leaptherapeutics

DKN-01 Program Update / Investigator Presentations

May 18th 2018

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, future financial position, future revenues, projected costs, prospects, plans and objectives of management, are forward-looking statements. 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. We assume no obligation to update any forward-looking statements, except as required by applicable law.

Agenda

Introduction
Dr. Cynthia Sirard, VP, Clinical Development, Leap Therapeutics

Immunotherapy Combinations and Initial Patient Results
Dr. Samuel Klempner
Director, Precision Medicine Program, The Angeles Clinic

Esophagogastric Cancer Background and Early Clinical Studies
Dr. John Strickler
Assistant Professor of Medicine, Duke Cancer Institute

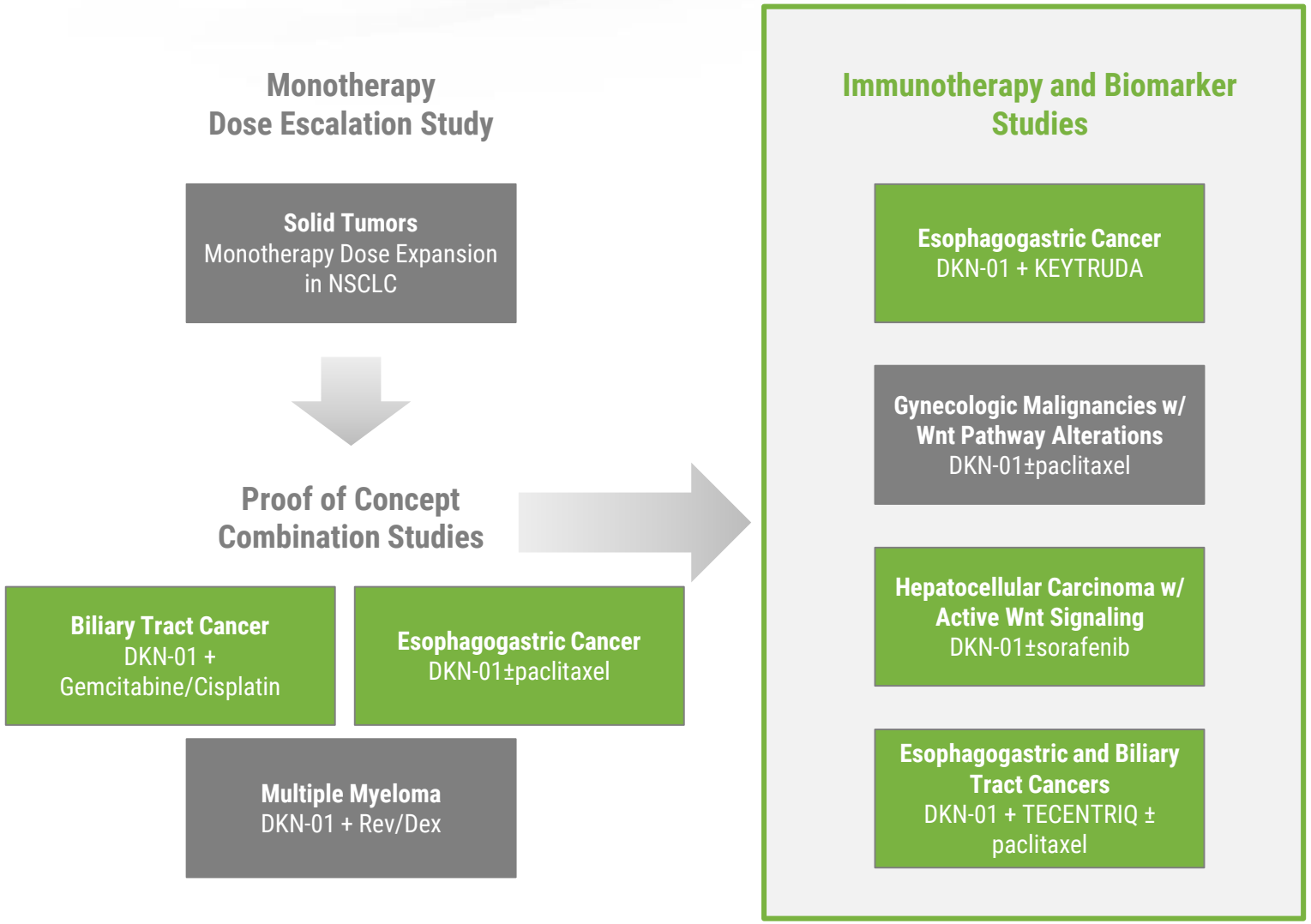
Hepatocellular Carcinoma, Biliary Tract Cancer, and Future Directions with DKN-01
Dr. Markus Möhler and Dr. Jens Marquardt
Professor and Lichtenberg Professor, University of Mainz, Germany

Q&A
Leap Therapeutics

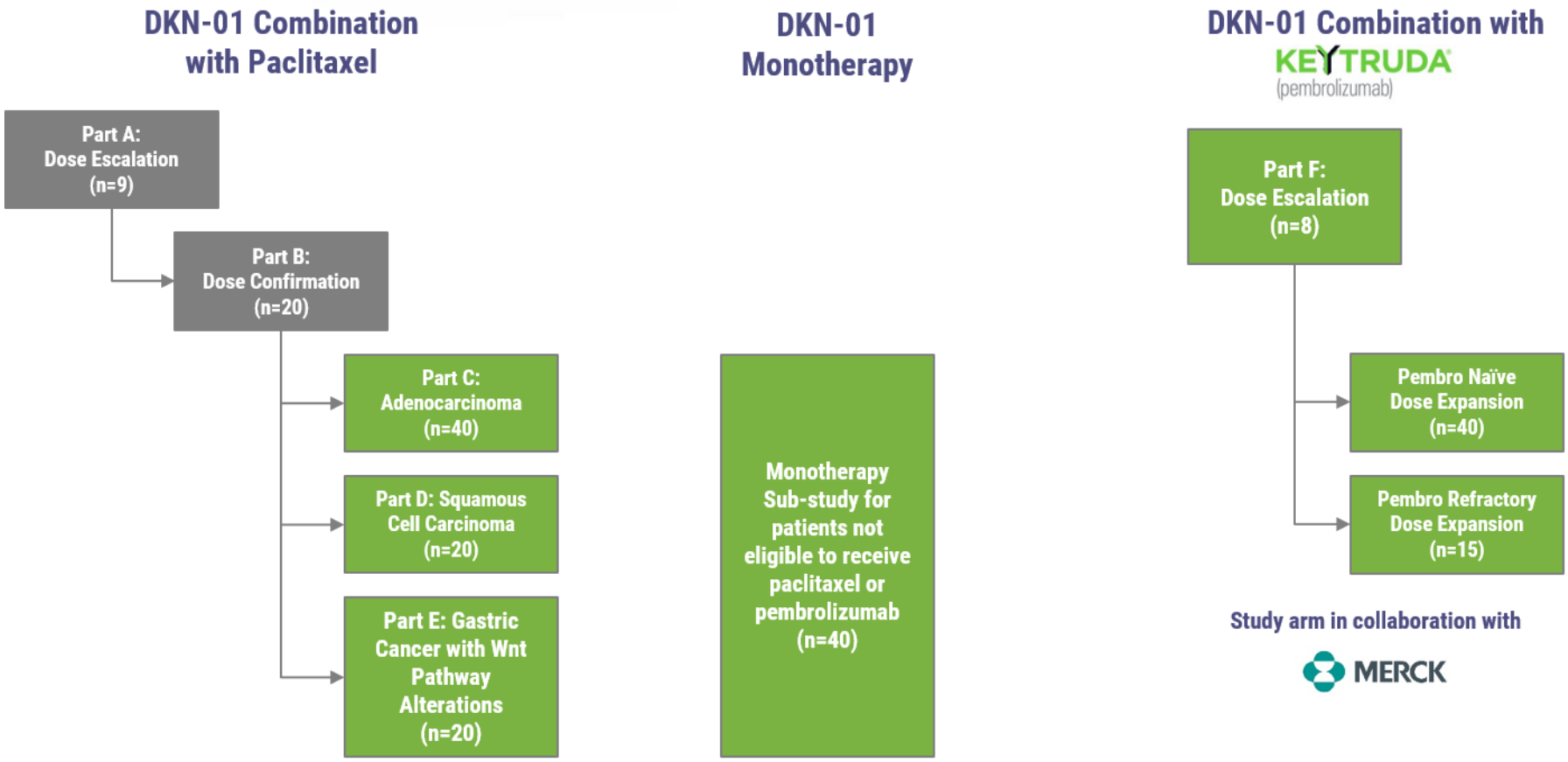
DKK1 and DKN-01 Overview

- Novel mechanism of action targeting both the tumor and tumor microenvironment
- Clinical activity and durable responses in NSCLC, esophageal cancer, biliary tract cancer
- DKN-01 therapy safe and well-tolerated with various backbone therapies
- Wnt pathway mutations identified as a biomarker to explore in future studies and additional indications
- Complementary with other immunotherapies

Today's Focus: Esophagogastric, Liver, and Biliary Cancers



DKN-01 Esophagogastric Cancer Study Overview



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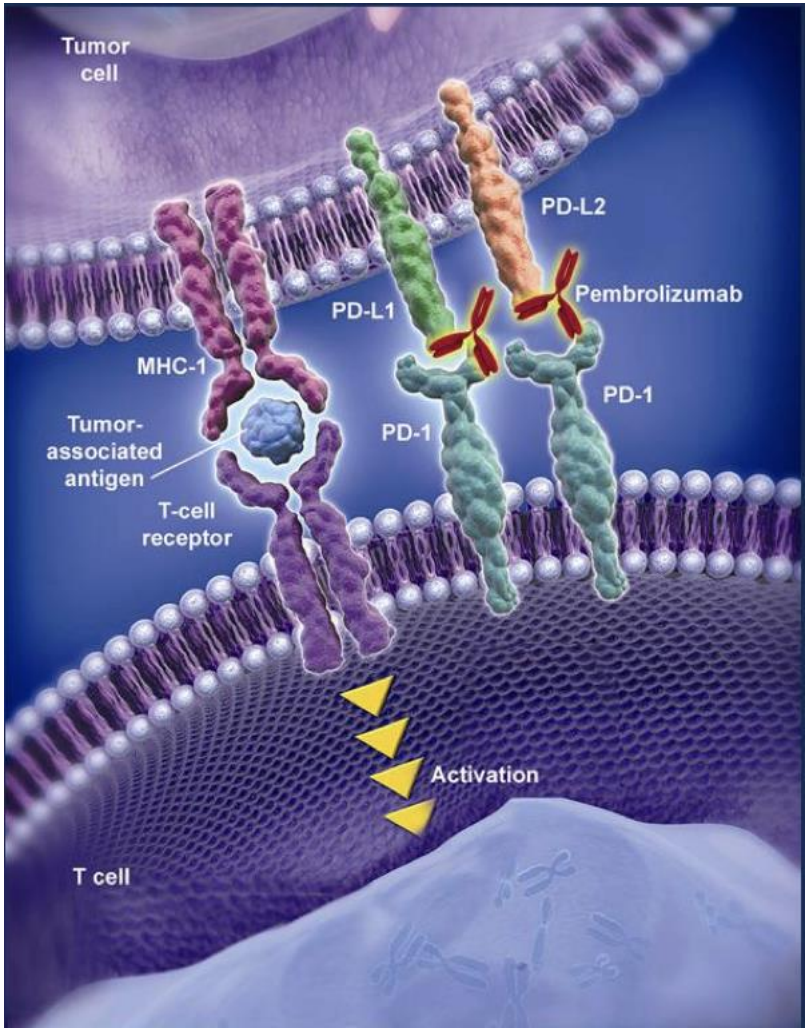
Immunotherapy Landscape in EGC

- PD-L1 and its cognate ligands are overexpressed in gastric and esophageal cancers
- Targeting the PD-1 axis has proven successful in multiple tumor types
- Early phase EGC trials suggested promising activity in both selected and unselected patients



Refs:
Gastric Cancer 2016:19;42-52
Hum Path 2016;53:25-34
Lancet Oncol 2016;17:717-726

Early Immunotherapy Trials in EGC

Table 2 Clinical activity of PD-1/PD-L1 and CTLA-4-directed therapies in advanced gastric cancer

Study	Phase	Trial population	*n*	ORR (%)	6 m PFS (%)	6 m OS (%)	12 m PFS (%)	12 m OS (%)	Median OS (m)	Median PFS (m)	Ref
KEYNOTE-012	Ib	Advanced GC	39	22	26	66	NR	42	11.4	1.9	43
KEYNOTE-028	Ib	Advanced esophageal	23	30	30	NR	21.7	NR	NR	NR	55
CheckMate-032 N 3 mg/kg	I/II	Advanced GC	59	14	18	49	7	36	5	1.3	52
CheckMate-032 N 3mg/kg, 1 1mg/kg	I/II	Advanced GC	52	10	9	43	NR	NR	4.6	1.6	52
CheckMate-032 N 1mg/kg, 1 3mg/kg	I/II	Advanced GC	49	26	18	54	18	34	6.9	1.5	52
JAVELIN	Ib	Advanced GC/GEJ, second line	62	9.7	NR	NR	NR	NR	NR	1.5	56
Tremelimumab	II	Advanced GC, esophageal	18	5	NR	NR	NR	33	4.8	2.8	73
ONO-4538	III	>2 prior lines, gastric, GEJ	493	11.2	NR	46.4	7.6	26.6	5.32	1.6	54

Gastrointestinal Cancer: Targets and Therapy 2017;7:1-11

PD-1 Monotherapy Has Limited Activity in Esophagogastric Cancer

- Outside MSI-H PD-1 has limited activity in advanced EGD
- PD-L1 selection does not completely distinguish responders from non-responders
- Novel combinations are needed to overcome innate resistance

eTable 3. Objective Tumor Response by PD-L1 Expression

	PD-L1 Positive (n = 148)		PD-L1 Negative (n = 109)	
Best overall response[a]	No.	% (95% CI)	No.	% (95% CI)
Objective response (CR + PR)	23	15.5 (10.1-22.4)	7	6.4 (2.6-12.8)
Disease control (CR + PR + SD ≥2 months)	49	33.1 (25.6-41.3)	21	19.3 (12.3-27.9)
CR	3	2.0 (0.4-5.8)	3	2.8 (0.6-7.8)
PR	20	13.5 (8.5-20.1)	4	3.7 (1.0-9.1)
SD	26	17.6 (11.8-24.7)	16	14.7 (8.6-22.7)
Progressive disease	79	53.4 (45.0-61.6)	65	59.6 (49.8-68.9)
Nonevaluable	3	2.0 (0.4-5.8)	3	2.8 (0.6-7.8)
No assessment[b]	17	11.5 (6.8-17.8)	18	16.5 (10.1-24.8)
Duration of response, median (range), mo	16.3 (1.6+ to 17.3+)		6.9 (2.4 to 7.0+)	

Abbreviations: CR, complete response; PD-L1, programmed death ligand 1; PR, partial response; NR, not reached; SD, stable disease.
[a]Only confirmed responses are included.
[b]No assessment represents patients who had a baseline assessment but no postbaseline assessment at the time of the data cutoff date. Reasons for no assessment include missing, treatment discontinuation, or death before the first postbaseline radiologic imaging study.
+No progressive disease at last assessment

eTable 6. Objective Response and Duration of Response by MSI Status

	MSI-High (n = 7)		Non–MSI-High (n = 167)	
Best overall response[a]	No.	% (95% CI)	No.	% (95% CI)
Objective response (CR + PR)	4	57.1 (18.4-90.1)	15	9.0 (5.1-14.4)
Disease control (CR + PR + SD ≥2 months)	5	71.4 (29.0-96.3)	37	22.2 (16.1-29.2)
CR	1	14.3 (0.4-57.9)	4	2.4 (0.7-6.0)
PR	3	42.9 (9.9-81.6)	11	6.6 (3.3-11.5)
SD	1	14.3 (0.4-57.9)	23	13.8 (8.9-19.9)
Progressive disease	0	0 (0.0-41.0)	102	61.1 (53.2-68.5)
Nonevaluable	0	0 (0.0-41.0)	4	2.4 (0.7-6.0)
No assessment[b]	2	28.6 (3.7-71.0)	23	13.8 (8.9-19.9)
Duration of response, median (range), mo	NR (5.3+ to 14.1+)		8.4 (2.4 to 19.4+)	

Fuchs CS, Doi T, Jang RW, et al. Safety and efficacy of pembrolizumab monotherapy in patients with previously treated advanced gastric and gastroesophageal junction cancer: phase 2 clinical KEYNOTE-059 trial. Published online March 15, 2018. *JAMA Oncol*. doi:10.1001/jamaoncol.2018.0013

PD-1 Monotherapy Fails to beat Taxol in Phase III 2L Trial

- KEYNOTE-061 is a randomized, open-label, pivotal phase III study investigating pembrolizumab as a monotherapy vs paclitaxel in patients with advanced gastric or GEJ adenocarcinoma whose disease progressed after first-line treatment with platinum and fluoropyrimidine doublet therapy

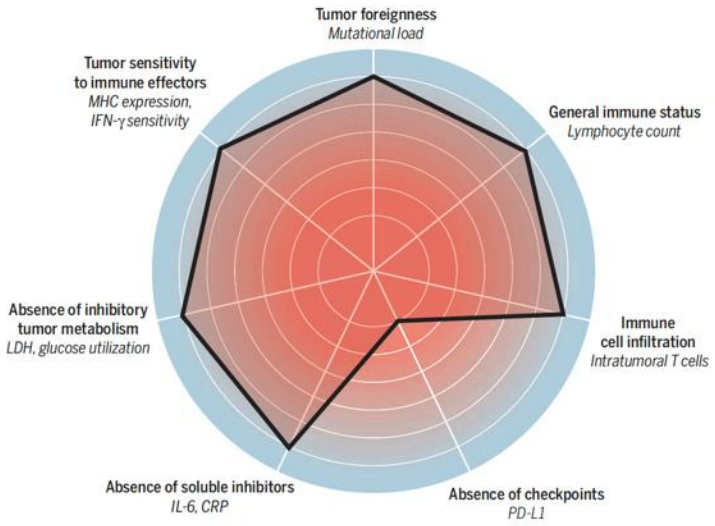
- The study randomized 592 patients to receive pembrolizumab (200 mg fixed dose every 3 weeks) or paclitaxel (80 mg/m^2 on days 1, 8, and 15 of each 28-day cycle).

- Keynote-061 did not meet its overall survival primary endpoint (OS) (hazard ratio [HR] = 0.82, 95% confidence interval [CI] = 0.66–1.03; *P* = .042 [one-sided]) in patients whose tumors expressed programmed cell death ligand 1 (PD-L1) (combined positive score [CPS] ≥ 1).

- Additionally, progression-free survival (PFS) in the PD-L1–positive population did not show statistical significance.

Unique Immunologic Activity of DKK1 Inhibition

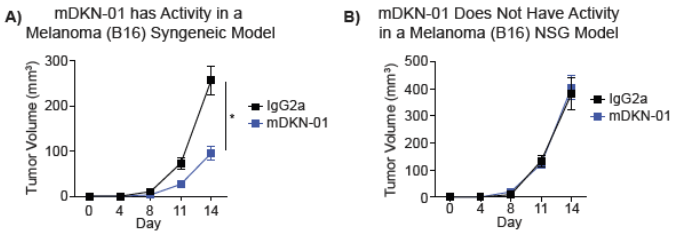
- Inhibition of DKK1 targets innate immunity
  - Reduces Myeloid Derived Suppressor Cells (MDSC)
  - Enhances NK cell activity
  - Increases expression of PD-L1
  - Induces transcription of T cell chemo-attractants



Science 2016;352:658-660

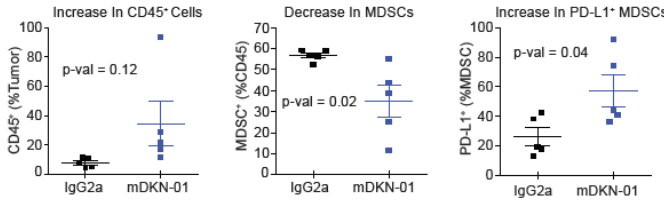
DKN-01 mechanism complementary with checkpoint inhibitors

Figure 2: Murine DKN-01 Activity Requires a Functioning Immune System



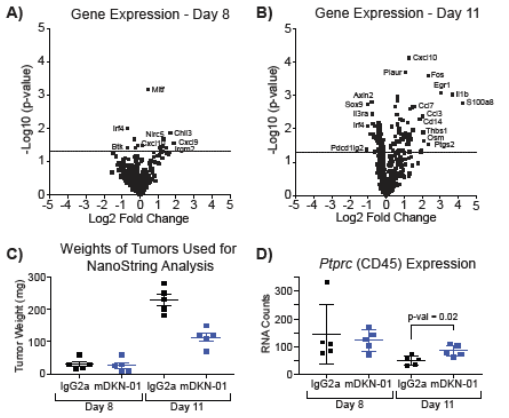
A) Immune competent C57BL/6J mice or **B)** immune incompetent NSG (NOD.Cg-Prkdcscid Il2rgtm1Wjl/SzJ) mice (10 per group) were inoculated subcutaneously with B16-F0 mouse melanoma cells on Day 0. The following day, bi-weekly intraperitoneal treatment of murine DKN-01 (mDKN-01) or IgG2a control was initiated at 10 mg/kg. Mean tumor volumes and SEM are plotted. *p-val = 0.0003.

Figure 3: Murine DKN-01 Alters the Immune Infiltrate in the Tumor Microenvironment



Flow cytometry analysis of the B16 tumor microenvironment following murine DKN-01 (mDKN-01) treatment. C57BL/6J mice were inoculated subcutaneously with B16-F0 mouse melanoma cells on Day 0. The following day, bi-weekly intraperitoneal treatment of mDKN-01 or IgG2a control was initiated at 10 mg/kg. Tumors were isolated on Day 11 (5 per group) and analyzed by flow cytometry for the presence of CD45, myeloid derived suppressor cells (MDSCs) identified as CD11b⁺ and GR-1⁺, and PD-L1⁺ MDSCs. Mean and SEM are shown.

Figure 4: Murine DKN-01 Induces Immune Gene Expression Changes



A and B) Volcano plots of NanoString gene expression data from the B16 tumor microenvironment following murine DKN-01 (mDKN-01) treatment. C57BL/6J mice were inoculated subcutaneously with B16-F0 mouse melanoma cells on Day 0. The following day, bi-weekly intraperitoneal treatment of mDKN-01 or IgG2a control antibody was initiated at 10 mg/kg. Tumors (5 per group) were isolated on Day 8 and 11, and purified RNA was analyzed by NanoString using the PanCancer Immune Profiling panel. Data was normalized and differential expression values relative to IgG2a control treatment were calculated with the NanoString nCounter Advanced Analysis Plugin. **C)** Weight of isolated tumors. Mean and SEM are shown **D)** Expression of *Ptprc* (CD45). Mean and standard deviation are shown.

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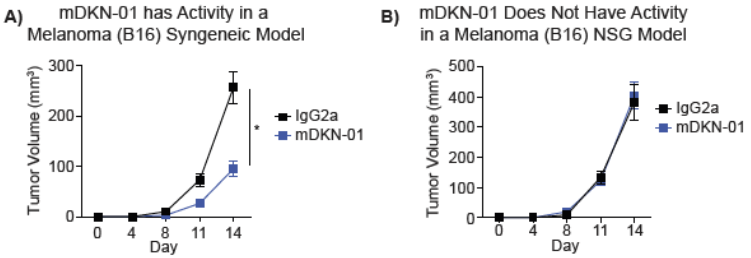

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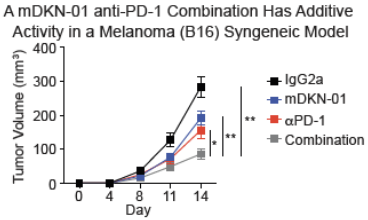
Figure 6: Murine DKN-01 Has Additive Activity With an anti-PD-1 Antibody



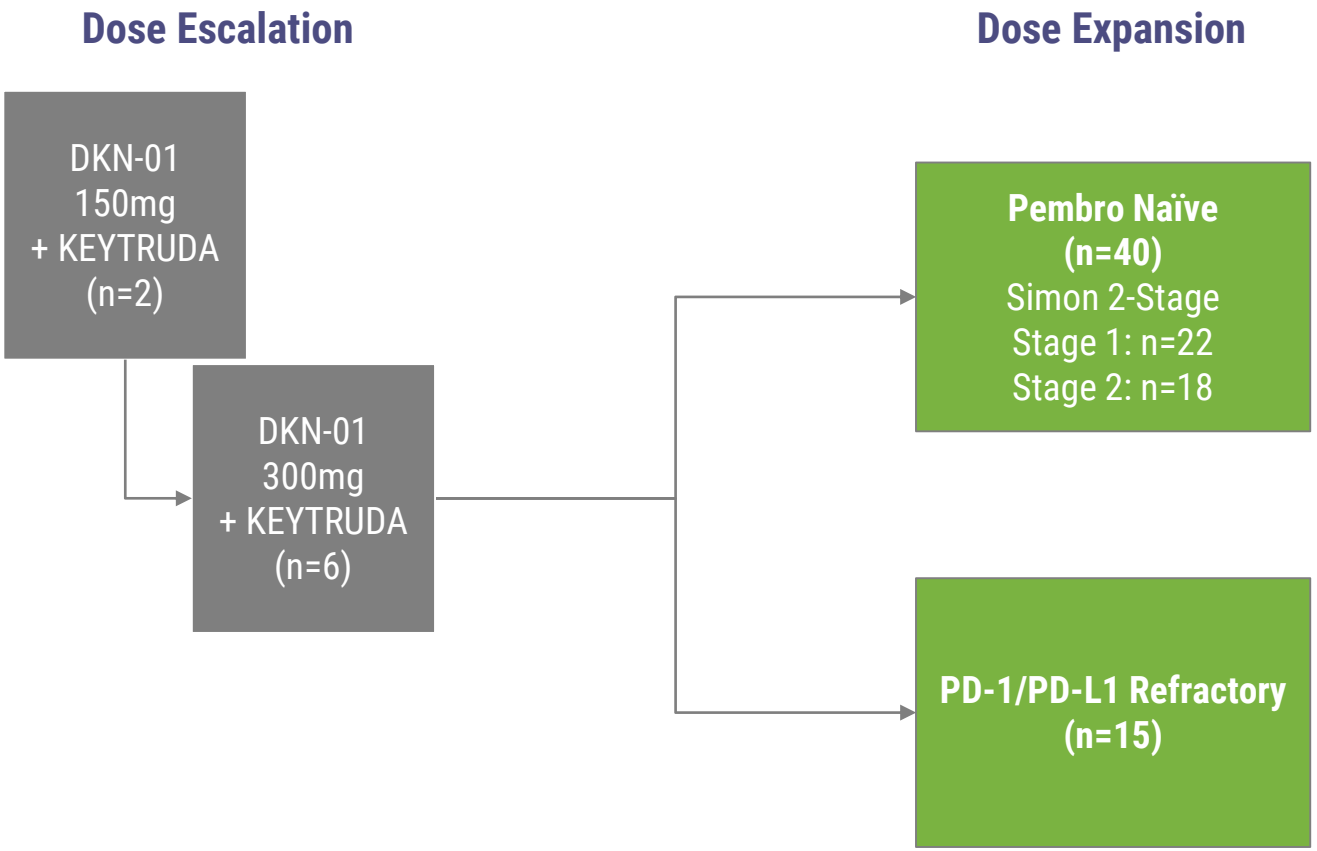
C57BL/6J mice (15 per group) were inoculated subcutaneously with B16-F0 mouse melanoma cells on Day 0. The following day, bi-weekly treatment with mDKN-01 (10 mg/kg), bi-weekly treatment with an anti-PD-1 antibody (250 ug/mouse), or combination treatment was initiated. The control animals were treated with rat IgG2a (250 ug/mouse). Mean tumor volumes are plotted. Error bars represent SEM. *p-value <0.001, **p-value <0.0001.

Challenges in Caring for Advanced EGC Patients

- Highly symptomatic disease complicates number of patients appropriate for clinical trials
- Nutritional Status: complicated by prior surgical treatment and/or tumor location
- Several large studies suggest only 40% of US EGC patients receive second line therapy
- Inter and intra-tumoral heterogeneity limit success of small molecule targeted therapies and trastuzumab

P102: DKN-01 + KEYTRUDA Study Design Overview

- Dose escalation followed by dose expansion into two groups
- 21-day cycle, D+K administered Day 1, D alone Day 15 each cycle



- *Stage 1: If 3 or more patients respond (i.e., experience CR or PR) proceed to stage 2*

Clinical Activity in Dose Escalation with Pembrolizumab

DKN-01 Dose	Prior a-PD-1 or a-PD-L1	Medical History	MSI	TMB	PD-L1	Best Overall Response	Status
300	Naive	53 M w/GEJ, s/p FOLFOX/trastuzumab, FOLFIRI	MSS	N/D	neg	**Partial Response (-66%)**	Cycle 6
	Naive	59 M w/GEJ s/p FOLFOX	MSS	I	neg	**Stable Disease (+7%)**	Cycle 5
	Naive	74 M w/GC s/p ECF and ramucirumab/paclitaxel	MSS	L	neg	**Stable Disease (non-measurable at baseline)**	Cycle 4
	Naïve	61 M w/GEJ s/p FOLFOX, ramucirumab/paclitaxel and irinotecan	MSS	N/D	N/D	**Stable Disease (+3%)**	Off Study - Cycle 3
	Naive	63 M w/ EC s/p FOLFOX and XELOX	MSS	L	pos	**Not Evaluable**	Off Study - Cycle 1 (death unrelated)
	Refractory	62 M w/GEJ s/p anti-PD1 (PD), and ramucirumab/paclitaxel	N/D	N/D	N/D	**Stable Disease (+10%)**	Cycle 3
150	Naïve	67 M w/EC, s/p FOLFOX, ramucirumab + paclitaxel, irinotecan	N/D	N/D	N/D	**Progressive Disease (+26%)**	Off Study - Cycle 1
	Refractory	69 F w/GC, s/p FOLFOX, anti-PDL1 for 2 years with PD	MSS	I	neg	**Stable Disease (-10%)**	Cycle 6

Note: MSI = Microsatellite Instability, MSS = Microsatellite Stable, TMB = Tumor Mutational Burden, I = Intermediate, L = Low, N/D = Not Done/Not Available

Data presented at AACR 2018.

Case Study: Patient 011 on DKN-01 + KEYTRUDA

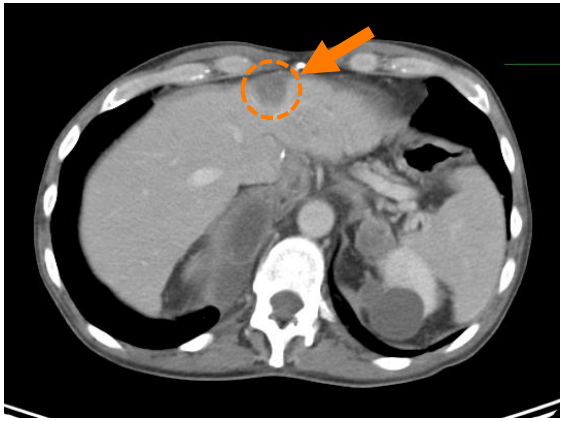
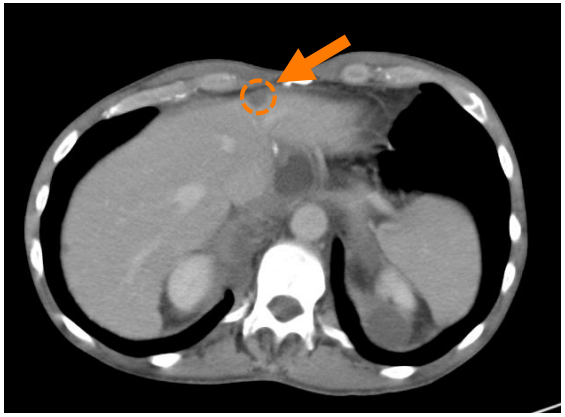
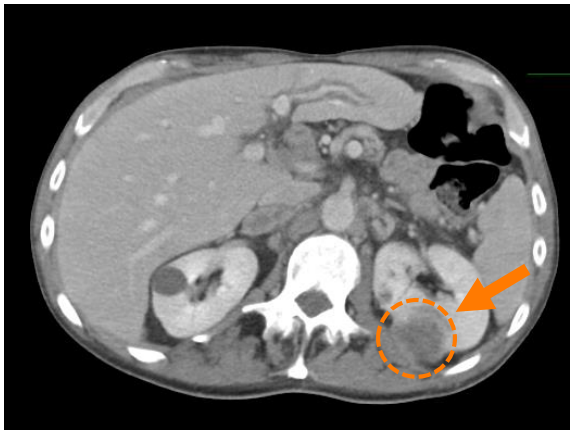
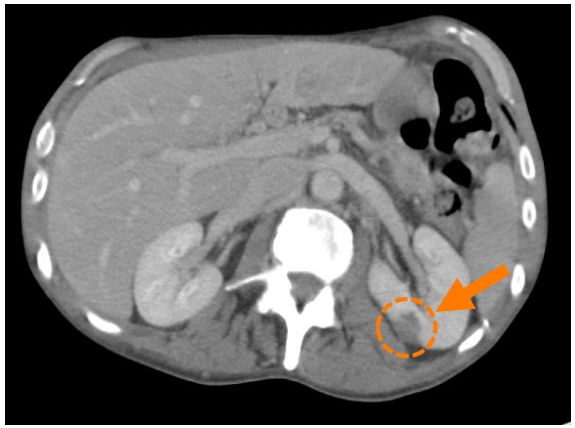
Immune resistant phenotype (KRAS amplified, MSS, and PD-L1 negative) patient treated with DKN-01+KEYTRUDA combination with documented PR.

- 53 year old male with advanced distal esophageal/GEJ adenocarcinoma
- Previously treated with carboplatin/paclitaxel/XRT, FOLFOX/trastuzumab, and FOLFIRI
- Rapid disease progression immediately preceding study entry

Study Performance

- Began combination therapy (DKN-01: 300 mg) in Dec 2017 with lesions in the liver, adrenals, hip, lungs, liver and sacrum
- ~66% reduction after 5 cycles, currently in Cycle 6
- No adverse events, dramatic improvement in QoL

Tumor Images from Patient 011

	December 2017	March 2018
Target Lesion: Hepatic Lobe		
Target Lesion: Renal/ Perirenal Mass		

Conclusions

- Gastric and esophageal cancers represent a major cause of global cancer-related deaths (2^{nd} -3^{rd} leading cause of global cancer-related death)

- Despite the approval of pembrolizumab for PD-L1+ patients who have received 2 or more lines of therapy, only the small minority respond to monotherapy.

- There is an urgent need for combinatorial approaches to expand the benefit to a larger proportion of patients

- DKN-01 in combination with pembrolizumab is a safe and tolerable combination with promising activity in EGC, including patient ineligible and/or less likely to benefit from single agent PD-1 therapy.

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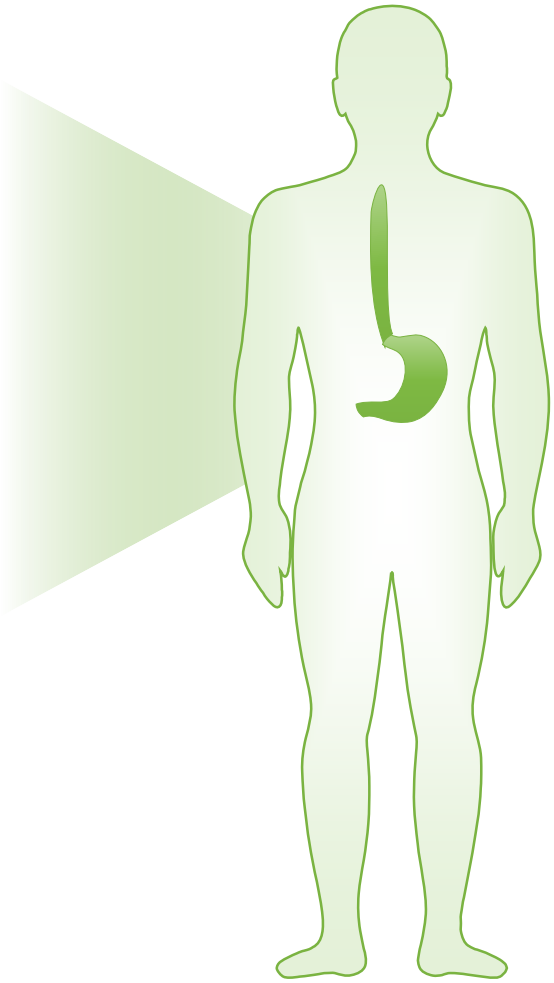
Esophagogastric Cancer

New Cases Each Year*

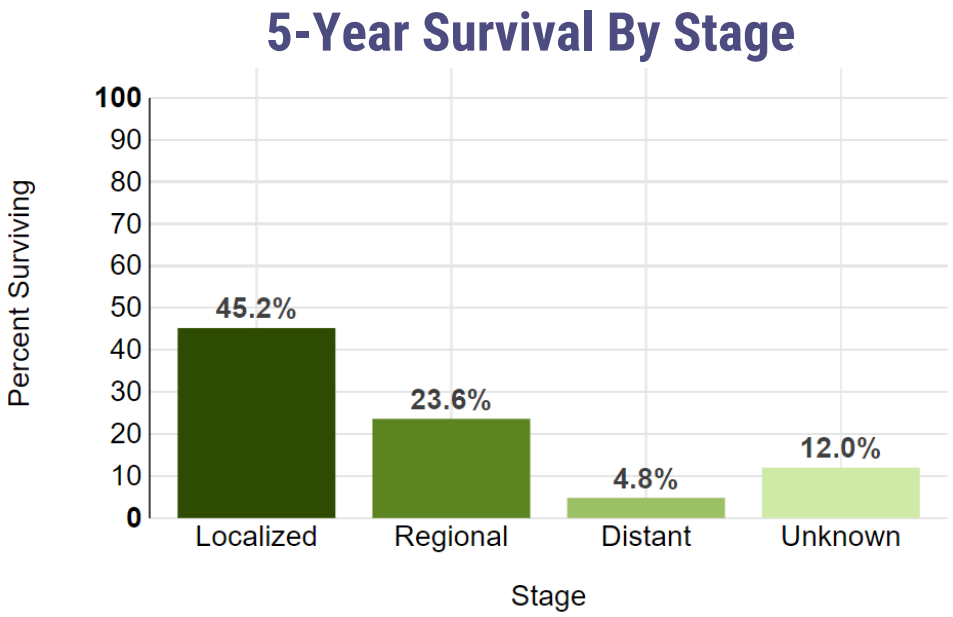
	Esophageal Cancer	Gastric Cancer
US	17,290	26,240
Worldwide	456,000	952,000



* SEER: US in 2018
WCRF: Worldwide 2012

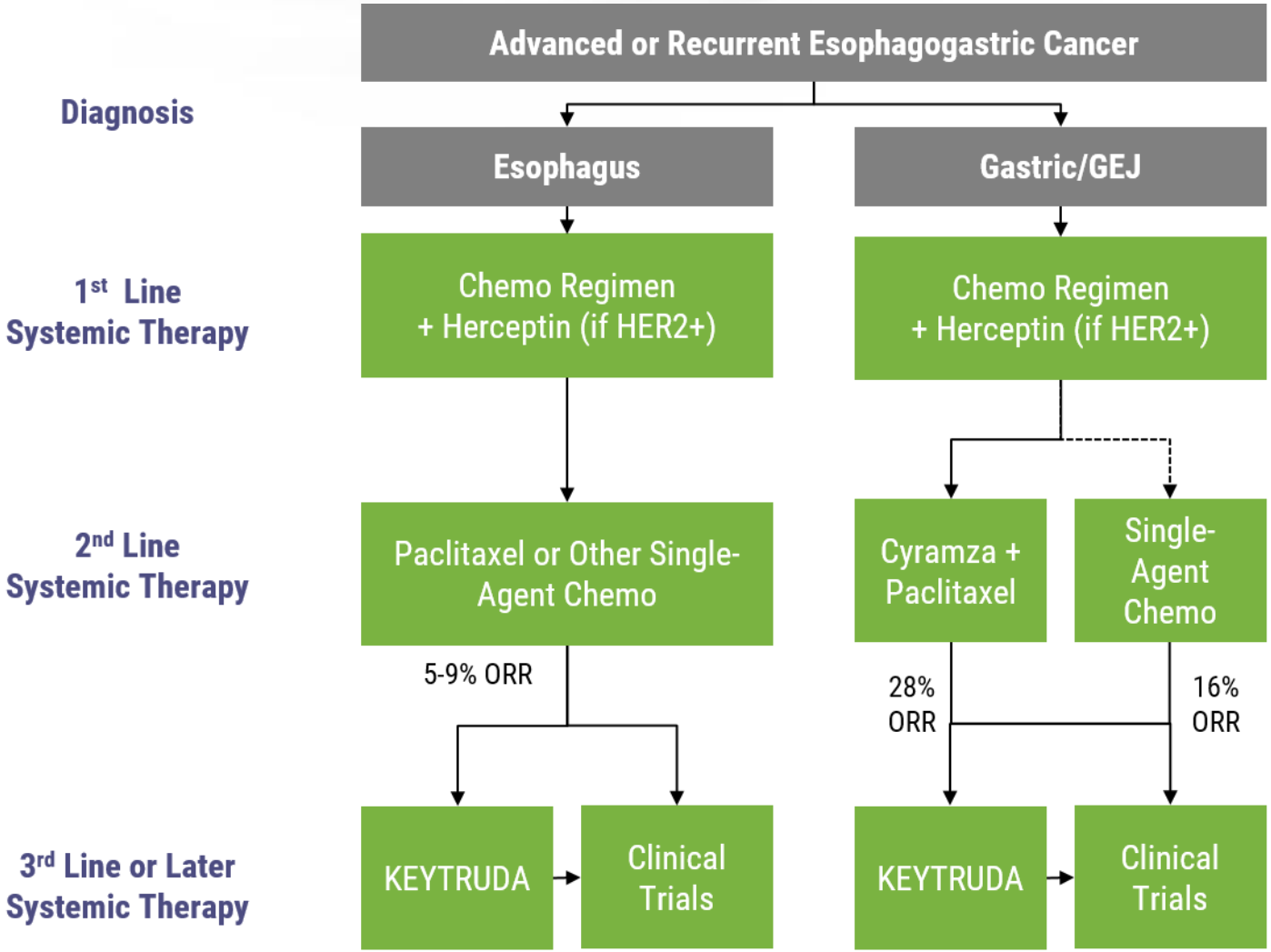
Esophagogastric Cancer: Grim Prognosis and Poor Quality of Life

- At diagnosis >50% percent of patients have advanced disease
- Limited treatment options available
- Standard of care has limited activity



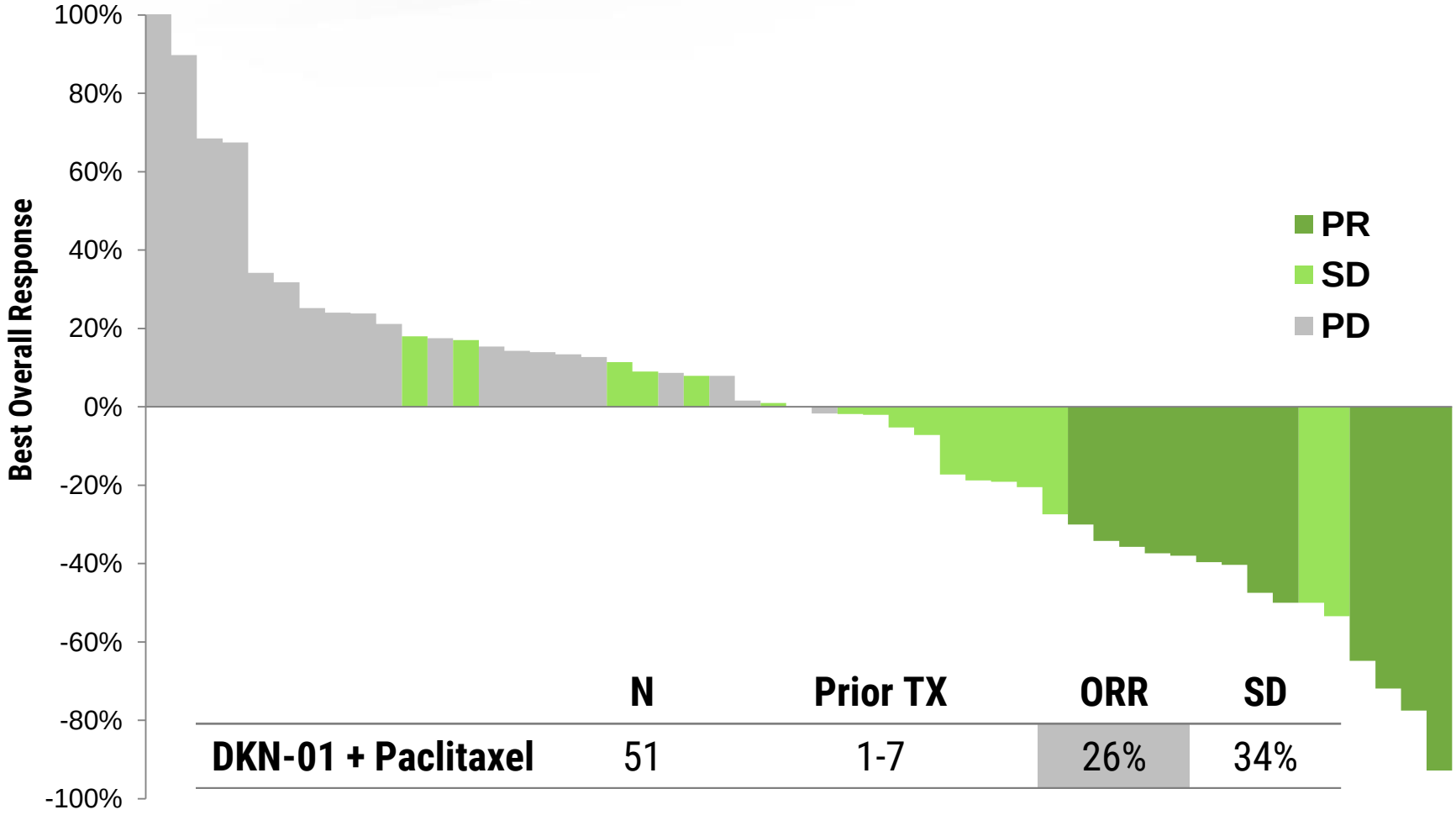
Source: SEER

Treatment Paradigm for Esophagogastric Cancer



Monotherapy	ORR
Cyramza (REGARD Study)	3.4%
Keytruda (KEYNOTE-059)	11.6%
Opdivo (ONO-4538-12)	11.2%

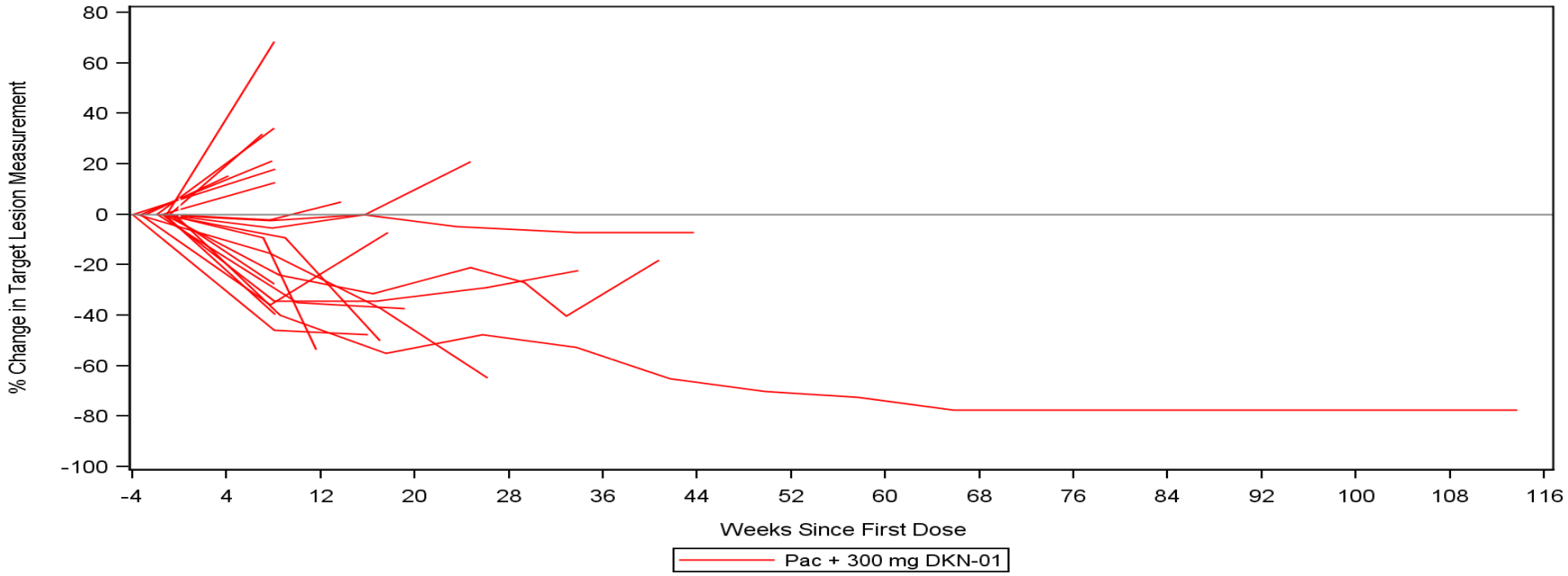
DKN-01 and Paclitaxel Efficacy in Esophagogastric Cancer



	N	Prior TX	ORR	SD
DKN-01 + Paclitaxel	51	1-7	26%	34%

DKN-01 + Paclitaxel in Taxane Naïve Patients

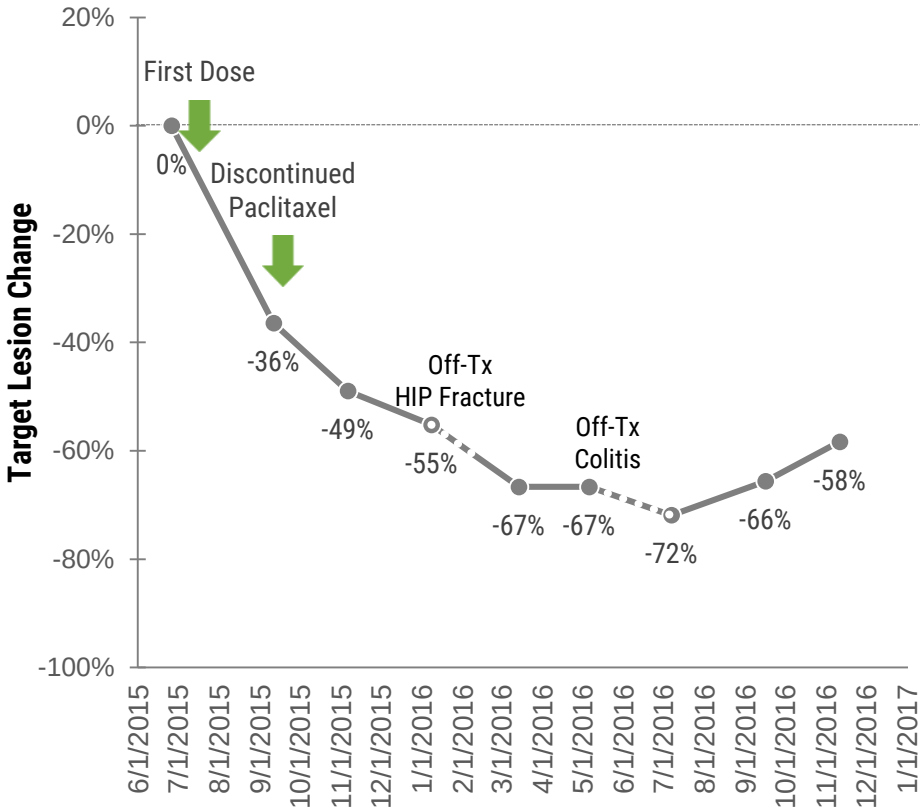
Tumor Burden Change Over Time
(Each Line Represents an Individual Patient)



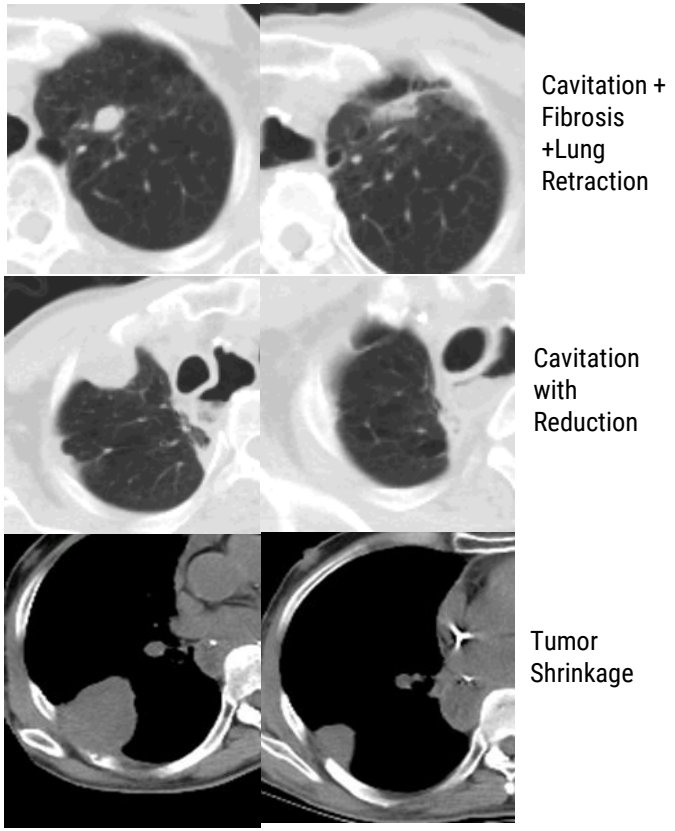
ORR	SD
41%	32%

Case Study: Patient with Squamous Cell Carcinoma

Tumor Volume Change



Baseline Cycle 8



Cavitation + Fibrosis +Lung Retraction

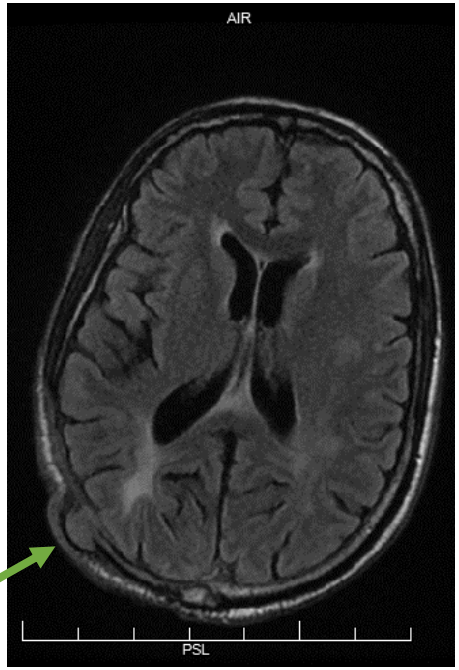
Cavitation with Reduction

Tumor Shrinkage

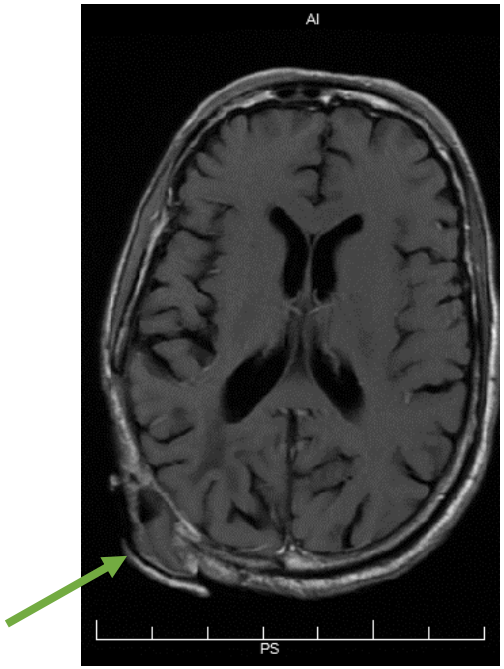
Case Study: Patient with Squamous Cell Carcinoma

Change in Non-Target Brain Lesion

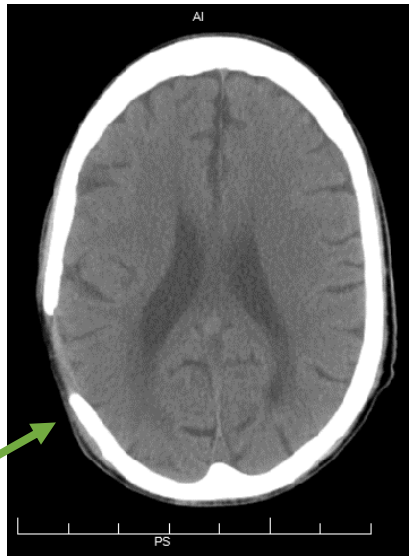
Two Months After Calvarium XRT



Five Months After Calvarium XRT Two weeks into DKN-01 Therapy



Two Months of DKN-01 Therapy



Case Study: PD-L1 Refractory Patient on DKN-01 + KEYTRUDA

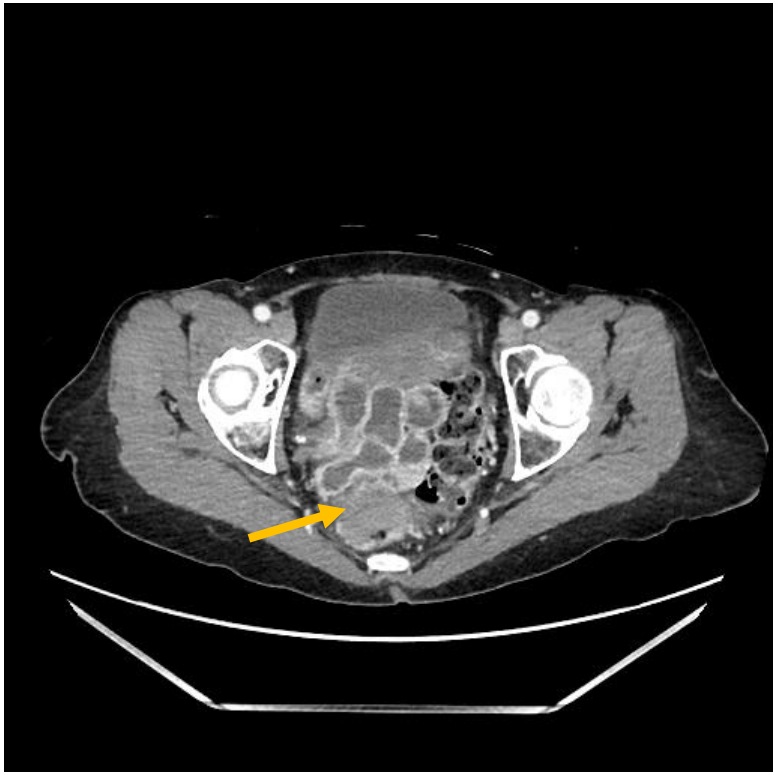
- 69 year old female with gastric adenocarcinoma

- Treatment History:
  - FOLFOX adjuvant (rapid progression)
  - Clinical trial with checkpoint inhibitor therapy (durable PR, developed oligometastatic disease and ultimately progressed through with new sites of disease in September 2017)

- Began combination therapy (DKN-01: 150 mg) on Nov 2017 with disease in pelvis and peritoneum

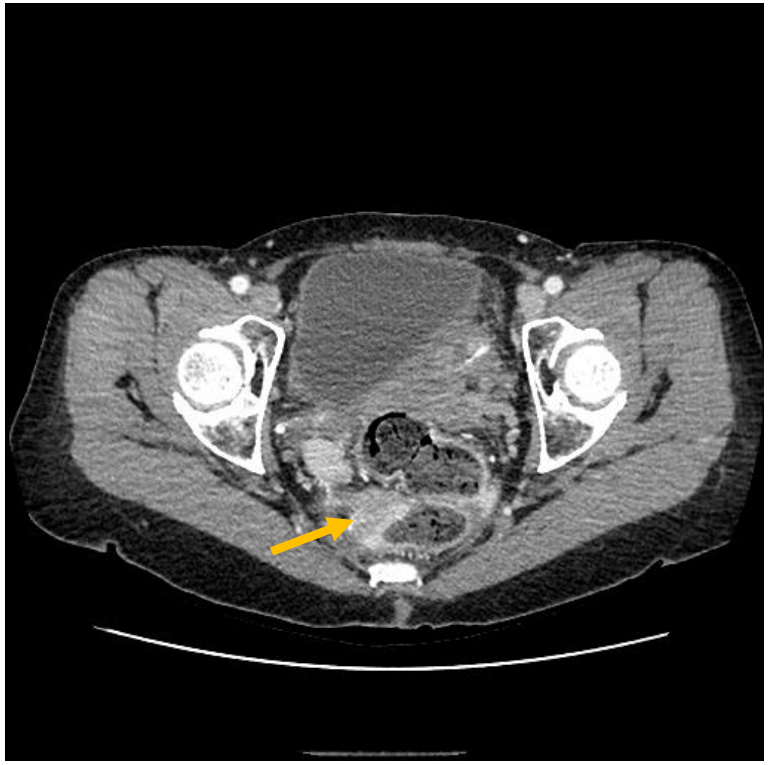
- Tumor burden reduction (~10%) at end of Cycle 2 scan

Clinical Benefit and Decrease in Pelvic Mass



November 2017

4.1 x 2.6 cm



January 2018

3.7 x 1.8 cm

Conclusions

- Esophagogastric cancer has few available treatment options for advanced disease
- DKN-01 well-tolerated with no new emerging safety trend
- DKN-01 early activity encouraging as both a single agent and in combination with paclitaxel or pembrolizumab

Agenda

Introduction
Dr. Cynthia Sirard, VP, Clinical Development, Leap Therapeutics

Immunotherapy Combinations and Initial Patient Results
Dr. Samuel Klempner
Director, Precision Medicine Program, The Angeles Clinic

Esophagogastric Cancer Background and Early Clinical Studies
Dr. John Strickler
Assistant Professor of Medicine, Duke Cancer Institute

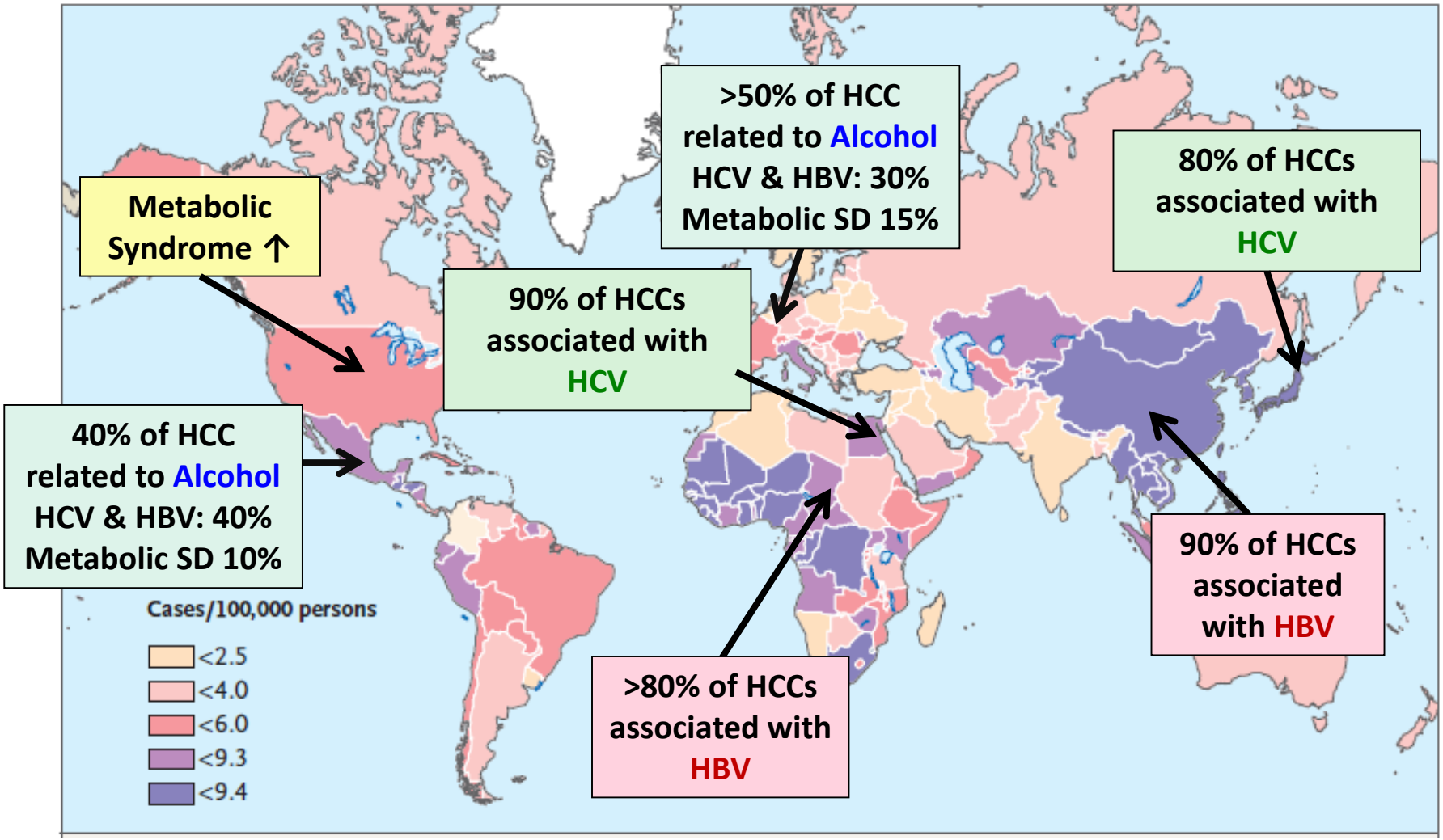
Hepatocellular Carcinoma, Biliary Tract Cancer, and Future Directions with DKN-01
Dr. Markus Möhler and Dr. Jens Marquardt
Professor and Lichtenberg Professor, University of Mainz, Germany

Q&A
Leap Therapeutics

Hepatocellular Carcinoma

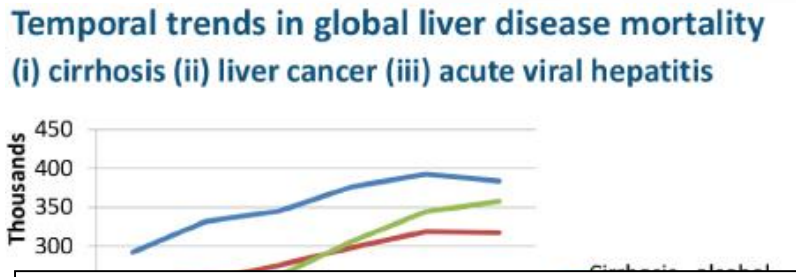
- 6th most common malignancy with rising incidence in the western world
- 3rd most common cause of cancer related deaths
- Heterogenous disease with diverse molecular pathogenesis
- HCC is multi-resistant to conventional irradiation or chemotherapy
- Less than 30% of the HCC patients are eligible for curative treatment (transplantation)
- Relapse occurs in most HCC patients after surgery

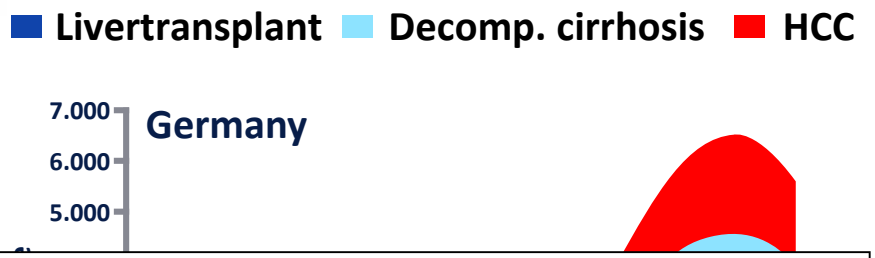
Epidemiology and Geographic Heterogeneity



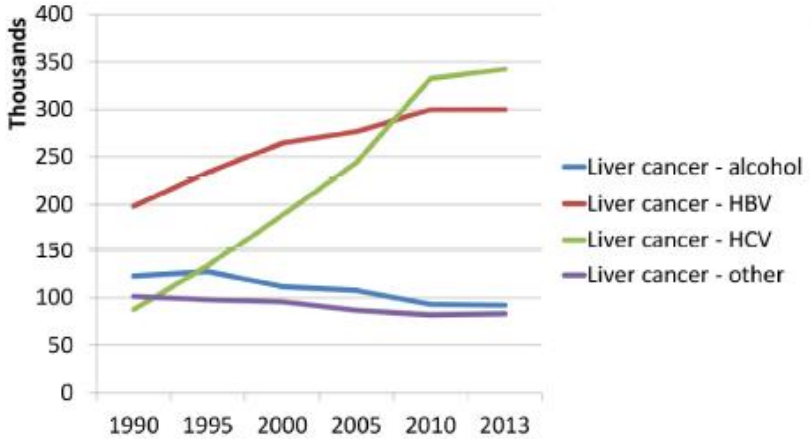
El-Serag NEJM 2011

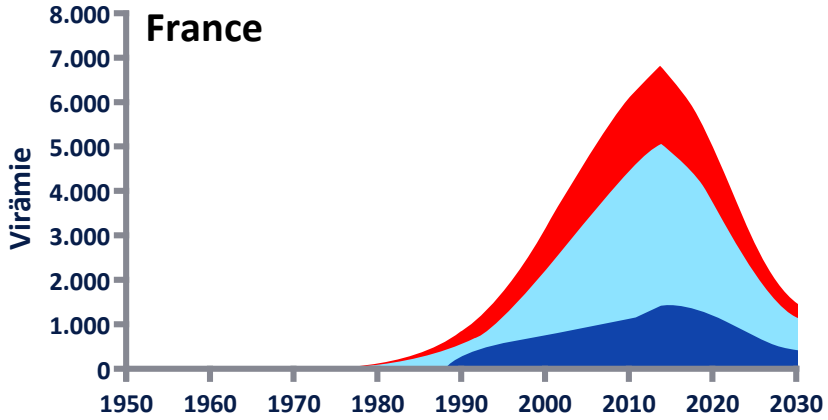
Global Burden of Liver Diseases





Liver cancer is an increasing health care problem!

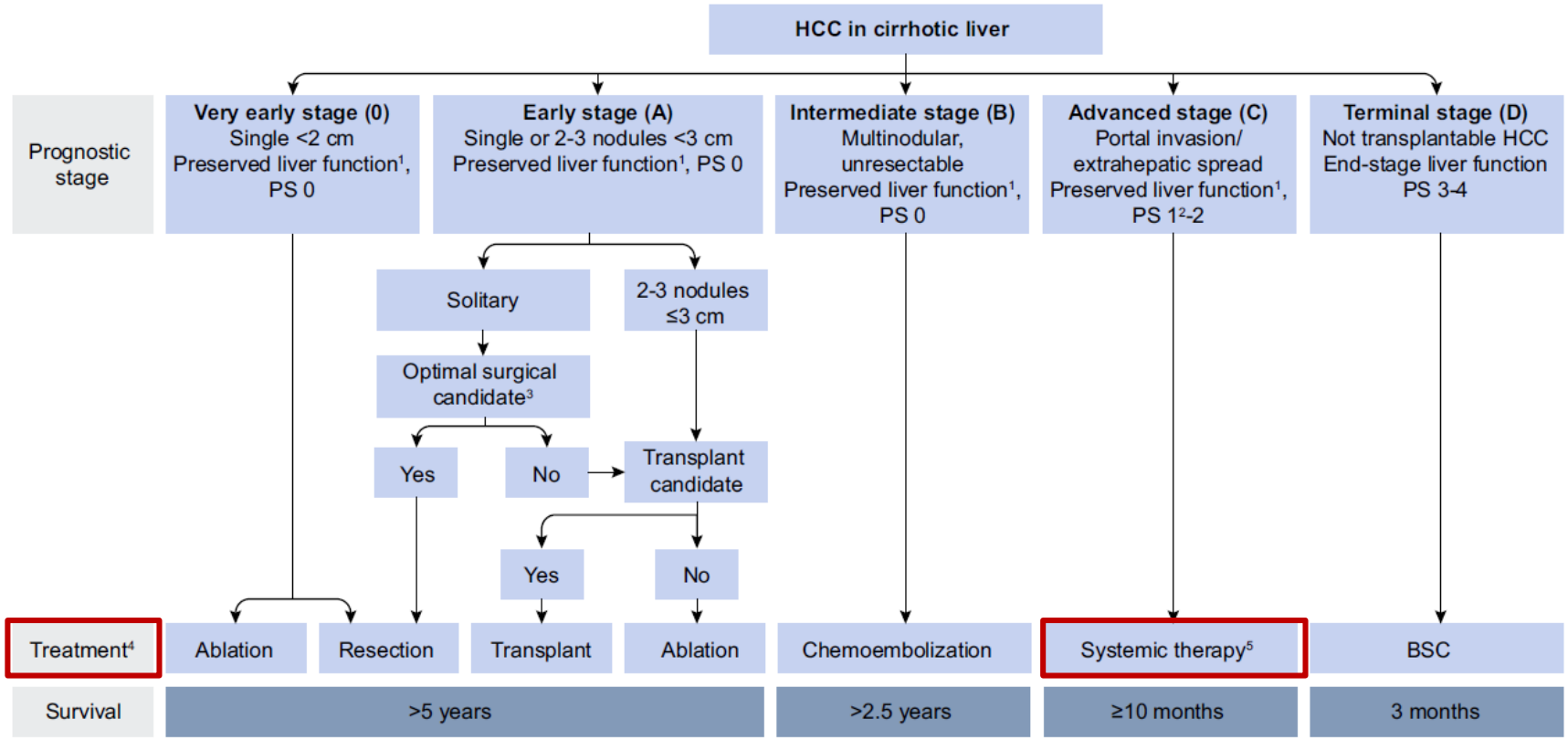




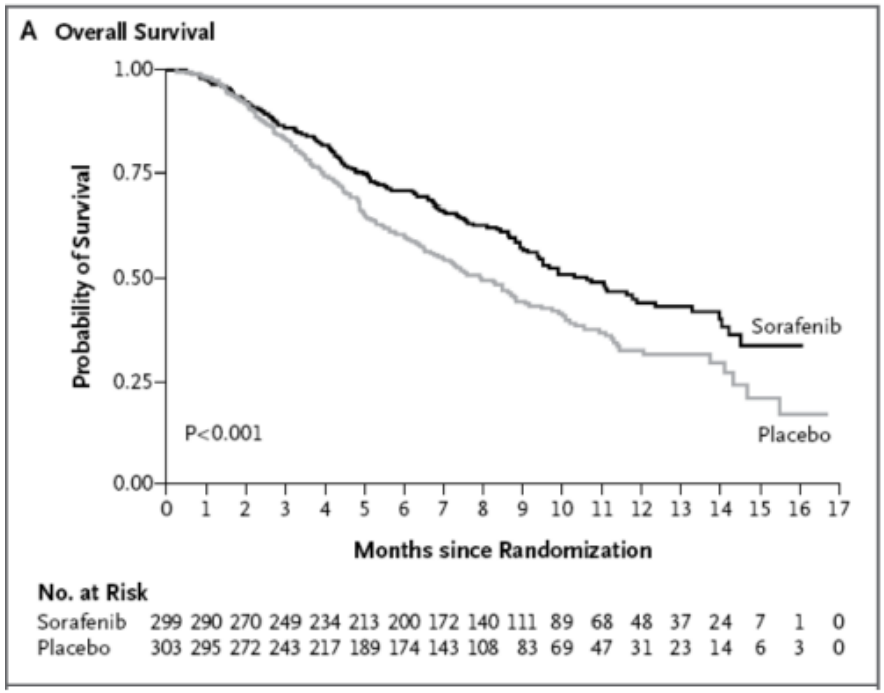
Razavi H, et al. J Viral Hepat 2014; 21(Suppl. 1):34–59; Cowie BC et al., EASL 2015; abstract 1256

Update BCLC Classification

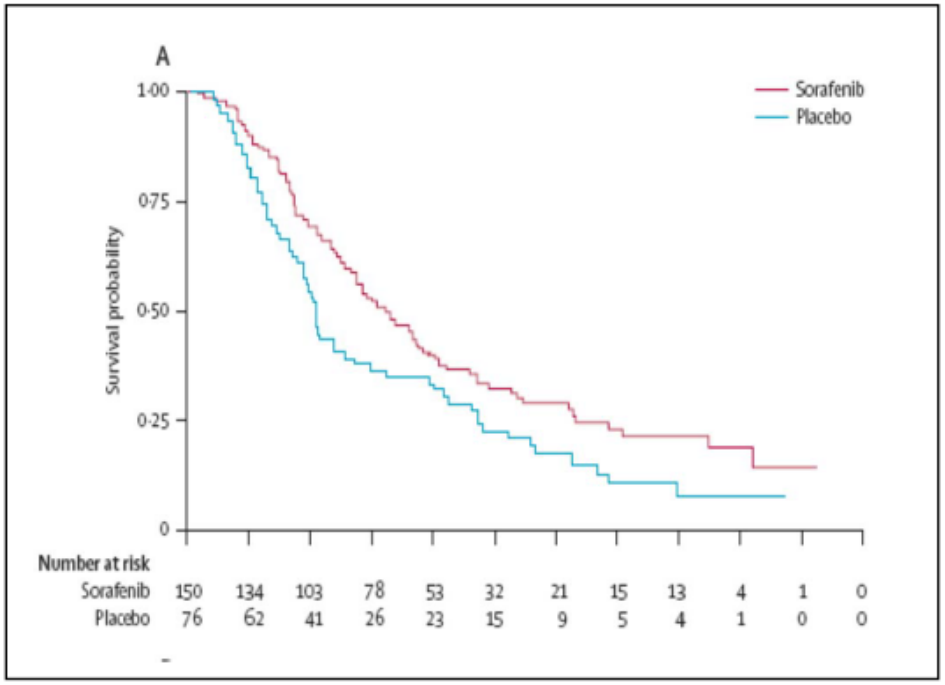
- EASL CPG, Galle et al. J Hepatol 2018 Apr 5. doi: 10.1016/j.jhep.2018.03.019



State of the Art 1st Line: Sorafenib (SHARP/Asia Pacific Trial)



OS
10.7 vs 7.9 Months



OS
6.5 vs 4.2 Months

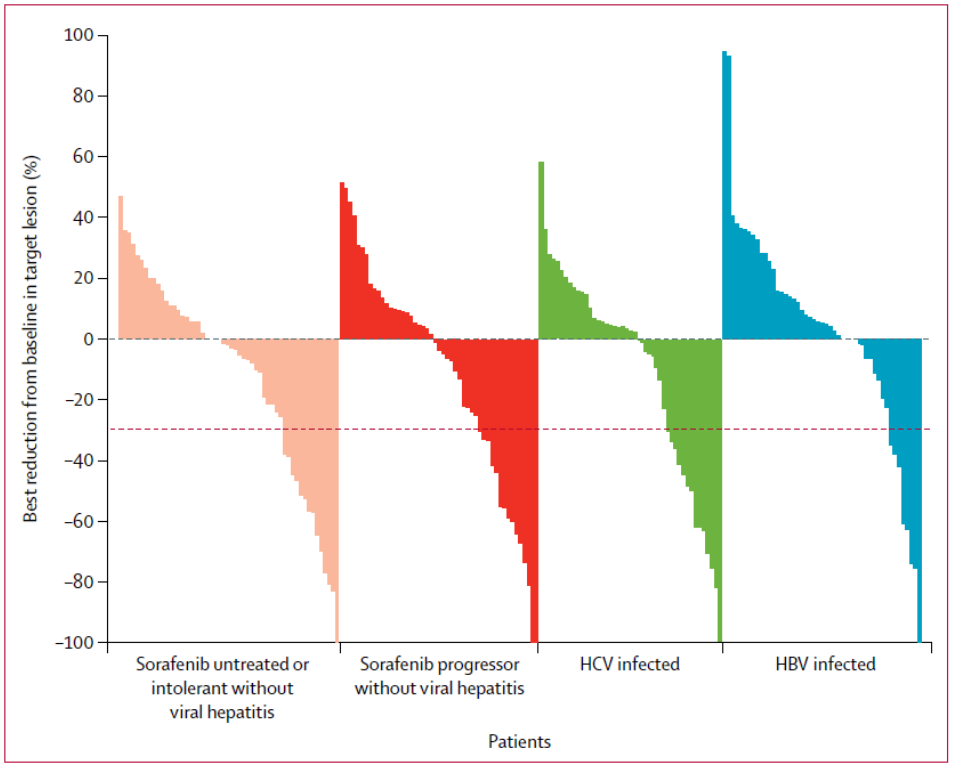
Llovet JM et al., N Engl J Med 2008; 359;379-390
Cheng AL et al., Lancet Oncol 2009;10:25-34

Completed Phase 3 Studies

Wörns MA et al., Nat Rev Gastroenterol Hepatol. 2014;11(7):447-452

Nivolumab – Phase I/II 1L/2L – CheckMate 040

- *El-Khoueiry AB et al., Lancet 2017; 389:2492-2502*

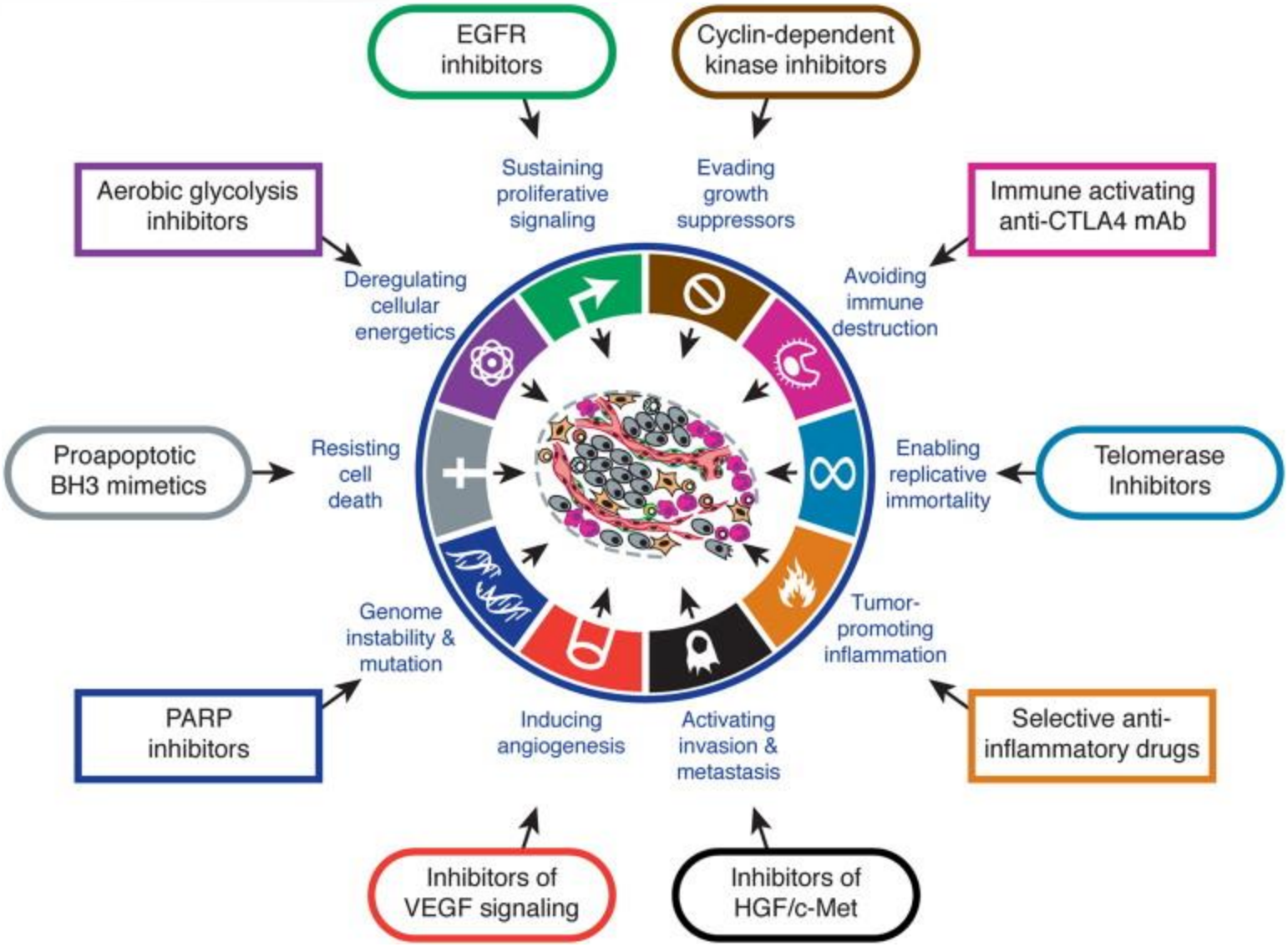


	Escalation phase (n=44)*	Expansion phase (n=174)*
PD-L1 ≥1%†	11 (25%)	34 (20%)
Objective response	3/11 (27%; 6–61)	9/34 (26%; 13–44)
Complete response	1 (9%)	1 (3%)
Partial response	2 (18%)	8 (24%)
Stable disease	0	16 (47%)
Progressive disease	7 (64%)	9 (26%)
Not determined	1 (9%)	0
PD-L1 <1%†	33 (75%)	140 (80%)
Objective response	4/33 (12%; 3–28)	26/140 (19%; 13–26)
Complete response	2 (6%)	2 (1%)
Partial response	2 (6%)	24 (17%)
Stable disease	19 (58%)	62 (44%)
Progressive disease	8 (24%)	46 (33%)
Not determined	2 (6%)	6 (4%)

Data are n (%); n/N (%; 95% CI). PD-L1=programmed death-ligand 1.
*Four patients in the dose-escalation phase and 40 patients in the dose-expansion phase did not have tumour PD-L1 expression data available.
†PD-L1 membrane expression on tumour cells.

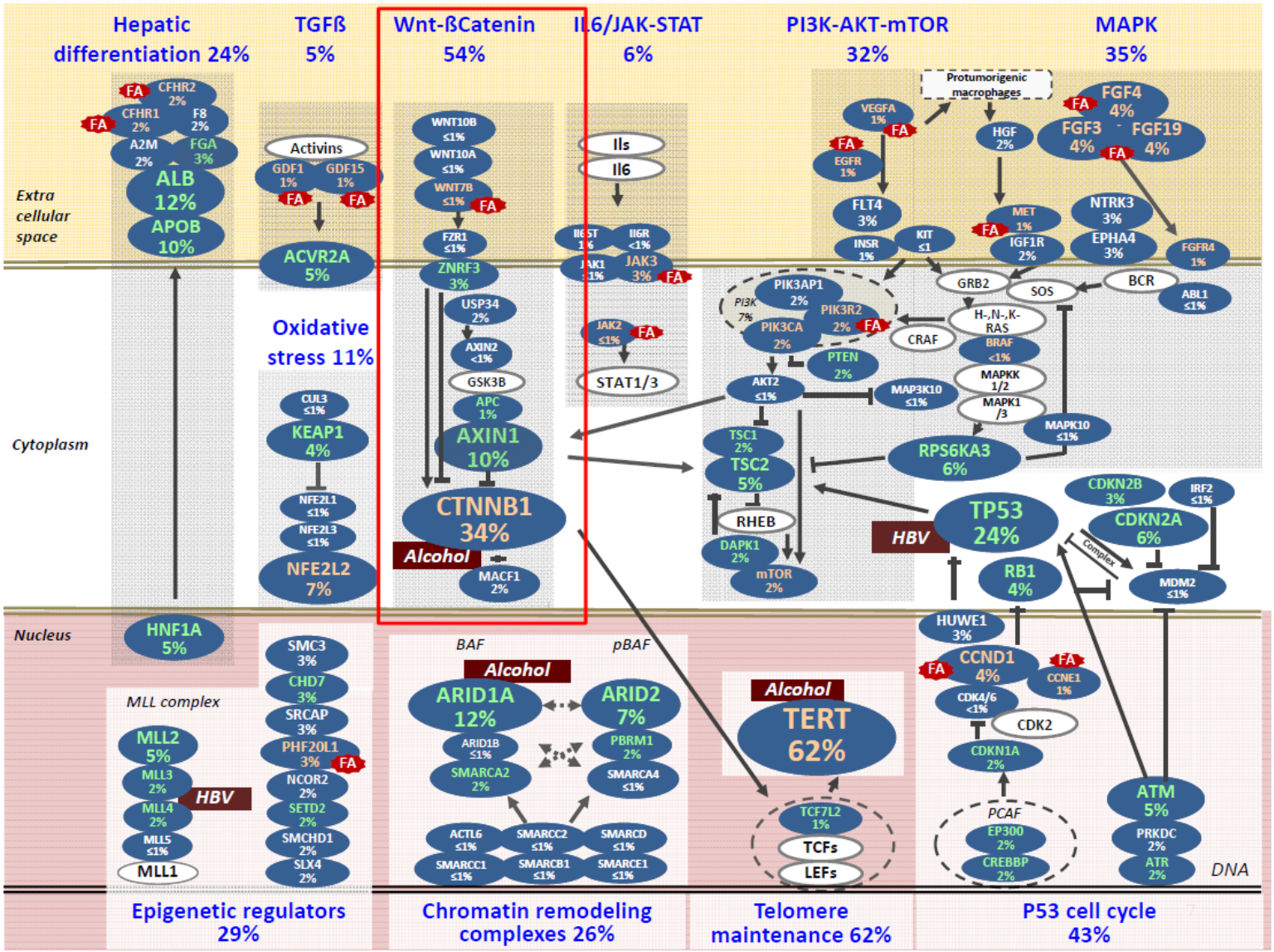
Table 5: PD-L1 expression on tumour cells and response

"Hallmarks" of Cancer



Hanahan and Weinberg Cell 2011

Landscape of Mutations in HCC



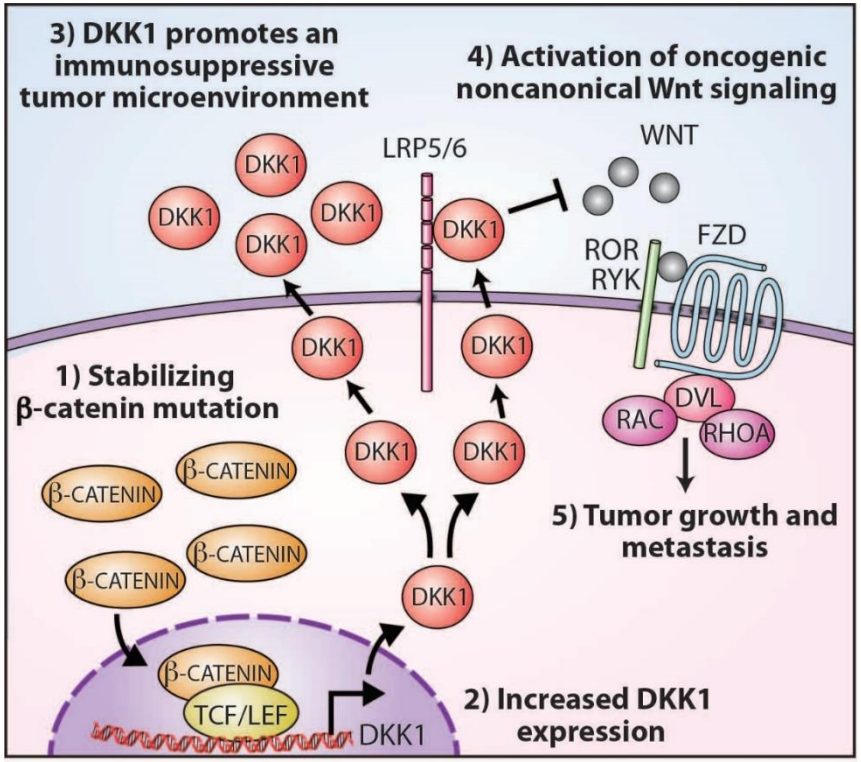
Schulze et al. Nat. Genet 2015

Rationale for DKN-01 Therapy in HCC

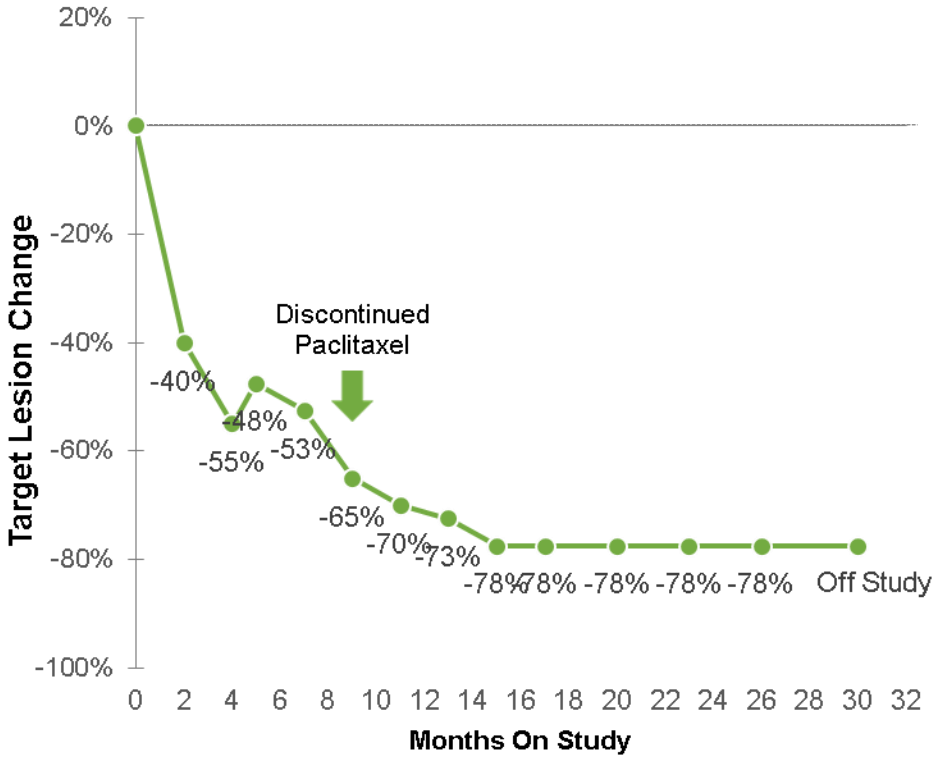
- Elevated expression of DKK1 observed in up to 70% of patients with HCC
- High DKK1 associated with a poor clinical outcome
- Elevated serum levels of DKK1 might complement current diagnostic strategies and improve identification of patients with AFP-negative HCC
- CTNNB1 mutations activating B-catenin are among the most frequent somatic events in HCC (11-37%)
- Alterations of this pathway can be considered a true driver of HCC development and progression
- Molecular targeted therapies against this pathway are particularly promising
- DKK1 modulates Wnt/B-catenin signaling

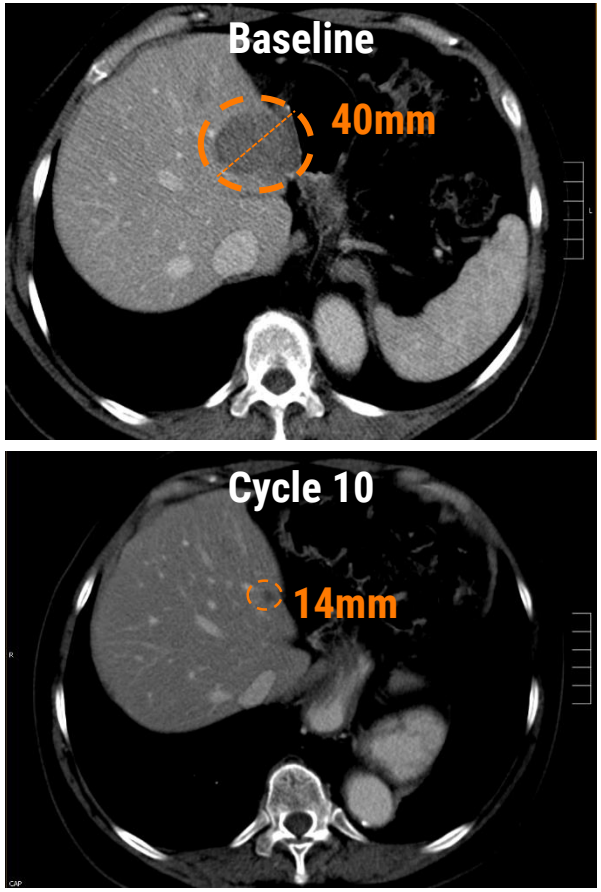
Rationale for DKN-01 Therapy in HCC

- Beta-catenin turns on production of DKK1
- DKK1 is overexpressed in cancers with beta catenin activating mutations
- Patients with mutations in beta-catenin and/or elevated levels of DKK1 have poor prognosis
- Patients with beta catenin mutations potentially more responsive to DKK1 targeted therapy



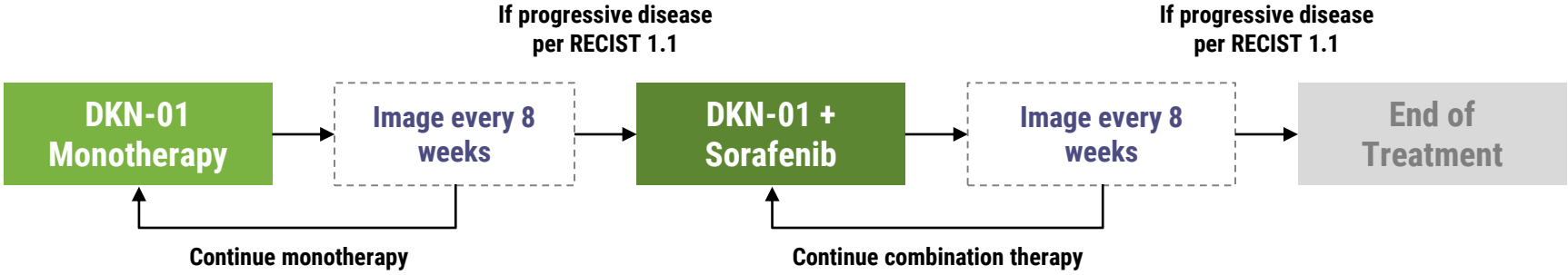
Durable DKN-01 Response in Patient with Beta-Catenin Mutation with Esophagogastric Cancer





Hepatocellular Carcinoma Study Design

- Study of patients with treatment-naïve advanced hepatocellular carcinoma with DKN-01 monotherapy and in combination with sorafenib

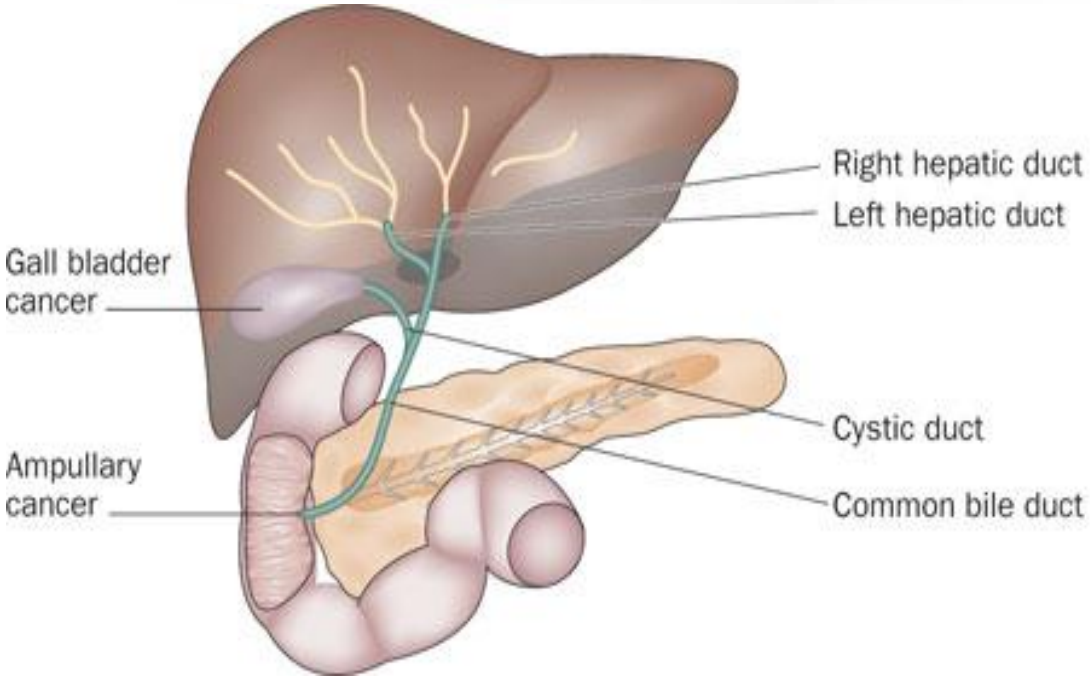


- Investigator sponsored study at 5+ sites, based at the University Medical Center of the Johannes Gutenberg-University Mainz in Germany
- Two-part study evaluating two DKN-01 dose levels (dose-escalation and dose expansion phases)
- Target sample size of 70 patients
  - Enriched for patients with Wnt pathway mutations

HCC Conclusions

- Liver cancer is an increasing health care problem
- Sorafenib is the standard of care for first line treatment in advanced stages
- Urgent and unmet clinical need for improved therapuetic strategies
- B-Catenin activation is a true molecular driver of hepatocarcinogenesis
- Targeting of the pathway by DKN-01 in enriched patient populations is highly promising

Biliary Tract Cancer Overview

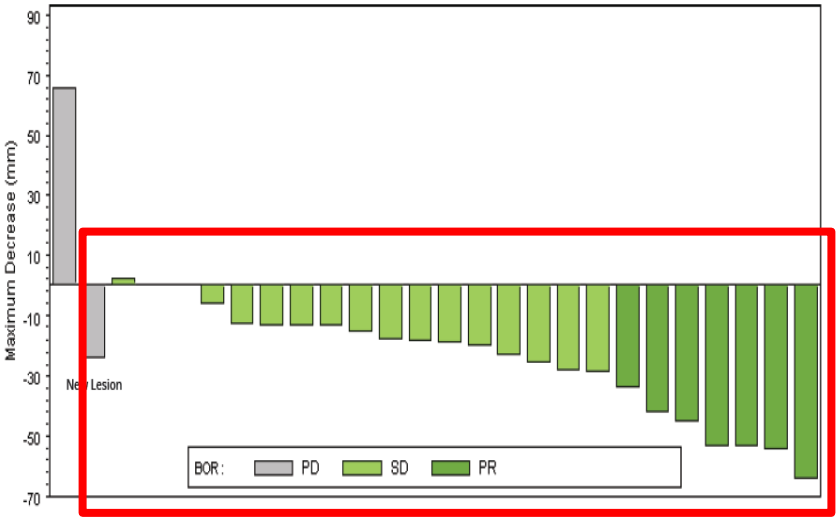


- Annual US incidence: 6,000
- Majority of cases are diagnosed with advanced stage disease
- 5 year survival less than 5%
- No approved therapies for advanced disease
- First-line therapy typically gemcitabine/cisplatin
  - Overall response rates: 19.5 to 25.5%
  - Disease control rate: 68.3 to 81.4%
  - PFS: 5.8 to 8 months

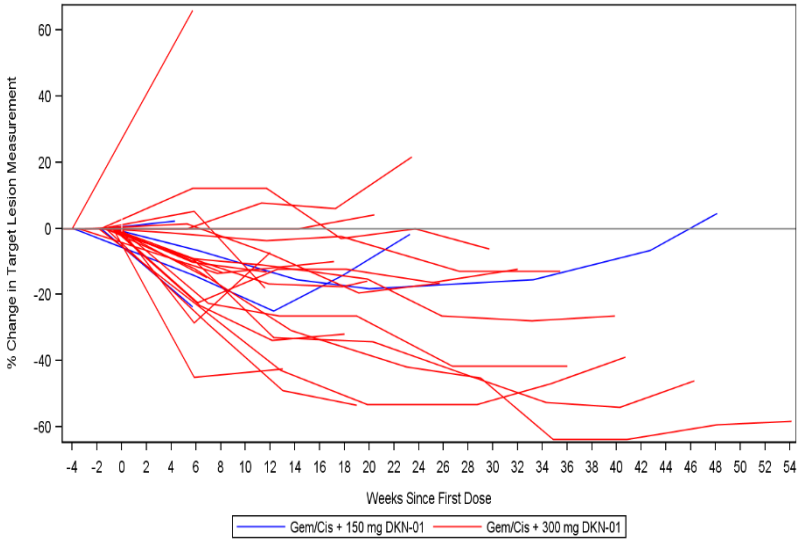
Valle et al. N Engl J Med. 2010 Apr 8;362(14):1273-81. doi: 10.1056/NEJMoa0908721.
Okusaka et al. Br J Cancer. 2010 Aug 10; 103(4): 469–474.

DKN-01 in Advanced Biliary Tract Cancer

ORR 31.8%, DCR 95.5%
PFS 9.4 months



DKN-01 + gemcitabine/cisplatin in treatment-naïve advanced BTC



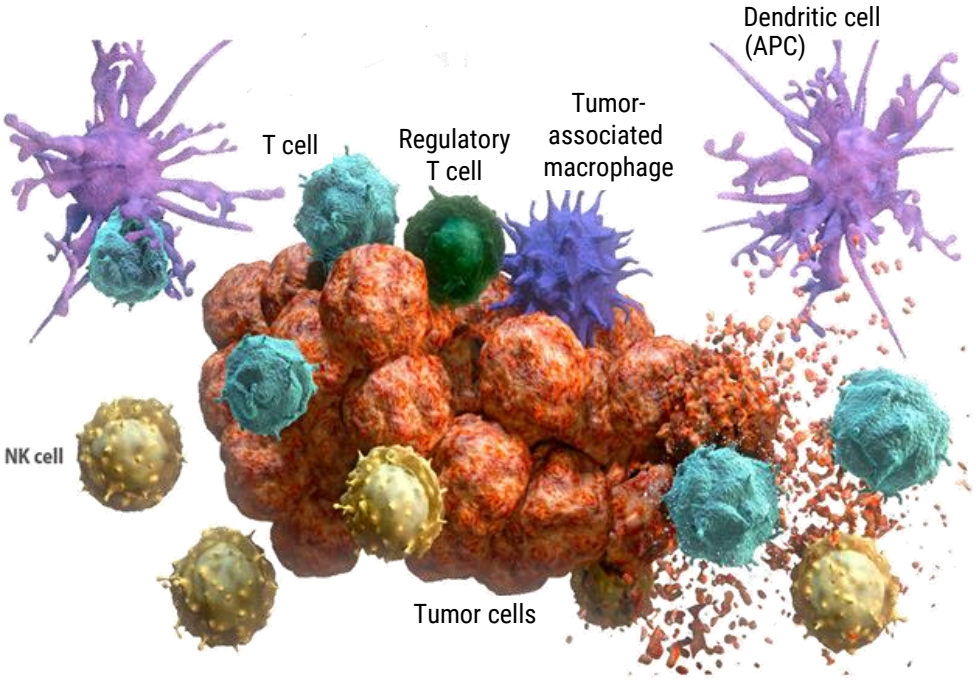
Historical gemcitabine/cisplatin studies:

- Overall response rates: 19.5 to 25.5%
- Disease control rate: 68.3 to 81.4%
- PFS: 5.8 to 8 months

Eads et al. A phase I study of DKN-01 (D), an anti-DKK1 monoclonal antibody, in combination with gemcitabine (G) and cisplatin (C) in patients (pts) for first-line therapy with advanced biliary tract cancer (BTC). ASCO 2017.

How to heat up “cold” tumors ?

Combination is key



Our next project

Checkpoint-Inhibitor

Atezolizumab TECENTRIQ® atezolizumab

with DKN-01±

chemotherapy

leaptherapeutics

Roche

EORTC
European Organization for Research and Treatment of Cancer

How to heat up “cold” tumors ?

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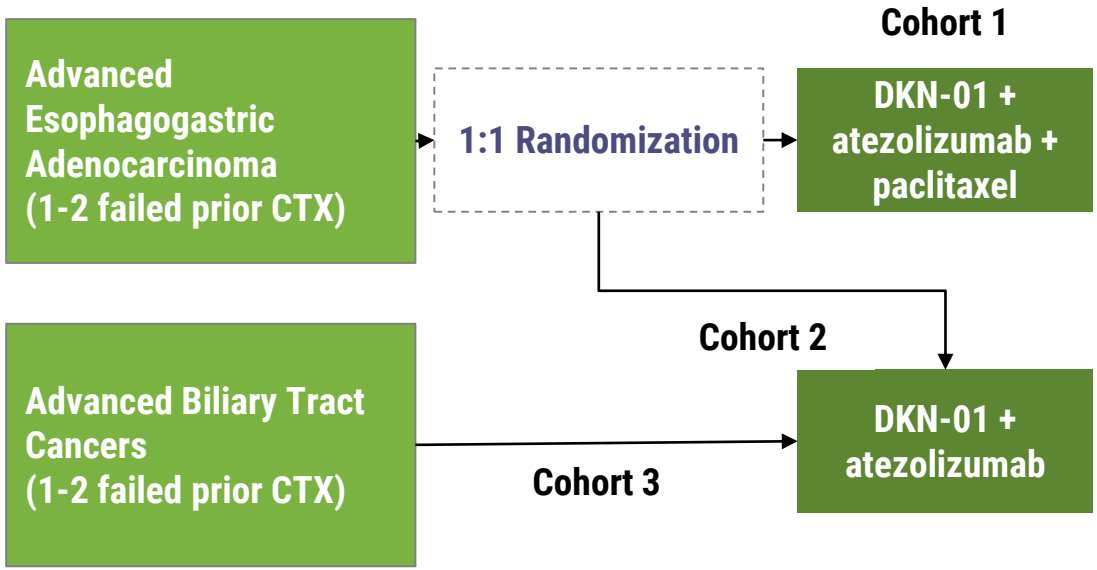

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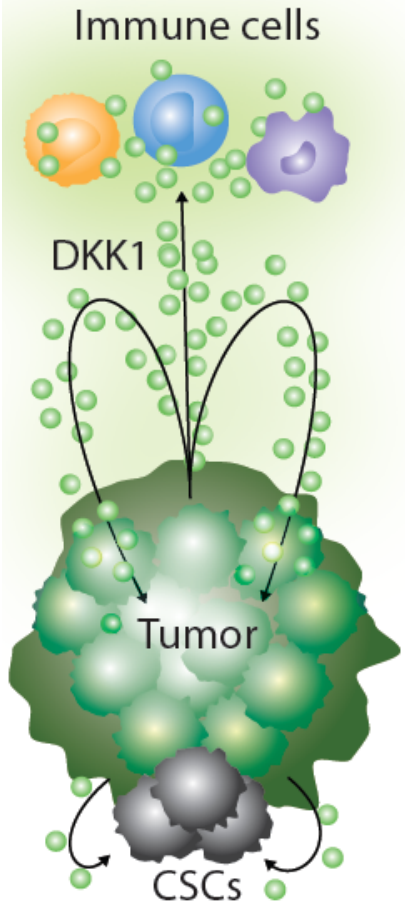


Immunosuppressive tumor microenvironment

DKK1 promotes an immunosuppressive tumor microenvironment[1]

- Increases MDSC and Treg suppressor activity[2,3]
- Downregulates NK activating ligands on tumor cells[4]
- Promotes Th2 polarization and decreases INFγ production[5]

Tumor growth

CSC phenotype and immune evasion

DKK1 has direct tumor promoting activity[1]

- Increases tumor growth and metastasis[1]
- Promotes a cancer stem cell (CSC) like phenotype[4]
- Enhances angiogenesis[1]

[1]Kagey and He, BJP, 2017; [2]D'Amico et al., JEM, 2016;
[3]Chae et al., Immunology, 2017; [4]Malladi et al., Cell, 2016; [5]Chae et al., Immunity, 2016

Model of DKK1 Tumor Promoting Activity

Future Directions: New Molecular Subtypes in Colorectal Cancer May Predict Response to Therapies

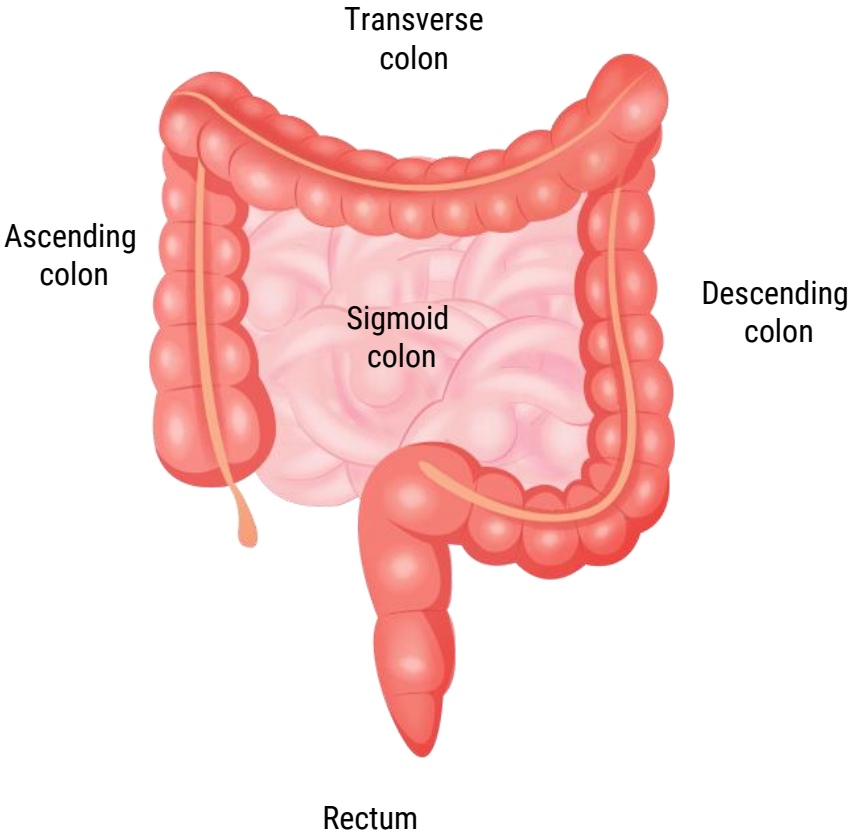
Colorectal cancer subtypes

MSI Immune (14%)
- MSI, CIMP high, hypermethylation
- *BRAF* mutations
- Immune infiltration/activation
- Worse survival after relapse

Canonical (37%)
- SCNA high
- WNT, DKK and MYC activation

Mesenchymal (23%)
- SCNA high
- Stromal infiltration, TGF-β activation, angiogenesis
- Worse relapse-free and overall survival

Metabolic (13%)
- Mixed MSI status, SCNA low, CIMP low
- *KRAS* mutations
- Metabolic deregulation



BRAF, B-Raf proto-oncogene; CIMP, CpG island methylator phenotype; *KRAS*, Kirsten rat sarcoma viral oncogene homolog; MSI, microsatellite instability; MYC, avian myelocytomatosis vial oncogene homolog; SCNA, somatic copy number alterations; TGF-β, transforming growth factor beta; WNT, wingless-related integration site.

Guinney J et al. *Nat Med*. 2015;21(11):1350-1356.11

Future Directions: New Molecular Subtypes in Colorectal Cancer May Predict Response to Therapies

Immune Subgroup	Molecular Subgroups	Escape Mechanisms	Immuno-Therapeutic Goals	Potential Approach
Immunogenic	CRC hypermutated	Immune checkpoints: PD-1 axis, LAG-3, CTLA-4	Boost intratumor CTLs	Checkpoint blockade
Inflammatory	CRC mesenchymal	• Hypoxia • TGF-β • PD-1 axis	• Dampen inflammation and suppression • Establish normoxia • Boost intratumor suppressed CTLs	• Anti-angiogenic • Anti-TGFβ • Checkpoint blockade
Immune-neglected	CRC canonical and metabolic	Low class I MHC expression	• Attract CTLs in tumors • Bypass class I MHC presentation	• CARs • DKN-01 • Bispecific antibodies

CAR, chimeric antigen receptors; CRC, colorectal cancer; CTL, cytotoxic T-lymphocyte; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; I-O, immuno-oncology; LAG3, lymphocyte-activation gene 3; MHC, major histocompatibility complex; PD-1, programmed death-1; TGFβ, transforming growth factor β; Th1, type 1 T helper cell.

Becht E et al. *Curr Opin Immunol*. 2016;39:7-13.

Future Directions: Wnt Biomarker Populations

	Esophagogastric Cancer	Liver Cancer	Uterine and Ovarian Cancer
			
US Incidence	Esophagus: 17,000 Stomach: 28,000	Liver: 40,000 Biliary: 6,000	Endometrial: 61,000 Ovarian: 22,000
β-catenin Mutational Frequency	Gastric 6-9% of patients	Hepatocellular Carcinoma 27-36% of patients	Endometrioid 29-30% of patients
Leap Clinical Plans	Expanded ongoing esophagogastric study	Initiating (University of Mainz)	Ongoing study

Agenda

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Hepatocellular Carcinoma, Biliary Tract Cancer, and Future Directions with DKN-01
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