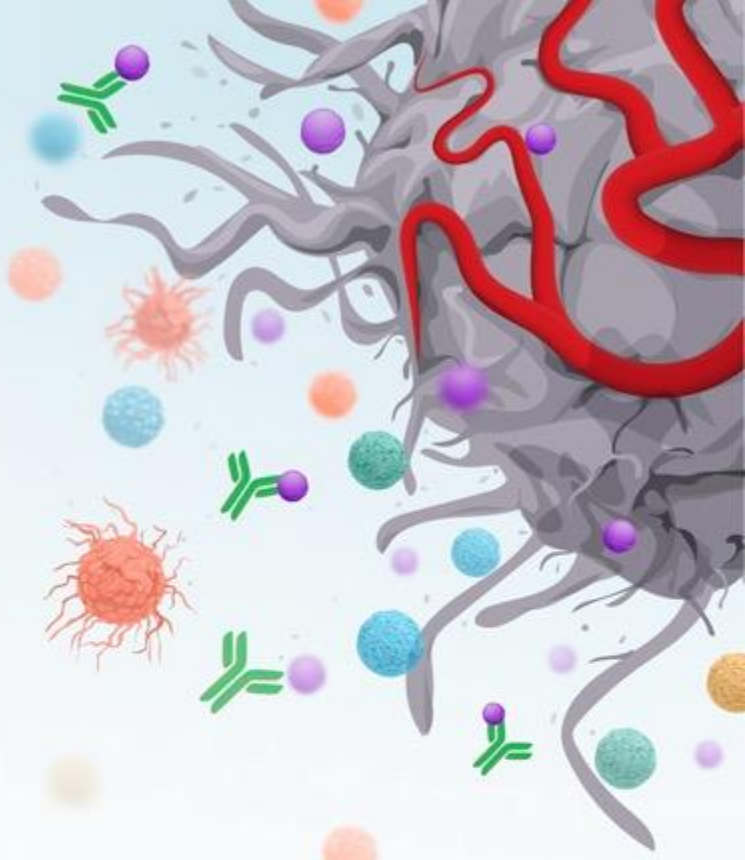
LEAP THERAPEUTICS

company presentation

January 15, 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.

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.

Because forward-looking statements relate to the future, they are subject to inherent uncertainties, risks and changes in circumstances that are difficult to predict and many of which are outside of our control. We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements we make. These and other risk factors are listed from time to time in reports filed with the Securities and Exchange Commission, including, but not limited to, our Annual Reports on Form 10-K and our Quarterly Reports on Form 10-Q. We assume no obligation to update any forward-looking statements, except as required by applicable law.

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

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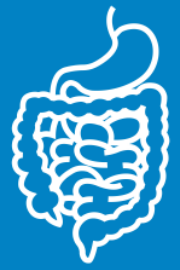
Developing biomarker-targeted antibody therapies for cancer patients

Lead clinical stage antibody program – sirexatamab (DKN-01) targeting DKK1

Multiple upcoming milestones from two randomized clinical trials



Biomarker strategy, focus on GI cancers

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

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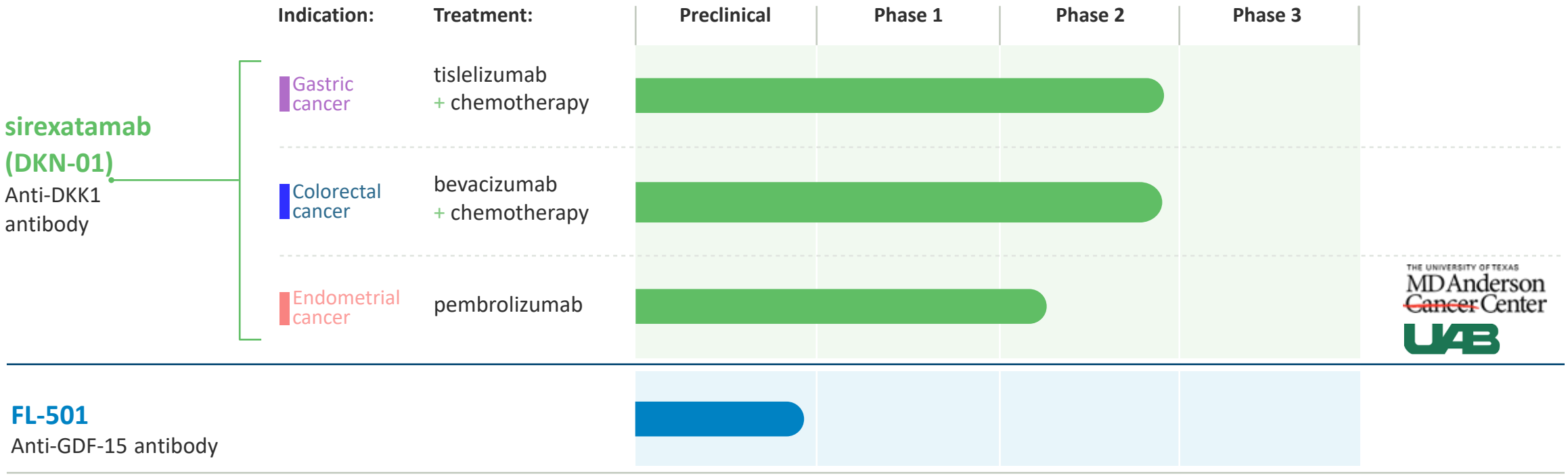
Pipeline



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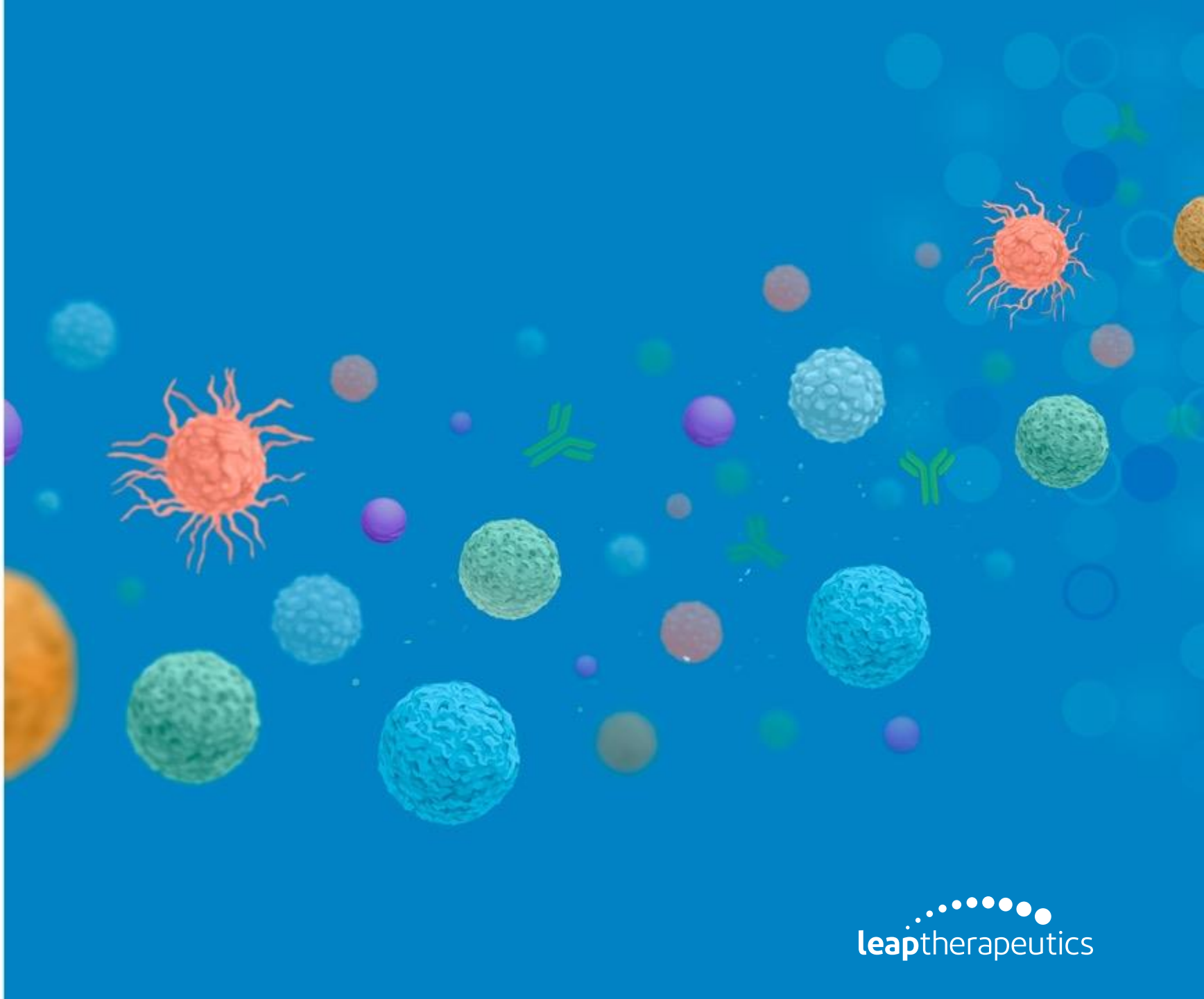
SIREXATAMAB (DKN-01)

Anti-DKK1 monoclonal antibody



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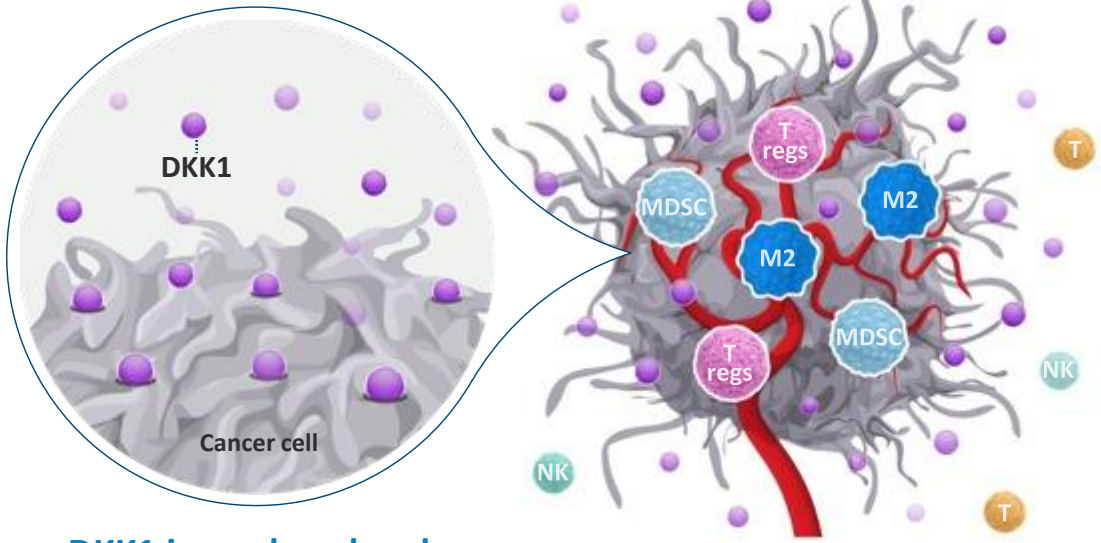
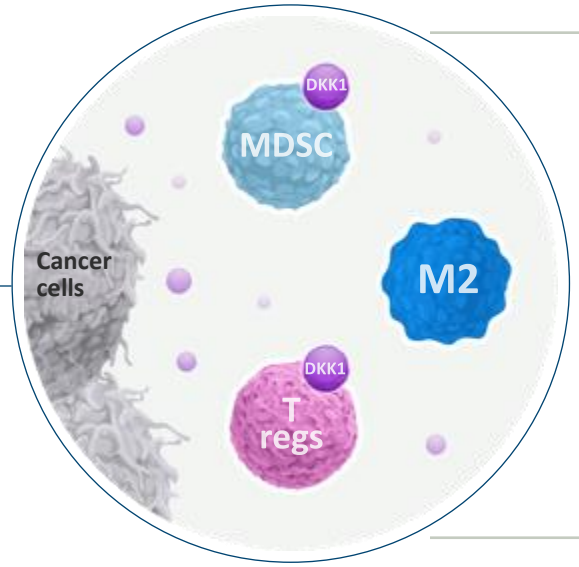
The role of DKK1 in cancer

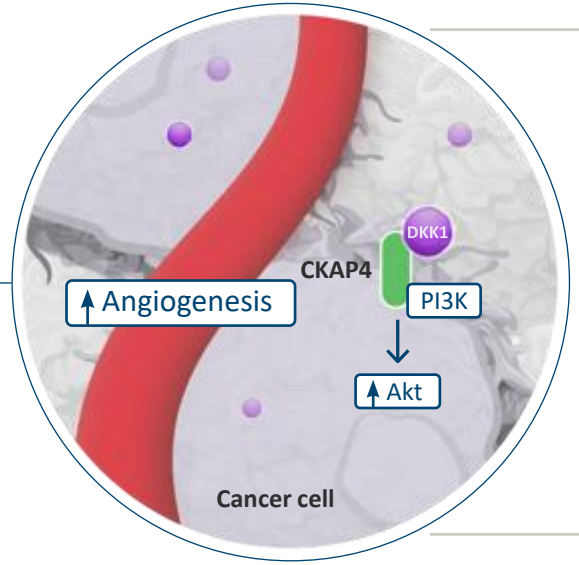


DKK1 is produced and secreted by cancer cells, and functions on several tumor pathways and nearby immune cells.



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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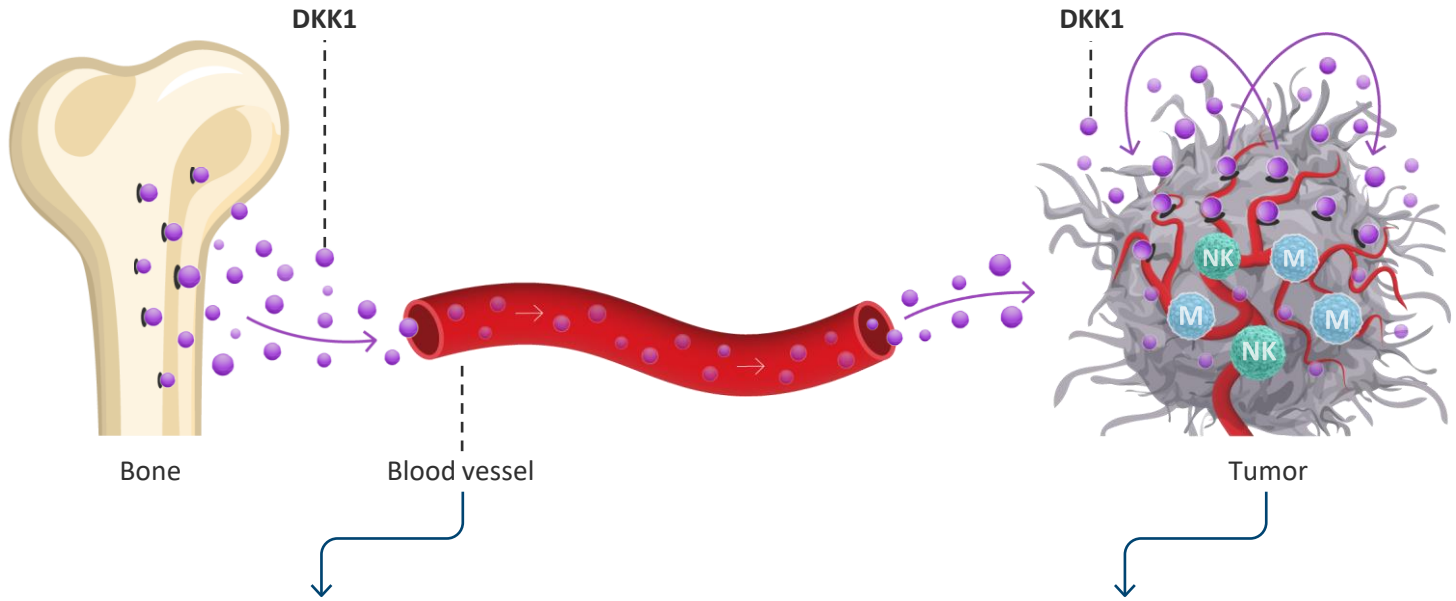
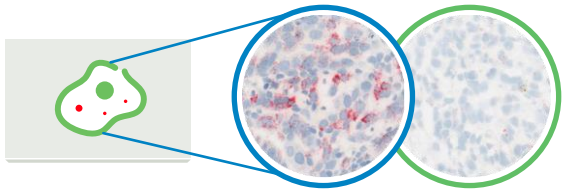
DKK1 production from multiple sources can drive tumor growth



DKK1 protein in circulation is measured by ELISA

ELISA
Enzyme-Linked Immunosorbent Assay

DKK1 RNA from the tumor is measured by RNAscope



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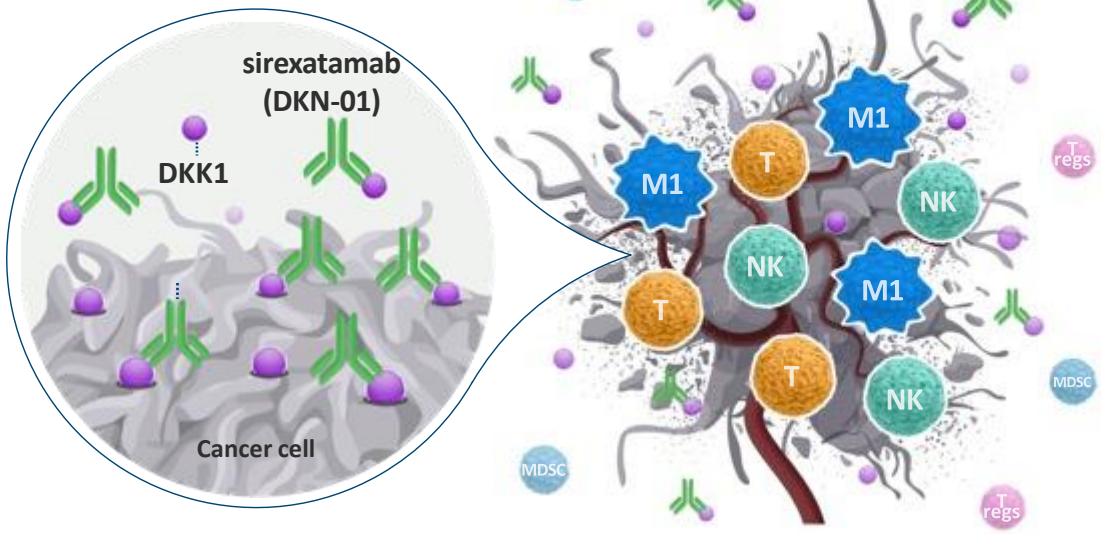
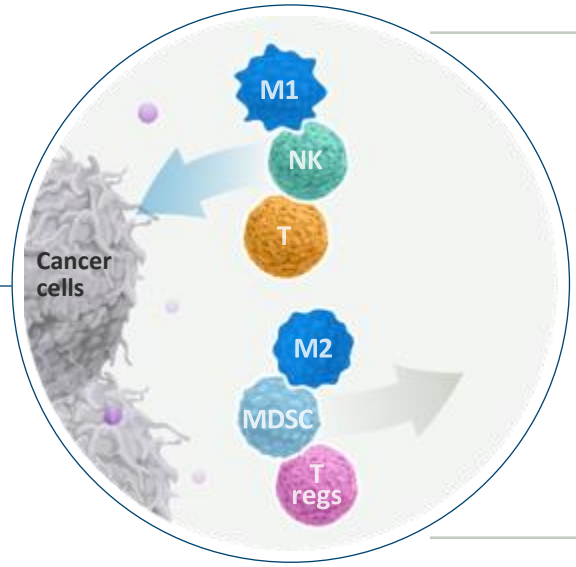
Activity of sirexatamab (DKN-01) to treat cancer

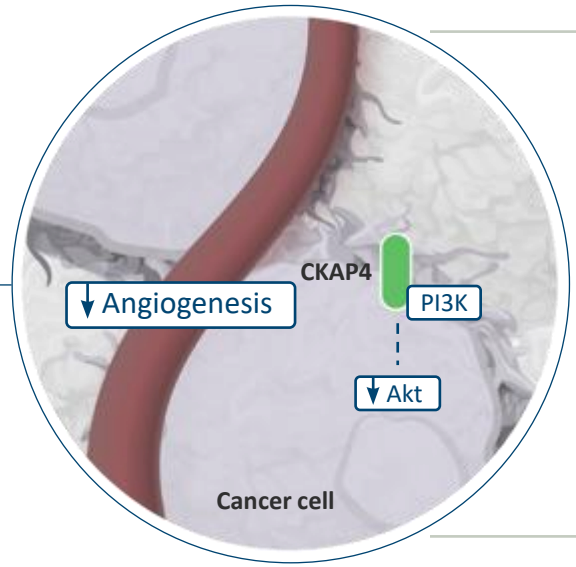


Sirexatamab (DKN-01) treatment neutralizes DKK1 and stimulates an immune mediated anti-tumor response.



Activates NK cells, reprograms macrophages into the tumor-attacking M1 subtype and promotes T cell infiltration.

Reduces MDSCs and tumor suppressive M2 macrophages in the TME.



Reduces angiogenesis and inhibits pro-oncogenic PI3K/AKT signaling.

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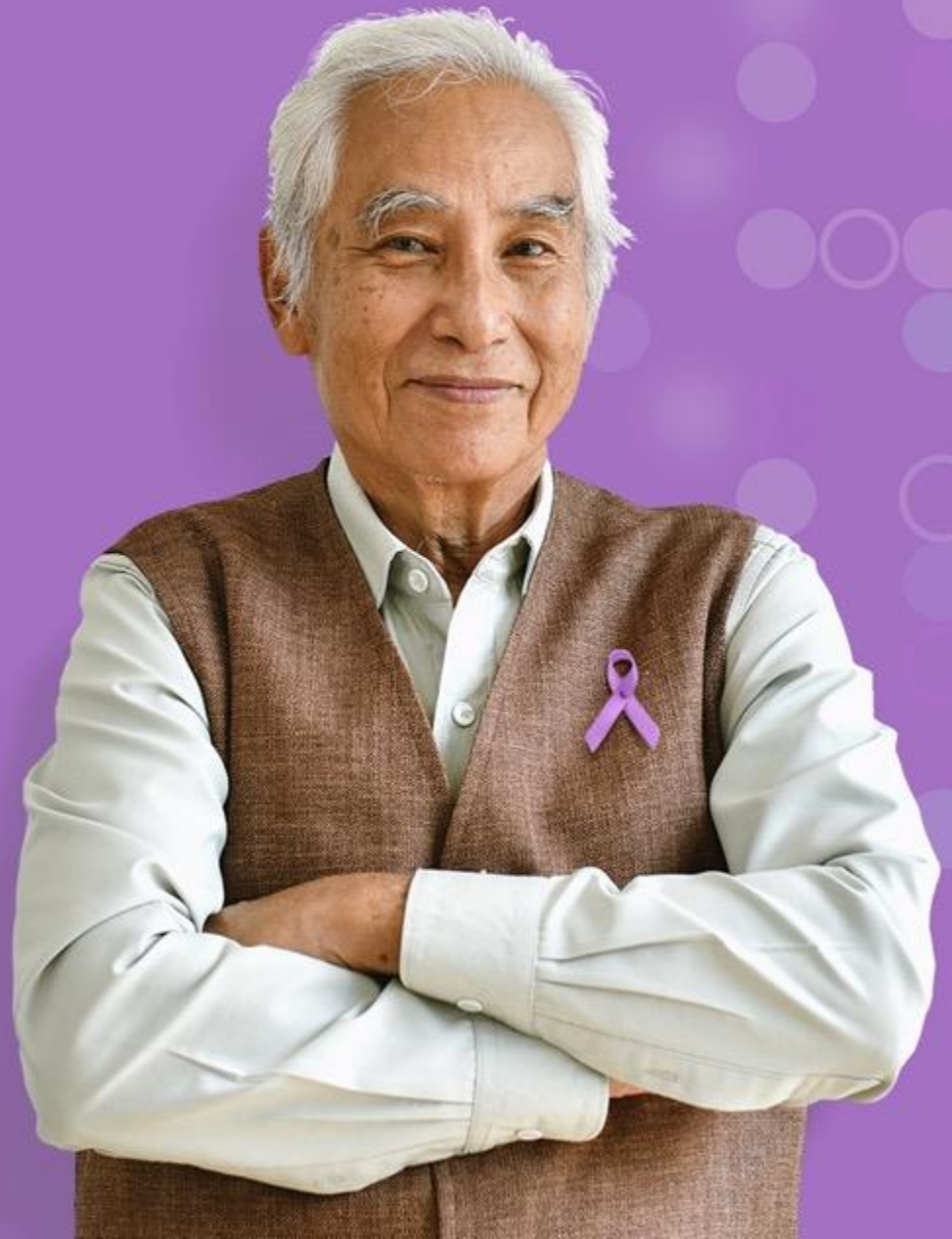
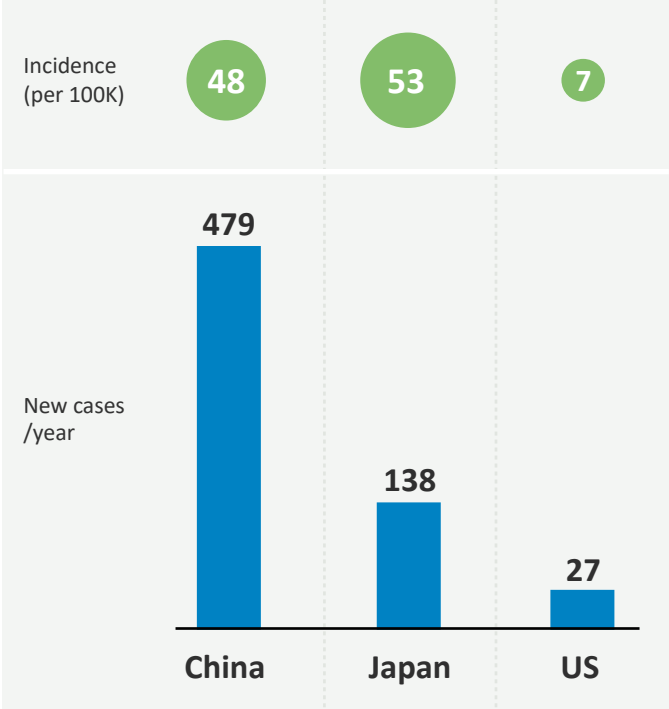
SIREXATAMAB (DKN-01)

Gastric cancer development



Gastric cancer background

Gastric cancer:



1,089,103
New cases 2020

768,793
Deaths 2020

High incidence of gastric cancer in Asia
Incidence of gastric cancer in China/Japan/US

- Includes gastroesophageal junction (GEJ) and gastric adenocarcinoma
- Often asymptomatic in the early stages. Substantial symptoms, such as indigestion, abdominal pain, nausea, weight loss, vomiting, and difficulty swallowing, are usually seen when tumor is fairly large and often spread to the liver or lungs.
- Fifth most frequent cancer globally and the fourth leading cause of cancer-related death
- Globally, 1,000,000 new cases in 2020, with over 750,000 deaths
- In the US, nearly 30,000 new cases and more than 10,000 deaths each year

Source: WHO Globocan 2020, American Cancer Society

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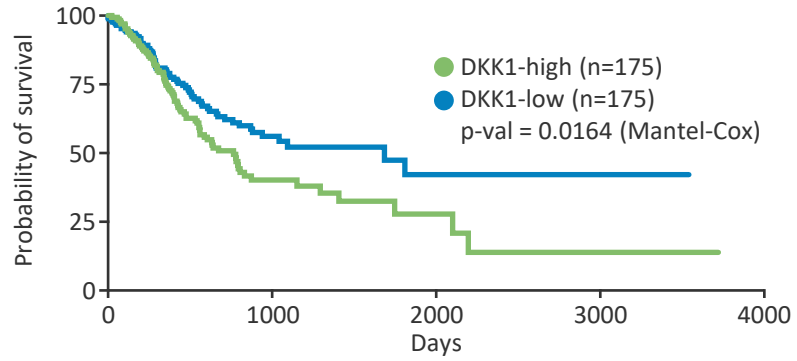
DKK1-high levels are associated with poor survival in gastric cancer

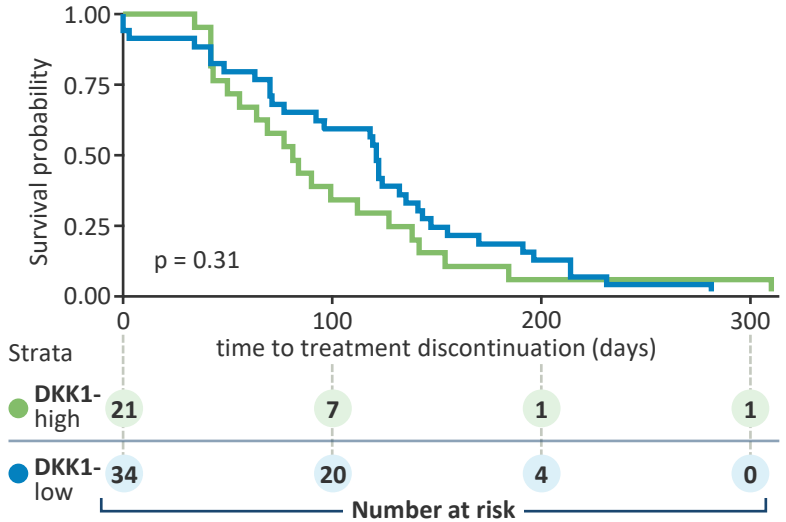
High levels of DKK1 correlate with shorter overall survival In gastric cancer

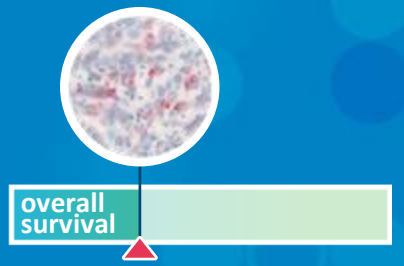
TCGA STAD dataset

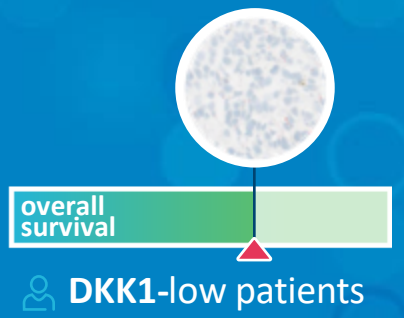


DKK1-high is associated with poor response to first-line platinum + fluoropyrimidine based therapies in GEJ/gastric cancer patients

Collaboration with Tempus







~2.5 years shorter OS in DKK1-high patients

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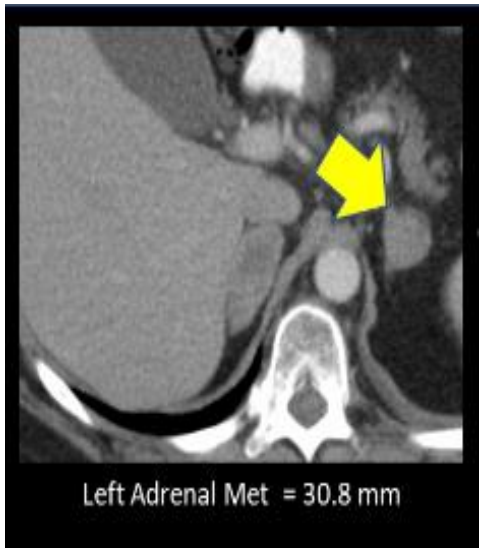
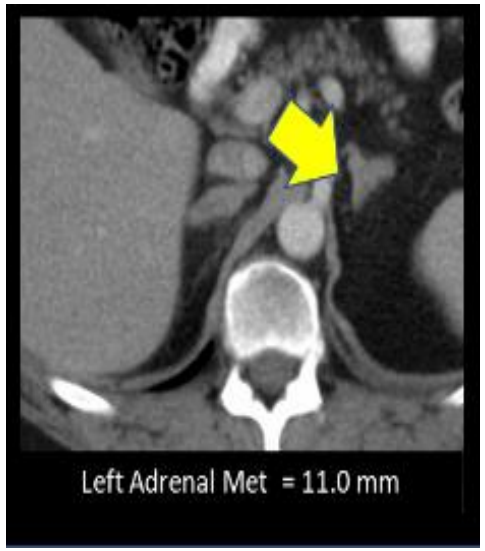
Sirexatamab (DKN-01) single agent activity in heavily pretreated esophagogastric cancer patients

2L+ EGC
sirexatamab (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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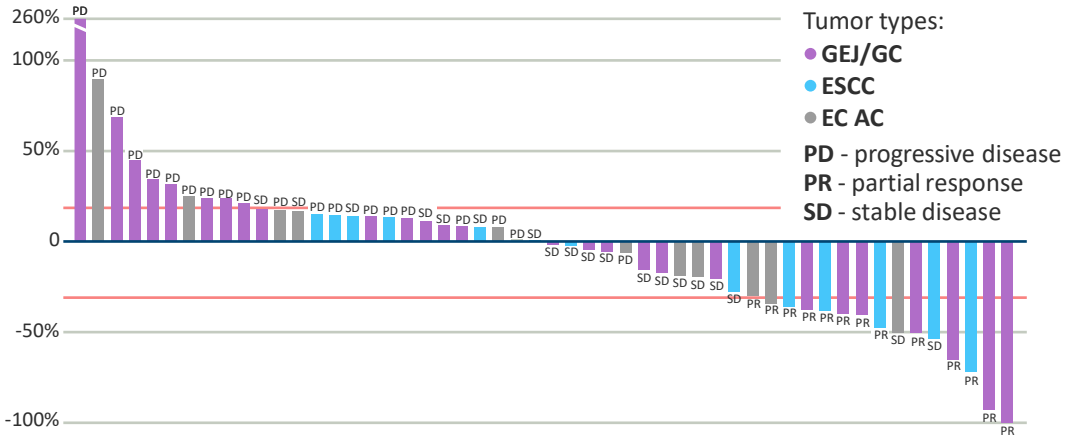
Clinical activity of sirexatmab (DKN-01) plus paclitaxel or anti-PD-1 antibody

GEJ/GC
sirexatamab (DKN-01)
Historical data

DKN-01 + paclitaxel — N=52 — **2L-8L esophagogastric pts**



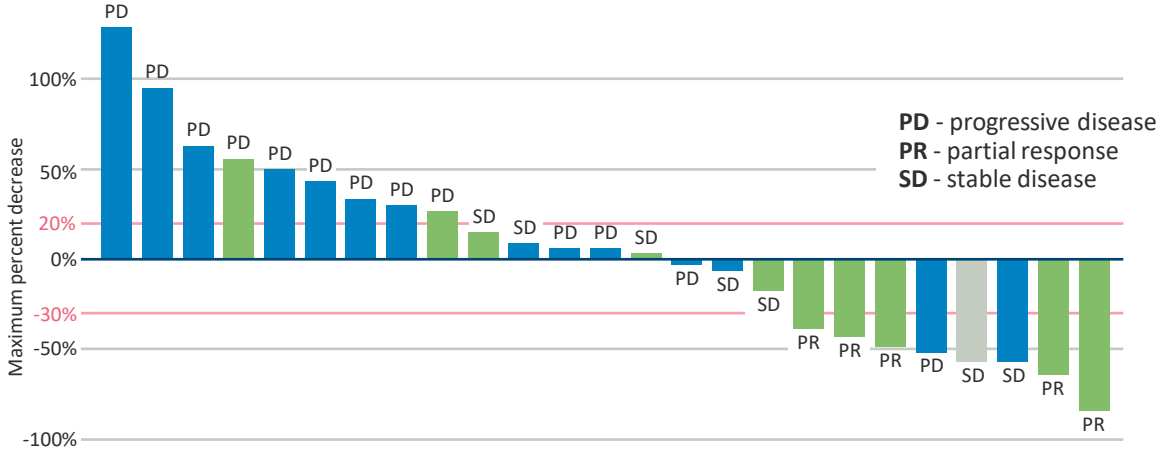
	Patients treated	Prior therapies	Overall response rate (ORR)	Disease control rate (DCR)
DKN-01 + paclitaxel	N=52	1-7	**25%**	**60%**

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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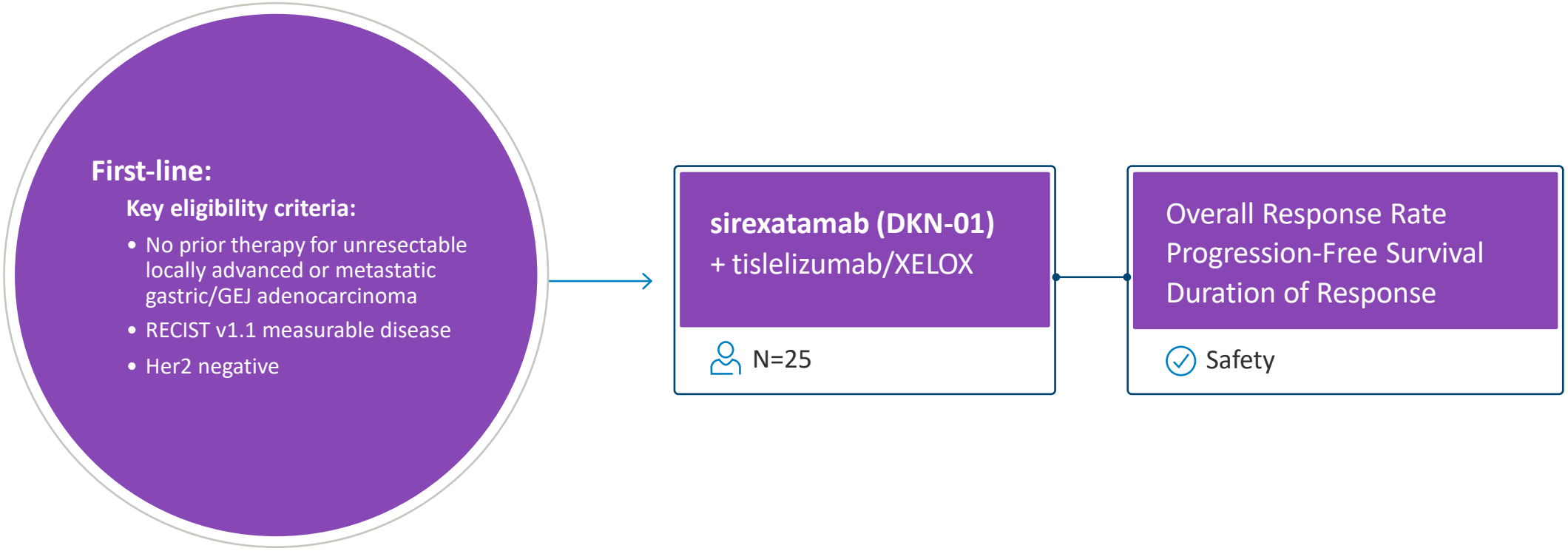
DisTinGuish Part A study design

1L GEJ/GC
sirexatmab (DKN-01)
+ tislelizumab
+ chemotherapy

Assess the safety and anti-tumor activity of sirexatamab (DKN-01) in combination with tislelizumab +/- chemotherapy



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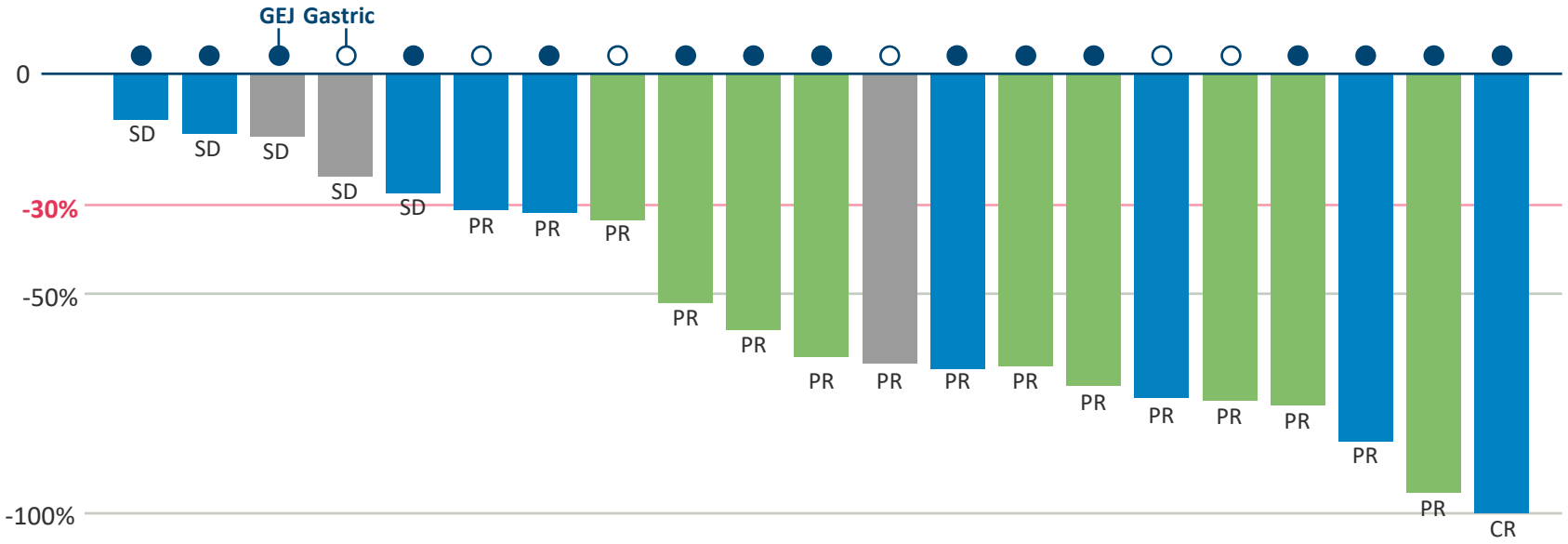
Response by DKK1 expression in first-line patients

1L GEJ/GC
sirexatmab (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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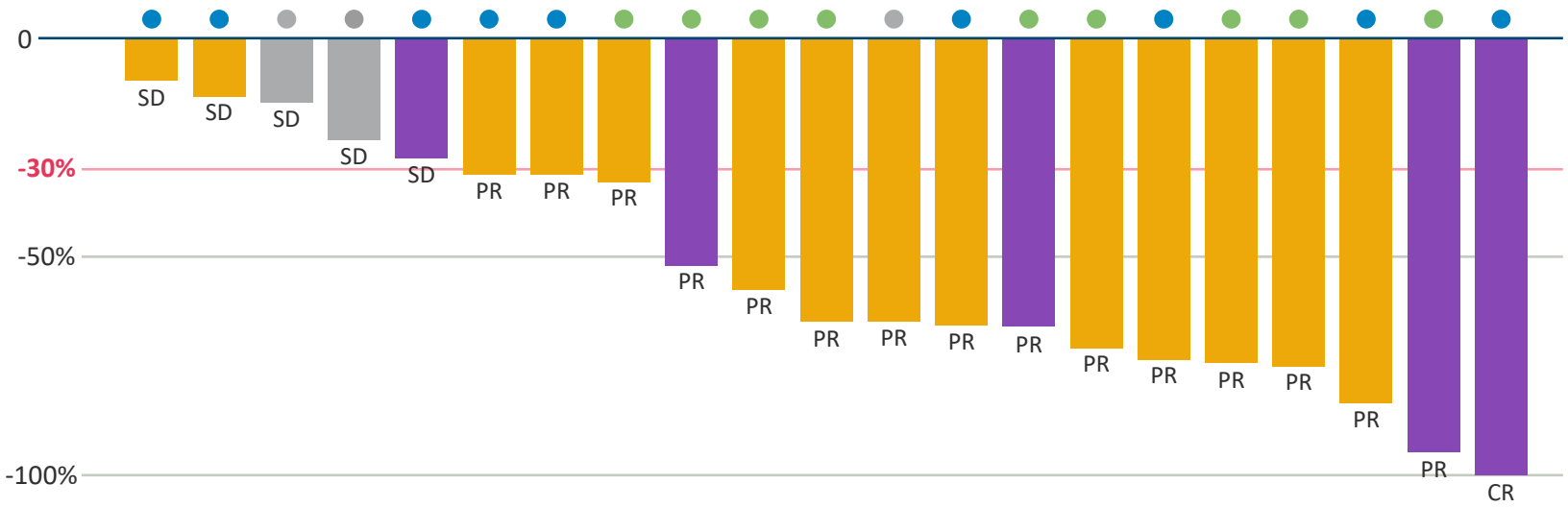
Response by PD-L1 expression

1L GEJ/GC
sirexatmab (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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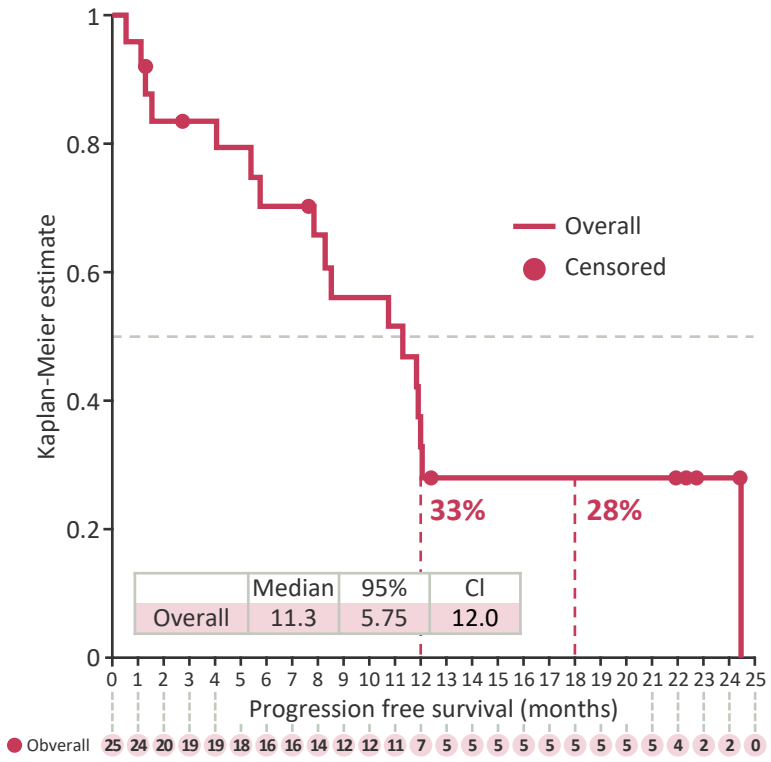
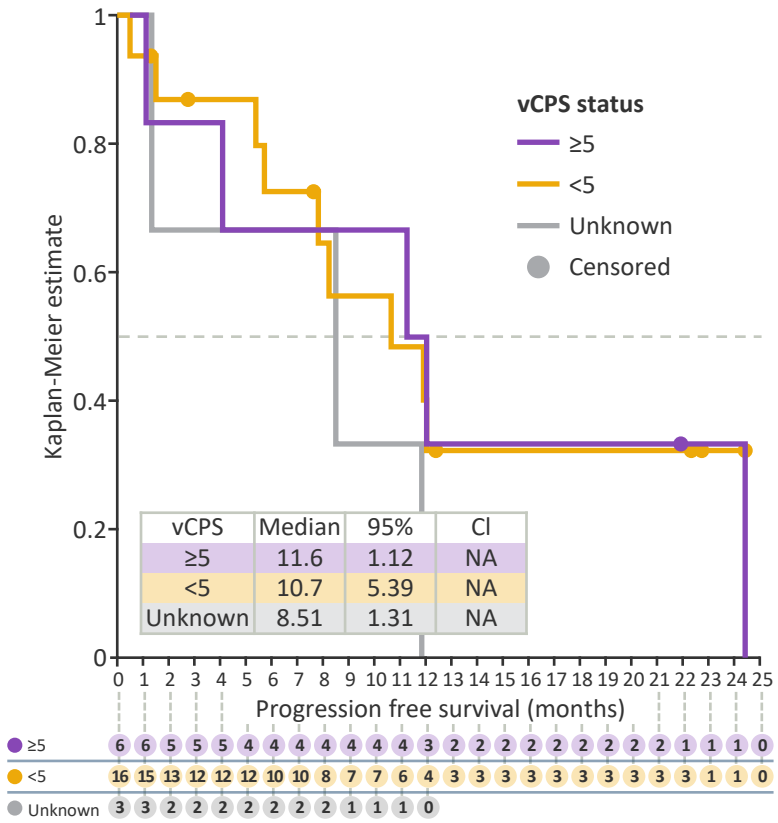
Progression-free survival

1L GEJ/GC
sirexatmab (DKN-01)
+ tislelizumab
+ chemotherapy

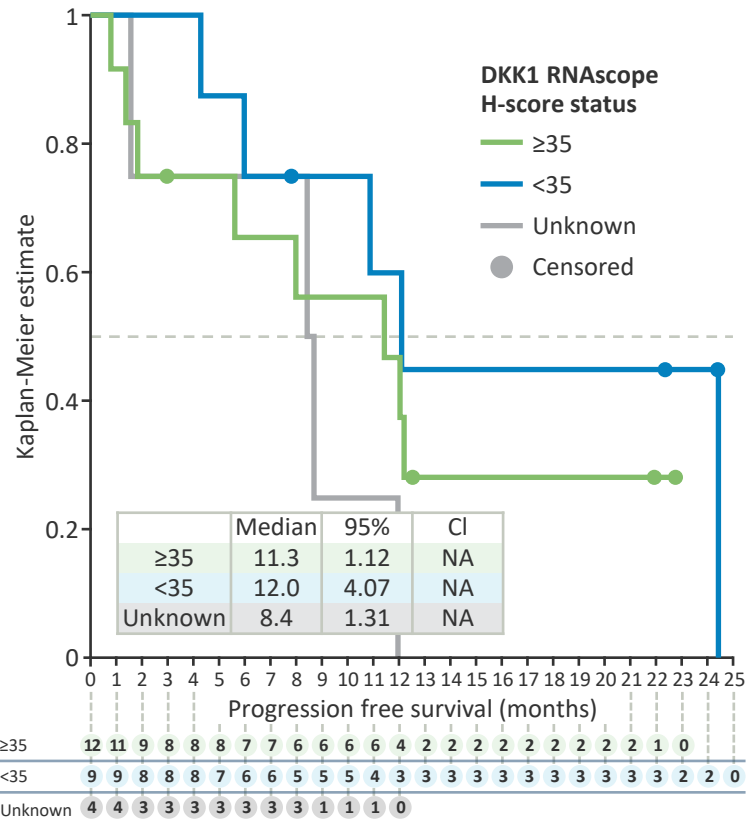
Overall Population



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
As presented at ASCO 2023

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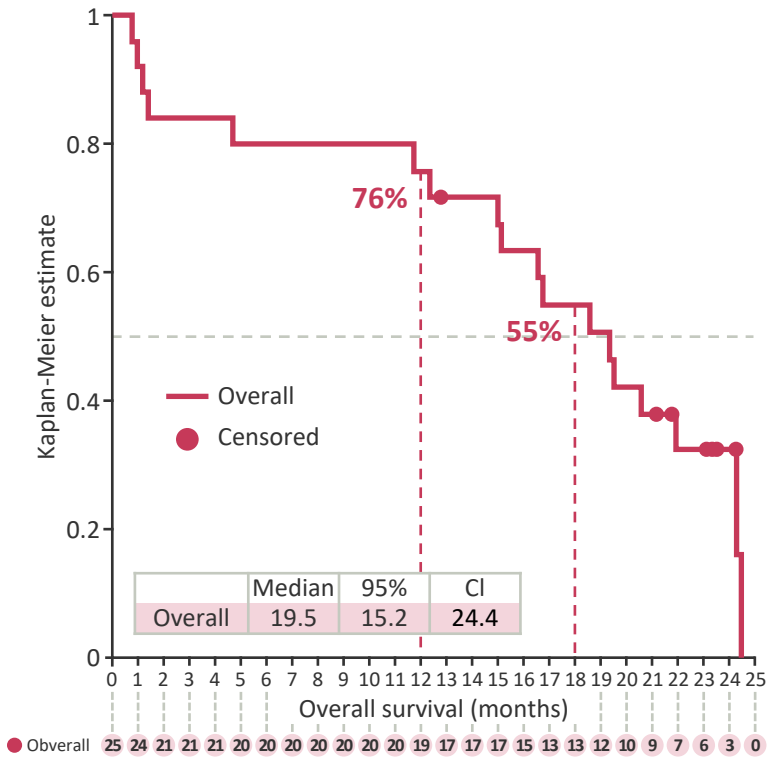
Overall survival

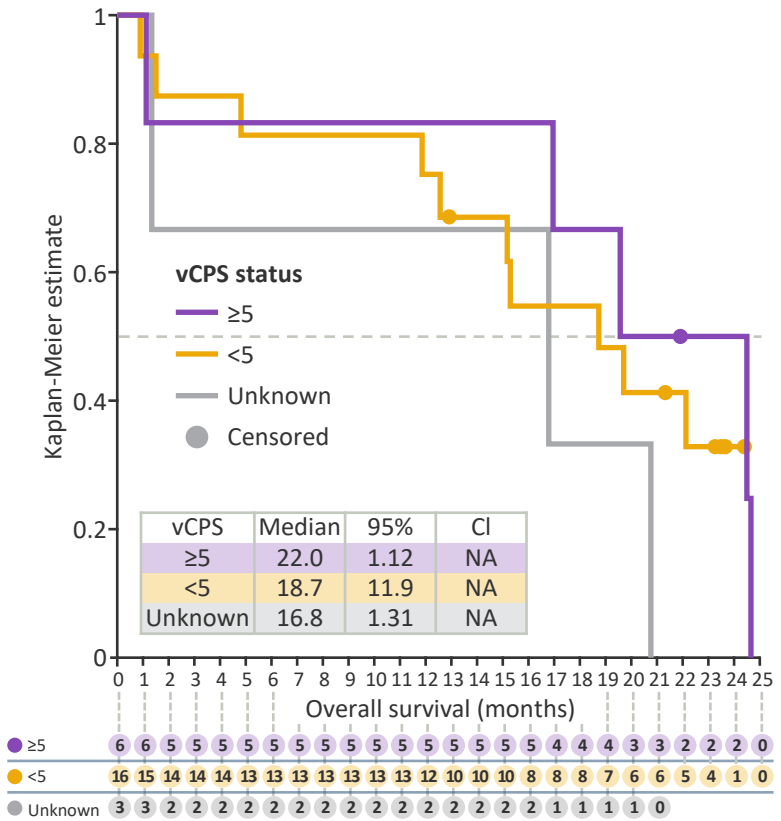
1L GEJ/GC
sirexatmab (DKN-01)
+ tislelizumab
+ chemotherapy

Overall Population



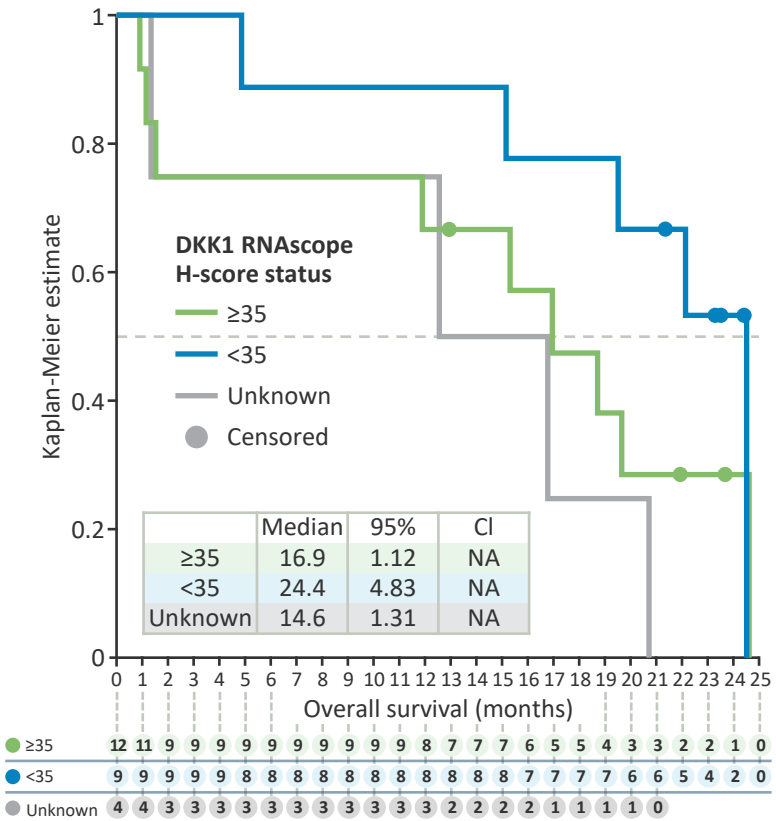
	Median	95%	CI
Overall	19.5	15.2	24.4

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

	All Patients			North America & Europe			PD-L1 CPS < 1		
	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 (0.69, 0.92)	11.0 (8.4, 13.9)	10.5 (8.1, 12.1)	0.71 (0.54, 0.94)	15.4 (8.4, 16.5)	13.8 (10.2, 17.8)	0.98 (0.64, 1.50)
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)		11.8 (4.3, NA)	18 (2.8, NA)	
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)	7.9 (5.6, 9.7)	6.9 (5.6, 15)	0.87 (0.54, 1.41)
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%)		44.9% (32.9%,57.4%)	34.9% (21%, 50.9%)	

All patients and PD-L1 < TAP 1 from September 26, 2024 FDA Briefing Document
North American & Europe as presented at ASCO GI 2024

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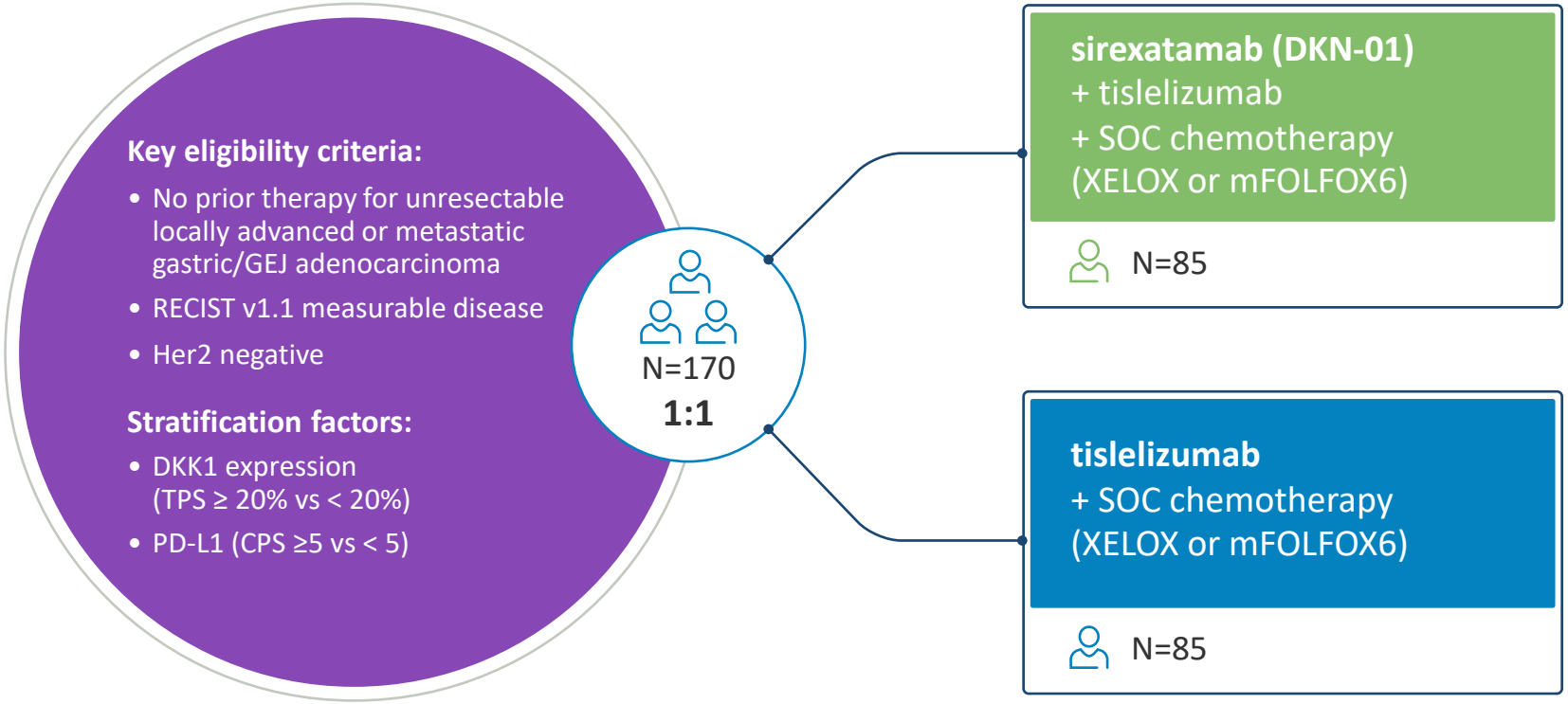
DisTinGuish Part C study design

1L GEJ/GC
sirexatmab (DKN-01)
+ tislelizumab
+ chemotherapy

Randomized phase 2 study of FOLFIRI/FOLFOX and tislelizumab +/- sirexatamab (DKN-01) as first-line treatment of advanced GEJ/gastric cancer



Primary objective:
PFS, DKK1-high and all

Secondary objectives:
– ORR
– DoR
– OS

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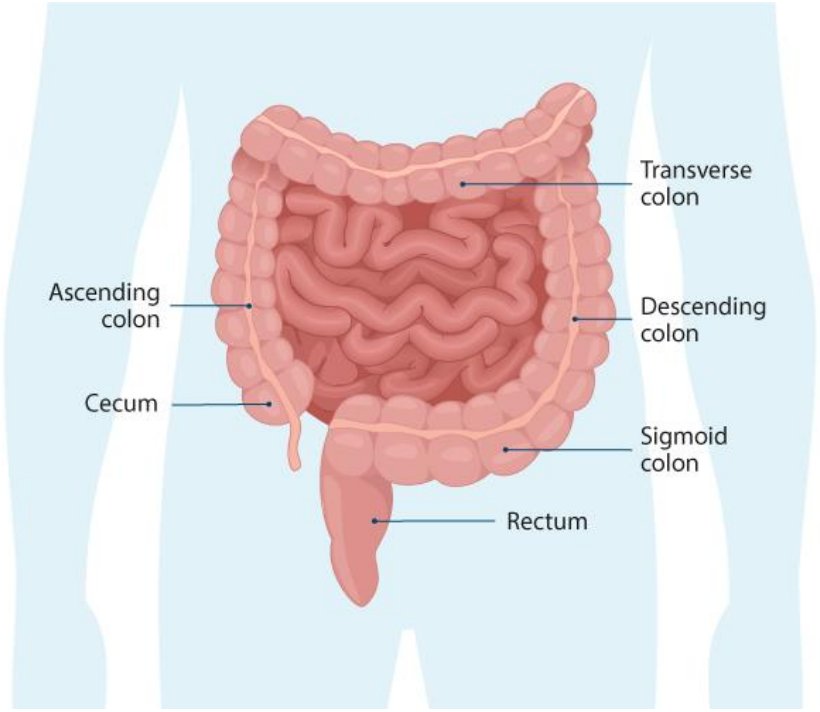
SIREXATAMAB (DKN-01)

Colorectal cancer development

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, nearly 2,000,000 new cases in 2020, with nearly 1,000,000 deaths.
- In the US, estimated that there will be approximately 150,000 cases each year, resulting in more than 50,000 deaths.

Source: WHO Globocan 2020, American Cancer Society

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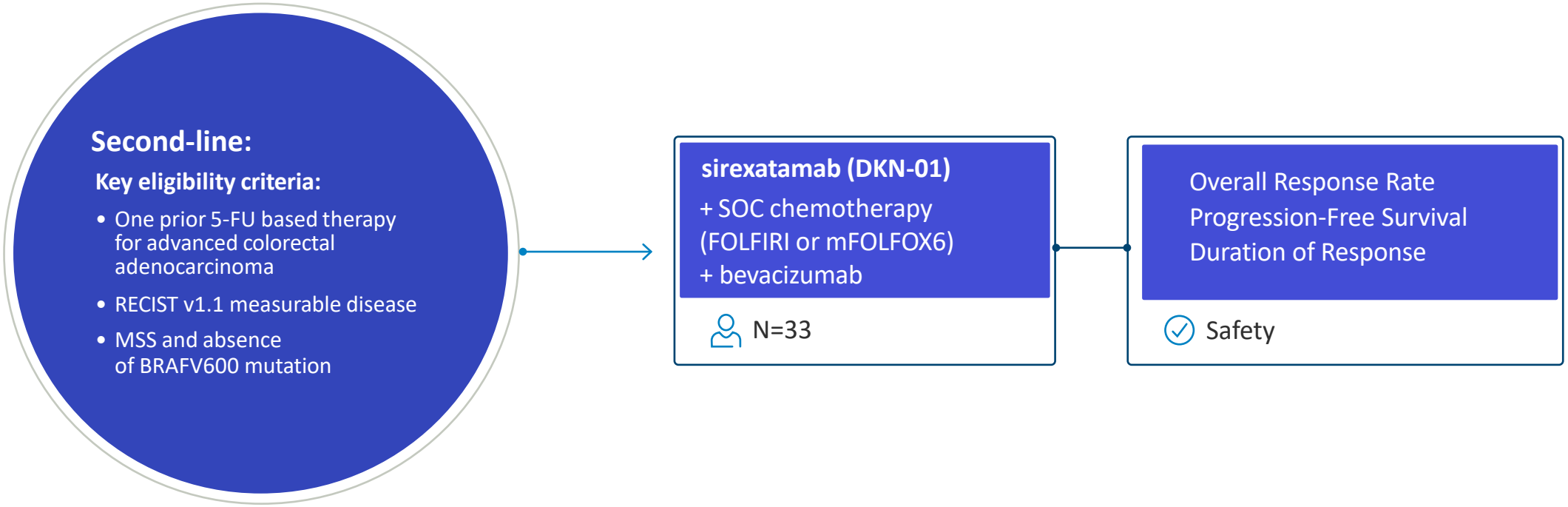
DeFianCe Part A study design

2L CRC
sirexatamab (DKN-01)
+ bevacizumab
+ chemotherapy

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



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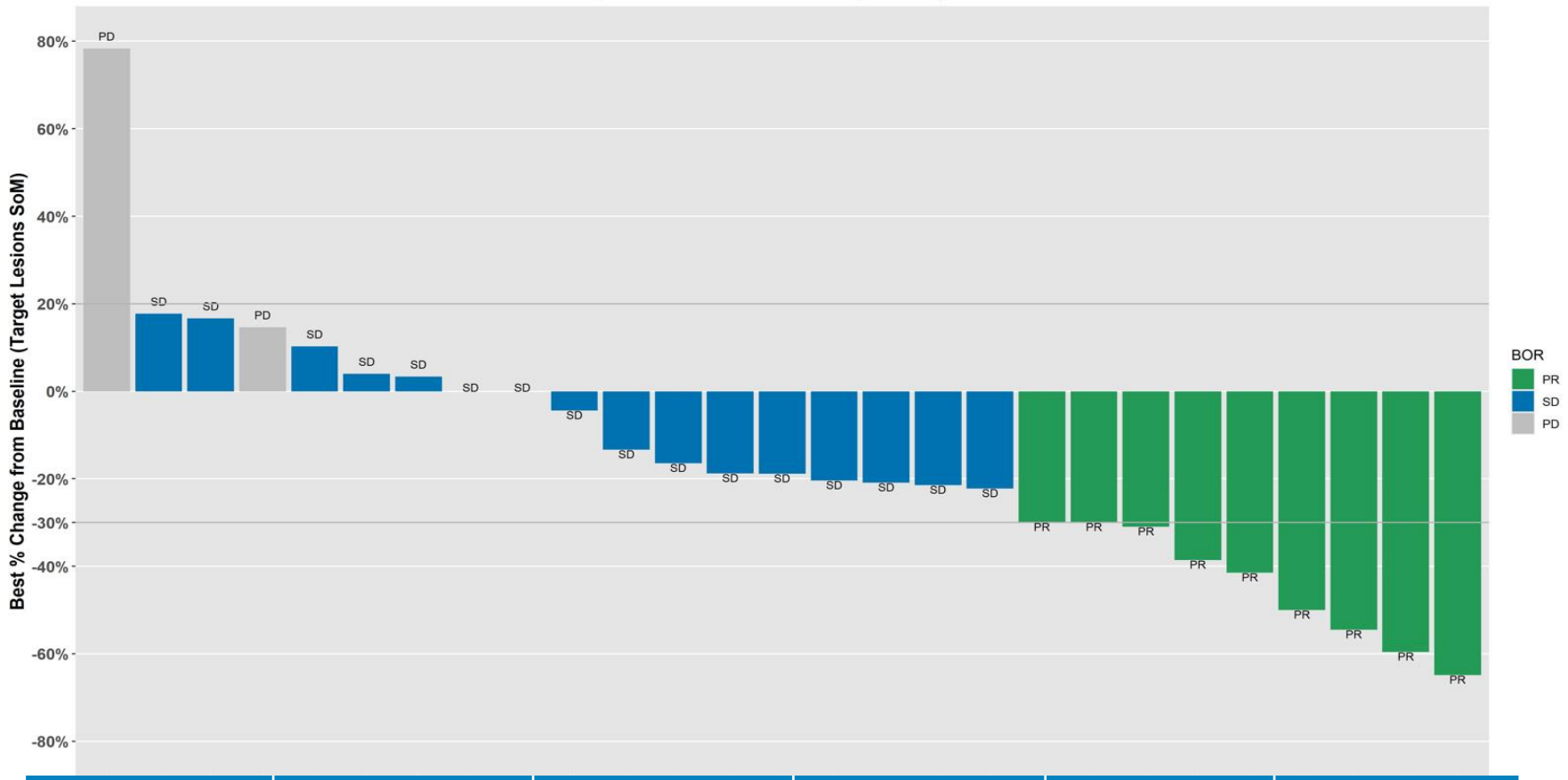
Overall response rate exceeded 20% target with high disease control rate

2L CRC
sirexatamab (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 October 1, 2024

ORR in RE patients:
9/27 = 33%

DCR in RE patients:
25/27 = 93%

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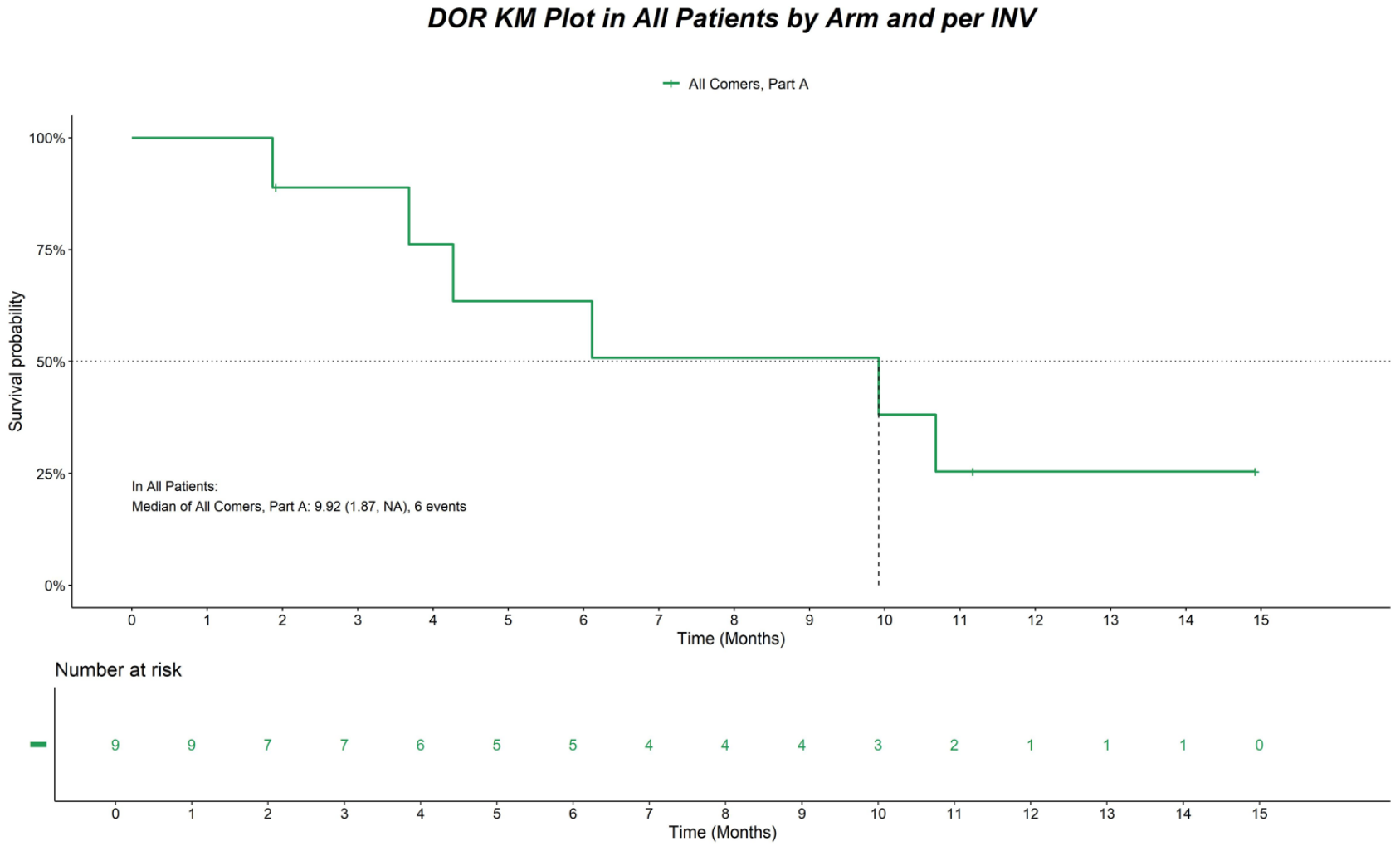
Duration of response

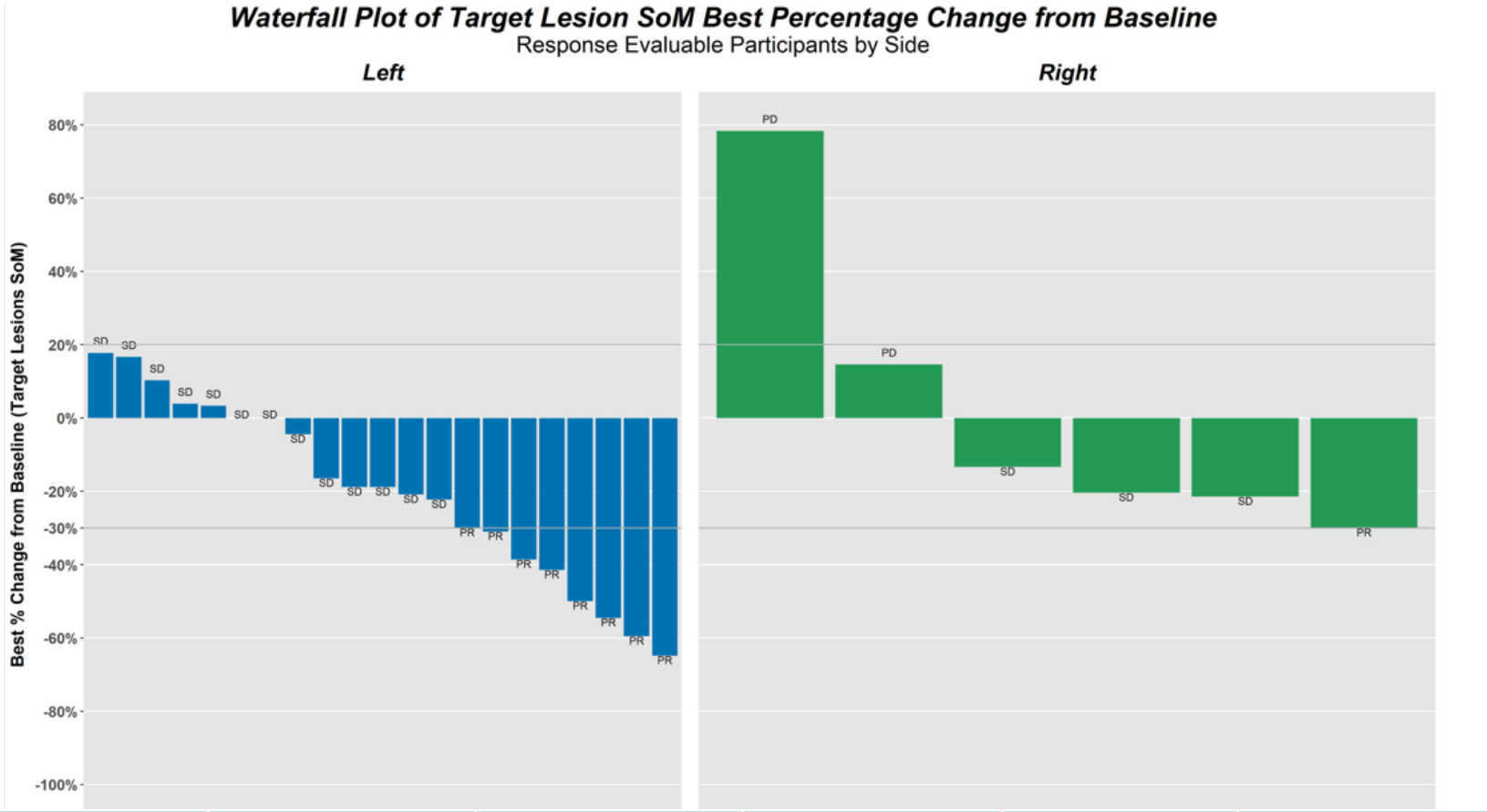
- Median DoR: 9.92 months

2L CRC
sirexatamab (DKN-01)
+ bevacizumab
+ chemotherapy



Best overall response based on tumor sidedness

2L CRC
sirexatamab (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 October 1, 2024

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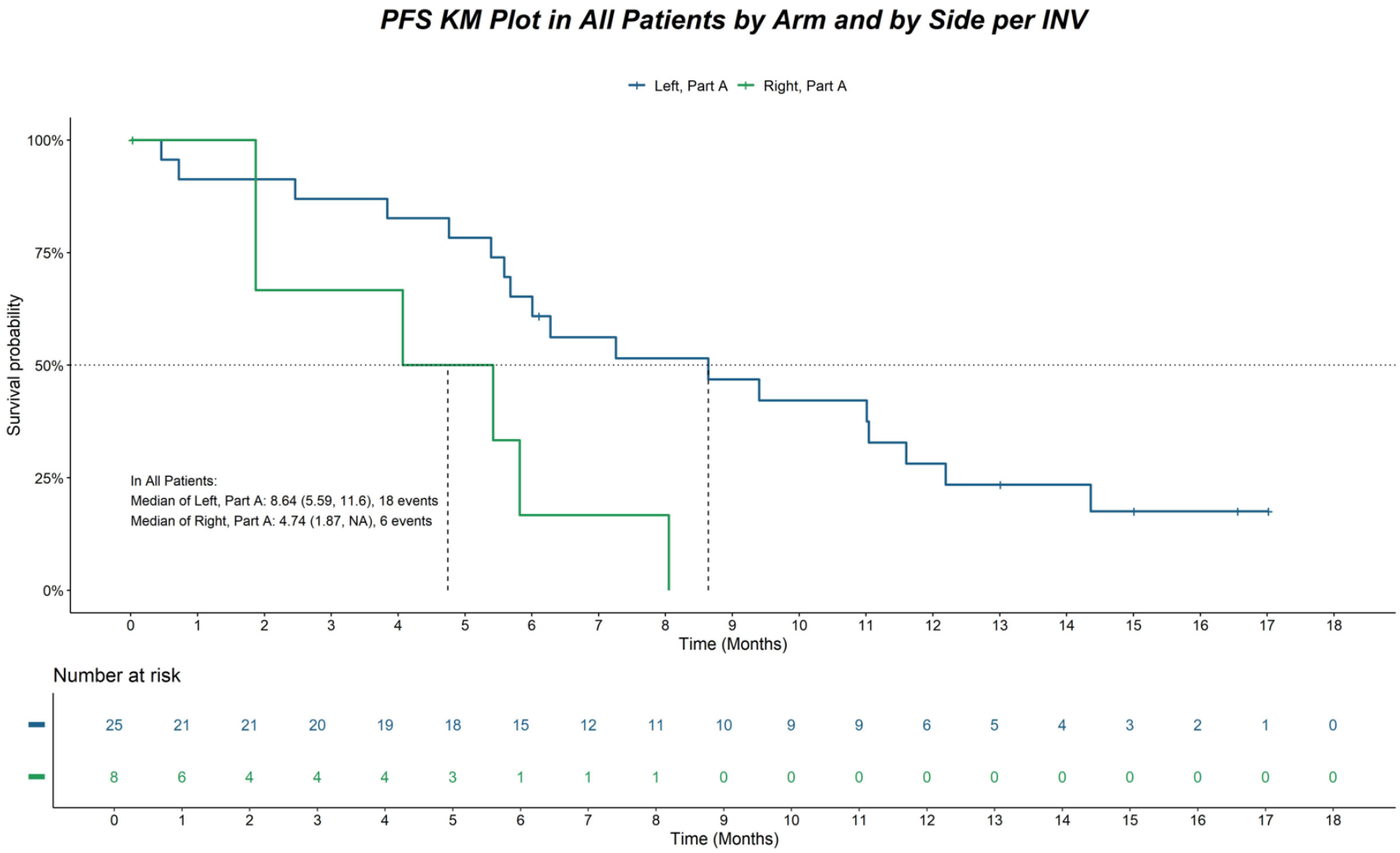
Longer progression-free survival in patients with left-sided tumors

2L CRC
sirexatamab (DKN-01)
+ bevacizumab
+ chemotherapy

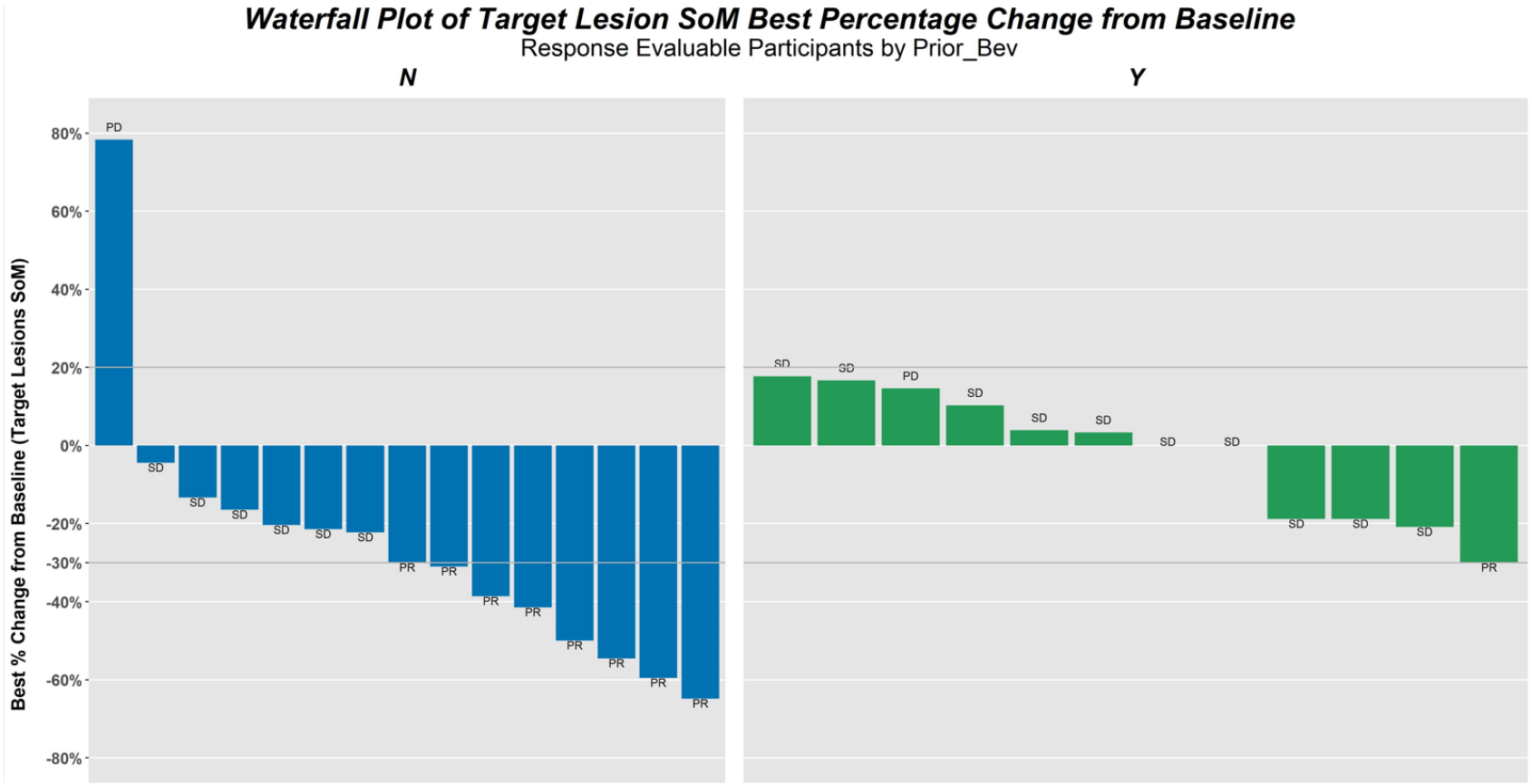
- Median PFS in left-sided tumors: 8.6 months



Data Cut-off: 2024-10-01

Best overall response based on prior bevacizumab exposure

2L CRC
sirexatamab (DKN-01)
+ bevacizumab
+ chemotherapy



Overall, n=27	Objective Response Rate (%)	Disease Control Rate (%)	Partial Response n (%)	Stable Disease n (%)	Progressive Disease n (%)
No Prior Bev (n=15)	53	93	8 (53)	6 (40)	1 (7)
Prior Bev (n=12)	8	83	1 (8)	10 (83)	1 (8)

As of October 1, 2024

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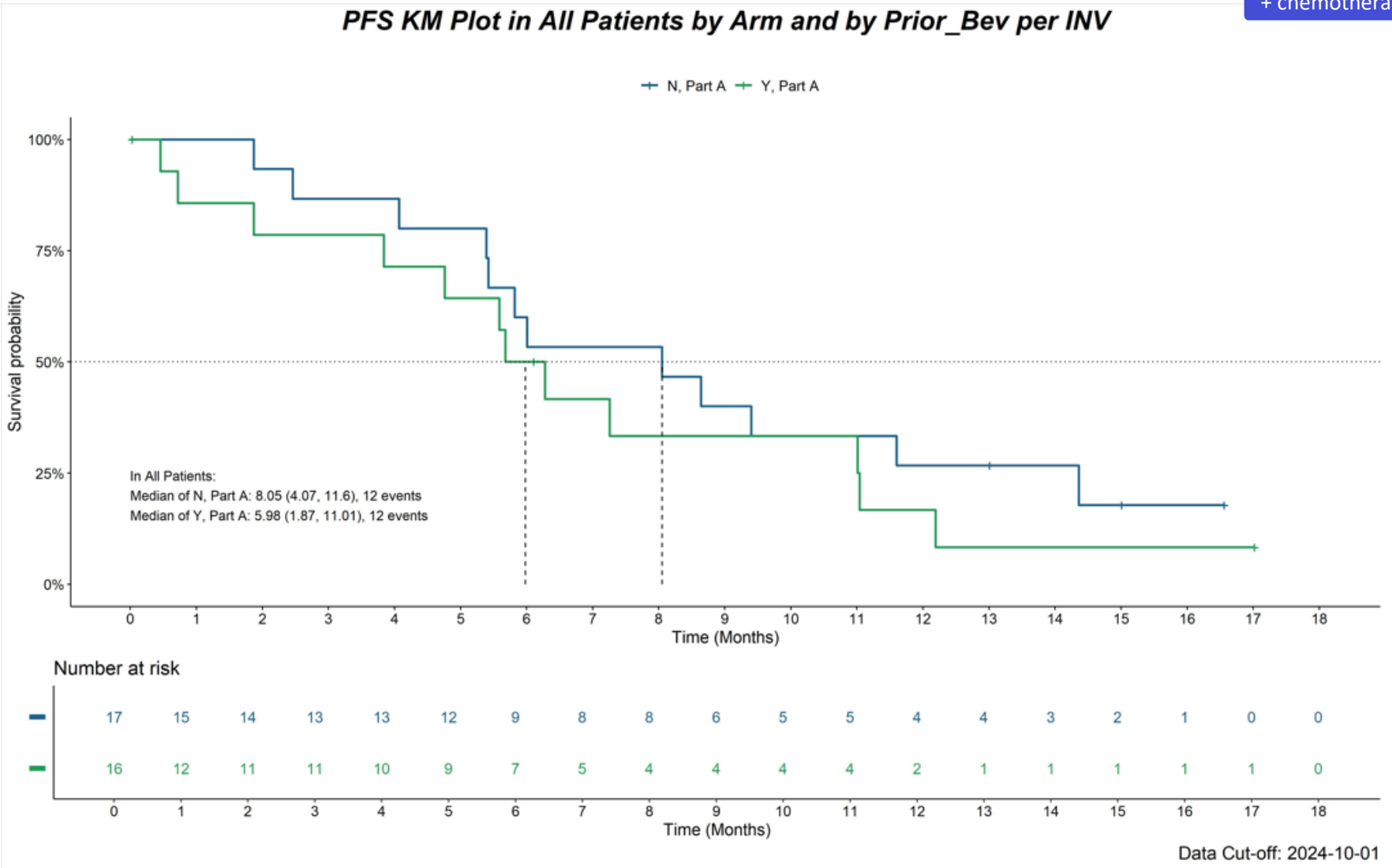
Progression-free survival
Bevacizumab exposure subgroup

2L CRC
sirexatamab (DKN-01)
+ bevacizumab
+ chemotherapy



Median PFS in bevacizumab naïve subgroup exceeds prior bevacizumab treated:
8.05 vs 5.98 months

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Significant Unmet Needs in 2L mCRC Patients

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

Treatment	Bevacizumab + Chemo[1]	Bevacizumab + Chemo[2]	Bevacizumab + Chemo[3]
Study	ML18147	E3200	SLAVE
Population	Bevacizumab-experienced	Bevacizumab-naïve	EGFR-experienced
👤	409	286	228
ORR	5.4%[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%

1. Avastin FDA Label
2. Giantonio et al. (2007)
3. Parisi et al. (2020)
4. Bennouna et al. (2012)

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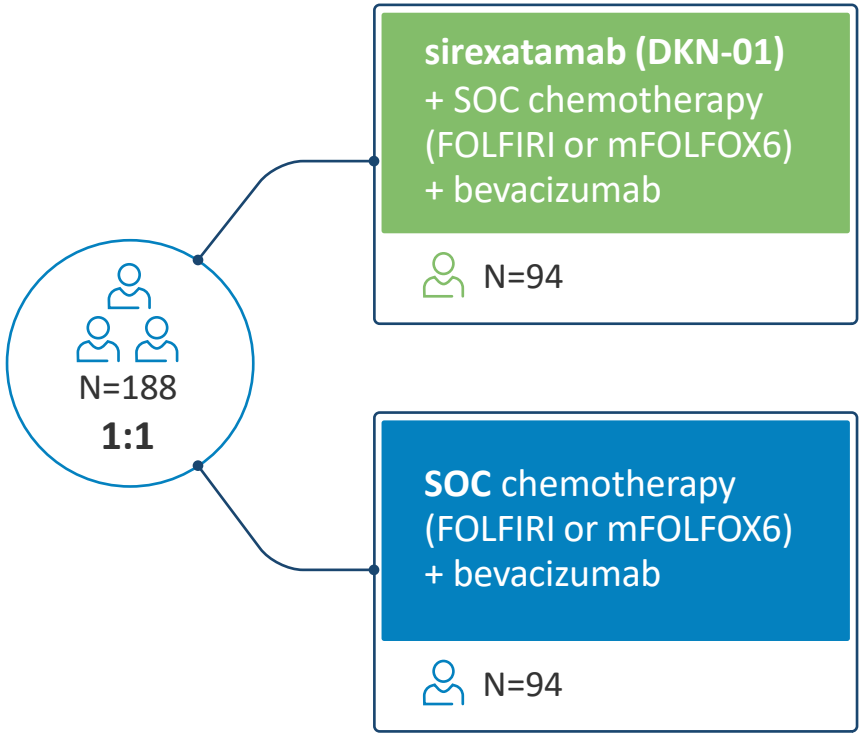
DeFianCe Part B study design

2L CRC
sirexatamab (DKN-01)
+ bevacizumab
+ chemotherapy

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

Key eligibility criteria:

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



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

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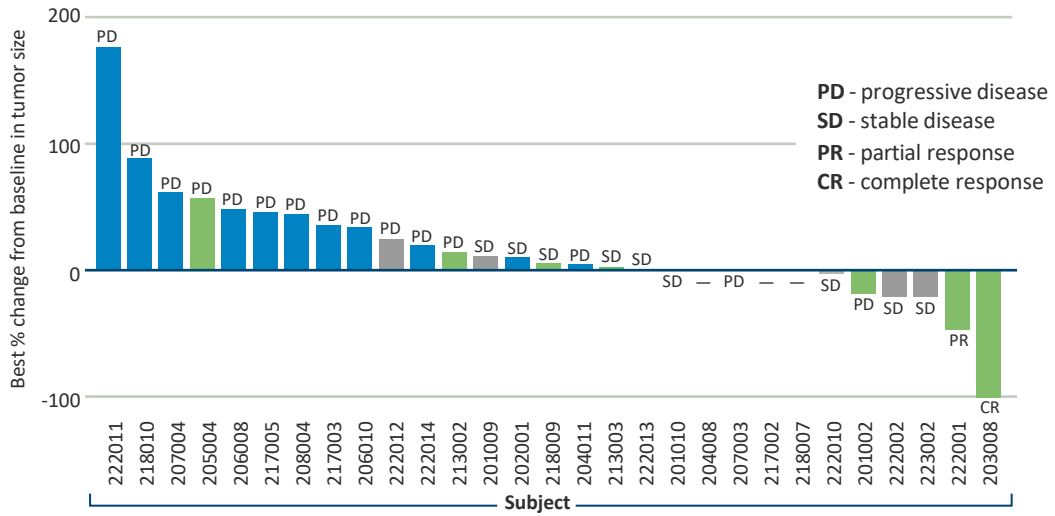
SIREXATAMAB (DKN-01)

Endometrial cancer development

Sirexatamab (DKN-01) monotherapy - response by DKK1 tumoral expression

2L+ EEC
sirexatamab (DKN-01)
monotherapy

Overall response by DKK1 tumoral expression



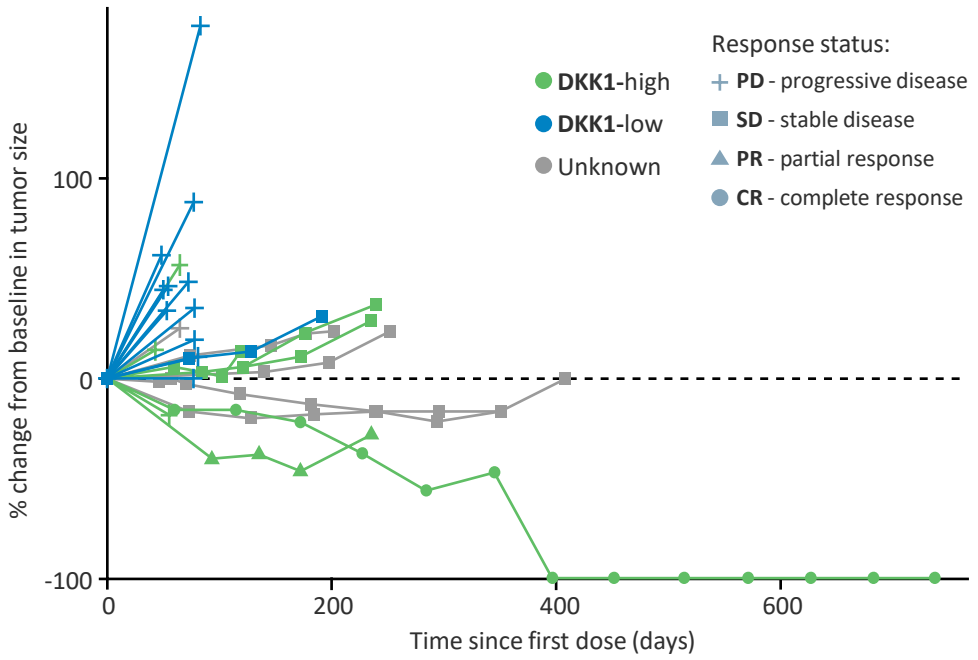
Status	Total	CR	PR	SD	PD	NE	ORR	DCR
DKK1-high (≥18)*	n=8	1	1	3	3	0	25%	63%
DKK1-low (<18)	n=15	0	0	1	11	3	0%	7%
Unknown	n=6	0	0	5	1	0	0%	83%

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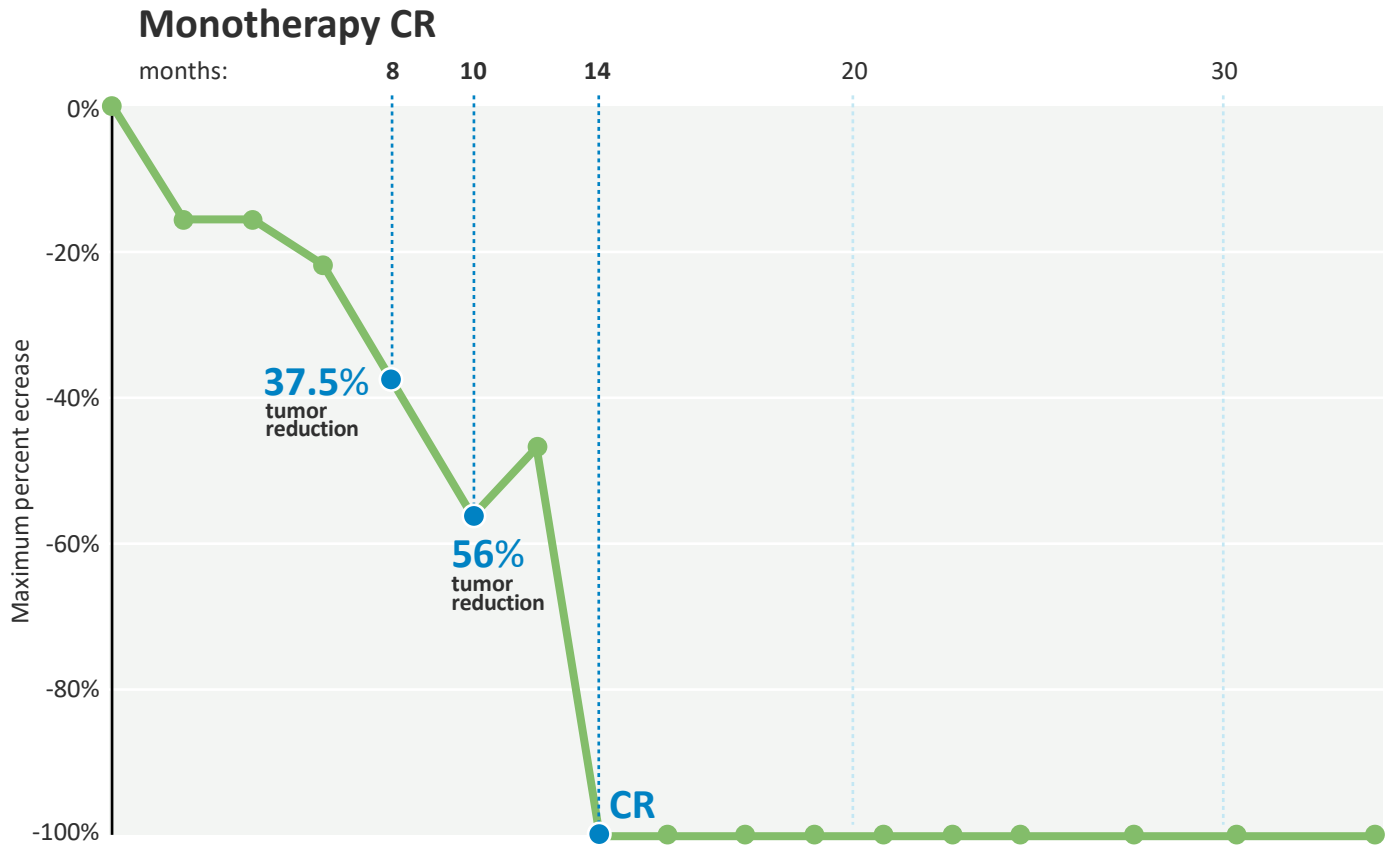
Complete response in endometrial cancer patient on sirexatamab (DKN-01) monotherapy

2L+ EEC
sirexatamab (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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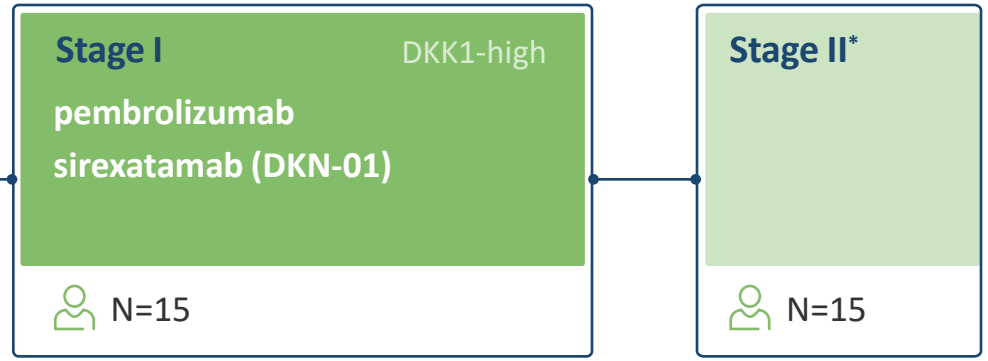
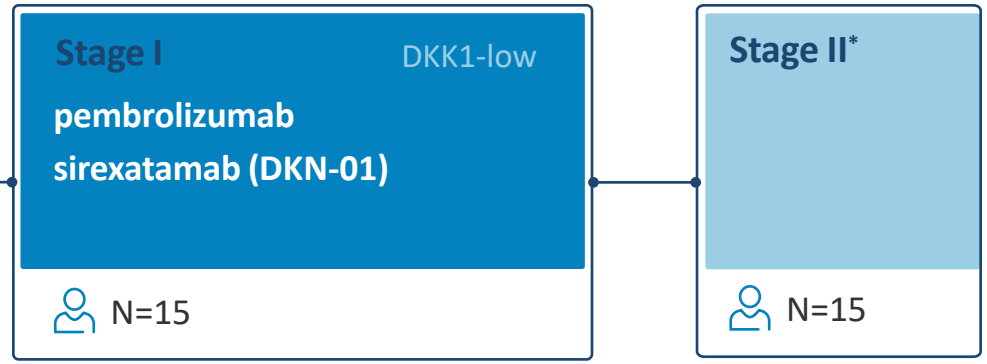
Sirexatamab (DKN-01) plus pembrolizumab endometrial cancer study

2-3L EEC
sirexatamab (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





Primary objective:
Objective response rate (ORR)

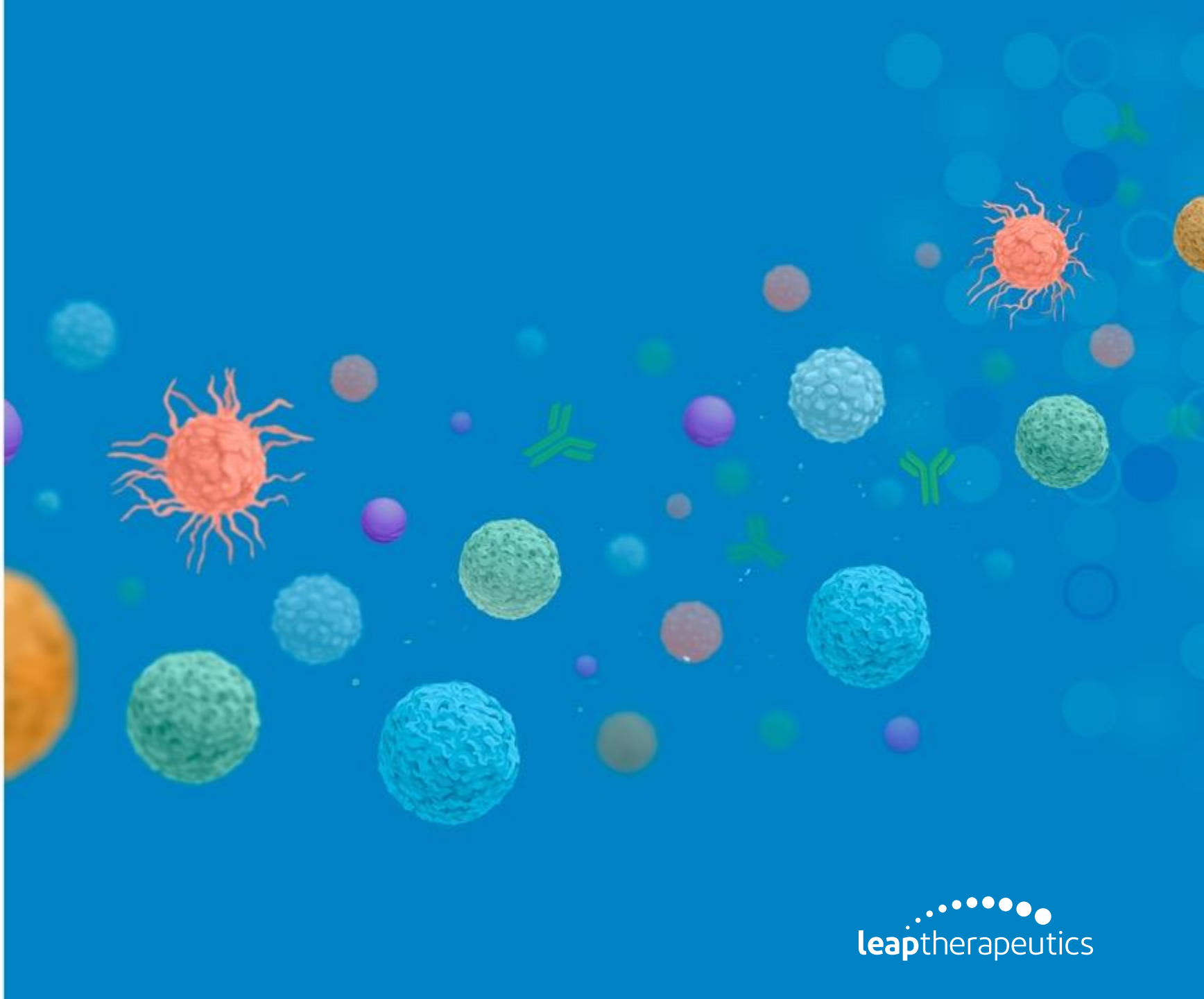
Secondary objectives:
Clinical benefit, PFS, OS, DOR

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

FL-501

Anti-GDF-15 monoclonal antibody



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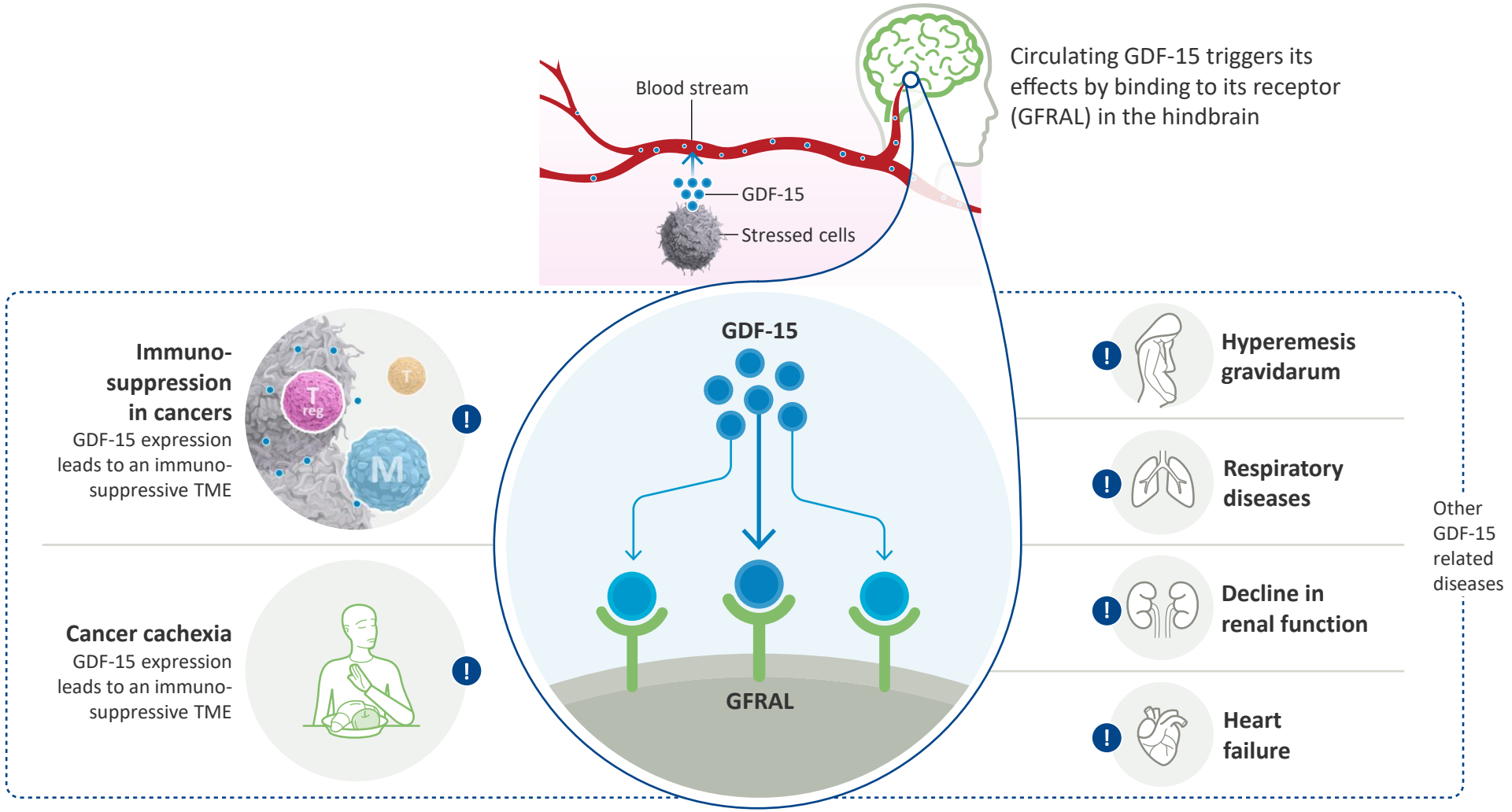
The role of GDF-15 in cachexia and cancer



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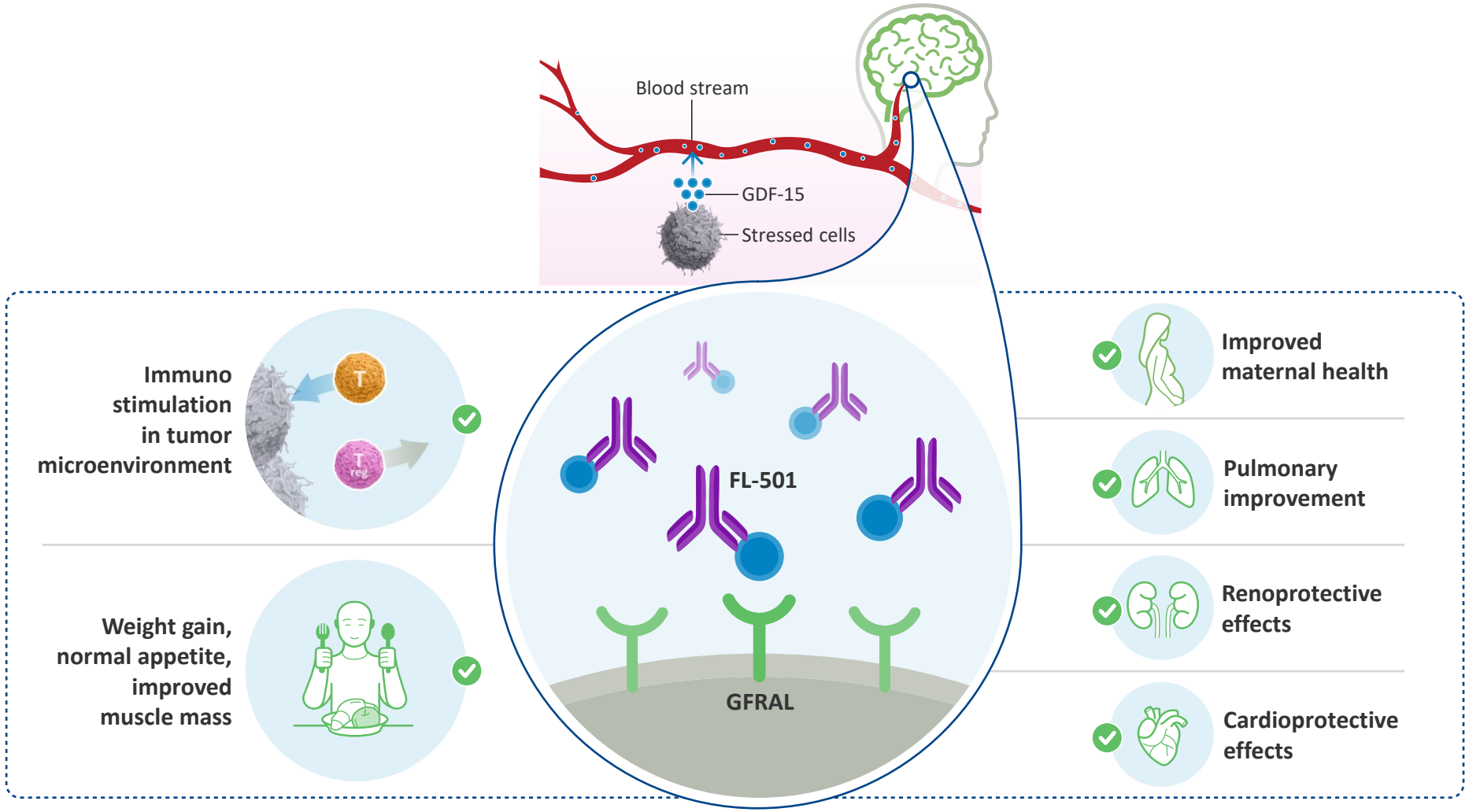
FL-501 mechanism of action



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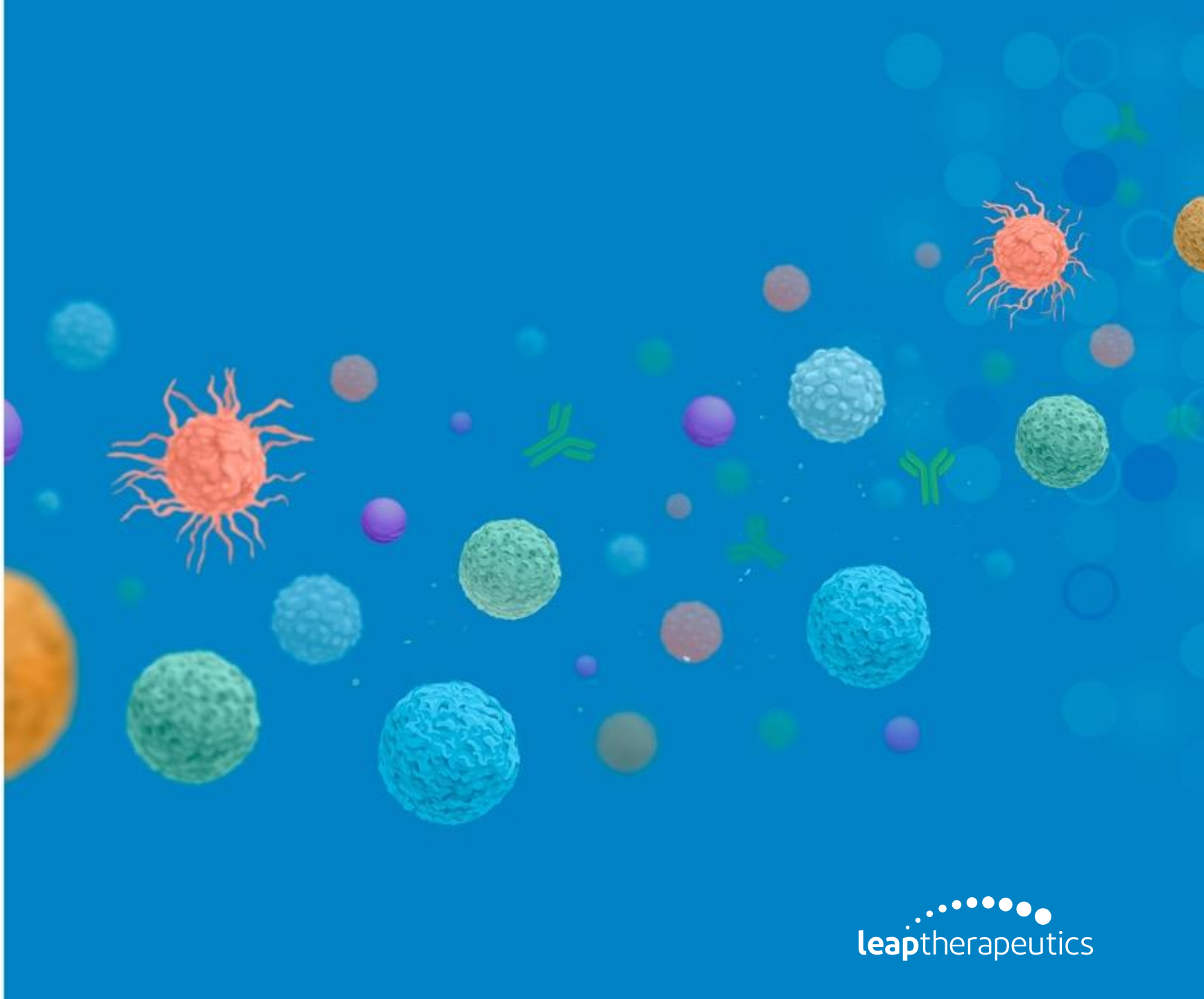
CORPORATE



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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

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2025 corporate milestones

- Sirexatamab (DKN-01)
  - Initial data disclosure from both randomized controlled clinical trials expected in Q1 2025
  - DisTinGuish study in first-line gastric cancer: ORR and PFS in all patients, DKK1-high and PD-L1 low subgroups
  - DeFianCe study in second-line colorectal cancer: ORR in all patients, left-side and bevacizumab-naïve subgroups
  - Identify the Phase 3 development strategy

- FL-501
  - Manufacturing development initiated with goal of initiating a clinical trial in H1 2026
  - Preclinical data presentation expected in early Q2 2025

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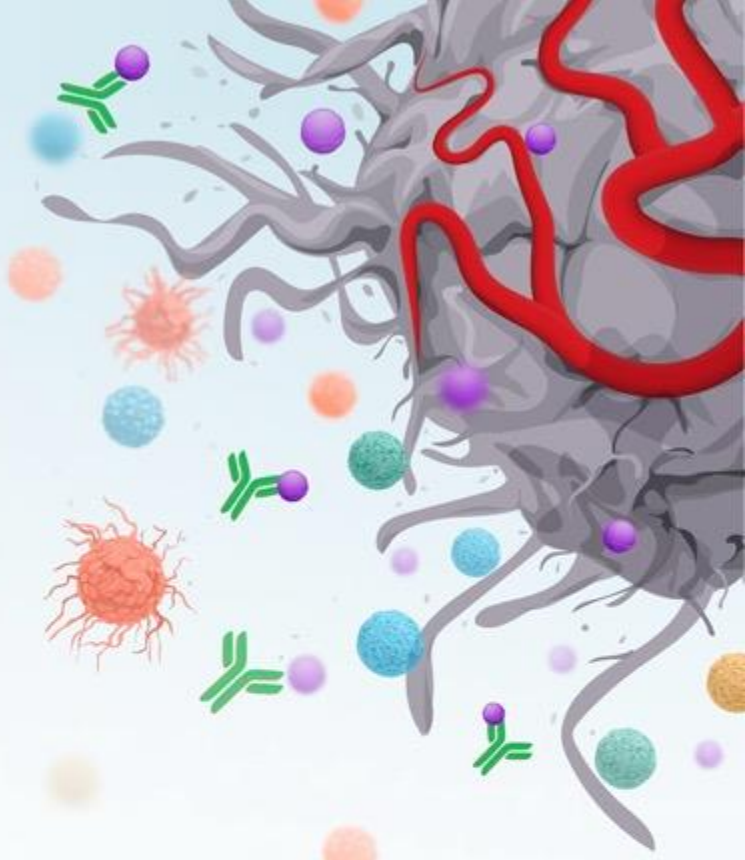
LEAP THERAPEUTICS

company presentation

January 15, 2025



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