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DeFianCe Trial: A randomized phase 2 trial of sirexatamab (DKN-01) plus bevacizumab and chemotherapy versus bevacizumab and chemotherapy as second-line therapy in advanced microsatellite stable (MSS) colorectal cancer (CRC)

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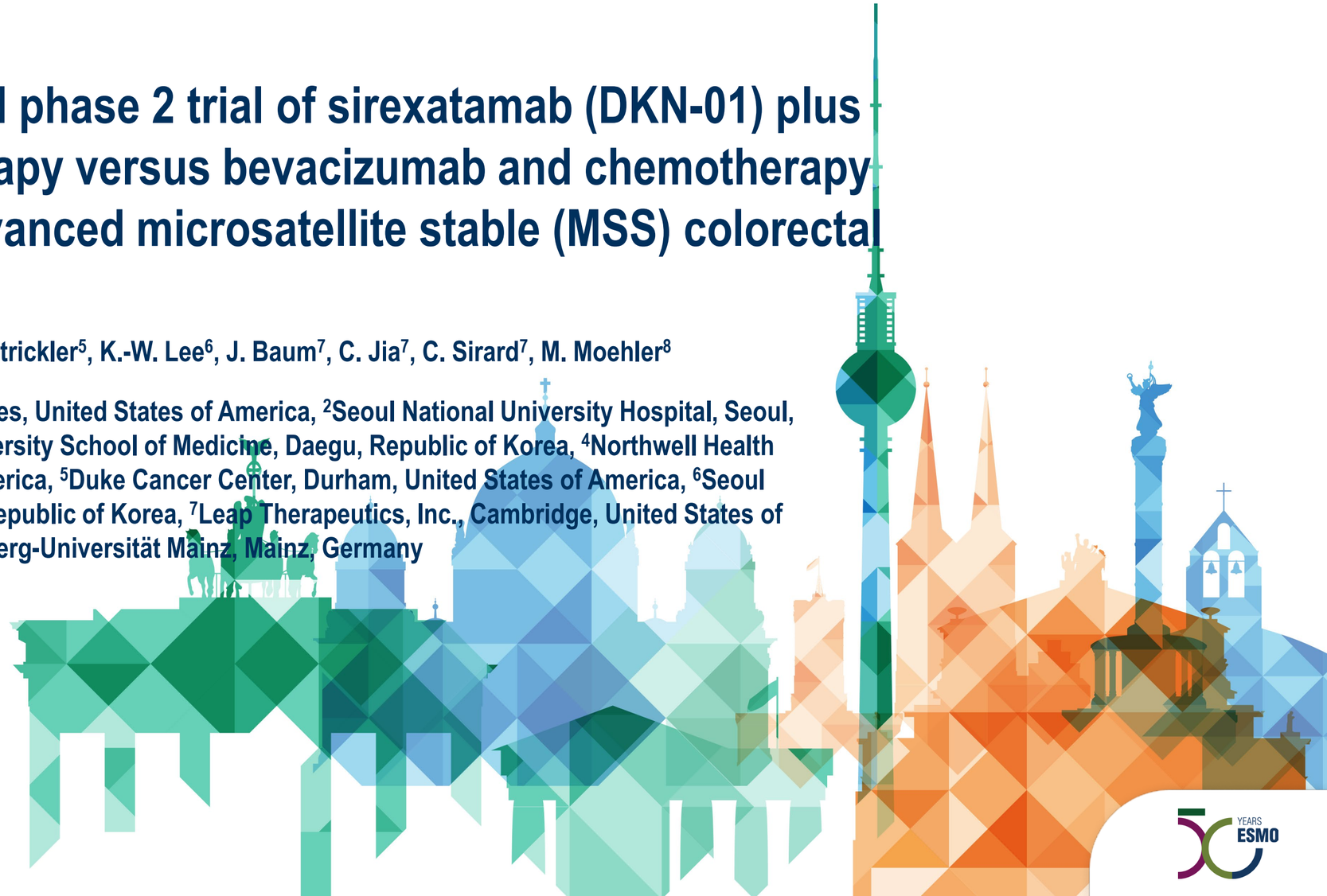

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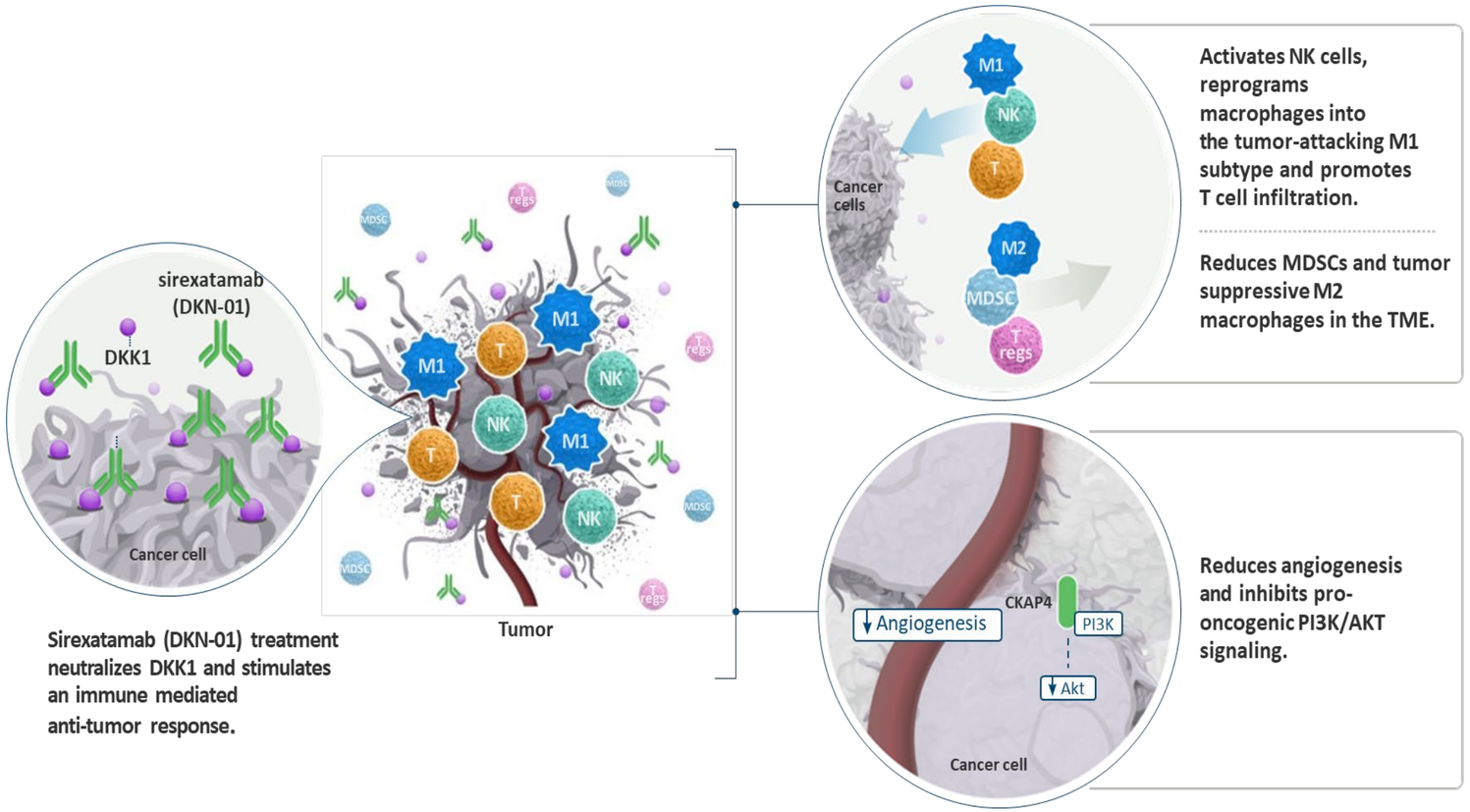
DECLARATION OF INTERESTS

- **Consulting:** Alligator Therapeutics, Amgen, AstraZeneca, Arcus, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi Sankyo Company, Eli Lilly and Company, EMD Serono, Roche AG, Genentech, Ipsen, Johnson & Johnson, Merus N.V., Merck, Novartis, Novocure, Pfizer, Servier, Verastem

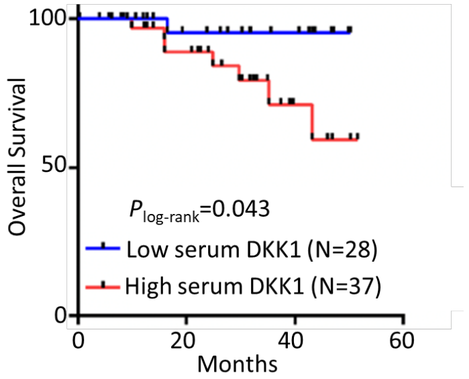
Zev Wainberg

Sirexatamab inhibits DKK1, a poor prognostic factor and key driver of CRC

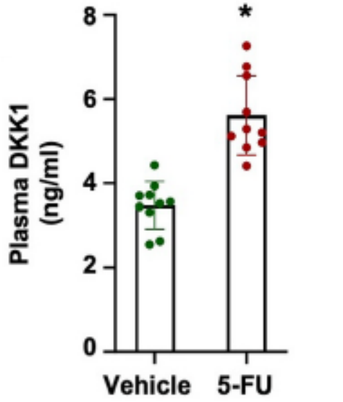
- Metastatic CRC is highly associated with alterations in the wnt signaling pathway.
- DKK1 is a key regulator of wnt signaling and implicated in disease progression, metastasis and angiogenesis.
- Circulating levels of DKK1 are higher in CRC patients than healthy volunteers and are associated with shorter survival.
- Sirexatamab is an IgG4 monoclonal antibody which potently inhibits DKK1.
- In preclinical models of CRC, sirexatamab synergizes with anti-angiogenesis agents, overcomes resistance to chemotherapies and inhibits metastasis.



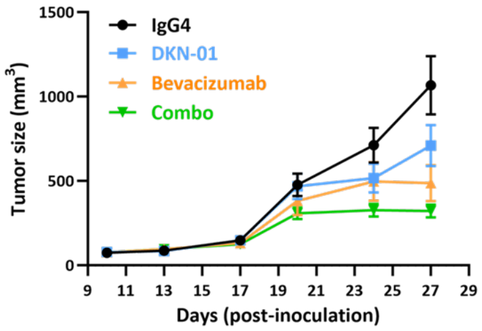
Sirexatamab (DKN-01) treatment neutralizes DKK1 and stimulates an immune mediated anti-tumor response.



Sui et al; 2019 BMC Cancer



Yin et al; 2025 Cancer Letters



DeFianCe study design

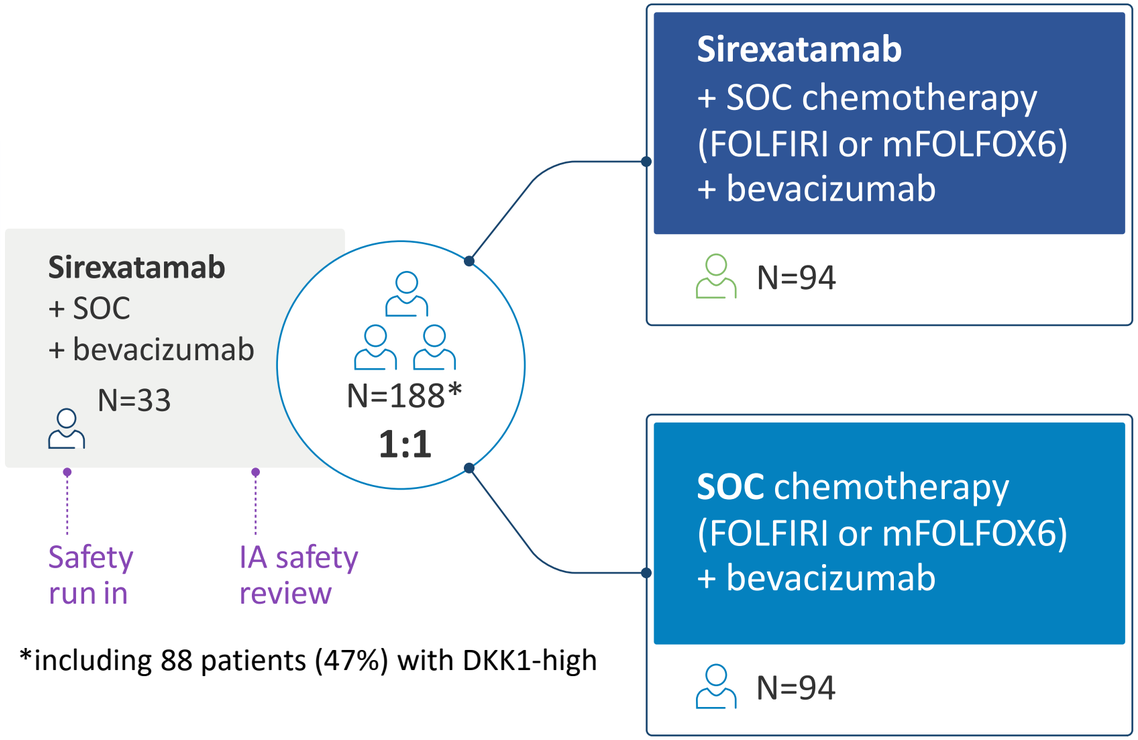
A randomized, open label, global phase 2 trial of sirexatamab plus bevacizumab and chemotherapy versus bevacizumab and chemotherapy as second-line therapy in mCRC

Key eligibility criteria:

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

Stratification factors:

- Tumor sidedness (left vs right)
- Prior anti-angiogenesis therapy (yes vs no)



*including 88 patients (47%) with DKK1-high

Objectives:

Primary:

- PFS (investigator assessed)

Secondary:

- Safety
- ORR
- OS

Key Exploratory:

- **PFS, ORR, OS DKK1-high subgroup**

Median study duration: 11.1 months at database lock on 17 Jul 2025

Clinicaltrials.gov number: NCT05480306, Right-sided mCRC capped at 45, DKK1-high was defined as upper median and performed on SomaScan platform (SomaLogic, Boulder CO).

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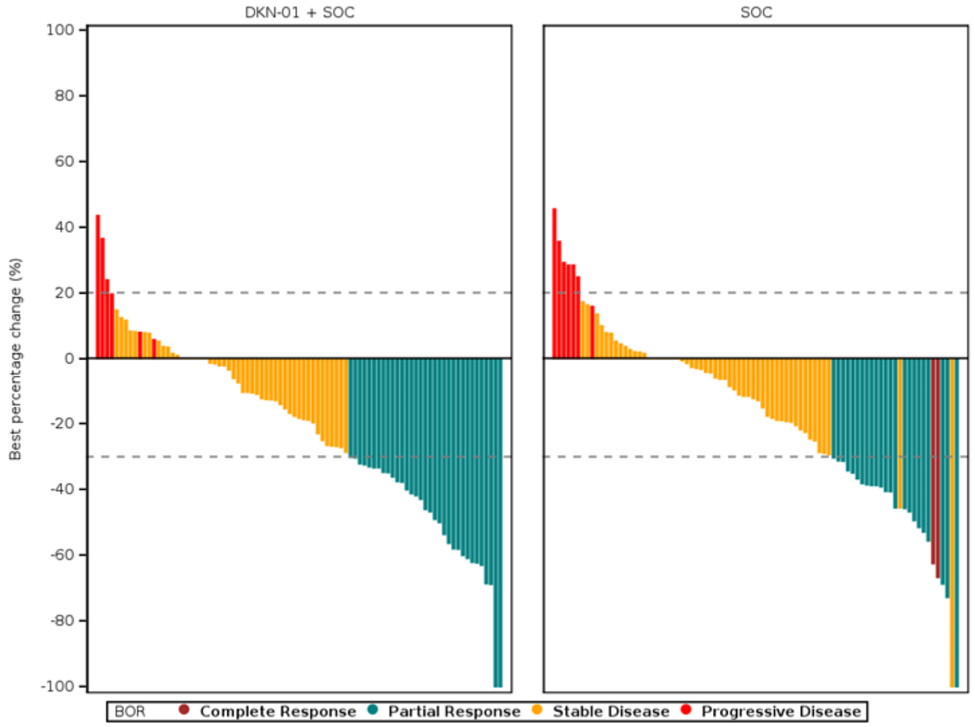
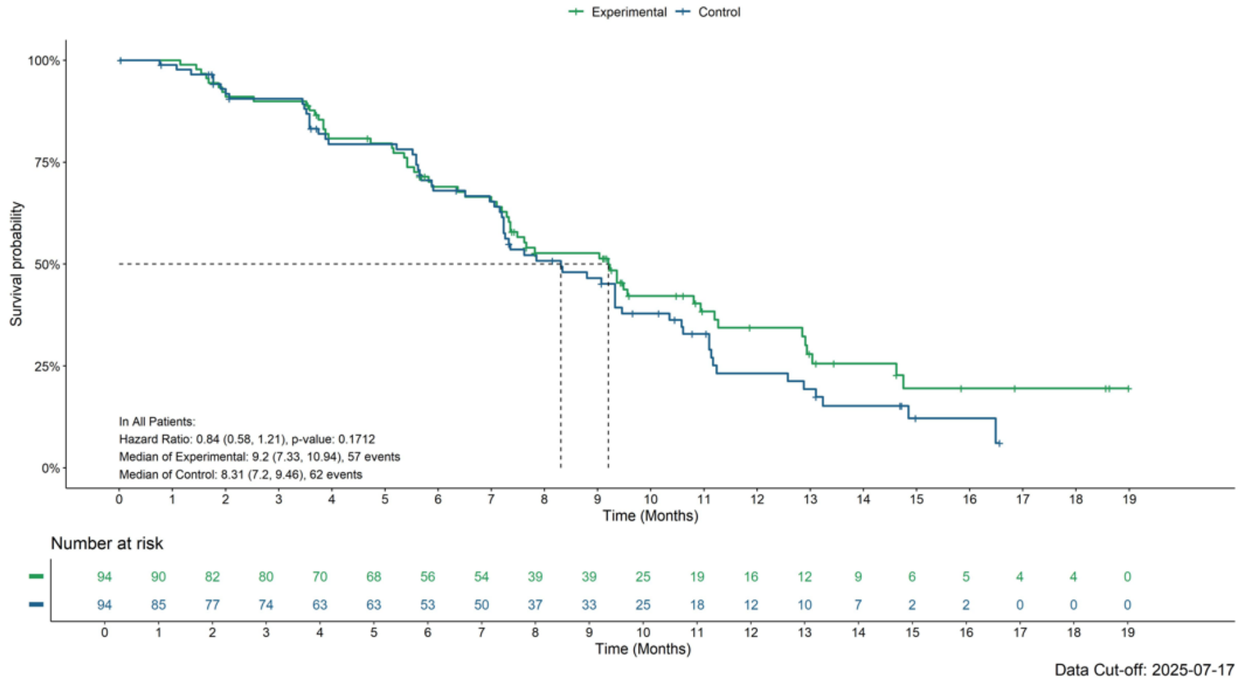
Baseline Demographics of DeFianCe Trial

N=188	Experimental Arm N=94 n (%)	Control Arm N=94 n (%)
Male	64 (68)	52 (55)
Age, mean (min, max)	59.6 (33, 84)	58.7 (29, 84)
Region		
United States	41 (44)	40 (43)
South Korea	50 (53)	45 (48)
Germany	3 (3)	9 (10)
Tumor Sidedness		
Right	24 (25)	23 (25)
Left	70 (75)	71 (75)
ECOG PS		
0	41 (44)	44 (47)
1	53 (56)	50 (53)
Liver metastasis		
Yes	72 (77)	67 (71)
RAS Mutated		
Yes	44 (47)	54 (57)
Prior Systemic Therapy- 5FU based		
Oxaliplatin based	76 (81)	84 (89)
Irinotecan based	19 (20)	13 (14)
Anti- VEGF	45 (48)	48 (51)
Anti- EGFR	29 (31)	23 (24)

Progression-free Survival and Overall Response Rate

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)**
SD	48 (51)	54 (57)
DCR	**86.2%**	**84.0%**
PD	6 (6)	7 (7)
No assessment	7 (7)	8 (9)

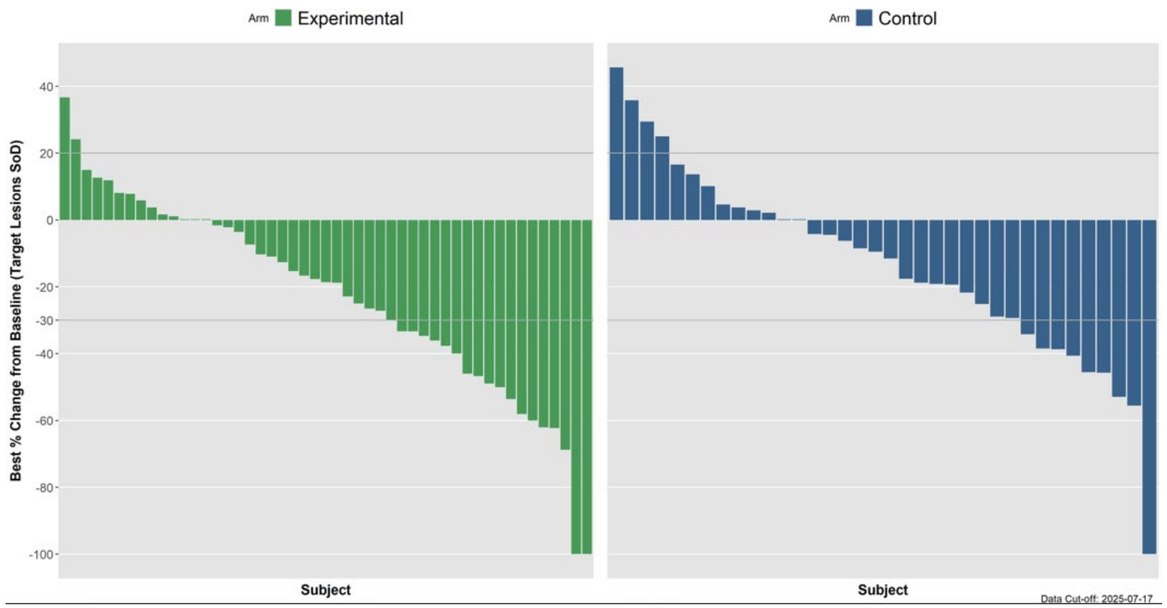
- Response rates were increased; p = 0.1009

- Median: 9.2 months sirexatamab vs. 8.3 months control arm
- 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%)

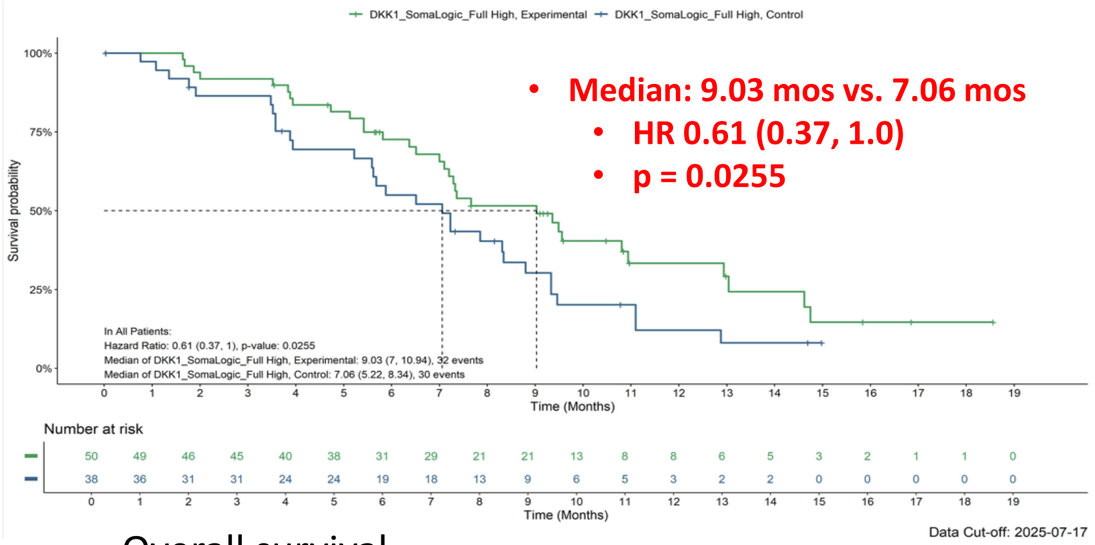
Sirexatamab significantly improves PFS and OS in DKK1-high patients

DKK1-high subgroup – Upper Median – Investigator Assessment



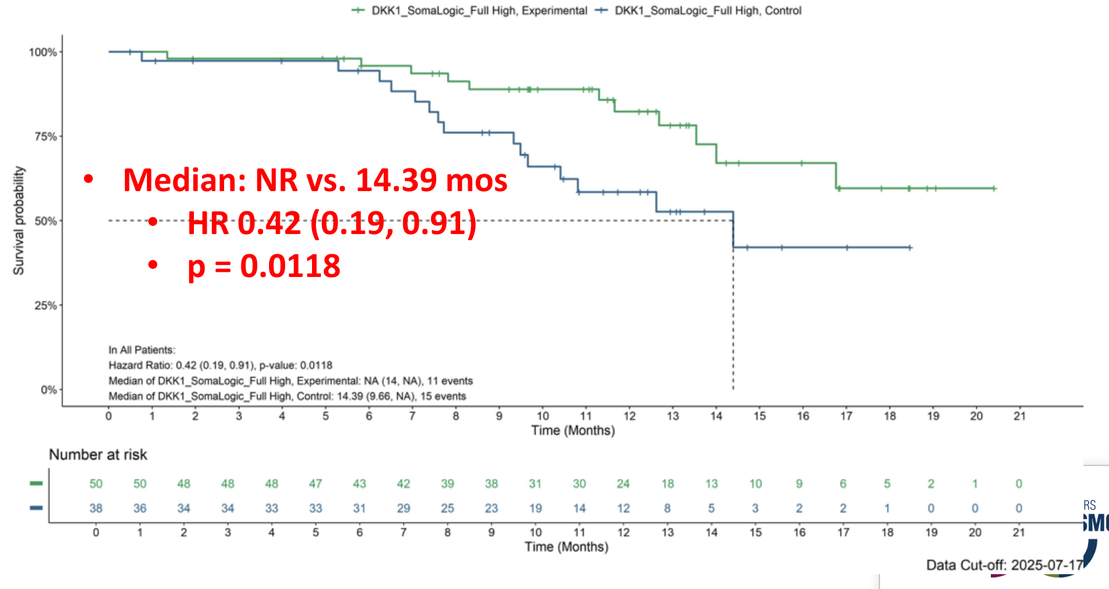
Response	Sirexatamab Experimental N=50 n (%)	Control N=38 n (%)
CR	0 (0)	0 (0)
PR	19 (38)	9 (24)
ORR	**38.0% (24.7, 52.8)**	**23.7% (11.4, 40.2)**
P value	**p=0.0706**	
SD	26 (52)	23 (61)
DCR	**90.0%**	**84.2%**
PD	4 (8)	4 (11)
No assessment	1 (2)	2 (5)

Progression free survival



- **Median: 9.03 mos vs. 7.06 mos**
  - **HR 0.61 (0.37, 1.0)**
  - **p = 0.0255**

Overall survival



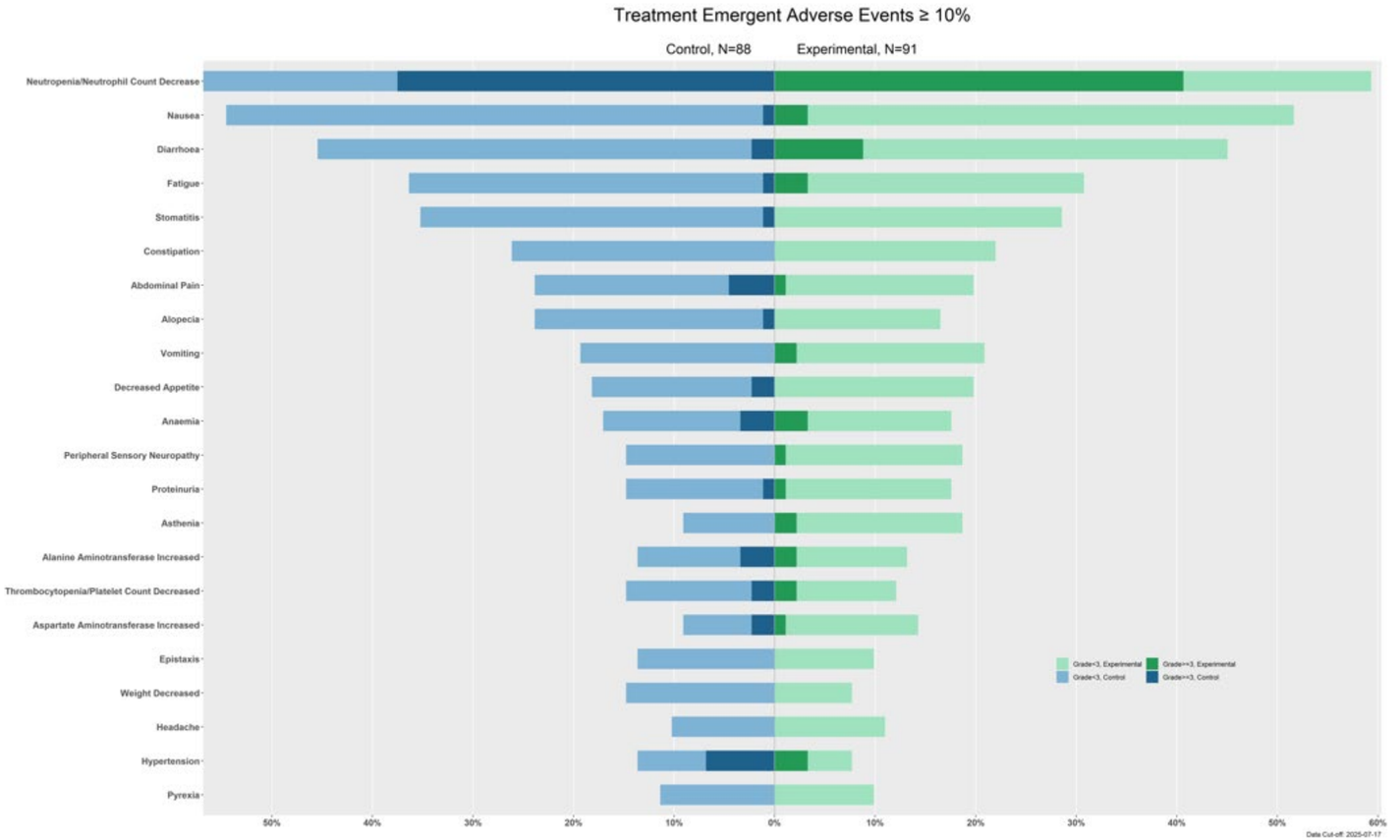
- **Median: NR vs. 14.39 mos**
  - **HR 0.42 (0.19, 0.91)**
  - **p = 0.0118**

Safety of sirexatamab

Overall TEAE profile is similar between the two arms suggesting the addition of sirexatamab does not adversely impact the safety profile of the combinatorial agents.

N=179	Experimental arm (n=91) n (%)	Control Arm (n=88) n (%)
Any TEAE	91 (100)	88 (100)
Regimen-related TEAE	90 (99)	86 (98)
≥ Grade 3 TEAE	54 (59)	59 (67)
Regimen-related ≥ Grade 3 TEAE[#]	50 (55)	50 (57)
Any SAE	18 (20)	17 (19)
Regimen-related SAEs[*]	12 (13)	4 (5)
AEs leading to death[+]	1 (1)	0 (0)
AEs leading to discontinuation of any regimen	14 (15)	17 (19)
AEs leading to discontinuation of DKN-01	4 (4)	N/A
AEs leading to dose reduction of any regimen	34 (37)	38 (43)
AEs leading to dose interruption of any regimen	66 (73)	62 (71)

[#] Only regimen related ≥ Grade 3 occurring in >10% in either arm was neutrophil count decreased
[*] SAEs assessed as related to DKN-01 occurred in 5 subjects and include diarrhea (n=2), vomiting (n=1), anal fistula (n=1), enterovesical fistula (n=1), infusion related reaction (n=1), and confusional state (n=1)
[+] Unrelated to DKN-01, cardiac arrest



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Conclusions

- 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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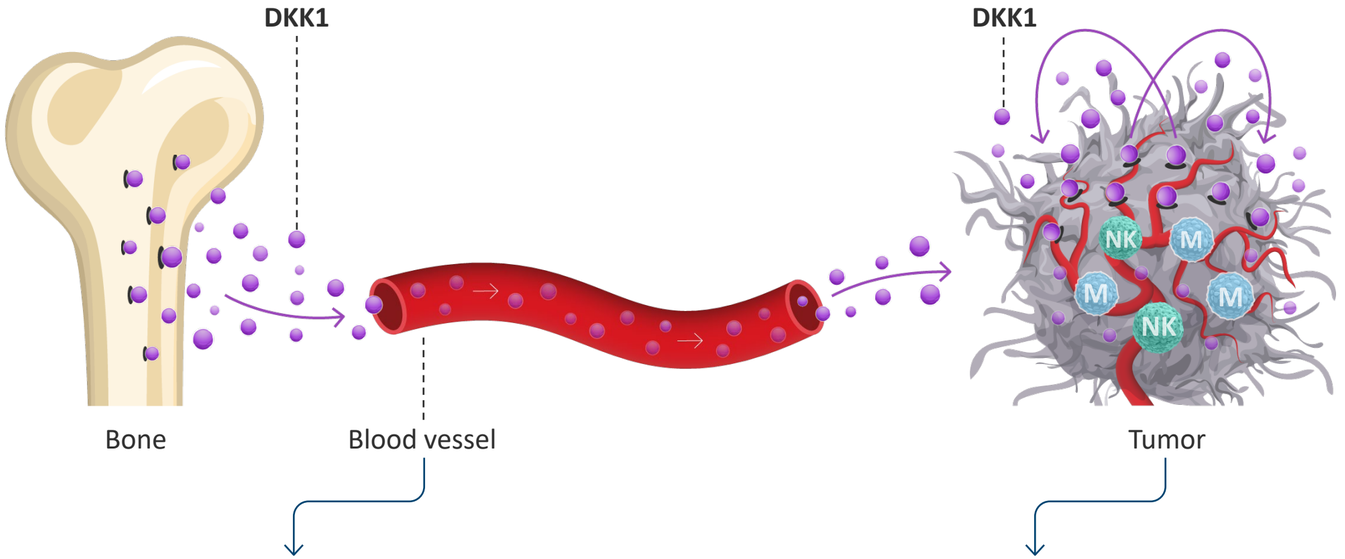
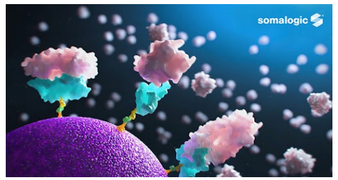
Backup

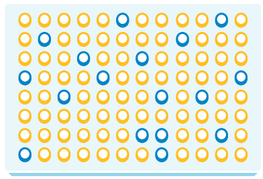
DKK1 production from multiple sources can drive tumor growth and is associated with poor prognosis in colorectal cancer



DKK1 protein in circulation is measured by SomaScan and ELISA

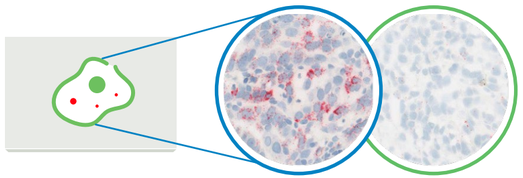


SomaScan platform (SomaLogic, Boulder CO).

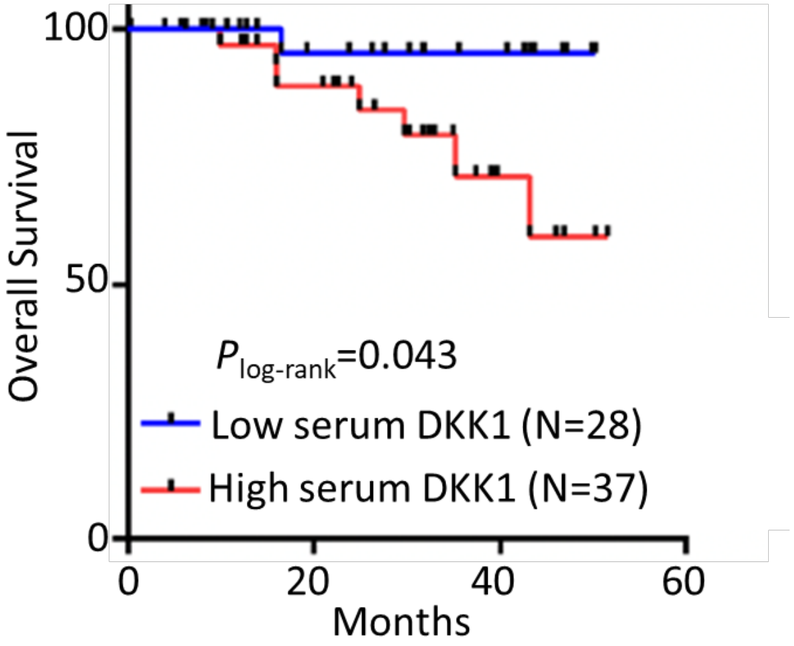


MSD ELISA

DKK1 RNA from the tumor is measured by RNAscope



DKK1 high DKK1 low



Sirexatamab activity is enhanced with increasing thresholds of baseline DKK1

	All Patients		DKK1-High (upper median)		DKK1-High (upper quartile)	
Endpoint	Sirexatamab Experimental n=94	Control n=94	Sirexatamab Experimental n=50	Control n=38	Sirexatamab Experimental n=25	Control n=19
ORR	35.1%	26.6%	38.0%	23.7%	44.0%	15.8%
	ORR difference: 8.34% p-value: 0.1009		ORR difference: 14.32% p-value: 0.0706		ORR difference: 28.21% p-value: 0.0149	
PFS	9.2 months	8.3 months	9.03 months	7.06 months	9.36 months	5.88 months
	HR: 0.84 (0.58, 1.21) p-value: 0.1712		HR: 0.61 (0.37, 1) p-value: 0.0255		HR: 0.46 (0.22,0.96) p-value: 0.0168	
OS	NA (15.08, NA)	NA (14.75, NA)	NA (14.0, NA)	14.39 months (9.66, NA)	NA (13.54, NA)	9.49 months (7.06, 12.62)
	HR: 0.83 (0.46, 1.48) p-value: 0.2632		HR: 0.42 (0.19, 0.91) p-value: 0.0118		HR: 0.17 (0.05, 0.53) p-value <0.001	