NASDAQ: BTAI

BXCL701 Key Opinion Leader Day

February 21, 2023

Forward-Looking Statements

This presentation includes "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995. We intend such forward-looking statements to be covered by the safe harbor provisions for forward-looking statements contained in Section 27A of the Securities Act of 1933, as amended (the “Securities Act”) and Section 21E of the Securities Exchange Act of 1934, as amended (the “Exchange Act”). Forward-looking statements in this presentation include but are not limited to: statements regarding BioXcel Therapeutics’ expected timing of, and data results from, trials and clinical studies involving its product candidates, in particular BXCL701; planned discussions with regulators and potential registrational trials; strategic options for OnkosXcel; and potential market size and opportunity for product candidates. The words “anticipate,” “believe,” “can,” “continue,” “could,” “designed,” “estimate,” “expect,” “forecast,” “goal,” “intend,” “may,” “might,” “plan,” “possible,” “potential,” “predict,” “project,” “should,” “target,” “will,” “would” and similar expressions are intended to identify forward-looking statements, though not all forward-looking statements use these words or expressions. In addition, any statements or information that refer to expectations, beliefs, plans, projections, objectives, performance, or other characterizations of future events or circumstances, including any underlying assumptions, are forward-looking. All forward-looking statements are based upon BioXcel Therapeutics’ current expectations and various assumptions. BioXcel Therapeutics believes there is a reasonable basis for its expectations and beliefs, but they are inherently uncertain.

BioXcel Therapeutics may not realize its expectations, and its beliefs may not prove correct. Actual results could differ materially from those described or implied by such forward-looking statements as a result of various important factors, including, without limitation: the Company’s limited operating history; its incurrence of significant losses; its need for substantial additional funding and ability to raise capital when needed; its limited experience in drug discovery and drug development; its dependence on the success and commercialization of IGALMI™, BXCL501, BXCL502 and BXCL701 and other product candidates; the Company has limited experience in marketing and selling drug products; IGALMI™ or the Company’s product candidates may not be accepted by physicians or the medical community in general; the failure of preliminary data from its clinical studies to predict final study results; failure of its early clinical studies or preclinical studies to predict future clinical studies; its ability to receive regulatory approval for its product candidates; its ability to enroll patients in its clinical trials; undesirable side effects caused by the Company’s product candidates; its novel approach to the discovery and development of product candidates based on EvolverAI; its exposure to patent infringement lawsuits; its ability to comply with the extensive regulations applicable to it; impacts from the COVID-19 pandemic; its ability to commercialize its product candidates; and the other important factors discussed under the caption "Risk Factors" in its Quarterly Report on Form 10-Q for the quarterly period ended September 30, 2022, as such factors may be updated from time to time in its other filings with the SEC, which are accessible on the SEC's website at www.sec.gov and the Investors section of our website at www.bioxceltherapeutics.com.

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Agenda and Speakers

- BioXcel Therapeutics: Corporate Overview
- Prostate Cancer Overview and Challenges with Current Immunotherapy
- BXCL701 Mechanism of Action
- Results of Phase 2 Trial of BXCL701 in Small Cell Neuroendocrine Prostate Cancer (SCNC)
- BXCL701 Current Trials and Future Direction
- Panel Q&A Session

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BioXcel Therapeutics: Corporate Overview

Vimal Mehta
Founder & CEO

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Building a Unique Biopharmaceutical Business Model

Transformative Drug Re-innovation Approach Using AI

BioXcel Therapeutics: Targeting High Unmet Needs in Neuroscience and Immuno-Oncology

- Optimize R&D, accelerate development, increase probability of success

Neuroscience (BXCL501): First-in-human trials to FDA approval in just under 3.5 years

- IGALMI™ (dexmedetomidine) sublingual film, acute treatment of agitation in schizophrenia and bipolar I and II disorder
- Multiple indications for BXCL501, $15B total market opportunity

AI Engine

OnkosXcel Therapeutics™ — Continuing Mission of Developing Transformative Medicine in Hard-to-Treat Tumors

A subsidiary of BioXcel Therapeutics, Inc.

Lead Oncology Drug Candidate: BXCL701

- Unique oral innate immune activator, designed to turn cold tumors hot via DPP8/9 inhibition
- Combination approach, BXCL701 plus KEYTRUDA®
- Extend the value of IO in large underserved patient populations
- Focusing on cold tumor types

High-Value Catalysts

- Positive Phase 2 data presented at ASCO GU, 2023
- SCNC Phase 2b trial initiation planned in 2023

*Subject to alignment with FDA | IO = Immuno-Oncology

Innovation Shaping the Immunotherapy "Cold" Solid Tumor Market

Similar to Hematological Market in the 2000s

Multiple Myeloma

INTERNATIONAL MYELOMA FOUNDATION

*"**The first effective new drug to treat MM in decades, Thalomid launched a new era of "novel therapies**." It gave rise to a next generation of immune modulators with increased efficacy and reduced side effects, or the drugs Revlimid® (lenalidomide) and Pomalyst® (pomalidomide)."*
– International Myeloma Foundation

GEN Genetic Engineering & Biotechnology News

*"Thalidomide is one of the drugs emerging in a **promising new class of therapeutics** for MDS. The **recently discovered uses of thalidomide have conferred upon the once derided drug the moniker "wonder drug."** Hematologists are working to discover **novel molecular pathways** in which the drug and its derivatives can be used in a combination regimen to treat various forms of leukemia." (2005)*

Addressing underserved patient population

Disrupting the treatment paradigm

Unlocking immuno-oncology potential

BXCL701 Transformative Potential

Leadership in DPP8/9 inhibition to turn "cold" tumors into "hot" tumors

- Human POC achieved in two cold tumor subtypes
- Broad potential application in multiple cold solid tumors

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Disruption is in Our DNA

Developing Transformative Medicines in Two Underserved Therapeutic Areas

Delivering innovation

First public AI company focused on neuroscience and Immuno-oncology (2018)

Disrupting drug development paradigm

IND to commercial launch of IGALMI™ in under 4 years

First drug approved and POC achieved with second drug candidate

AI-based drug development and commercialization capability

$260m strategic financing in April 2022

Advanced commercial launch activities and clinical pipeline development

Neuro franchise

Poised to potentially capture 139-million-episode[1] U.S. agitation market[2]

OnkosXcel Therapeutics™
A subsidiary of BioXcel Therapeutics, Inc.

Poised to potentially impact cold, solid tumor market

1 Data on file. BioXcel Therapeutics, Inc., New Haven, CT
2 For Bipolar disorders, schizophrenia & Alzheimer's-related agitation

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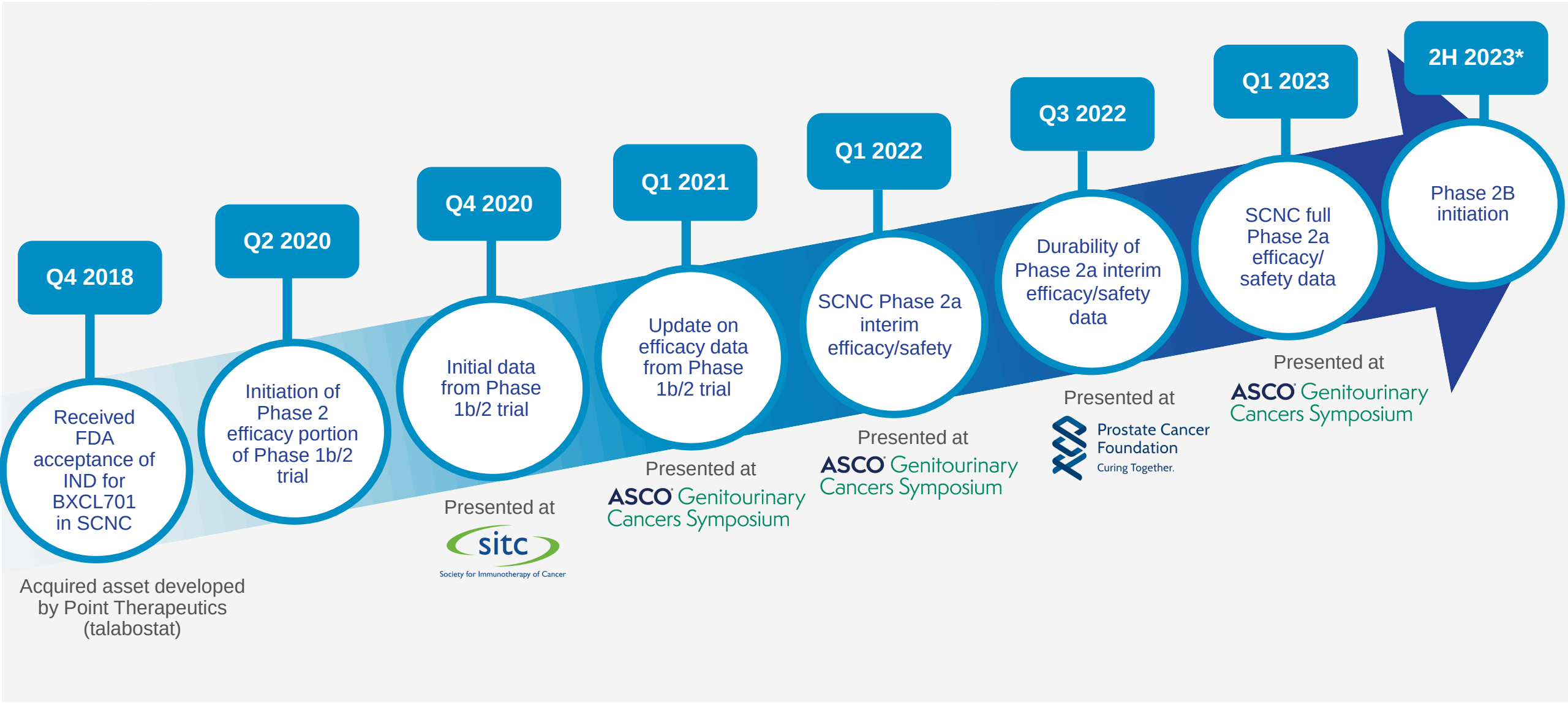
First AI Derived Human POC for Oral Innate Immune Activator

Utilizing Extensive Data from 11 Prior Clinical Trials and ~700 Subjects



*Subject to FDA alignment

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BXCL701: Strong Value Proposition in Hard-to-Treat Tumors

Mechanism of Action
Data Published in JITC

One of the most clinically advanced oral innate immune activators, designed to activate inflammasome via DPP8/9 inhibition*

Full Phase 2 Data for SCNC Presented at ASCO GU

- Composite response rate: 25%
- Median duration of response: 6+ months**
- Generally well tolerated in combination with KEYTRUDA

Clinical Proof of Concept
Cold Tumors

- Demonstrated positive efficacy results in two cancer types: mCRPC small cell neuroendocrine prostate cancer (SCNC) and adenocarcinoma
- ~800-subject clinical safety database

Leadership Position in Innate Immunity
DPP8/9 Biology

FortySeven

Acquired for ~$5B by

GILEAD

Scarcity of assets in innate immunity

TRILLIUM THERAPEUTICS INC.

Acquired for ~$2.3B by

Pfizer

OnkosXcel Therapeutics

Exploring Strategic Options

*Source: www.clinicaltrials.gov
**As of data cutoff on December 19, 2022

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Prostate Cancer Overview and Challenges with Current Immunotherapy

Daniel P. Petrylak, M.D.

Yale Medicine

Speaker is acting on behalf of and is a paid consultant to BioXcel Therapeutics, Inc.
This material is intended for an investor audience only.
The information contained in the following material is intended to provide background and educational information only and does not constitute medical advice. Individual results will vary among patients and depend on many factors. A patient's healthcare provider should consider the circumstances of each patient.

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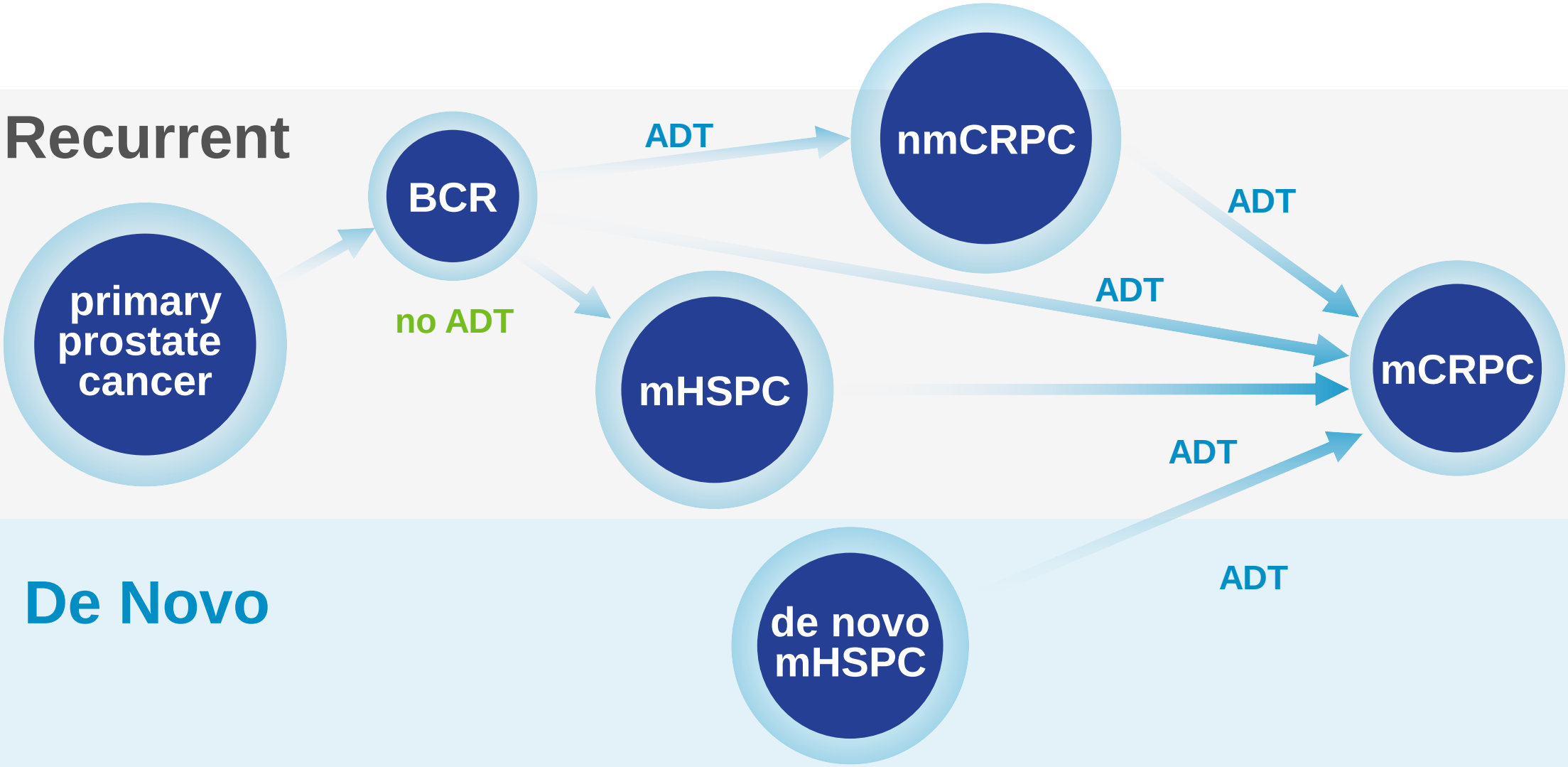
Prostate Cancer 2023

- Leading male US cancer, 2nd cancer deaths (lung #1)
- **New:** 288,300 **Deaths:** 34,700
- Prevalence of metastatic disease: 100,000
- Lifetime US risk:
  - Diagnosis: ~17% Death: ~3%
- Every **2 Minutes** an American is diagnosed with prostate cancer and every **18 Minutes** an American dies of prostate cancer
- Since 2014, the incidence rate has increased by 3% per year overall and by about 5% per year for advanced-stage prostate cancer

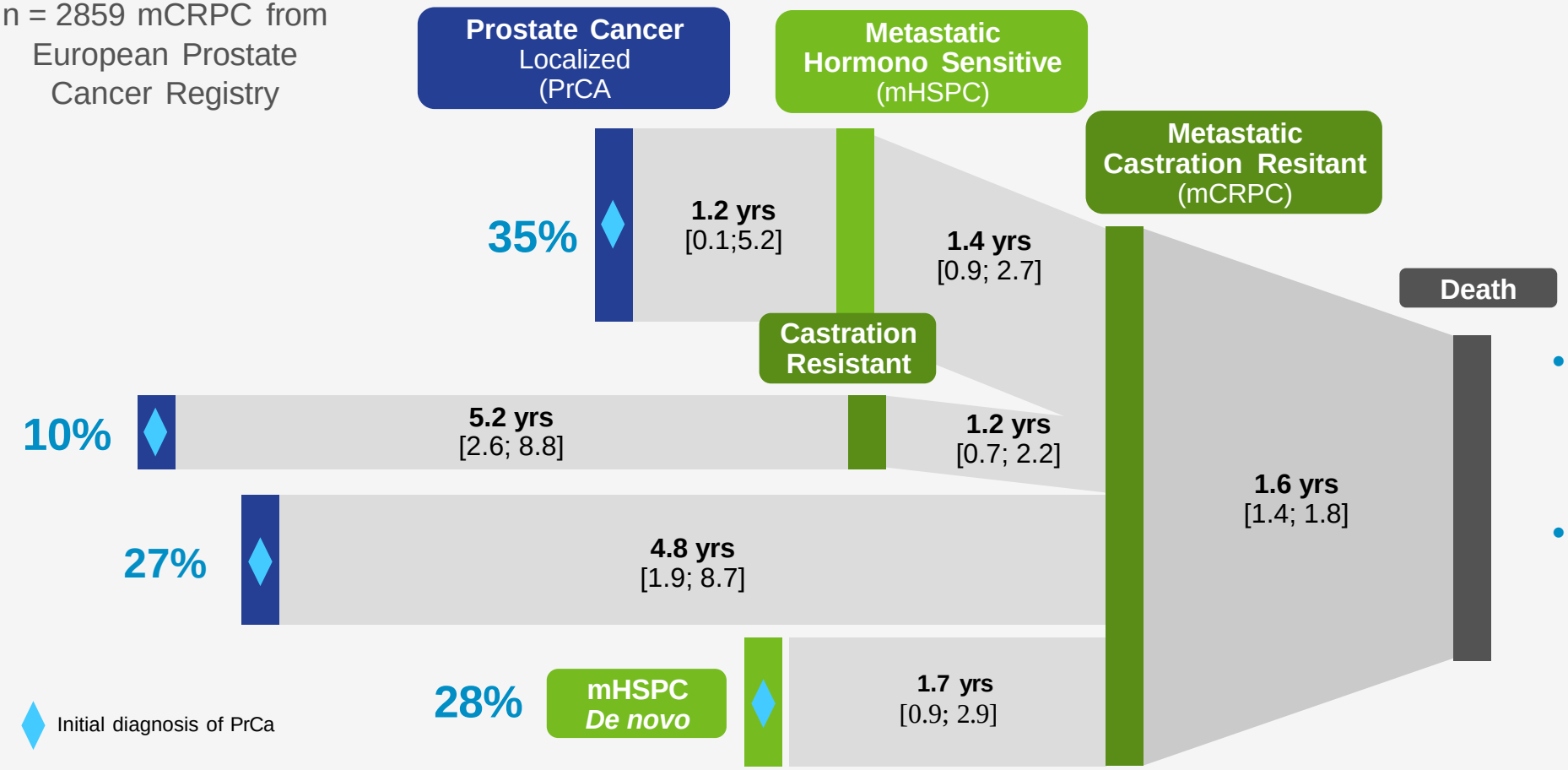
CA CANCER J CLIN 2019

What Was the Path to mCRPC?



Differing Natural Histories

n = 2859 mCRPC from European Prostate Cancer Registry



- OS comparable after progression to mCRCP
- De nova mHSPC has a shorter natural history than recurrent disease

Verry et al. *Targeted Oncology*. 2022;17:441-451.

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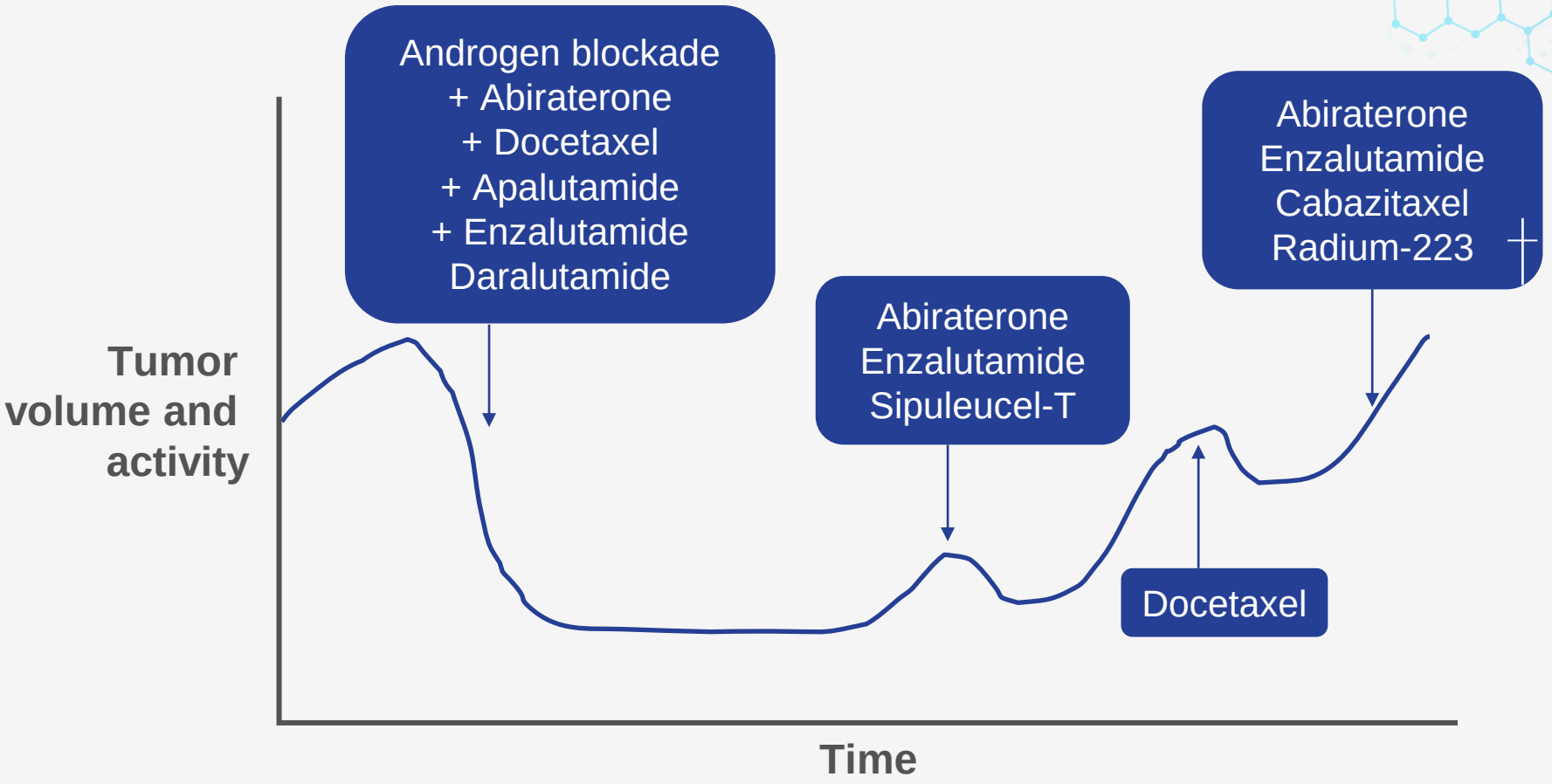
Treatment of Metastatic Prostate Cancer



Classes of Agents

- **Immunotherapeutic**
  - Sipuleucel-T
  - Pembrolizumab MSI-high
- **Hormonal**
  - Enzalutamide, apalutamide, darolutamide, abiraterone
- **Cytotoxic**
  - Docetaxel, cabazitaxel
- **DNA damage**
  - Rad223
  - Olaparib, rucaparib

Updated WHO Classification in Prostate Cancer

Table 1 - The 2022 WHO classification of the Prostate and Seminal Vesicle

Epithelial tumors of the prostate	
Glandular neoplasms of the prostate	
8440/0	Cystadenoma
8148/2	Prostatic intraepithelial neoplasia, high grade
8500/2	Intraductal carcinoma
8140/3	Acinar adenocarcinoma
8490/3	*Signet ring cell-like acinar adenocarcinoma*
8140/3	*Pleomorphic giant cell acinar adenocarcinoma*
8572/3	*Sarcomatoid acinar adenocarcinoma*
8140/3	*Prostatic intraepithelial neoplasia-like carcinoma*
8500/3	Ductal adenocarcinoma
85743	Treatment-related neuroendocrine prostatic carcinomas
Squamous neoplasms of the prostate	
8560/3	Adenosquamous carcinoma
8070/3	Squamous cell carcinoma
8147/3	Adenoid cystic (basal cell) carcinoma
Mesenchymal tumors unique to the prostate	
Stromal tumors of the prostate	
8935/1	Stromal tumor of uncertain malignant potential
8935/3	Stromal sarcoma

- No distinction between small cell, large cell, or mixed morphologies
- No comment on the use of IHC markers

Netto et al, Eur Urol 2022

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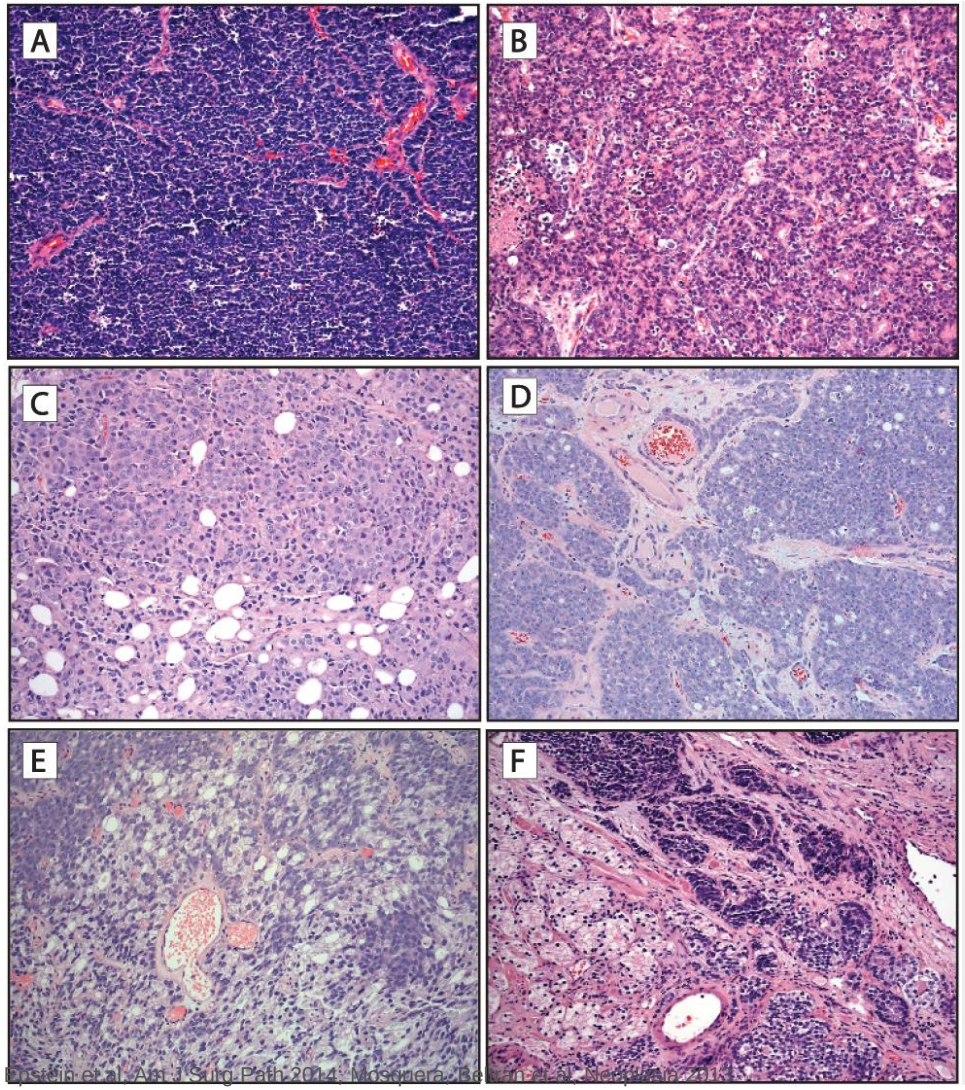
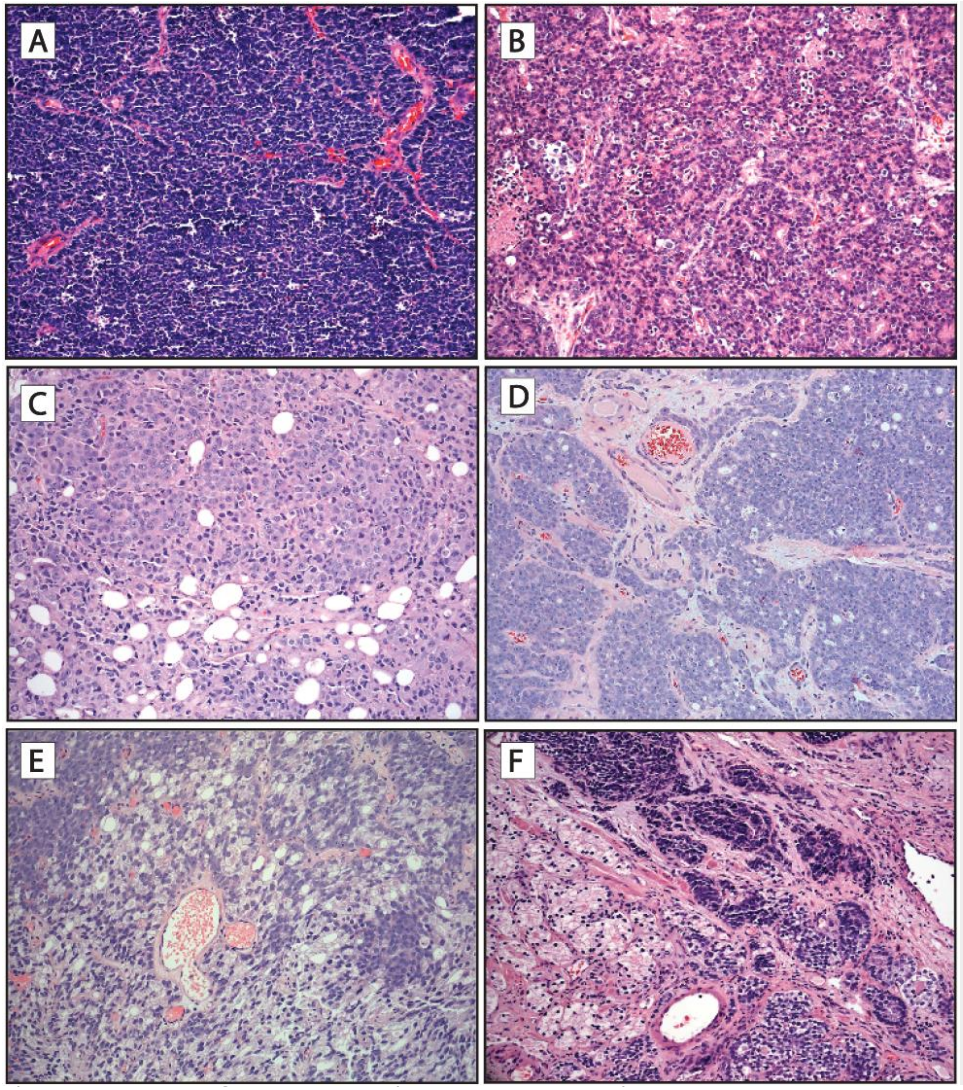
Neuroendocrine Prostate Cancer Terminology



- Morphology-based definition
  - Small cell carcinoma, large cell carcinoma, mixed/NED, other NE

Epstein et al. Am J Surg Path 2014; Mosquera, Beltran et al. Neoplasia 2013

Neuroendocrine Prostate Cancer Terminology



- Morphology-based definition
  - Small cell carcinoma, large cell carcinoma, mixed/NED, other NE
- IHC not required for diagnosis but is often:
  - (+) for at least 1 NE marker
    - e.g., INSM1, SYP, NSE
  - (-) androgen receptor (AR)
  - (-) Luminal markers
    - Eg, PSA, ERG, NKX3.1

Exceptions are common!

IHC is used variably

Current Diagnosis of NEPC is Imperfect

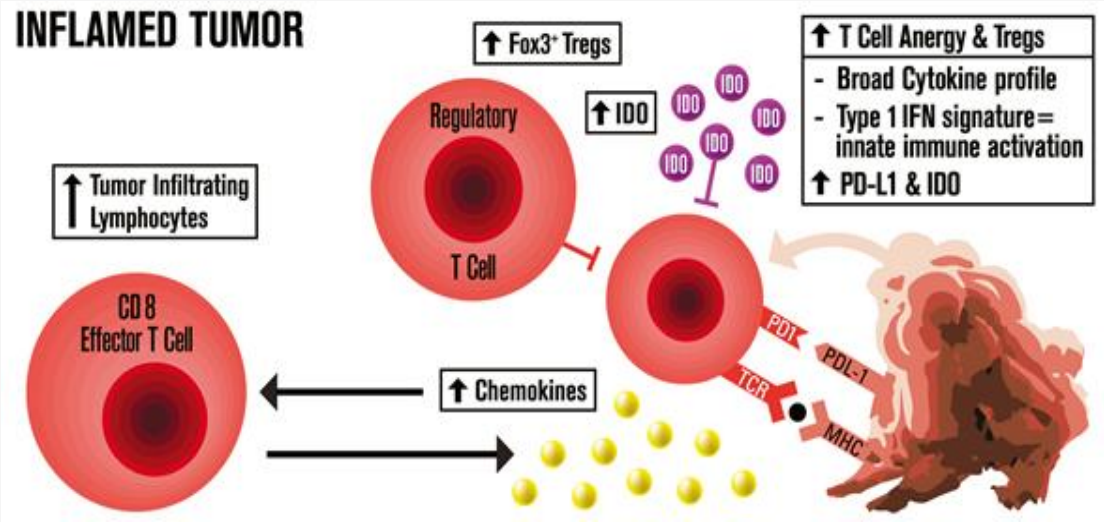
Some people report never or rarely seeing a case of NEPC

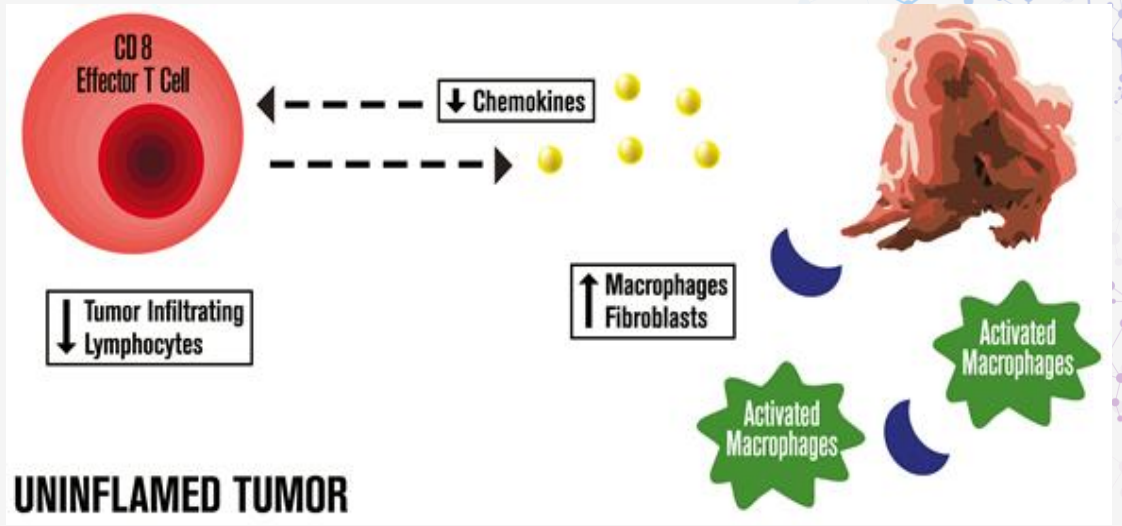
Others report up to 15–20% of CRPC tumors

POSSIBLE EXPLANATIONS:

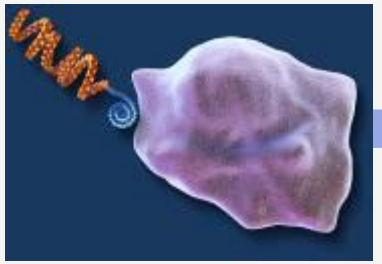
- Repeat biopsies are not standardly done in mCRPC
- Variability amongst pathologists – evaluation and nomenclature not standardized
- Intra-patient heterogeneity

Tumors Exhibiting a T Cell–Inflamed or Non-T-Cell-Inflamed Phenotype

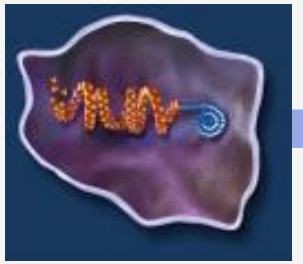




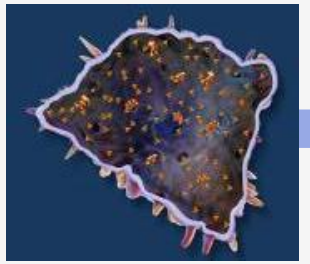
Sipuleucel-T: Autologous APC Cultured with PAP-Cytokine Fusion Protein



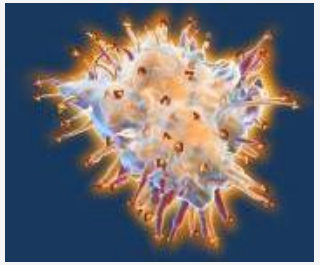
Recombinant Prostatic Acid Phosphatase (PAP) antigen combines with resting antigen presenting cell (APC)



APC takes up the antigen

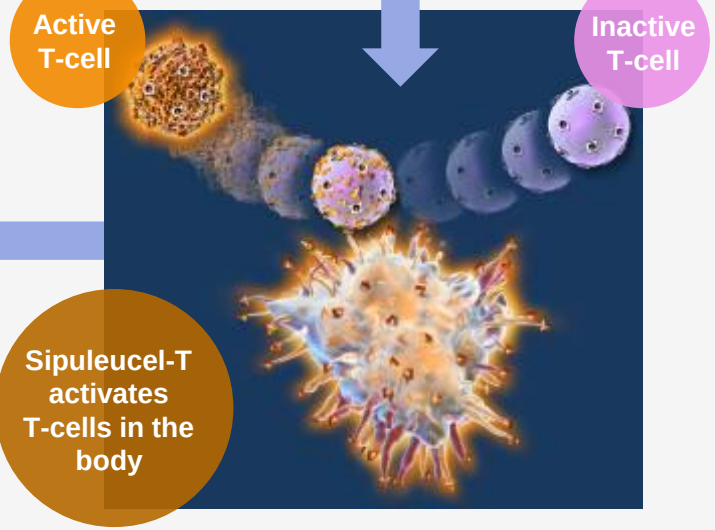


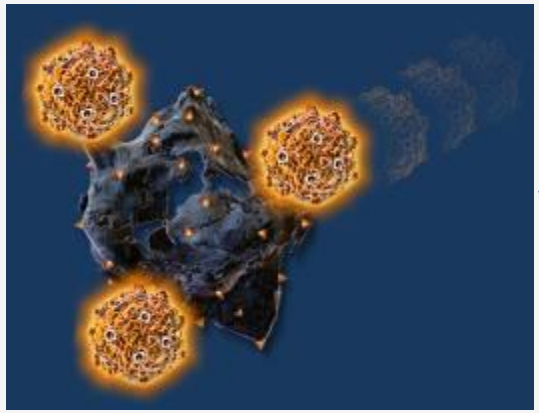
Antigen is processed and presented on surface of the APC



Fully activated, the APC is now sipuleucel-T

INFUSE PATIENT





T-cells proliferate and attack cancer cells

The precise mechanism of sipuleucel-T in prostate cancer has not been established.

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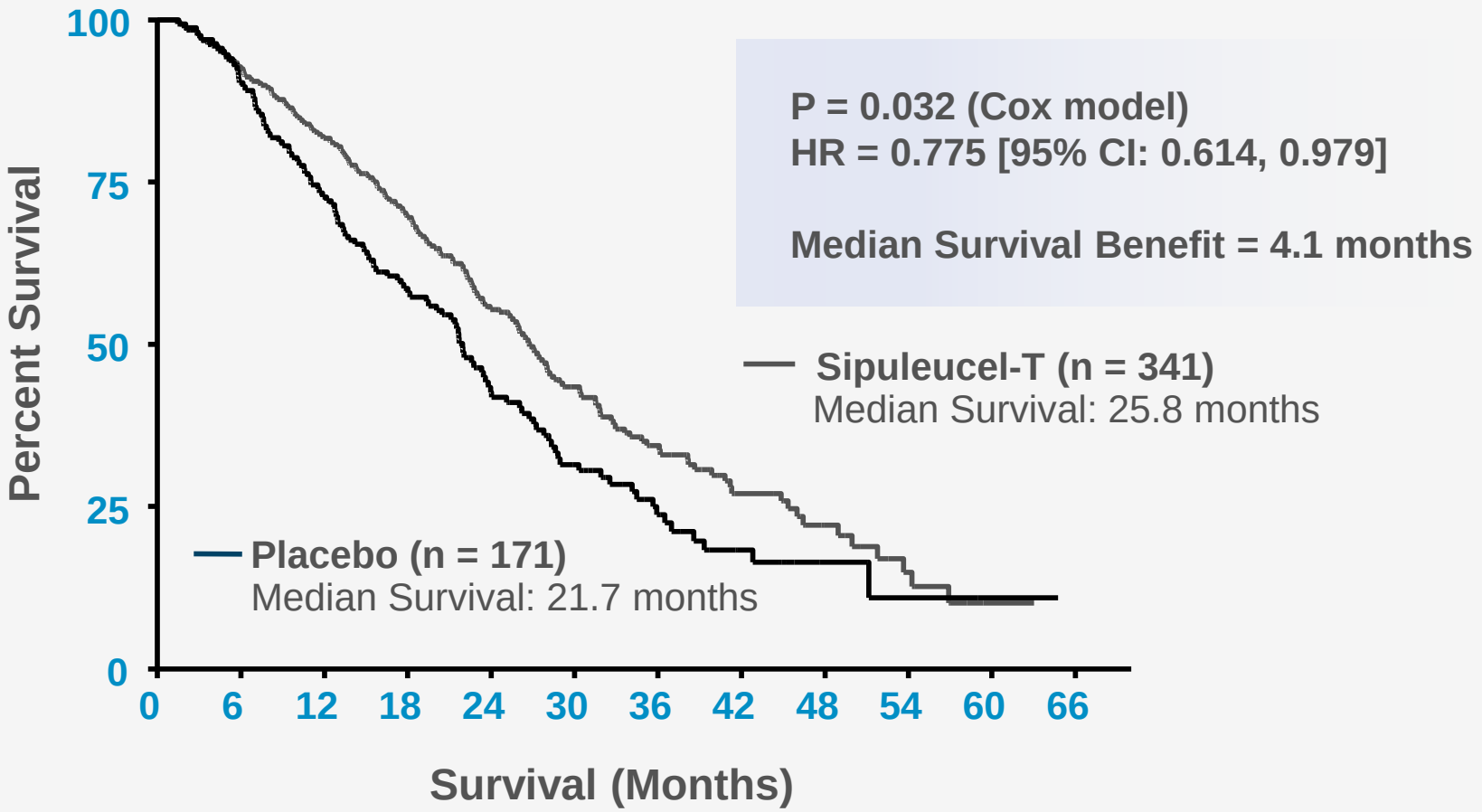
IMPACT Overall Survival

Intent-to-Treat Population



Key Data From Anti-PD-1 / PD-L1 Alone in mCRPC

- **Phase I atezolizumab study in mCRPC cohort 1**
  - Unresectable or recurrent patients with prior treatment with sipuleucel-T or enzalutamide
  - ORR (RECIST 1.1) 0%, ORR (irRECIST) 7.0%, mPFS 3.4 months, and mOS 18.6 months
  - 60% of patients had TRAEs (20% had treatment interruptions/modifications, and 7% discontinued because of TRAEs)
- **KEYNOTE 199: Phase II pembrolizumab study in mCRPC cohorts post docetaxel2-4**
  - N=259, Cohort 1 (PD-L1+), Cohort 2 (PD-L1–), Cohort 3 (any PD-L1, bone predominant)
  - ORR (RECIST 1.1) ranged from 3%-6%, mPFS 2.0-4.0 months, and mOS 8.0-14.0 months among all 3 cohorts
  - 15%-17% (cohorts 1-3) had grade 3-5 TRAEs*

TRAEs = Treatment-Related Adverse Events

TABLE. Subtypes of Prostate Cancer Sensitive to Checkpoint Inhibitors

NAME	INTERVENTION	TRIAL TYPE	PATIENTS	OUTCOME
dMMR/MSI-H				
NCT02312557[5]	Pembrolizumab 200 mg/kg IV/3 wk	Phase 2	10	PSA50 30% PR 20%
Abida et al[7]	Anti–PD-1/PD-L1	Retrospective	11	PSA50 55%
PD-1/PD-L1 positive				
KEYNOTE-028[2]	Pembrolizumab 10 mg/kg IV/2 wk	Phase 1b	23	ORR 17% DOR 14 mo OS 8 mo
KEYNOTE-199[8]	Pembrolizumab 200 mg/kg IV/3 wk	Phase 2	133	ORR 7% DOR 17 mo OS 9.5 mo
High TMB				
CHECKMATE-650[10]	Ipilimumab+nivolumab	Phase 2	33	ORR 58%
CDK12				
Antonorakis et al[11]	Pembrolizumab	Retrospective	8	PSA50 38%
Antonorakis et al[11]	Nivolumab	Retrospective	3	PFS 6.6 mo
Reimers et al[15]	Anti–PD-1	Retrospective	5	PSA50 40%
Antonorakis et al[16]	Pembrolizumab	Retrospective	5	PSA50 33%
Antonorakis et al[16]	Nivolumab	Retrospective	4	PFS 5 mo
POLE/POLD				
Lee et al[18]	Pembrolizumab 200 mg/kg IV/3 wk	Case report POLE V411L	1	PSA <0.1 ng/mL DOR 17 mo OS 10 mo
Guedes et al[19]	Pembrolizumab 200 mg/kg IV/3 wk	Case report POLD1 D402N	1	"Exceptional response"

dMMR/MSI-H, deficient mismatch repair genes/microsatellite instability-high; DOR, duration of response; IV, intravenous; ORR, overall response rate; OS, overall survival; NR, not reached; PD-1/PD-L1, programmed death-1/PD-1 ligand; PFS, progression-free survival; PR, partial response; PSA50, PSA decrease >50%; TMB, tumor mutational burden.

Source: Miguel Gonzalez-Velez, MD, and Alan H. Bryce, MD

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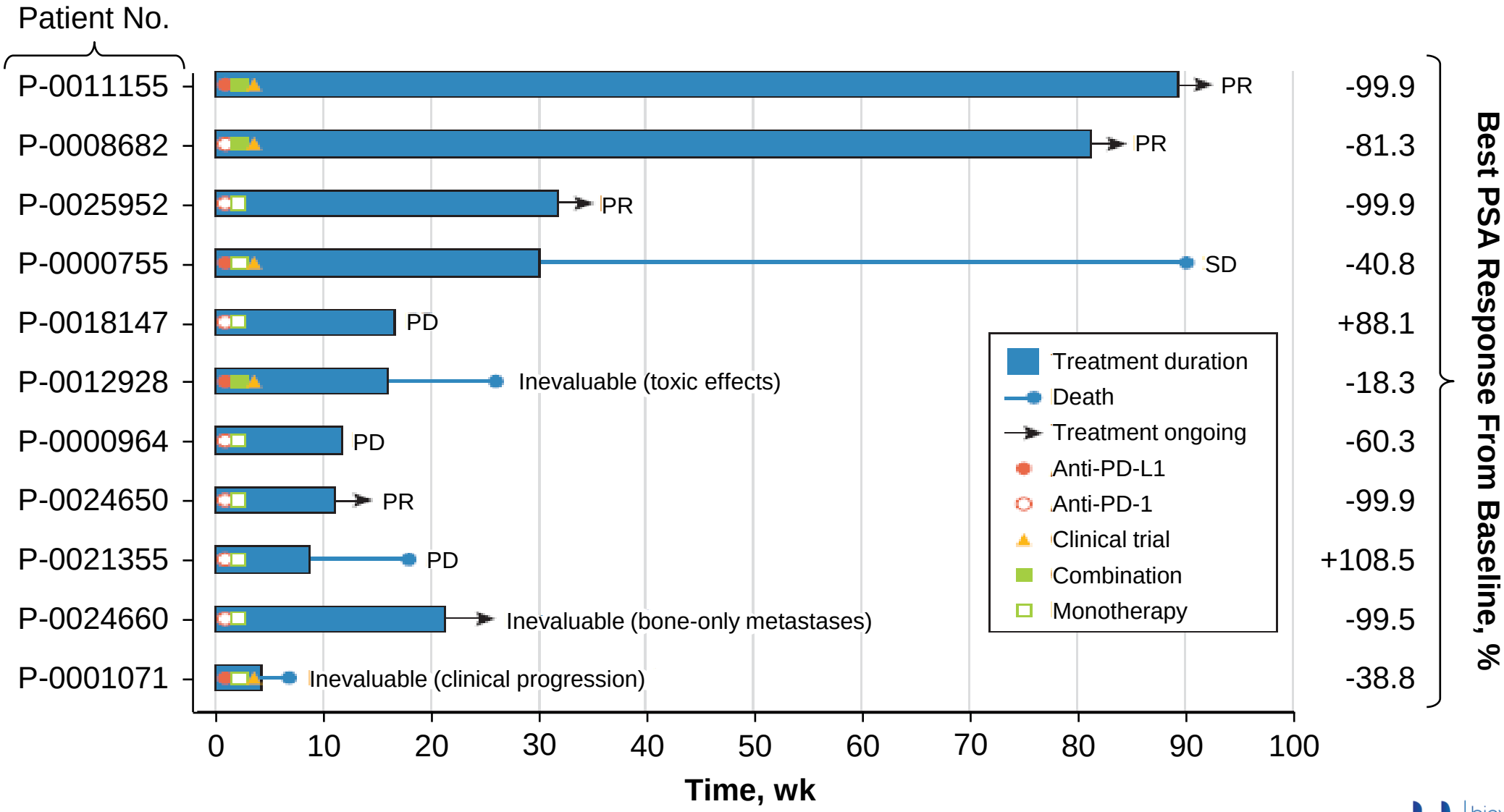
MSI in Castration-Resistant Prostate Cancer



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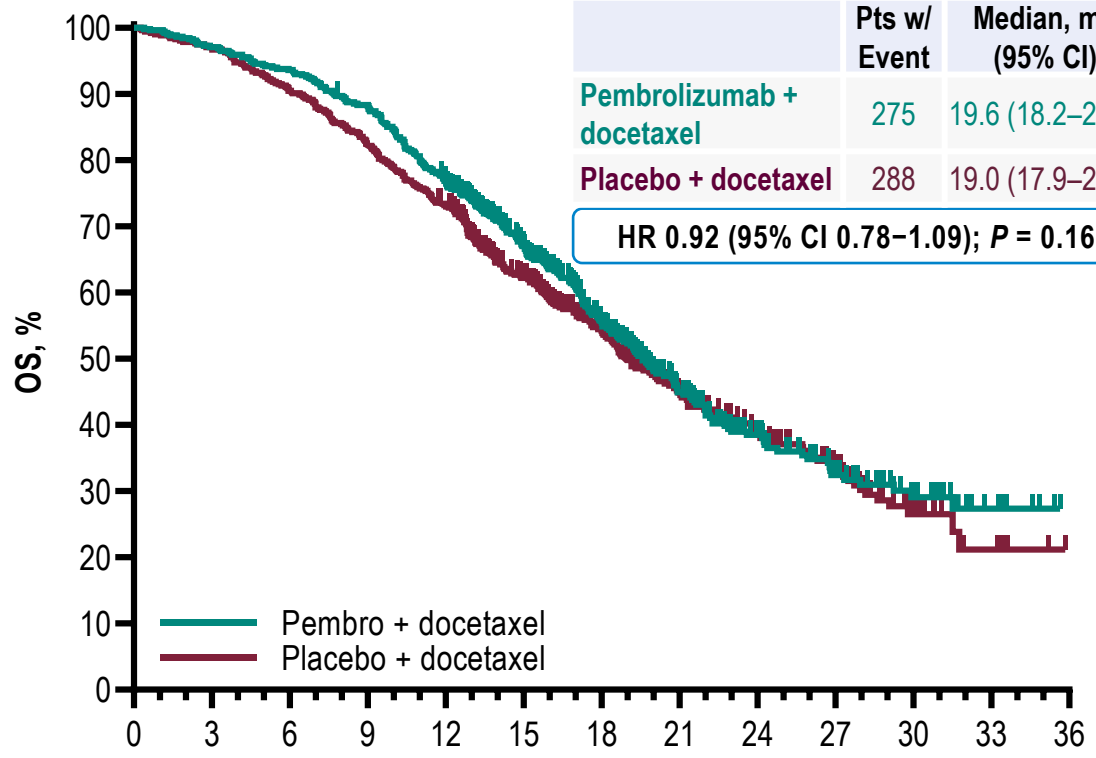
Primary Endpoint: OS at Final Analysis, ITT Population

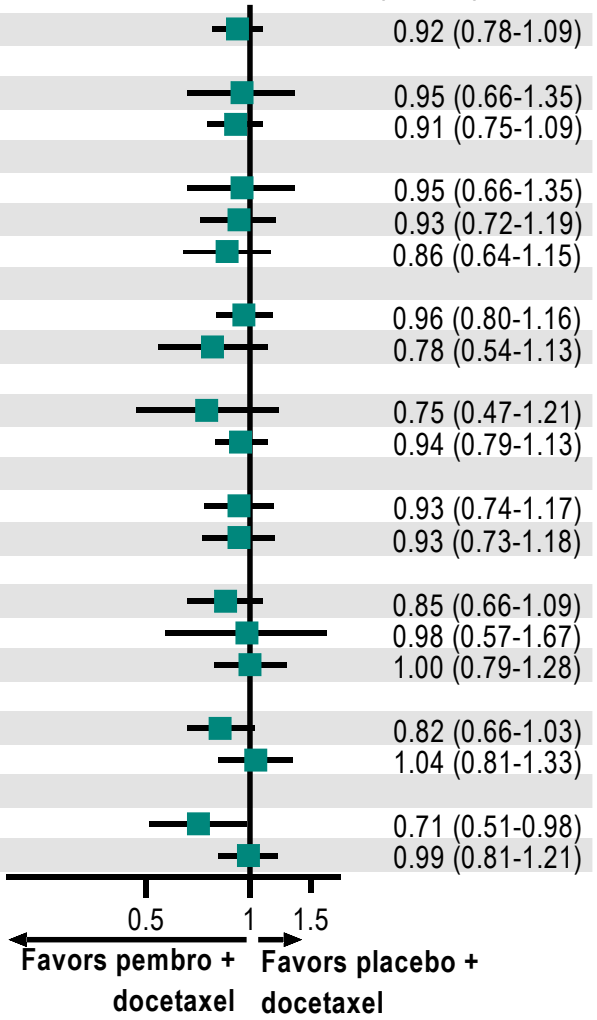


	Pts w/ Event	Median, mo (95% CI)
Pembrolizumab + docetaxel	275	19.6 (18.2–20.9)
Placebo + docetaxel	288	19.0 (17.9–20.9)

HR 0.92 (95% CI 0.78−1.09); *P* = 0.1677

No. at Risk													
Pembro + docetaxel	515	500	482	454	393	292	198	124	79	50	28	7	0
Placebo + docetaxel	515	500	466	424	375	268	192	127	89	58	21	7	0

	Events/Participants	Hazard Ratio (95% CI)
Overall	563/1030	0.92 (0.78-1.09)
Age		
<65 years	123/225	0.95 (0.66-1.35)
≥65 years	440/805	0.91 (0.75-1.09)
Age (EU categories)		
<65 years	123/225	0.95 (0.66-1.35)
65 to 74 years	248/496	0.93 (0.72-1.19)
75 to 84 years	183/297	0.86 (0.64-1.15)
Race		
White	450/800	0.96 (0.80-1.16)
All others	113/228	0.78 (0.54-1.13)
Region		
North America	70/144	0.75 (0.47-1.21)
Outside North America	493/886	0.94 (0.79-1.13)
ECOG PS		
0	294/584	0.93 (0.74-1.17)
≥1	266/440	0.93 (0.73-1.18)
Metastases at baseline		
Bone only	247/507	0.85 (0.66-1.09)
Liver	55/67	0.98 (0.57-1.67)
Other	261/456	1.00 (0.79-1.28)
Prior abiraterone		
Yes	314/555	0.82 (0.66-1.03)
No	249/475	1.04 (0.81-1.33)
PD-L1 status		
PD-L1 positive	148/228	0.71 (0.51-0.98)
PD-L1 negative	375/718	0.99 (0.81-1.21)



ITT population included all randomized participants. Data cutoff date, FA: June 20, 2022. Median (range) time from randomization to data cutoff date: 22.7 months (12.1−36.7).

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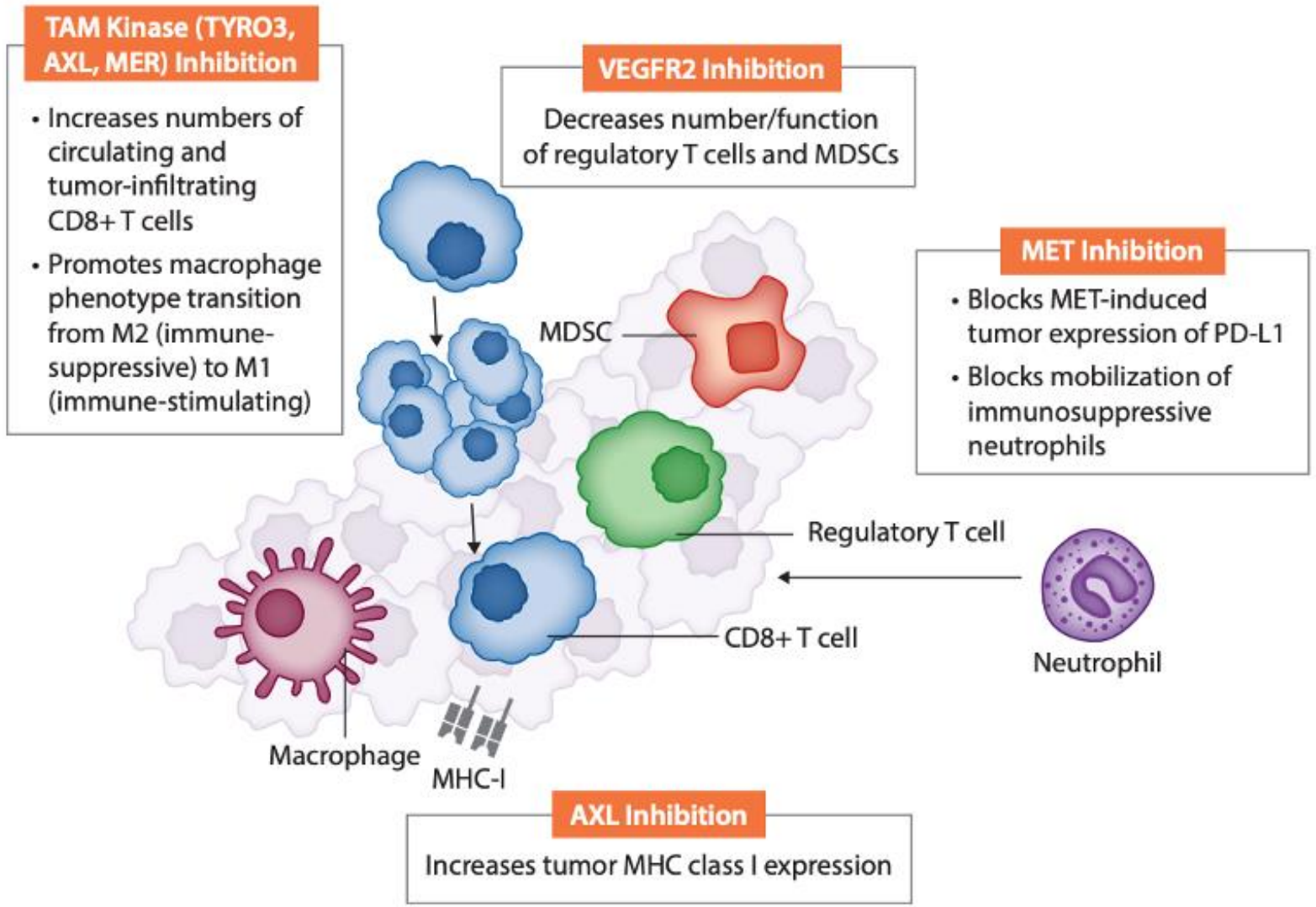
Figure 1. Cabozantinib Targets Pathways Associated With Tumor Immune-Suppression



Atezolizumab / Cabozantanib

	Tumour response per investigator		Tumour response per BIRC	
	All patients (n=132)	Visceral metastases or measurable extrapelvic lymphadeno-pathy (n=101)	All patients (n=132)	Visceral metastases or measurable extrapelvic lymphadeno-pathy (n=101)
Objective response rate	31 (23%; 17–32)	27 (27%; 18–37)	20 (15%; 10–22)	18 (18%; 11–27)
Best overall response				
Confirmed complete response	3 (2%)	2 (2%)	0	0
Confirmed partial response	28 (21%)	25 (25%)	20 (15%)	18 (18%)
Stable disease	80 (61%)	62 (61%)	87 (66%)	67 (66%)
Progressive disease	19 (14%)	11 (11%)	23 (17%)	15 (15%)
Missing	2 (2%)	1 (1%)	2 (2%)	1 (1%)
Disease control rate*	111 (84%; 77–90)	89 (88%; 80–94)	107 (81%; 73–87)	85 (84%; 76–91)
Duration of objective response, months†	8·3 (4·6–11·0)	6·9 (4·2–9·8)	6·9 (4·1–8·4)	6·9 (4·1–9·5)
Time to objective response, months‡	1·7 (1·4–2·8)	1·7 (1·4–3·2)	2·8 (1·5–3·9)	2·8 (1·6–4·0)

Data are n (%; 95% CI), n (%), or median (IQR). BIRC=blinded independent radiology committee. RECIST=Response Evaluation Criteria in Solid Tumors. *Patients with a complete response, partial response, or stable disease. †Kaplan-Meier estimate. ‡Arithmetic estimate.

Table 2: **Tumour response per RECIST version 1.1**

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CONTACT-02 Trial Design

Patients

Key eligibility

- Prior treatment with one, and only one, NHT (e.g., abiraterone, apalutamide, darolutamide, or enzalutamide)
- Surgical or medical castration
- Measurable visceral disease per RECIST 1.1; OR measurable extrapelvic adenopathy
- Progressive disease at study entry
- ECOG PS ≤1

Exclusion criteria

- Any prior nonhormonal therapy initiated for the treatment of mCRPC

RANDOMIZED 1:1

Cabozantinib (40 mg daily) Atezolizumab (1200 mg /20 mL q3w) (n = 290)

2nd NHT (Abiraterone or Enzalutamide) (n = 290)

Efficacy Endpoints

Primary:

- PFS per RECIST 1.1
- Overall survival (37 months after randomization)

Secondary:

- ORR per RECIST 1.1 (37 months after randomization)

ClinicalTrials.gov Identifier: NCT04446117

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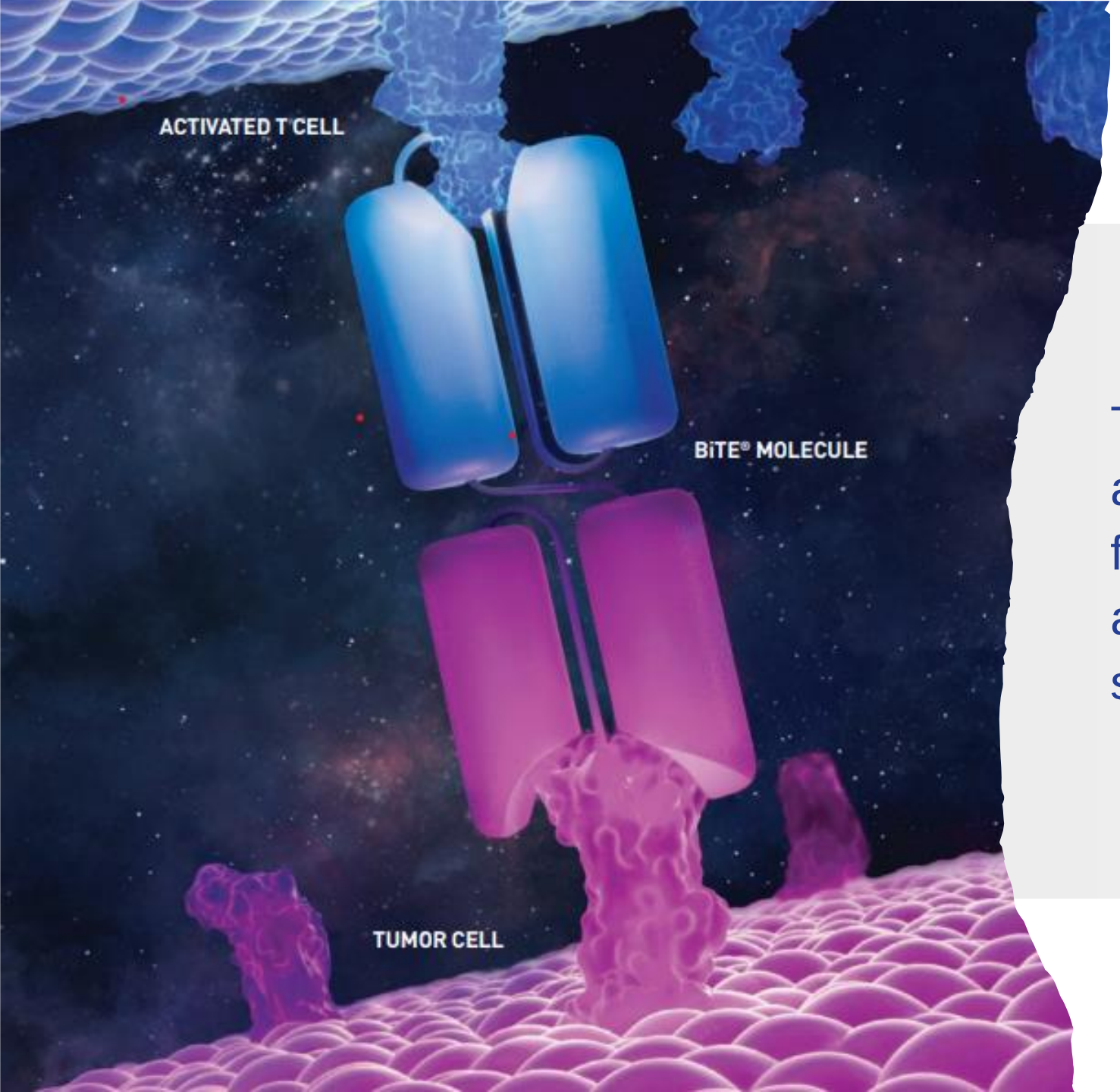
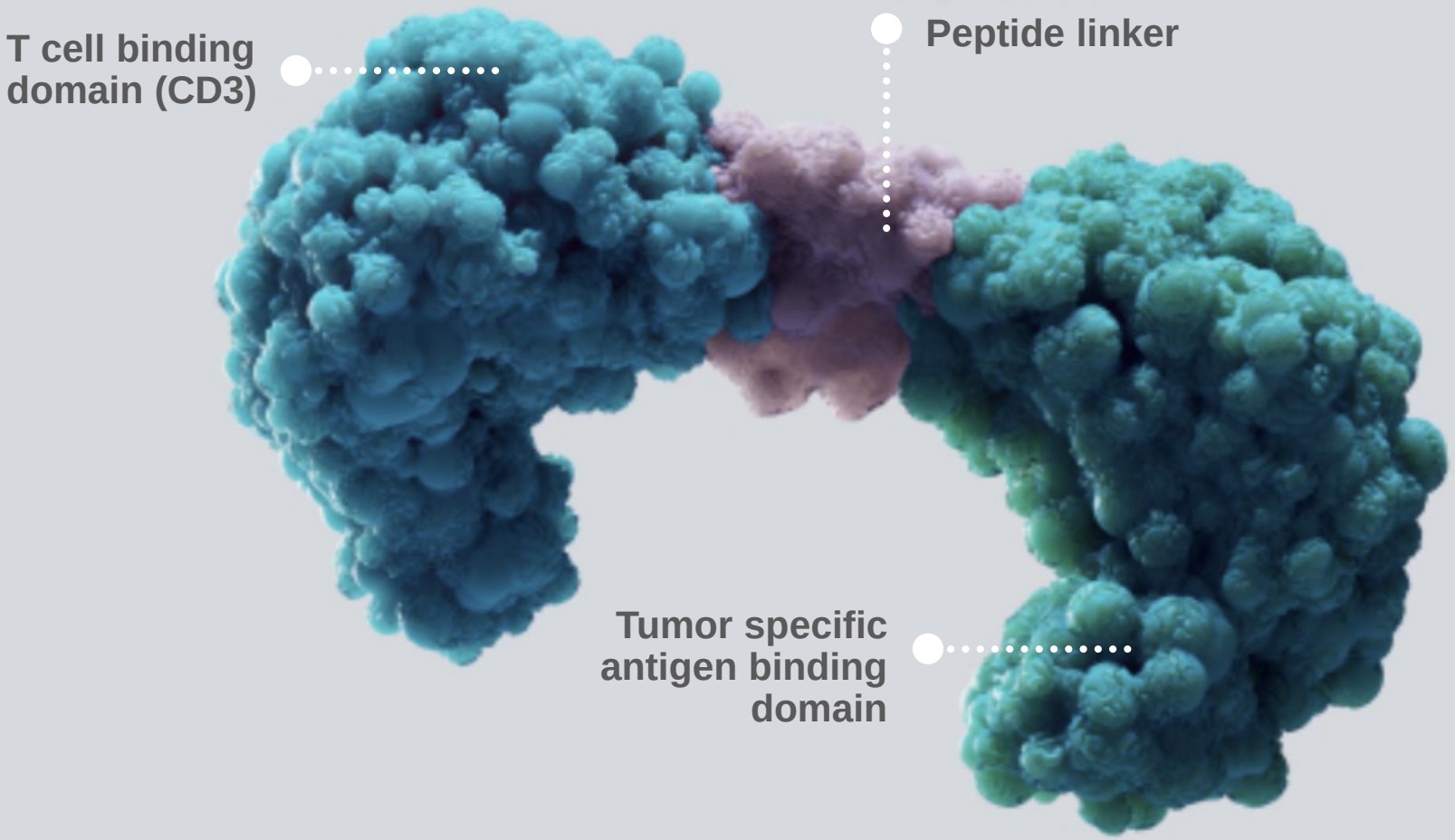
Bi-Specific T Cell Engager (BiTE®)…

- Once T cells are activated by a BiTE molecule, the T cells may induce further T-cell proliferation and cytokine production
- Induces apoptosis; activated T cells release cytokines and produce additional perforin/granzymes that may allow T cells to target surrounding cancer cells
- Potentially results in the serial lysis of multiple cancer cells by a single T cell
- **Sustained activation** of a single activated cytotoxic T cell theoretically results in local proliferation and expansion of polyclonal memory T cells



Two flexibly linked, single-chain antibodies, with one that is specific for a selected tumor-associated antigen and the other that is specific for CD3 found on T cells

Pasotuxizumab



Hummel HD et al. Immunotherapy. 2021;13(2):125-141

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Therapeutic Targets

- DLL3 in NEPC (AMG 757)
- STEAP1 (AMG 509)
- Human Kallikrein-2 (KLK2)
- TMEFF2: ESMO 2022 poster
- PD-1 x CTLA-4 (Vudalimab = XmAb20717)
- PSMA
- PSCA

BiTE Molecules

- Pasotuxizumab - AMG 212 = BAY 2010112
- Acapatamab - AMG 160: half-life extended
- HPN424
- JNJ-081
- REGN5678

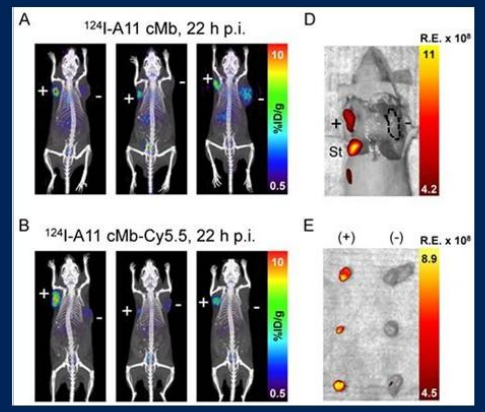
PSCA Targeted CAR T

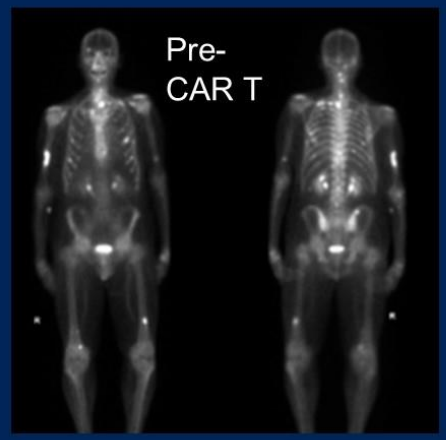
Phase 1 Study

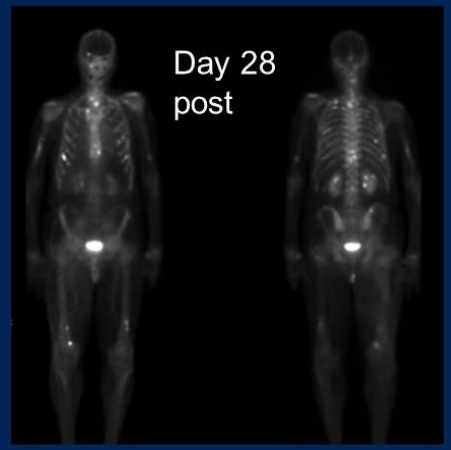
PSCA targeted CAR T in mCRPC: phase 1 results

- Radiographic and PSA responses have occurred (abstr #91, poster E5)
  - On-target, off-tumor toxicity = cystitis
- PSCA PET imaging feasible

Tsai WK et al. Theranostics 2018; 5903-14







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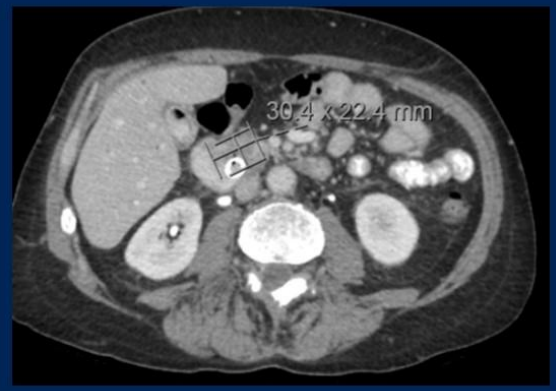
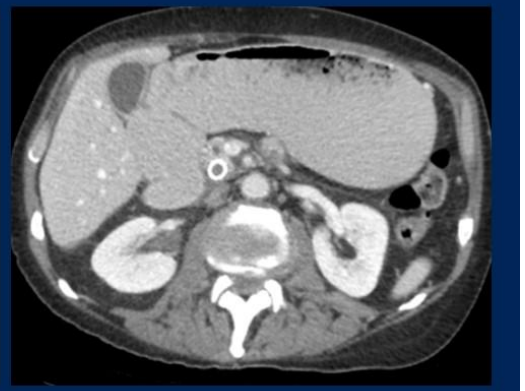


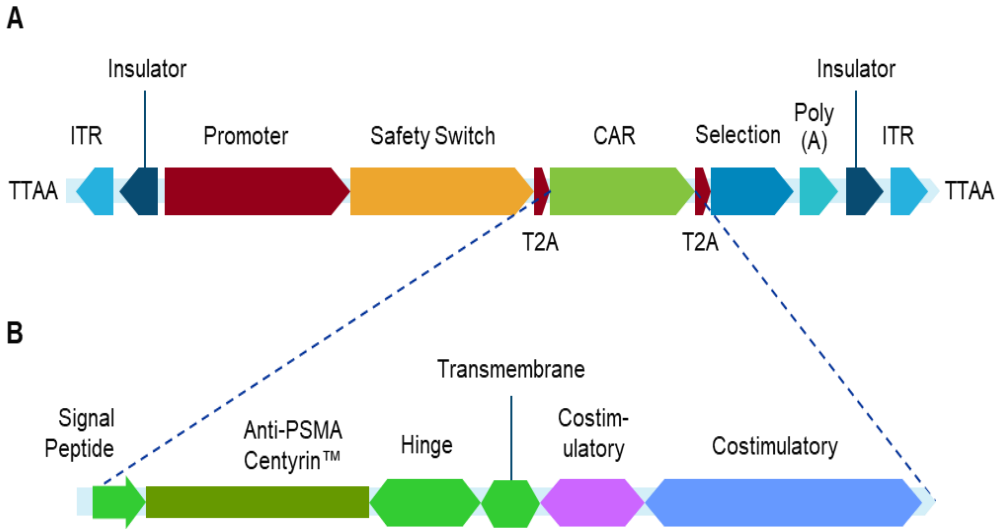


P-PSMA-101

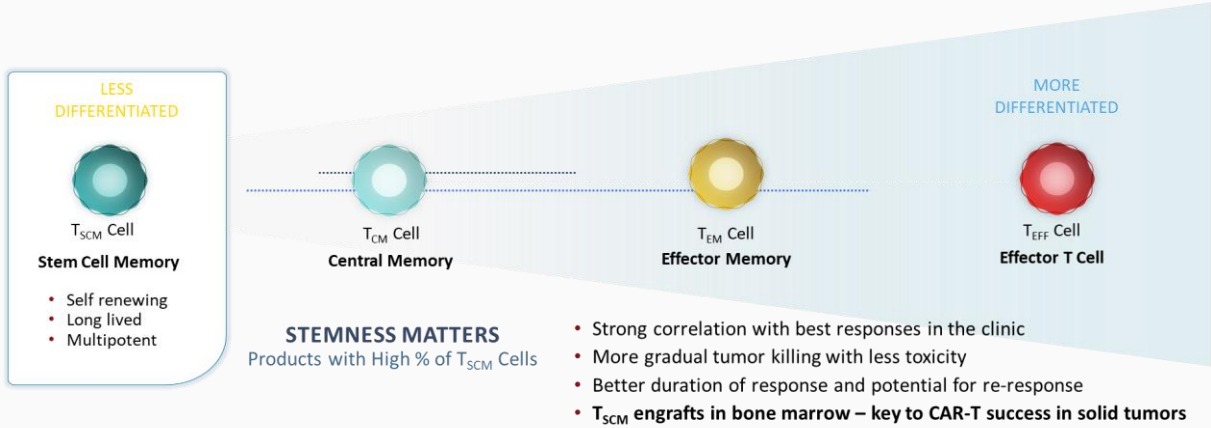
PSMA Targeted CAR T, Phase 1 Study

CAR encodes intracellular 4-1BB signaling domain and a T-cell receptor (TCR) ζ chain signaling domain expresses three major components from a transposed transgene that is stably integrated into the genome

1) An anti-PSMA Centyrin™-based CAR gene,
2) Dihydrofolate reductase (DHFR) mutein gene for selection of transposed cells during manufacture,
3) (3) an inducible caspase 9 (iCasp9)-based safety switch gene (activated by the small molecule rimiducid) for rapid ablation of CAR T-cells for SAE



- P-PSMA-101 is an autologous CAR-T therapy targeting PSMA and is made using a unique non-viral transposon system (piggyBac®) that results in a CAR-T product composed of a high percentage of stem cell memory T cells (T_{SCM})



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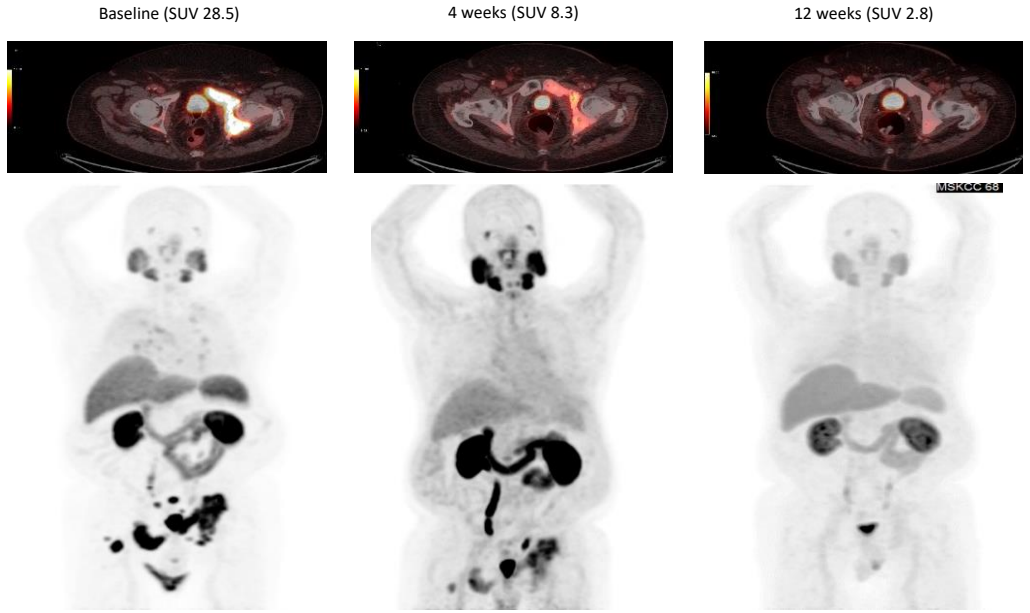
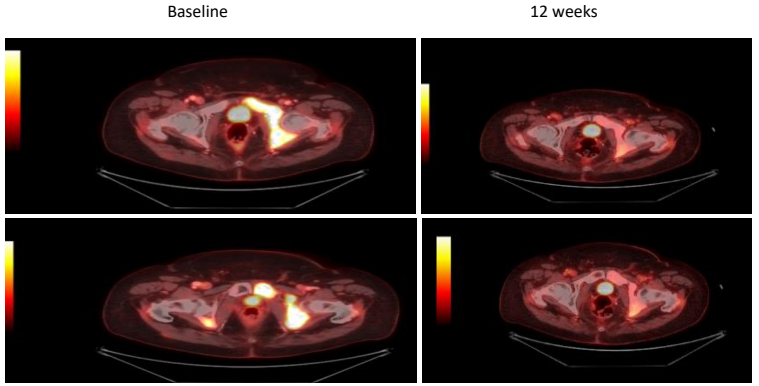
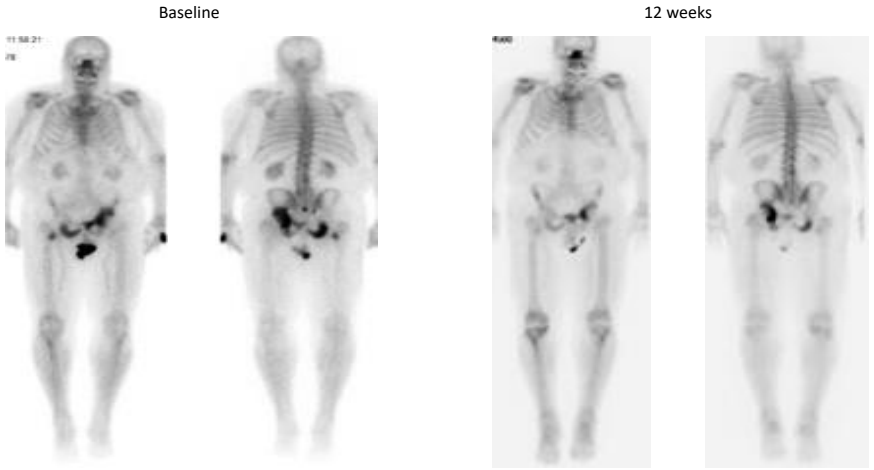
A



B



C



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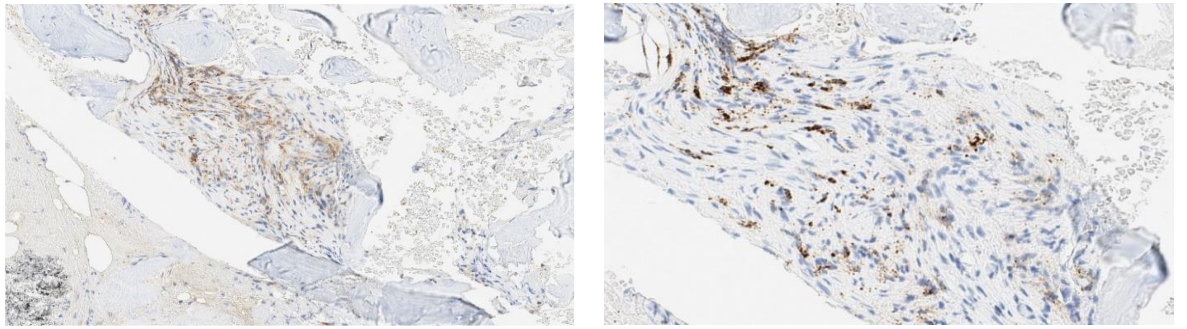
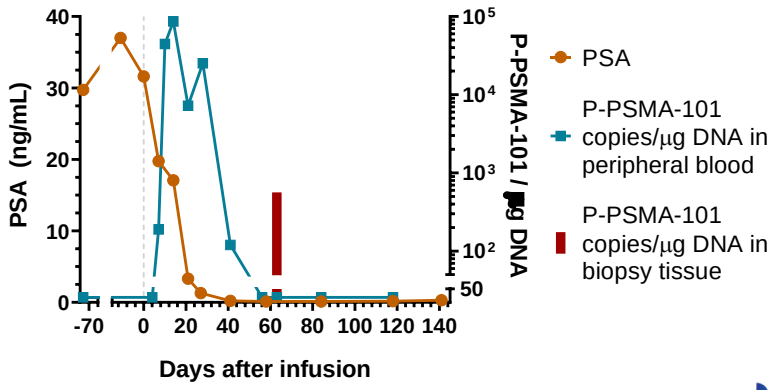


E



Slovin SF et al. *J Clin Oncol*. 2022;40(suppl _6):98-98.

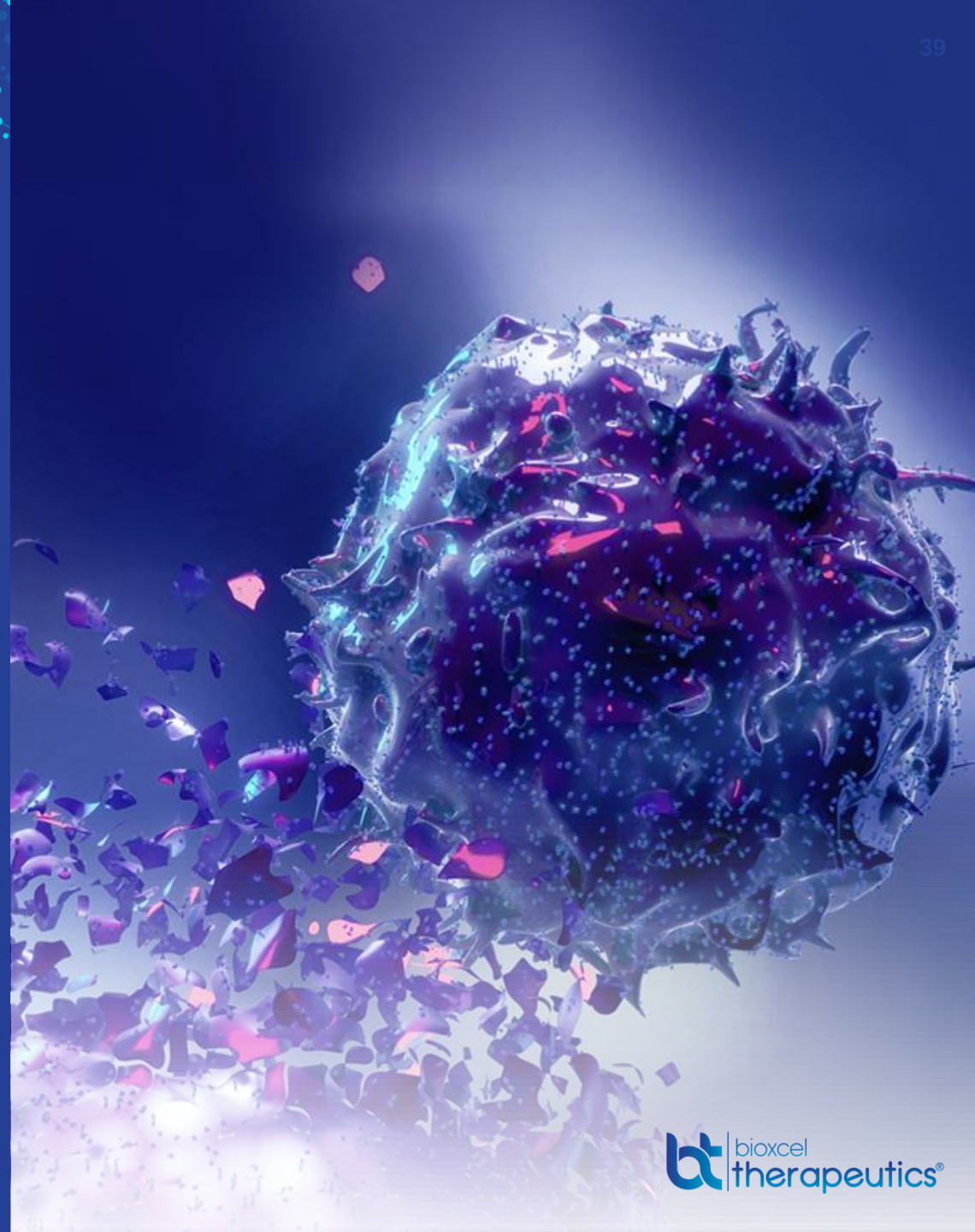
Conclusions

- Sipuleucel-T is FDA approved for CRPC in patients who are minimally symptomatic/asymptomatic with non-hepatic metastases
- Checkpoint inhibition therapy is effective in the MSI high subgroup, results in unselected patients are disappointing
- Further treatment should be designed to convert a cold tumor to hot

BXCL701 Mechanism of Action

Louis M. Weiner, M.D.

Georgetown | Lombardi
COMPREHENSIVE CANCER CENTER



Speaker is acting on behalf of and is a paid consultant to BioXcel Therapeutics, Inc.
This material is intended for an investor audience only.
The information contained in the following material is intended to provide background and educational information only and does not constitute medical advice. Individual results will vary among patients and depend on many factors. A patient's healthcare provider should consider the circumstances of each patient.

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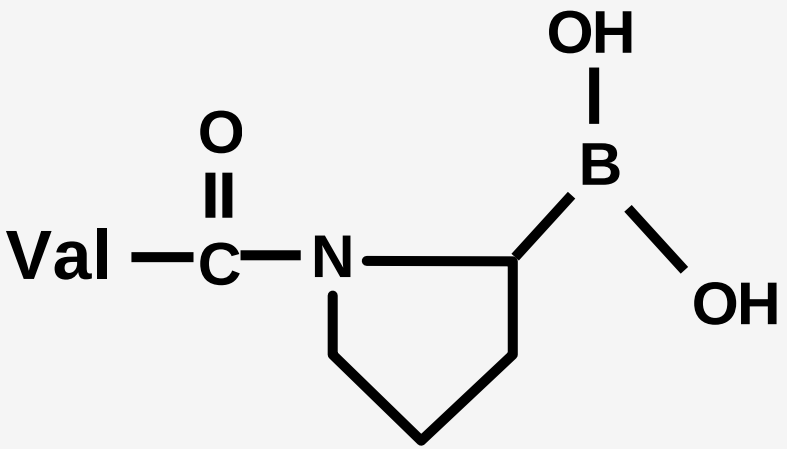
Disclosures

- I receive no monetary compensation from BioXcel Therapeutics*
- My laboratory has a contract for work that will be discussed
- Co-PI of open clinical trial of BXCL701 + pembrolizumab in metastatic pancreatic adenocarcinoma

*Travel was arranged by BioXcel Therapeutics

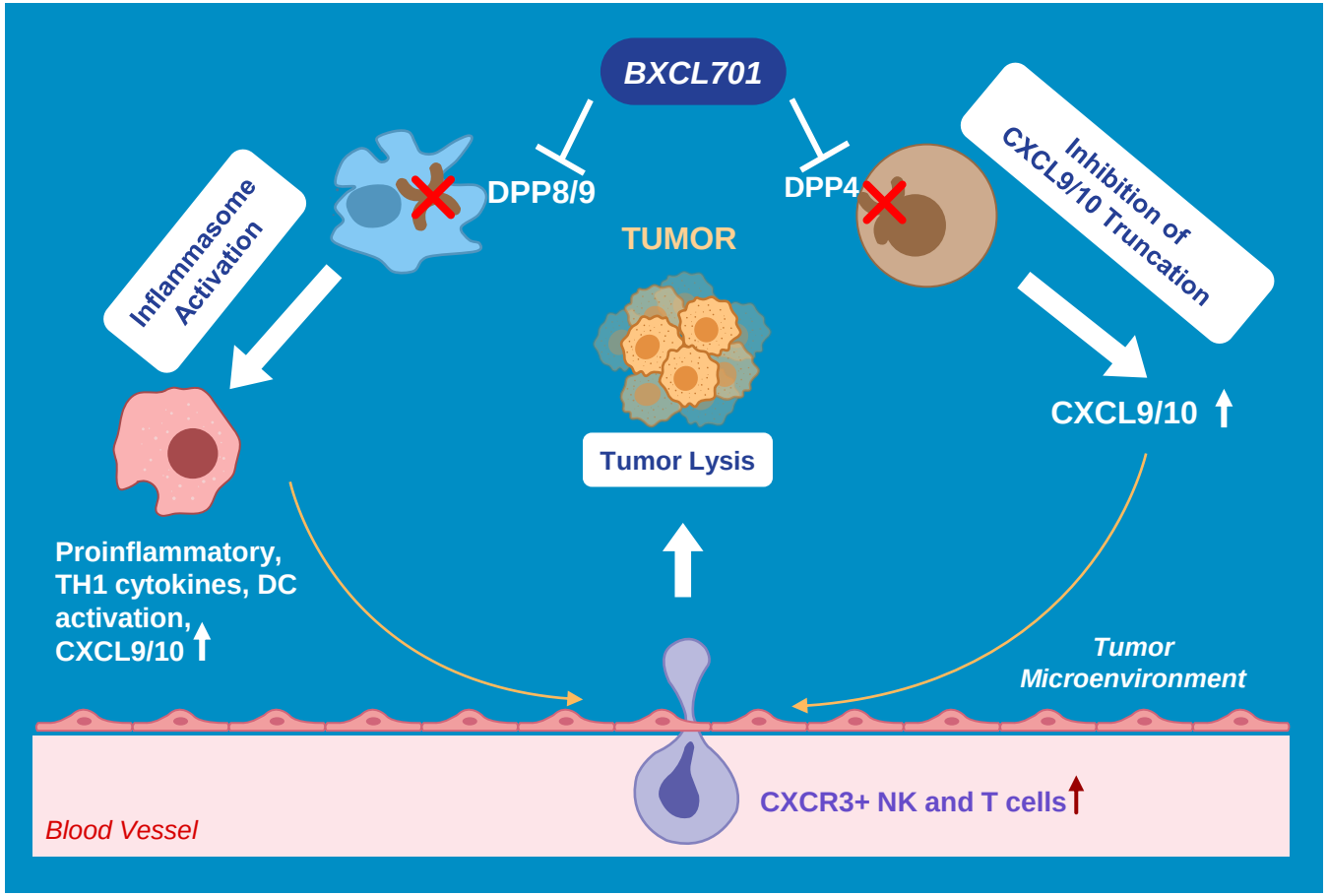
BXCL701 (Talabostat): Biochemical Activities



DPP8	DPP9	DPPIV	FAP
IC50 (nM)	IC50 (nM)	IC50 (nM)	IC50 (nM)
3	3	1	30

Mechanism of Action of BXCL701

BXCL701 Modulates the Tumor Microenvironment by Activating the Innate Immunity Followed by Adaptive Immunity Leading to Cancer Cell Death



- DPP8/9 inhibition by BXCL701 activates inflammasome leading to proinflammatory cytokines, Th1 cytokines and CXCL9/10 increase that enhances CXCR3+ NK and CD8+ T cell infiltration to improve anti-PD1 activity resulting in tumor lysis
- CXCL9/10 increase by inhibition of DPP4 also enhances CXCR3+ NK and CD8+ T cell infiltration

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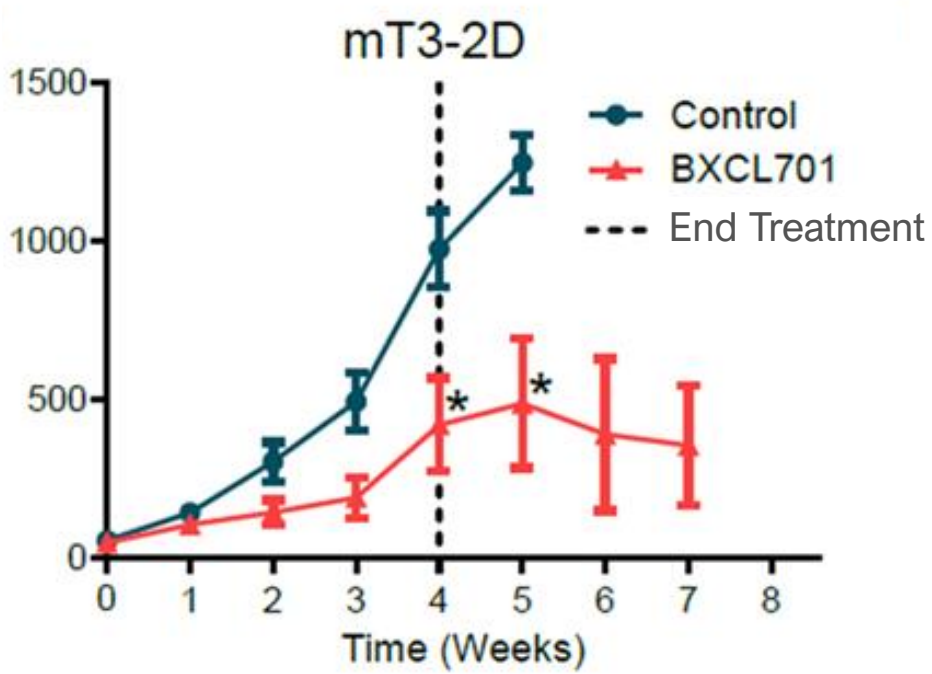
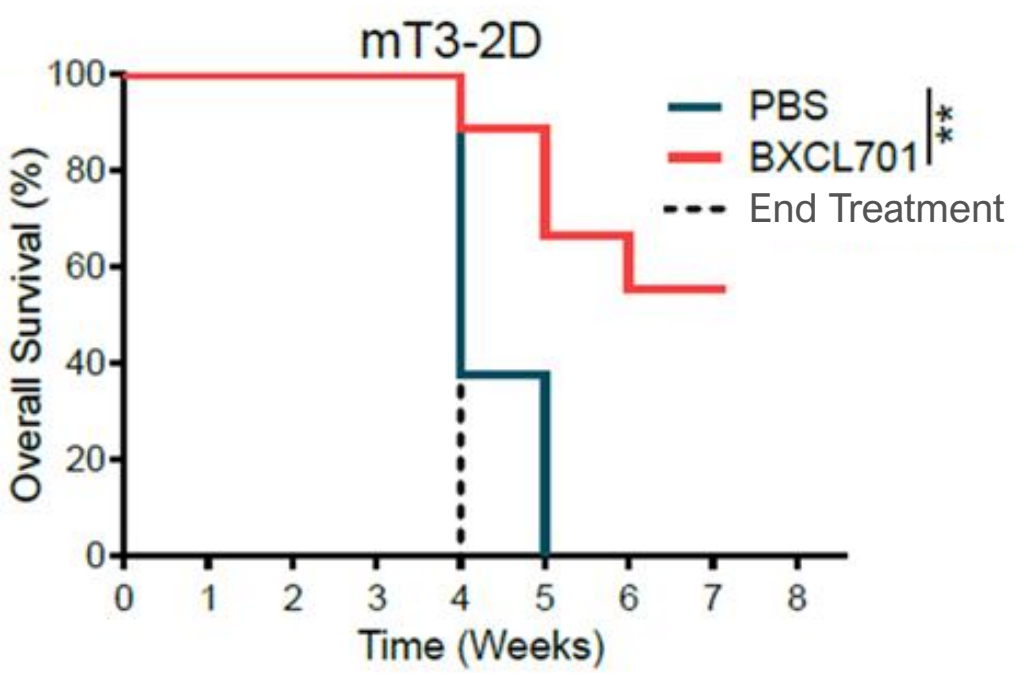
DPP Inhibition by BXCL701 Reduces Tumor Growth in a Murine Pancreatic Ductal Adenocarcinoma (PDAC) Model





Tumor Growth Curves

Survival curves of mice

Journal for ImmunoTherapy of Cancer 2021; 9:e002837. doi:10.1136/jitc-2021-002837

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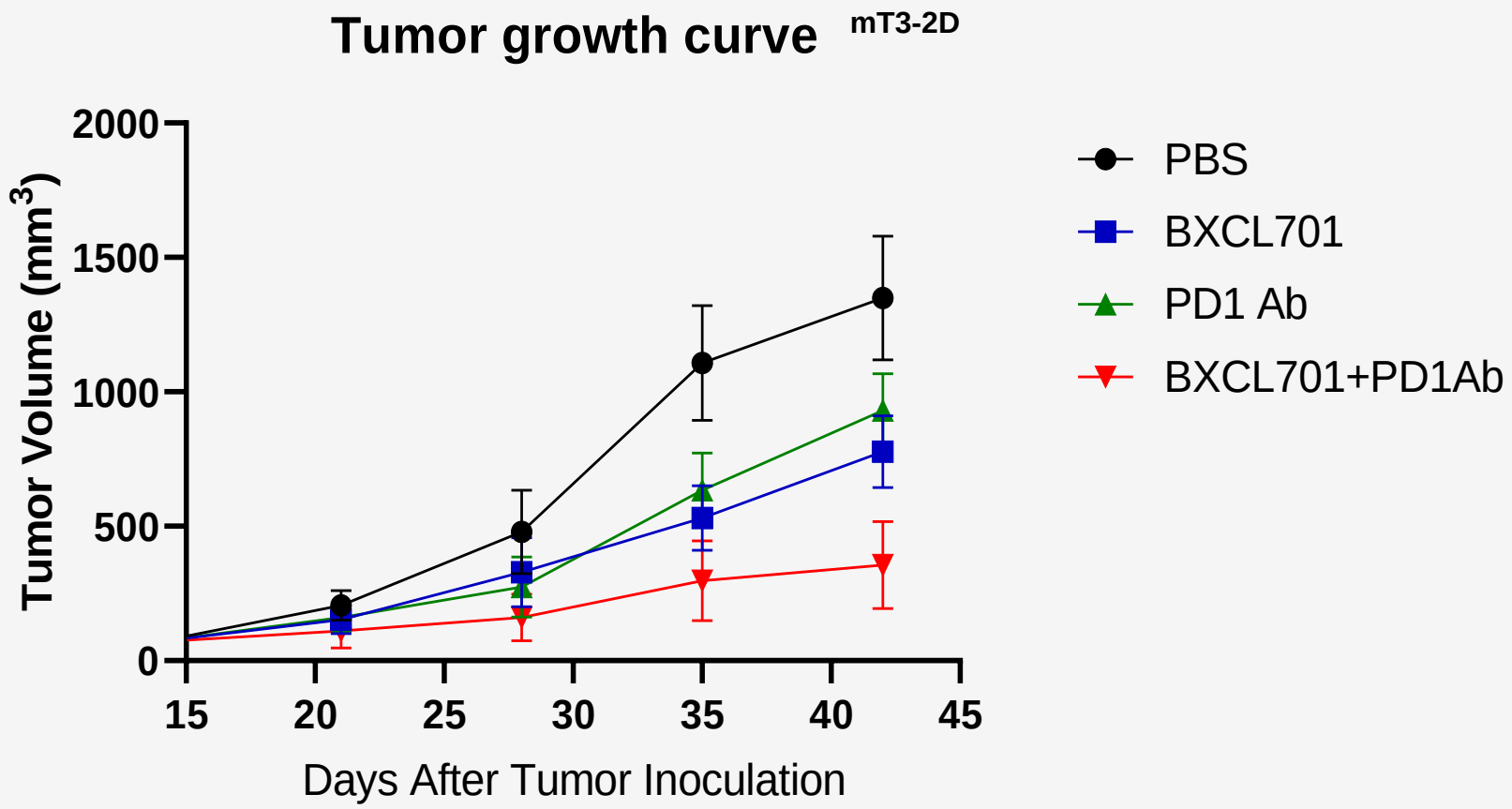
BXCL701 Synergizes with Anti-PD-1 in Reducing Tumor Growth in a Murine Pancreatic Ductal Adenocarcinoma (PDAC) Model



Journal for ImmunoTherapy of Cancer 2021; 9:e002837. doi:10.1136/jitc-2021-002837

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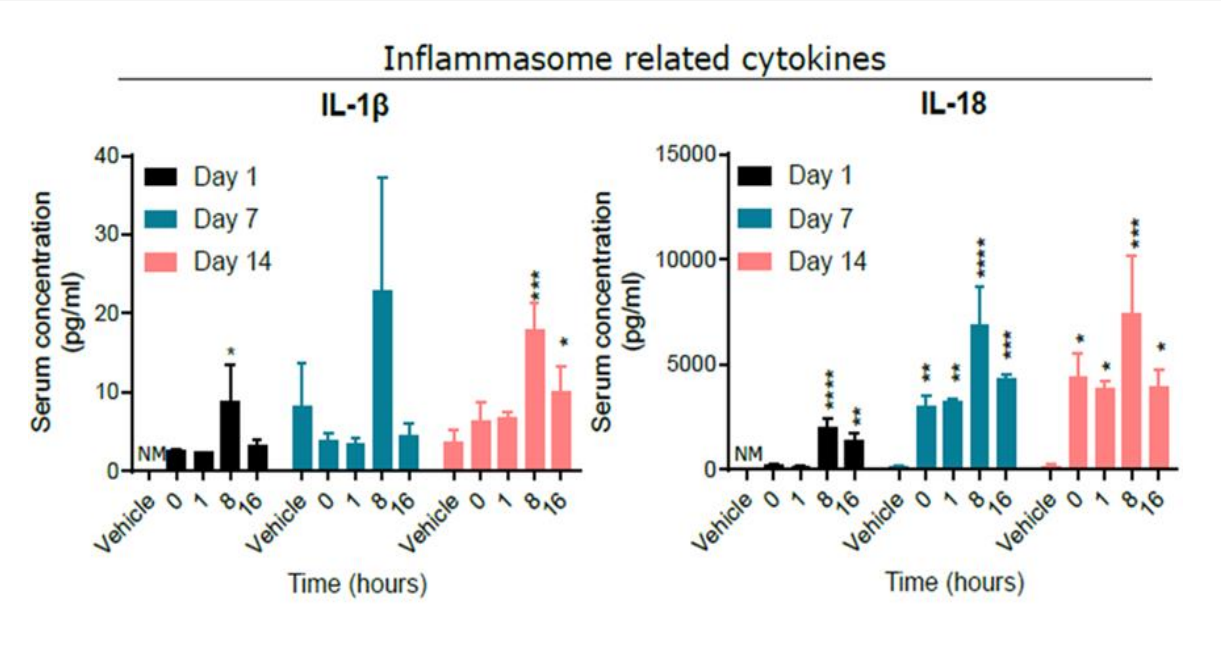
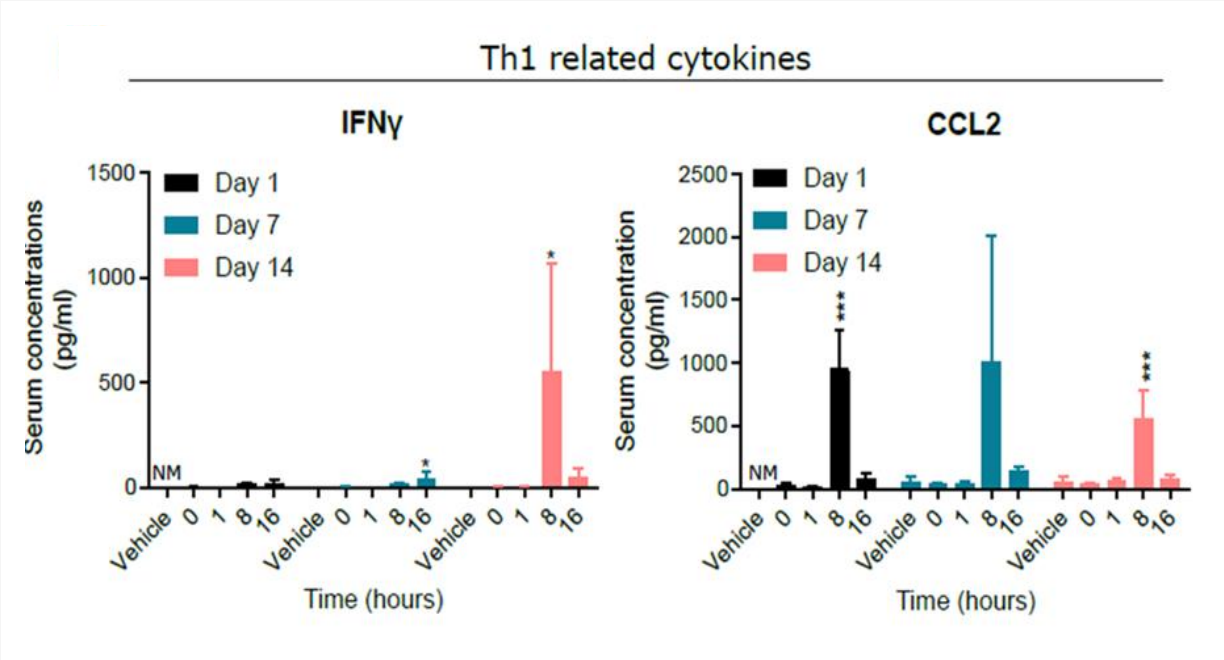
BXCL701 Increases Circulating Inflammasome and Th1-Related Cytokines in a Syngeneic PDAC Mouse Model of Pancreatic Cancer





Journal for ImmunoTherapy of Cancer 2021; 9:e002837. doi:10.1136/jitc-2021-002837

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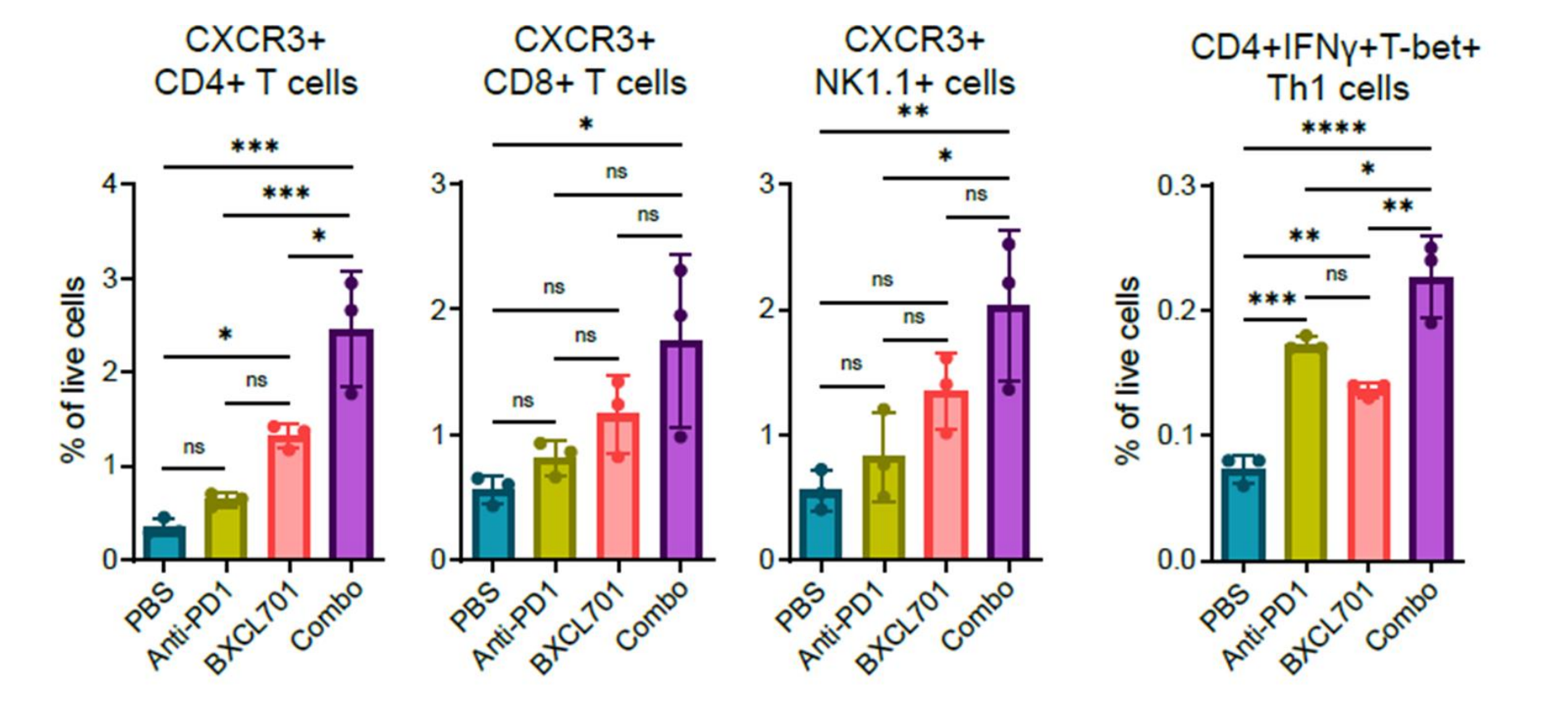
BXCL701 Alone and in Combination with Anti-PD-1 Increases Tumor Levels of CXCR3+ and Innate Immune Cells in a Syngeneic Mouse Model (mT3-2D) of Pancreatic Ductal Adenocarcinoma



Journal for ImmunoTherapy of Cancer 2021; 9:e002837. doi:10.1136/jitc-2021-002837

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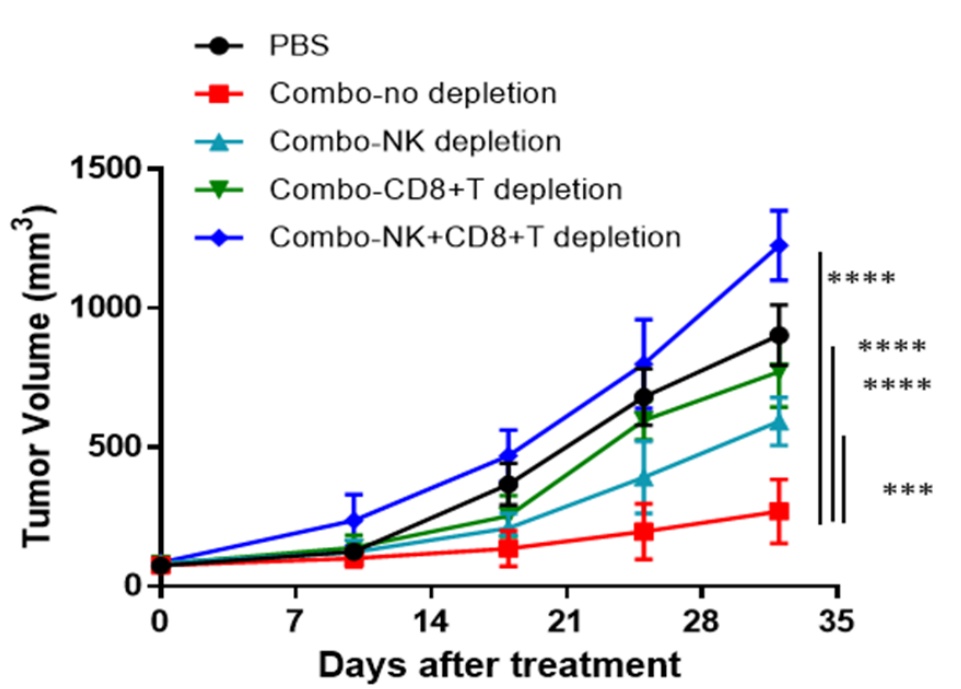
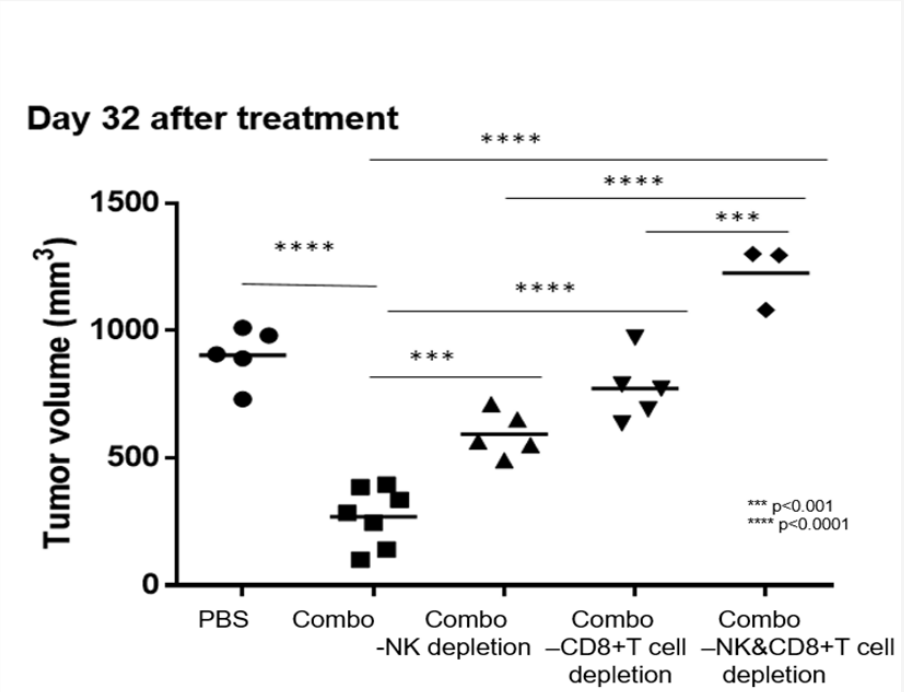
BXCL701 + Anti-PD-1 Engages Both NK and CD8+ T Cells in a Syngeneic Mouse Model (mT3-2D) of Pancreatic Ductal Adenocarcinoma

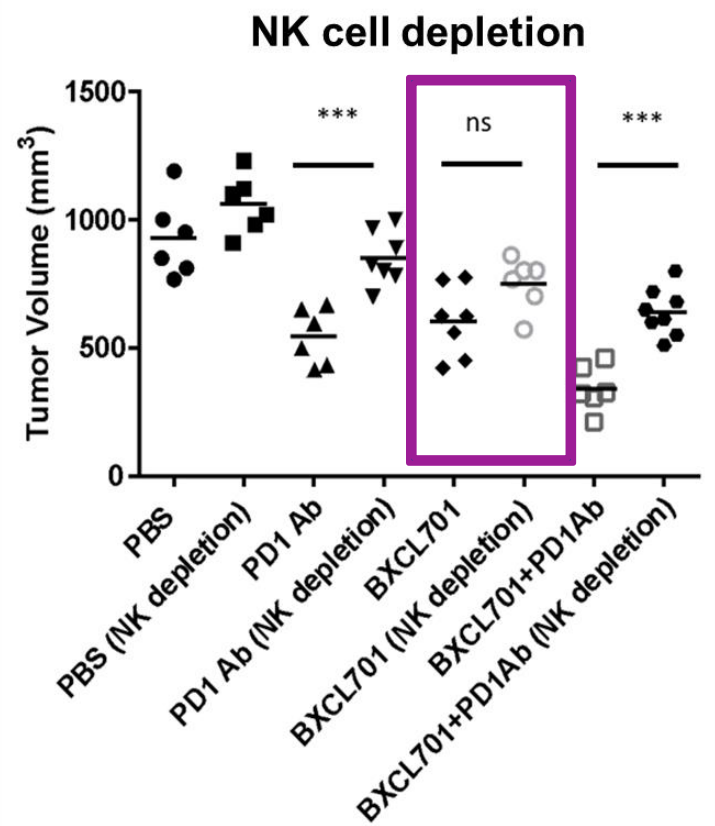




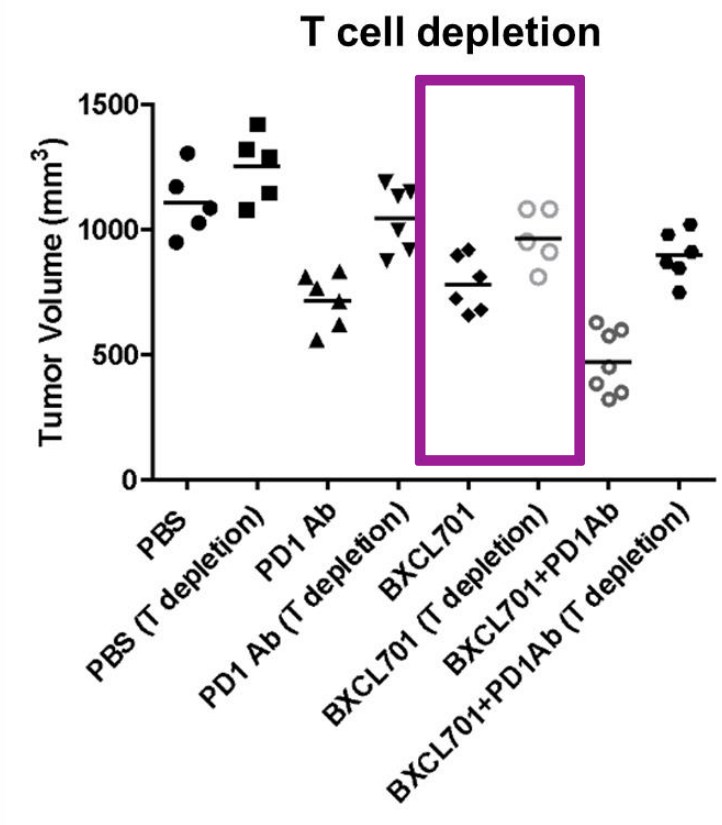
- NK and CD8+T cells both contribute to tumor growth inhibition by PD-1 / BXCL701combination treatment
- Depletion of either immune cell type or especially both types simultaneously has a large impact on tumor growth

Journal for ImmunoTherapy of Cancer 2021; 9:e002837. doi:10.1136/jitc-2021-002837

NK Cell and T Cell Depletion Influences Treatment Outcomes for 701 Treatment Alone



Day 18 after treatment



Day 28 after treatment

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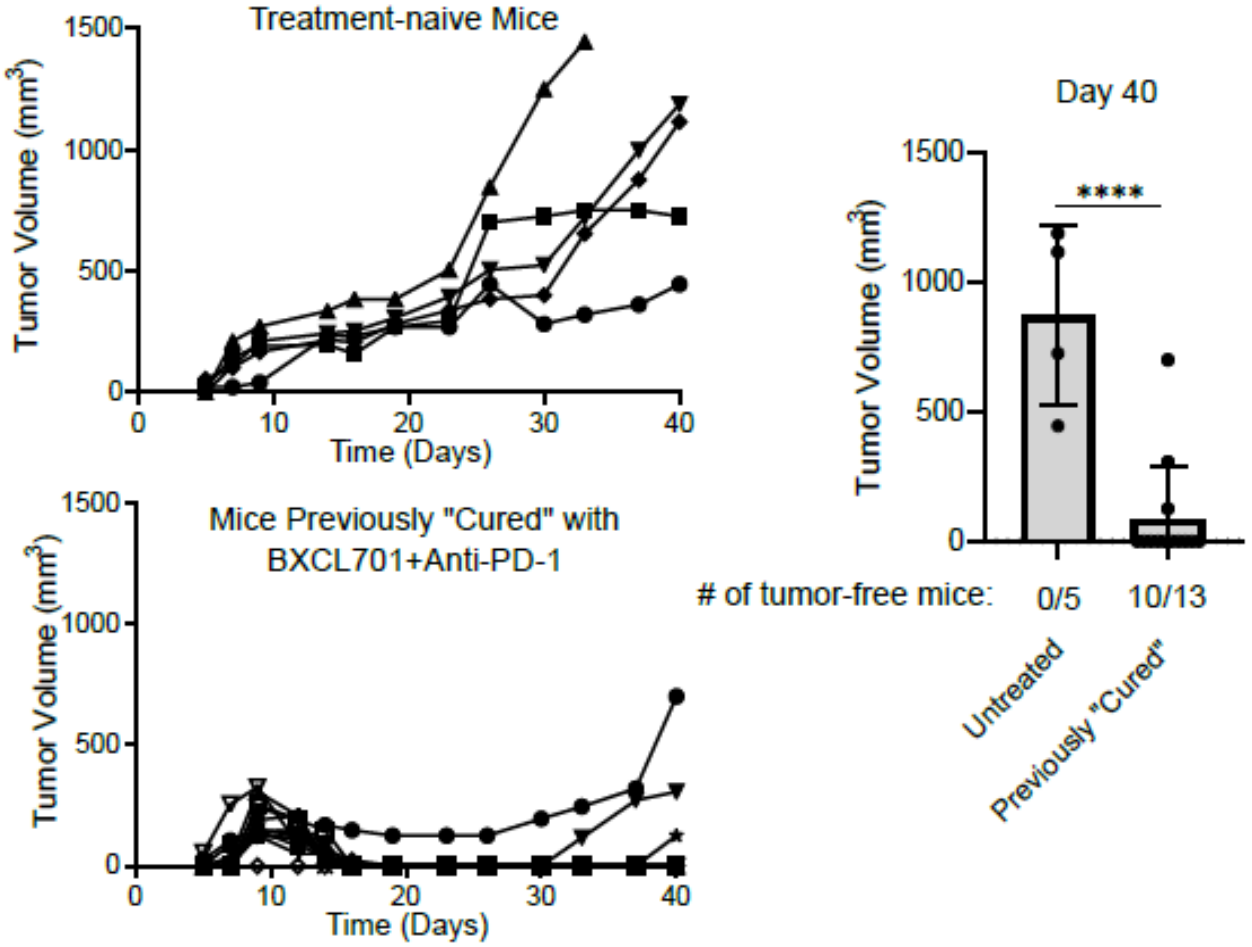
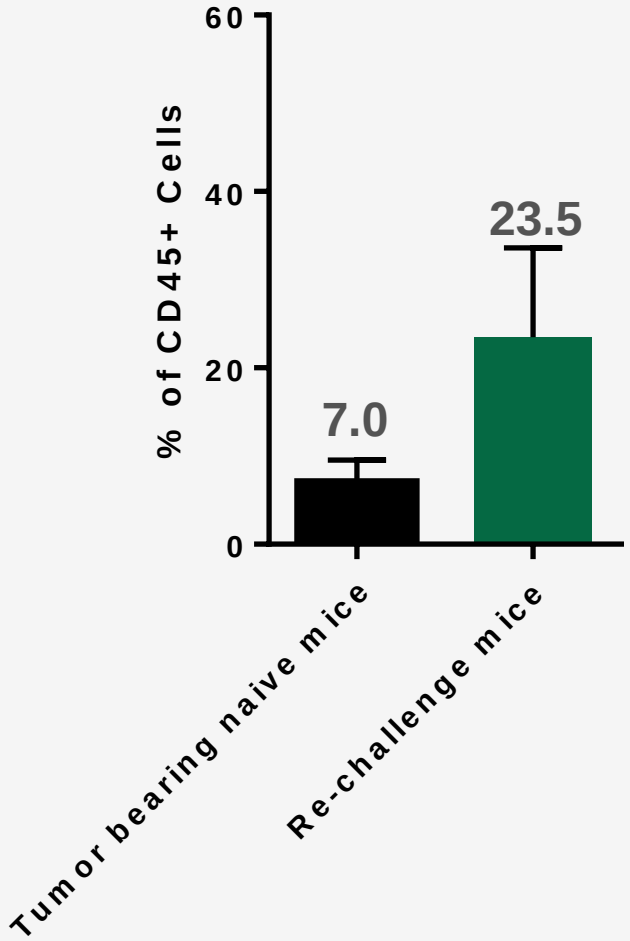
BXCL701 + Anti-PD-1 Induces Memory Response Against Rechallenge



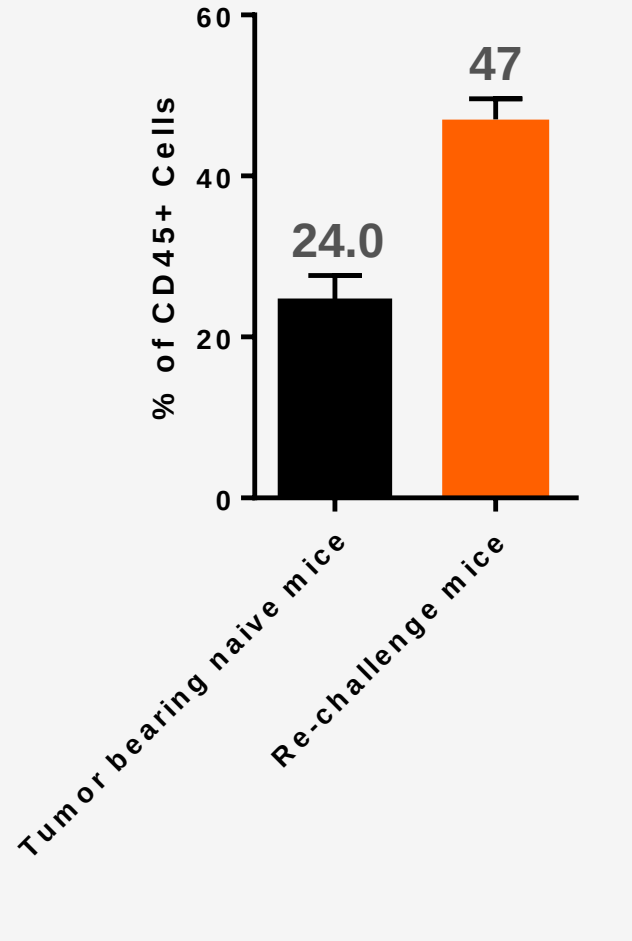
- Tumor-free mice from previous experiment (BXCL701 + anti-PD-1 Ab) were re-challenged with 5-fold excess (i.e., 5 x 10^5) tumor cells compared with original challenge
- 5 tumor-naive mice used as controls
- Tumor growth was monitored without administering any additional treatment.
- ****p <0.0001 by unpaired two-tailed t-test

Journal for ImmunoTherapy of Cancer 2021; 9:e002837. doi:10.1136/jitc-2021-002837

Percentage of CD45+ Cells (Effector Memory T Cells) Were Increased in Re-Challenged Mice

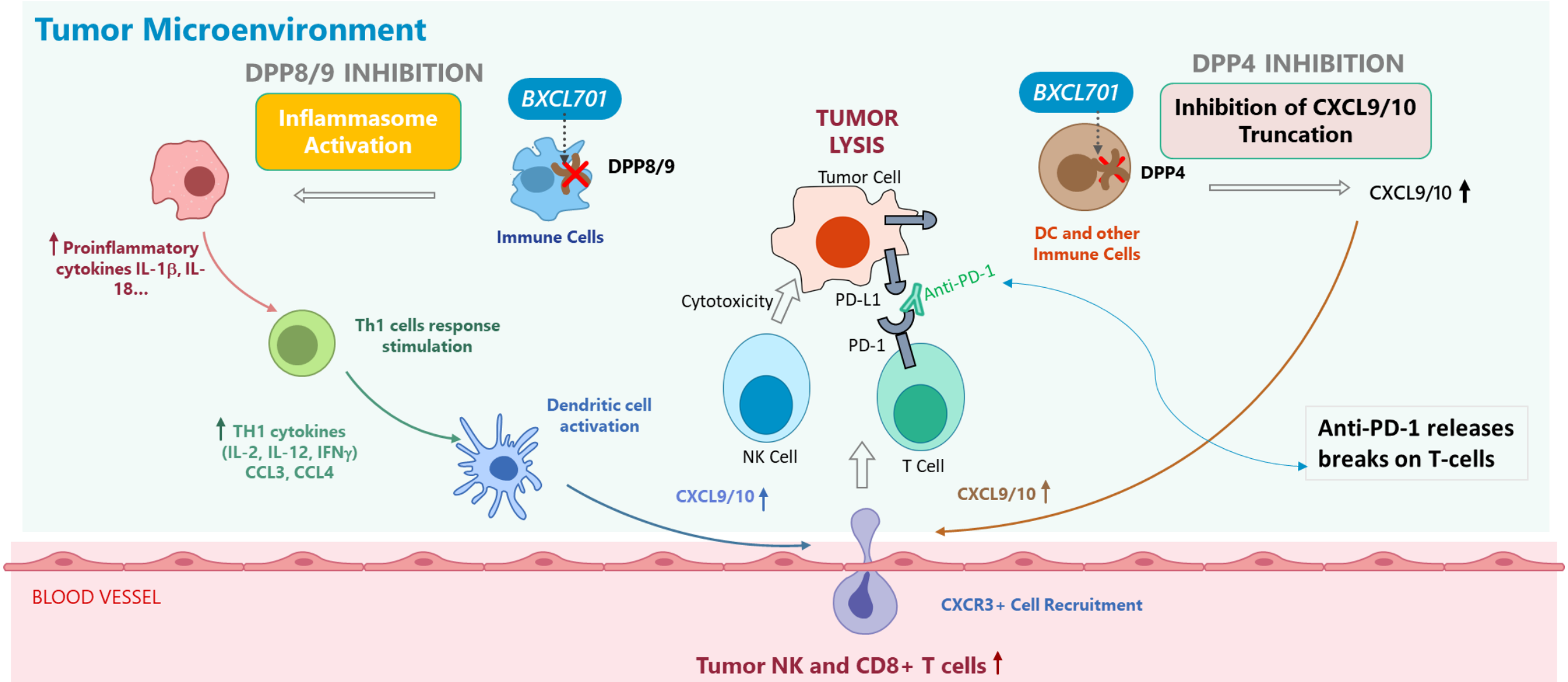


$CD8^{+}\ CD44^{high}\ CD62L^{low}$



$CD4^{+}\ CD44^{high}\ CD62L^{low}$

Well-Understood Mechanism of Action of BXCL701 and Pembrolizumab Combination



Adapted from **Journal for ImmunoTherapy of Cancer 2021**; 9:e002837. doi:10.1136/jitc-2021-002837

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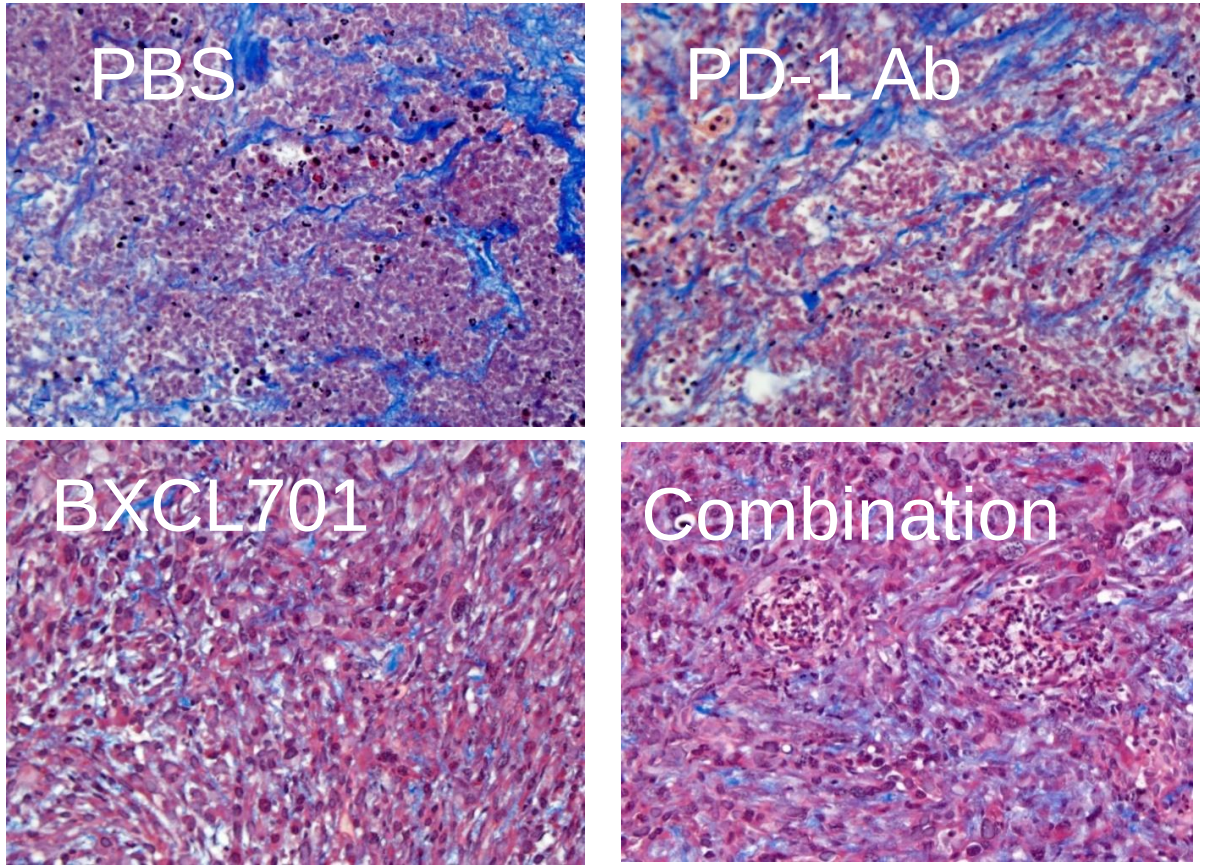
BXCL701 or BXCL701 + PD1 Antibody Treatment Reduces Fibrosis in Tumor Micro-Environment

A



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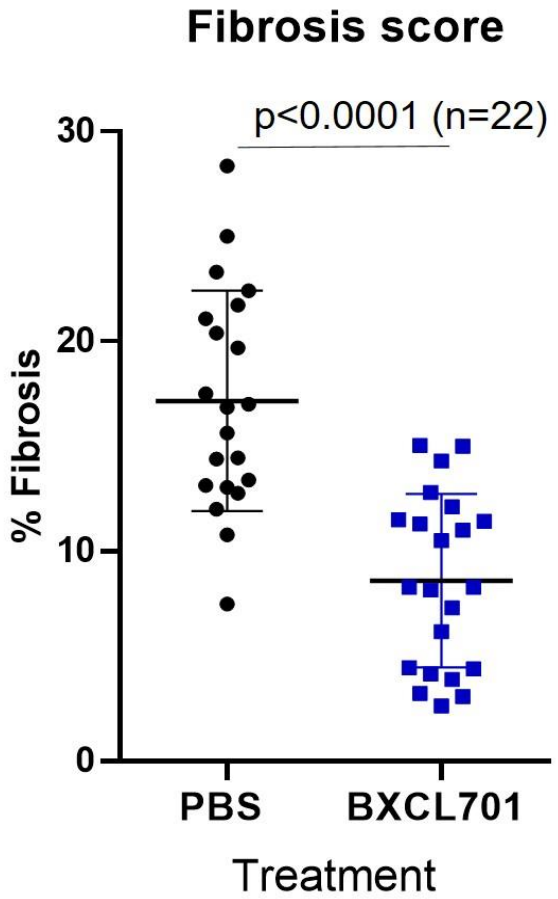

(A) Masson's Trichrome stain demonstrating intense fibrosis formation in a representative mT3-2D pancreatic tumor from a PBS treated mouse, while BXCL701 or combined Rx markedly decreased fibrosis. (B) Fibrosis scoring was performed using quantitative morphometry by Image J. BXCL701 treated mouse tumors showed significantly decreased fibrosis compared to PBS treatment (n=22 pooling results from two separate experiments).

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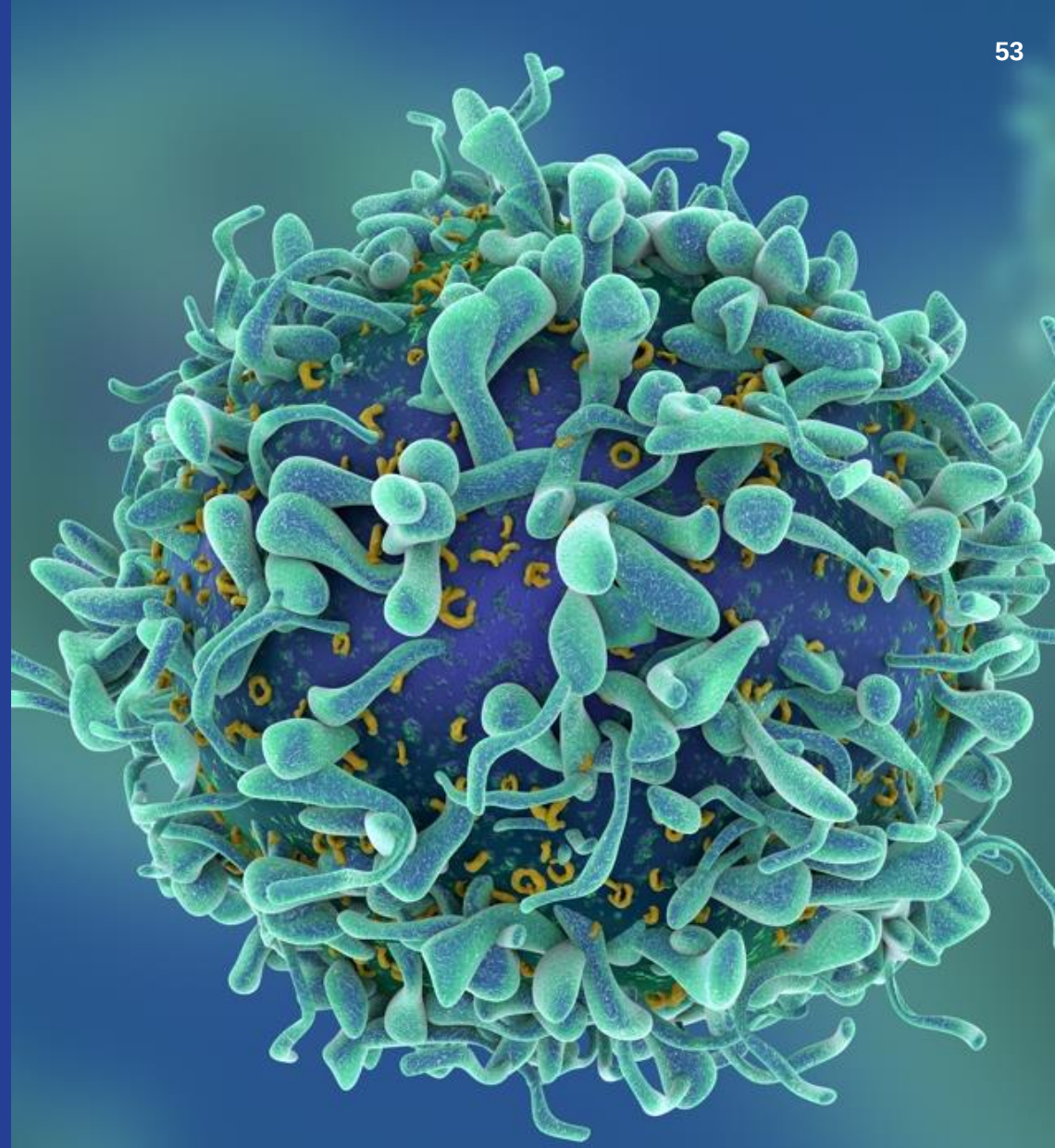
BXCL701: Potential Combination Opportunities in Addition to Anti-PD-1



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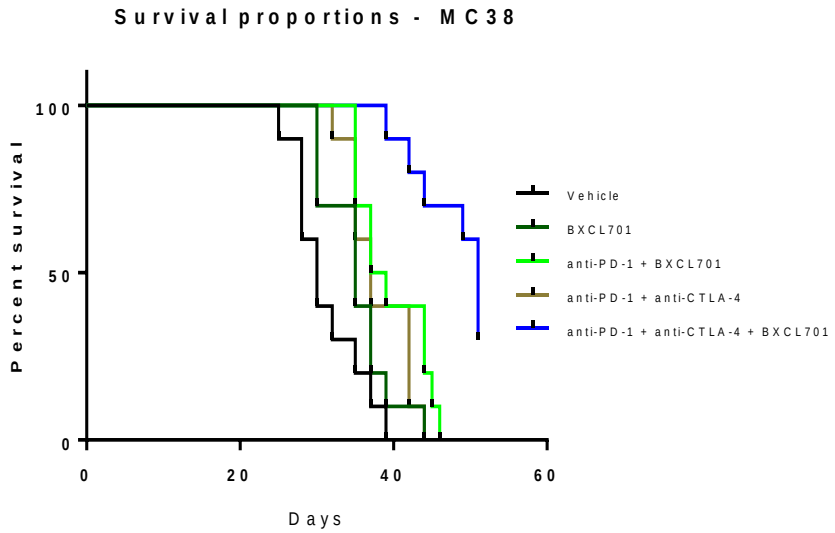
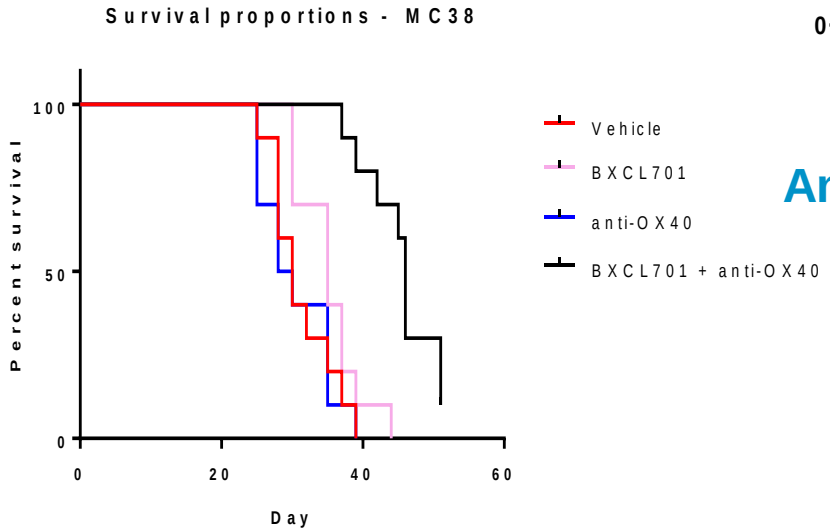
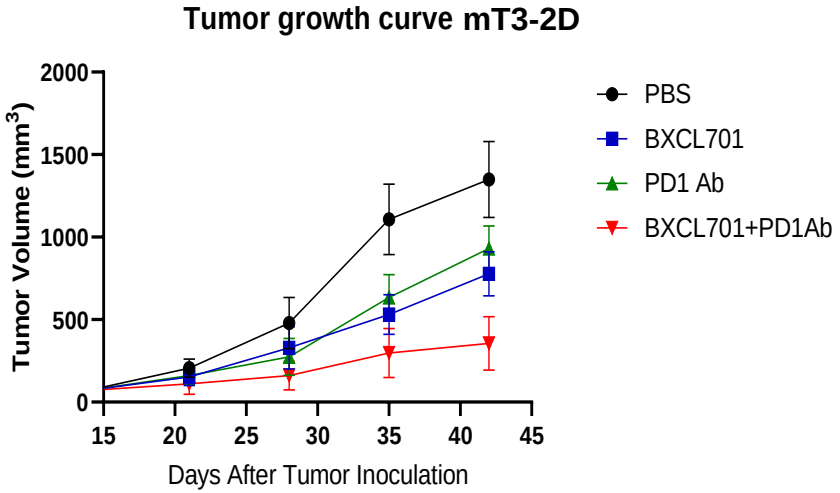
BXCL701 Synergizes with Multiple T Cell Activating Therapies



Anti-CTLA-4 (checkpoint antagonist)



Anti-OX40 (co-stimulator)



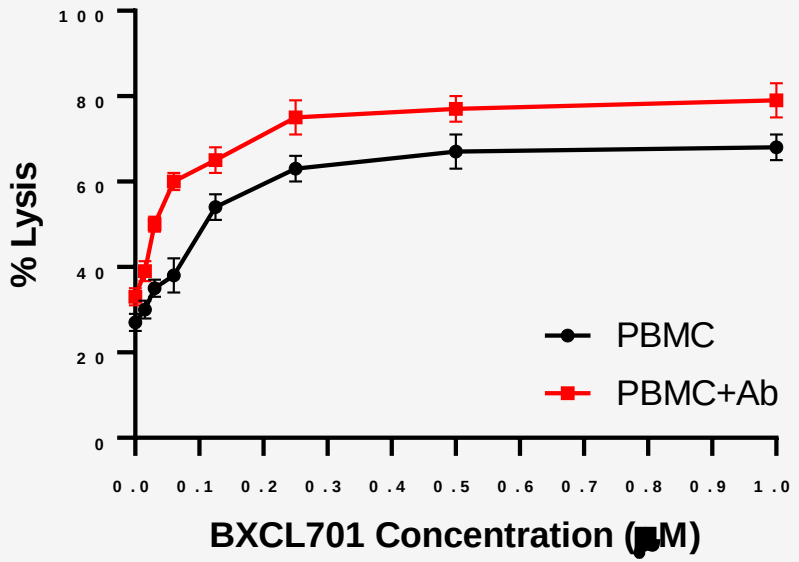
Anti-PD1 (checkpoint antagonist)

BXCL701 Has Shown Synergistic Antitumor Activity with Different Checkpoint Modulators

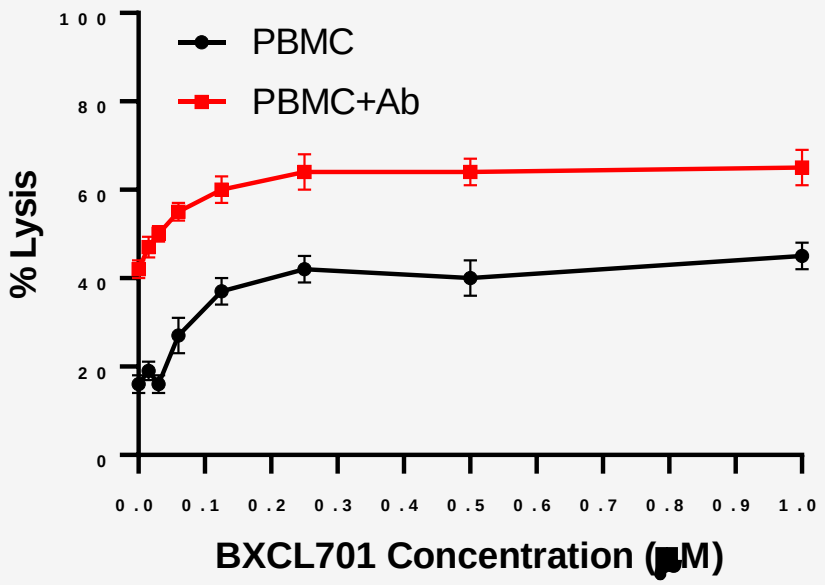
bioxcel therapeutics®

BXCL701 Induces Antibody Dependent Cell Cytotoxicity (ADCC) Effect *In Vitro*

PBMC+SKOV3 (E:T =15:1)+Trastuzumab



PBMC+A431 (E:T =15:1)+Cetuximab



BXCL701 (0.01-0.03 μM) induces peak ADCC by PBMCs + Ab against A431 and SKOV3 cells with 3 days of exposure in 2 separate donors

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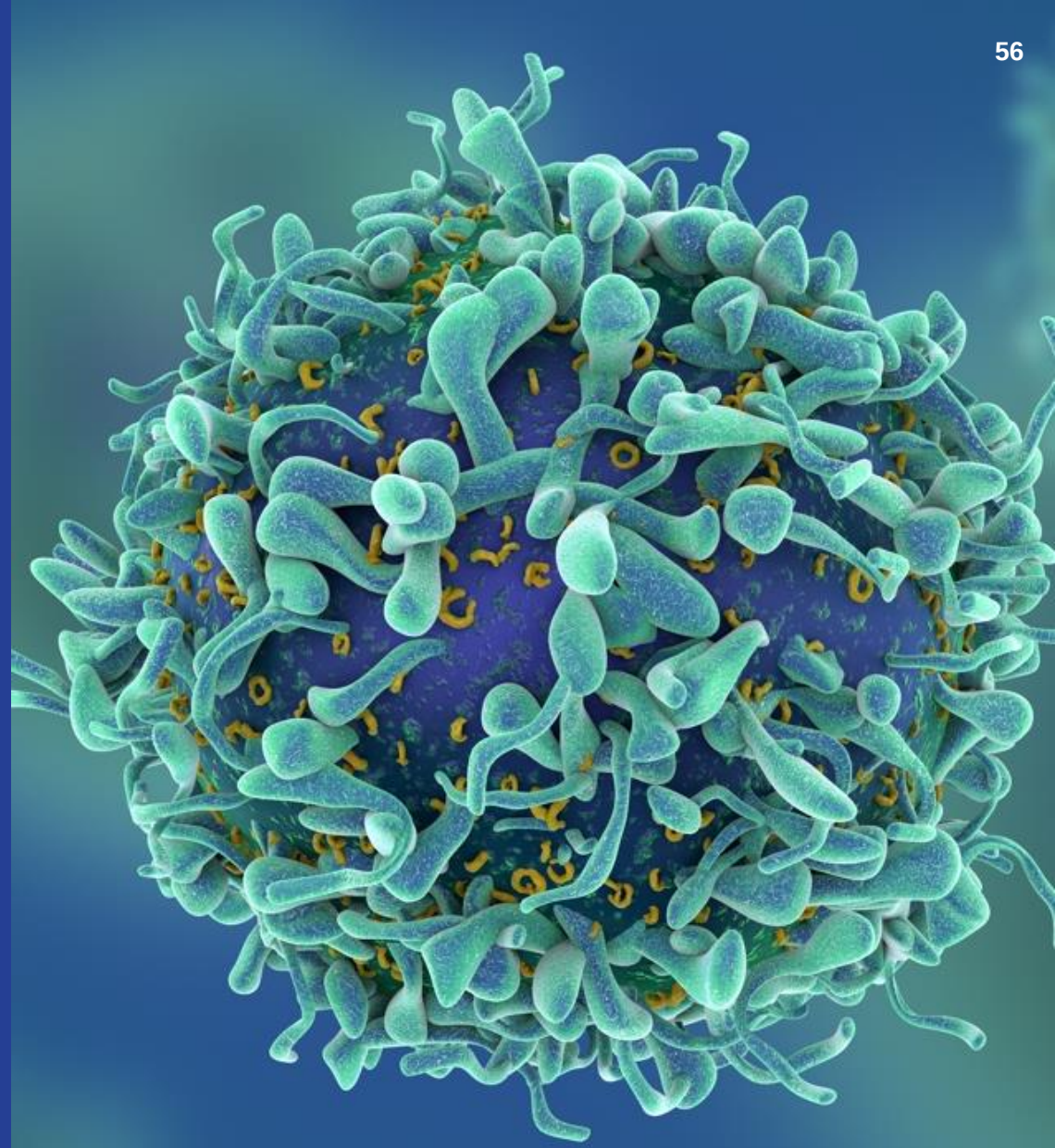
BXCL701: Potential Predictive Biomarker



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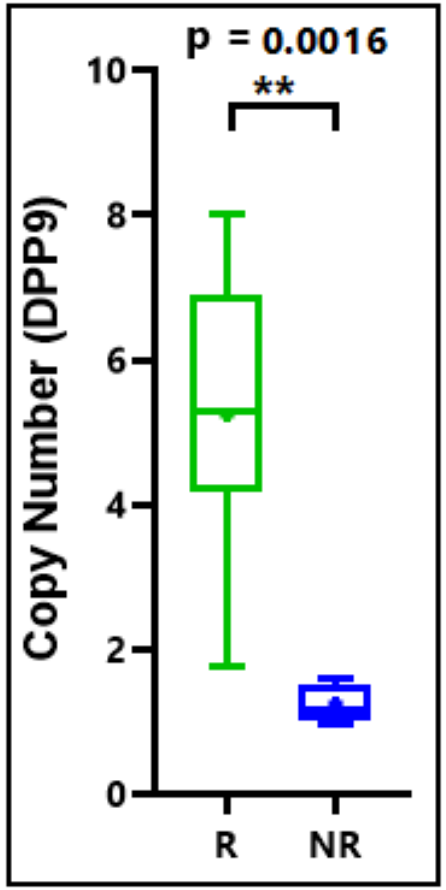
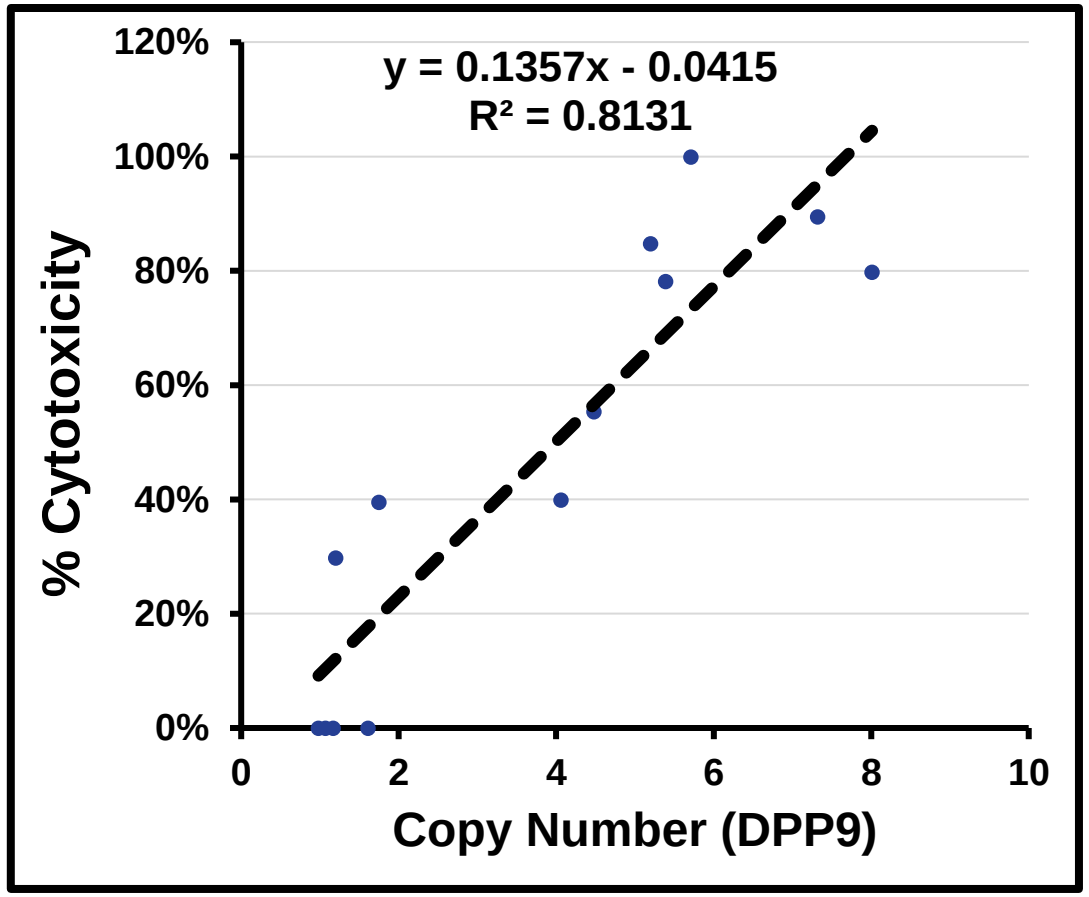
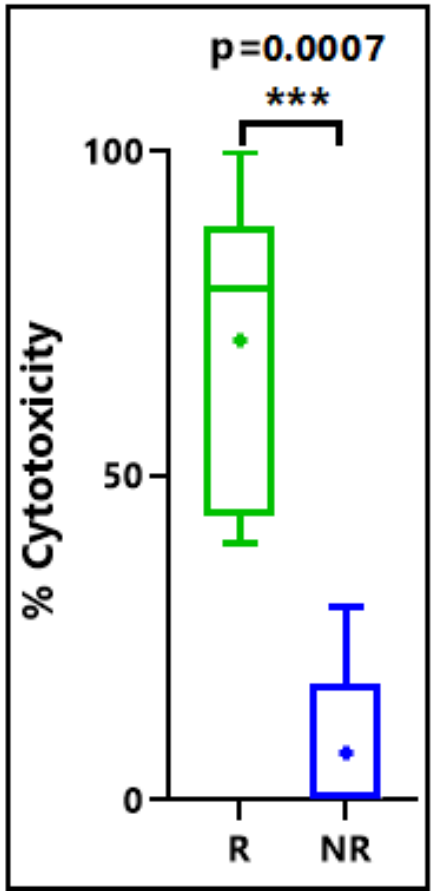
DPP9 Copy Number Correlates with BXCL701 Cytotoxicity in Leukemic Cell Lines and is a Potential Predictive Biomarker in Leukemias

Society for Immunotherapy of Cancer

Out of total 13 cell lines 10 were AML cell lines







*** p-value calculated by non-parametric Mann-Whitney Test,

R – Responder Cell Lines, **NR** – Non-Responder Cell Lines

Aggarwal et al. SITC 2022, Abstract #25

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Results of Phase 2 Trial of BXCL701 in SCNC

Rahul Aggarwal, M.D.

UCSF
University of California
San Francisco

Speaker is acting on behalf of and is a paid consultant to BioXcel Therapeutics, Inc.
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The information contained in the following material is intended to provide background and educational information only and does not constitute medical advice. Individual results will vary among patients and depend on many factors. A patient's healthcare provider should consider the circumstances of each patient.

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ASCO Genitourinary Cancers Symposium

First-in-class Oral Innate Immune Activator BXCL701 Combined with Pembrolizumab in Patients with Metastatic Castration-resistant Prostate Cancer (mCRPC) of Small Cell Neuroendocrine (SCNC) Phenotype: Phase 2a Final Results

Rahul R. Aggarwal[1], Jingsong Zhang[2], Paul Monk[3], Xinhua Zhu[4], Rob Jones[5], Mark Linch[6], Dan Costin[7], Johann de Bono[8], Lawrence I. Karsh[9], Daniel Petrylak[10], Pascal Borderies[11], Rashmi Deshpande[12], Amir Hafeez[13], Vincent O'Neill[14], Scott T. Tagawa[15]

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4. Monter Cancer Center, Northwell Health Center for Advanced Medicine, New Hyde Park, NY, USA
5. Beatson West of Scotland Cancer Centre, University of Glasgow, Glasgow, UK
6. Uro-Oncology, University College London Hospital, London, UK
7. Center for Cancer Care, White Plains Hospital, White Plains, NY, USA
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15. Hematology and Medical Oncology, Weill Cornell Medicine, New York, NY, USA

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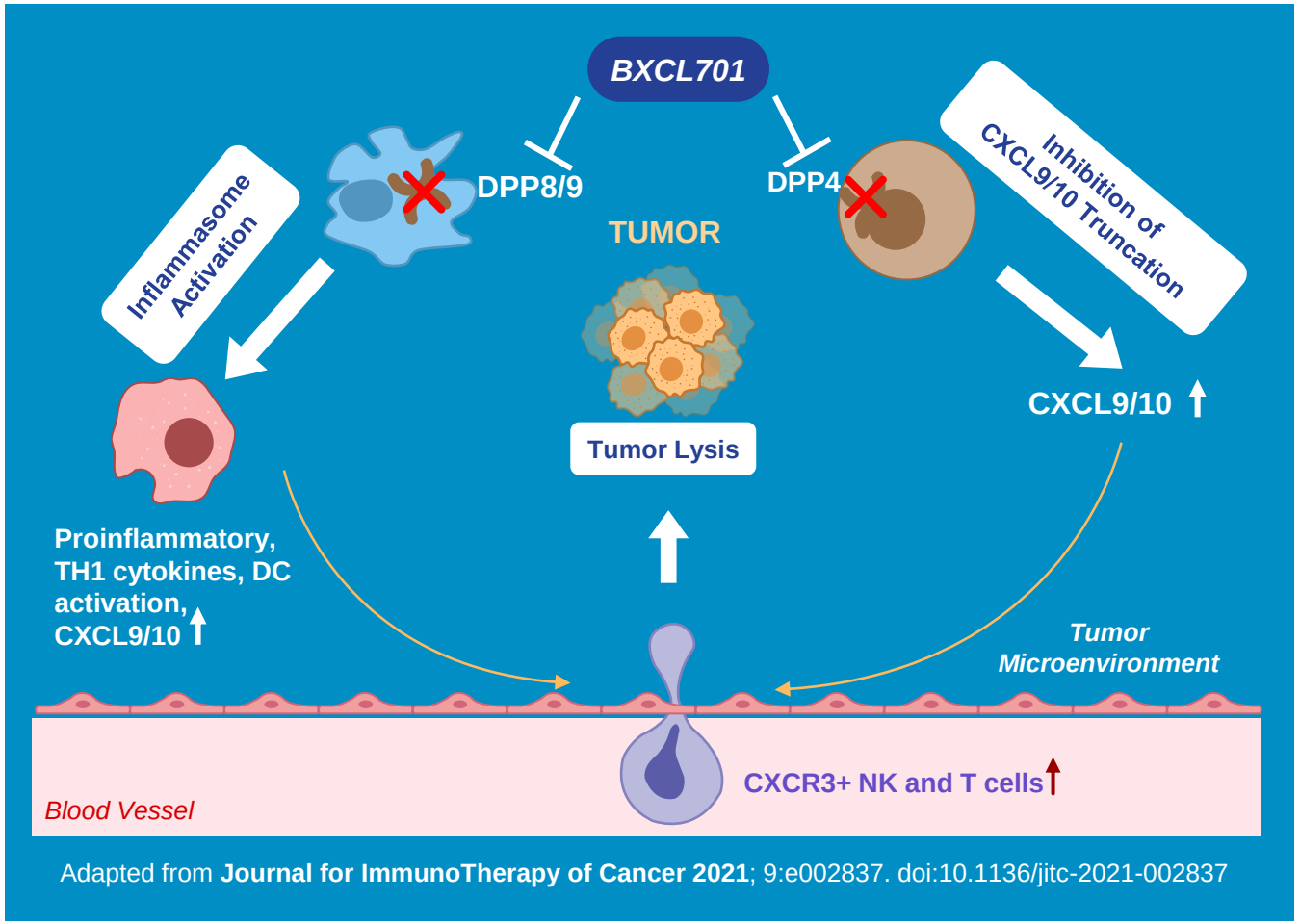
Background



Adapted from **Journal for ImmunoTherapy of Cancer 2021**; 9:e002837. doi:10.1136/jitc-2021-002837

- *De novo* and treatment-emergent SCNC are associated with adverse survival outcomes
- BXCL701 modulates tumor microenvironment by activating innate immunity followed by adaptive immunity leading to cancer cell death
- Phase 1b safety lead-in tested 2 total daily doses of BXCL701 (0.4 mg and 0.6 mg) [SITC 2020]
  - On-target AEs consistent with cytokine activation seen at highest daily dose (0.6 mg)
  - Splitting daily dose + step-up dosing → improved tolerability (no reported DLTs and lower rates of AEs of interest hypotension and peripheral edema)

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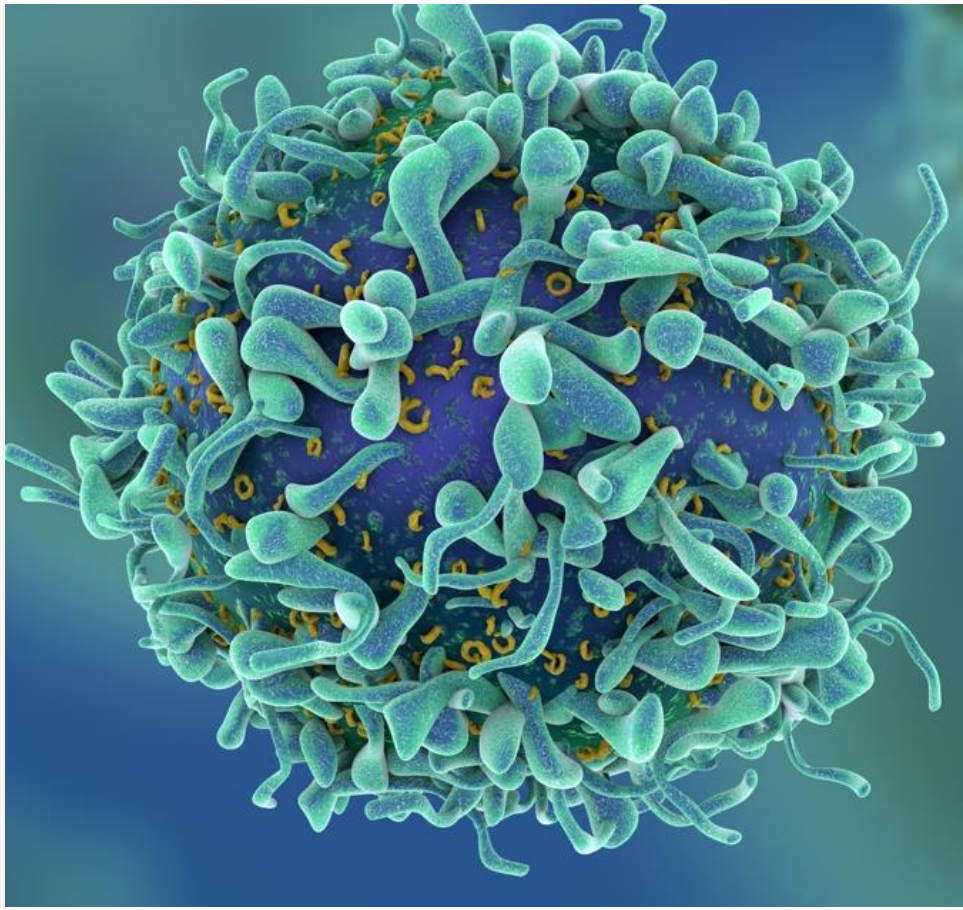
High Unmet Need in SCNC with no FDA Approved Therapy and Incidence is Increasing

288,300 Men Diagnosed with Prostate Cancer in U.S. in 2023*; ~20% Expected to Progress to More Aggressive mCRPC

- **~20% of these mCRPC patients will develop SCNC phenotype**, characterized by poor prognosis and low survival rate
- Current treatment protocols that are sub-optimal include platinum-based cytotoxic chemotherapies despite short duration of response and considerable toxicities
- Current CPIs targeting PD-1 and CTLA-4 have not demonstrated meaningful single-agent therapeutic benefit in SCNC



* American Cancer Society's estimates for prostate cancer in the United States for 2023

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Methods

KEY INCLUSION CRITERIA

- Histologically confirmed *de novo* SCNC or treatment-emergent SCNC
- ≥1 prior line of systemic therapy
- Progression as defined by PCWG3 criteria
- Serum testosterone <50 ng/dL during screening, except for patients with *de novo* SCNC
- ECOG performance status of 0-2

KEY EXCLUSION CRITERIA

- >2 cytotoxic chemotherapy regimens for mCRPC
- Prior treatment with anti-PD-1, anti-PD-L1, anti-programmed death-ligand 2 (PD-L2) agent or with agent directed to another co-inhibitory T-cell receptor

Pembrolizumab 200 mg IV q3w Day 1 + BXCL701 0.3 mg PO BID Days 1-14 of 21-day cycle
Step-up dosing in Cycle 1: BXCL701 0.2 mg PO BID Days 1-7 then BXCL701 0.3 mg PO BID Days 8-14

Primary objective: Composite Response Rate, either objective response by RECIST 1.1 criteria, and/or CTC conversion from ≥5/7.5 mL to <5/7.5 mL, and/or ≥-50% PSA decline from baseline

Secondary objectives: Duration of response, safety, and changes in circulating cytokines

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Baseline Characteristics

Phase 2a Cohort (n = 34)		n (%)
Median Age, years (range)		**67.5** (54 – 80)
ECOG Performance Status (%)	0 1 2	**16** (47%) **16** (47%) **2** (6%)
Visceral Metastases (%)	Any site Liver	**21** (62%) **11** (32%)
Median number of lines of prior systemic therapy (range)		**3** (1 – 8)
Prior Systemic Treatment	Androgen signaling inhibitor(s) Platinum-based Chemotherapy Taxane Chemotherapy	**25** (89%) **19** (68%) **17** (50%)

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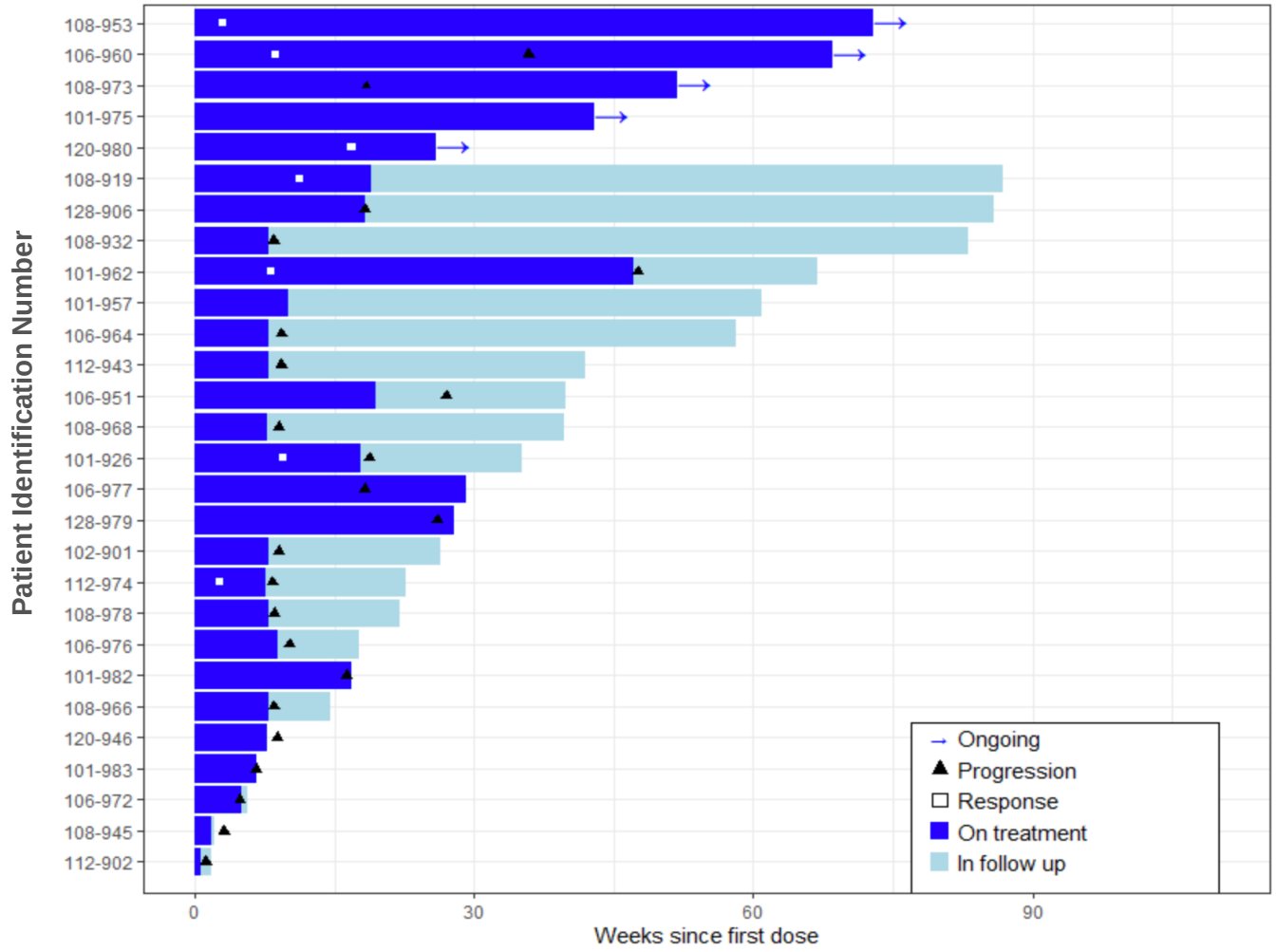
Treatment Duration



- **Median duration of follow up = 30.8 weeks** (range 1.9 – 86.9 weeks)
- **Median duration of treatment = 9 weeks** (range: 0.7 to 73 weeks)

28 Evaluable Patients - Data as of 19-DEC-22

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Best Overall Response

	n (%)
RECIST Evaluable[a] (%)	**25 (89)**
Objective Response Rate (%)	**5 (20)**
Confirmed Partial Response (%)	*4 (16)*
Unconfirmed Partial Response (%)	*1 (4)*
SD (any duration)	7 (28)
PD	13 (52)
Disease Control Rate (PR + SD)	**12 (48)**
Non-RECIST Evaluable	**3 (11)**
CTC[b] Evaluable[c]	**1**
CTC Response[d]	*1*
PSA Evaluable[e]	**1**
PSA_{50} Response	*1*
Composite Response Rate (%)	**7 (25)**

Objective response rate: 20%

- 4 confirmed partial responses +
  1 unconfirmed partial response

Median duration of response:

- 6+ months
  (range: 1.8 - 9.8 months)

[a] Patients who received ≥2 cycles of study therapy and had 1 on-treatment tumor assessment [b] Circulating tumor cell [c] Baseline CTC value ≥5/7.5 mL and 1 measurable on-treatment assessment [d] CTC conversion from ≥5/7.5 mL to <5/7.5 mL; [e] Baseline PSA >4 ng/mL and 1 on-treatment PSA assessment

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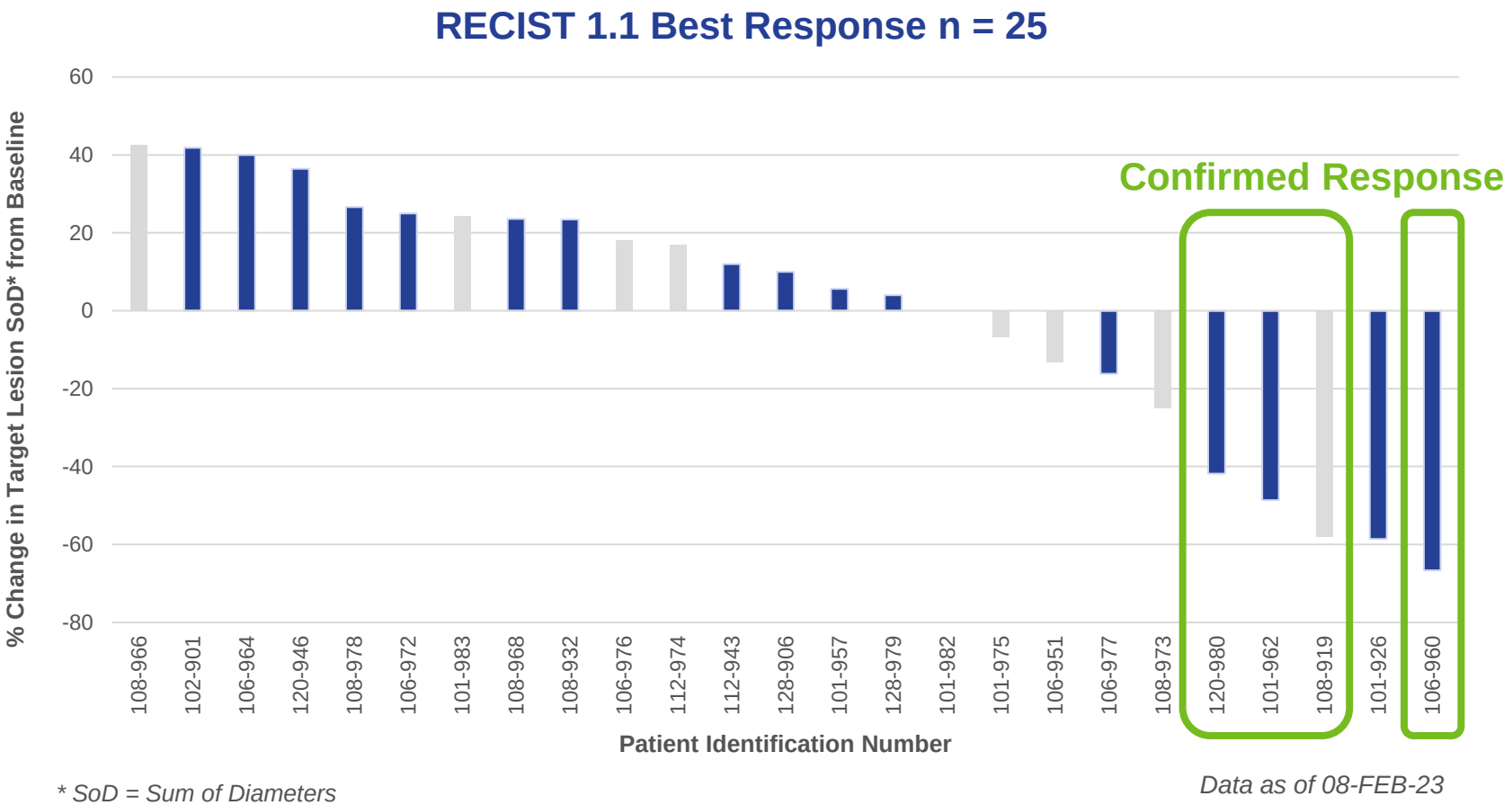
Change in Tumor Size from Baseline



* SoD = Sum of Diameters

Data as of 08-FEB-23

- All responders are MSS and/or TMB low

Prior Platinum Chemotherapy

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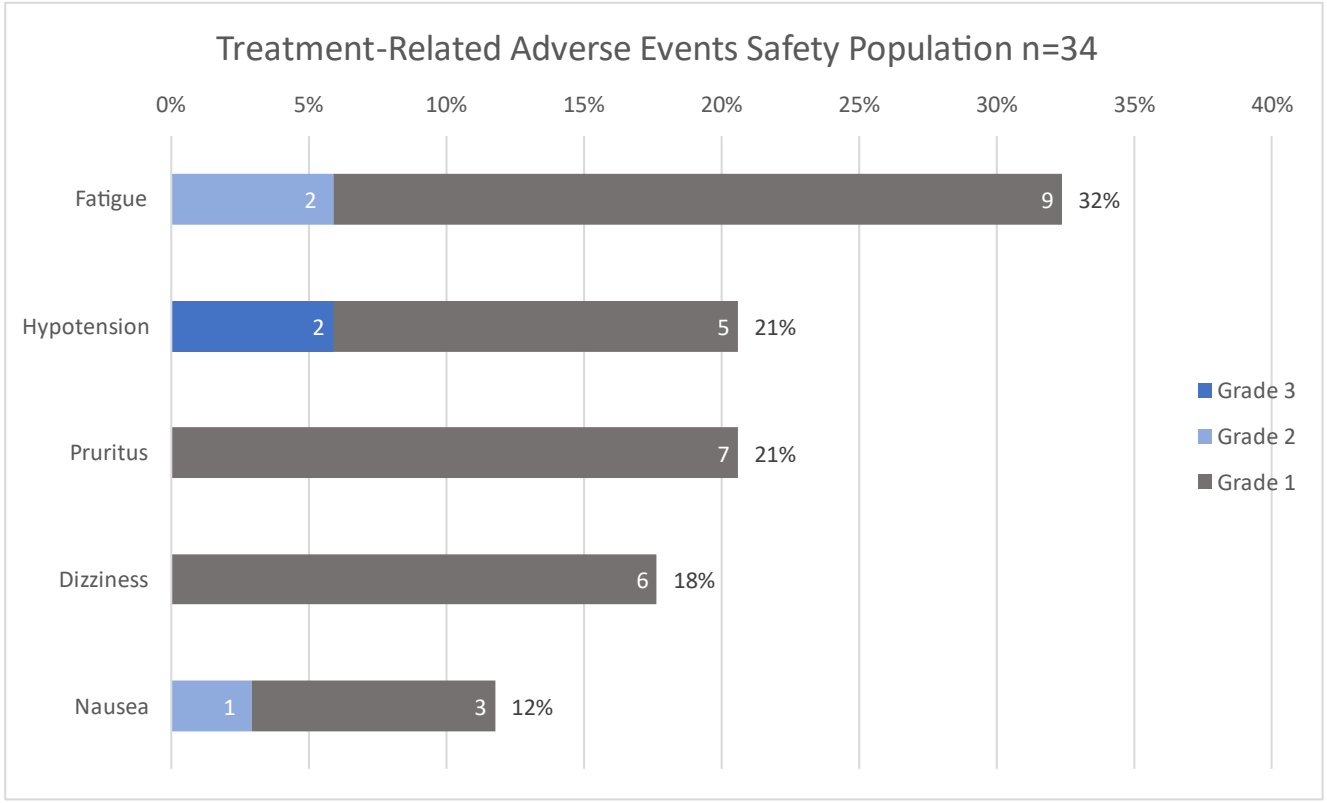
Safety

Treatment-Emergent Adverse Events (n = 34)	n (%)
Any Grade	**33** (97)
Attributed to BXCL701	***29*** *(85)*
Attributed to Pembrolizumab	***23*** *(68)*
Grade 3	**16** (47)
Attributed to BXCL701	***6*** *(18)*
Attributed to Pembrolizumab	***6*** *(18)*
Grade 4	**0**
Grade 5	**1*** (3)
AE Leading to Treatment Discontinuation	**6** (18)
BXCL701 Discontinuation	***6*** *(18)*
Pembrolizumab Discontinuation	***5*** *(15)*
Immune Related Adverse Events Any Grade	**14** (41)
Grade ≥3	***1^*** *(7)*



At least possibly related to BXCL701 or pembrolizumab, occurring in >10% of patients

** Grade 5 tumor lysis*
^ Grade 3 colitis

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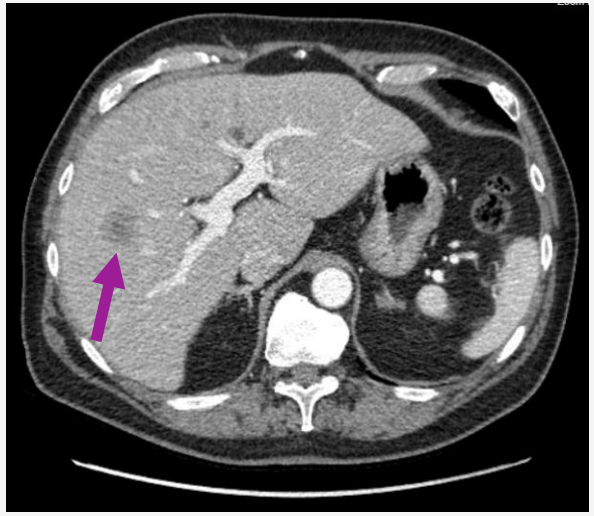
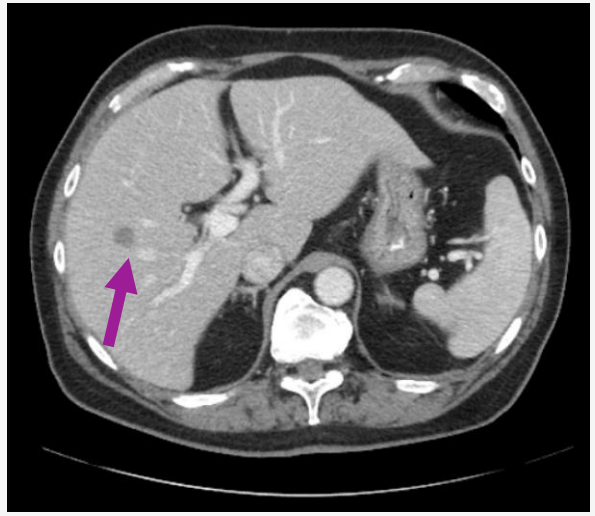
Response in a Patient with Treatment-Emergent SCNC with Liver Metastases

- Prior systemic therapies: LHRH agonist, abiraterone + prednisone, cisplatin + etoposide
- Microsatellite stable, low TMB
- 58% reduction in target lesions following three cycles of treatment

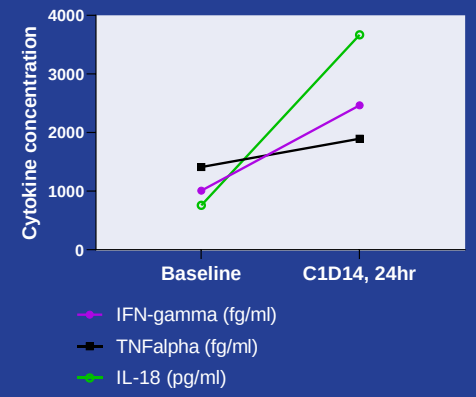
Liver – Baseline
JAN-21



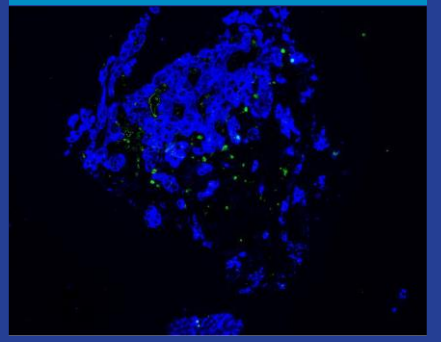
Liver – Post Cycle 3
APR-21



Cytokine expression in the circulation

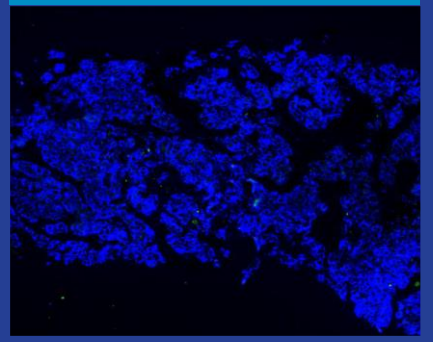


Responder



DPP9 PanCK

Non-responder



DPP9 PanCK

Responder patient 101-926:
DPP9 overexpressed *vs* non-responder

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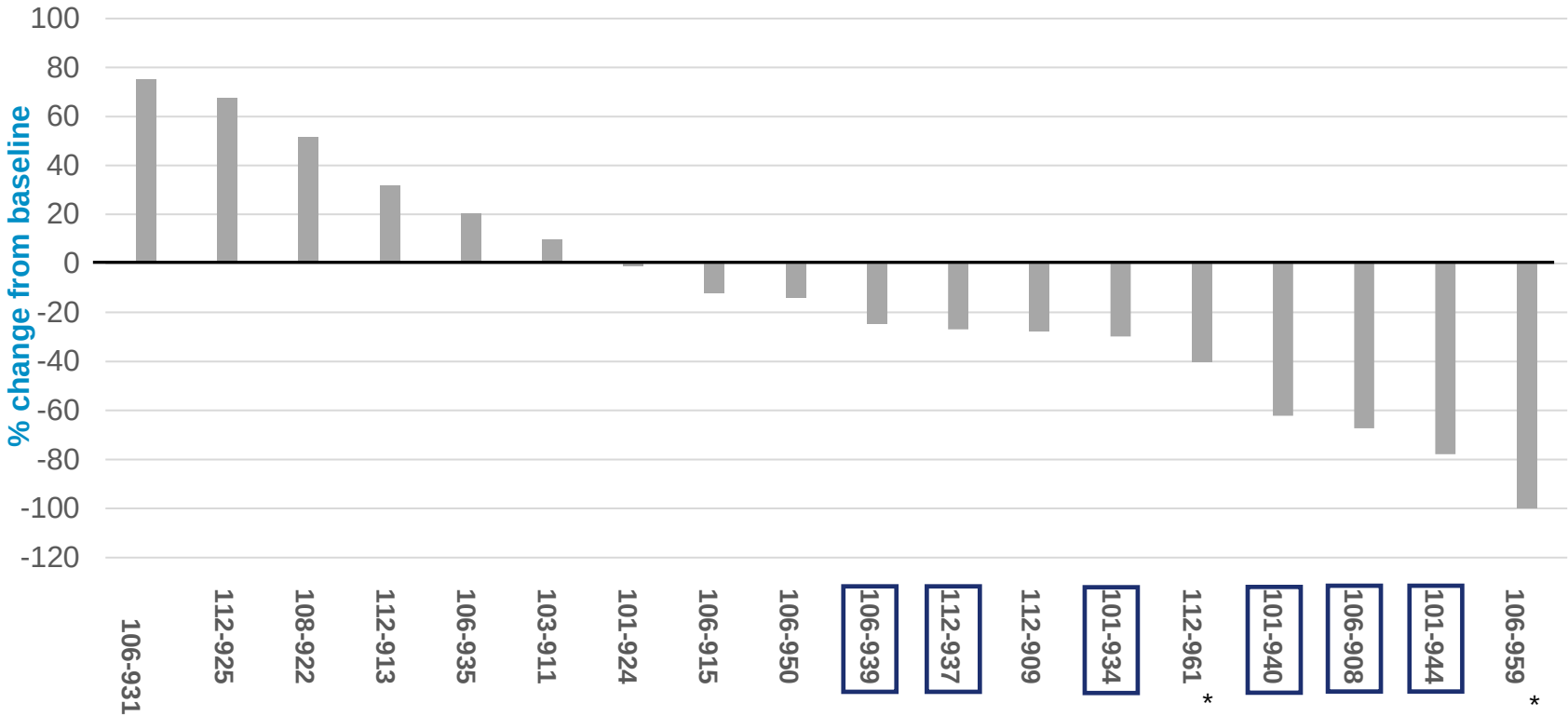
Results from Adenocarcinoma Cohort BXCL701 + Pembrolizumab

ASCO Genitourinary Cancers Symposium

2022

Best Tumor Response (n = 18)



Only Patients with measurable disease
(not shown 11 patients with only non-target lesions)

Composite Responders

*Bony Progression

Composite response rate: **21%**

- RECIST-defined PR*: **22%**
- Disease control rate: **83%**
- PSA_{50}: **17%**—including 5 patients with -100% to -57% PSA decrease
- CTC response: **18%**

** Includes confirmed and unconfirmed PRs*

Data cut-off date: 24-NOV-21

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Conclusions

- **BXCL701 + pembrolizumab demonstrated encouraging activity with durable responses observed in a subset of patients with platinum pre-treated, small cell neuroendocrine prostate cancer**
  - All responders were MSS and/or TMB low, with low probability of response to pembrolizumab monotherapy
- **BXCL701 + pembrolizumab demonstrated manageable safety profile**
  - Split and step-up dosing to mitigate cytokine release
  - No evidence of potentiation of immune-related AEs
- **BXCL701 + pembrolizumab demonstrated similar activity in adenocarcinoma**
- **Evaluation of DPP9 overexpression as a predictive biomarker is ongoing**
- **Planned Phase 2b randomized study in SCNC expected to commence in 2H23**

Acknowledgements

- Patients and their families
- Co-Investigators and study staff
- BioXcel Therapeutics

UCSF

University of California
San Francisco

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BXCL701 Current Trials and Future Direction

Vincent J. O’Neill, M.D.

BXCL701: Pipeline Within a Product Plan and Next-Generation Candidate

Compound	Proposed Indication	Preclinical	Phase 1	Phase 2	Expected Upcoming Milestone	Collaborator
BXCL701	Small Cell Neuroendocrine Prostate Cancer (SCNC)				Initiate Phase 2b	
	Small Cell Lung Cancer (SCLC)				Initiate Phase 1b/2	
	Acute Myeloid Leukemia (AML) IST*				Initiate Phase 1b/2	Dana-Farber Cancer Institute
	Metastatic Pancreatic Ductal Adenocarcinoma IST*				Initiate Phase 2	Georgetown | Lombardi COMPREHENSIVE CANCER CENTER MERCK supply agreement
Next-Generation DPP8/9 Inhibitor	Solid and Liquid Tumors				Initiate novel candidate development	

*Investigator Sponsored Trial

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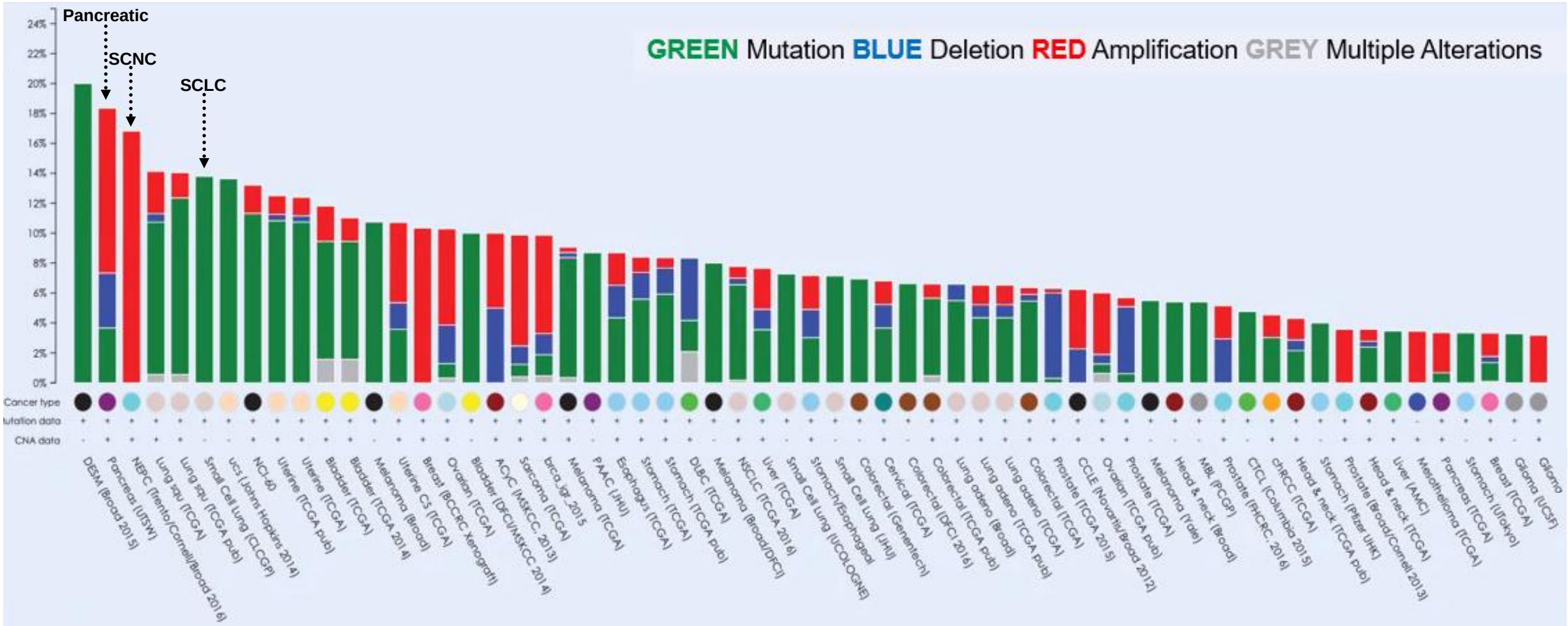
Frequency of DPP Alterations in Solid Tumors



TCGA Data; AACR 2017

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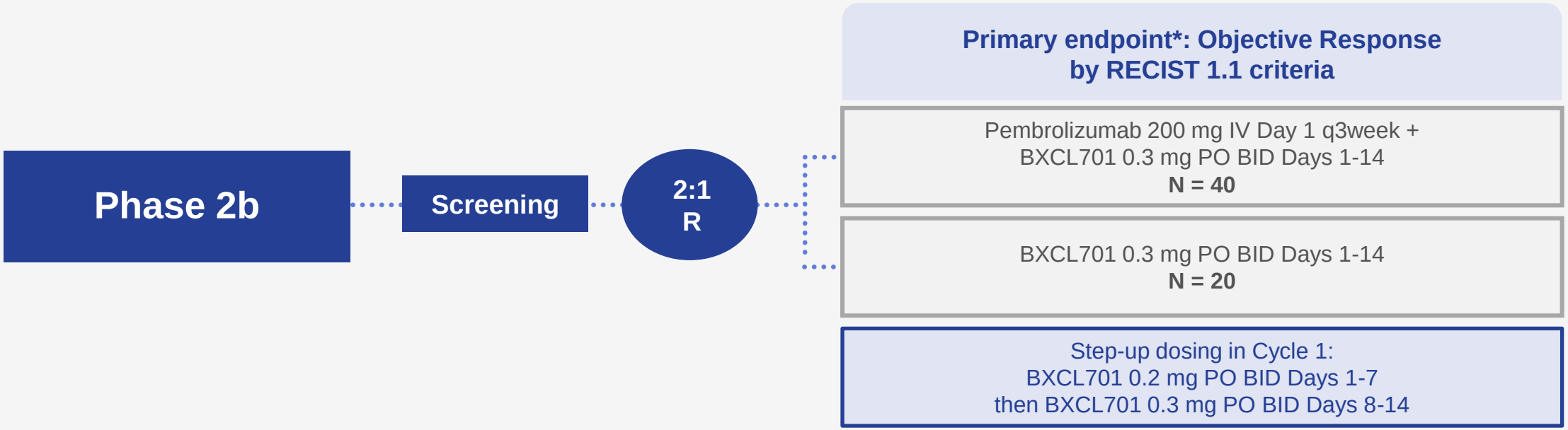
SCNC Phase 2a Results Support Further Development of BXCL701 + KEYTRUDA

Phase 2b Potential Registrational Trial in SCNC Expected to Initiate in 2H 2023*



Biomarker evaluation to be performed retrospectively

*Initial discussions with the FDA regarding the development pathway and registrational strategy for BCXL701 in SCNC expected in mid-2023.

RECIST 1.1 = Response Evaluation Criteria in Solid Tumors Version 1.1 | R = Randomization * *Additional objectives: CRR, OS, duration of response, rPFS, and PSA PFS*

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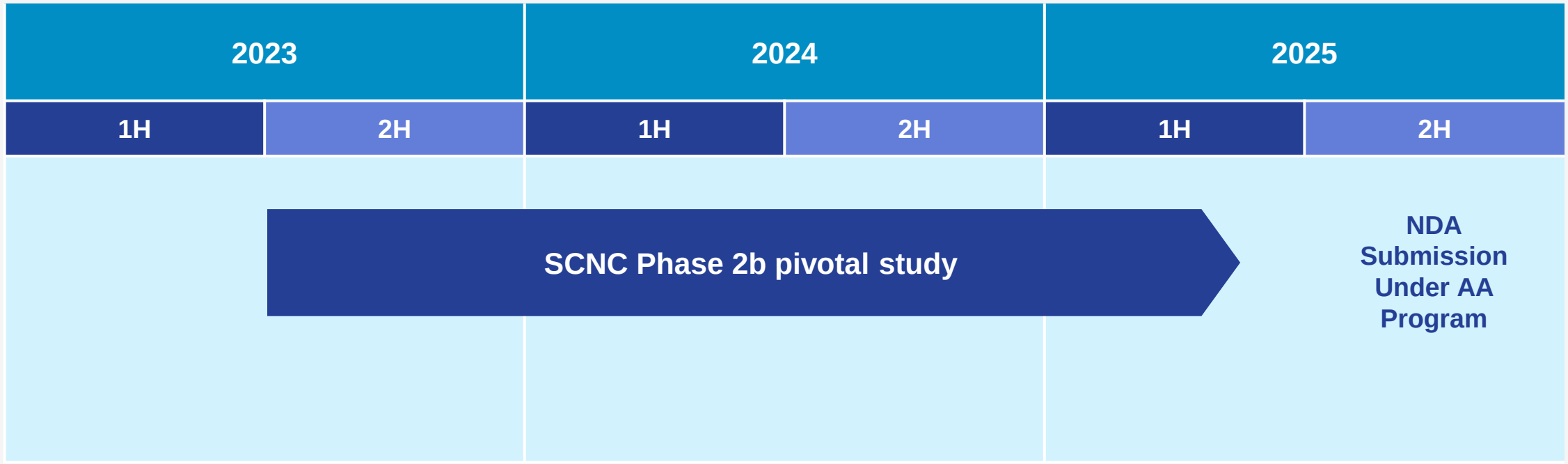
SCNC Clinical Development Timeline*



*Initial discussions with the FDA regarding the development pathway and registrational strategy for BCXL701 in SCNC expected in mid-2023.
| AA = Accelerated Approval

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BXCL701: Extensive Stage Small Cell Lung Cancer (SCLC)

Current Therapy Remains Sub-optimal

- SCLC is an aggressive disease with early metastasis
- 2 CPIs approved in combination with carboplatin / etoposide for Extensive Stage SCLC
  - TECENTRIQ® (atezolizumab)
  - IMFINZI® (durvalumab)
- Median overall survival remains about 1 year
  - TECENTRIQ® 12.3 months
  - IMFINZI® 13 months

U.S. Patients 2023

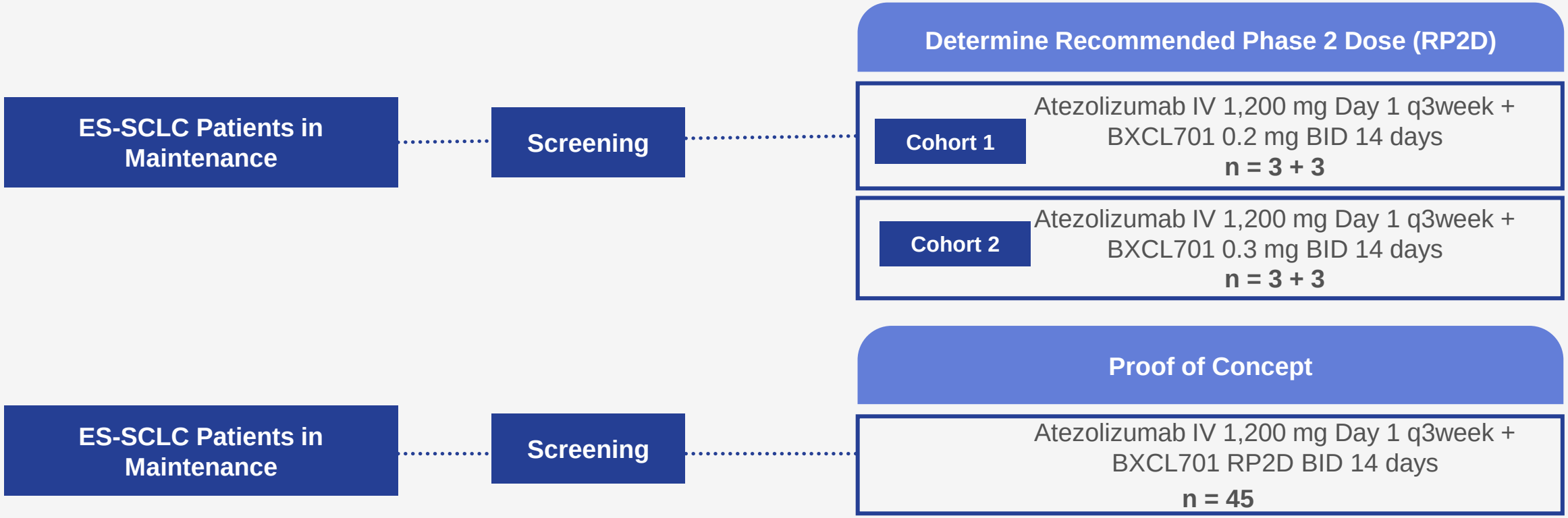
New SCLC patients
36K[1]

75% Extensive Stage SCLC
27K

60% maintenance therapy with checkpoint inhibitor + carboplatin / etoposide
16K

1 The American Cancer Society's estimates for lung cancer in the United States for 2023

Planned Phase 1b/2 SCLC Clinical Trial Design*



Proceed to Phase 3 if 6-month PFS rate is superior to SoC

***Trial design subject to agreement with FDA** | SoC = Standard of Care

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SCLC Clinical Development Timeline

BXCL701: Acute Myeloid Leukemia (AML)

Significant Underserved Patient Population

- BXCL701 is directly cytotoxic in AML cell lines[1]
- Conventional chemotherapy is a mainstay in AML therapy, response rates 35-75%
- Standard of care for patients unfit for induction chemotherapy: combination of decitabine or azacitidine and venetoclax
  - All oral combination is preferable
- BXCL701 cytotoxicity in human AML cell lines highly correlates with DPP9 copy number[4]

U.S. Patients 2023

New AML Patients

20K[2]

60% AML patients unfit for induction chemotherapy

12K[3]

[1] Johnson et al. Nature Med. 2018:1151-6 [2] The American Cancer Society's estimates for Acute Myeloid Leukemia (AML) in the United States for 2023 [3] Sonal Agarwal, Andrew Kowalski, Molly Schiffer, Jennifer Zhao, Jan Philipp Bewersdorf & Amer M. Zeidan (2021) Venetoclax for the treatment of elderly or chemotherapy-ineligible patients with acute myeloid leukemia: a step in the right direction or a game changer?, Expert Review of Hematology, 14:2, 199-210, DOI: 10.1080/17474086.2021.1876559; [4] V. R. Agarwal et al. (2022) Potential Predictive Biomarkers for BXCL701 in Acute Myeloid Leukemia (AML). Society for Immunotherapy of Cancer Annual Meeting 2022

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Initiating Phase 1b/2 AML Clinical Trial

Dana-Farber Cancer Institute

3 + 3 Dose Escalation Study Design
n = 12 - 30

Screening

Starting Dose

Level (-1)	BXCL701 0.2 mg BID Pulse Dosing
Level 1	BXCL701 0.3 mg BID Pulse Dosing
Level 2	BXCL701 0.4 mg BID Pulse Dosing
Level 3	BXCL701 0.6 mg BID Pulse Dosing
Level 4	BXCL701 0.8 mg BID Pulse Dosing

BXCL701 Pulse Dosing:
dose BID on Days 1-3, 8-10, 15-17, 22-24 on a 28-day cycle

Primary objective

Determine MTD and establish recommended Phase 2 dose

RP2D + SoC

MTD = Maximum Tolerated Dose | RP2D = Recommended Phase 2 Dose | SoC = Standard of Care

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BXCL701: Pancreatic Cancer

Significant Underserved Patient Population

- Pancreatic cancer has among the highest levels of overexpression and amplification of DPPs
- Preclinical models demonstrate synergy between DPP inhibition with BXCL701 and anti-PD-1 antibody in PDAC tumor microenvironment
- Immunotherapy not been demonstrated to have significant clinical impact in patients with mPDAC
- 2nd line standard of care varies:
  - FOLFIRINOX: RR 2.5% - 24% and mOS 4 - 6 months

U.S. Patients 2023

New Pancreatic Cancer Patients

64K[1]

2nd-line treatment

20K

[1] The American Cancer Society's estimates for pancreatic cancer in the United States for 2023 | RR = Response Rate | mOS = Median Overall Survival

Initiating Phase 2 Pancreatic Clinical Trial

Georgetown | Lombardi
COMPREHENSIVE CANCER CENTER

Screening + pre-treatment core tumor biopsy

Safety Lead-In n = 6

Pembrolizumab 200 mg IV q3w Day 1 +
BXCL701 0.3 mg PO BID Days 1-14 of 21-day cycle

Simon's 2-stage, single-arm, open label n = 19-43

Pembrolizumab 200 mg IV q3w Day 1 +
BXCL701 0.3 mg PO BID Days 1-14 of 21-day cycle

Step-up dosing in Cycle 1:
BXCL701 0.2 mg PO BID Days 1-7
then BXCL701 0.3 mg PO BID Days 8-14

Primary objective

Determine 18-week progression-free survival rate of BXCL701 + pembrolizumab

On-treatment tumor biopsy

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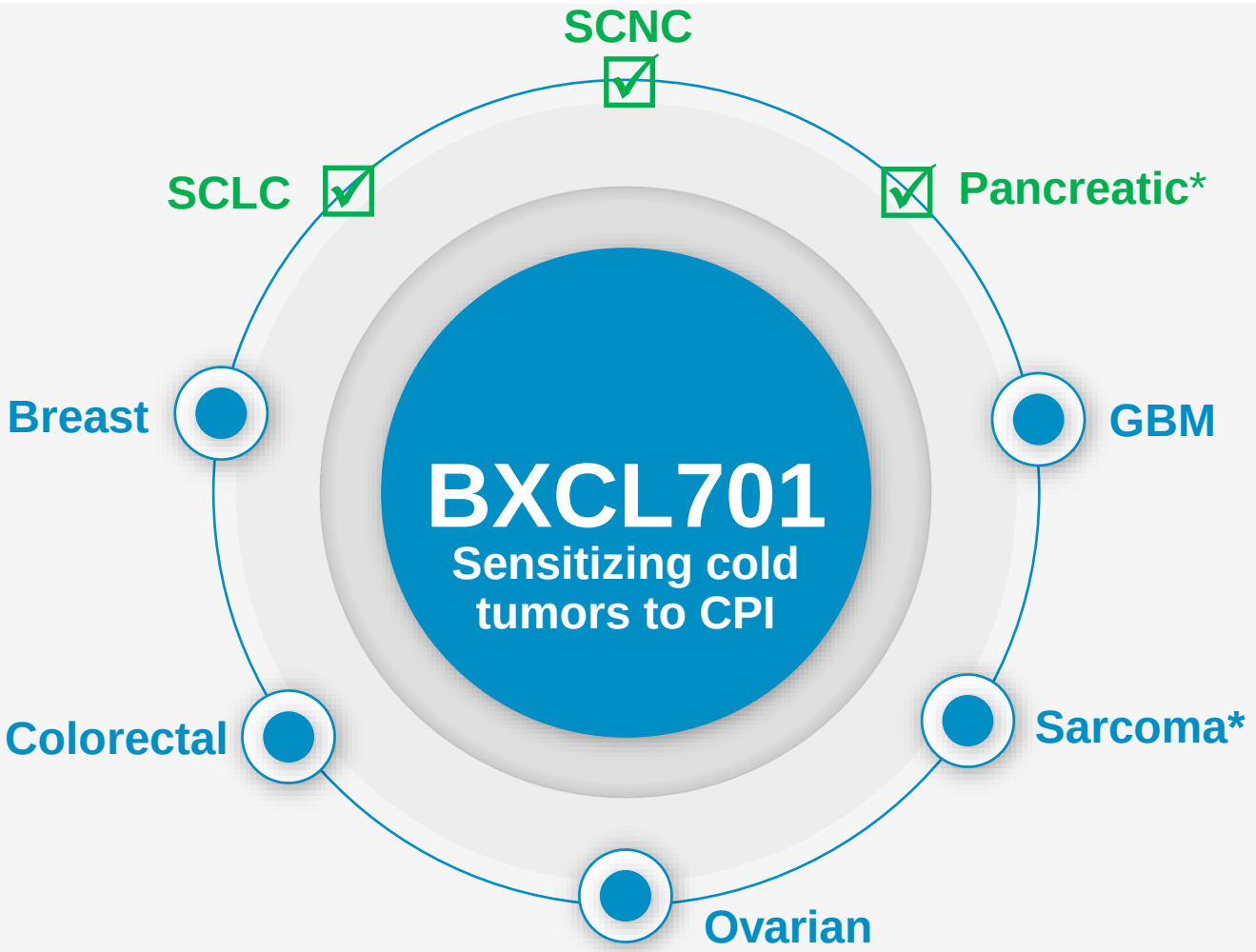
BXCL701 Potential Pipeline Within a Product in Cold Tumors



* Orphan Drug Designation

Conclusions

- **BXCL701 is an oral innate immune activator with a novel mechanism of action**, described in peer-reviewed publication
- **BXCL701 has demonstrated clinical POC, in combination with KEYTRUDA, in two cold tumor settings**
  - Adenocarcinoma
  - SCNC
- Initial discussions with the FDA regarding development pathway and registrational strategy for BCXL701 in SCNC expected in **mid-2023**.
- **Strong scientific rationale** to guide choice of indications
- Foundation for a **precision medicine strategy** (DPP9 overexpression)
- **Potentially extending the value of IO** into large underserved patient populations

Panel Discussion