# Spotlight on XTX301, a Novel Tumor-Activated, Engineered IL-12

**Program Spotlight**

**December 1, 2022**

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# Today’s Agenda

| Unmet Need in Cancer | XTX301 | XTX301 Development Plan |
| --- | --- | --- |
| "Cold" vs "Hot" Tumors & Differences in Their TMEs | Tumor-Activated IL-12 Product Candidate | 3-Pronged Approach |

TME: tumor microenvironment

# Today's Speakers

## Featured Key Opinion Leader

**Diwakar Davar, MBBS, M.Sc**
Diwakar Davar, MBBS, M.Sc is an assistant professor of medicine and a medical oncologist/hematologist at UPMC Hillman Cancer Center. He specializes in the management of advanced melanoma and the development of early phase studies to test novel immunotherapeutic approaches to treat advanced cancers.

Dr. Davar is board-certified in internal medicine and medical oncology. He received his medical degree from National University of Singapore, and completed both his residency and fellowship at UPMC.

Dr. Davar is a member of many professional organizations, including the American Association for Cancer Research, American Society of Clinical Oncology, Allegheny County Medical Society, American College of Physicians, and Singapore Medical Association.

## Xilio Management

**René Russo, Pharm. D.**
**Chief Executive Officer, Director**

**Martin Huber, M.D.**
**President and Head of R&D**

**Uli Bialucha, Ph.D.**
**Chief Scientific Officer**

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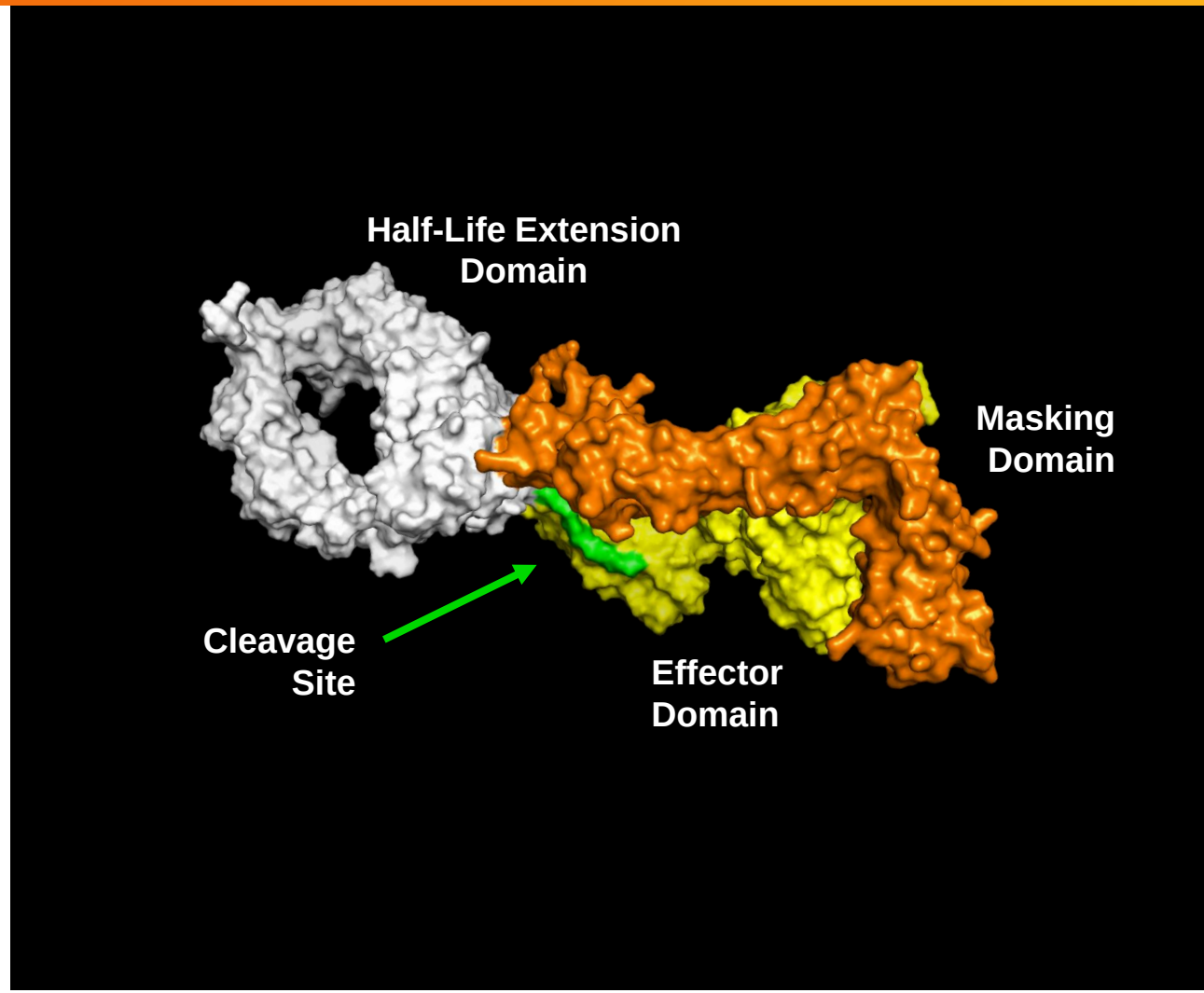
# Xilio's Tumor-Activated Precision Immuno-Oncology

- We are passionate about **harnessing and focusing** the power of the immune system to treat cancer
- We have developed a novel approach designed to **outsmart tumors** by using the tumor's growth activities against itself
  - Tumor proteases **activate a switch** in our molecules, which unleashes the active agent once it is inside the tumor microenvironment
- Each of our molecules has a custom masking domain designed to prevent it from interacting with healthy tissues and cells
  - The mask is released by the tumor's **dysregulated matrix metalloproteinases (MMPs),** which are present but inhibited outside of the tumor microenvironment

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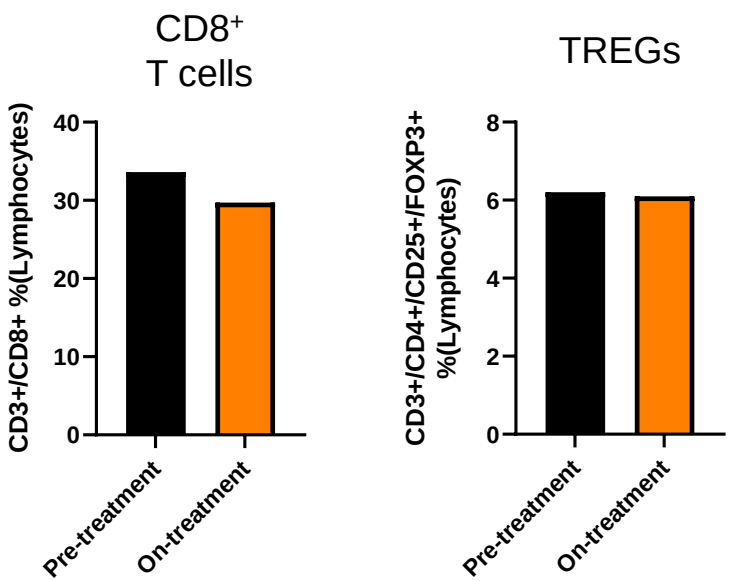
# Xilio's First Demonstration of Activation in a Patient Tumor (XTX202)

## Preliminary Evidence of Intra-tumoral Pharmacodynamic Effects Consistent with Known IL-2 Biology

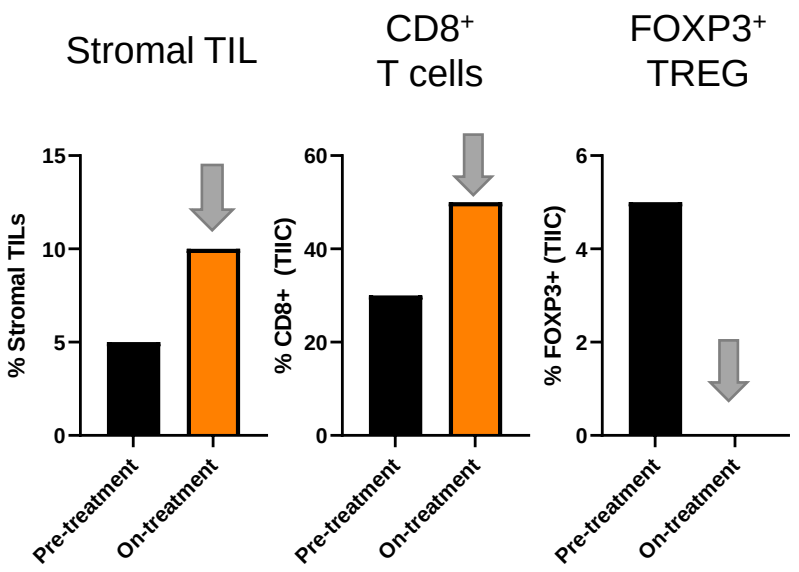
### Patient Details

- 51-year-old male with stage 4 melanoma
- Previously treated with dabrafenib, trametinib, pembrolizumab, ipilimumab, nivolumab,
- XTX202 dose level 2 (0.38 mg/kg, Q3W)
- Fresh biopsies at pre-treatment and on-treatment cycle 2, day 20
- No evidence of vascular leak syndrome

### XTX202 treatment resulted in minimal pharmacodynamic changes in peripheral blood




### XTX202 treated tumor featured increased CD8+ T cells and decreased TREG post-treatment (compared to pre-treatment)




Patient had an optional on-treatment tumor biopsy and was the first patient for whom a tumor biopsy analysis was available as of November 7, 2022.
TREG: Regulatory T cell; TIL: Tumor infiltrating lymphocyte; TIIC: Tumor infiltrating immune cell.

# A Spotlight on XTX301, a Tumor-Activated IL-12

| Program | Disease Indication | Mechanism of Action | Discovery | IND-Enabling | Phase 1 | Phase 2 | Phase 3 |
|---|---|---|---|---|---|---|---|
| **Cytokine Programs** | | | | | | | |
| XTX202 | Oncology | IL-2 | | | | | |
| **XTX301[1]** | Oncology | IL-12 | | | | | |
| Discovery Stage | Oncology | Tumor-Activated Cytokine | | | | | |
| **Antibody Program** | | | | | | | |
| XTX101 | Oncology | Anti-CTLA-4 | | | | | |

Plan to seek partnership for further investment

1. Plan to initially evaluate XTX301 as a monotherapy for the treatment of advanced solid tumors.

# Unmet Need in Cancer

## "Cold" vs "Hot" Tumors & Differences in Their TMEs

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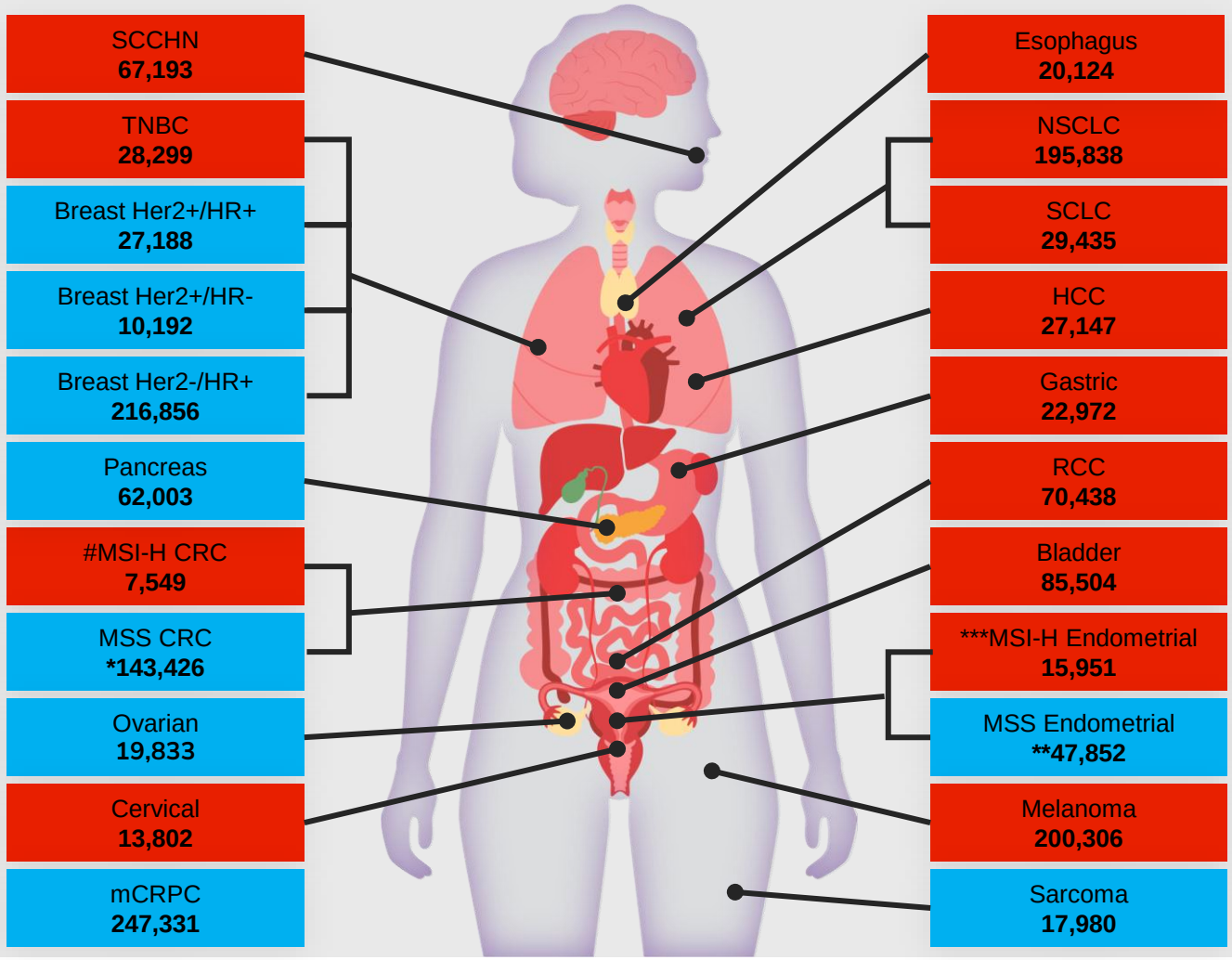
# Overwhelming Unmet Need Remains: 2022 US Incidence by Tumor Type and Category

| Hot Tumors | Cold Tumors |
|---|---|
| **784,558** | **792,661** |

Categories assigned based on approval of a checkpoint inhibitor (CPI) in that tumor and relative efficacy

**Per Cerner Enviza CancerMPact Epidemiology Database**




* Estimated by taking incidence of CRC patients and removing 5% for MSI-H. # Estimated by taking 5% of incident CRC patients. ** Estimated by taking incidence of endometrial patients and removing 25% for MSI-H. *** Estimated by taking 25% of incident endometrial patients.
CRC: colorectal cancer; HCC: hepatocellular lung cancer; NSCLC: non-small cell lung cancer; SCLC: squamous cell lung cancer; SCSCHN: squamous cell cancer of head and neck; TNBC: triple negative breast cancer.

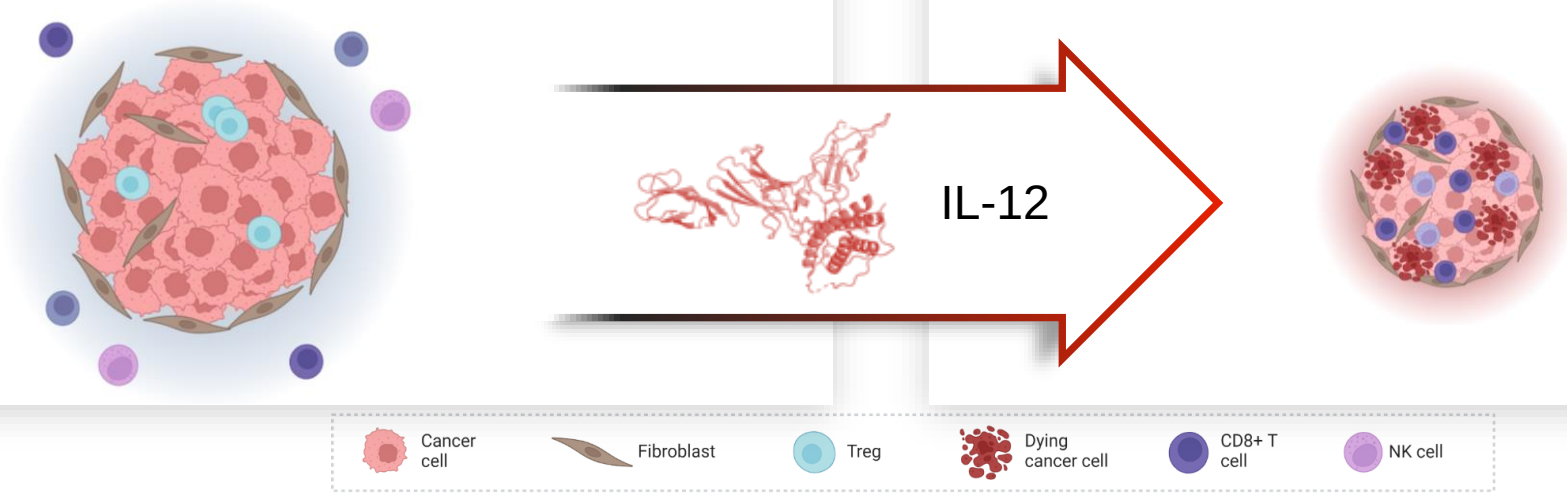
# IL-12 Can Remodel Cold Tumor Microenvironment Towards a Pro-Inflammatory (Hot) State That Favors Anti-Tumor Immunity

## Cold Tumor

- Lack of CD8 T and NK cells within tumor
- Presence of immune suppressive cells (TREGs, MDSCs)
- Poor response to checkpoint inhibitors

## Hot Tumor

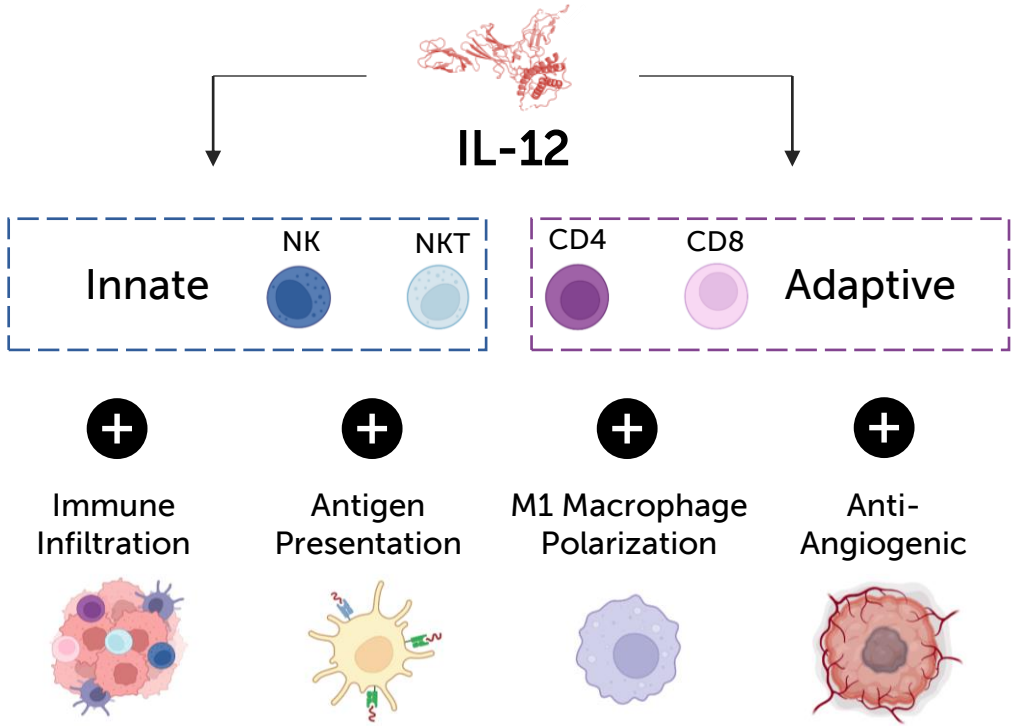
- Abundant CD8 T and NK cells in tumor
- Pro-inflammatory microenvironment
- Improved prognosis and effective killing of tumor cells with immunotherapy treatment




Adapted from “Cold vs Hot Tumors”, by BioRender.com, 2022. Retrieved from https://app.biorender.com/biorender-templates.
Barraondo et al., Clin. Cancer Res., 2018. Nguyen et al., Front. Immunol., 2020.

# IL-12: Compelling Biology For IO Applications – But Limited Without Engineering

## IL-12: A key cytokine bridging innate and adaptive cellular immunity




## IL-12 properties highlight potential in IO, but tolerability remains limiting

- Exquisitely potent stimulator of NK and T cell cytotoxicity and INFγ production.[1-2]
- Capable of polarizing naïve CD4 T-cells towards Th1 phenotype, thus driving cellular immunity against infection and cancer.[1-2]
- Robust INFγ induction results in broad remodeling of the TME towards a more immune-permissive environment.[1-2]
- Demonstrated single agent objective responses in patients, but poorly tolerated (MTD <500 ng/kg).[3]
- Synergy with TIL and a-PD-1 preclinically.[4-5]

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[1]Carter LL, J Exp Med 1999
[2]Berraondo P, Clin Cancer Res 2018
[3]Gollob JA, Clin Cancer Res 2000
[4]Mazzolini G, Hum Gene Ther 2000
[5]Garris CS, Immunity 2018

# Novel Systemic Deliver Approaches Overcome Limitations and Provides Possible Synergies

## Existing IL-12 modalities

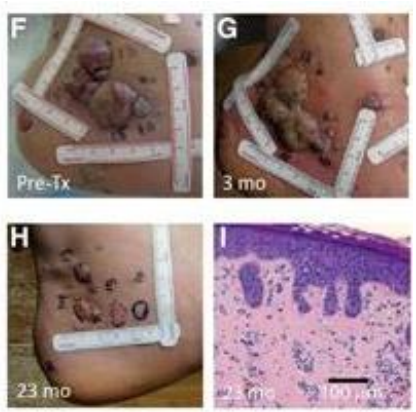
Tavokinogene telseplasmid.

- Requires intra-tumoral administration.[1]
- Activity observed in melanoma and Merkel cell carcinoma both as single agent and in combination with anti-PD-1.[2-4]
- Response is associated with antigen-specific circulating immune responses.[5]

Other approaches: lipid-nanoparticle mRNA encoding IL-12[6], NDV encoding IL-12[7] and gene therapy approaches[8].

## Limitations and need for systemic administration

- Local administration is effective in injected lesions, but distant effects are rare.
- Greatest unmet needs for IL-12 are often in tumors with inaccessible lesions.




[1]Canton DA, Immunotherapy 2017
[2]Algazi AP, Clin Cancer Res 2020
[3]Algazi AP, Ann Oncol 2020
[4]Bhatia S, Clin Cancer Res 2020
[5]Graney SK, Cancer Immunol Res 2020
[6]Hewitt SL, Clin Cancer Res 2020
[7]Purroy N, AACR 2022
[8]Chiocca EA, Sci Transl Med 2019

# XTX301

## Tumor-Activated IL-12 Product Candidate

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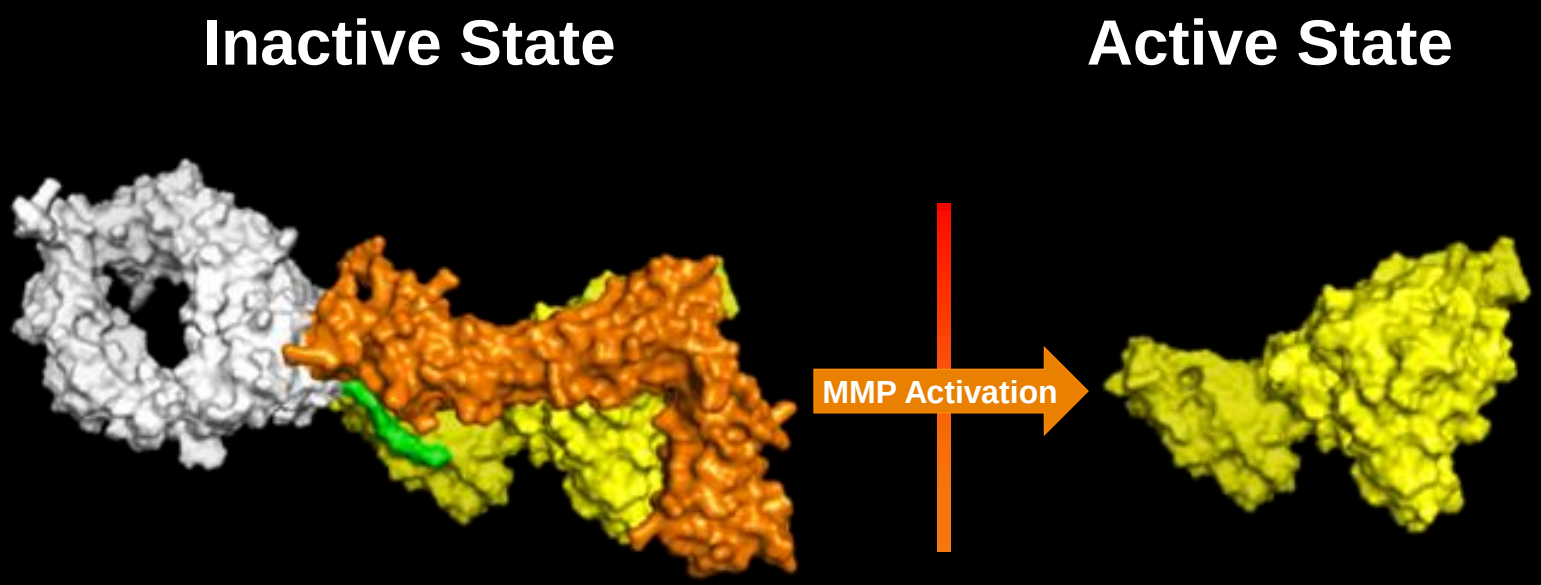
# XTX301: Tumor-Activated IL-12

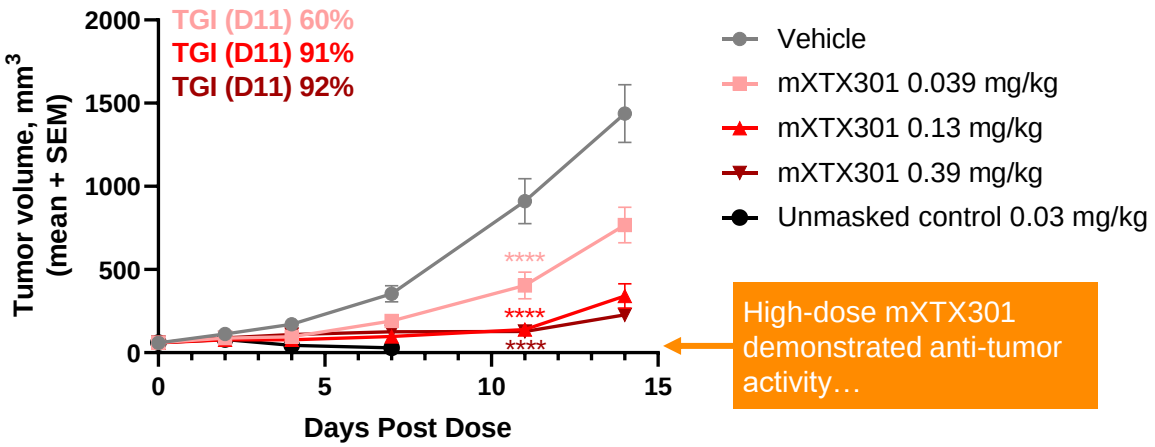



## Designed to Outsmart Tumors

XTX301 custom mask designed to address unique challenges presented by the complex heterodimer structure of IL-12

# mXTX301, a Murine Surrogate for XTX301, Demonstrated Dose-Dependent Anti-Tumor Activity Without Body Weight Loss

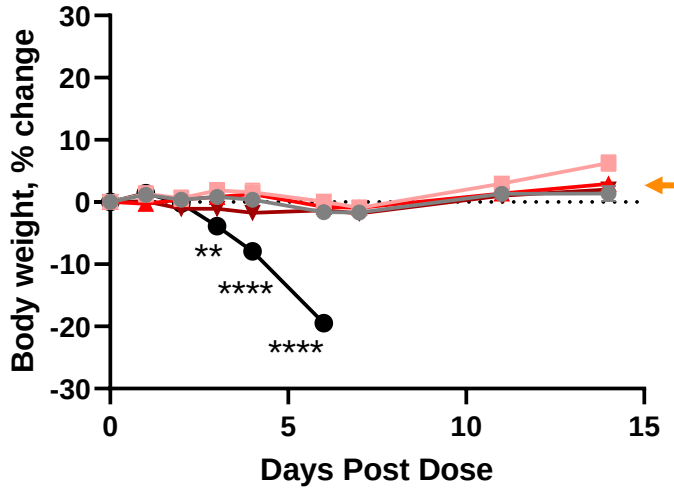
## Tumor Growth




High-dose mXTX301 demonstrated anti-tumor activity…

- mXTX301 demonstrated dose-dependent anti-tumor activity in MC38 murine model at all tested doses
- Dosing with mXTX301 at 0.13 and 0.39 mg/kg resulted in complete tumor regression in individual mice

## Body Weight




…without causing body weight loss

- mXTX301 was well-tolerated in MC38 murine model with no significant body weight loss at all tested doses
- Unmasked control (mXTX302) not tolerated at 0.03 mg/kg dose; 75% (9/12) mice were euthanized by Day 11 due to body weight loss

**Data presented at New York Academy of Sciences' Frontiers in Cancer Immunotherapy in May 2022**

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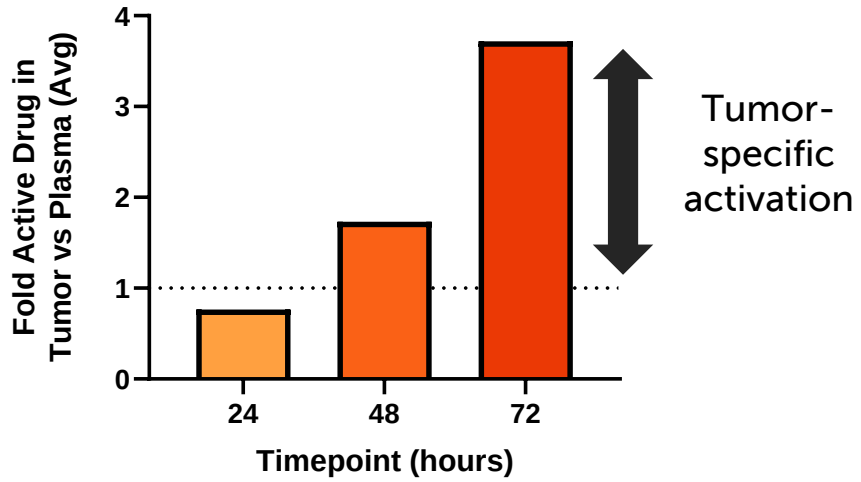
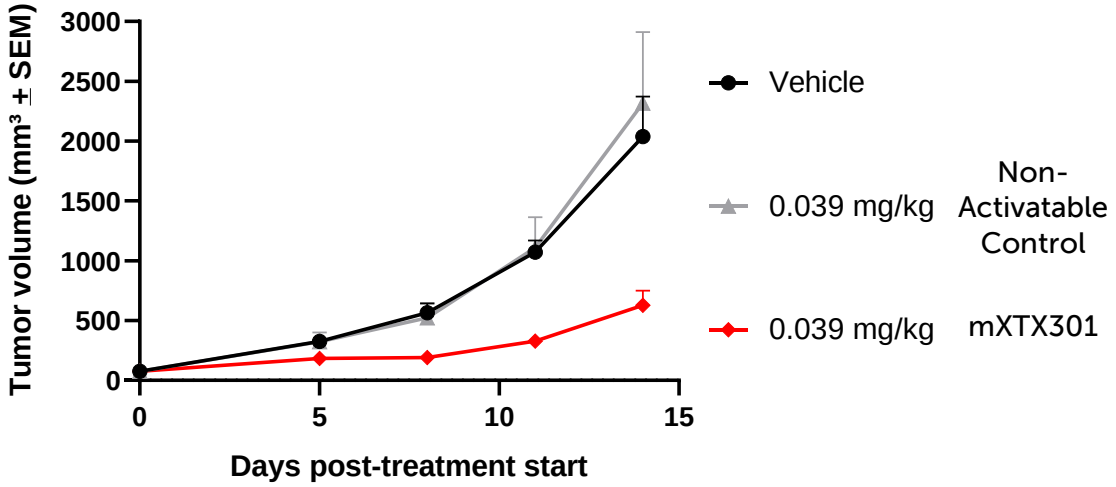
TGI: tumor growth inhibition.
MC38 model: s.c. $0.5x10^6$ cells; single IV dose of mXTX301 and mXTX302 on Day 0. Tumor growth data shown as mean±SEM. Tumor volume data was assessed by a two-way ANOVA followed by Bonferroni post hoc test on Day 11 compared to vehicle treated animals. ****p<0.0001 for all mXTX301 treatment groups. Body weight data are shown as mean ±SEM. A two-way ANOVA followed by Bonferroni post hoc test compared to vehicle treated animals was performed **p<0.005, ****p<0.0001.

# mXTX301 was Preferentially Activated in Tumors vs Plasma and Resulted in Cleavage-Dependent Activity *In Vivo*

## mXTX301 demonstrated tumor-specific activation *in vivo*




## mXTX301 treatment resulted in cleavage-dependent enhancement in activity vs. non-activatable control

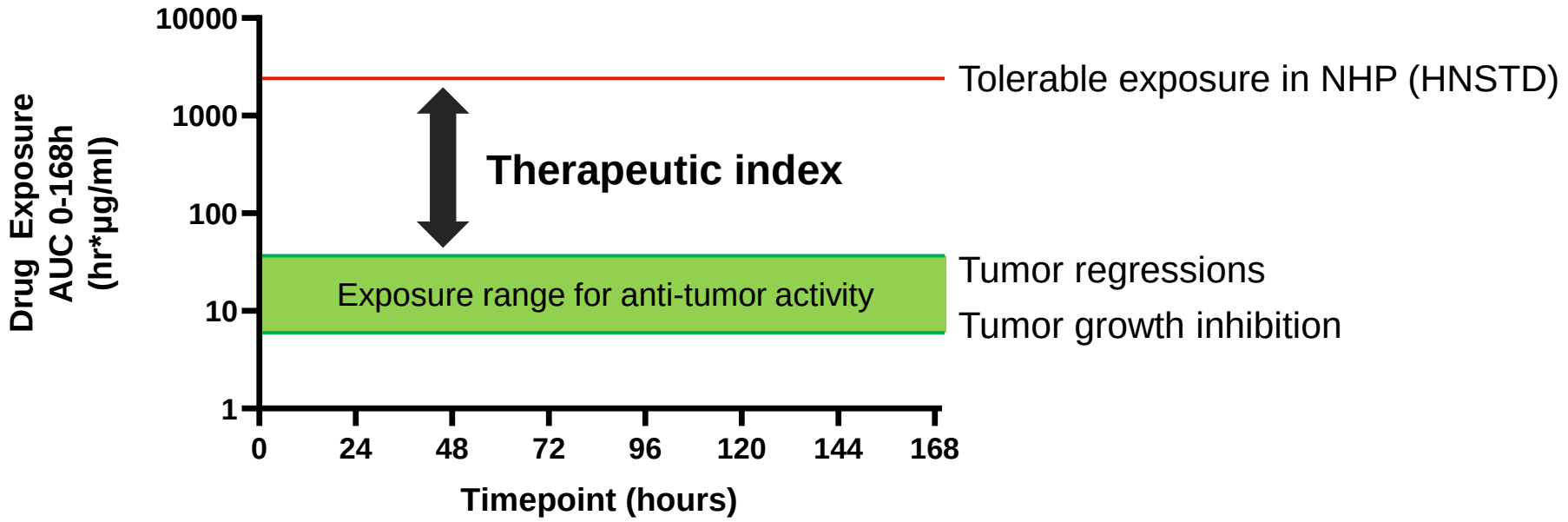



**Data presented at Protein Engineering Summit Europe, November 2022**

Left panel: Mice bearing MC38 syngeneic colorectal carcinoma tumors were dosed with mXTX301 (murine surrogate for XTX301) and the percent activated drug was measured over time in tumors and plasma.
Right panel: Mice bearing MC38 syngeneic colorectal carcinoma tumors were dosed once with mXTX301 or a non-activatable control and tumor growth was monitored over time.

# XTX301 Preclinical Data Support Potential for Broad Therapeutic Index

- XTX301 was tolerated at doses up to 2.0 mg/kg Q1W x4 in NHP (HNSTD)
- mXTX301 induced tumor regressions in murine model following a **single dose** of 0.13 mg/kg



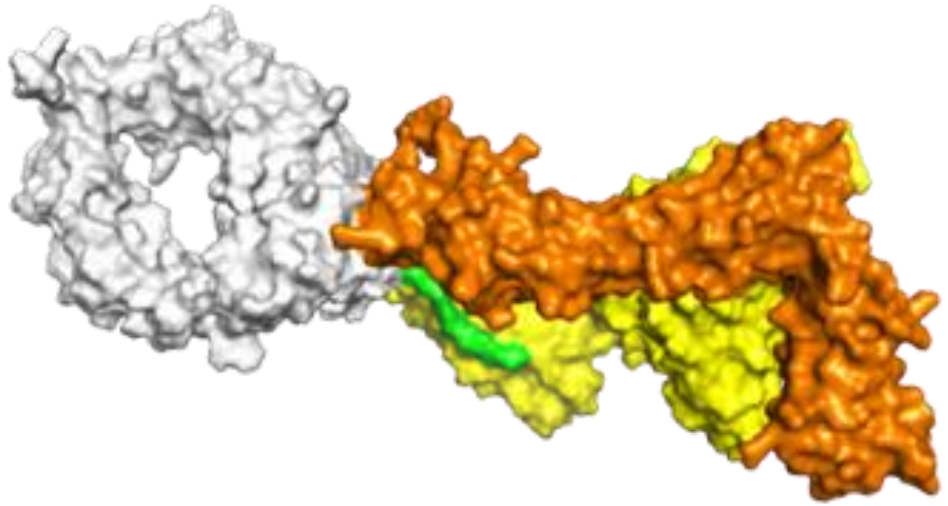

| Compound | In vivo model | Dose (mg/kg) | $AUC_{0\text{-}168}$ (hr*µg/mL) | Estimated Therapeutic Index ($AUC_{Safety}$ / $AUC_{Activity}$) |
|---|---|---|---|---|
| mXTX301 | **Anti-tumor activity** (murine) | 0.13 | 37.8 | **66** |
| XTX301 | **Safety** (NHP) | 2.0 | 2510 | |

HNSTD: highest non-severely toxic dose; NHP: non-human primates; Q1W: once every week.

# XTX301: A Tumor Activated, Engineered IL-12 Designed to Potently Stimulate Innate and Adaptive Immunity

## Unique benefits of XTX301 design

- **Exquisitely Potent, With Preclinical Evidence of Tolerability**
  - Complete tumor regressions in preclinical studies in response to single-dose administration
  - Order of magnitude higher dose tolerable with masked molecules compared to unmasked control in preclinical studies
  - Preclinical safety data supports outpatient administration in clinical protocol
- **Designed to be Precise**
  - Single optimized cleavage site for enhanced tumor selectivity
- **Optimized for Simplicity**
  - Use of Fc backbone enables an antibody-like dosing regimen
  - Well-established and understood precedent for Fc-based fusion proteins



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# XTX301 Development Plan

## 3-Pronged Approach

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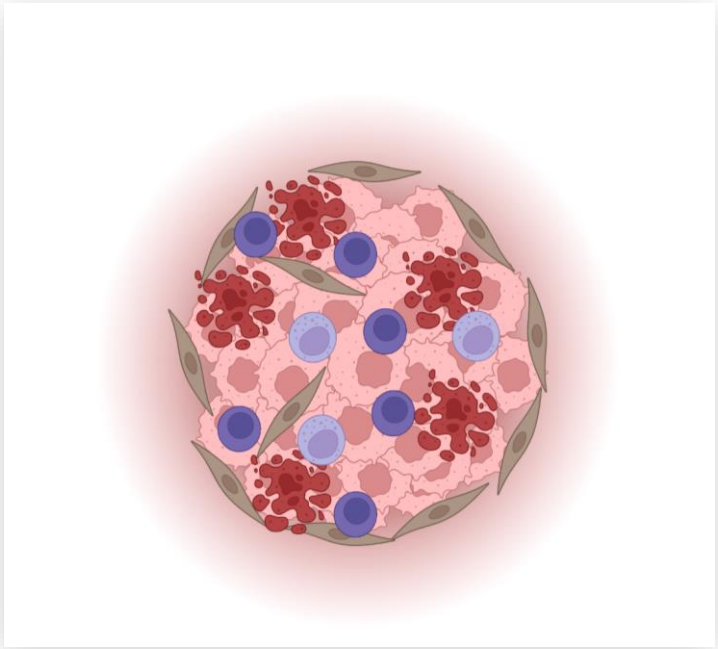
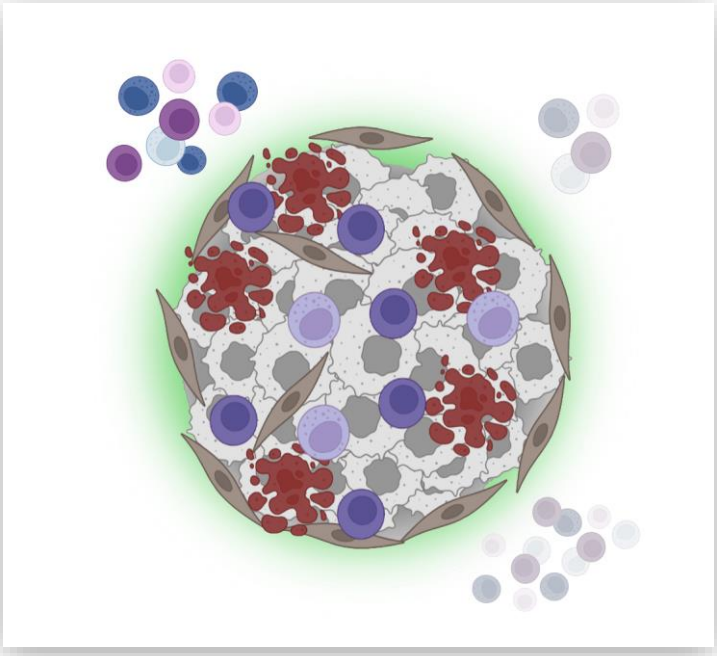
# XTX301 Clinical Development Strategy

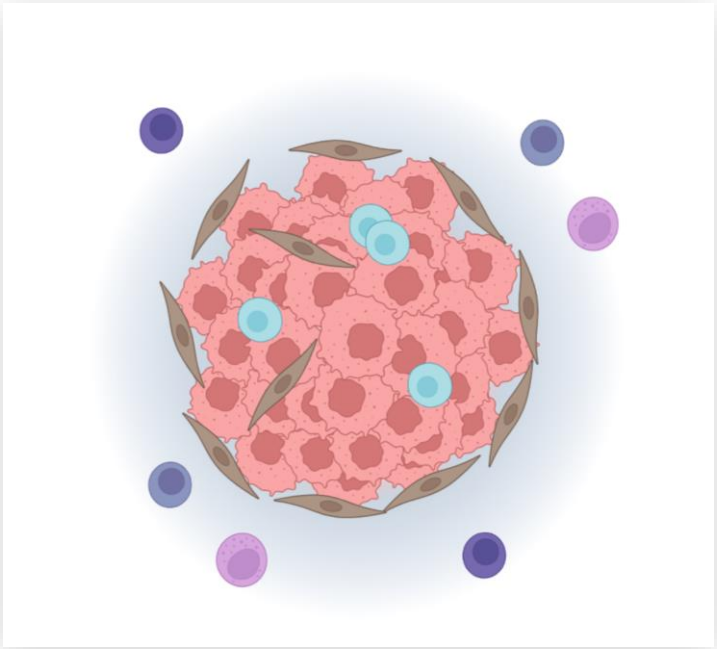
Initiating Monotherapy Phase 1 in Hot Tumors to Observe Activity; Anticipate Patient Enrollment in Q1 2023



Select Promising Solid Tumors & Identify Active Dose



Explore Strategic Combination Strategies in Cold Tumors

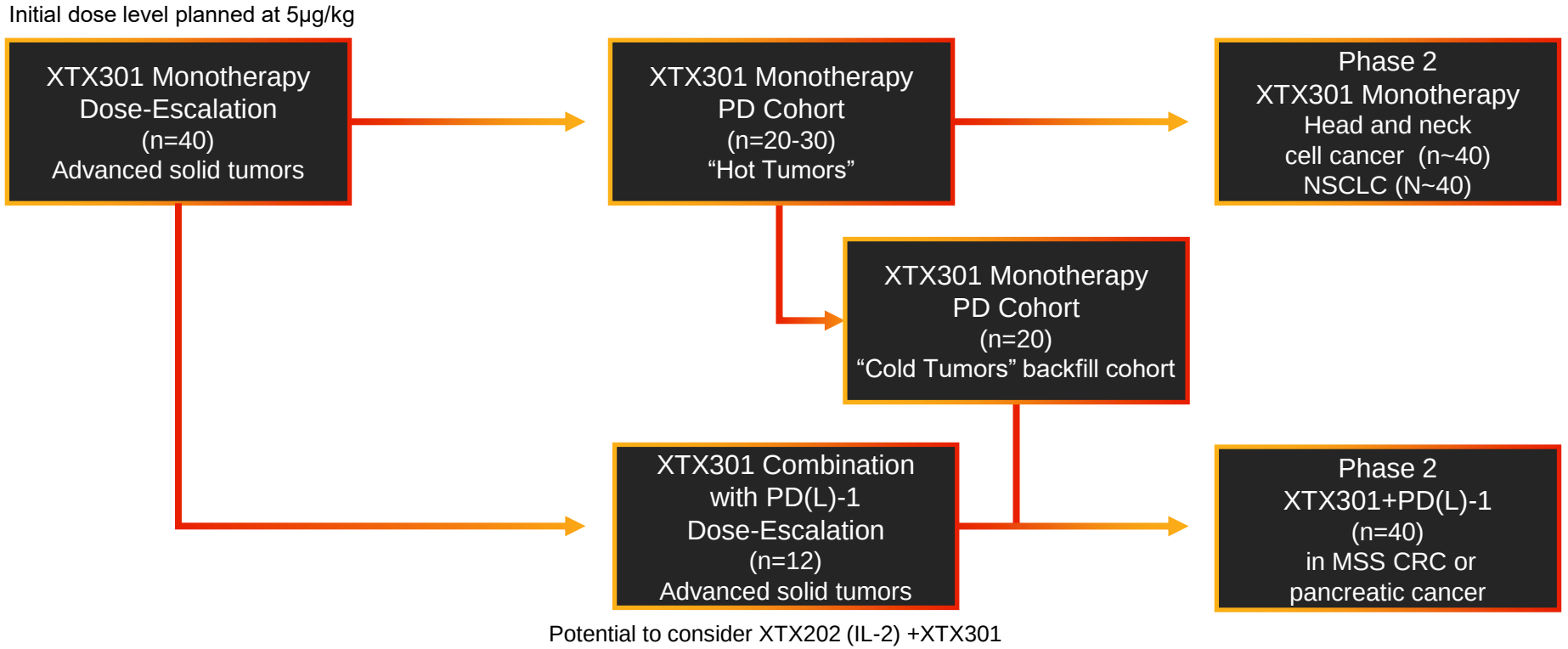


# XTX301 (IL-12) Trial Designed to Enable Multiple Monotherapy and Combination Opportunities for Expansion in Both Hot and Cold Solid Tumors

**As of November 7, 2022:**

- IND cleared in November 2022
- Anticipate initiating enrollment in monotherapy dose-escalation in planned Phase 1 trial in Q1 2023
- Initial dose level planned at 5µg/kg
- Anticipate reporting preliminary safety data from Phase 1 trial in Q4 2023

## Planned Phase 1 / 2 Trial Design




**Multiple Opportunities with Monotherapy and Combination Strategies**

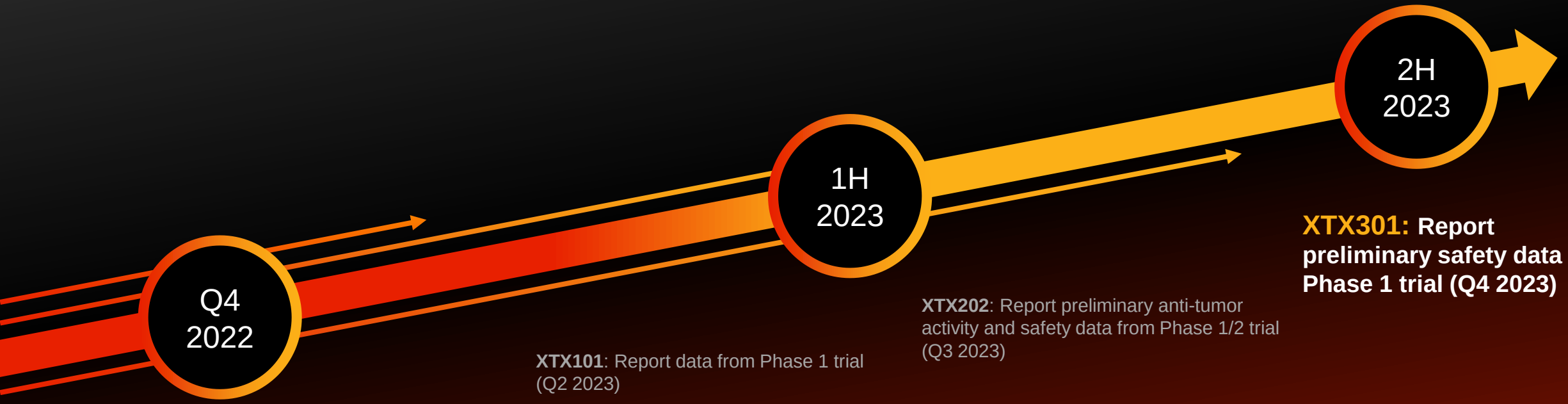
NSCLC, head & neck, melanoma, TNBC, MSI high CRC, Prostate, Ovarian, Pancreas, Colorectal MSS

CRC: colorectal cancer; NSCLC: non-small cell lung cancer; TNBC; triple negative breast cancer.
µg: micrograms.

# XTX301 (IL-12) Key Takeaways

- IL-12 has significant therapeutic potential across both “hot” and “cold” tumor types
  - “Hot” tumors include lung, bladder, head & neck, kidney, liver, melanoma, MSI high CRC
  - “Cold” tumors include prostate, ovarian, breast, pancreatic, brain, MSS CRC
- No approved IL-12 agents to date due to fatal dose limiting toxicities
- XTX301 compelling preclinical data supportive of broad clinical development approach
  - XTX301 tumor-activation designed to overcome significant toxicities of earlier IL-12 agents
  - IND accepted in November 2022; anticipate initiating Phase 1 trial in advanced solid tumors in Q1 2023
  - Preclinical data show anti-tumor activity in both “hot” and “cold” tumor models, often with a single dose
- Adaptive design of Phase 1/2 trial with preliminary safety data anticipated in Q4 2023
  - Patients will receive treatment with XTX301 in the outpatient setting
  - Initial dose level planned at 5µg/kg (10x MTD for recombinant human IL-12 of 0.5 µg/kg IV)
  - Trial design incorporates both “hot” and “cold” tumor cohorts

# XTX301: Preliminary Safety Data Anticipated in Q4 2023




**XTX101**: Complete monotherapy dose-escalation cohort *

**XTX202**: Initiate enrollment in monotherapy expansion cohort (Q4 2022)

**XTX301: IND cleared (November 2022)**

**XTX101**: Report data from Phase 1 trial (Q2 2023)

**XTX202**: Initiate enrollment in Phase 2 (monotherapy) trial (1H 2023)

**XTX301: Initiate enrollment in monotherapy dose-escalation (Q1 2023)**

**XTX202**: Report preliminary anti-tumor activity and safety data from Phase 1/2 trial (Q3 2023)

**XTX301: Report preliminary safety data from Phase 1 trial (Q4 2023)**

Anticipate existing cash and cash equivalents will be sufficient to fund operating expenses and capital expenditure requirements into Q2 2024

RP2D: recommended Phase 2 dose.

* Plan to evaluate XTX101 as a monotherapy for the treatment of advanced solid tumors and explore opportunities for strategic collaborations to advance XTX101. Do not plan to initiate an anti-PD-1 combination cohort in the Phase 1 trial or initiate a Phase 2 trial without a development partner.

# Acknowledgements

Xilio would like to thank the patients participating in our clinical trials, as well as their families and caregivers.

We are humbled by their commitment and support in bringing us closer to achieving our mission to design and deliver tumor-activated immuno-oncology therapies that provide effective, tolerable and durable therapeutic options for patients with solid tumors.

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