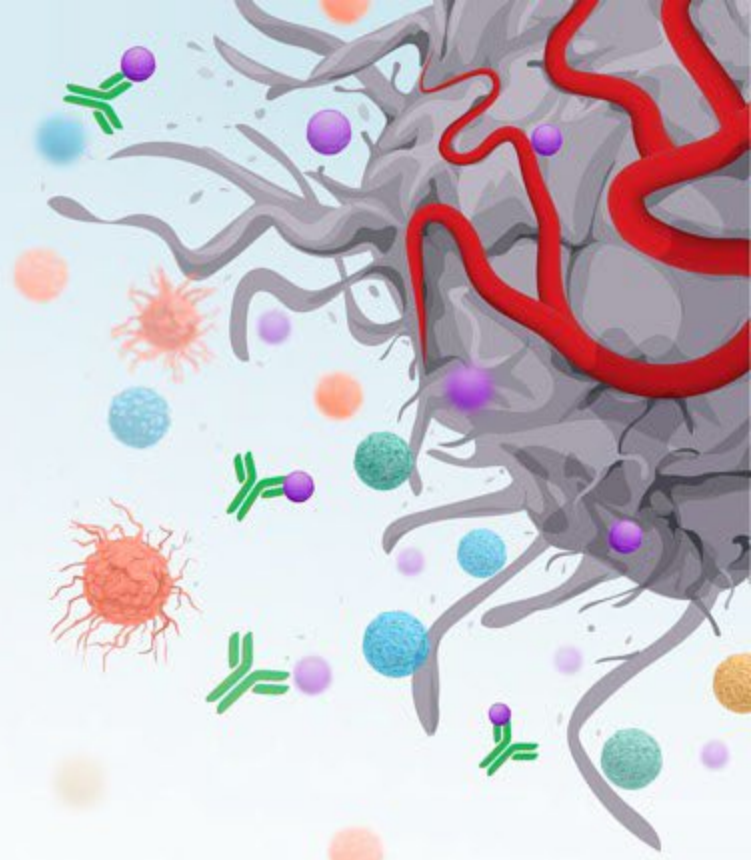
LEAP THERAPEUTICS

company presentation

October 20, 2025



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Forward looking statements

This presentation contains forward-looking statements that involve substantial risks and uncertainties. All statements, other than statements of historical facts, contained in this presentation, including statements regarding our strategy, future operations, clinical trials, collaborations and partnerships, future financial position, future revenues, projected costs, prospects, plans and objectives of management, are forward-looking statements within the meaning of U.S. securities laws. The words “anticipate,” “believe,” “estimate,” “expect,” “intend,” “may,” “plan,” “predict,” “project,” “target,” “potential,” “will,” “would,” “could,” “should,” “continue,” and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words.

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This presentation does not constitute an offer to sell, or the solicitation of an offer to buy, any securities.

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Corporate overview

Drug Development Strategy

- Sirexatamab (DKN-01) for patients with colorectal cancer
- FL-501 for treatment of cachexia-related diseases

Digital Asset Treasury Strategy

- $58.88 million strategic investment led by Winklevoss Capital

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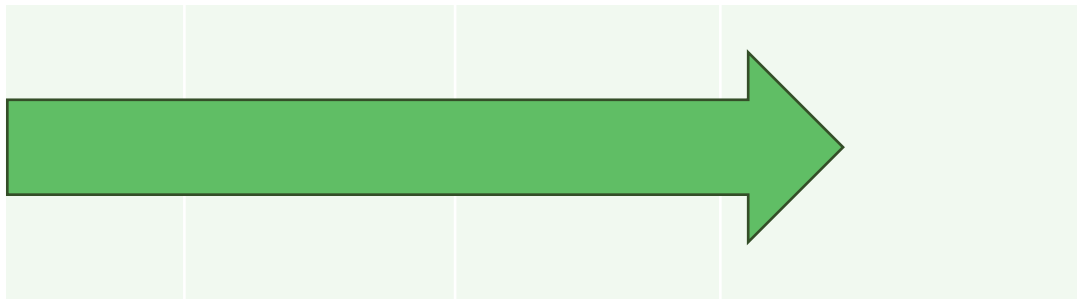
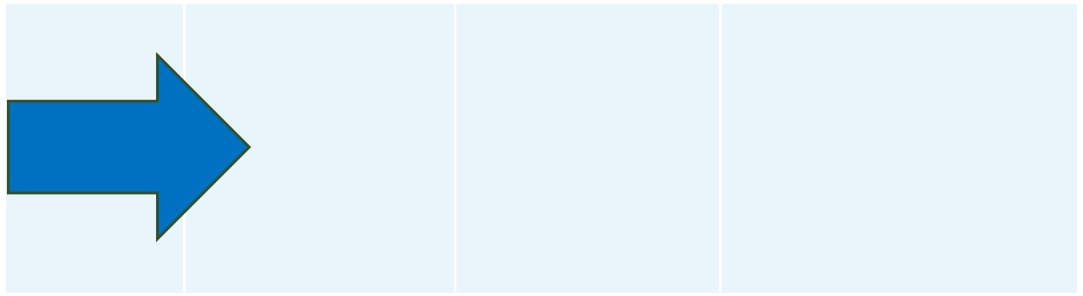
Pipeline

	Indication:	Treatment:	Preclinical	Phase 1	Phase 2	Phase 3
sirexatamab (DKN-01) Anti-DKK1 antibody	Colorectal cancer	bevacizumab + chemotherapy				
FL-501 Anti-GDF-15 antibody						





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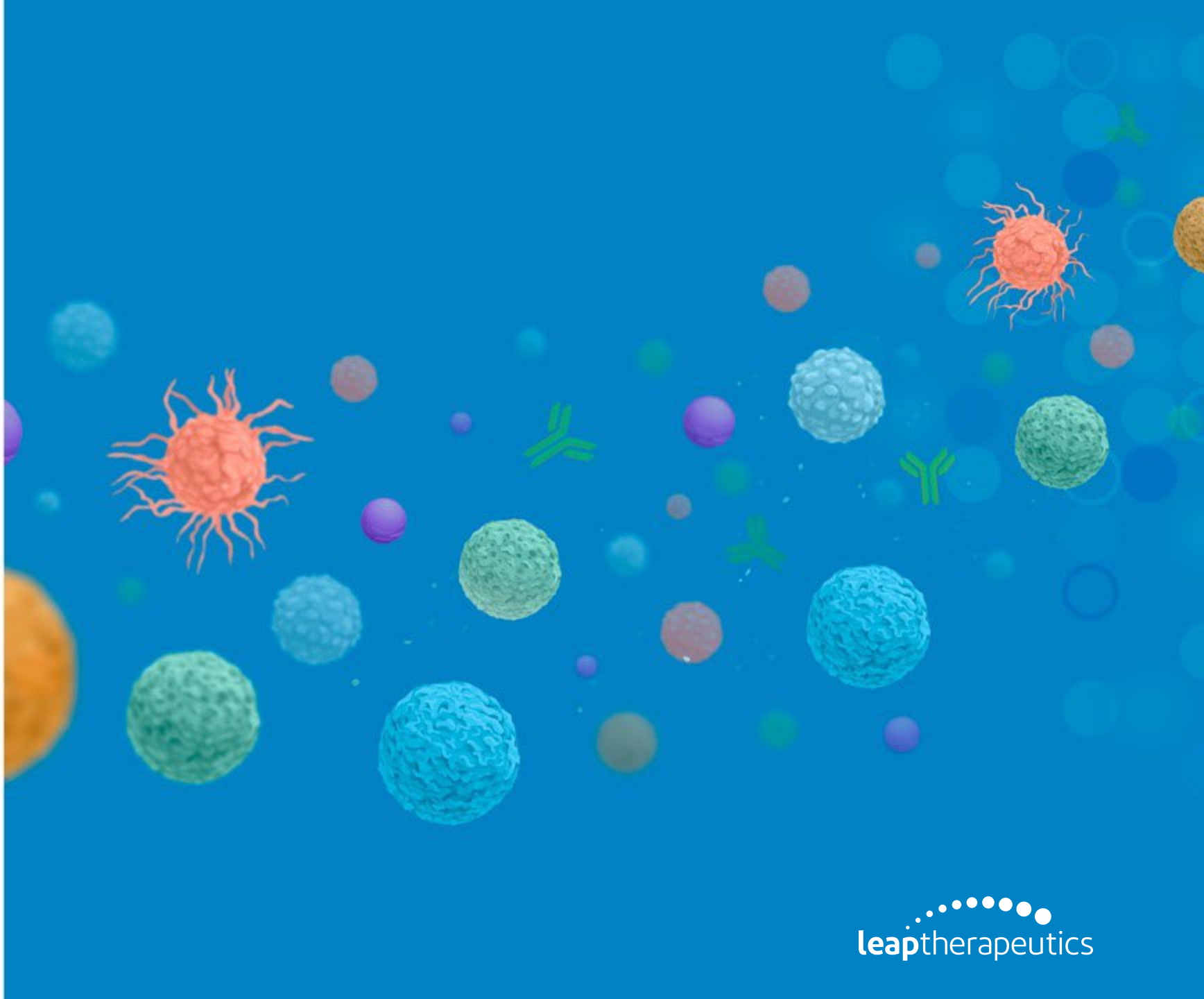
SIREXATAMAB (DKN-01)

Anti-DKK1 monoclonal antibody



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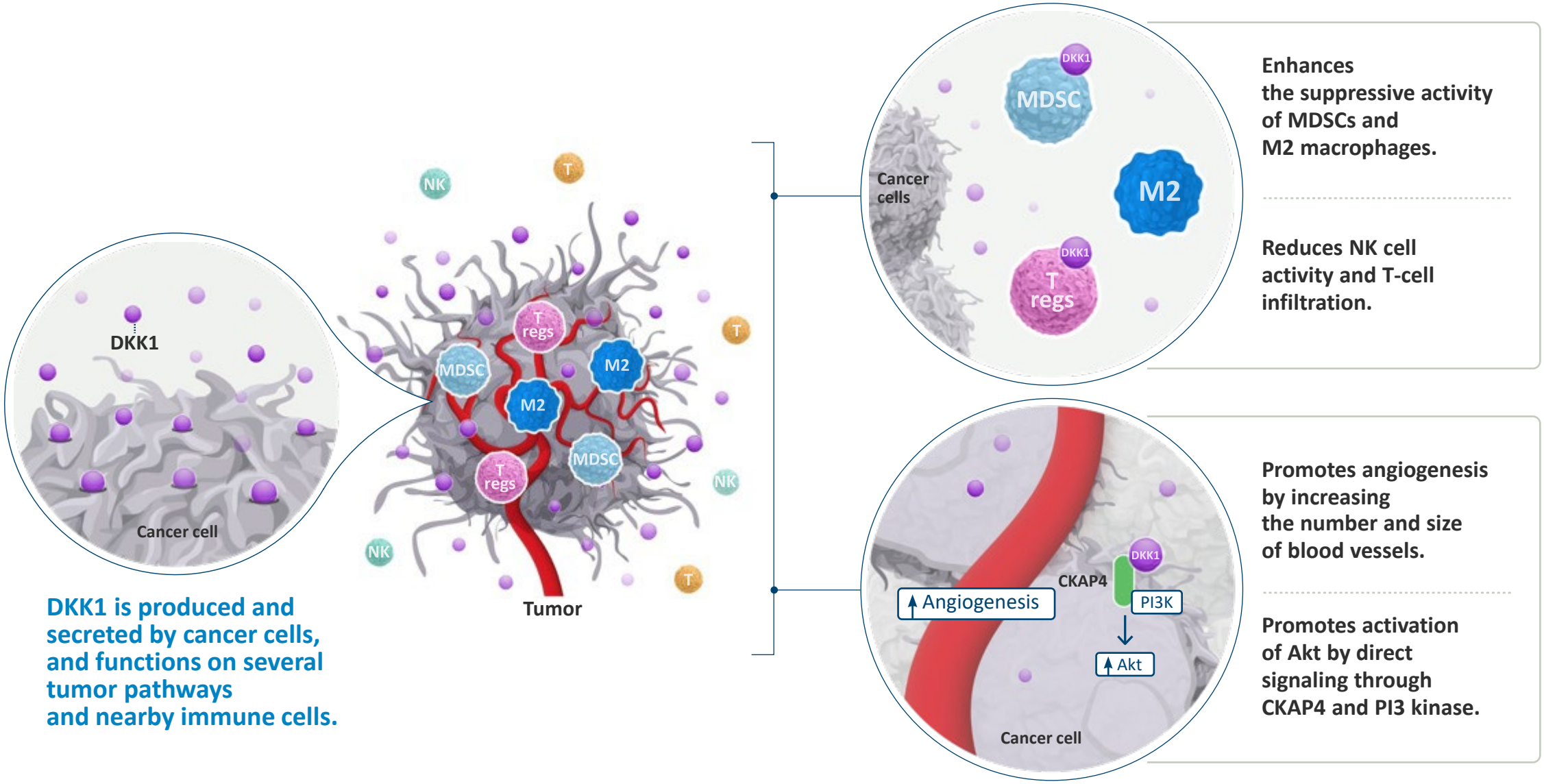
The role of DKK1 in cancer



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

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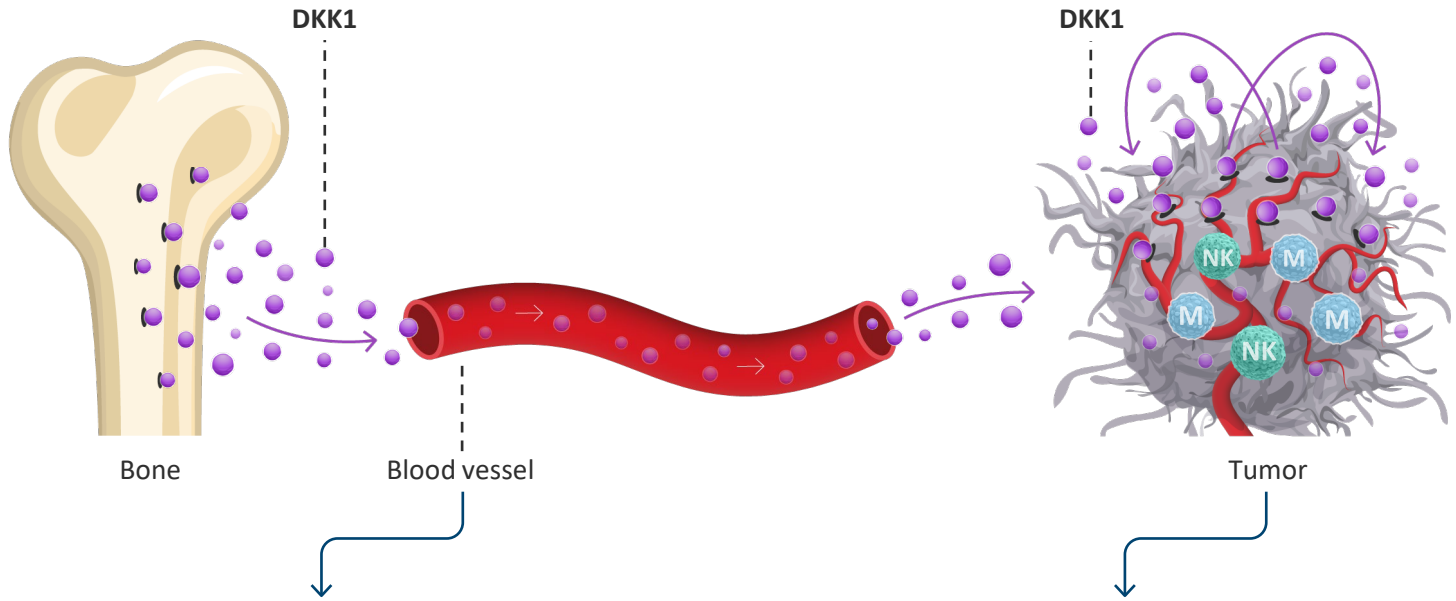
DKK1 production from multiple sources can drive tumor growth



DKK1 protein in circulation is measured by ELISA

ELISA
Enzyme-Linked Immunosorbent Assay

DKK1 RNA from the tumor is measured by RNAscope

DKK1 high DKK1 low

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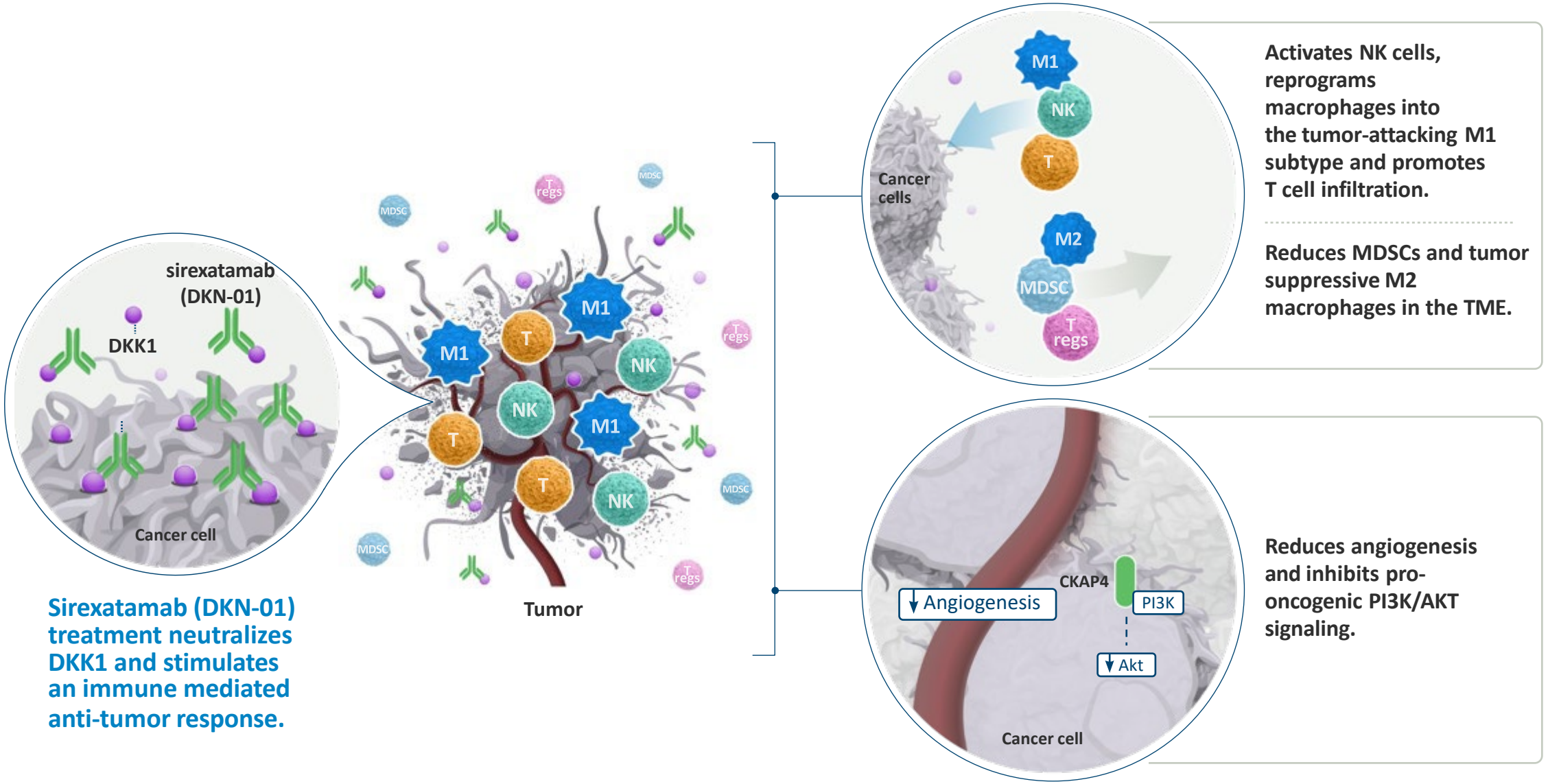
Activity of sirexatamab (DKN-01) to treat cancer



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

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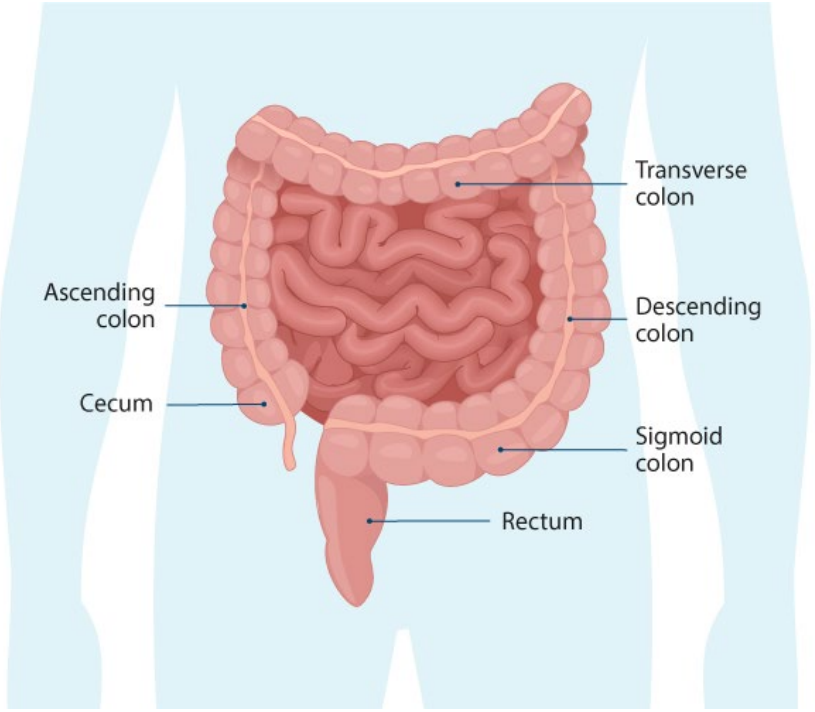
SIREXATAMAB (DKN-01)

Colorectal cancer

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, over 2,000,000 new cases and 1,000,000 deaths per year
- In the US, estimated 155,000 cases and more than 50,000 deaths per year

Source: WHO, American Cancer Society

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Significant unmet needs in 2L patients

Bevacizumab benchmark studies demonstrate need for new options for today's heterogeneous second-line patient population

Treatment	Bevacizumab + Chemo	Bevacizumab + Chemo	Bevacizumab + Chemo*
Study	ML18147	E3200	SLAVE
Population	Bevacizumab-experienced	Bevacizumab-naïve	EGFR-experienced
👤	409	286	228
ORR	5.4%	22.7%	25.7%
PFS	5.7	7.3	7.1
OS	11.2	12.9	16.2

*SLAVE included N=198 left sided CRC patients. This subgroup has an ORR of 22.7%

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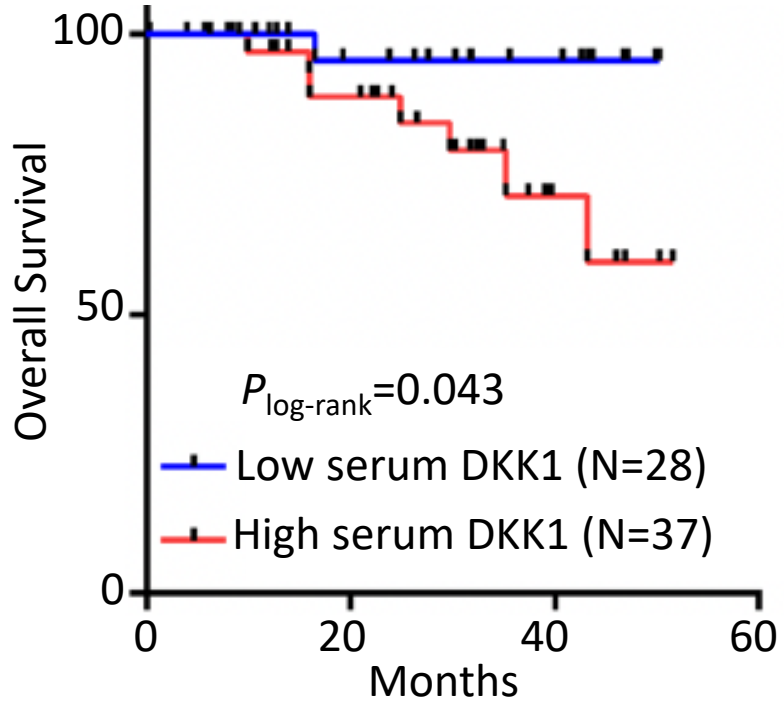
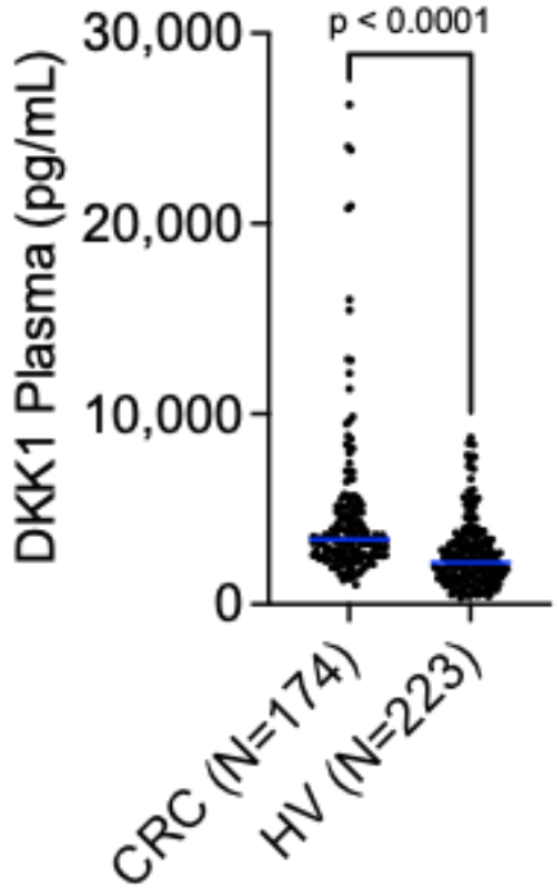
Circulating DKK1 levels are elevated in CRC and prognostic of worse outcomes

Elevated serum levels of DKK1 are associated with a worse clinical prognosis for CRC



DKK1 plasma levels are elevated in CRC patients



Gurluler et al., ERMPS, 2014; Sui et al., JITC, 2021; Sui et al. BMC Cancer, 2019

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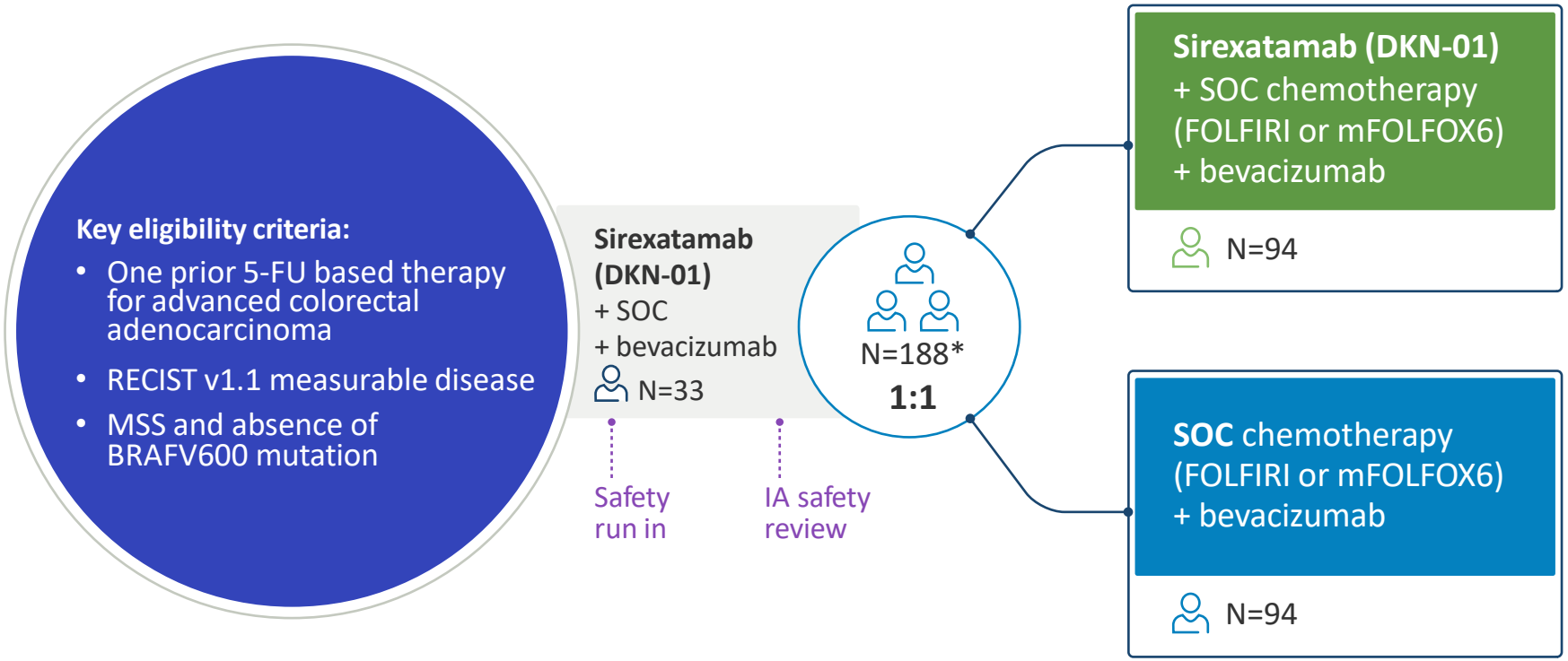
DeFianCe study design

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



*Right-sided mCRC capped at 45

Database lock: July 18, 2025
Median study duration: 11.1 months

Clinicaltrials.gov number: NCT05480306

OBJECTIVES

Primary:
PFS (Investigator assessed)

Secondary:
- ORR
- OS

Key Exploratory Populations:
- DKK1 biomarker high
- VEGF-naive

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INTENT-TO-TREAT POPULATION

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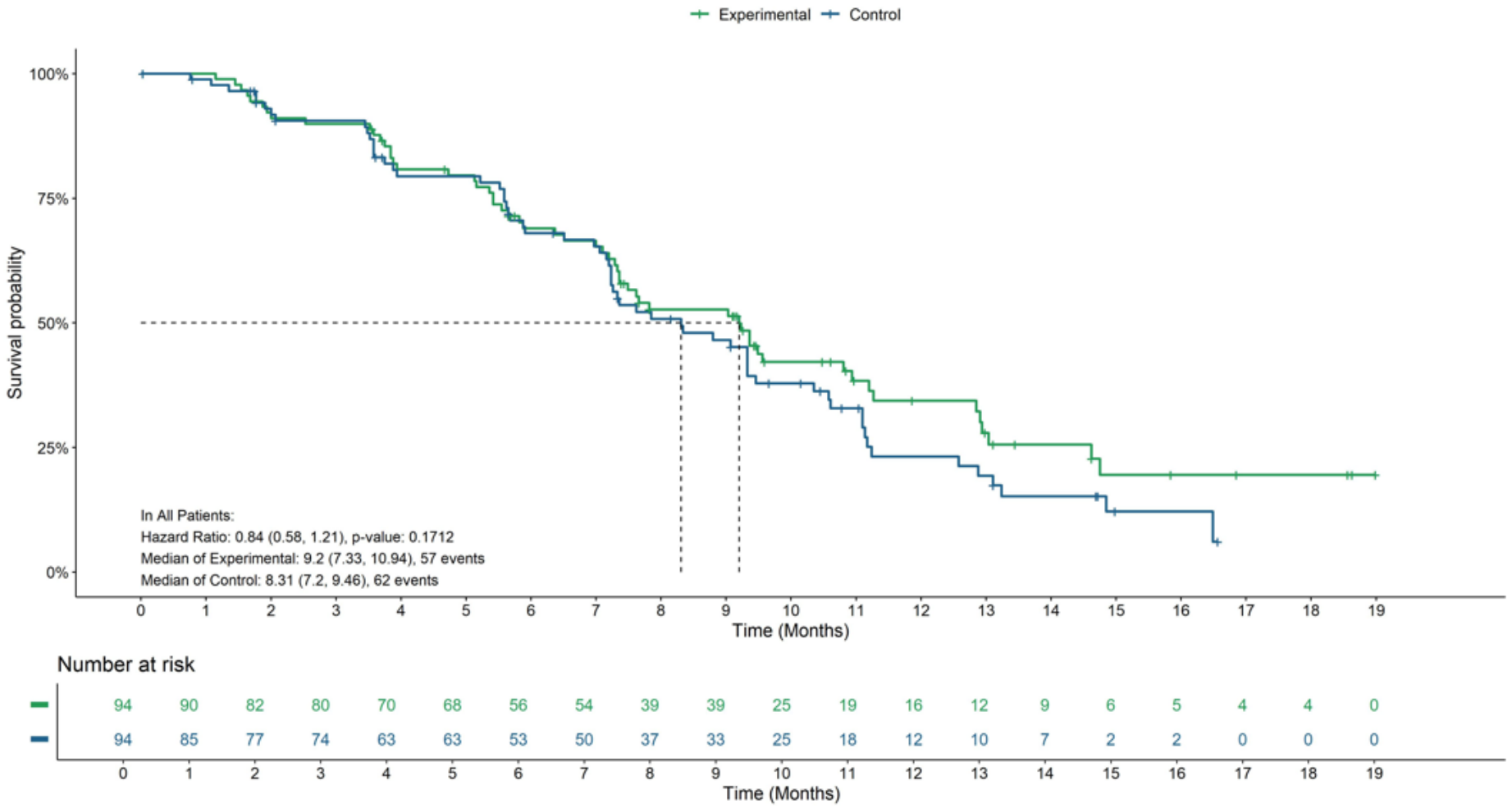
Sirexatamab increased median PFS by ~1 month

Intent-to-Treat (ITT) population – Investigator Assessment



Data Cut-off: 2025-07-17

PFS demonstrates ~1 month advantage

- **Median: 9.2 vs. 8.3 months**
- **HR 0.84**
- **p = 0.1712 (pre-defined SAP primary endpoint p = 0.10)**

Event-free rate favors sirexatamab arm beginning at month 9 (53 vs 47%) and further separation at month 12 (34 vs 23%)

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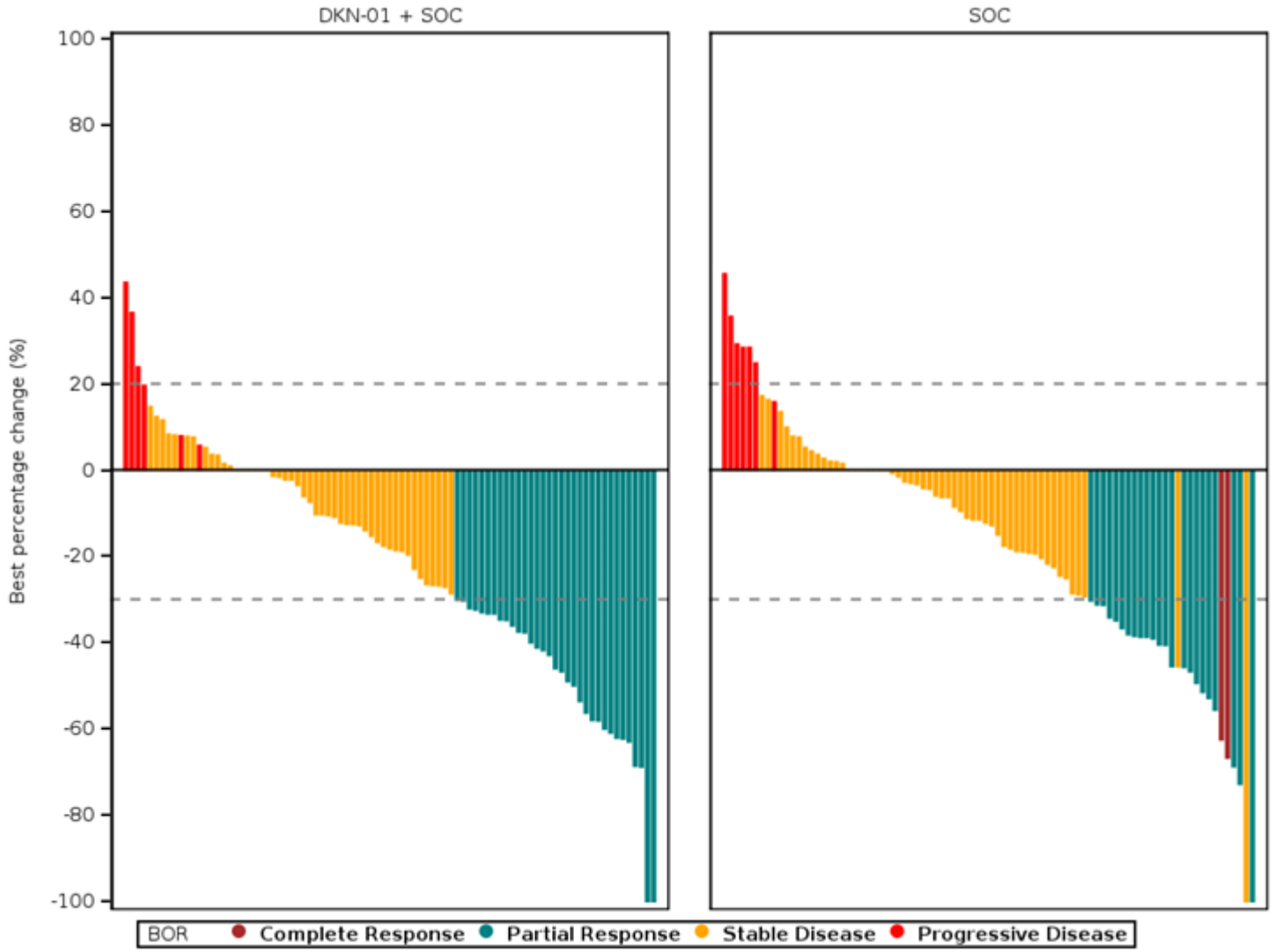
Sirexatamab improved ORR by 8% (35% vs. 27%)

Intent-to-Treat (ITT) population – Investigator Assessment

Response	Sirexatamab Experimental N=94 n (%)	Control N=94 n (%)
CR	0 (0)	2 (2)
PR	33 (35)	23 (25)
ORR 95% CI	**35.1% (25.5, 45.6)**	**26.6% (18.0, 36.7)**
p value	**p=0.1009**	
SD	48 (51)	54 (57)
DCR	**86.2%**	**84.0%**
PD	6 (6)	7 (7)
No assessment	7 (7)	8 (9)



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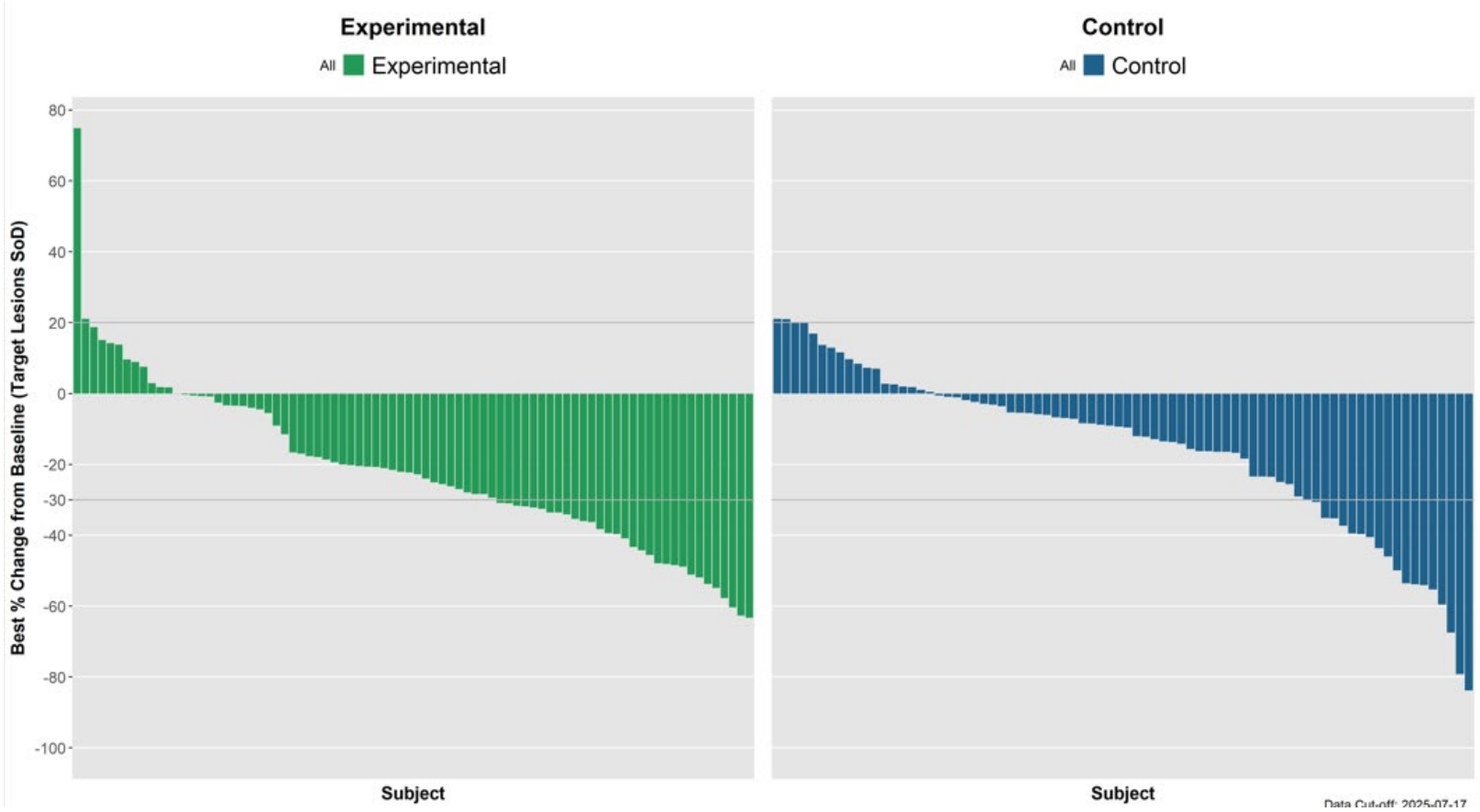
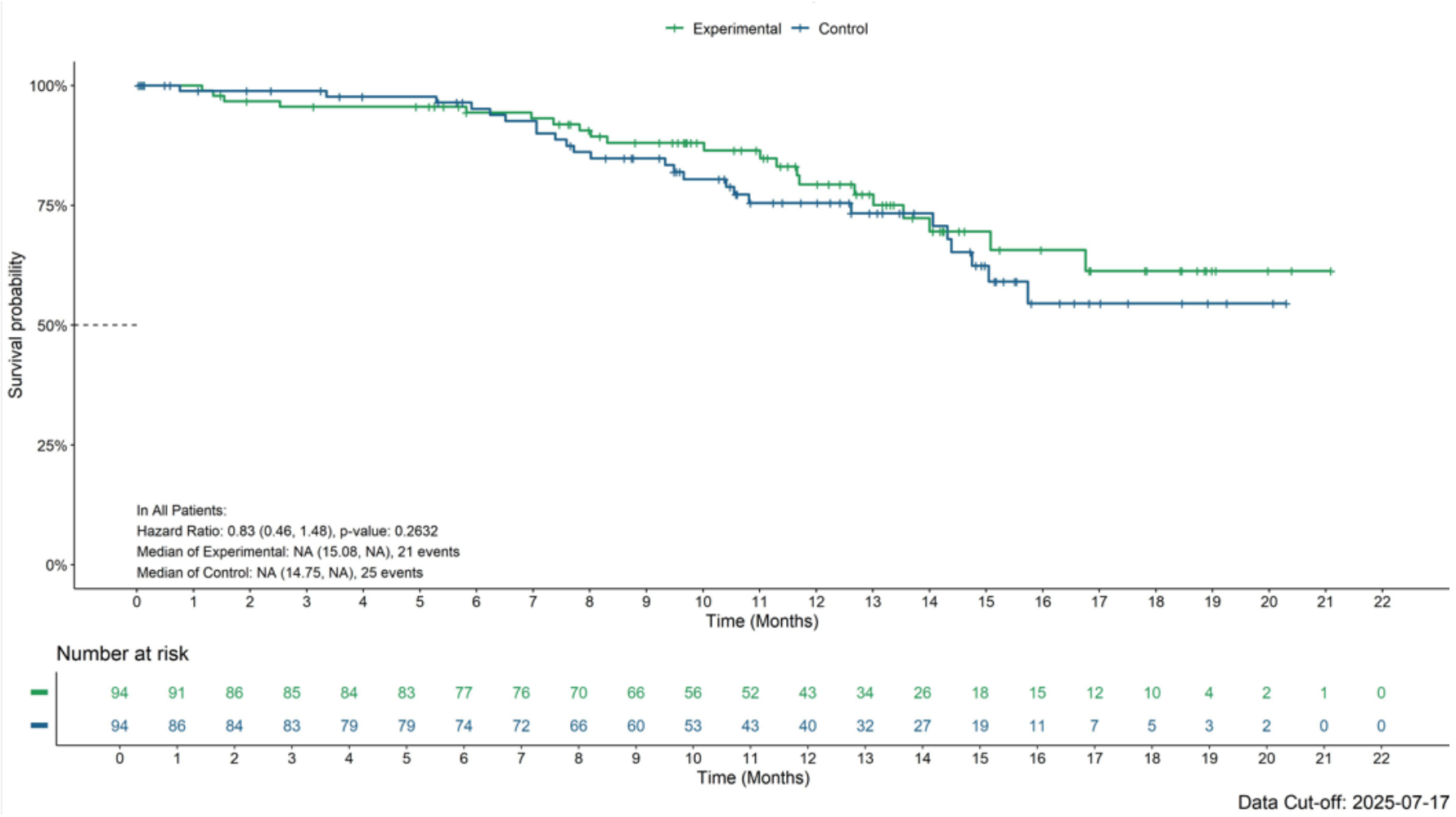
Sirexatamab improved ORR by 13% (33% vs. 20%) assessed by BICR

Intent-to-Treat (ITT) population - BICR

Response	Sirexatamab Experimental N=94 n (%)	Control N=94 n (%)
CR	1 (1)	2 (2)
PR	30 (32)	17 (18)
ORR 95% CI	**33.0% (23.6, 43.4)**	**20.2% (12.6, 29.8)**
p value	**p=0.0203**	
SD	47 (50)	52 (55)
Non-CR / Non-PD	2 (2)	5 (5)
DCR	**82.9%**	**75.5%**
PD	6 (6)	9 (10)
NE/NA	8 (9)	9 (10)



Overall Survival
Intent-to-Treat (ITT) population



- OS not mature due to limited number of events
  - 25 deaths Control Arm vs. 21 deaths Experimental Arm

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DKK1 BIOMARKER – UPPER QUARTILE (TOP 25%)

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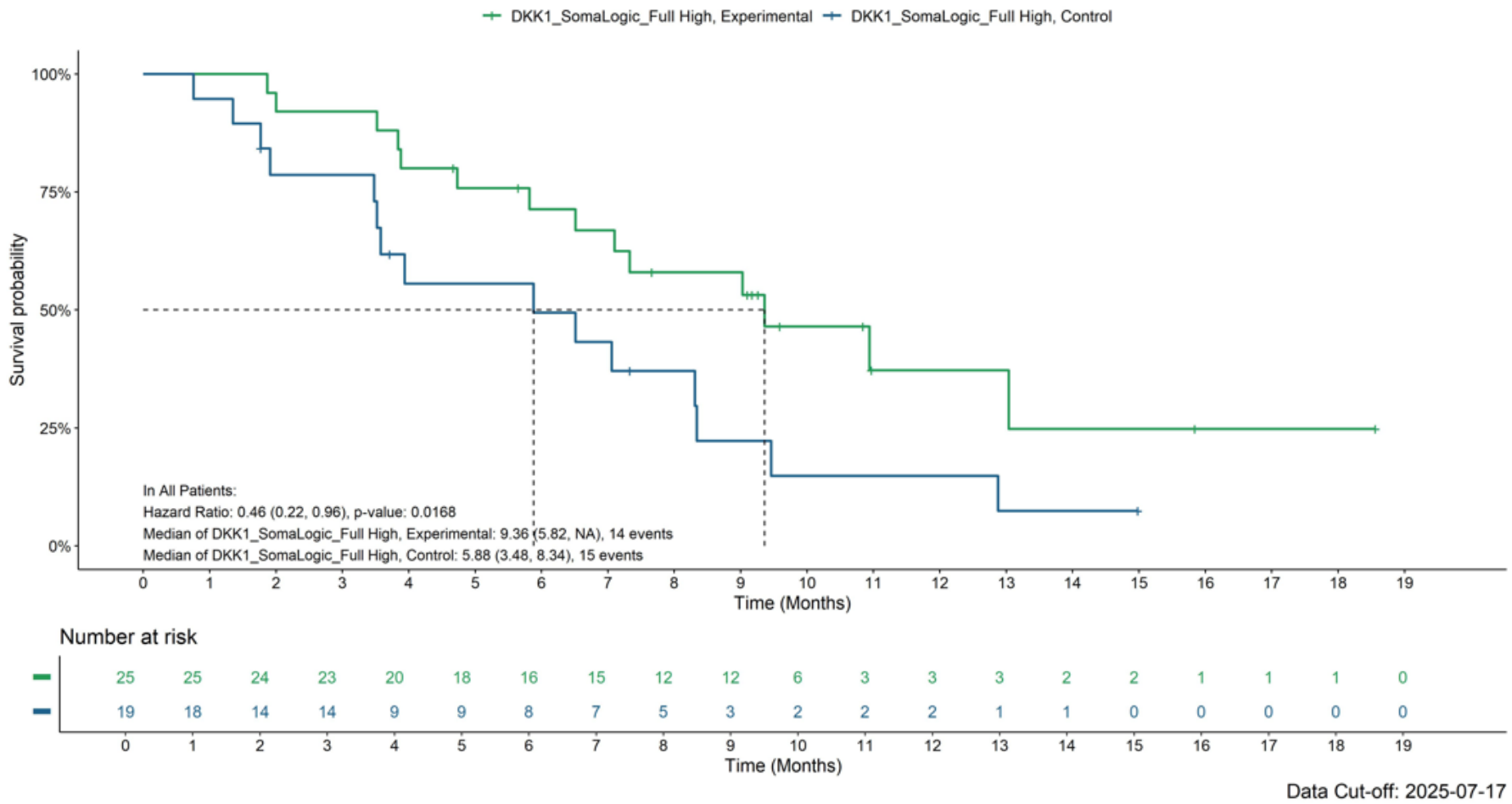
3.5 months longer Progression-free Survival with sirexatamab

DKK1-high subgroup – Upper Quartile



- Statistically significant improvement in PFS
  - Median: 9.36 vs. 5.88 months
  - HR 0.46
  - p = 0.0168
- Enhanced, statistically significant 5 month improvement in PFS by BICR
  - Median: 9.0 vs. 3.9 months
  - HR 0.36
  - p = 0.0065

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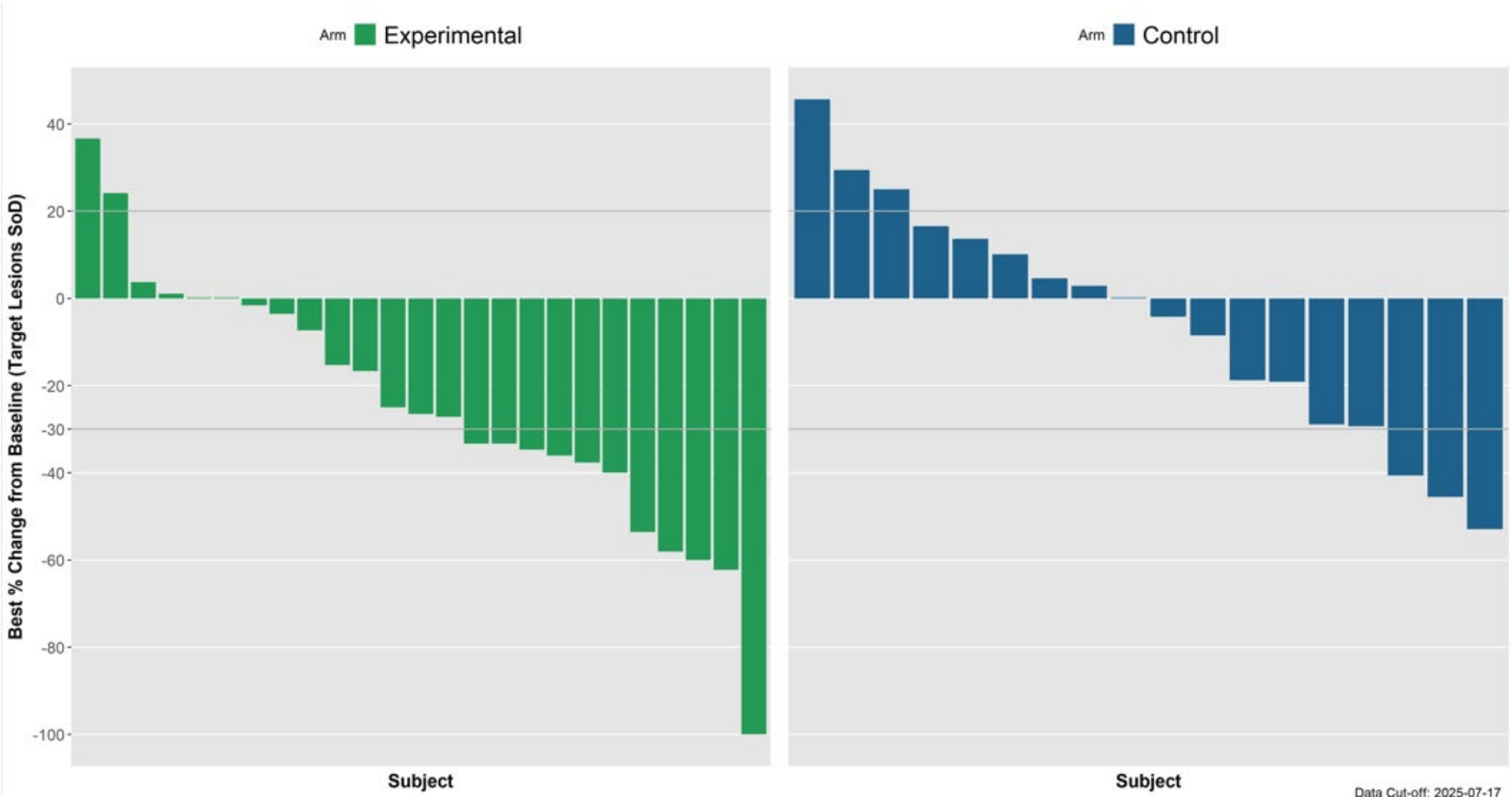
28% higher response rate (44% vs 16%) with sirexatamab

DKK1-high subgroup – Upper Quartile

Response	Sirexatamab Experimental N=25 n (%)	Control N=19 n (%)
CR	0 (0)	0 (0)
PR	11 (44)	3 (16)
ORR 95% CI	**44.0% (24.4, 65.1)**	**15.8% (3.4, 39.6)**
p value	**p=0.0149**	
SD	12 (48)	12 (63)
DCR	**92.0%**	**78.9%**
PD	2 (8)	3 (16)
No assessment	0 (0)	1 (5)



- BICR: ORR (40.0% v 15.8%; p=0.0301), DCR (88.0% v 68.4%)

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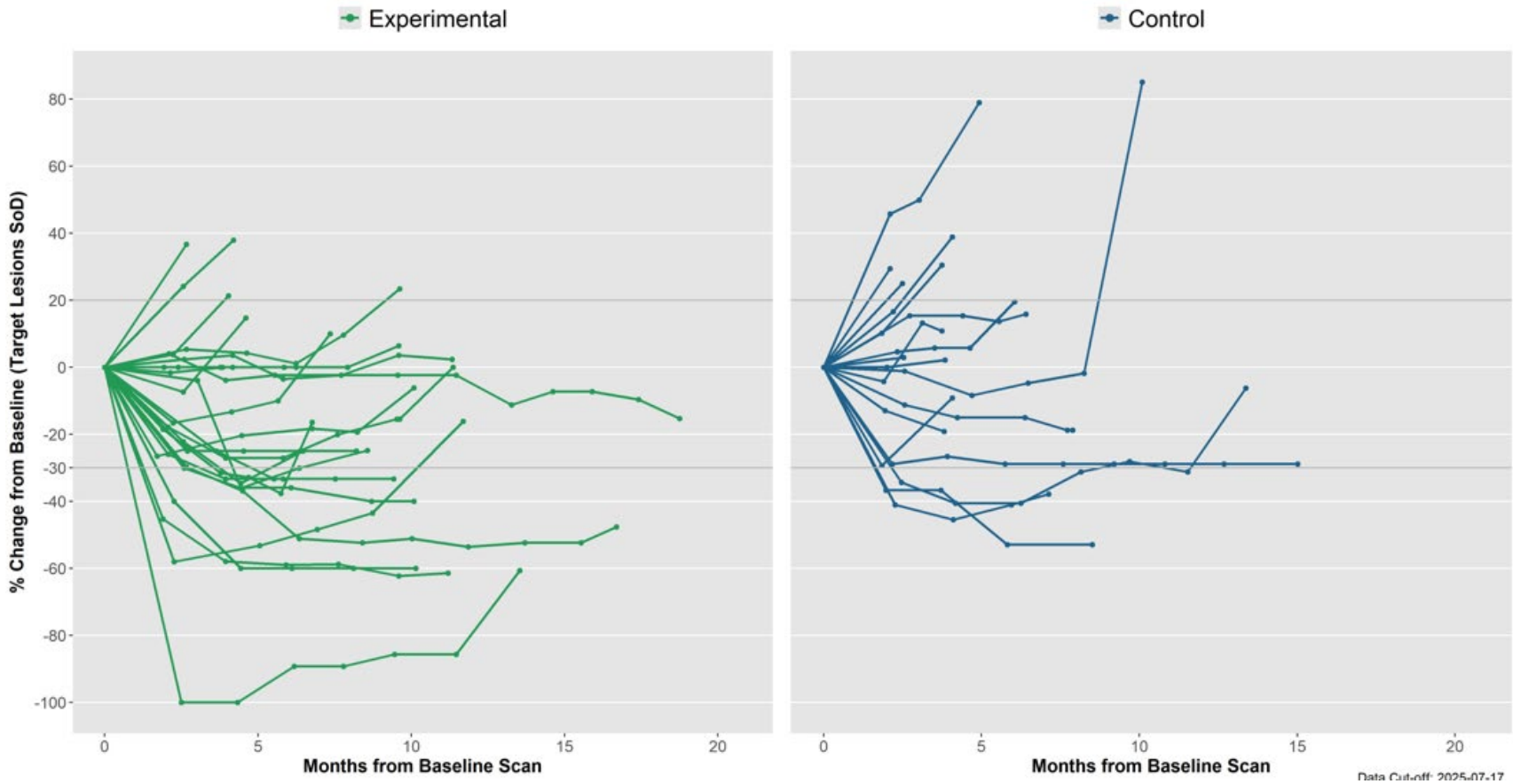
28% higher response rate (44% vs 16%) with sirexatamab

DKK1-high subgroup – Upper Quartile

Response	Sirexatamab Experimental N=25 n (%)	Control N=19 n (%)
CR	0 (0)	0 (0)
PR	11 (44)	3 (16)
ORR 95% CI	**44.0% (24.4, 65.1)**	**15.8% (3.4, 39.6)**
p value	**p=0.0149**	
SD	12 (48)	12 (63)
DCR	**92.0%**	**78.9%**
PD	2 (8)	3 (16)
No assessment	0 (0)	1 (5)



- BICR: ORR (40.0% v 15.8%; p=0.0301), DCR (88.0% v 68.4%)

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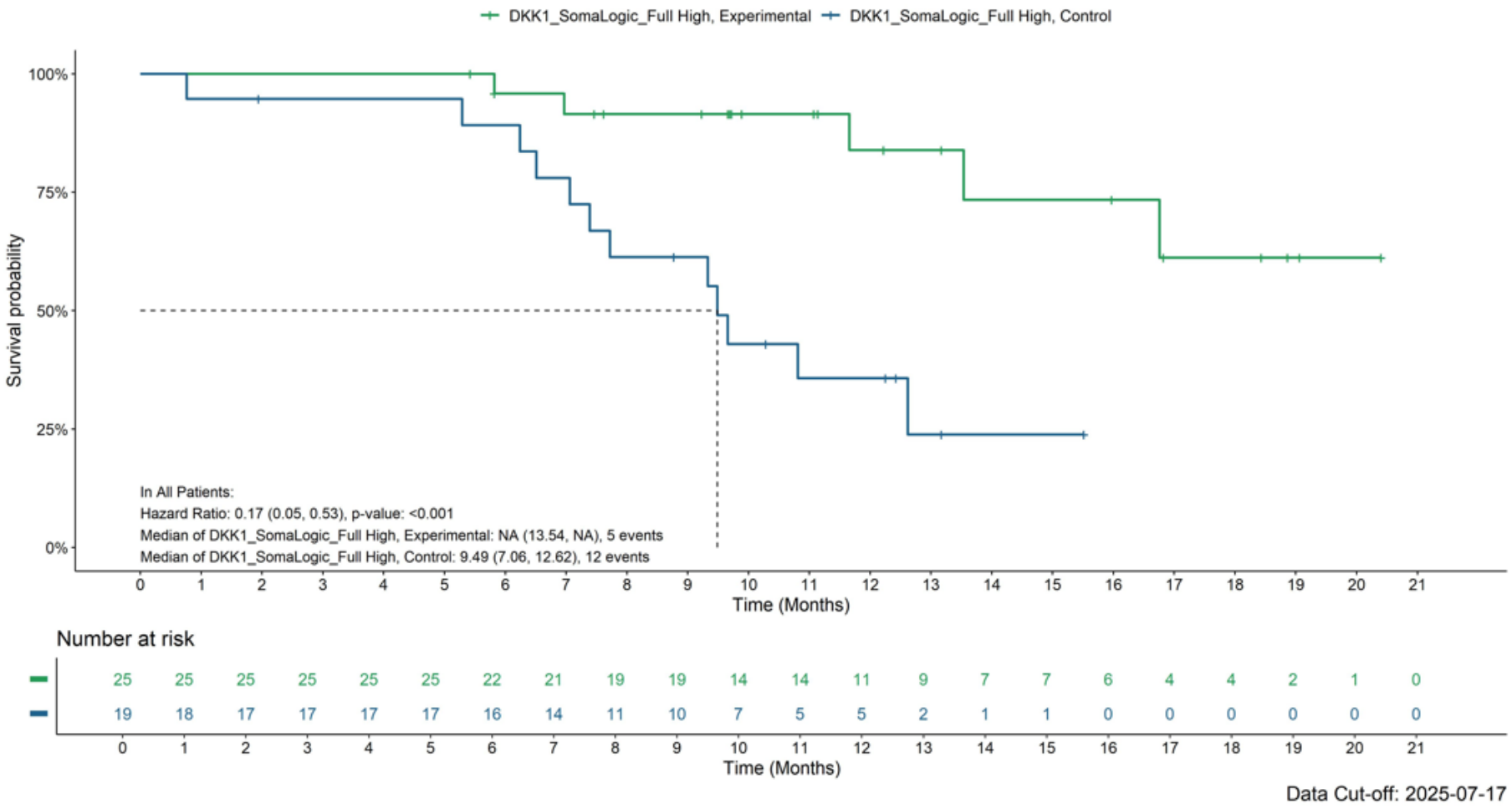
Sirexatamab significantly improved Overall Survival

DKK1-high subgroup – Upper Quartile



Data Cut-off: 2025-07-17

- **Statistically significant improvement in OS**
  - **12 deaths Control Arm vs. 5 deaths Experimental Arm**
  - **Median: Not Yet Reached vs. 9.49 months**
  - **HR 0.17**
  - **p < 0.001**

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DKK1 BIOMARKER – UPPER MEDIAN (TOP 50%)

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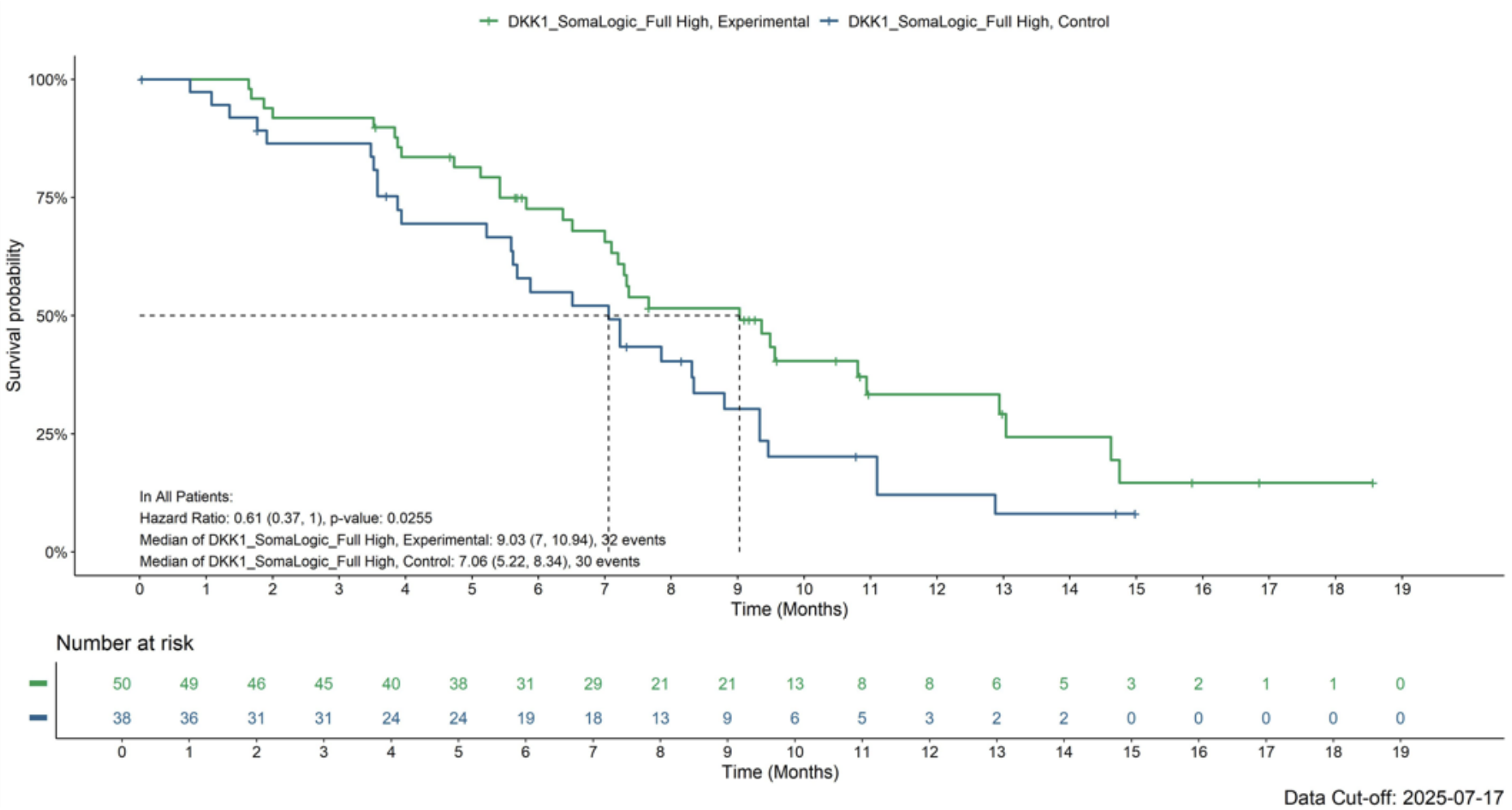
~2 months longer PFS with sirexatamab

DKK1-high subgroup – Upper Median



- **Statistically significant improvement in PFS**
  - **Median: 9.03 vs. 7.06 months**
  - **HR 0.61**
  - **p = 0.0255**
- **Consistent 2 month improvement in PFS by BICR**
  - **Median: 9.5 vs. 7.2 months**
  - **HR 0.64**
  - **p = 0.0763**

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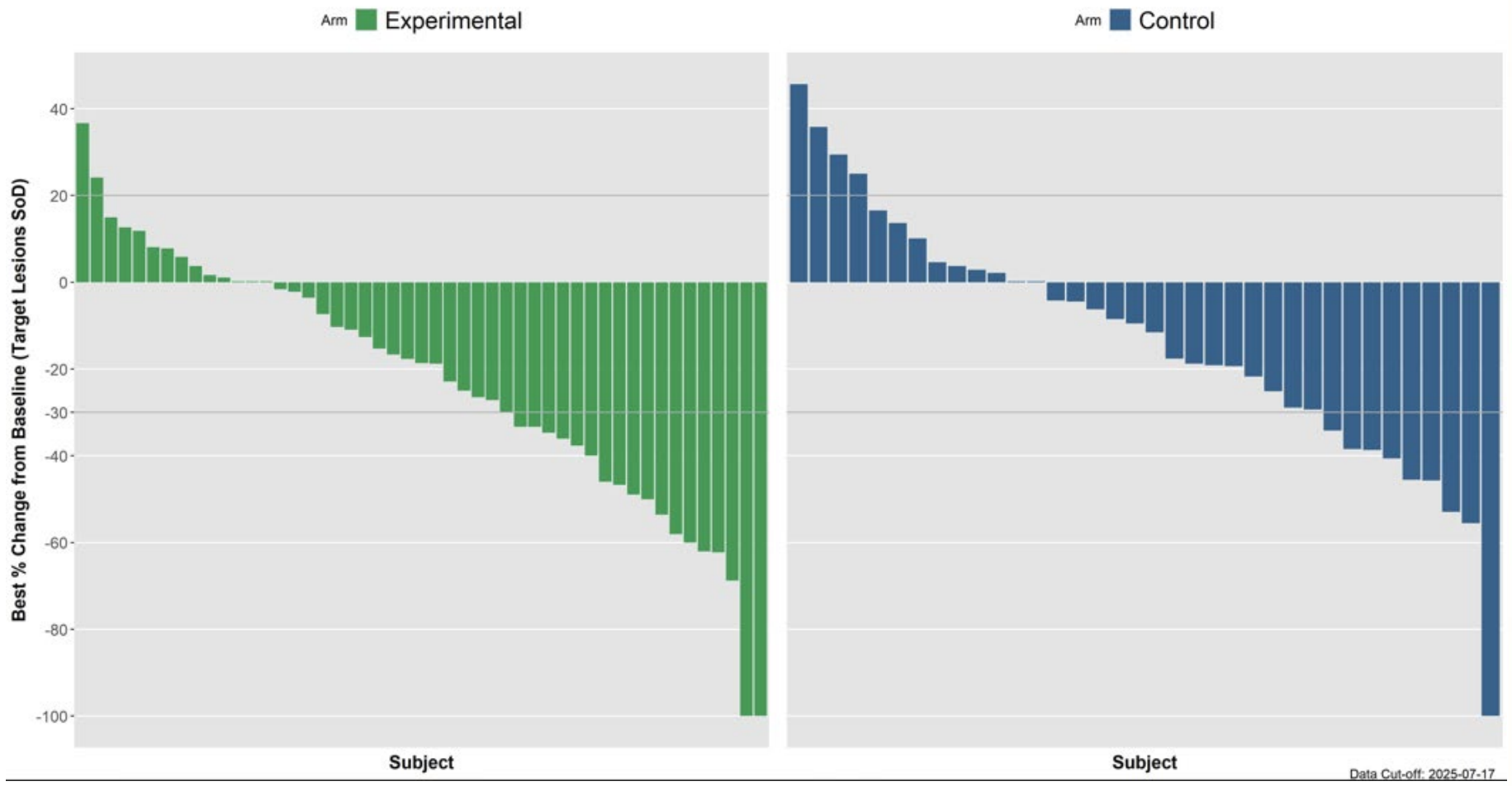
14% higher response rate (38% vs 24%) with sirexatamab

DKK1-high subgroup – Upper Median

Response	Sirexatamab Experimental N=50 n (%)	Control N=38 n (%)
CR	0 (0)	0 (0)
PR	19 (38)	9 (24)
ORR	**38.0% (24.7, 52.8)**	**23.7% (11.4, 40.2)**
P value	**p=0.0706**	
SD	26 (52)	23 (61)
DCR	**90.0%**	**84.2%**
PD	4 (8)	4 (11)
No assessment	1 (2)	2 (5)



- BICR: ORR (40.0% v 15.8%; p=0.0039), DCR (88.0% v 78.9%)

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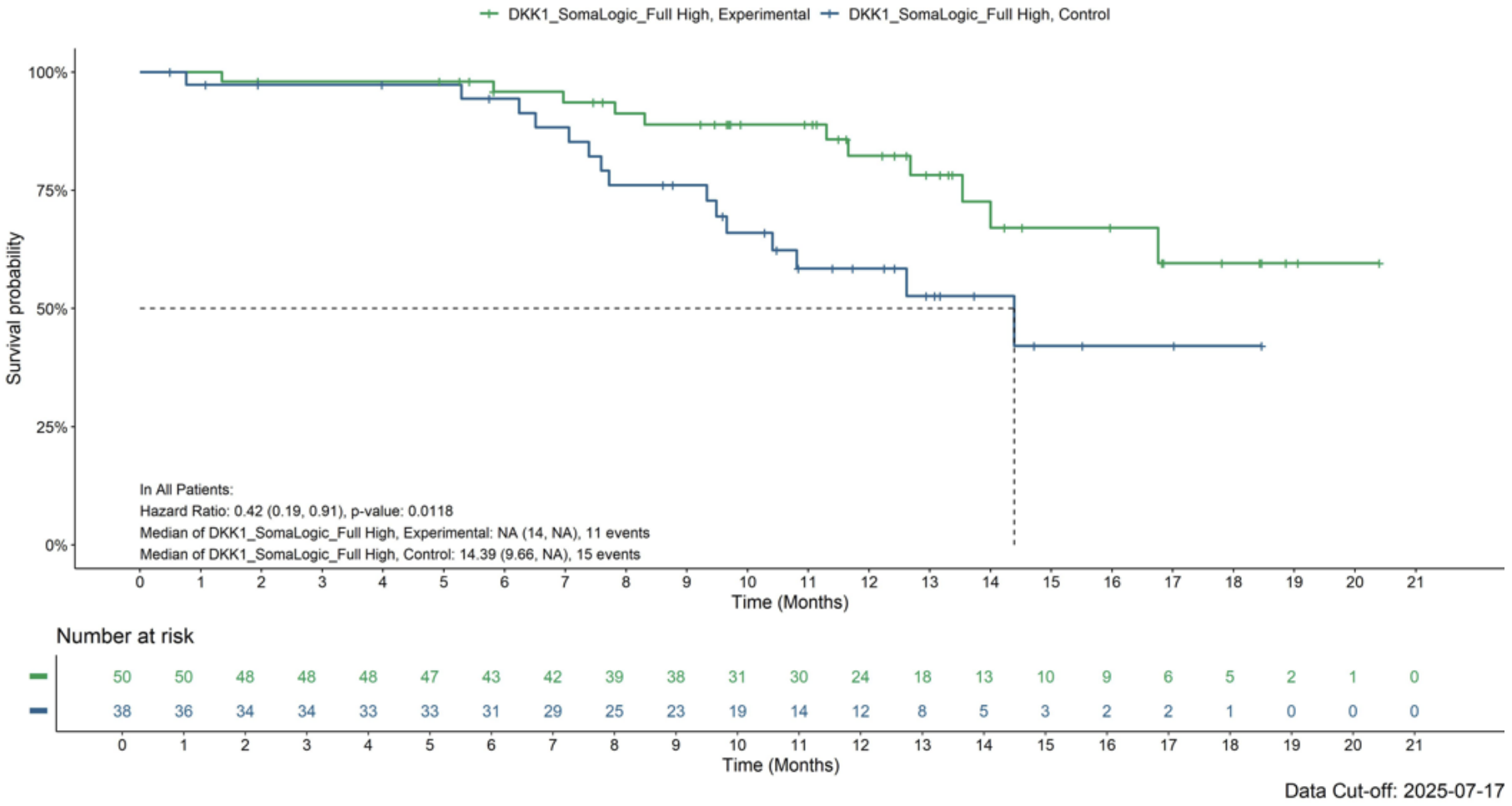
Sirexatamab significantly improved Overall Survival

DKK1-high subgroup – Upper Median



- **Statistically significant improvement in OS**
  - **15 deaths Control Arm vs. 11 deaths Experimental Arm**
  - **Median: Not Yet Reached vs. 14.39 months**
  - **HR 0.42**
  - **p = 0.0118**

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NO PRIOR ANTI-VEGF POPULATION

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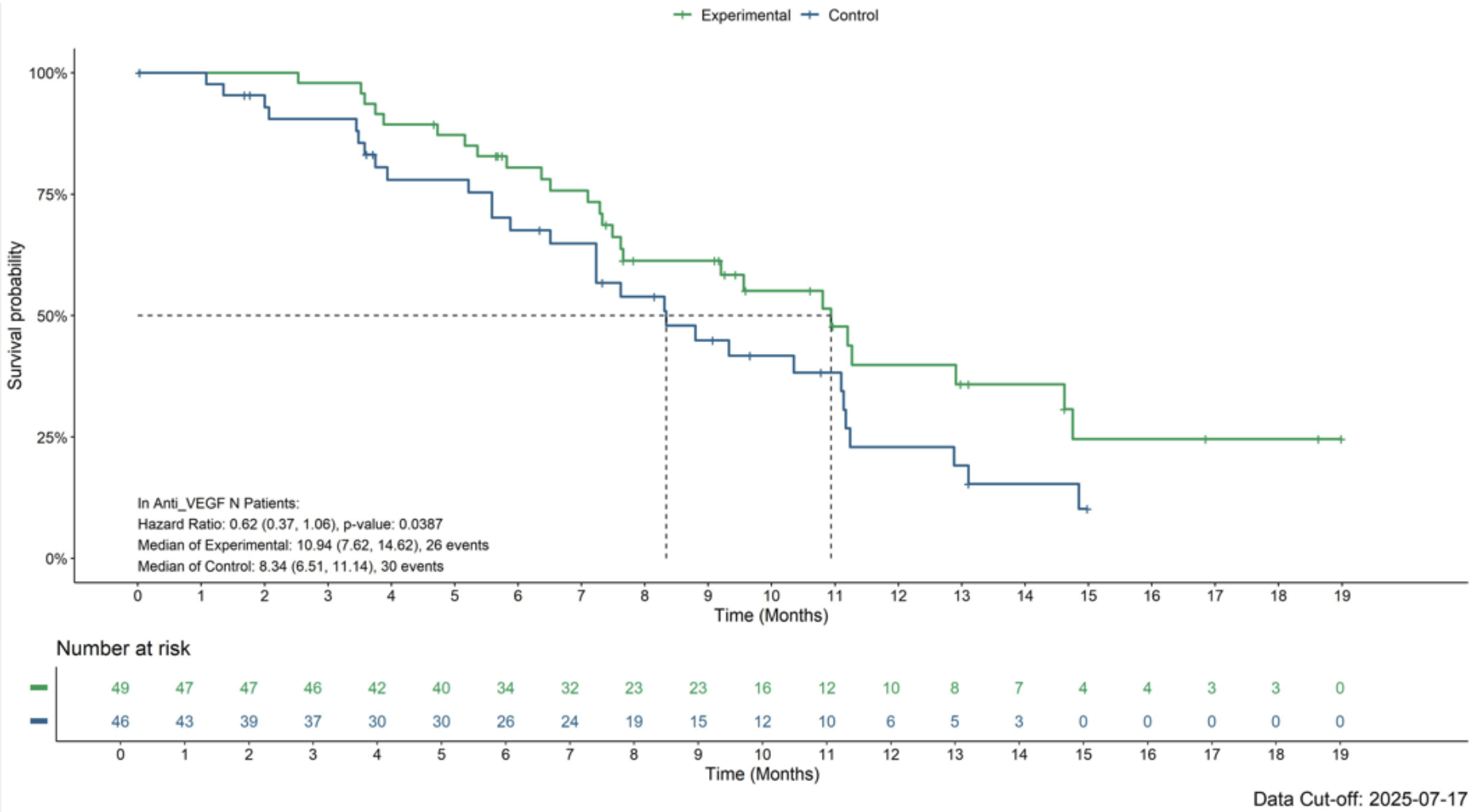
~2.6 months longer Progression-free Survival with sirexatamab

No prior anti-VEGF subgroup



Data Cut-off: 2025-07-17

- **Statistically significant improvement in PFS**
  - **Median: 10.94 vs. 8.34 months**
  - **HR 0.62**
  - **p = 0.0387**
- **Enhanced, statistically significant ~4.6 month improvement in PFS by BICR**
  - **Median: 14.7 vs. 9.3 months**
  - **HR 0.50**
  - **p = 0.0251**

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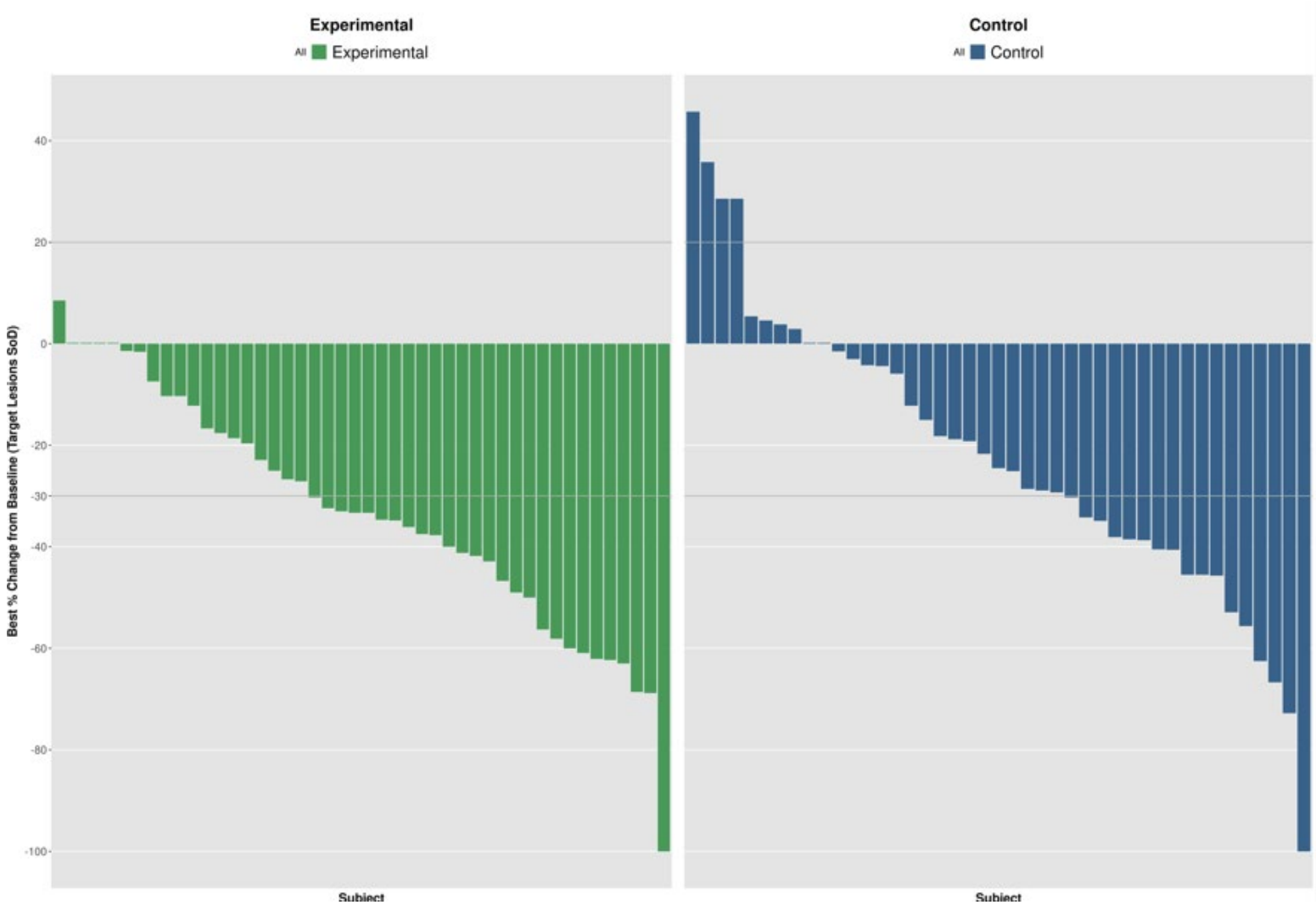
Sirexatamab improved ORR by 22% (55% vs. 33%)

No prior anti-VEGF subgroup

Response	Sirexatamab Experimental N=49 n (%)	Control N=46 n (%)
CR	0 (0)	2 (4)
PR	27 (55)	13 (28)
ORR 95% CI	**55.1% (40.2, 69.3)**	**32.6% (19.5, 48.0)**
p value	**p=0.0116**	
SD	19 (39)	24 (52)
DCR	**93.9%**	**84.8%**
PD	0 (0)	4 (9)
No assessment	3 (6)	3 (7)



- BICR: ORR (44.9% v 26.1%; p=0.0252), DCR (91.8% v 82.6%)

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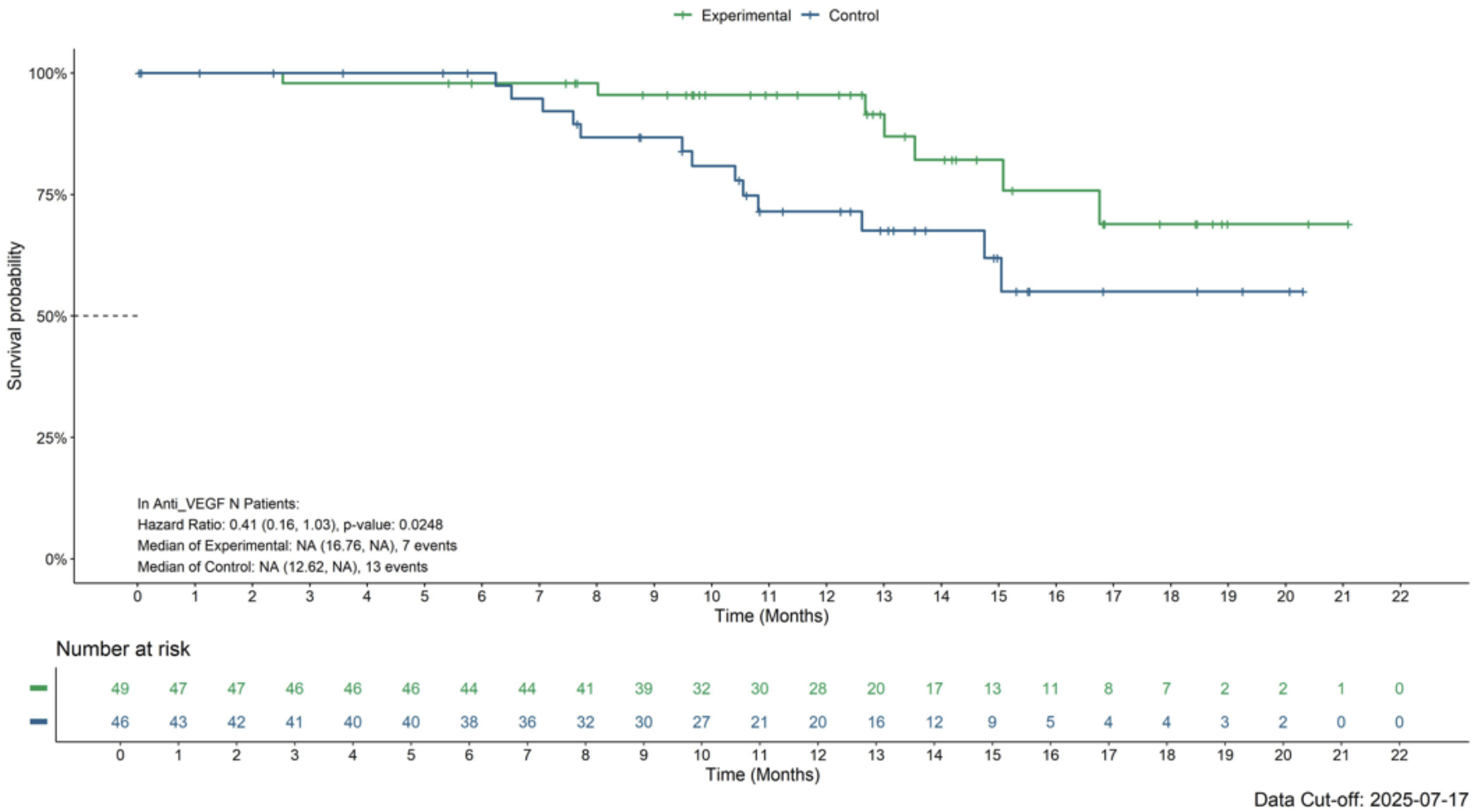
Overall Survival
No prior anti-VEGF subgroup



Data Cut-off: 2025-07-17

- Early advantage in OS with limited number of events
  - 13 deaths Control Arm vs. 7 deaths Experimental Arm
  - Median: Not Yet Reached vs. Not Yet Reached
  - HR 0.41
  - p = 0.0248

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LIVER METASTASIS POPULATION

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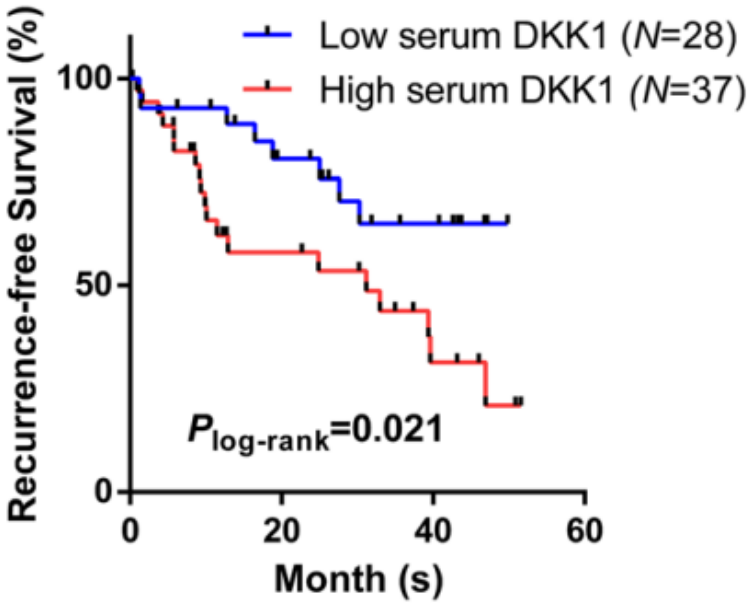
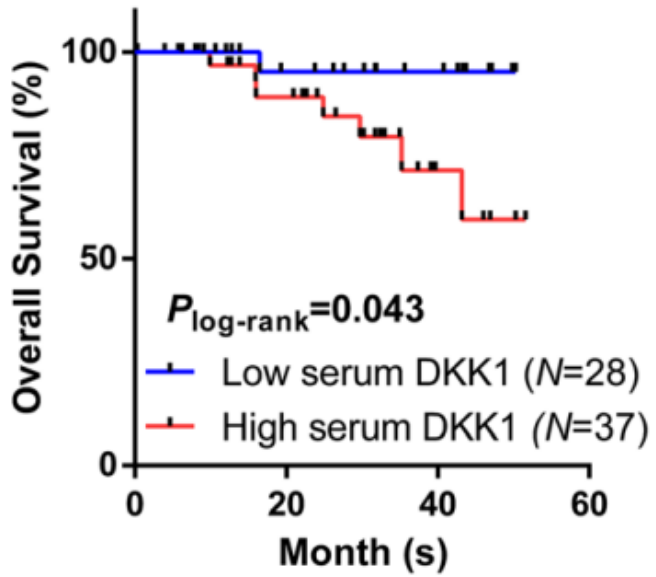
High circulating DKK1 is associated with liver metastasis and poor prognosis in CRC





CRC liver metastases patients with high and low serum DKK1

Sui et al; 2019, BMC Cancer

DeFianCe Part B Patients

DKK1-High Cutoff	Full ITT	≥25%	≥50%	≥75%
% of patients with liver mets	72% (136/188)	71% (94/132)	76% (67/88)	82% (36/44)

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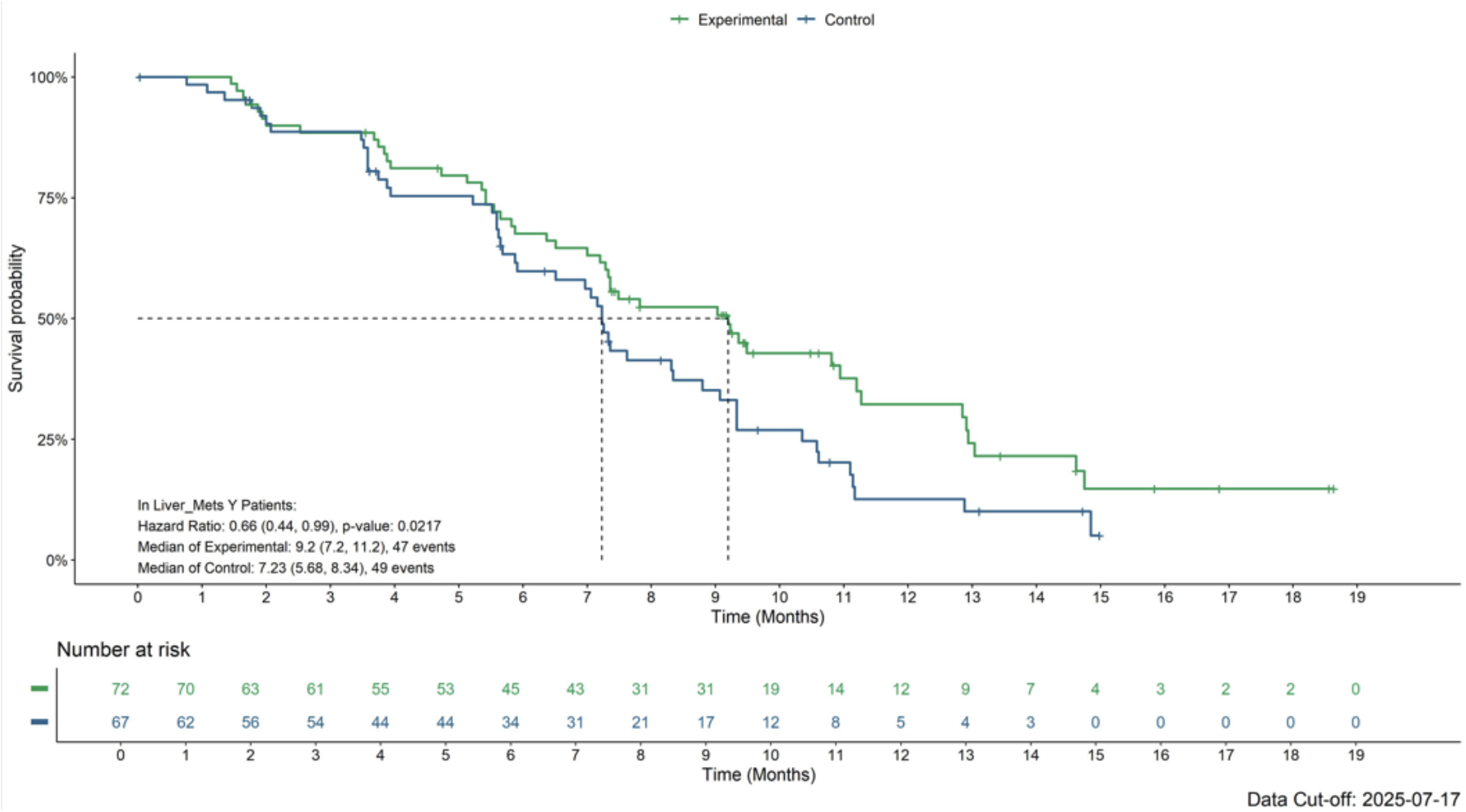
~2 months longer Progression-free Survival with sirexatamab

Liver Mets subgroup



- ~2 month and 34% risk reduction favoring the Experimental Arm
  - Median: 9.20 vs. 7.23 months
  - HR 0.66
  - p = 0.0217
- Enhanced advantage for Experimental Arm in biomarker high patients
  - DKK1 Upper Median PFS:
    - HR 0.46
    - p = 0.0039
  - DKK1 Upper Quartile PFS:
    - HR 0.34
    - p = 0.0042

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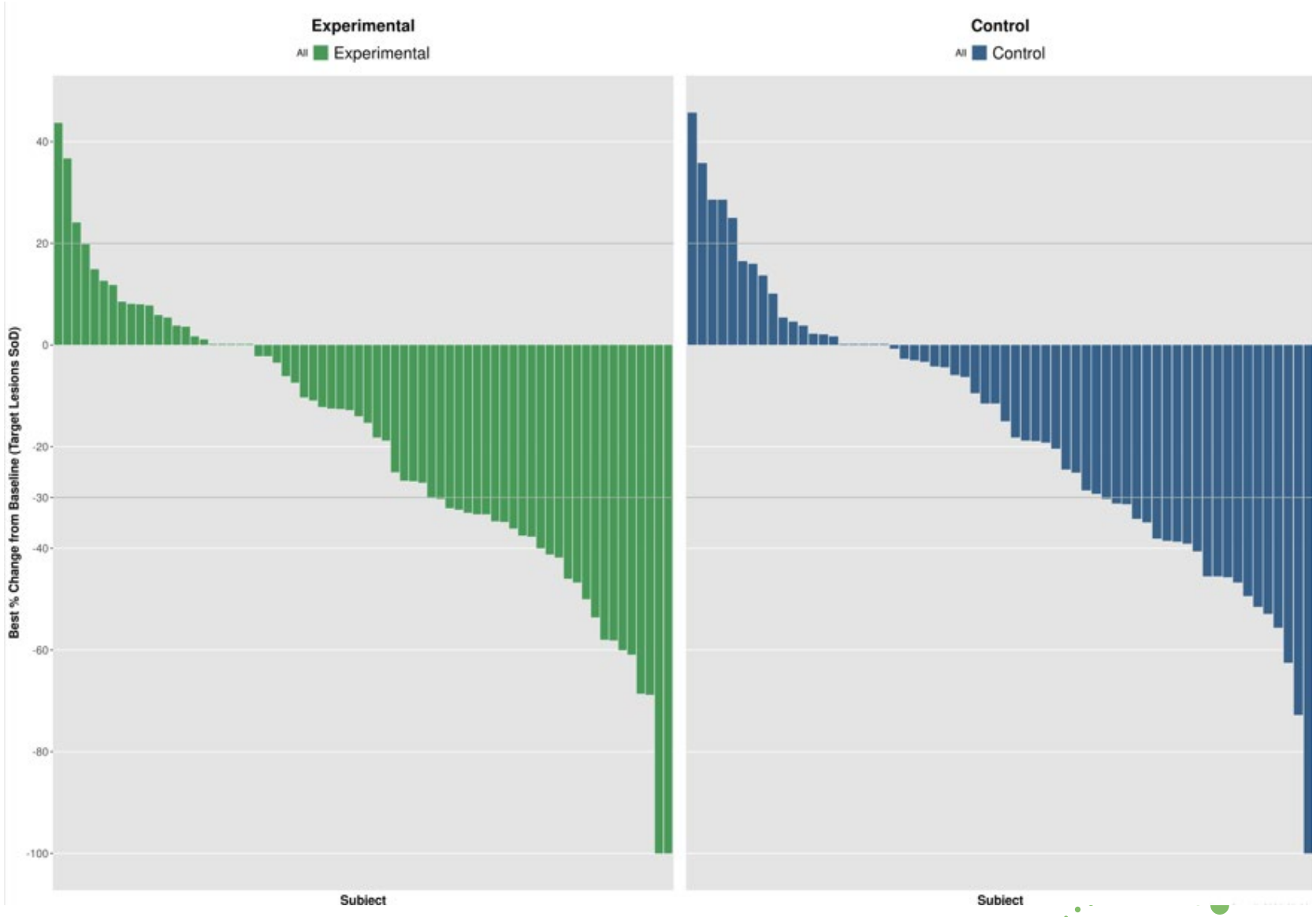
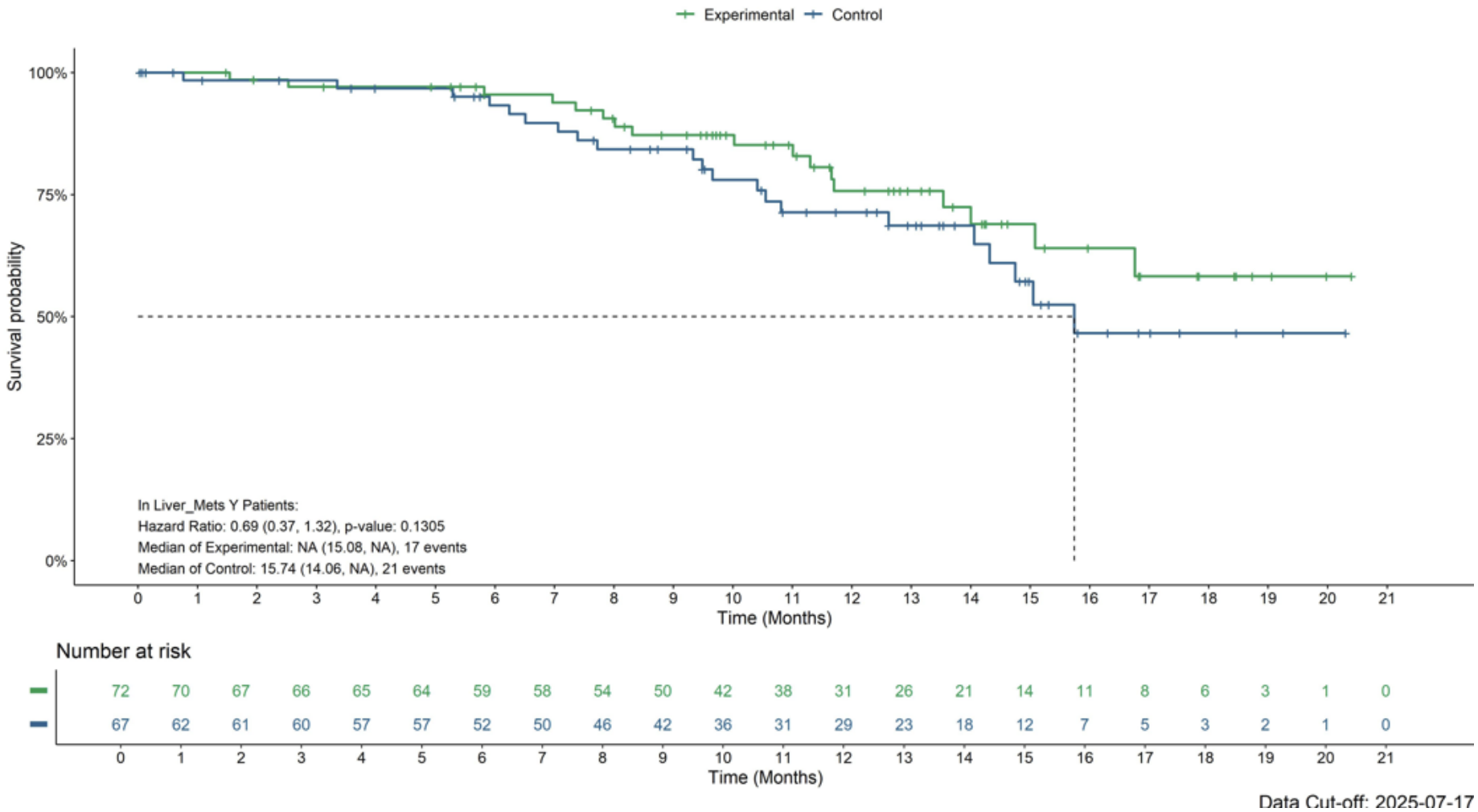
9% higher response rate with sirexatamab

Liver Mets subgroup

Response	Sirexatamab Experimental N=72 n (%)	Control N=67 n (%)
CR	0 (0)	1 (1)
PR	27 (38)	18 (27)
ORR 95% CI	**37.5% (26.4, 49.7)**	**28.4% (18.0, 40.7)**
p value	**p=0.1245**	
SD	35 (48)	37 (55)
DCR	**86.1%**	**83.6%**
PD	6 (8)	6 (9)
No assessment	4 (5)	5 (7)



Overall Survival
Liver Mets subgroup



- OS trending advantage for sirexatamab
  - 21 deaths Control Arm vs. 17 deaths Experimental Arm
  - Median: Not Yet Reached vs. 15.74 months
  - HR 0.69
  - p = 0.1305

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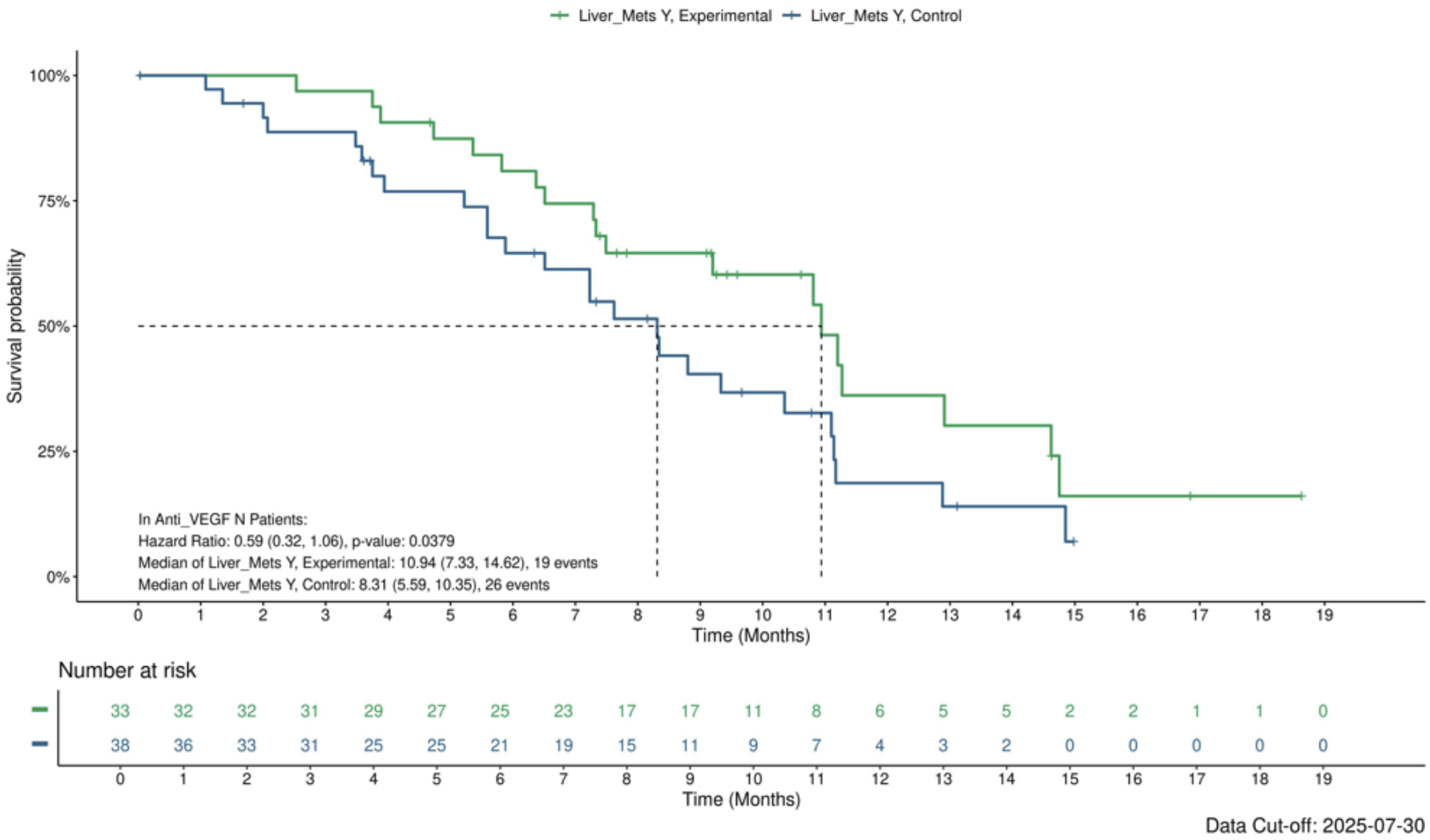
~2.6 months longer Progression-free Survival with sirexatamab

Liver Mets subgroup without prior VEGF



Data Cut-off: 2025-07-30

- Nearly 3 month improvement favoring the Experimental Arm in patients with liver mets and no prior anti-VEGF exposure
  - Median: 10.94 vs. 8.31 months
  - HR 0.59
  - p = 0.0379

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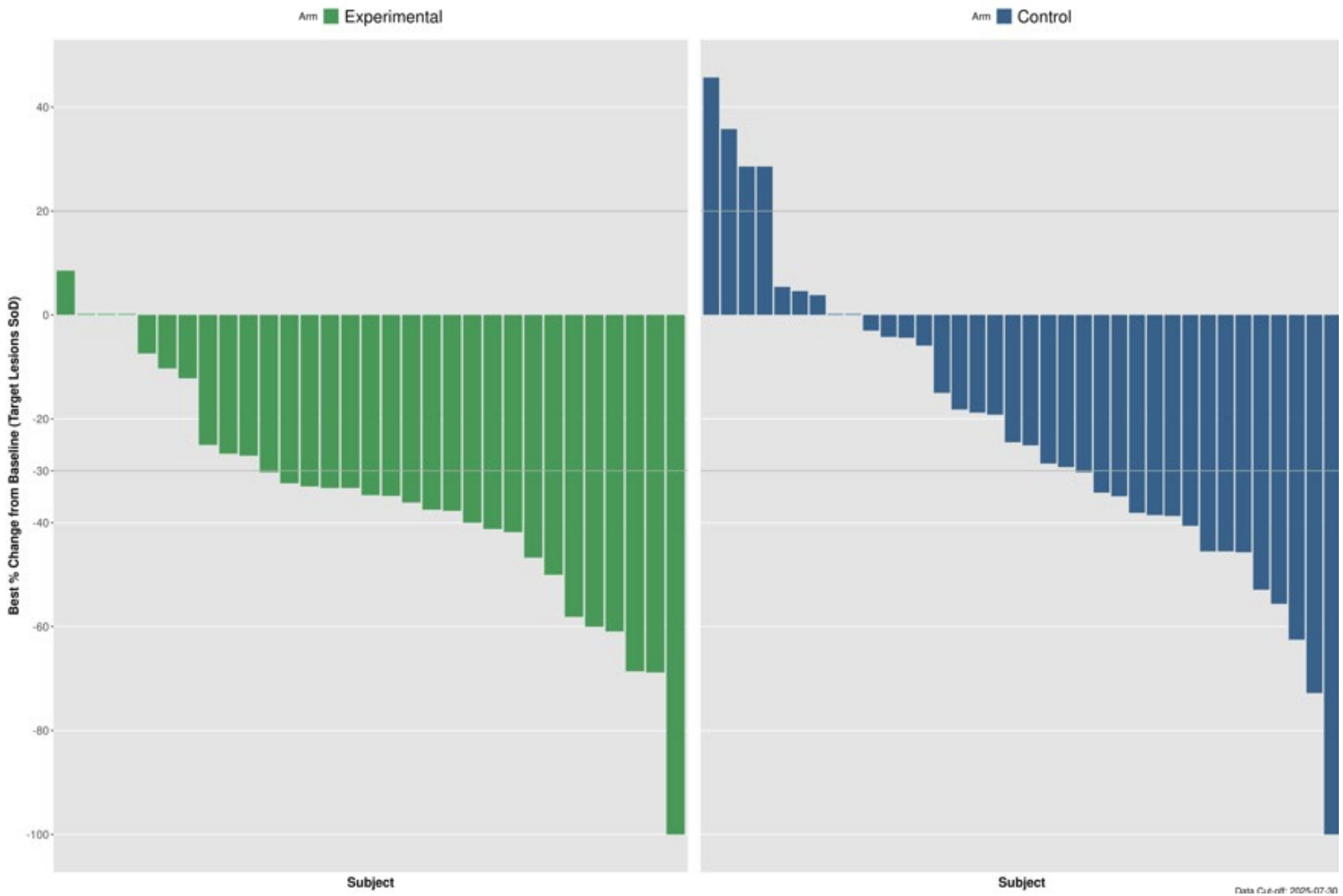
29% higher response rate with sirexatamab

Liver Mets subgroup without prior VEGF

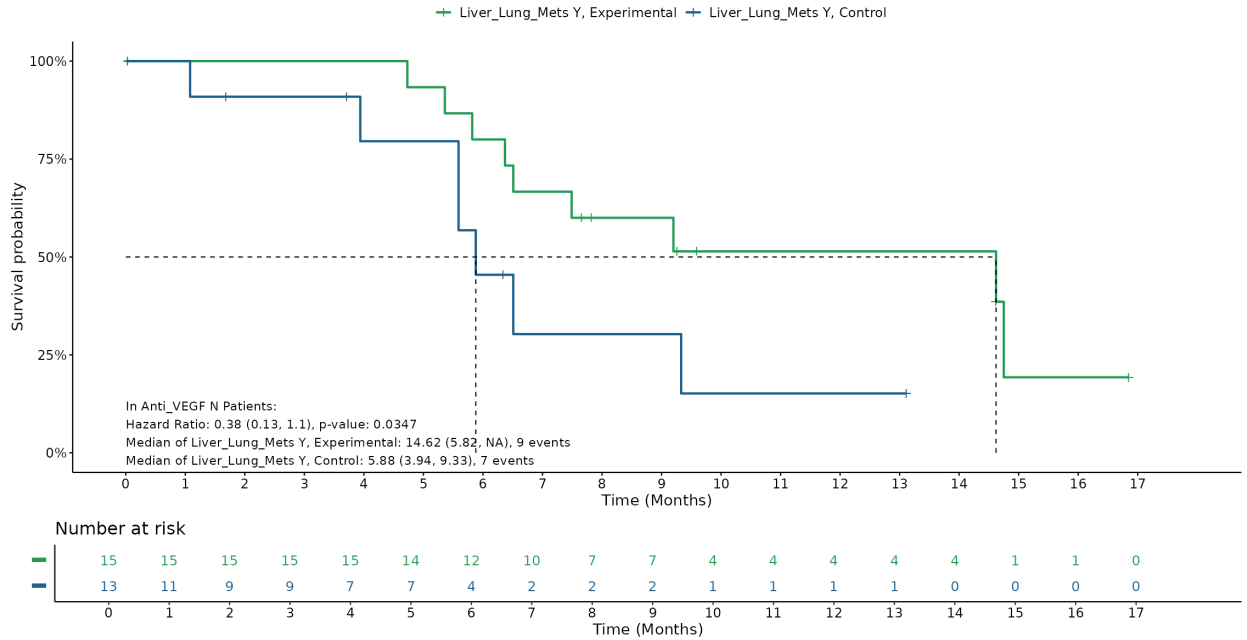
Response	Sirexatamab Experimental N=33 n (%)	Control N=38 n (%)
CR	0 (0)	1 (3)
PR	21 (64)	12 (32)
ORR	**63.6%**	**34.2%**
p value	**p=0.0048**	
SD	10 (30)	19 (50)
DCR	**93.9%**	**84.2%**
PD	0 (0)	4 (11)
No assessment	2 (6)	2 (5)

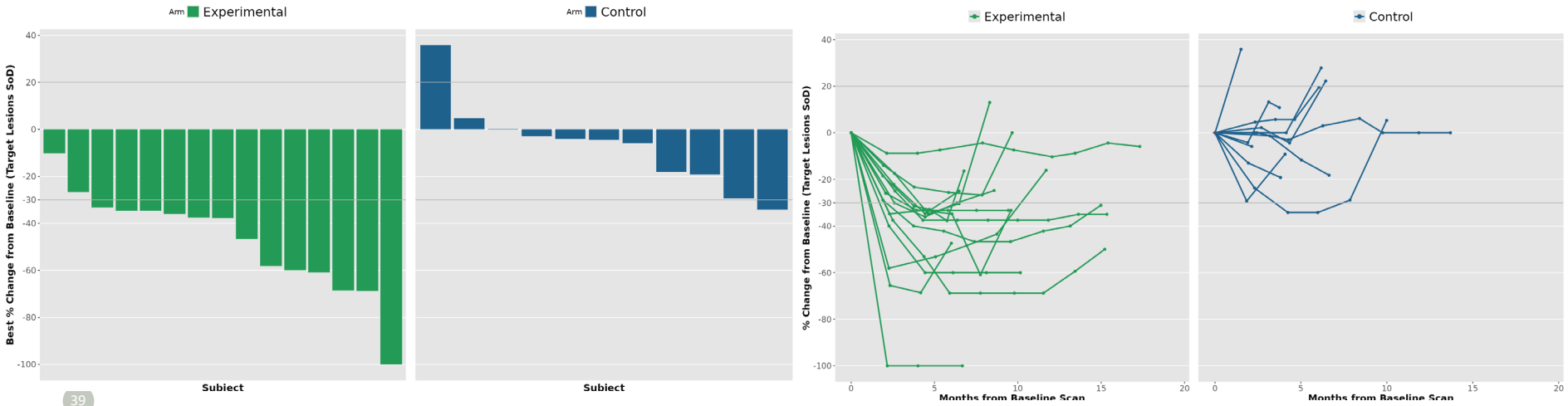


Sirexatamab enhanced outcomes in patients with liver & lung mets

Patients with Both Liver and Lung Mets and no prior anti-VEGF

P207B PFS KM Plot in Anti_VEGF N Patients by Arm and by Liver_Lung_Mets





- More advanced, poorer prognostic groups perform well on sirexatamab
- Anti-VEGF naïve patients with both liver and lung mets
  - ORR: 86.7% v 7.7% (p<0.001)
  - DCR: 100% v 76.9% (p=0.0241)
  - PFS: 14.62 v 5.88 months
    - HR: 0.38, p=0.0347
  - OS: NYR v 12.78 months
    - HR: 0.15, p=0.0046

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MARKET OPPORTUNITY

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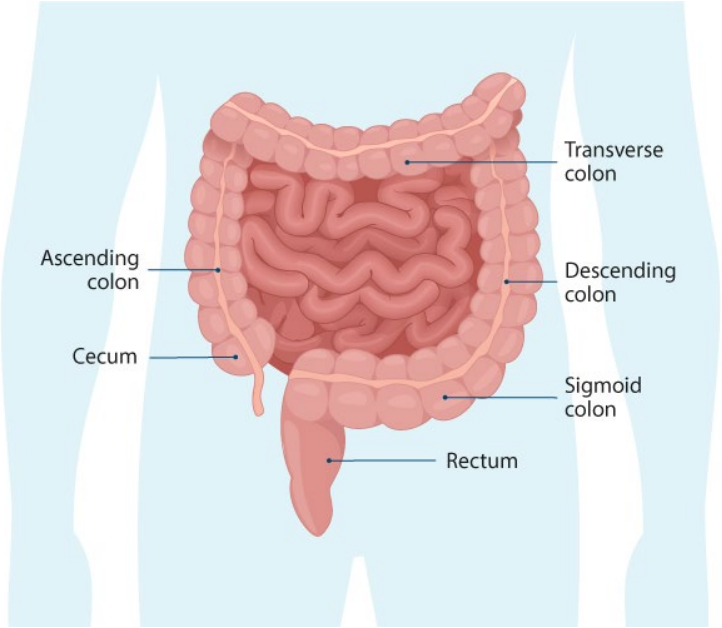
Large potential colorectal cancer market opportunity



Global Incidence and Deaths
US: 155,000 patients and 53,000 deaths
ROW: 1,900,000 patients and 910,000 deaths

First-Line Treated Patients for Advanced Disease
US: 45,000 patients
Largest 7 non-US markets: 265,000 patients

~5%	~10%	~10%	~25%	~50%
HER2-amplified + RAS/BRAF wt	MSI-H	BRAF V600E	RAS/BRAF wt Left Sided	Other
HER2 agent combination	Checkpoint Inhibitor	encorafenib + EGFR inhibitor + Chemo	EGFR inhibitor + Chemo	Bevacizumab + Chemo

Second-Line Treated Patients
US: 30,000 patients
Largest 7 non-US markets: 160,000 patients

- **DKK1 biomarker high = ~25% - ~50%**
- **VEGF-naïve = ~50%**

Sources: American Cancer Society, World Health Organization, Company estimates

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Sirexatamab ORR is enhanced by increasing DKK1 across biomarker subgroups

	All Patients		DKK1-High (upper median)		DKK1-High (upper quartile)	
Group	Sirexatamab Experimental	Control	Sirexatamab Experimental	Control	Sirexatamab Experimental	Control
ITT	35.1%	26.6%	38.0%	23.7%	44.0%	15.8%
VEGF-naïve	55.1%	32.6%	55.6%	36.4%	56.3%	25.0%
VEGF-experienced	13.3%	20.8%	17.4%	6.3%	22.2%	0%
Liver metastasis	37.5%	28.4%	41.0%	28.6%	50.0%	20.0%
Lung metastasis	36.0%	11.8%	39.3%	9.5%	58.3%	0%
Liver & Lung mets	41.7%	12.1%	43.5%	7.1%	63.6%	0%

- Control arm demonstrates decreasing response with higher DKK1 across subgroups
- Experimental arm demonstrates increasing response with higher DKK1 across subgroups

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Summary of final results

- Circulating DKK1 is a negative prognostic factor in CRC and is elevated in patients with advanced mCRC; Sirexatamab, a first in class antibody neutralizes DKK1.
- Sirexatamab was safe and well tolerated in combination with chemotherapy and bevacizumab.
- Positive trend in the overall population favoring the sirexatamab arm
- Statistically significant improvement in PFS and OS in the prospectively identified DKK1-high population.
- Increasing DKK1 above upper median further improved PFS, OS, and ORR for the sirexatamab arm.
- These data support continued development of sirexatamab in DKK1-high previously treated patients with mCRC.

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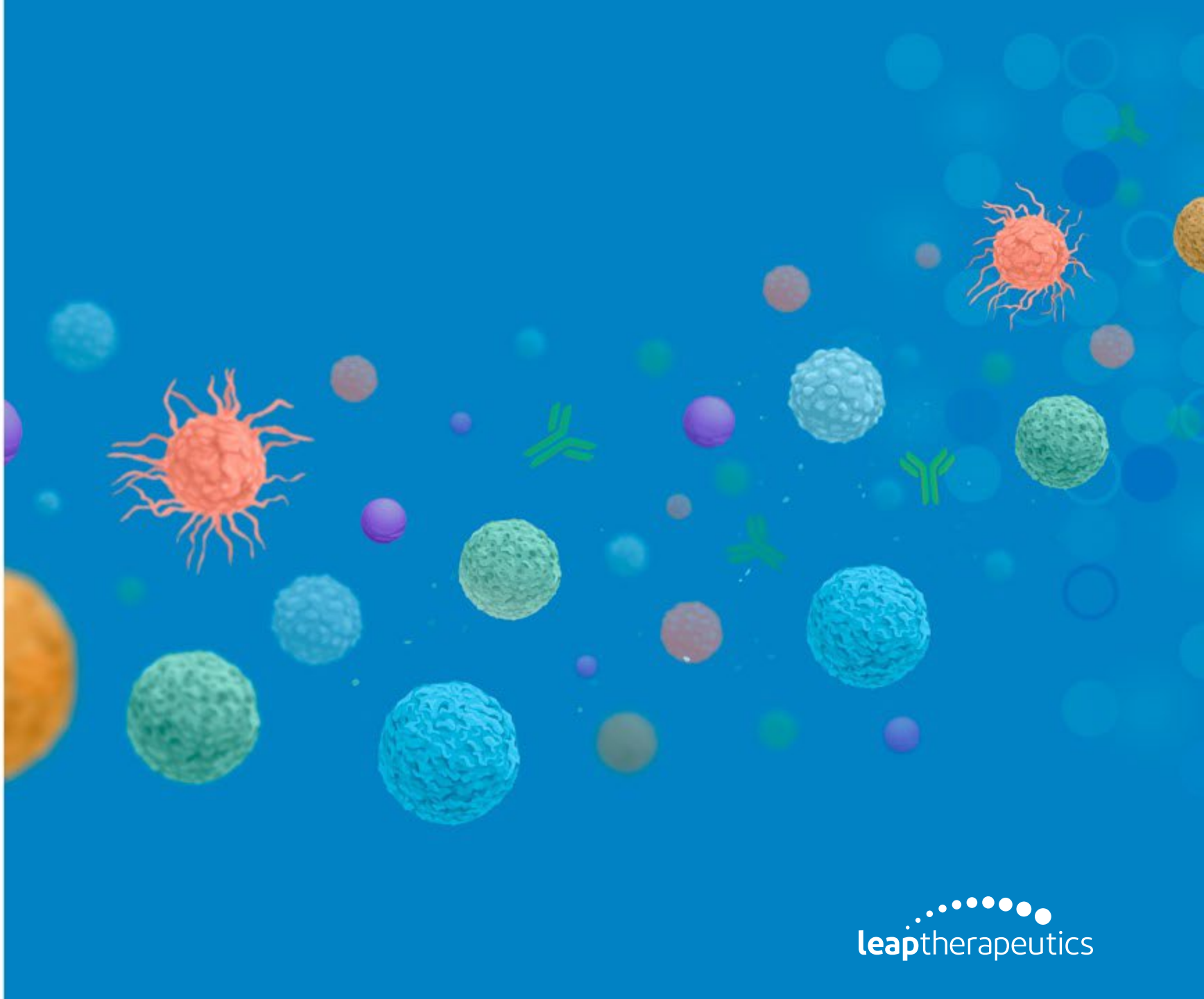
FL-501

Anti-GDF-15 monoclonal antibody



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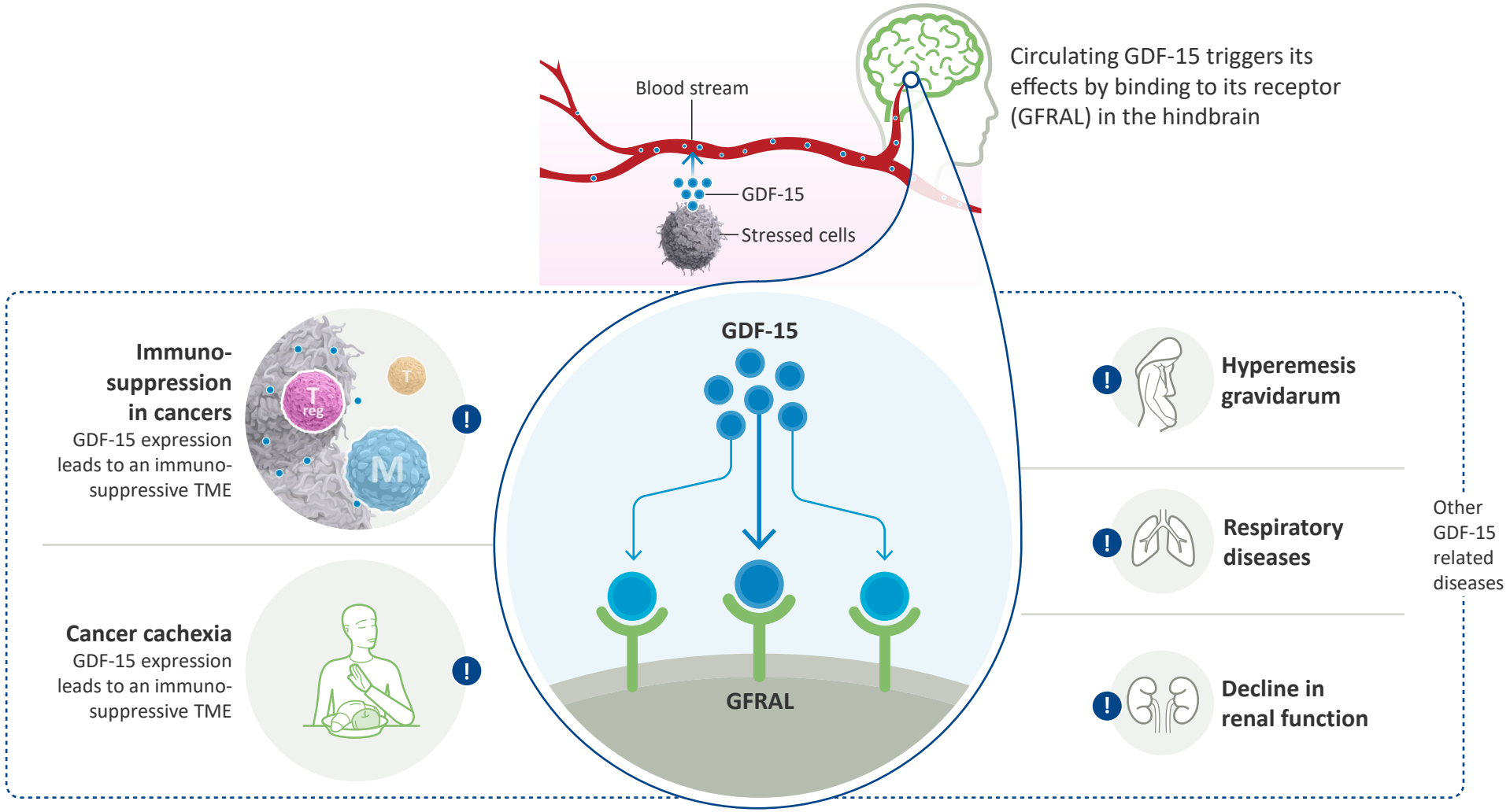
The role of GDF-15 in cachexia and cancer



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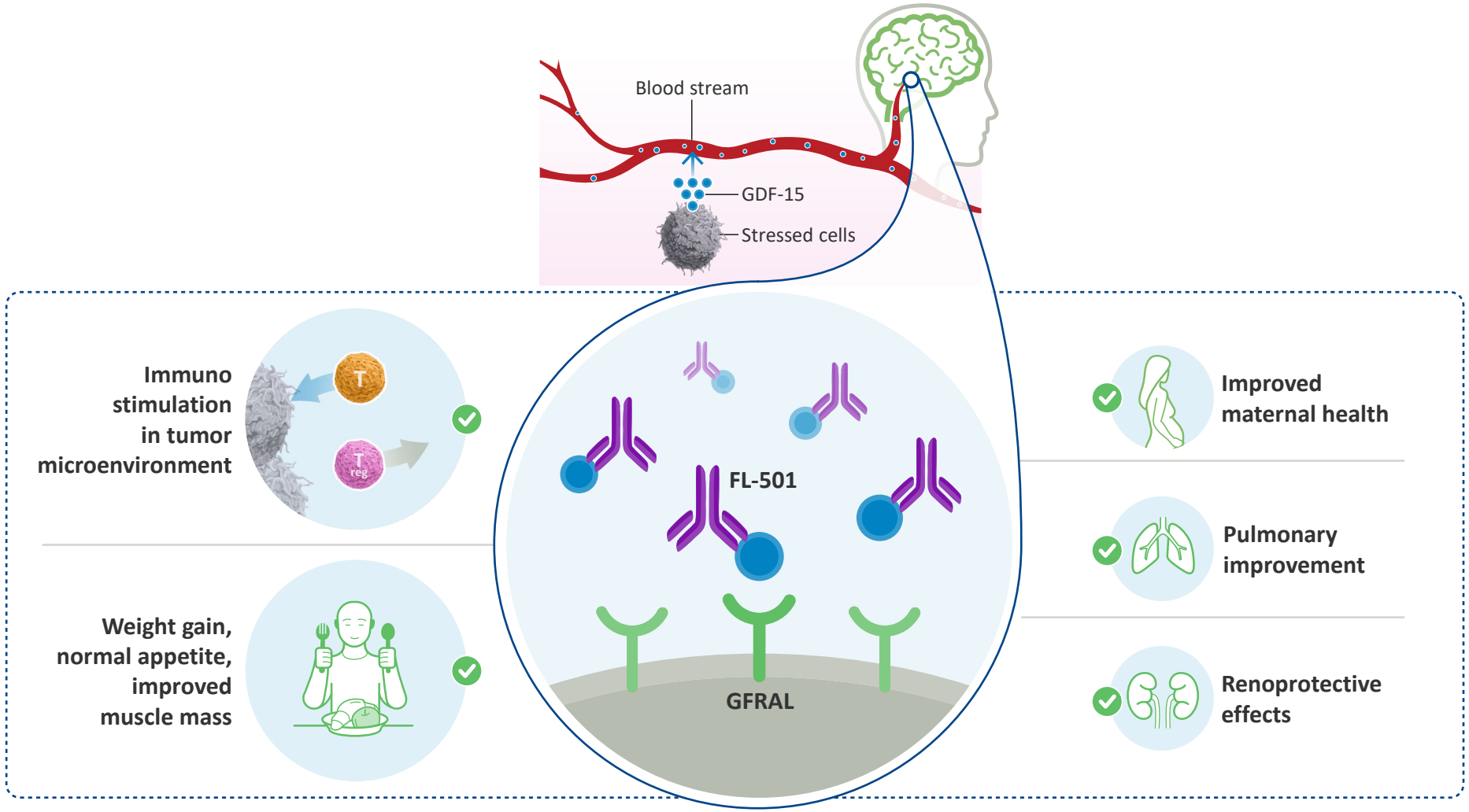
FL-501 mechanism of action



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