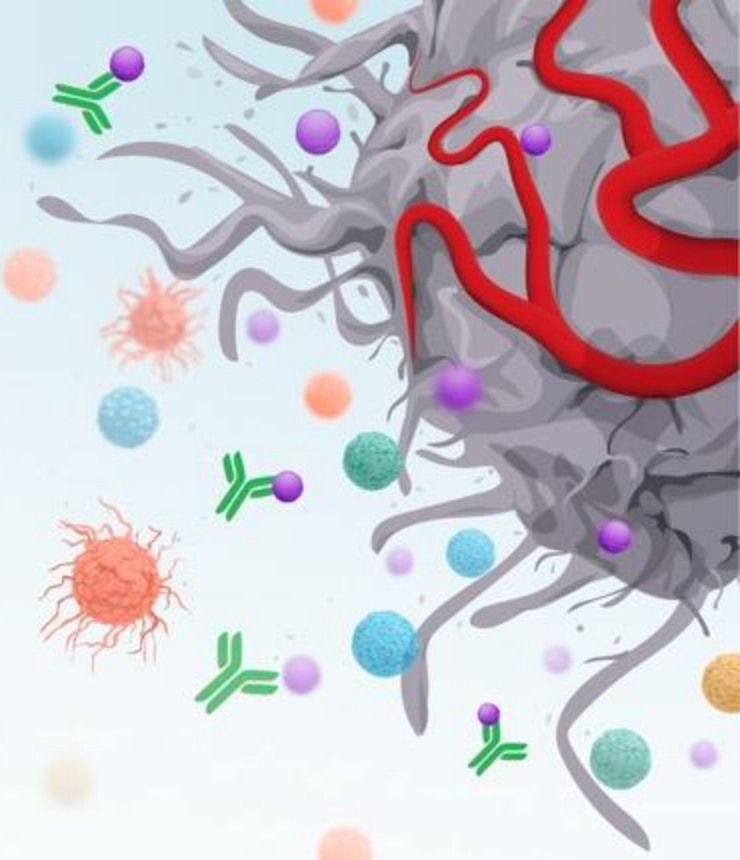
LEAP THERAPEUTICS

company presentation

November 13, 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.

Forward-looking statements are neither historical facts nor assurances of future performance. Instead, they are based only on our current beliefs, expectations and assumptions regarding the future of our business, future plans and strategies, projections, anticipated events and trends, the economy and other future conditions.

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Developing biomarker-targeted antibody therapies for cancer patients

Lead clinical stage antibody program – DKN-01 targeting DKK1

Upcoming multiple milestones from two randomized clinical trials

Biomarker strategy, focus on GI cancers

Cash runaway to Q2 2026 with $62.8M cash at September 30, 2024

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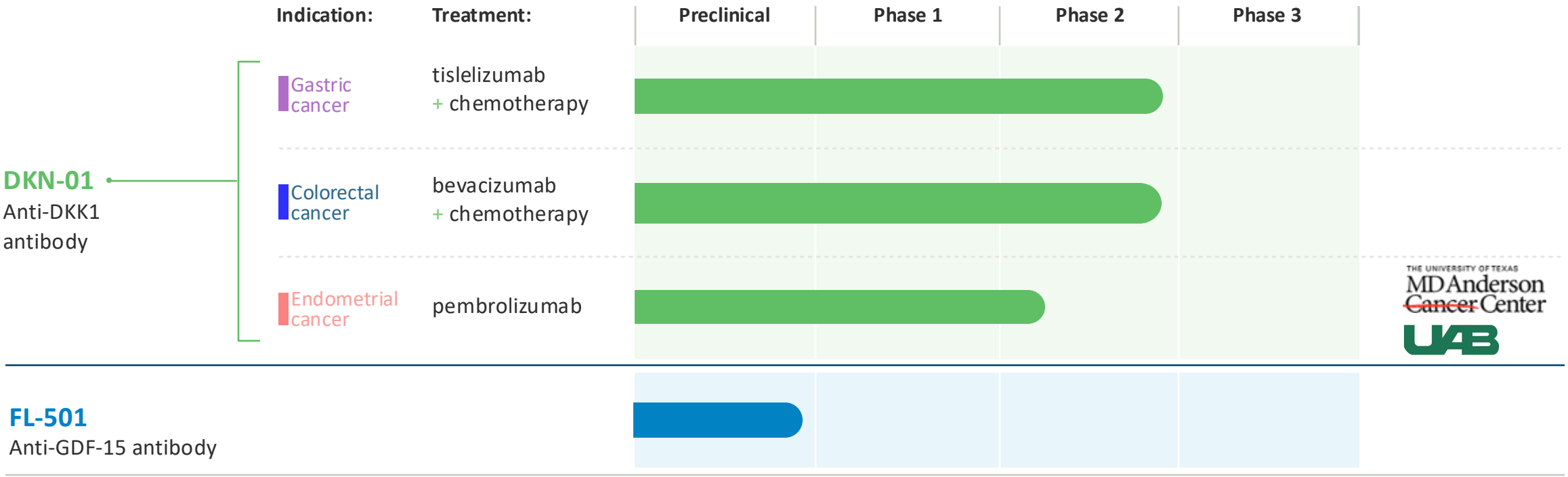
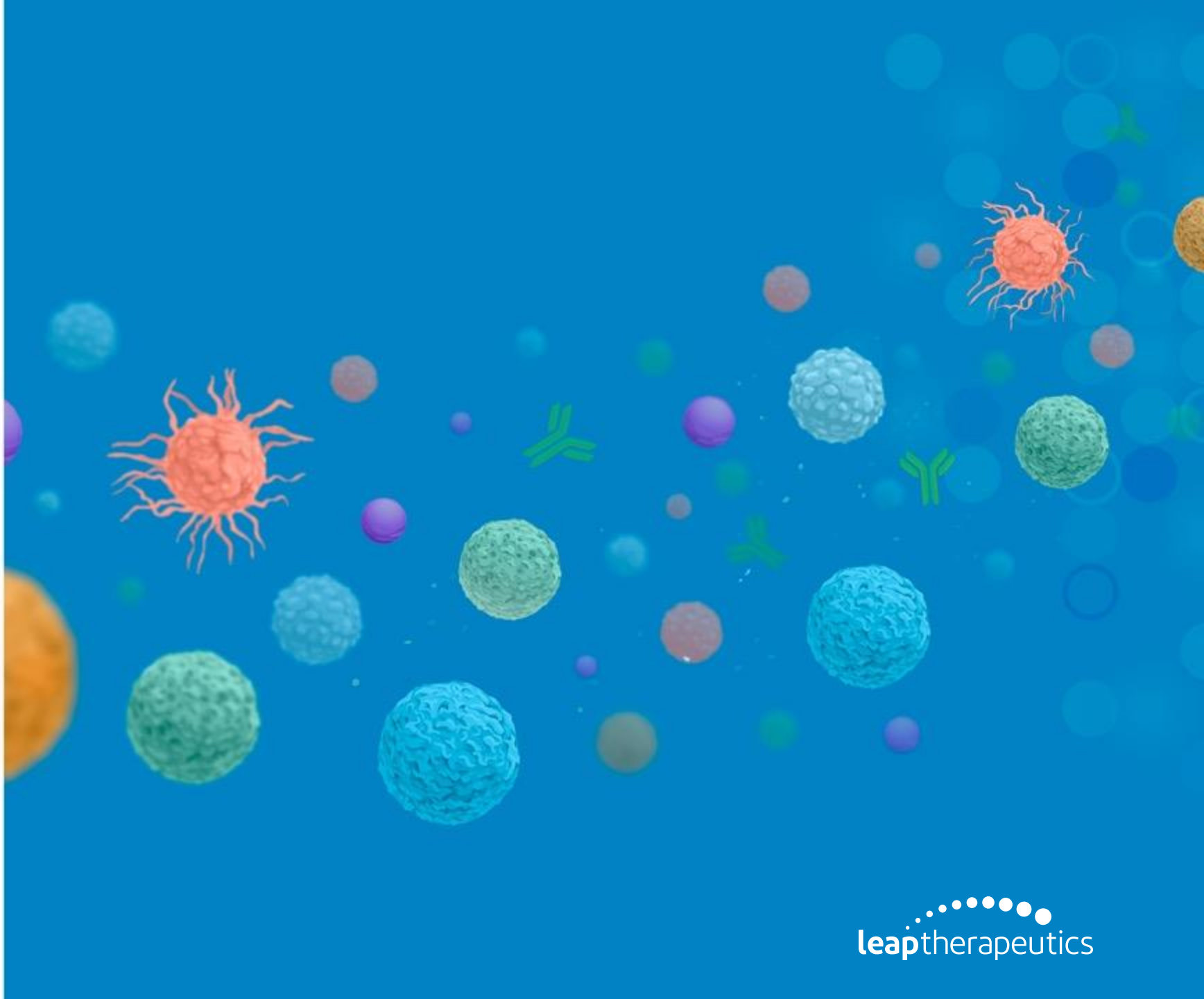
Pipeline


Indication:
Treatment:
Preclinical
Phase 1
Phase 2
Phase 3
DKN-01
Anti-DKK1 antibody
Gastric cancer
tislelizumab + chemotherapy
Colorectal cancer
bevacizumab + chemotherapy
Endometrial cancer
pembrolizumab
FL-501
Anti-GDF-15 antibody

DKN-01

Anti-DKK1 monoclonal antibody



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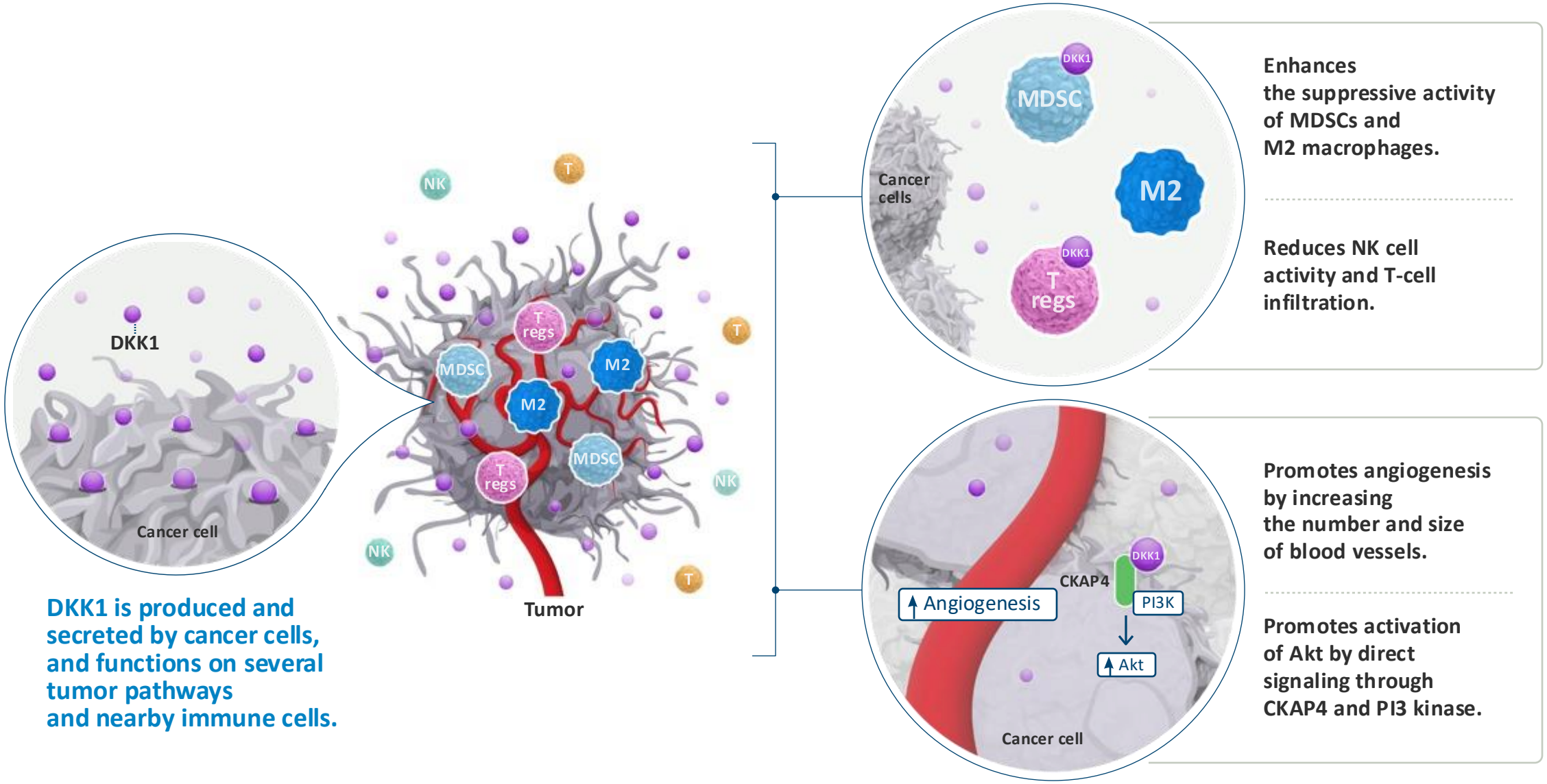
The role of DKK1 in cancer



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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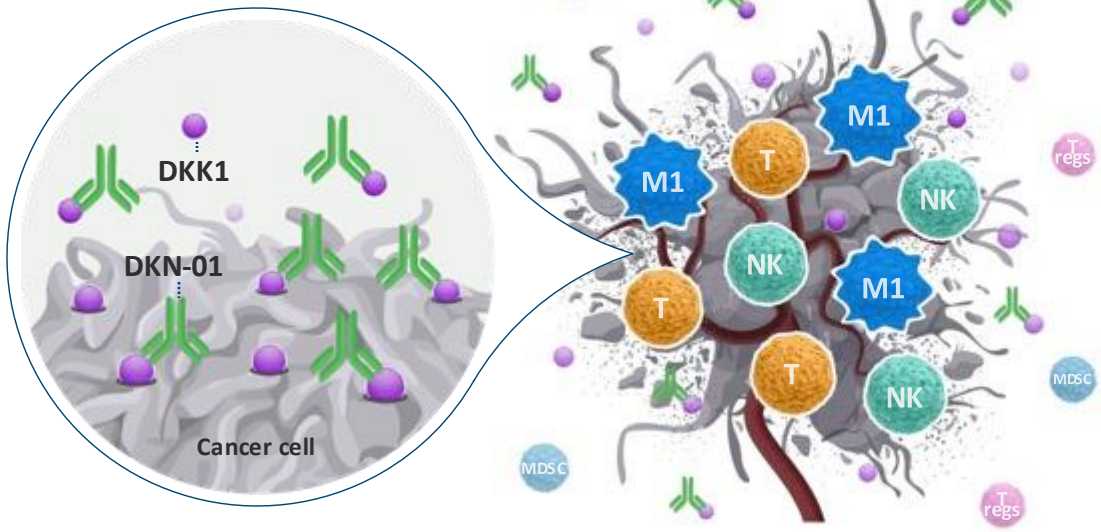
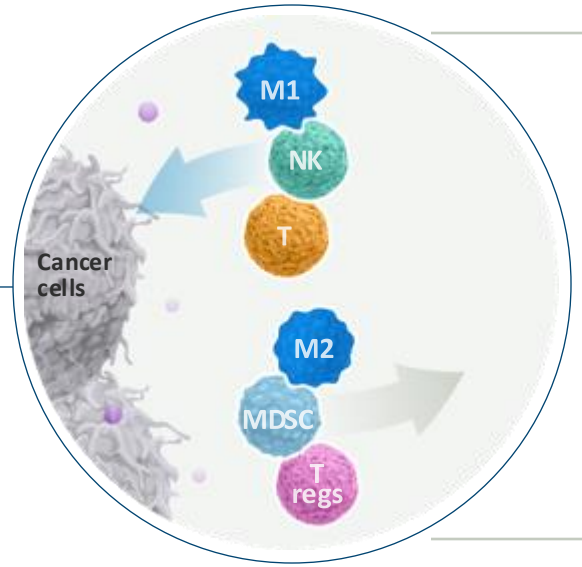
Activity of DKN-01 to treat cancer

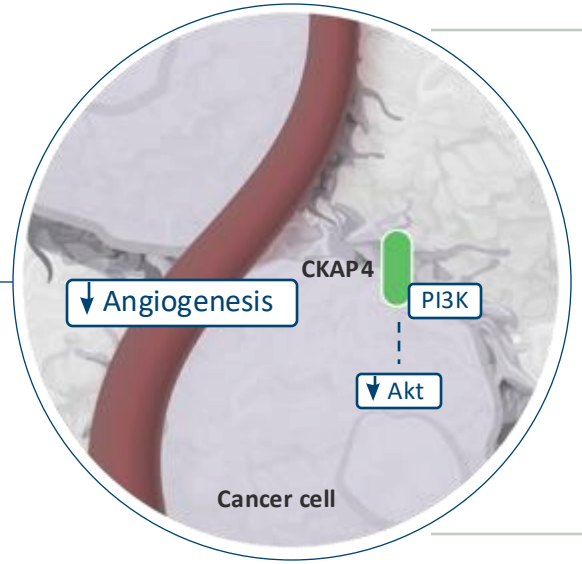


DKN-01 treatment neutralizes DKK1 and stimulates an immune mediated anti-tumor response.



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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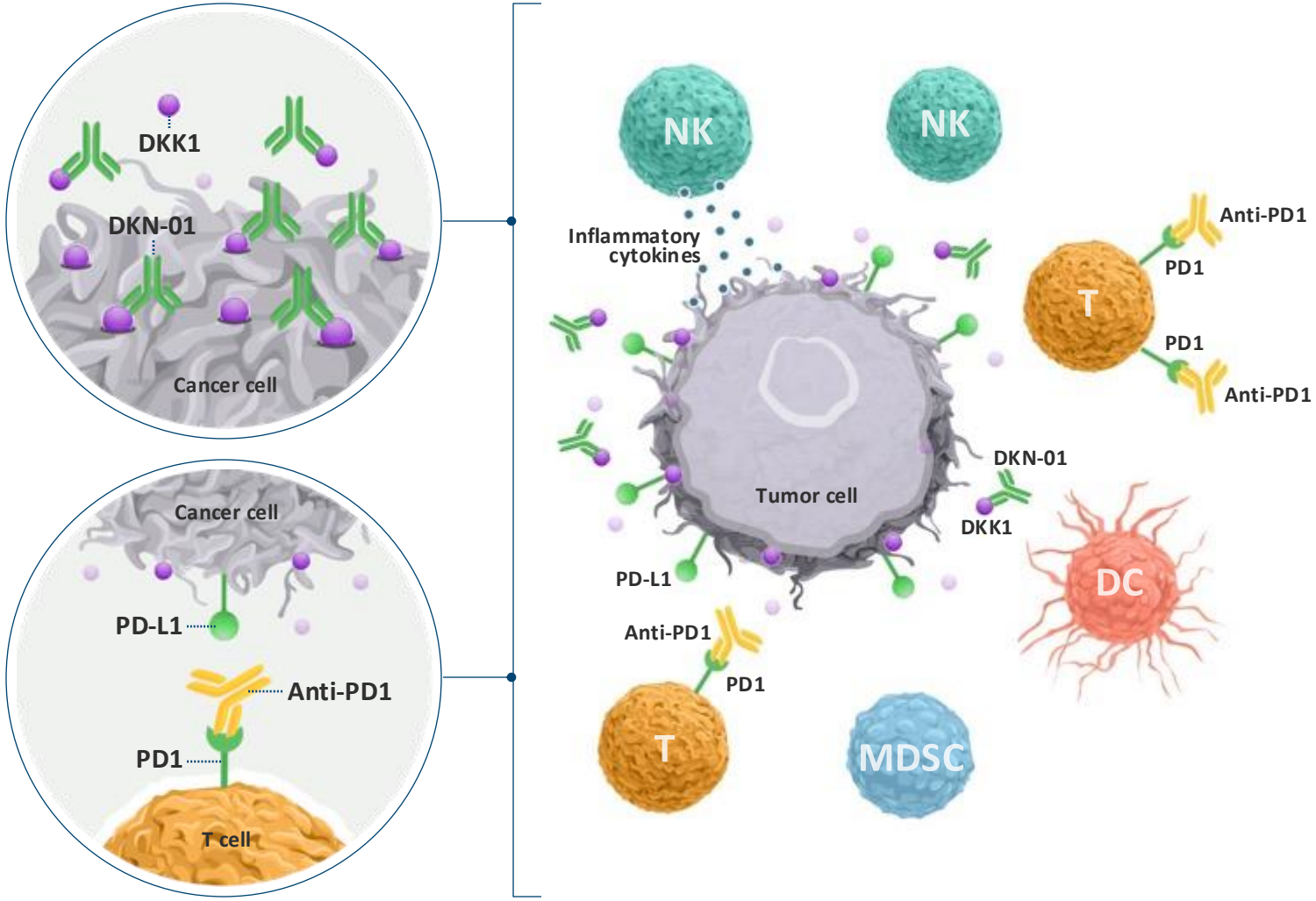
DKN-01 and anti-PD-1 cooperativity



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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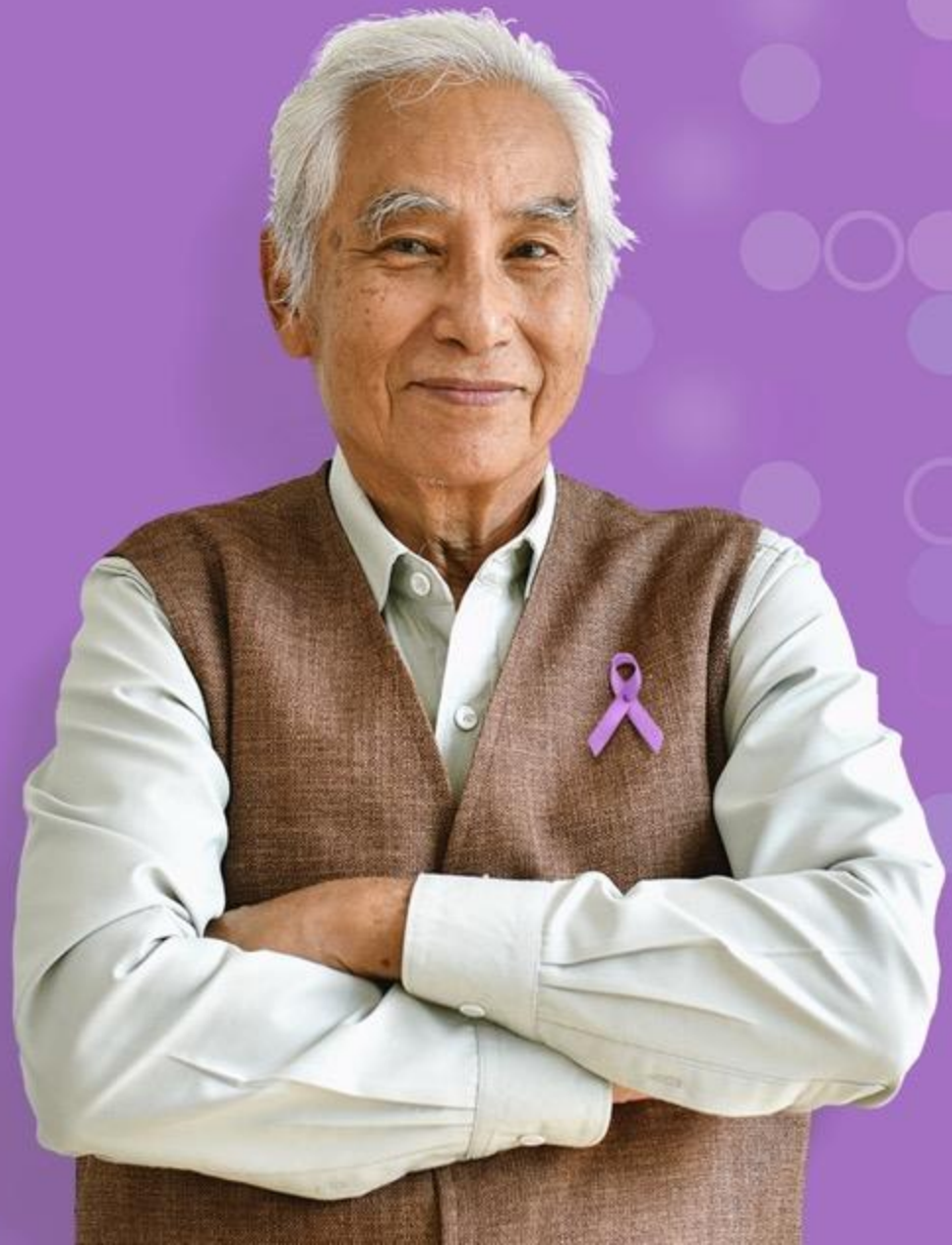
DKN-01

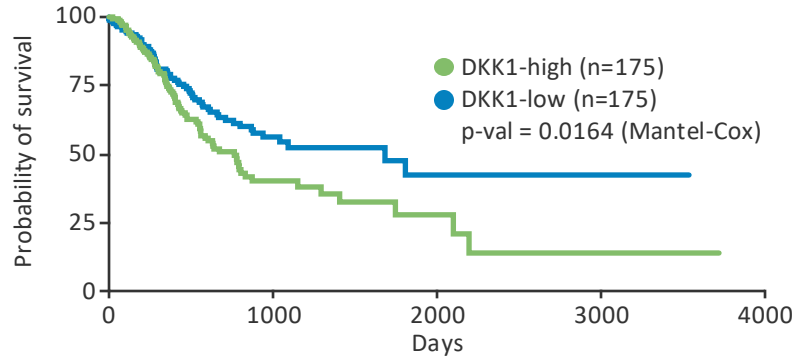
Gastric cancer development



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

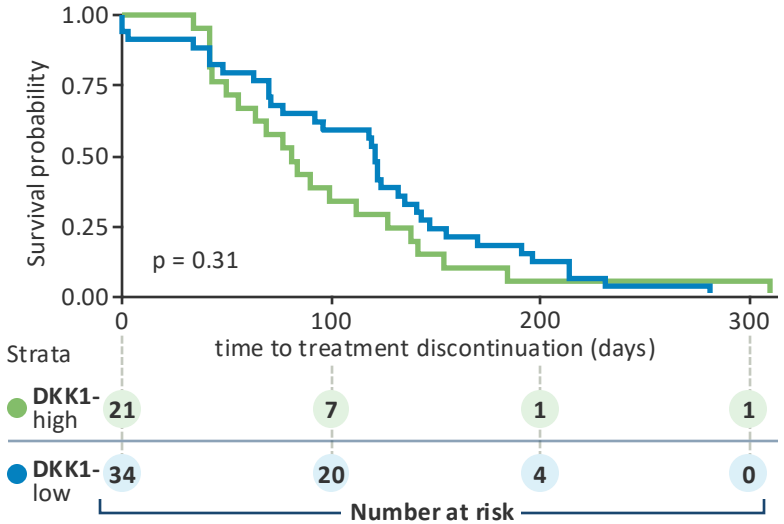
High levels of DKK1 correlate with shorter overall survival In gastric cancer

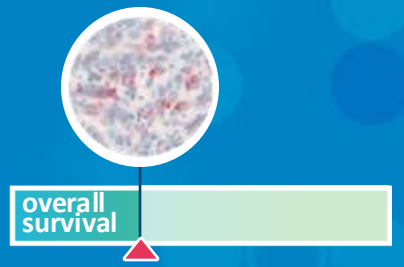
TCGA STAD dataset

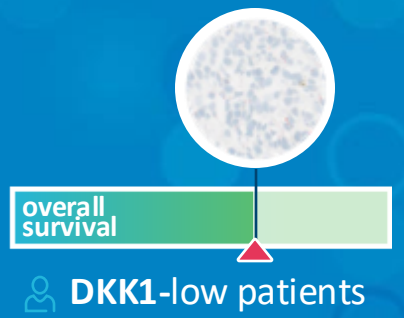


DKK1-high is associated with poor response to first-line platinum + fluoropyrimidine based therapies in GEJ/gastric cancer patients

Collaboration with Tempus







~2.5 years shorter OS in DKK1-high patients

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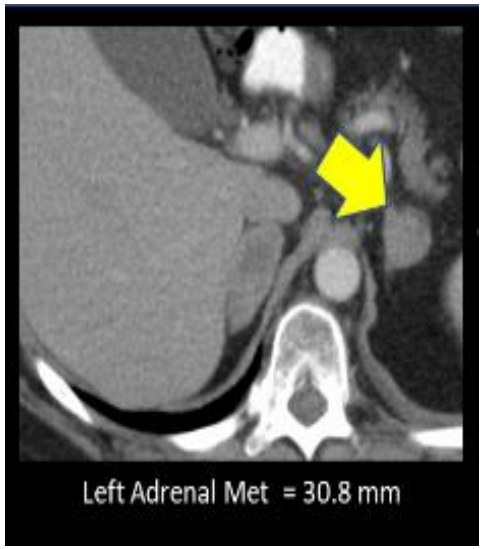
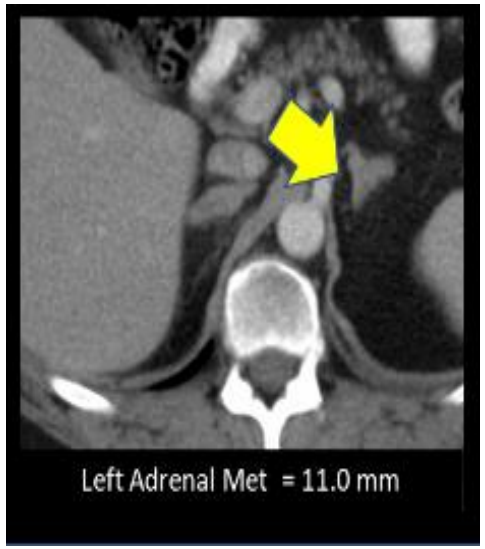
DKN-01 single agent activity in heavily pretreated esophagogastric cancer patients

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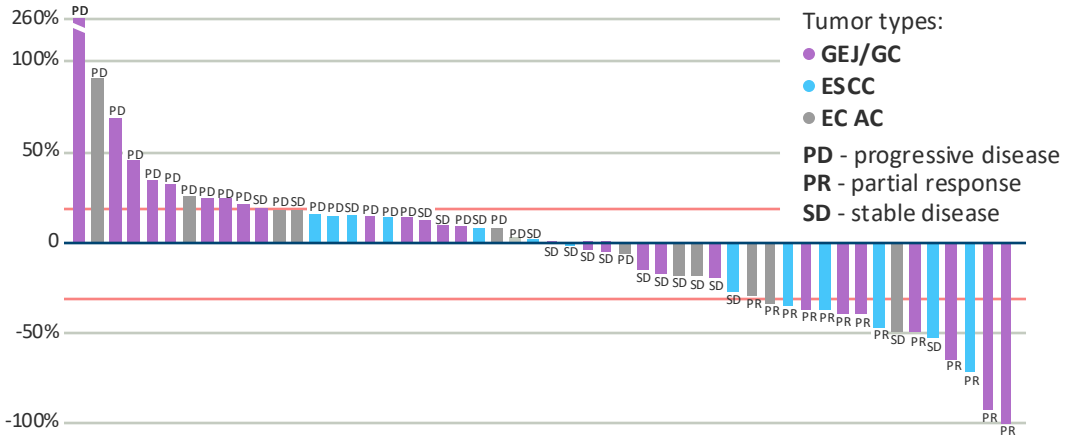
Clinical activity of DKN-01 plus paclitaxel or anti-PD-1 antibody

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%**

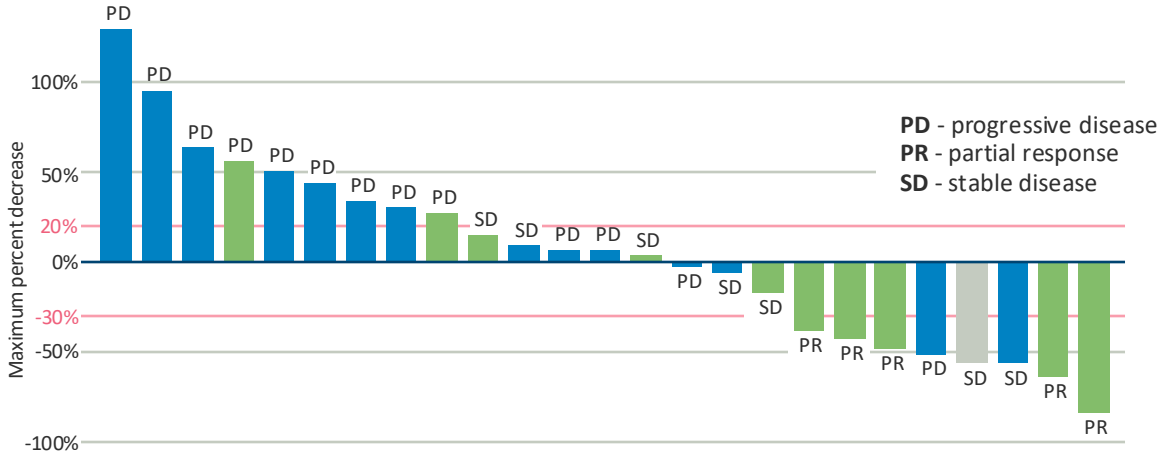
Strong broad activity in esophagogastric cancer in heavily pretreated patients

	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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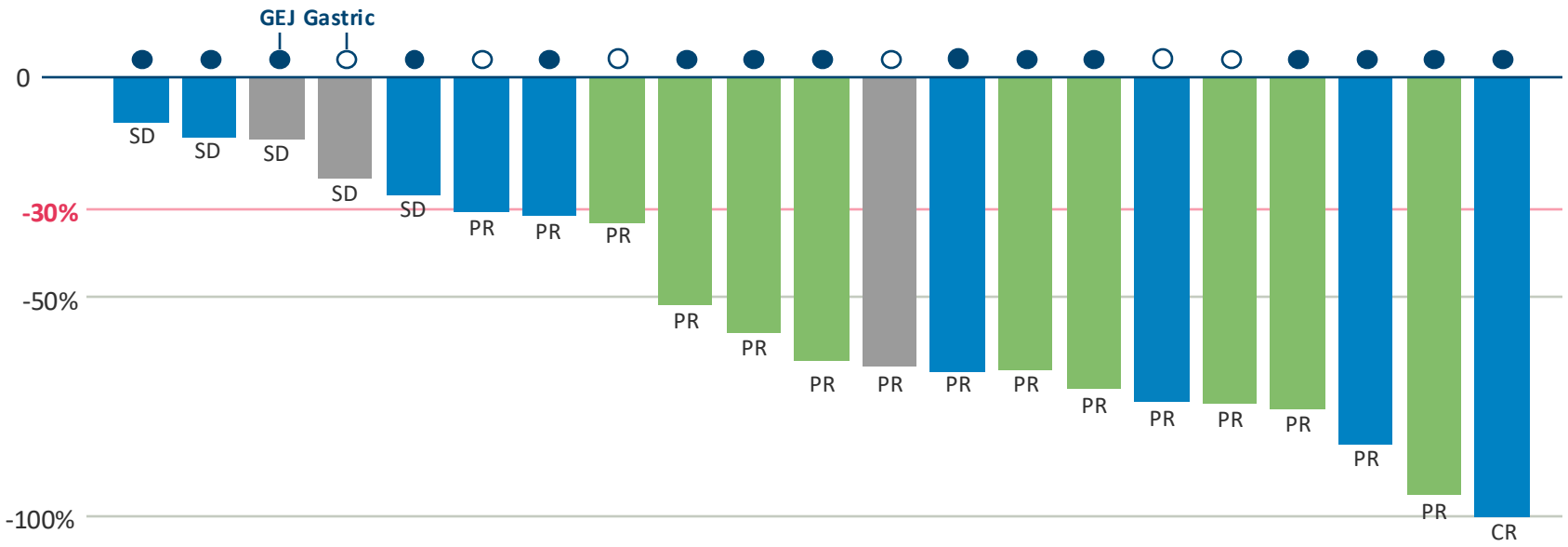
Response by DKK1 expression in first-line patients

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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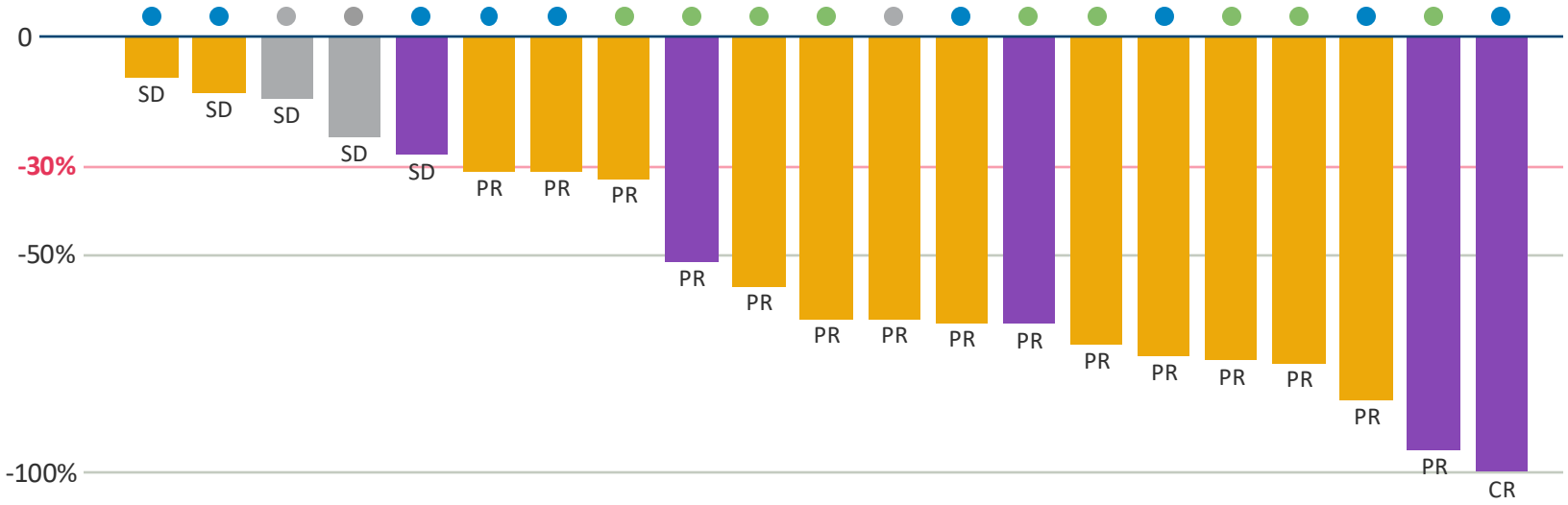
Response by PD-L1 expression

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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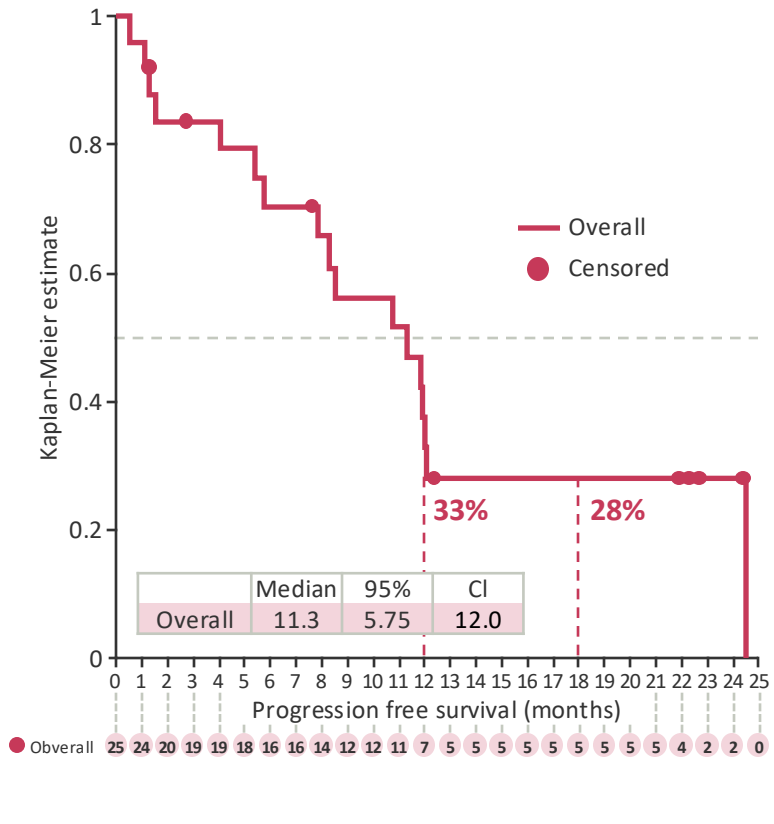
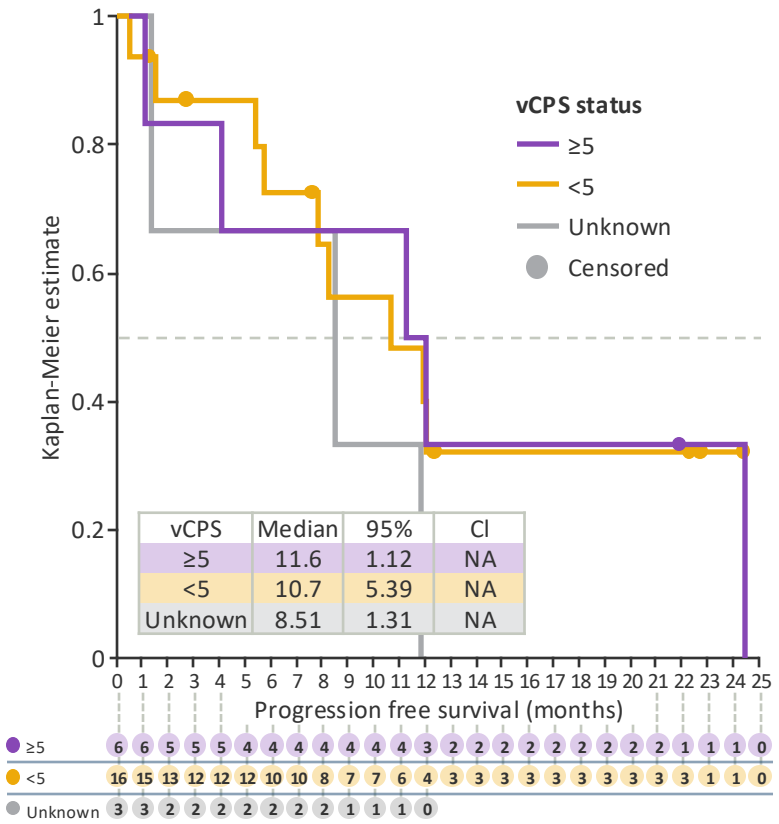
Progression-free survival

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

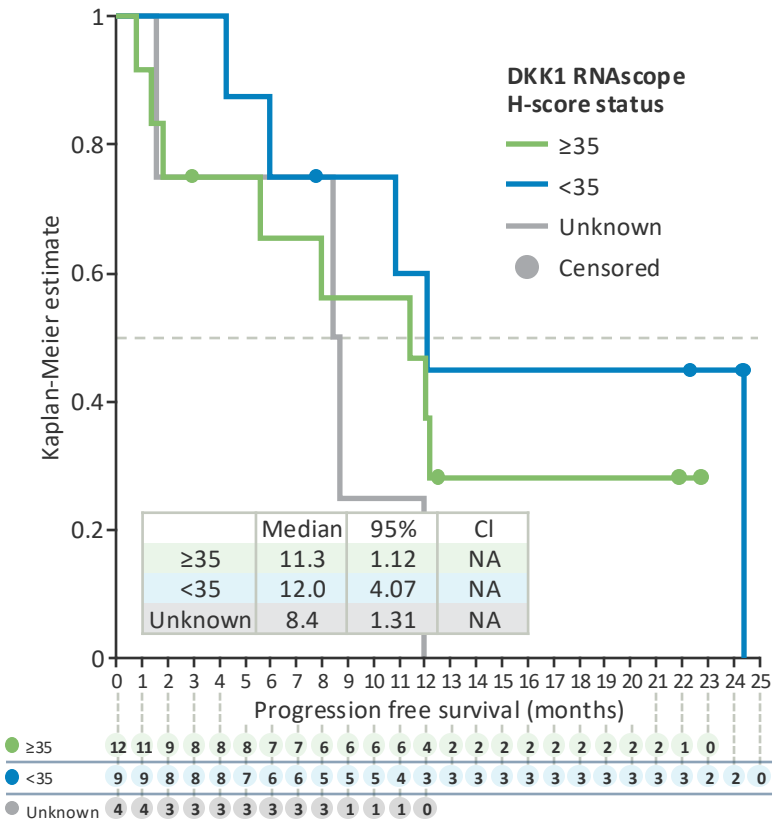
Overall Population



By PD-L1 Expression



By DKK1 Expression



DKK1-high: H-score ≥35; | DKK1-low: H-score <35 | PD-L1: Programmed Death-Ligand 1 | vCPS: Visually-Estimated Combined Positive Score
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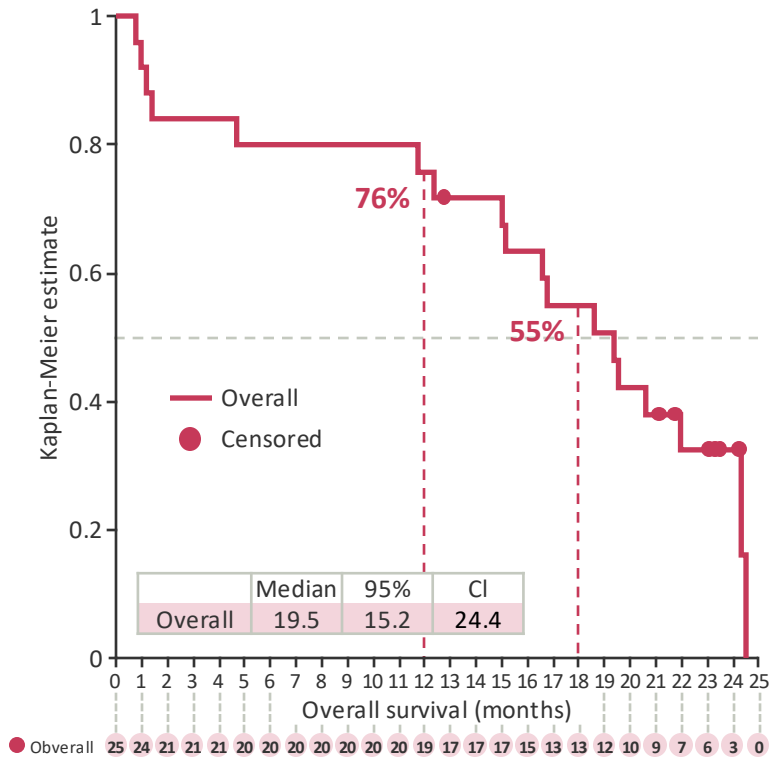
Overall survival

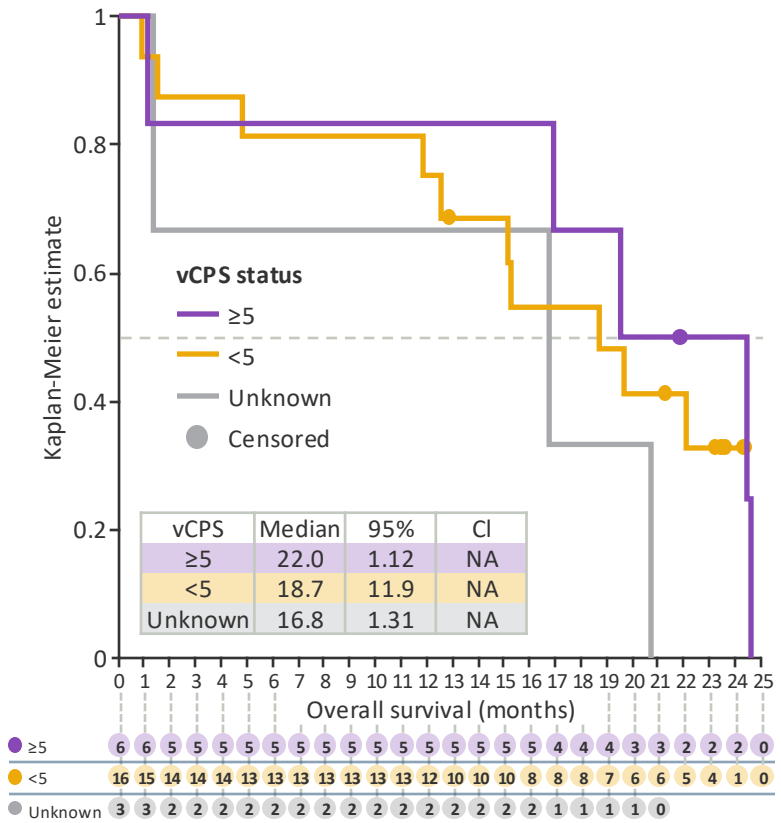
1L GEJ/GC
DKN-01
+ tislelizumab
+ chemotherapy

Overall Population



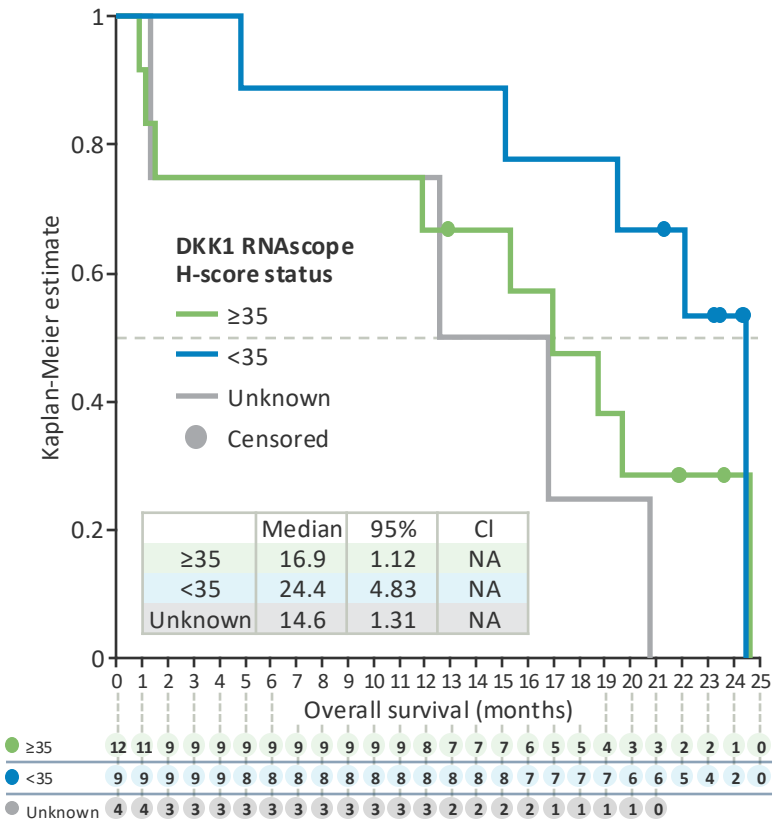
	Median	95%	CI
Overall	19.5	15.2	24.4

By PD-L1 Expression



vCPS	Median	95%	CI
≥5	22.0	1.12	NA
<5	18.7	11.9	NA
Unknown	16.8	1.31	NA

By DKK1 Expression



	Median	95%	CI
≥35	16.9	1.12	NA
<35	24.4	4.83	NA
Unknown	14.6	1.31	NA

DKK1-high: H-score ≥35; | DKK1-low: H-score <35 | PD-L1: Programmed Death-Ligand 1 | vCPS: Visually-Estimated Combined Positive Score
As presented at ASCO 2023

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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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Rationale-305 study: tislelizumab + chemotherapy in 1L GEJ/GC patients

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

	All Patients			North America & Europe			PD-L1 ↑ CPS ≥ 5		
	Tislelizumab + Chemo N= 501	Control N= 496	HR (95% CI)	Tislelizumab + Chemo N= 125	Control N= 124	HR (95% CI)	Tislelizumab + Chemo N= 274	Control N= 272	HR (95% CI)
OS months (95% CI)	15.0 (13.6, 16.5)	12.9 (12.1, 14.1)	0.80 (0.70, 0.92)	11.0 (8.4, 13.9)	10.5 (8.1, 12.1)	0.71 (0.54, 0.94)	17.2 (13.9, 21.3)	12.6 (12.0, 14.4)	0.74 (0.59, 0.94)
DOR months (95% CI)	8.6 (7.9, 11.0)	7.2 (6.0, 8.5)		7.5 (4.4, 12.0)	5.0 (3.9, 6.7)		9.0 (8.2, 19.4)	7.1 (5.7, 8.3)	
PFS months (95% CI)	6.9 (5.7, 7.2)	6.2 (5.6, 6.9)	0.78 (0.67, 0.90)	5.6 (4.4, 7.0)	5.4 (4.3, 5.9)	0.84 (0.63, 1.11)	7.2 (5.8, 8.4)	5.9 (5.6, 7.0)	0.67 (0.55, 0.83)
ORR (%) (95% CI)	47.3% (42.9%, 51.8%)	40.5% (36.2%, 45.0%)		36.0% (27.6%, 45.1%)	31.5% (23.4%, 40.4%)		50.4% (44.3%, 56.4%)	43.0% (37.1%, 49.1%)	

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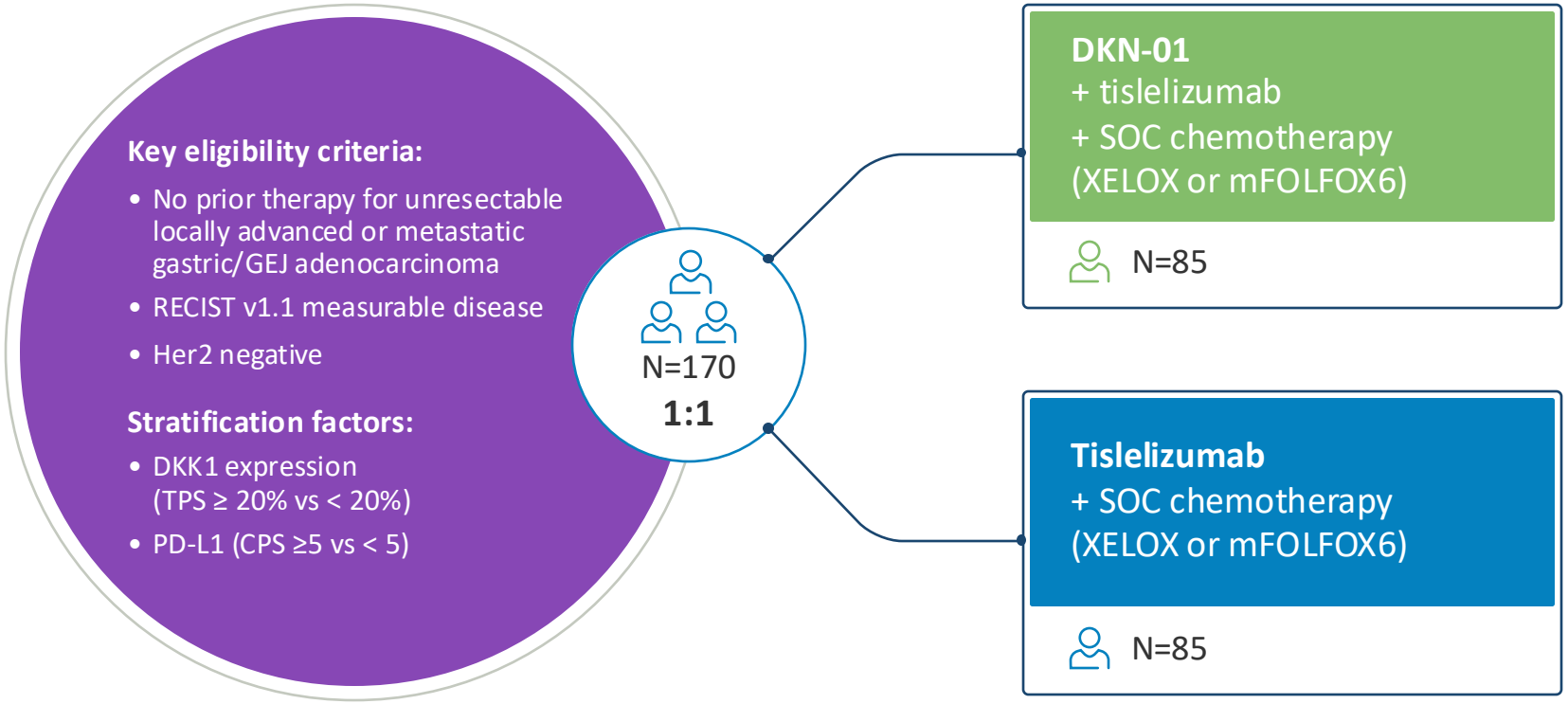
DisTinGuish Part C randomized study

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



Primary objective:
PFS, DKK-high and all

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

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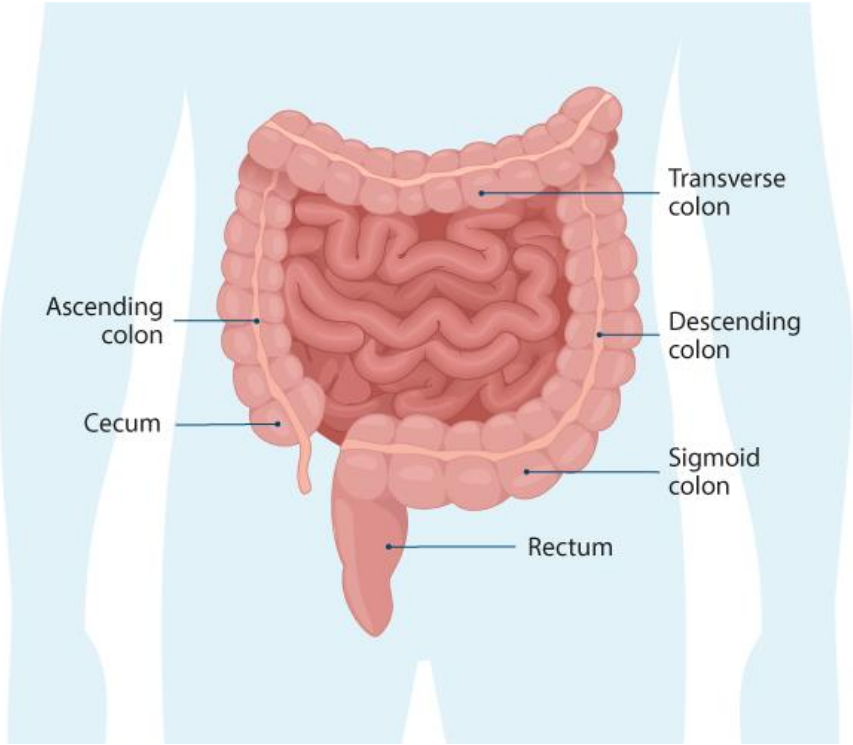
DKN-01

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
  - Consensus Molecular Subtype 2 primarily 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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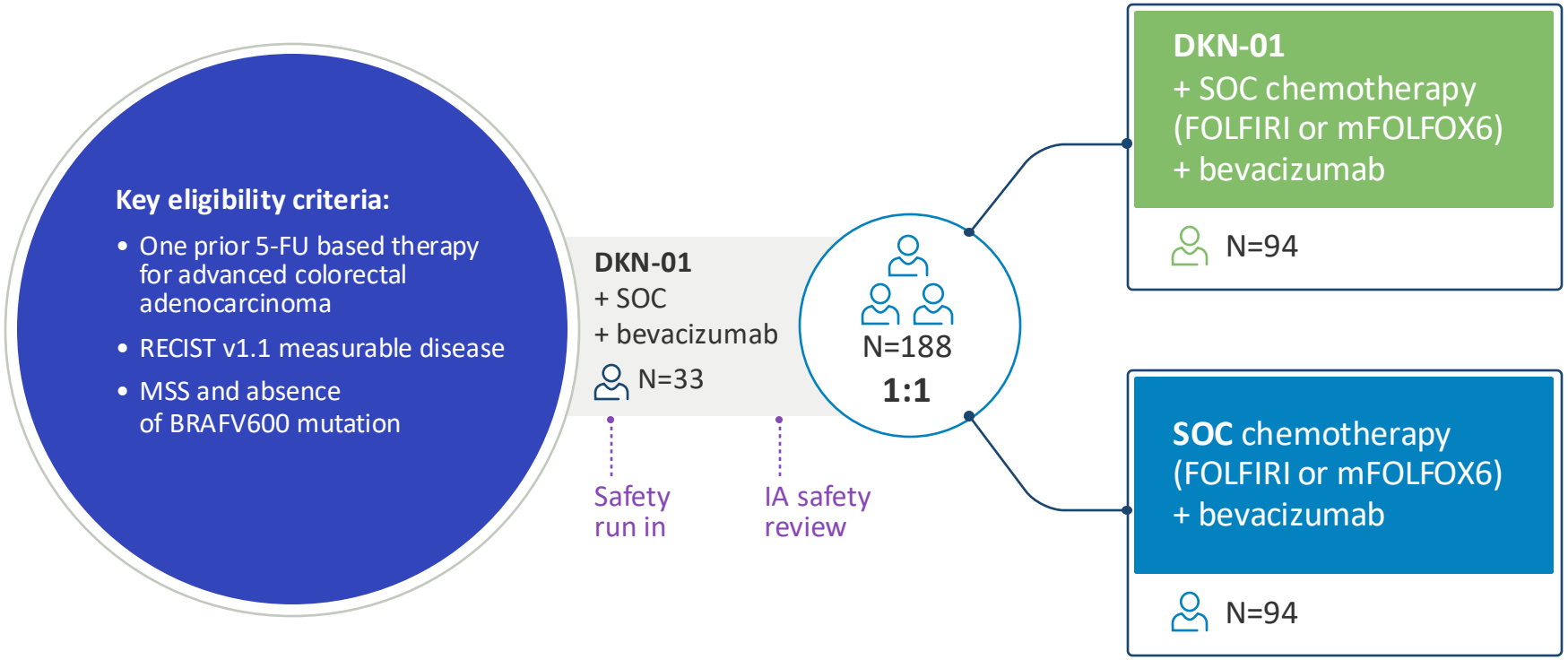
DeFianCe study design: advanced colorectal cancer

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, left-side and all
- **Secondary objectives:**
  – ORR
  – DoR
  – OS

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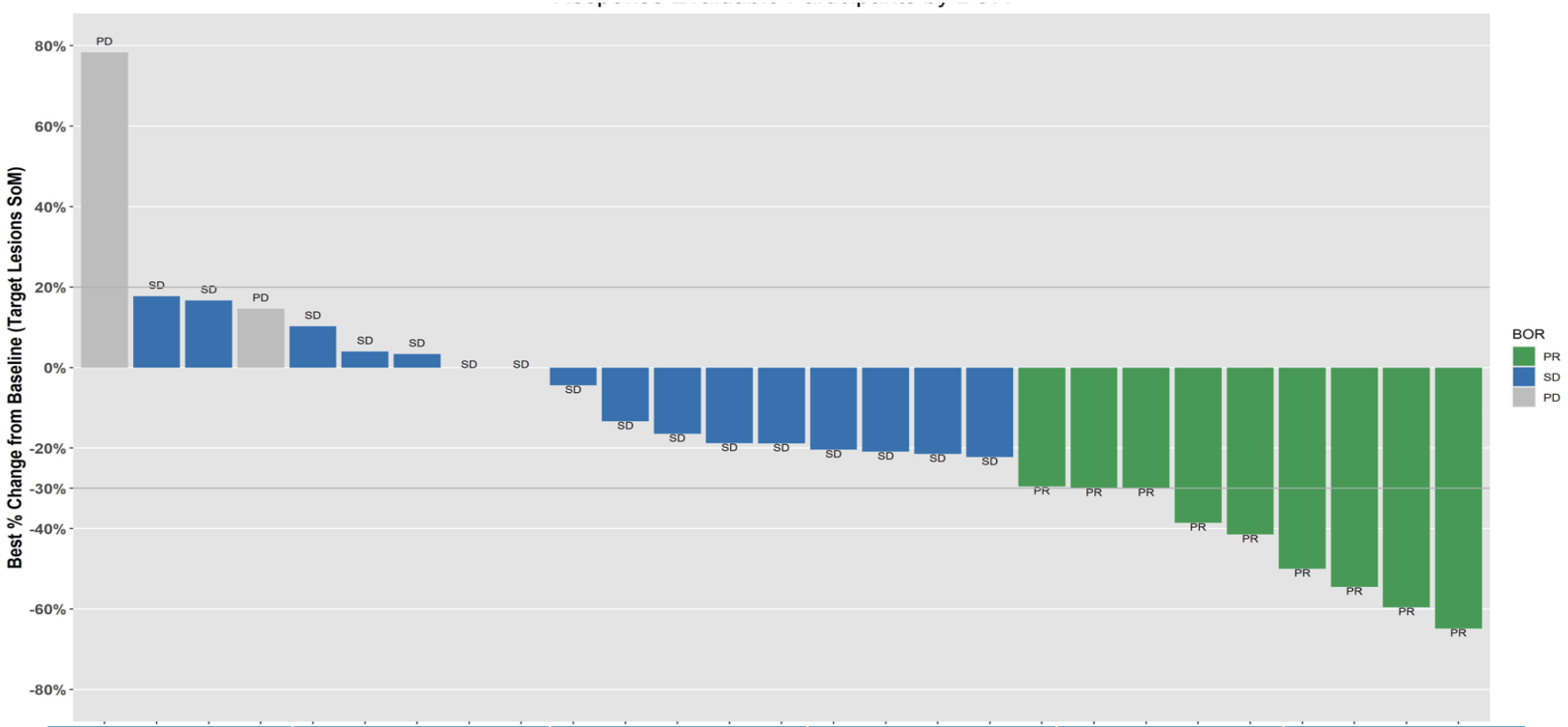
Overall response rate exceeded 20% target with high disease control rate

2L CRC
DKN-01
+ bevacizumab
+ chemotherapy



	Objective Response Rate (%)	Disease Control Rate (%)	Partial Response n (%)	Stable Disease n (%)	Progressive Disease n (%)
Overall, n=27	33	93	9 (33)	16 (59)	2 (7)

As of June 7, 2024

ORR in RE patients:
9/27 = 33%

DCR in RE patients:
25/27 = 93%

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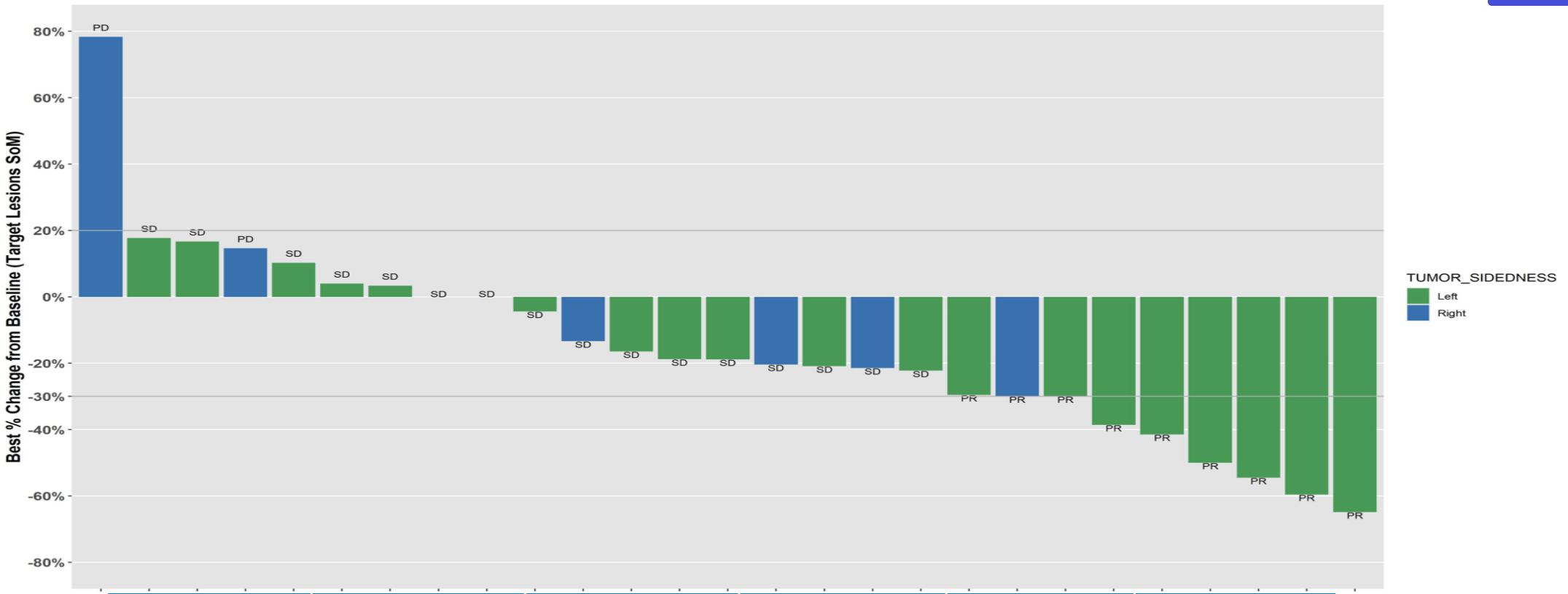
Greater activity in left-sided tumors subgroup

2L CRC
DKN-01
+ bevacizumab
+ chemotherapy



Overall, n=27	Objective Response Rate (%)	Disease Control Rate (%)	Partial Response n (%)	Stable Disease n (%)	Progressive Disease n (%)
Left (n=21)	38	100	8 (38)	13 (62)	0 (0)
Right (n=6)	17	67	1 (17)	3 (50)	2 (33)

As of June 7, 2024

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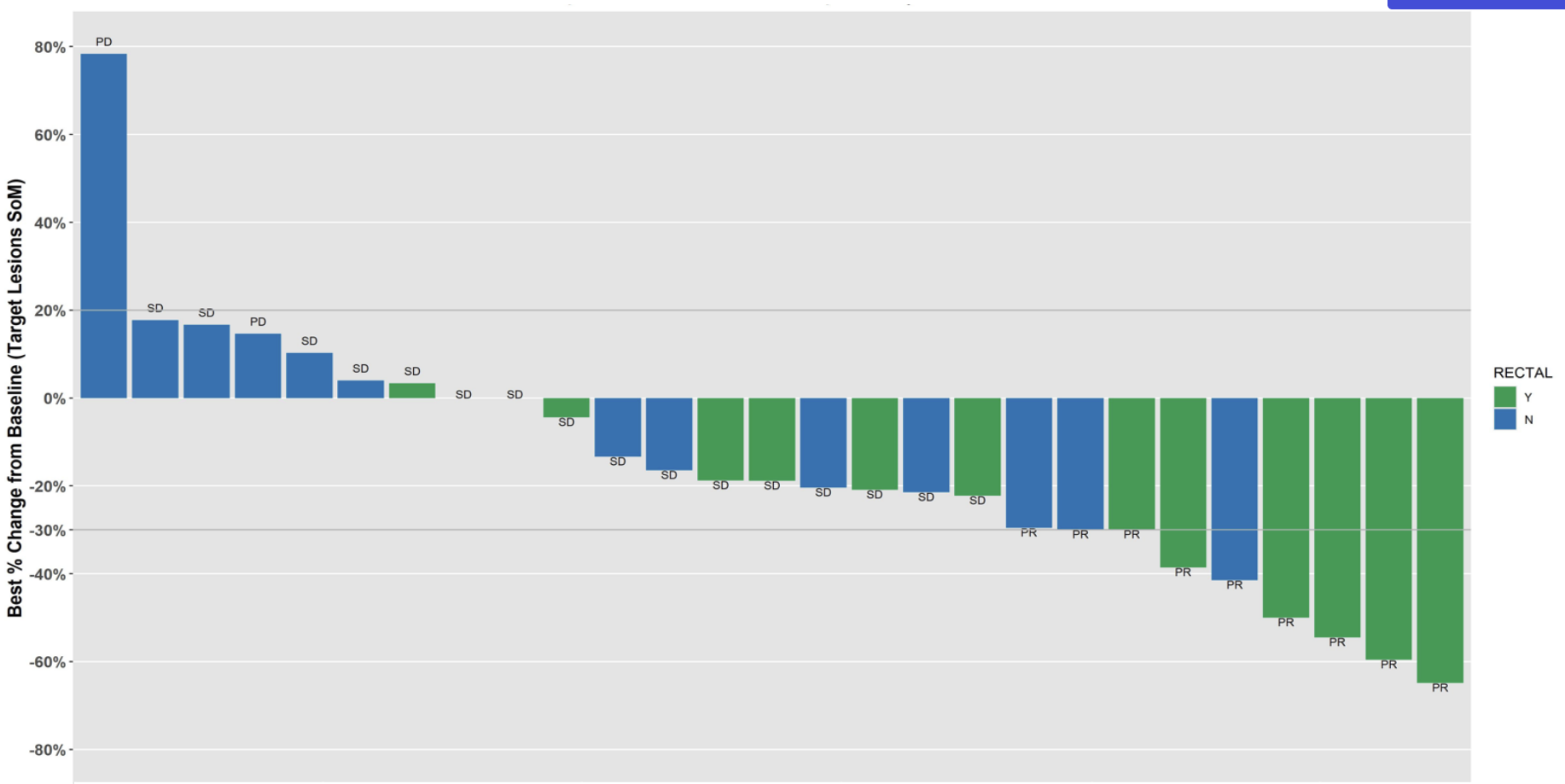
Enriched responses in rectal/rectosigmoid cancer patients

2L CRC
DKN-01
+ bevacizumab
+ chemotherapy



Overall, n=27	Objective Response Rate (%)	Disease Control Rate (%)	Partial Response n (%)	Stable Disease n (%)	Progressive Disease n (%)
Left (n=21)	38	100	8 (38)	13 (62)	0 (0)
Rectal (n=13)	**46**	**100**	**6 (46)**	**7 (54)**	**0 (0)**

As of June 7, 2024

6 of the 9 responding patients were in the rectal/rectosigmoid subgroup

ORR RE: 46%

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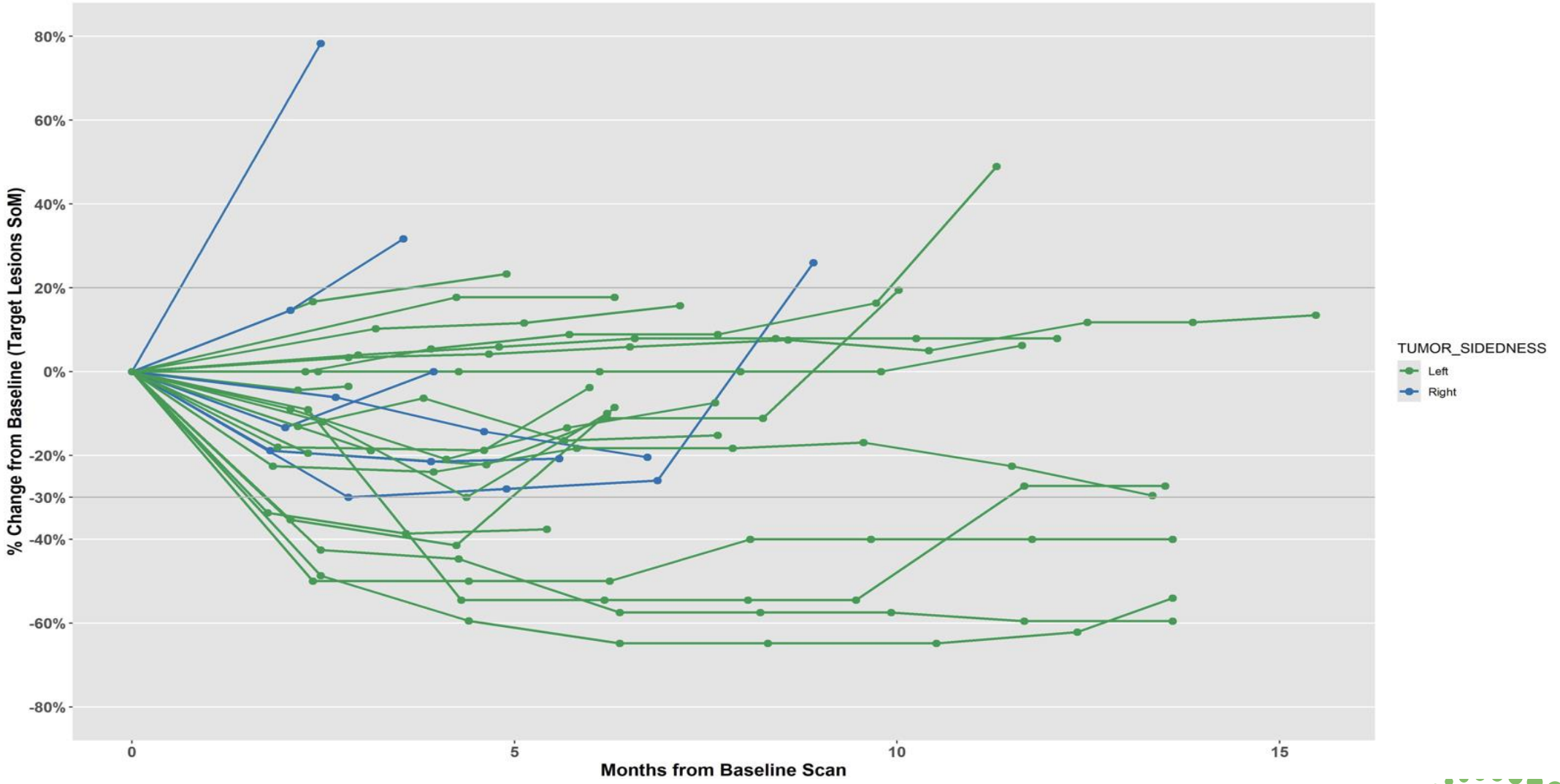
Duration of clinical benefit
Tumor sidedness subgroup



As of June 7, 2024

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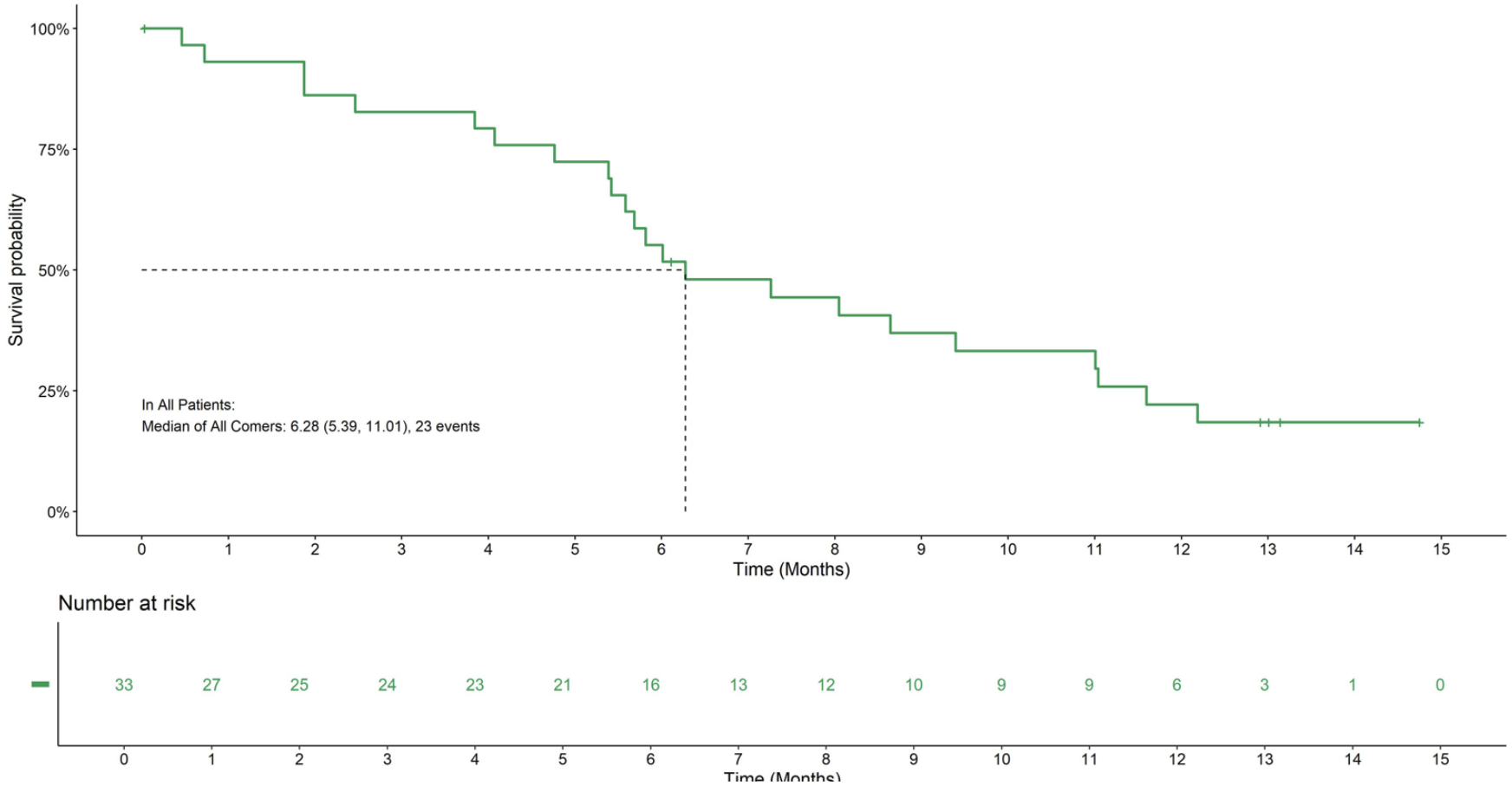
Progression-free survival

2L CRC
DKN-01
+ bevacizumab
+ chemotherapy

- Heterogeneous population included many unfavorable subgroups



Median PFS:
6.3 months

6-month PFS rate:
55.2%

As of June 7, 2024

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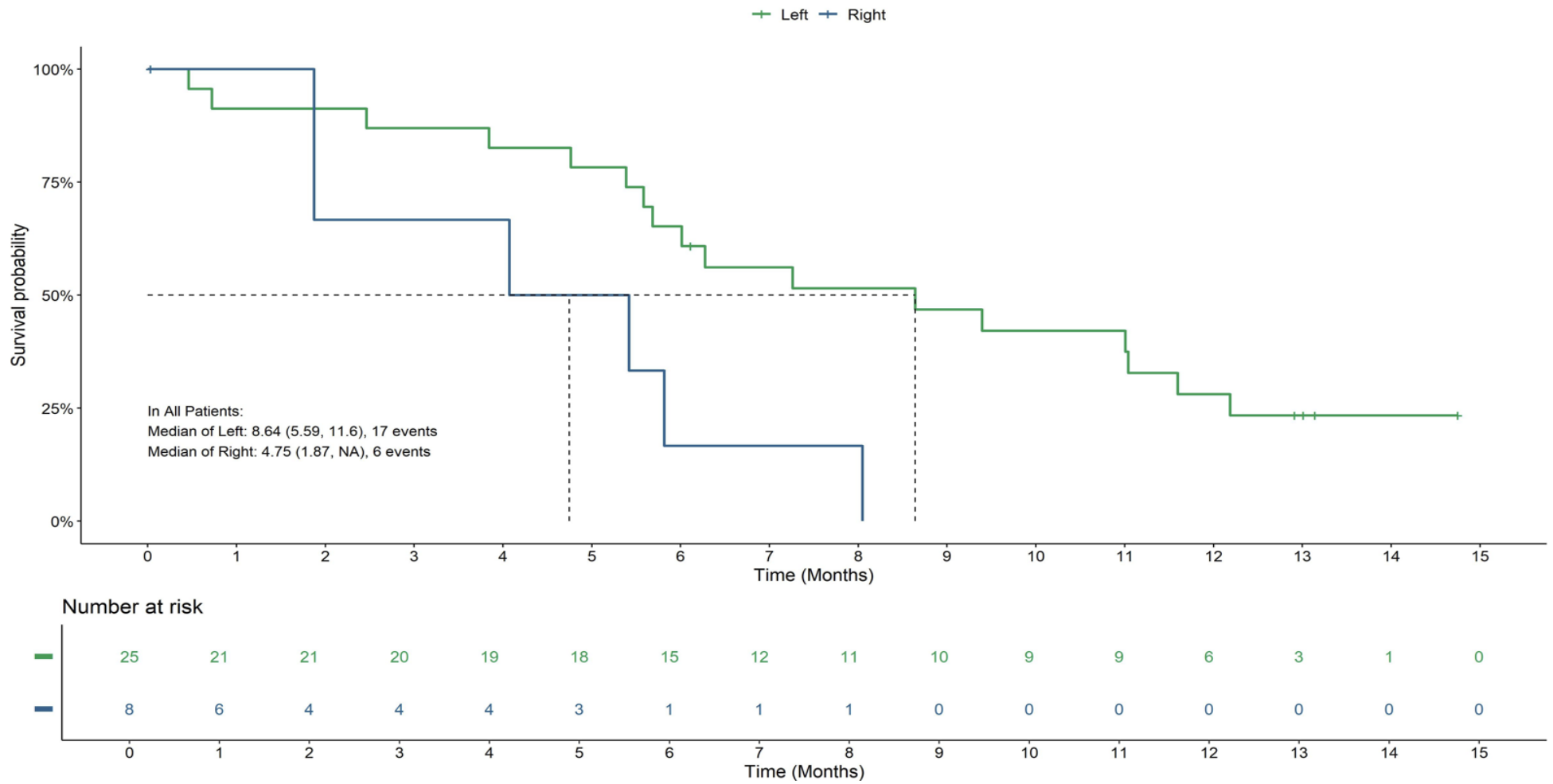
Longer progression-free survival in patients with left-sided tumors

2L CRC
DKN-01
+ bevacizumab
+ chemotherapy

- Median PFS in left-sided tumors: 8.6 months



As of June 7, 2024

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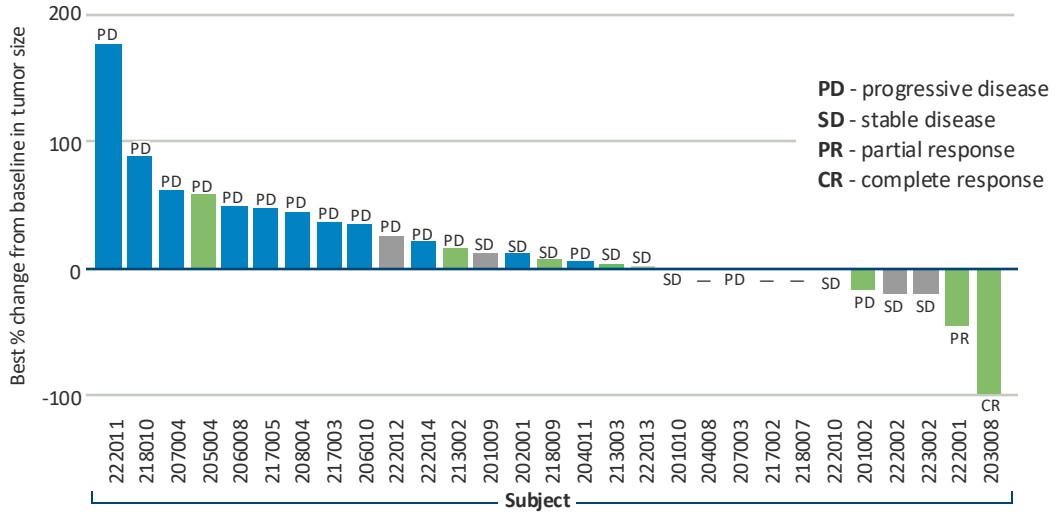
DKN-01

Endometrial cancer development

DKN-01 monotherapy - overall response by DKK1 tumoral expression

2L+ EEC
DKN-01
monotherapy

Overall response by DKK1 tumoral expression



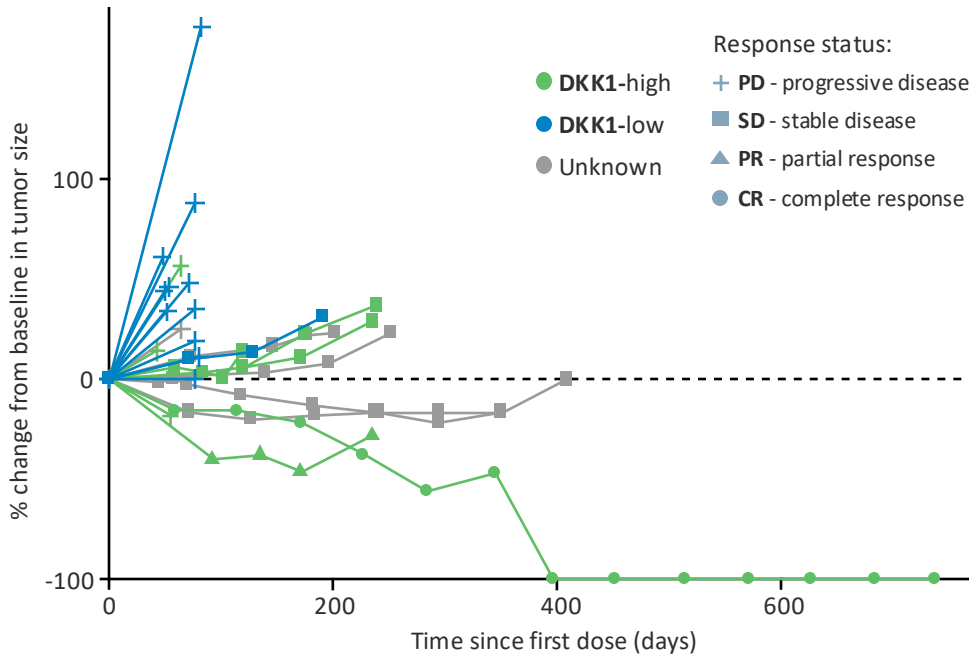
Status	Total	CR	PR	SD	PD	NE	ORR	DCR
DKK1-high (≥18)*	n=8	1	1	3	3	0	25%	63%
DKK1-low (<18)	n=15	0	0	1	11	3	0%	7%
Unknown	n=6	0	0	5	1	0	0%	83%

*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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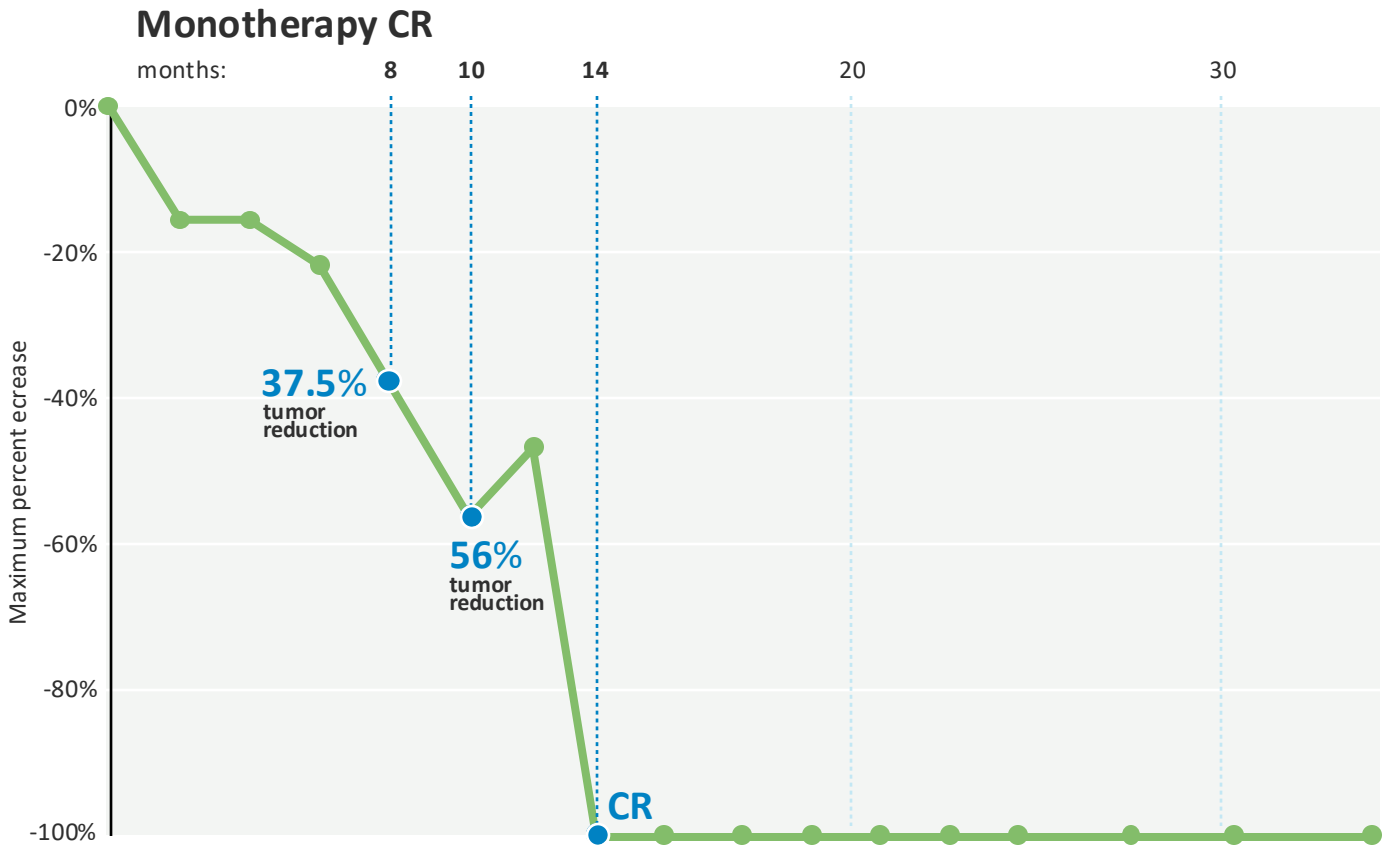
Complete response in endometrial cancer patient on DKN-01 monotherapy

2L+ EEC
DKN-01
monotherapy

- **Patient:** 60 yo female with recurrent endometrial cancer
- **Prior treatment:** radiation and chemotherapy poorly tolerated (neuropathy and thrombocytopenia)
- **Baseline disease characteristics:** MSI-H, TMB: 46.65
- **Genetics:** ARID1A, PIK3CA; DKK1-high

Treatment:
DKN-01 monotherapy

Enrolled in July 2018



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DKN-01 plus pembrolizumab endometrial cancer study

2-3L EEC
DKN-01
+ pembrolizumab

Key eligibility criteria:

- ≥ 18 years of age
- Pathology-confirmed advanced or recurrent endometrial carcinoma
- Non-endometrioid histologies included with a Wnt activating mutation
- No more than 2 prior chemotherapy regimens
- No prior PD-1 or PD-L1 therapy
- No known dMMR or MSI-H tumors

Stage I DKK1-high
Pembrolizumab 200mg IV Day 1
DKN-01 300mg IV Day 1 and 15
Cycle 21 days
N=15

Stage II*
N=15

Stage I DKK1-low
Pembrolizumab 200mg IV Day 1
DKN-01 300mg IV Day 1 and 15
Cycle 21 days
N=15

Stage II*
N=15

Primary objective:
Objective response rate (ORR)

Secondary objectives:
Clinical benefit, PFS, OS, DOR

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

* Move to Stage II based on ORR in Stage I

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
UAB
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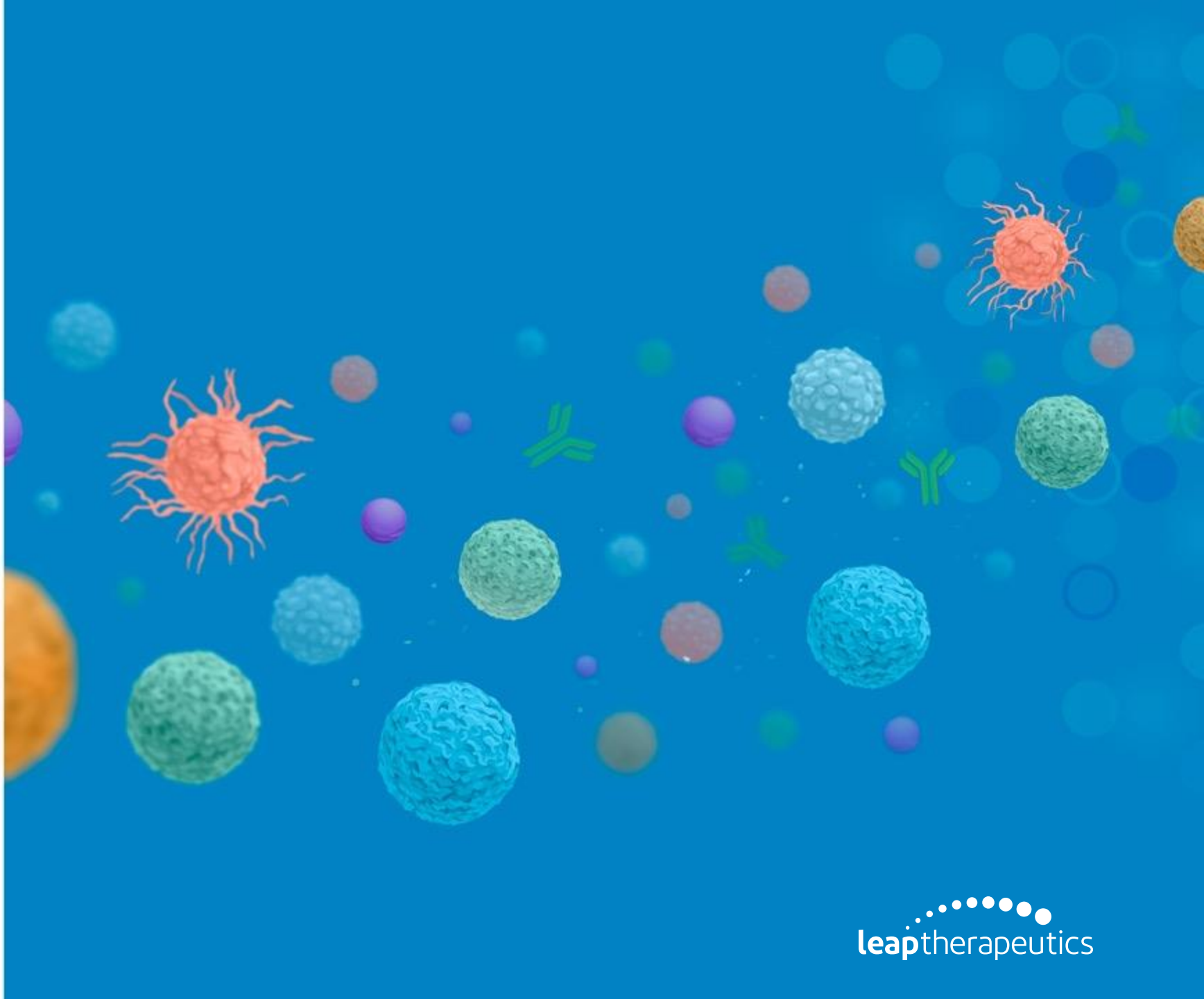
FL-501

Anti-GDF-15 monoclonal antibody



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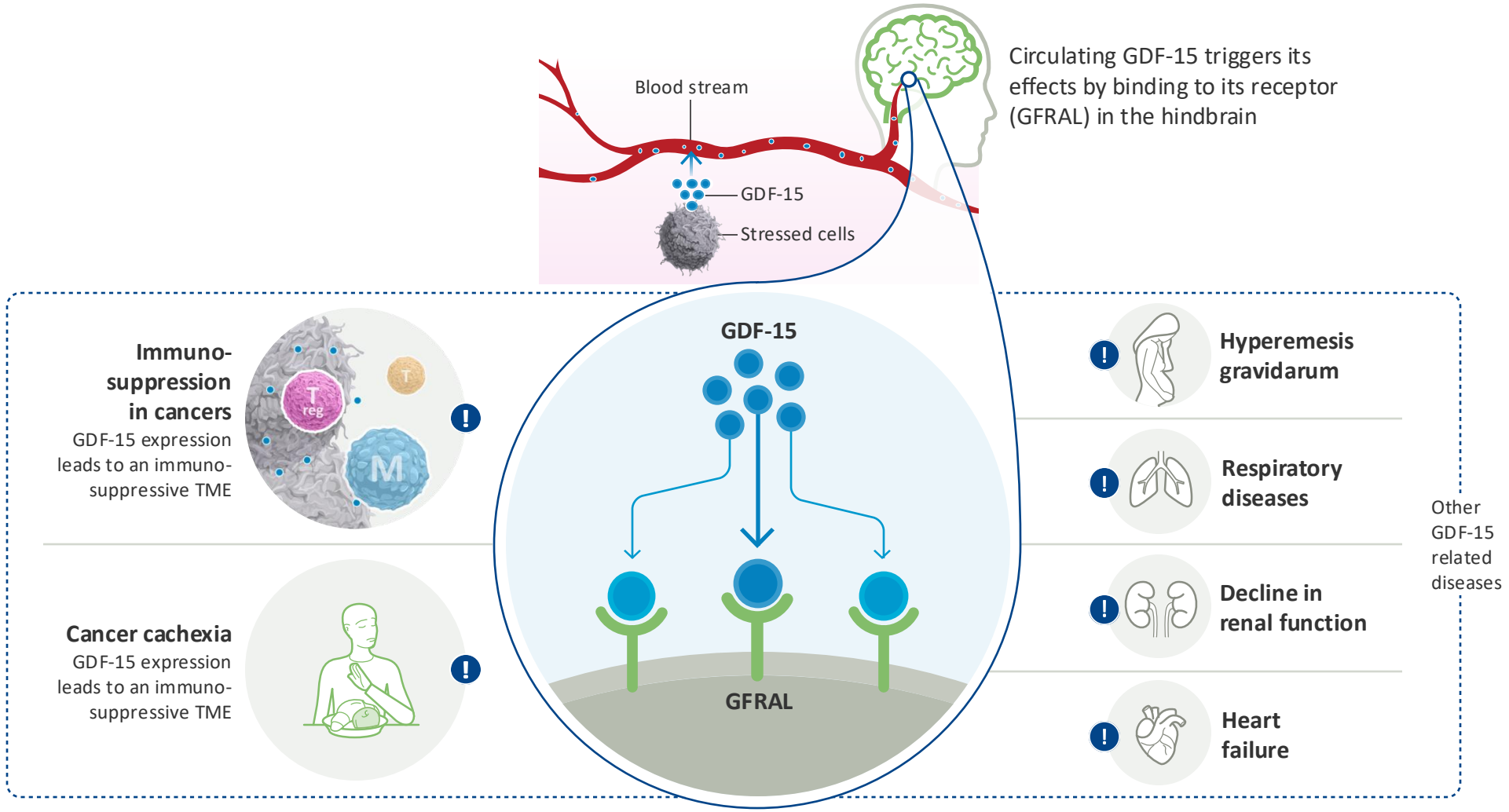
The role of GDF-15 in cachexia and cancer



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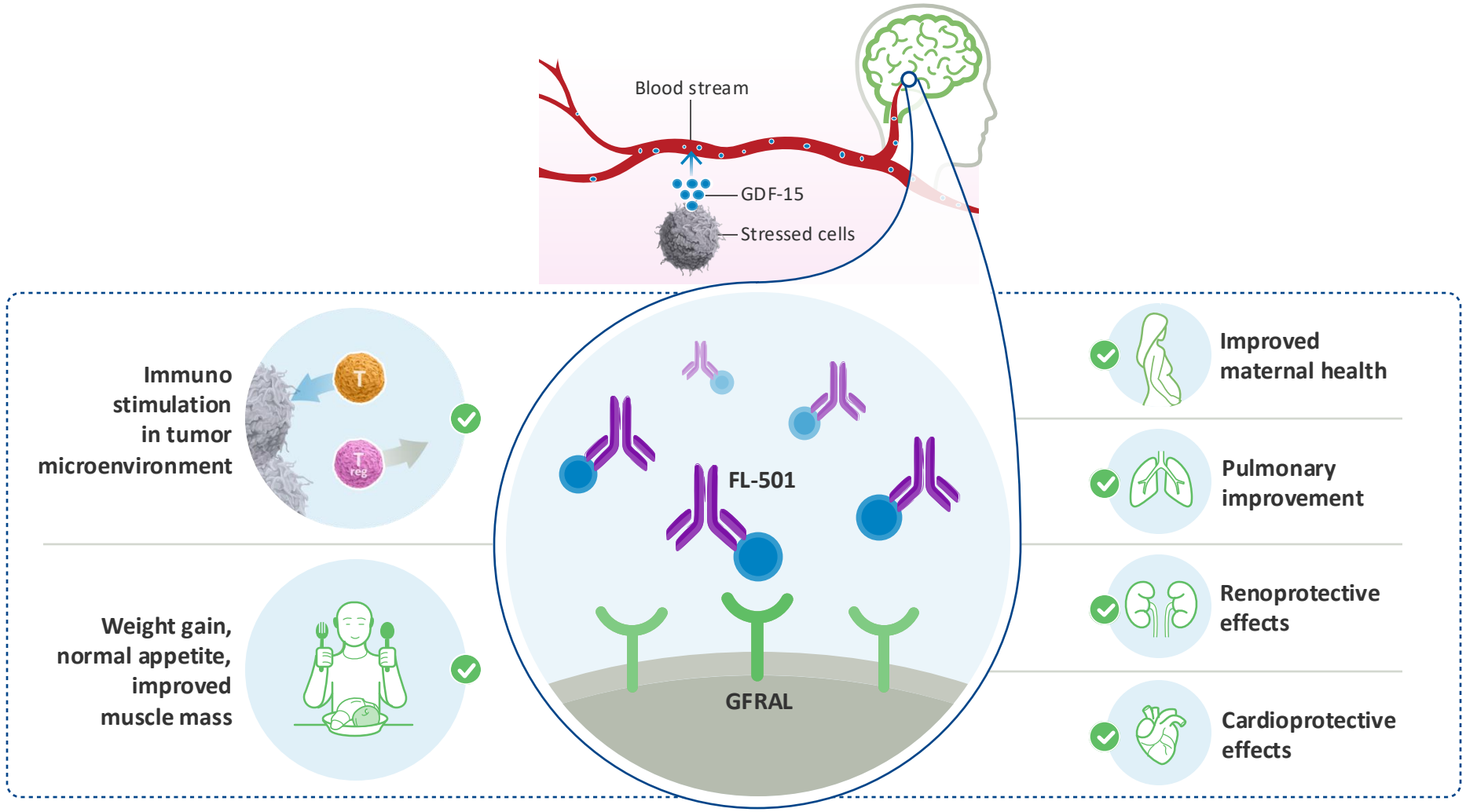
FL-501 mechanism of action



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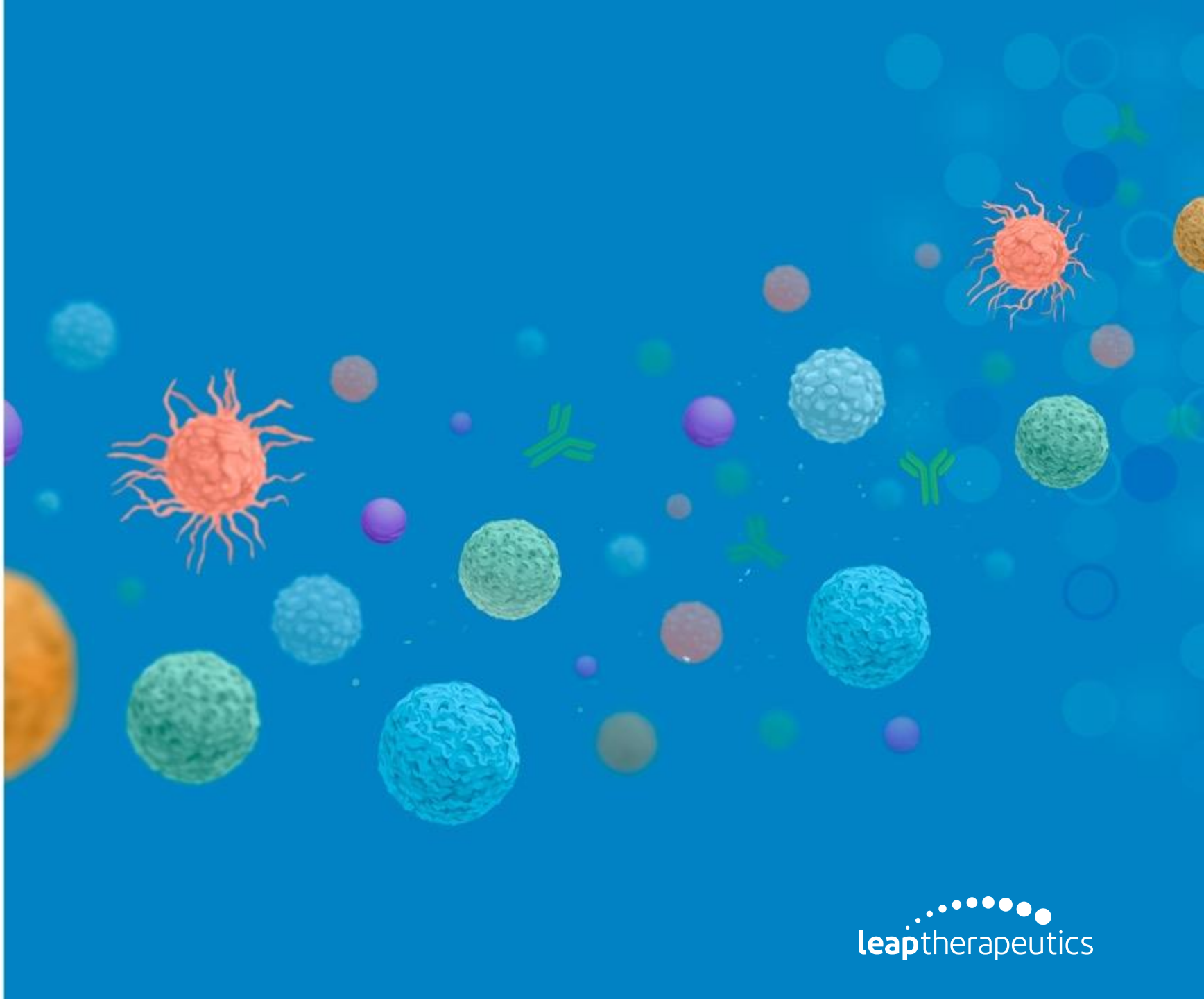
CORPORATE



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Management team

Christopher Mirabelli, PhD
Chairman of the board

Gus Lawlor
Chief operating officer

Cyndi Sirard, MD
Chief medical officer

Mark O'Mahony
Chief manufacturing officer

Douglas Onsi
President & chief executive officer

Walter Newman, PhD
Senior research fellow

Jason Baum, PhD
Chief scientific officer

Christine Granfield
Vice president, head of regulatory affairs and quality

DKN-01 clinical milestones 2024-2025

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