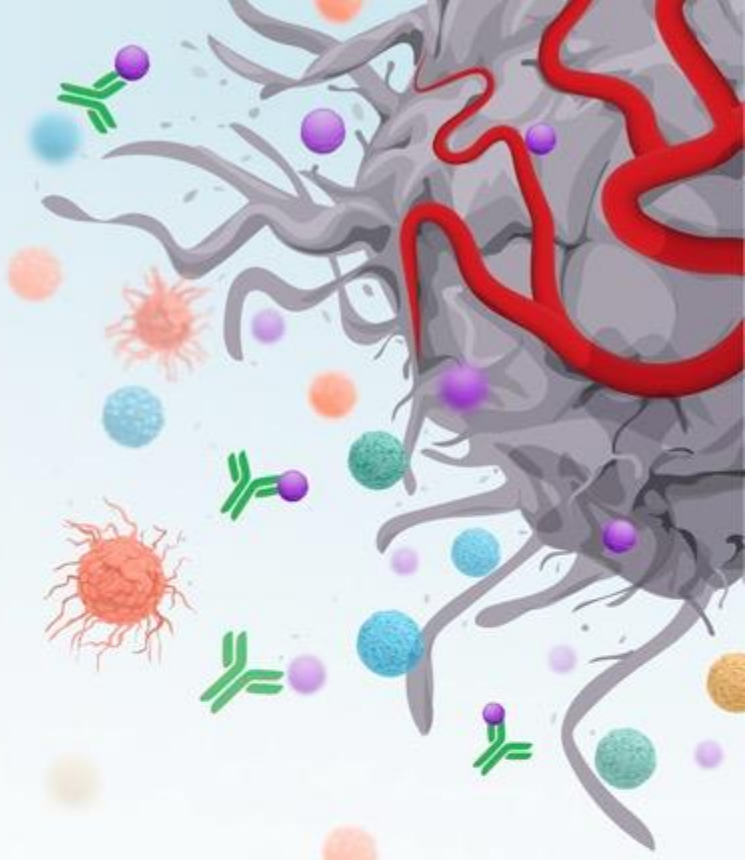
LEAP THERAPEUTICS

company presentation

42nd Annual J.P. Morgan Healthcare Conference

January 10, 2024



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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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Developing biomarker-targeted antibody therapies for cancer patients

Two clinical stage antibody programs –
DKN-01 targeting DKK1
FL-301 targeting CLDN18.2

Upcoming multiple milestones from two randomized clinical trials

Biomarker strategy, focus on GI cancers

Cash runaway to mid H1 2025 with $70M at December 31, 2023

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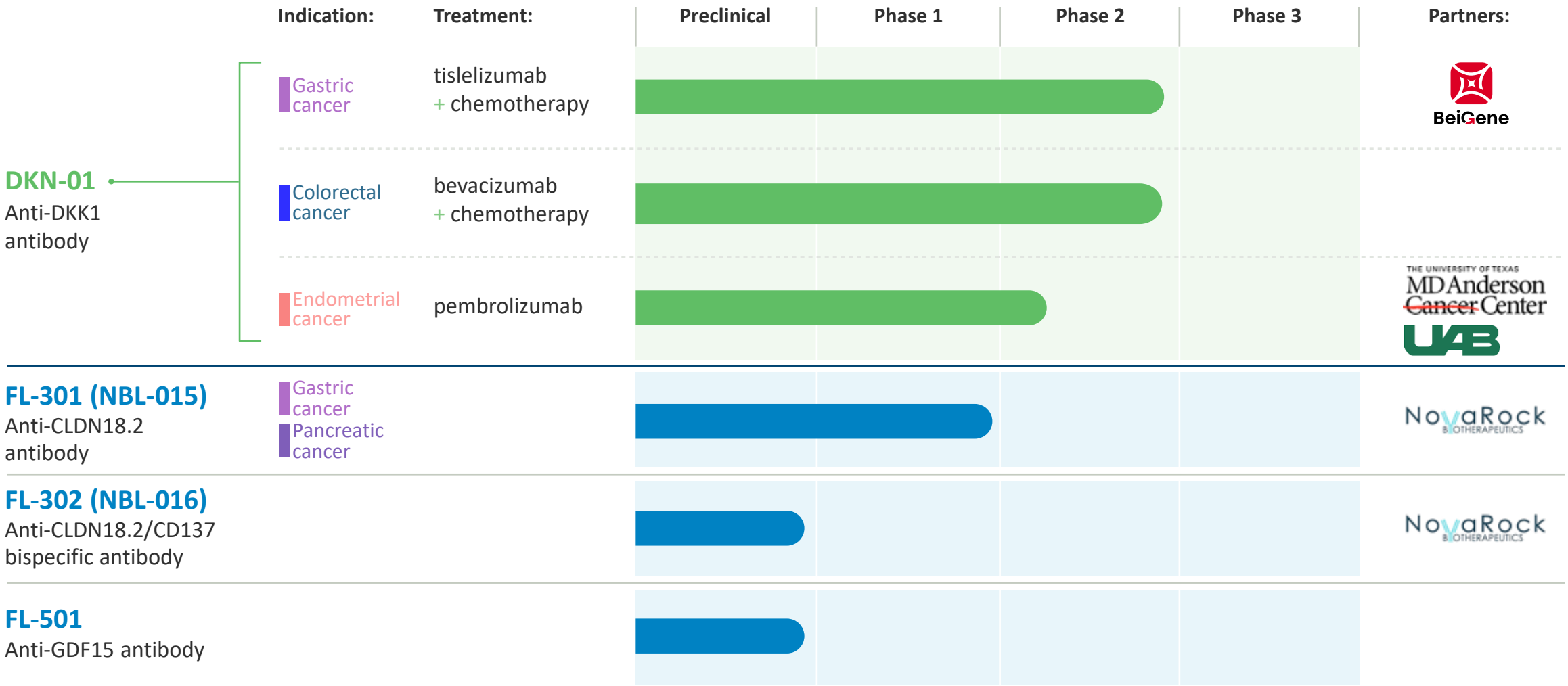
Pipeline



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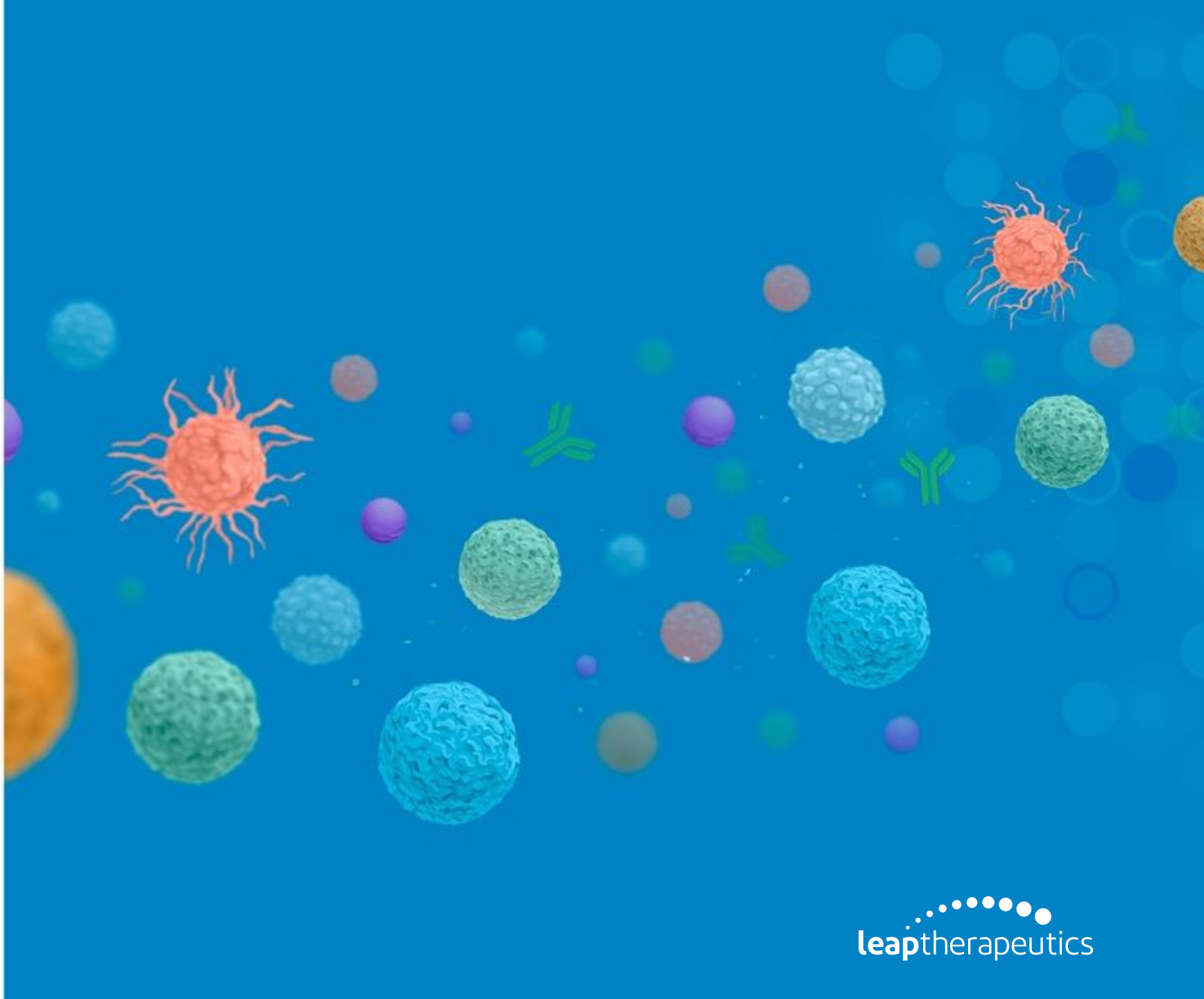
DKN-01

Anti-DKK1 monoclonal antibody



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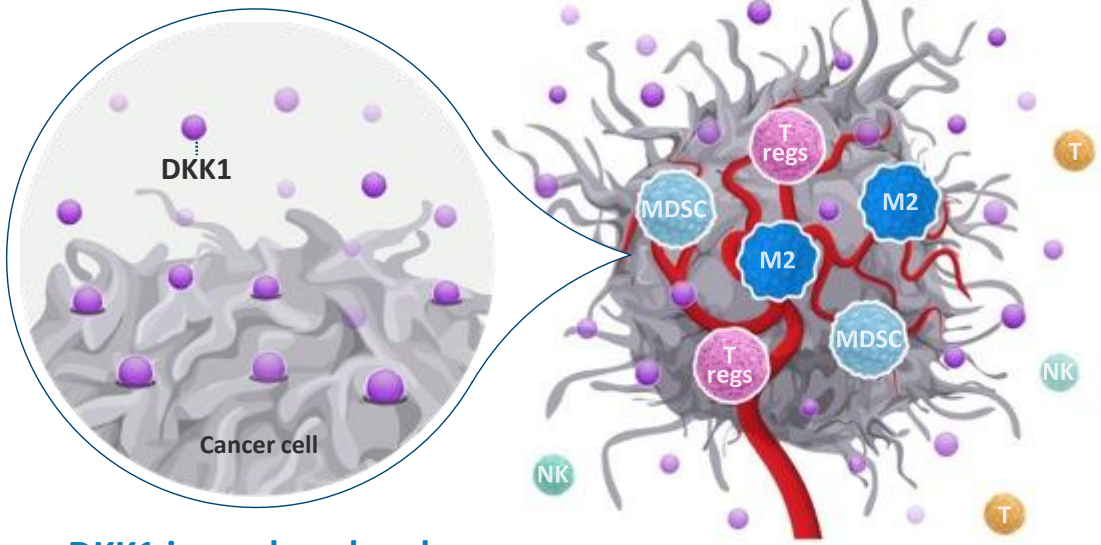
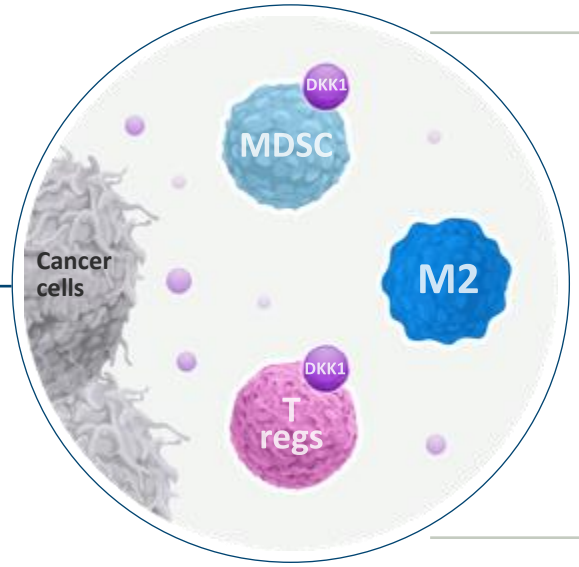
The role of DKK1 in cancer

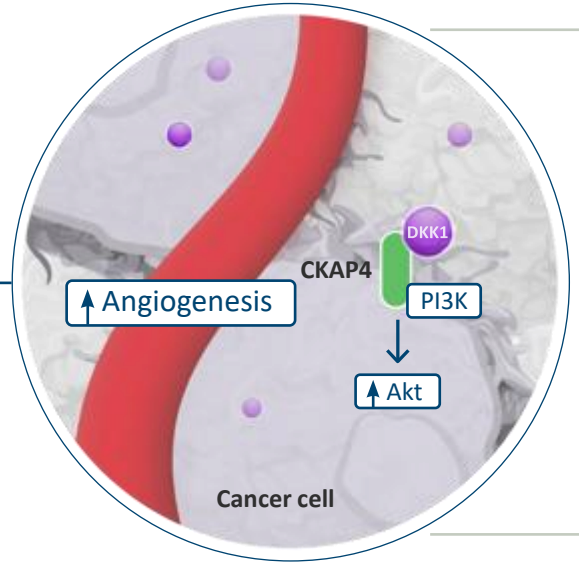


DKK1 is produced and secreted by cancer cells, and functions on several tumor pathways and nearby immune cells.



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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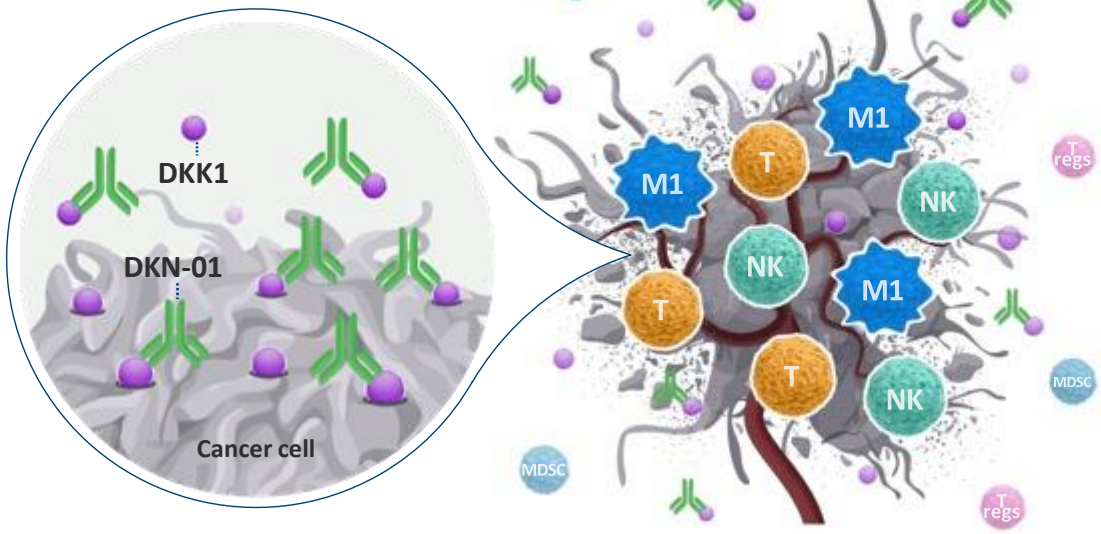
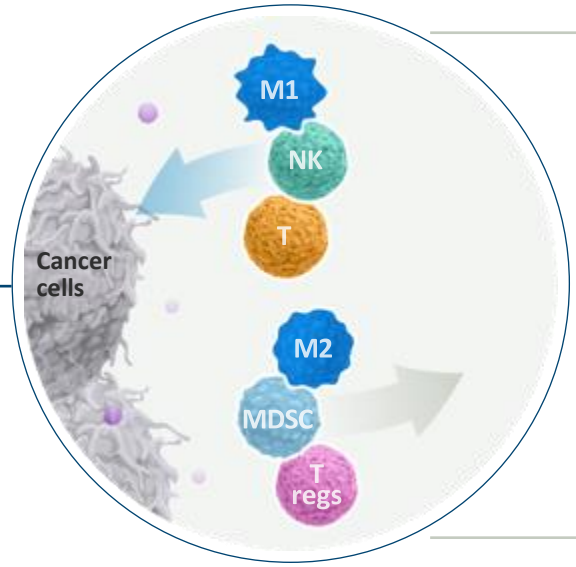
Activity of DKN-01 to treat cancer

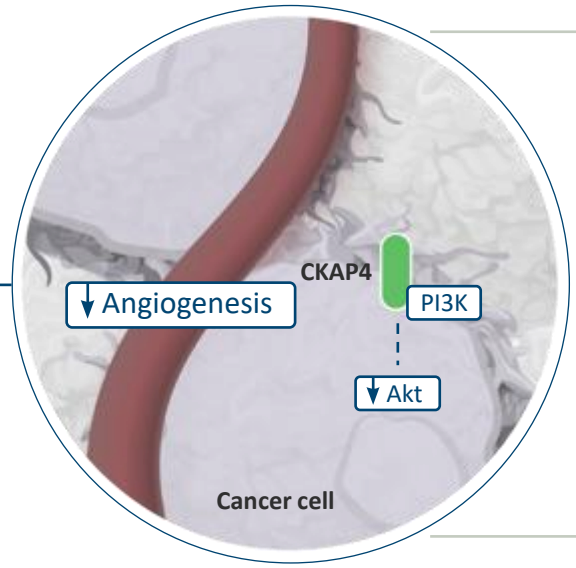


DKN-01 treatment neutralizes DKK1 and stimulates an immune mediated anti-tumor response.



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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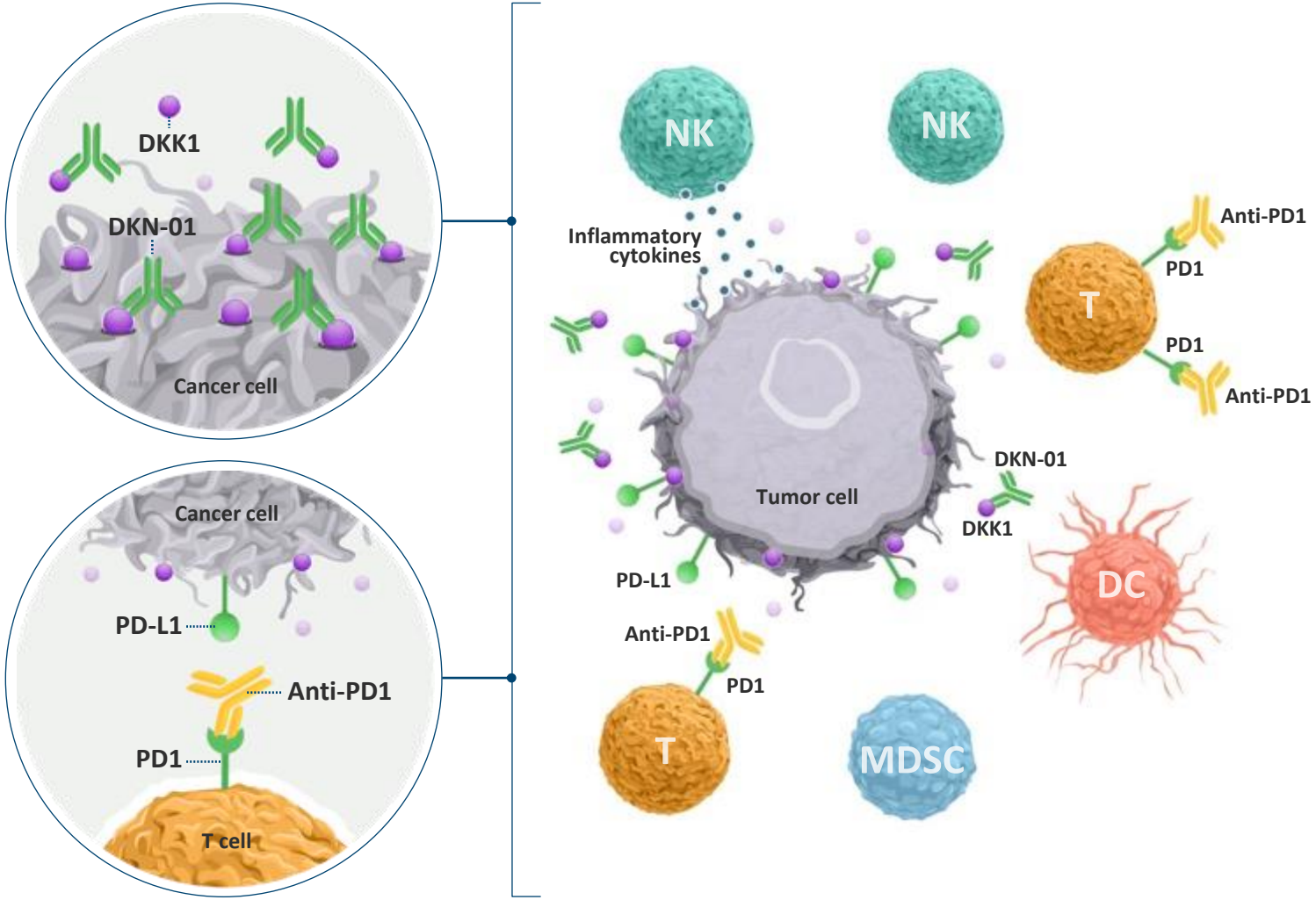
DKN-01 and anti-PD-1 cooperativity



DKN-01 targets innate immunity by activating NK cells, reprogramming Macrophages and inhibiting MDSCs, thus setting the stage for an enhanced adaptive immune response by anti-PD-1.

Promotes a pro-inflammatory M1 macrophage phenotype.

DKN-01 sensitizes tumors to anti-PD-1 therapies through upregulation of PD-L1.

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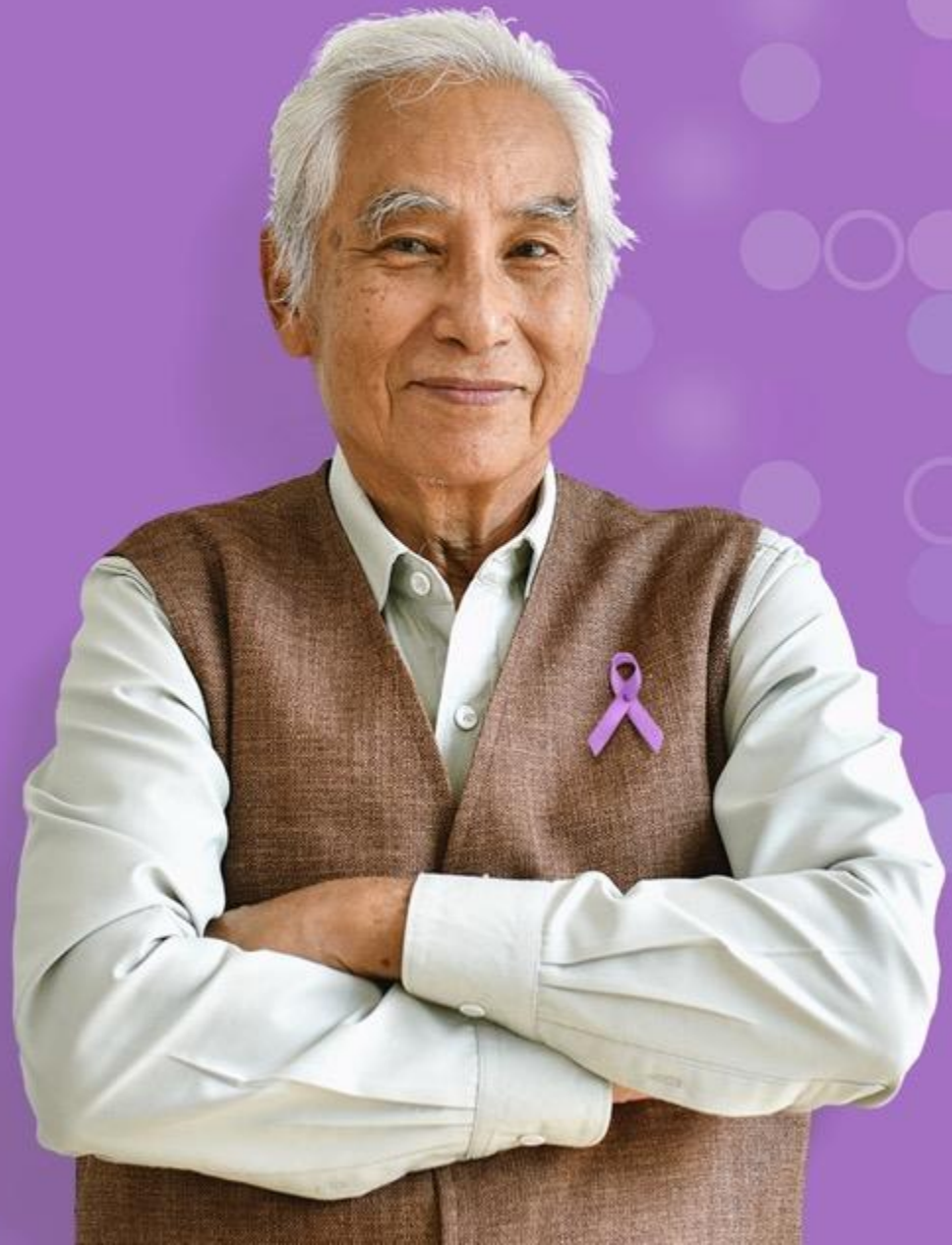
DKN-01

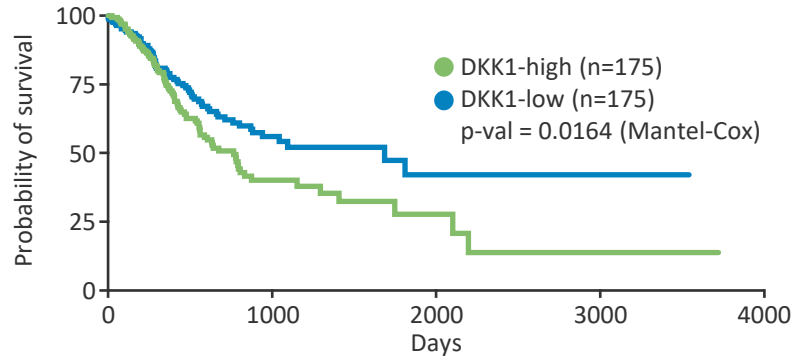
Gastric cancer development



DKK1-high levels are associated with poor survival in gastric cancer

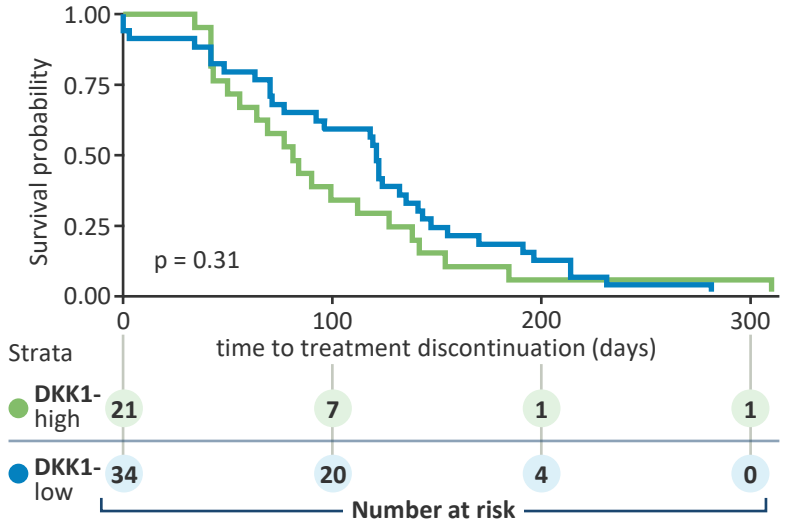
High levels of DKK1 correlate with shorter overall survival In gastric cancer

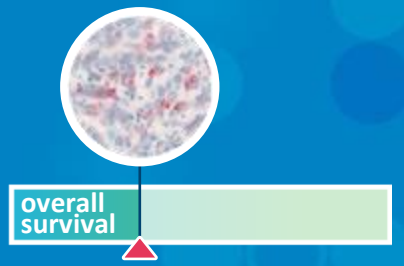
TCGA STAD dataset

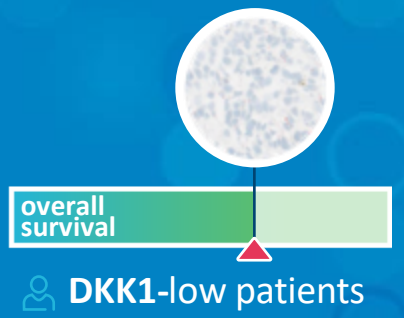


DKK1-high is associated with poor response to first-line platinum + fluoropyrimidine based therapies in GEJ/gastric cancer patients

Collaboration with Tempus







~2.5 years shorter OS in DKK1-high patients

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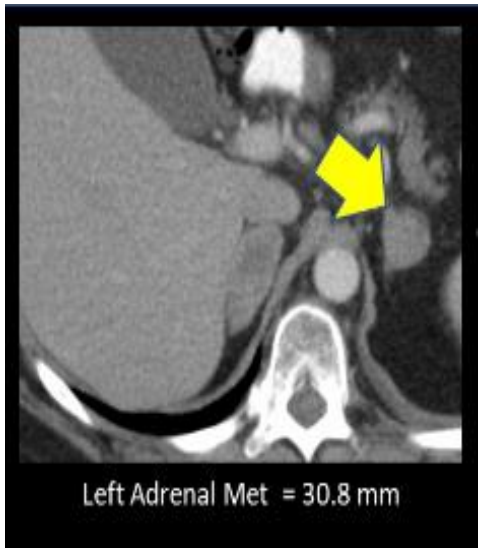
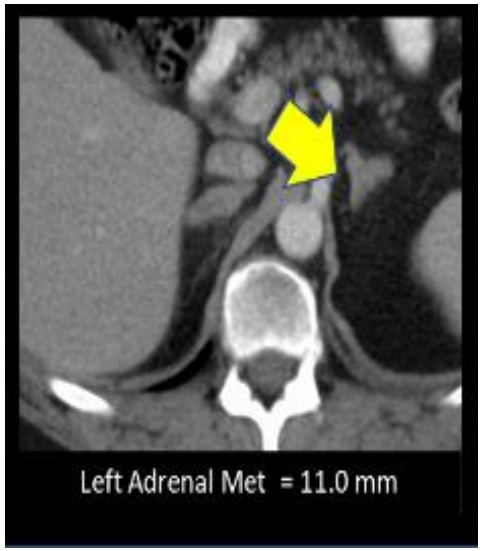
DKN-01 single agent activity in heavily pretreated esophagogastric cancer patients

2L+ EGC
DKN-01

On Study 1 Year, Reduction -33.9%
Failed Prior anti-PD-L1 + IDOi



Baseline



4-month scan

Best Overall Response of 20 Evaluable Patients*	
Partial Response	2
Stable Disease	6
Progressive Disease	12

2 Monotherapy PRs

Clinical Benefit Rate 40%

*By Blinded Independent Central Review

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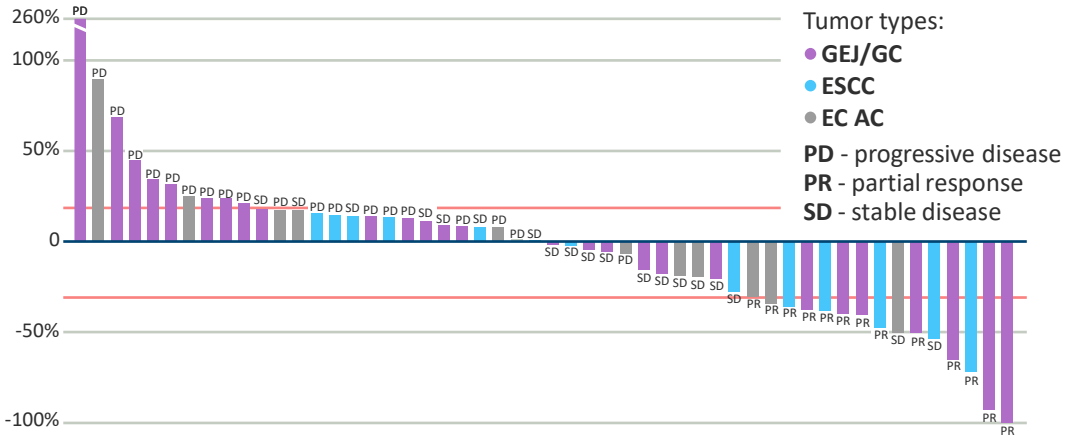
Clinical activity of DKN-01 plus paclitaxel or anti-PD-1 antibody

GEJ/GC
Historical data

DKN-01
+ paclitaxel

N=52
2L-8L esophagogastric pts



	Patients treated	Prior therapies	Overall response rate (ORR)	Disease control rate (DCR)
DKN-01 + paclitaxel	N=52	1-7	**25%**	**60%**

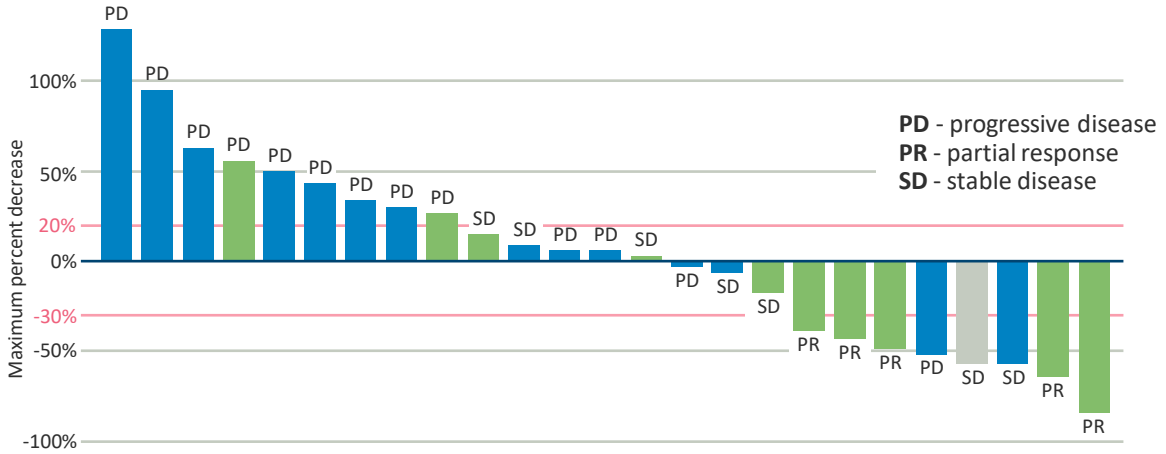
Strong broad activity in esophagogastric cancer in heavily pretreated patients

	Patients treated	PFS (months)	OS (months)	Overall response rate (ORR)	Disease control rate (DCR)
DKN-01 + paclitaxel	N=15	4.5	12.7	**46.7%**	**73.3%**

ORR in 2L patients is ~47%

DKN-01
+ pembro

N=31
2L+ GEJ/GC pts



location	Total (n)	PFS (mo)	OS (mo)	RE (n)	PR (n)	SD (n)	PD (n)	NE (n)	Overall response rate (ORR)	Disease control rate (DCR)
DKK1-high	n=11	5.1	7.3	10	5	3	2	1	**5 (50%)**	**8 (80%)**
DKK1-low	n=20	1.4	4	15	0	3	12	5	**0 (0%)**	**3 (20%)**

*DKK1-high ≥ upper tertile (35)

Achieved improved ORR, PFS, and OS in DKK1-high patients
Identified H-score threshold for DKK1 high/low expression

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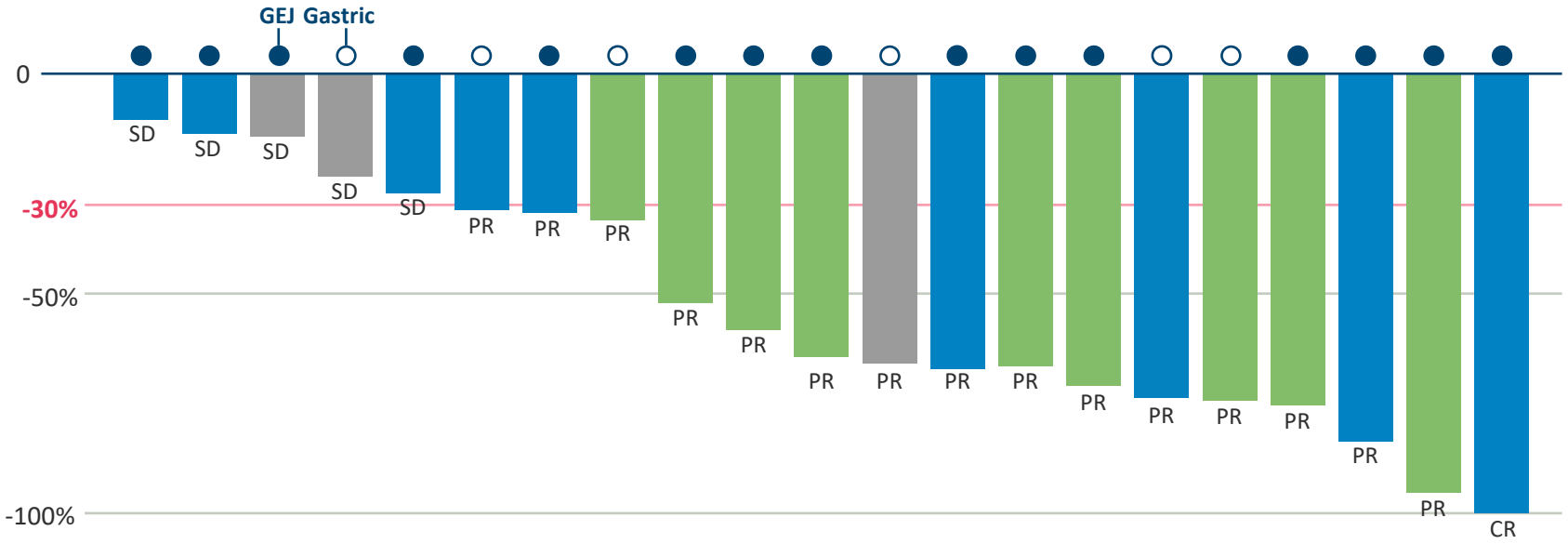
Response by DKK1 expression in first-line patients

1L GEJ/GC
DKN-01
+ tislelizumab
+ chemotherapy

Best % change in sum of diameters



	mITT* population N=22	**DKK1**-high N=10	**DKK1**-low N=9	**DKK1**-unknown N=3
CR - complete response	1 (5%)	0	1 (11%)	0
PR - partial response	15 (68%)	9 (90%)	5 (56%)	1 (33%)
SD - stable disease	5 (23%)	0	3 (33%)	2 (67%)
PD - progressive disease	0	0	0	0
NE - non-evaluable	1 (5%)	1 (10%)	0	0

All 9 of the evaluable DKK1-high patients had a partial response

1 PR went to curative surgery with pathological CR

73%
ORR in the mITT Population

(1 CR; 15 PR)

*mITT population includes all patients who received > 1 dose of DKN-01
As presented at ASCO 2023

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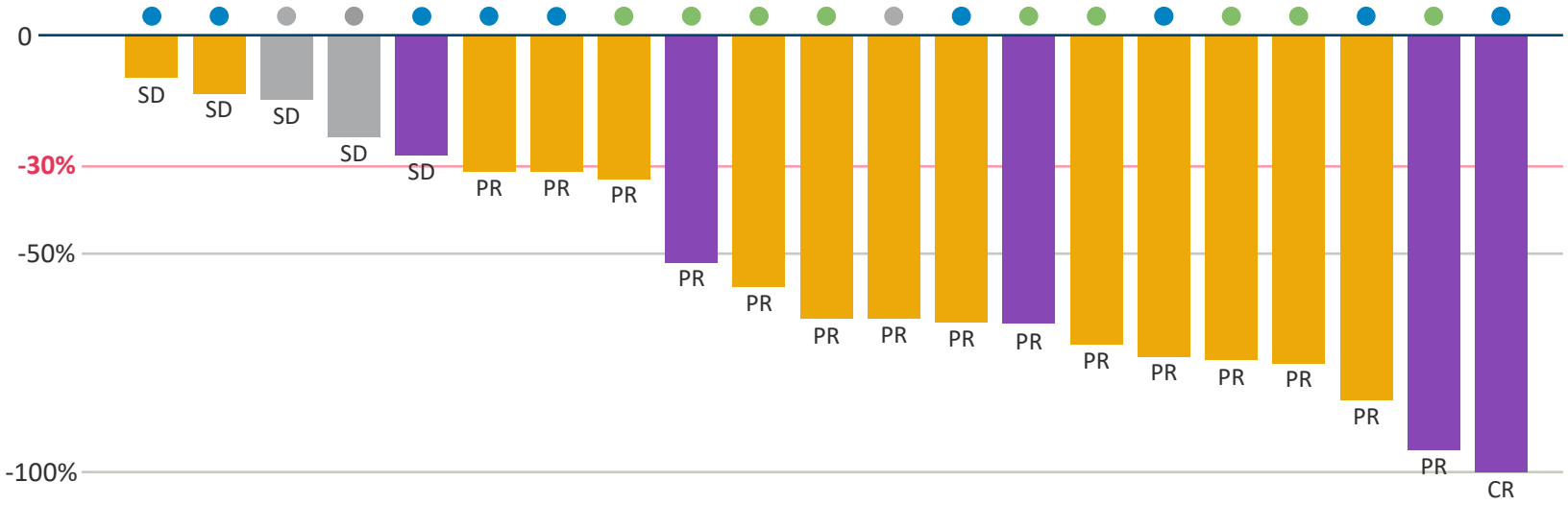
Response by PD-L1 expression

1L GEJ/GC
DKN-01
+ tislelizumab
+ chemotherapy

Best % change in sum of diameters



	PD-L1 CPS ≥5		PD-L1 CPS <5		
	DKK1-high N=4	**DKK1**-low N=2	**DKK1**-high N=6	**DKK1**-low N=7	**DKK1**-unknown N=1
CR - complete response		1 (50%)			
PR - partial response	3 (75%)	0	6 (100%)	5 (71%)*	1 (100%)
SD - stable disease	0	1 (50%)	0	2 (29%)	0
PD - progressive disease	0	0	0	0	0
NE - non-evaluable	1 (25%)	0	0	0	0
	N=6 **67% ORR**		N=14 **86% ORR**		

vCPS: visually-estimated combined positive score; PD-L1: programmed death-ligand 1
*Includes one pathologic CR
As presented at ASCO 2023

86%
ORR in PD-L1 low patients

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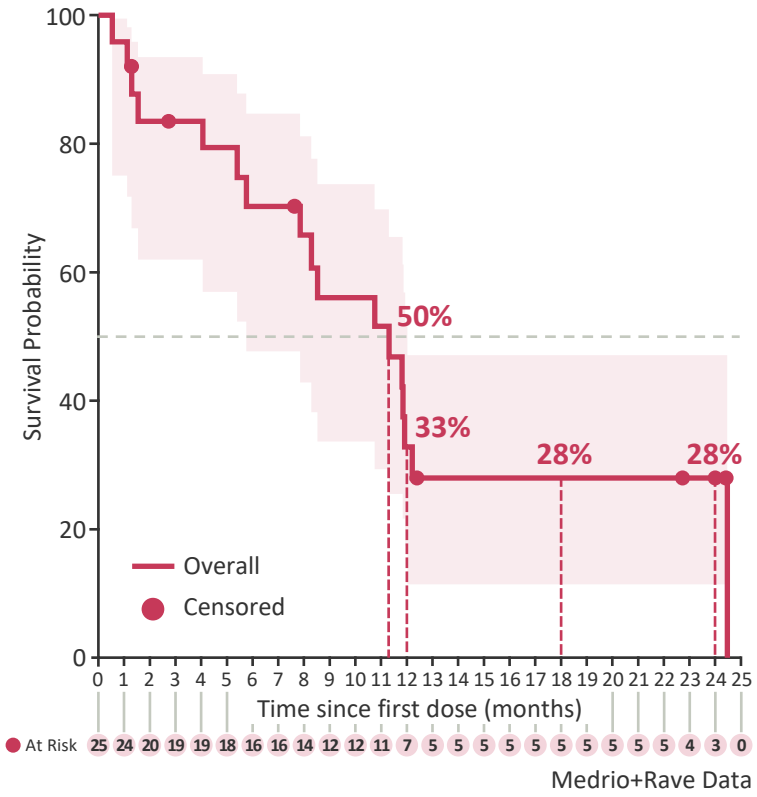
Survival outcomes in the overall population

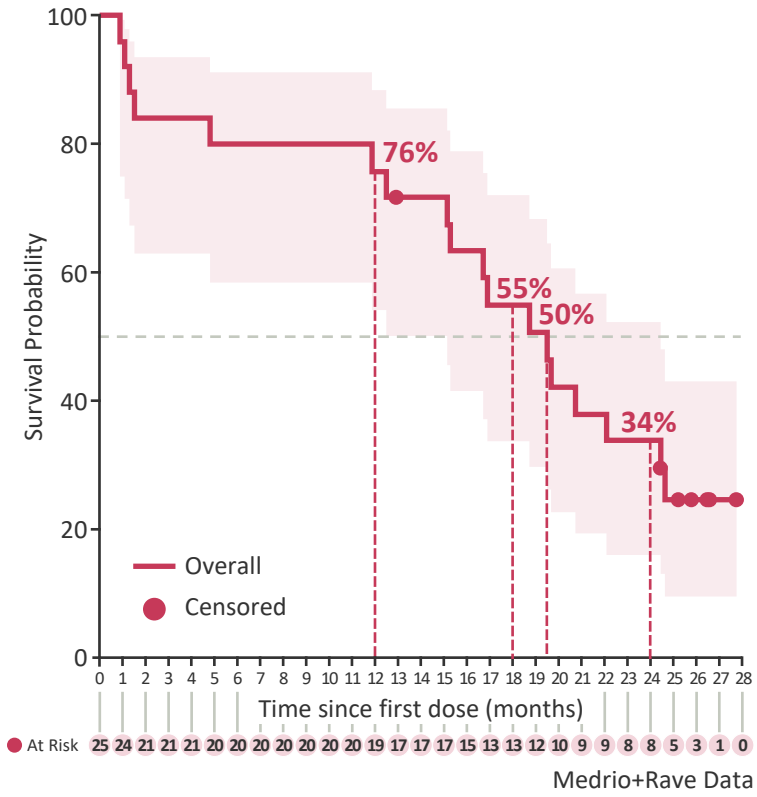
1L GEJ/GC
DKN-01
+ tislelizumab
+ chemotherapy

Progression-free survival



	Median	95%	CI
Overall	11.3	5.75	12.0

Overall survival



	Median	95%	CI
Overall	19.5	15.2	24.4

Median PFS:
11.3 months

Median OS:
19.5 months

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Competitive benchmarks for anti-PD-1 + chemotherapy in 1L GEJ/GC patients

1L GEJ/GC
DKN-01
+ tislelizumab
+ chemotherapy

PD-1 antibodies plus chemotherapy

	Nivolumab		Tislelizumab		Pembrolizumab
	Checkmate-649 (All) N=789	Checkmate-649 PD-L1 ↑ CPS ≥ 5 N=473	Rationale-305 (All) N=501	Rationale-305 PD-L1 ↑ CPS ≥ 5 N=274	Keynote-859 (All) N=790
OS months (95% CI)	13.7 (12.4, 14.5)	14.4 (13.1, 16.2)	15.0 (13.6, 16.5)	16.4 (13.6, 19.1)	12.9 (11.9, 14.0)
DOR months (95% CI)	8.5 (7.7, 9.9)	9.6 (8.2, 12.4)	8.6 (7.9, 11.1)	9.0 (8.2, 19.4)	8.0 (7.0, 9.7)
PFS months (95% CI)	7.7 (7.1, 8.6))	8.3 (7.0, 9.3)	6.9 (5.7, 7.2)	7.2 (5.8, 8.4)	6.9 (6.3, 7.2)
ORR (%) (95% CI)	47% (43%, 50%)	50% (46%, 55%)	47.3% (42.9%, 51.8%)	50.4% (44.3%, 56.4%)	51.3% (47.7%, 54.8%)

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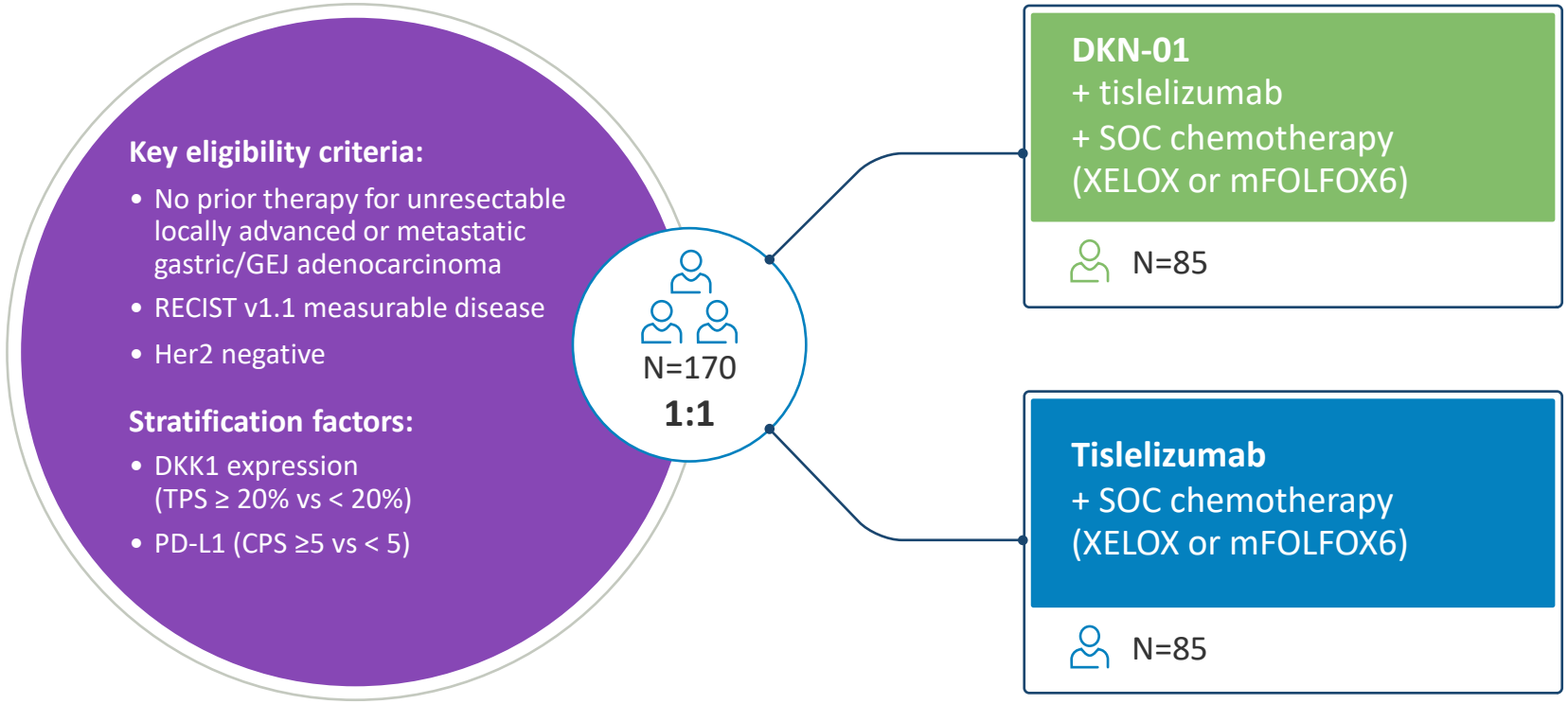
DisTinGuish Part C randomized study

1L GEJ/GC
DKN-01
+ tislelizumab
+ chemotherapy



Primary objective:
PFS, DKK-high and all

Secondary objectives:
– OS, DKK1-high and all
– ORR, DKK1-high and all

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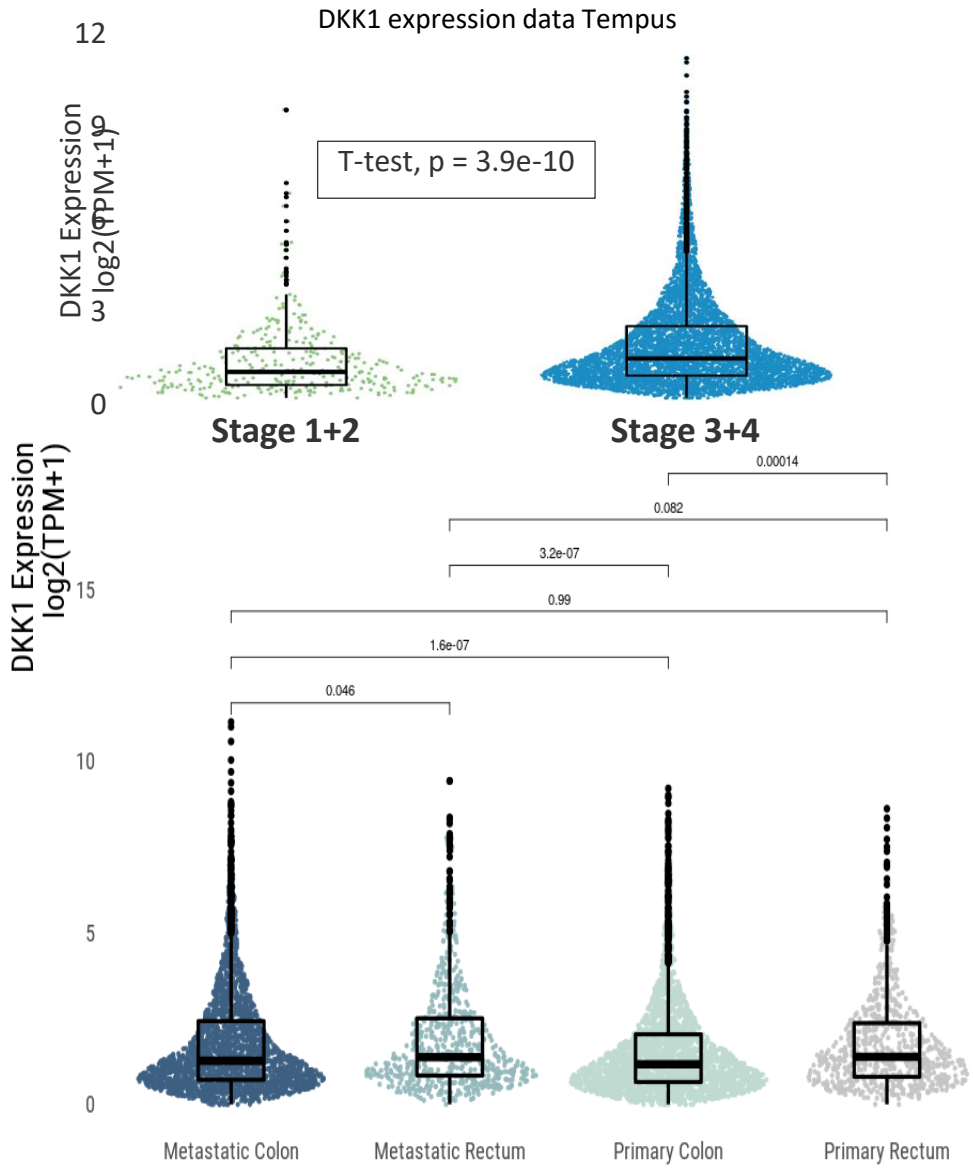
DKN-01

Colorectal cancer development

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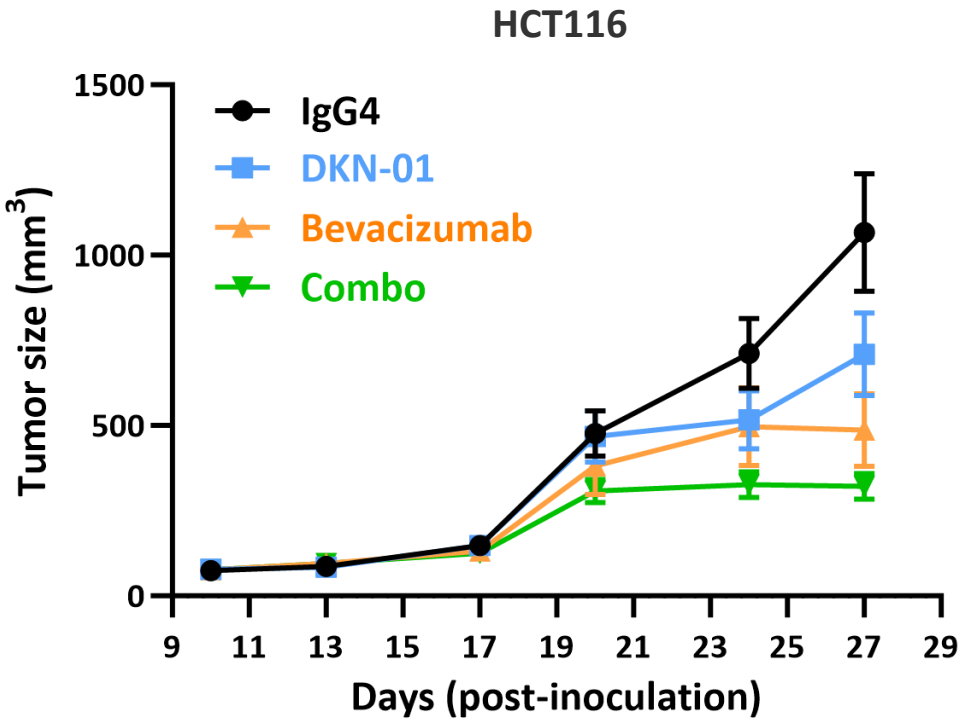
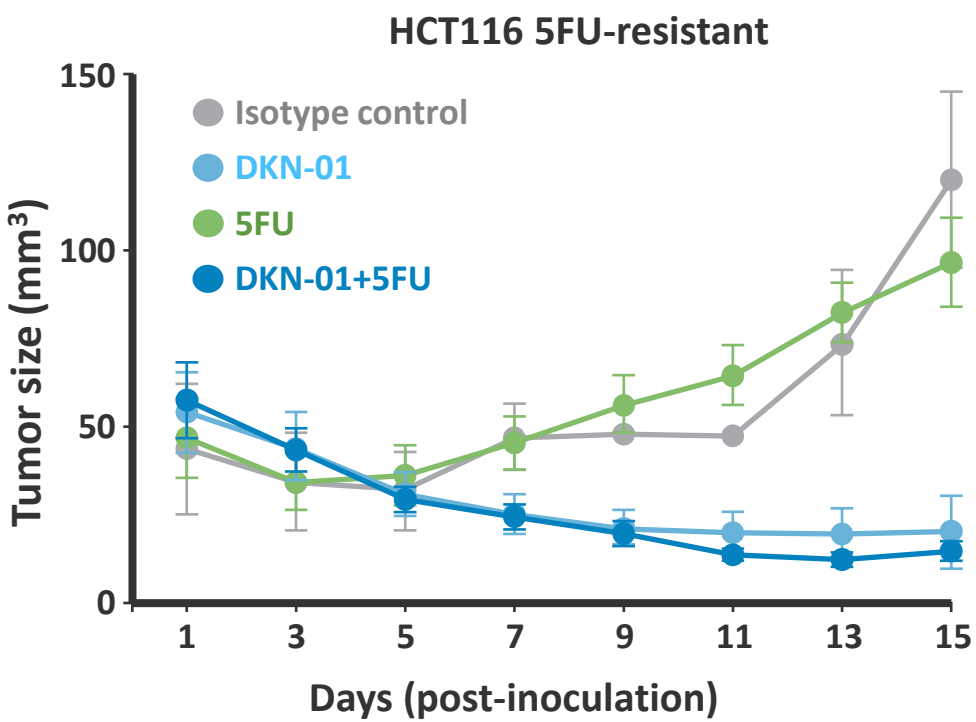
DKN-01 has activity in CRC models in combination with bevacizumab or 5FU

- 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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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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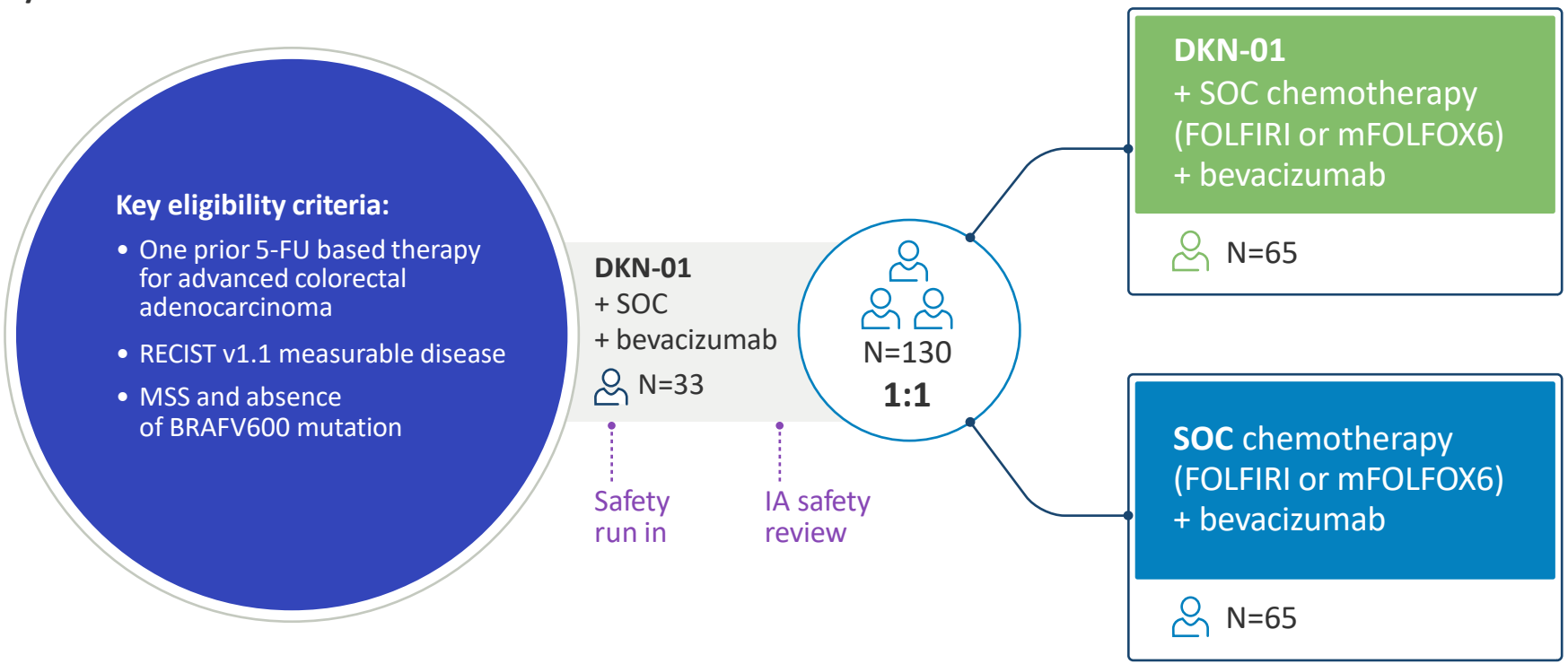
DeFianCe study design: advanced colorectal cancer

2L CRC
DKN-01
+ bevacizumab
+ chemotherapy

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

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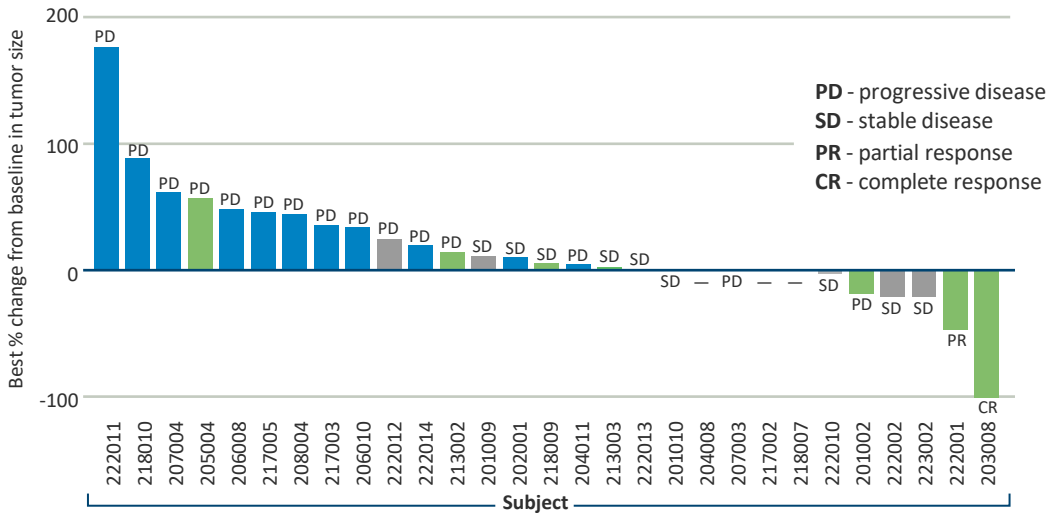
DKN-01

Endometrial cancer development

DKN-01 monotherapy - overall response by DKK1 tumoral expression

2L+ EEC
DKN-01
monotherapy

Overall response by DKK1 tumoral expression



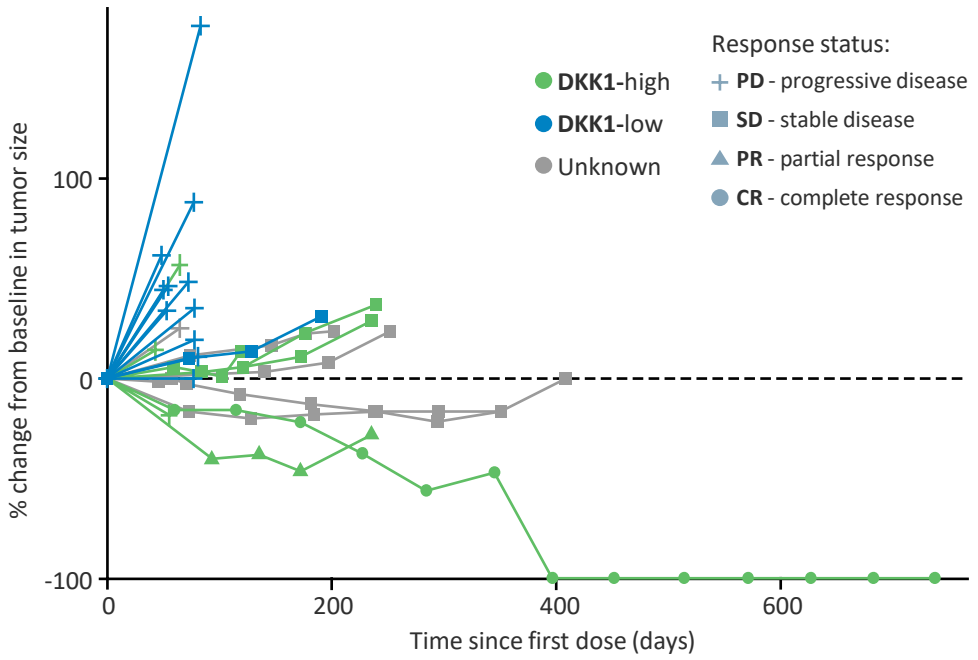
Status	Total	CR	PR	SD	PD	NE	ORR	DCR
DKK1-high (≥18)*	n=8	1	1	3	3	0	25%	63%
DKK1-low (<18)	n=15	0	0	1	11	3	0%	7%
Unknown	n=6	0	0	5	1	0	0%	83%

*H-score ≥ 18, upper tertile of overall study population

DKK1-high tumors have better ORR (25% vs. 0%) and clinical benefit (63% vs. 7%)

Patients with unknown DKK1 expression include 3 patients with durable SD and Wnt activating mutations

Durable clinical benefit in DKK1-high tumors



DKK1-high patients have longer progression-free survival (4.3 vs. 1.8 months [HR 0.26; 95 CI: 0.09, 0.75])

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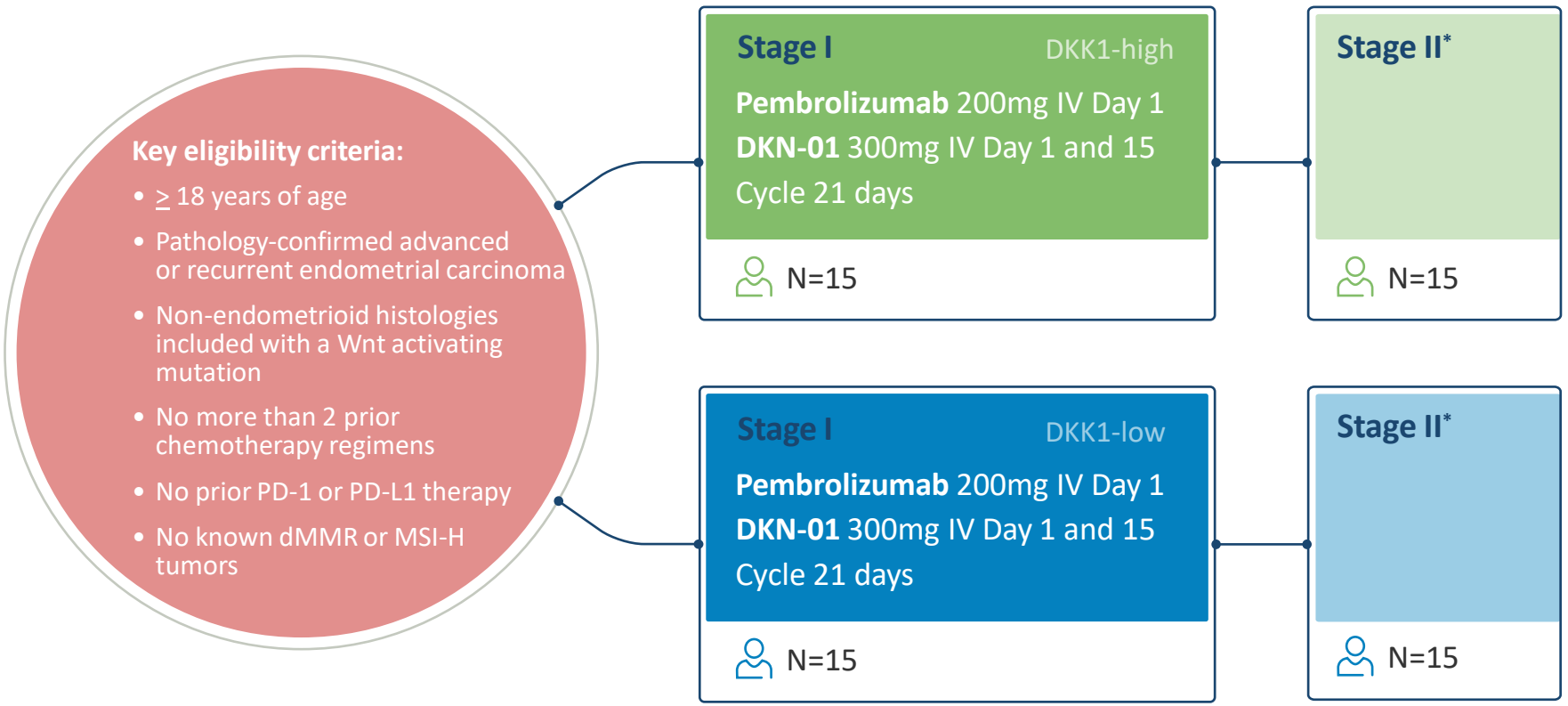
DKN-01 plus pembrolizumab endometrial cancer study

2-3L EEC
DKN-01
+ pembrolizumab



Open-label, phase 2 trial,
Bayesian optimal phase II design,
Investigator-initiated study with pembrolizumab supplied by Merck.

Primary objective:
Objective response rate (ORR)

Secondary objectives:
Clinical benefit,
PFS, OS, DOR

* Move to Stage II based on ORR in Stage I

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

UAB

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DKN-01 clinical milestones