Elevated Baseline DKK1 Plasma is a Biomarker for Sirexatamab Treated Colorectal Cancer Patients

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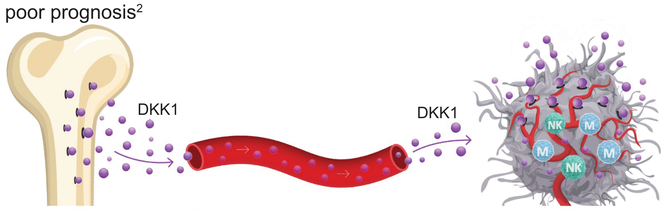
Abstract

Sirexatamab is an IgG4 monoclonal antibody that potently neutralizes dickkopf-related protein 1 (DKK1). DKK1 is a secreted protein that has been implicated as a poor prognostic marker and as an oncogenic driver for colorectal cancer (CRC). The DeFianCe (NCT05480306) Phase 2 randomized, global, open-label, multicenter study was conducted to evaluate the efficacy and safety of sirexatamab plus the current standard of care (SOC) treatment regimen (FOLFIRI/FOLFOX and bevacizumab) versus SOC as second-line treatment for participants with advanced CRC (n=188). A retrospective analysis of baseline plasma levels of DKK1 using a research assay identified a significant improvement in progression free and overall survival favoring the experimental arm in patients with elevated levels of DKK1. In order to enable future prospective patient selection, an optimized DKK1 assay using the Meso Scale Discovery (MSD) platform was developed and underwent feasibility at a central laboratory. DeFianCe samples were retested with the optimized assay. Consistent with the research assay, patients whose DKK1 levels were above the median showed improved clinical outcomes in the experimental arm compared to SOC. Furthermore, approximately 500 commercial CRC plasma samples were evaluated to determine the prevalence of patients with elevated DKK1 in a real-world data set and understand the association between demographics and DKK1 levels. Future work will include completing the development and validation of the assay as a potential companion diagnostic and determining the appropriate threshold of DKK1 plasma levels for CRC patients who would be most likely to derive clinical benefit from a sirexatamab-based therapy.

Background

- Sirexatamab (DKN-01) is a highly potent DKK1 neutralizing therapeutic antibody
- Bone produced DKK1 stimulates tumor cell proliferation and an immune suppressive tumor microenvironment[1]
- CRC patients have elevated blood levels of DKK1 and it is a marker of poor prognosis[2]

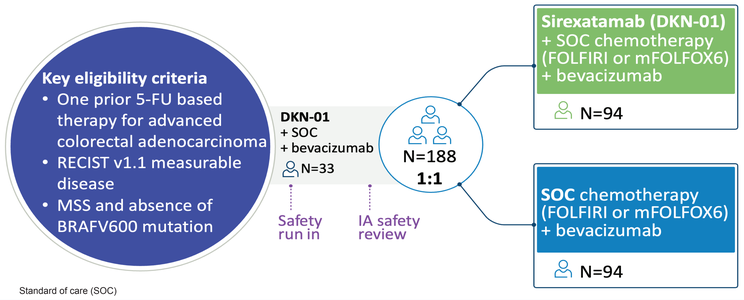


[1]Kagey and He, BJP (2017); D'Amico et al., JEM (2016); Shi et al., Cancer Cell (2025)
[2]Gurluler et al., ERMPS (2014); Sui et al., JITC (2021); Sui et al. BMC Cancer (2019); Disc et al., Medicina (2024)
Macrophage (M); Natural Killer Cell (NK)

DeFianCe Study Design

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

Objectives
- Primary: PFS
- Secondary: ORR and OS
- Exploratory: DKK1 biomarker high (plasma)



Improved ORR In Patients with Elevated Plasma DKK1

All Patients with Baseline DKK1 Plasma Data

Response	Experimental Arm N=89 n (%)	Control Arm N=85 n (%)
CR	1 (1%)	2 (2%)
PR	30 (34%)	17 (20%)
ORR	**35%**	**22%**
p-value	p=0.033	
SD	45 (51%)	49 (58%)
Non-CR/PD	2 (2%)	5 (6%)
DCR	78 (88%)	73 (86%)
PD	6 (7%)	9 (11%)
NE/NA	5 (6%)	3 (4%)

DKK1 High Subgroup - Upper Median (>380 pg/mL)

Response	Experimental Arm N=43 n (%)	Control Arm N=44 n (%)
CR	1 (2%)	0 (0%)
PR	17 (40%)	7 (16%)
ORR	**42%**	**16%**
p-value	p=0.003	
SD	17 (40%)	26 (59%)
Non-CR/PD	1 (2%)	3 (7%)
DCR	36 (84%)	36 (82%)
PD	4 (9%)	5 (11%)
NE/NA	3 (7%)	3 (7%)

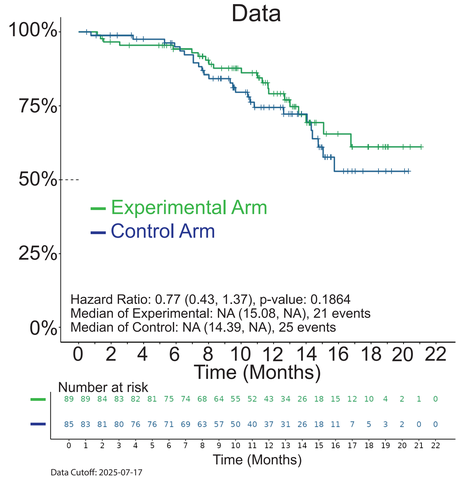
DKK1 High Subgroup - Upper Quartile (>580 pg/mL)

Response	Experimental Arm N=18 n (%)	Control Arm N=26 n (%)
CR	1 (6%)	0 (0%)
PR	6 (33%)	3 (12%)
ORR	**39%**	**12%**
p-value	p=0.018	
SD	9 (50%)	16 (62%)
Non-CR/PD	0 (0%)	1 (4%)
DCR	16 (89%)	20 (77%)
PD	0 (0%)	5 (19%)
NE/NA	2 (11%)	1 (4%)

Non evaluable (NE); Non assessment (NA)
Blinded Independent Central Review (BICR); Data Cutoff: 2025-07-17

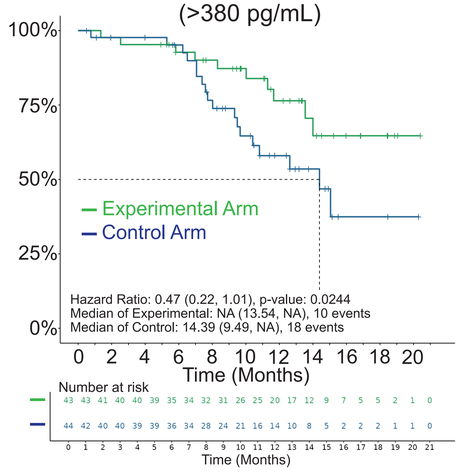
Improved Overall Survival In Patients with Elevated Plasma DKK1

All Patients with Baseline DKK1 Plasma Data

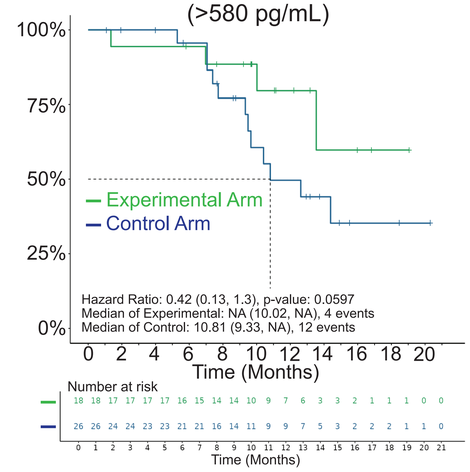


Data Cutoff: 2025-07-17

DKK1 High Subgroup - Upper Median (>380 pg/mL)

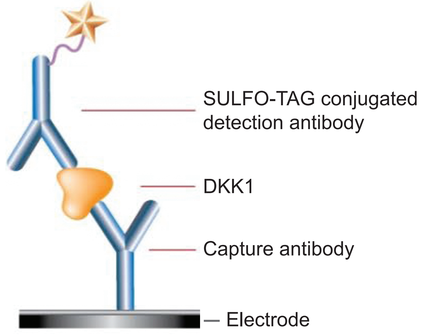


DKK1 High Subgroup - Upper Quartile (>580 pg/mL)



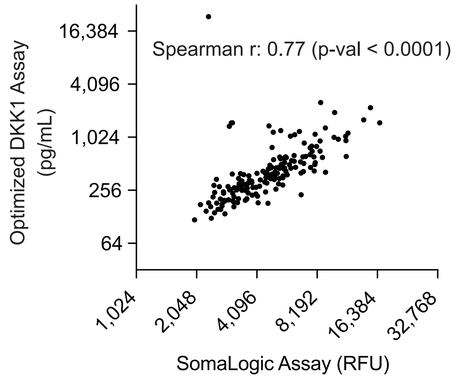
DKK1 Plasma Assay

- ARUP Laboratories developed an optimized DKK1 plasma assay on the Meso Scale Discovery (MSD) platform
- Tested 72 antibody combinations and selected the best pair based on sensitivity and dynamic range
- Assay has undergone feasibility studies and is acceptable for Companion Diagnostic (CDx) development



DKK1 Plasma Assay Accuracy

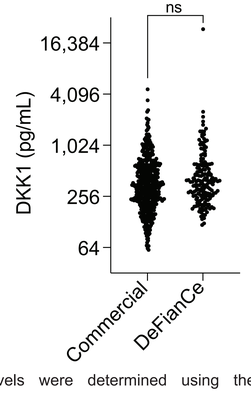
The Optimized DKK1 Plasma Assay Correlates with an Orthogonal Technique



Baseline plasma samples from the DeFianCe Study were analyzed for DKK1 levels with the optimized assay and compared to an orthogonal SomaLogic assay. Relative fluorescent units (RFU).

DKK1 Real World Data

DKK1 Plasma Levels from the DeFianCe Trial are Similar to Commercially Acquired Samples



DKK1 levels were determined using the optimized assay. Commercial (N=465) stage IV CRC patient plasma samples were acquired from multiple vendors and compared to baseline DeFianCe (N=174) patient plasma samples. Non significant (ns).

Conclusions

- Sirexatamab has efficacy in advanced CRC
- Plasma DKK1 is a biomarker for Sirexatamab and a negative prognostic factor for CRC
- Data supports the continued development of sirexatamab in advanced CRC patients with elevated plasma DKK1

ARUP LABORATORIES

leaptherapeutics