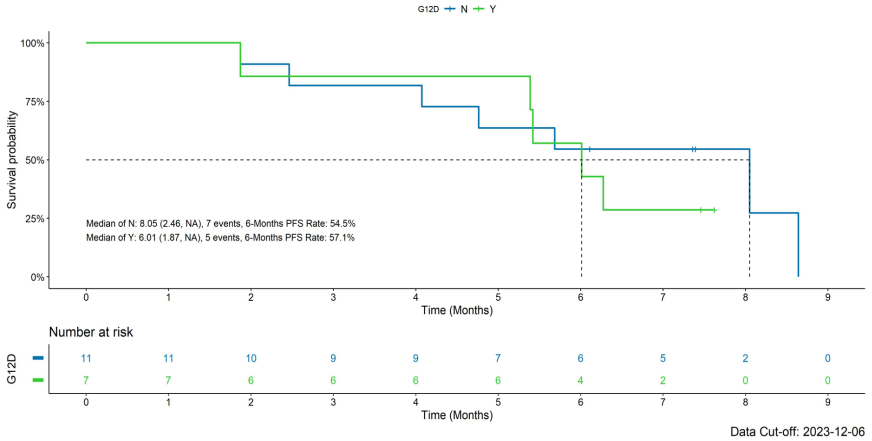
Clinical activity and durability in patients with KRAS mutations and KRAS wildtype

Progression-free survival by KRAS mutations status



Progression-free survival of patients with KRAS mutations by KRAS G12D status



Overall, n=24*	Objective Response Rate (RE %)	Disease Control Rate (RE %)	Median PFS months
KRAS mutated (n=18)	28	89	6.1
G12D (n=7)	43	86	6.0
No G12D (n=11)	24	94	8.0
KRAS wildtype (n=6)	33	100	11.6

* Baseline ctDNA analysis

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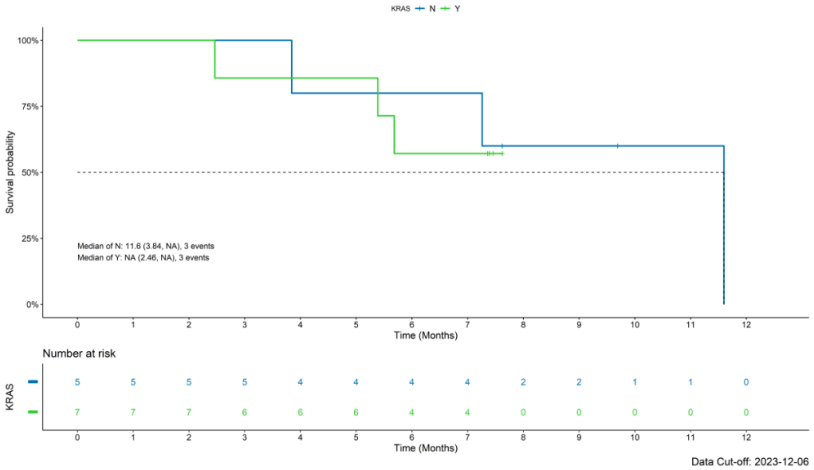
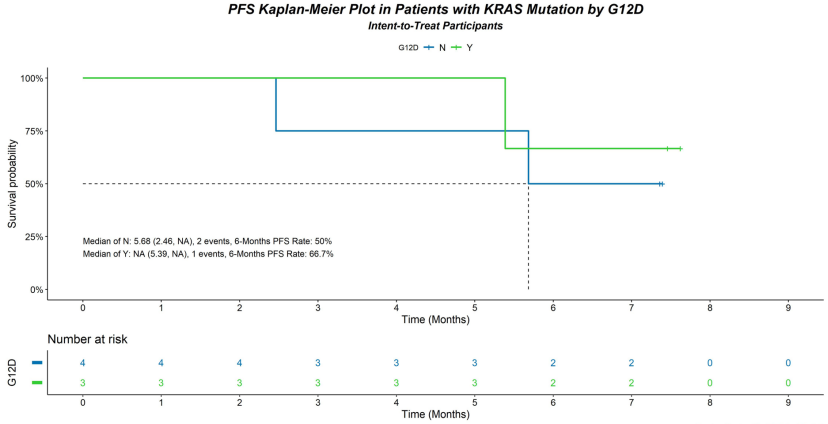
Clinical activity and durability in patients with KRAS mutations and KRAS wildtype
Rectal/Rectosigmoid cancer subgroup

Progression-free survival by KRAS mutations status



Data Cut-off: 2023-12-06

Progression-free survival of patients with KRAS mutations by KRAS G12D status



Data Cut-off: 2023-12-06

Overall, n=12*	Objective Response Rate (RE %)	Disease Control Rate (RE %)	Median PFS months
KRAS mutated (n=7)	43	100	NR
G12D (n=3)	67	100	NR
No G12D (n=4)	33	100	5.7+
KRAS wildtype (n=5)	40	100	11.6

* Baseline ctDNA analysis

PRIOR BEVACIZUMAB

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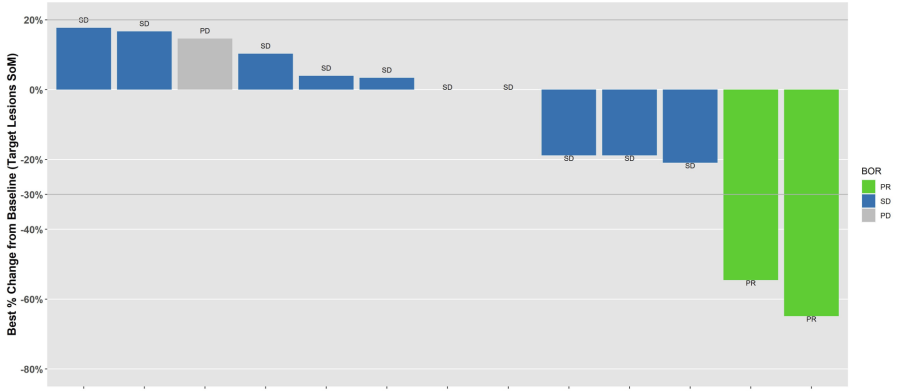
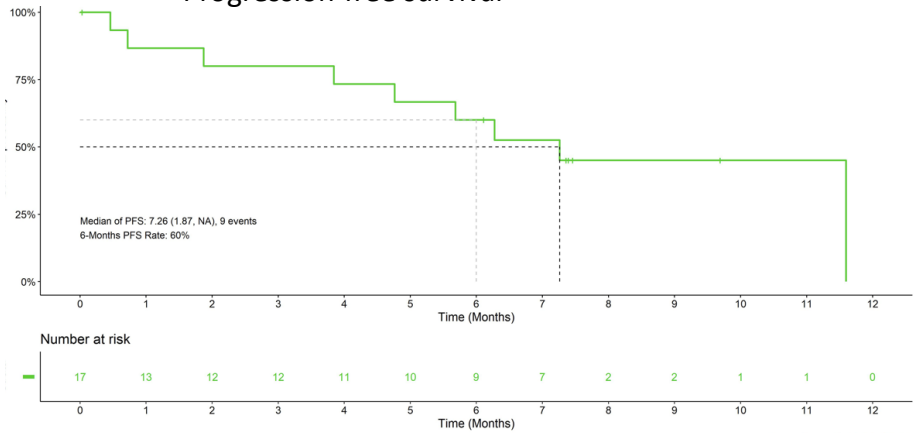
Response rate and PFS favorable in bevacizumab-experienced patients compared to benchmark from ML18147 study

- 6-month PFS rate: 60%
- Preliminary median PFS: 7.3 months, with 5 patients continuing on study beyond 8.5 months

Best overall tumor reduction from baseline



Progression-free survival



Data Cut-off: 2023-12-06

Overall, n=17	Objective Response Rate (RE %)	Disease Control Rate (RE %)	Partial Response n (RE %)	Stable Disease n (RE %)	Progressive Disease n (RE %)	PFS Median months
Prior bev	15	92	2 (15)	10 (77)	1 (8)	7.3

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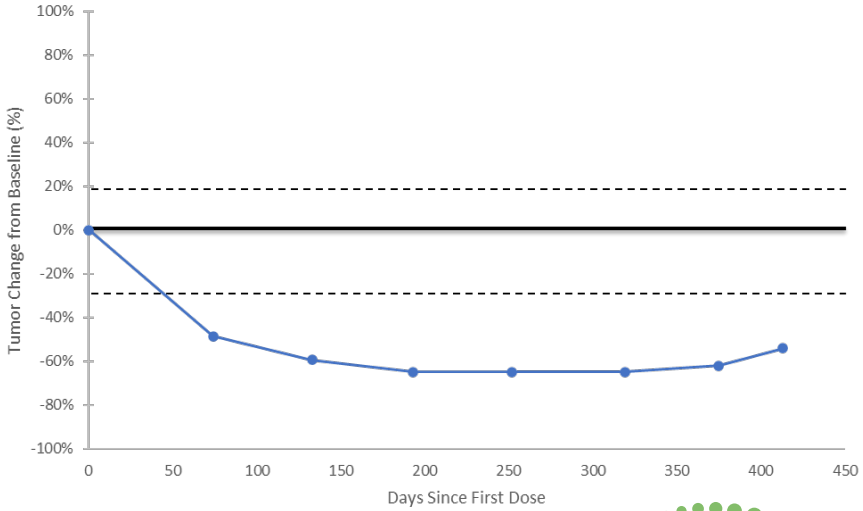
Patient with Metastatic Rectal MSS CRC
Prolonged Partial Response ~10 months

- Patient history
  - 43 yo male diagnosed in May 2020 with metastatic rectal adenocarcinoma, treated with 1L FOLFOX/bevacizumab followed by robotic low anterior resection with diverting loop ileostomy in December 2020.
  - No evidence of disease until May 2022 when he had recurrence of liver metastasis treated with microwave ablation to the liver
  - Enrolled on DeFianCe trial in October 2022 with disease in the retroperitoneal lymph nodes, sum of target lesions 37 mm, and treated with FOLFIRI + bevacizumab + DKN-01

- Tumor characteristics
  - ctDNA: TP53, APC, BRAF, SMAD, PTEN, FLT3, CDK8, BRIP1 mutations

- Durable partial response
  - CT scans on study revealed a PR at 8-week scans (-49%)
  - Confirmed with deepening at 16-week scans (-59%)
  - Further deepening at 24-week scans (-65%)
  - Remained on study for 13 months



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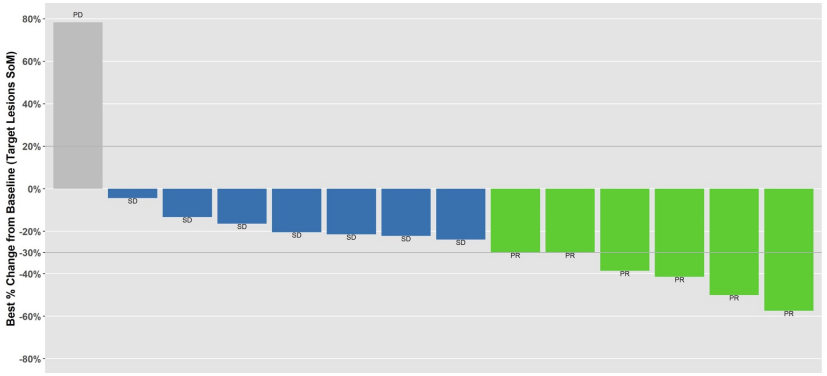
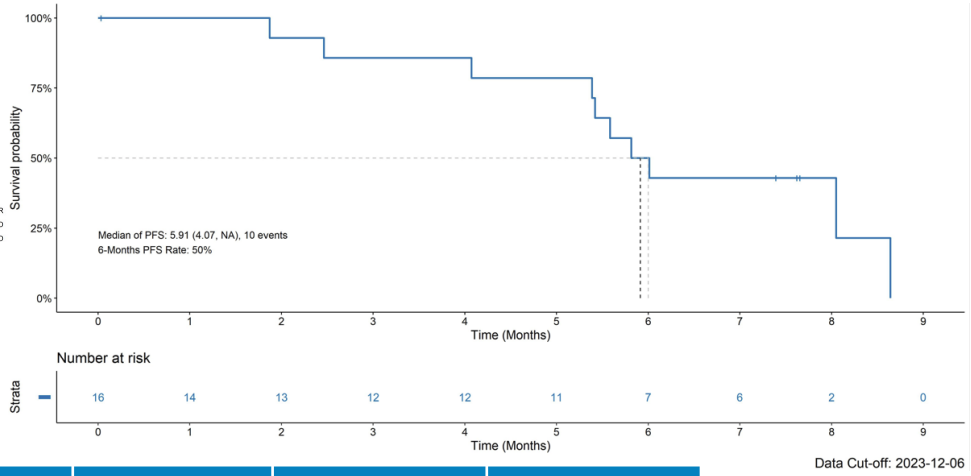
High overall response rate in patients without prior bevacizumab exposure

- Patient population includes rapid progressors on first-line therapy
- 6 patients with PFS exceeding 8 months, 4 continuing on therapy

Best overall tumor reduction from baseline



Progression-free survival



Data Cut-off: 2023-12-06

Overall, n=16	Objective Response Rate (RE %)	Disease Control Rate (RE %)	Partial Response n (RE %)	Stable Disease n (RE %)	Progressive Disease n (RE %)	PFS Median months
No prior bev	43	93	6 (43)	7 (50)	1 (7)	5.9

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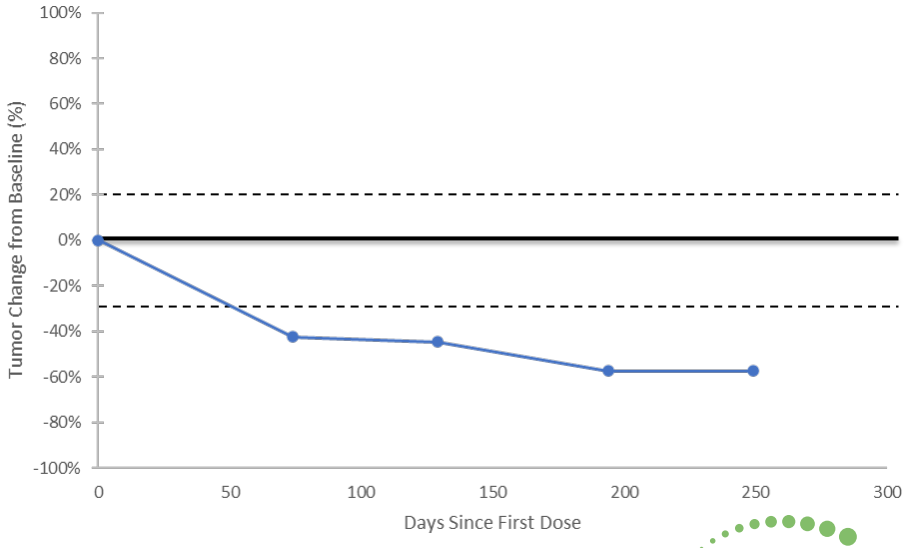
Patient with Metastatic Rectal MSS CRC
Ongoing PR ~8+ months

- Patient history
  - 71 yo female diagnosed with rectal adenocarcinoma in January 2022, treated with neoadjuvant FOLFOX (March 2022-July 2022) + XRT followed by Xeloda until September 2022
  - December 2022 underwent a colectomy and then recurred
  - Enrolled on DeFianCe study in March 2023 and treated with FOLFIRI + bevacizumab + DKN-01

- Tumor characteristics
  - ctDNA: TP53, CHEK2, DNMT3A, FBXW7, APC mutations

- Durable partial response ongoing
  - CT scans on study revealed a PR at 8-week scans (-43%)
  - Confirmed PR with deepening at 16-week scans (-45%)
  - Further deepening at 24-week and 32-week scans (-57%),
  - Continues on therapy in Cycle 19



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SUMMARY

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DeFianCe Part A summary

- DKN-01 + SOC chemotherapy (FOLFIRI or FOLFOX) + bevacizumab was well tolerated
- Promising clinical activity in a heterogeneous 2L MSS population with poor prognostic features
  - Response evaluable ORR 30%, DCR 93%
  - Median PFS: 6.3 months
    - 9 subjects remain on study therapy beyond 8.5 months
- Subgroup analysis demonstrated the greatest benefit in rectal/rectosigmoid cancer patients
  - ORR 46%, DCR 100%
  - Preliminary median PFS 9.4 months
  - Elevated baseline plasma DKK1 levels correlate with greater clinical response
- Additional subgroups reflect the breadth of the clinical activity
  - Prior bevacizumab: ORR 15%, DCR 92%, PFS 7.3 months
  - Without prior bevacizumab: ORR 43%, DCR 93%, PFS 5.9 months
  - KRAS wildtype: ORR 33%, DCR 100%, PFS 11.6 months
  - KRAS mutations: ORR 28%, DCR 89%, PFS 6.1 months
- Enrollment in the randomized controlled trial (Part B) is strong with 54 patients enrolled to date

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QUESTIONS & ANSWERS

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