



Biolnvent

**UNLEASHING IMMUNITY
TO FIGHT CANCER**

December 2024

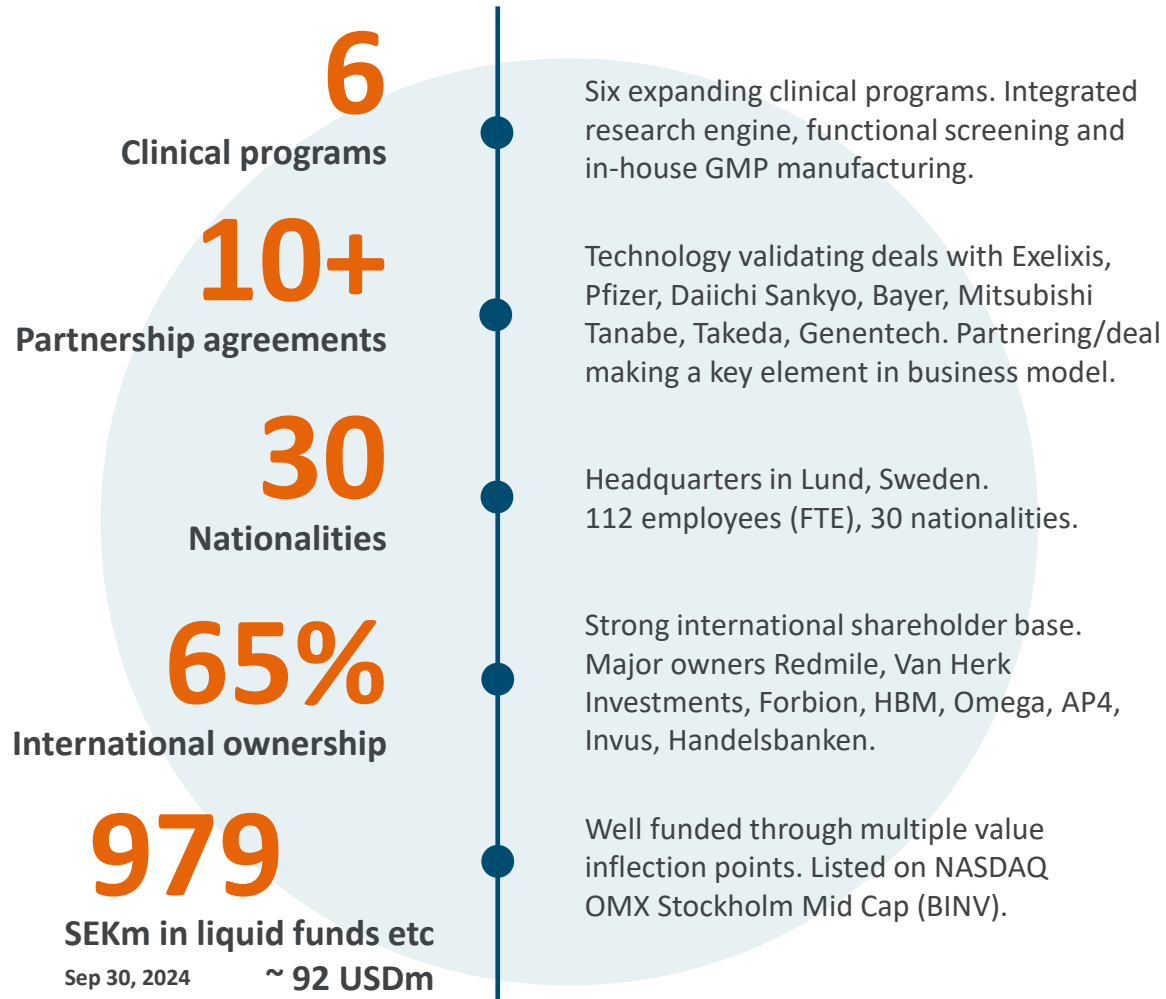
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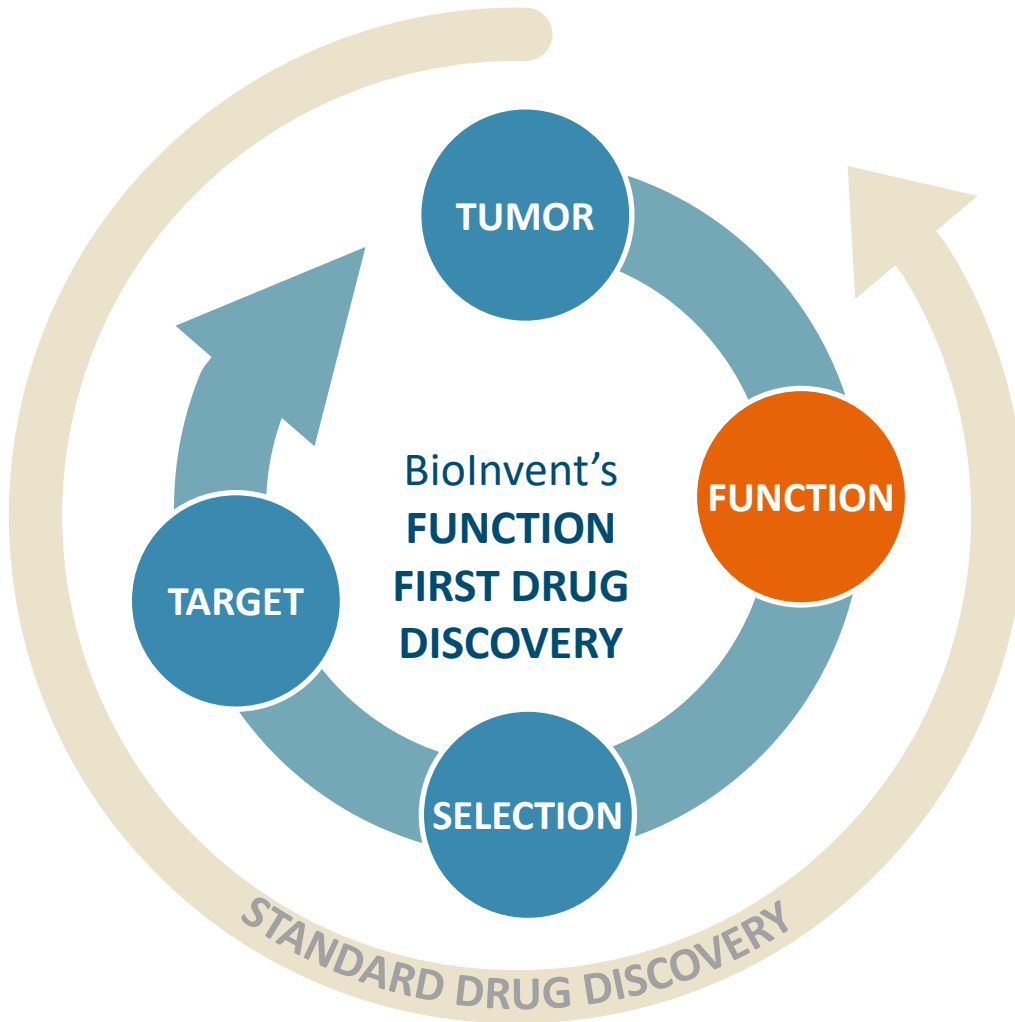
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Translating complex cancer biology into innovative antibody therapies

BUILDING A PIPELINE: OUR STATE-OF-THE ART ANTIBODY TECHNOLOGY

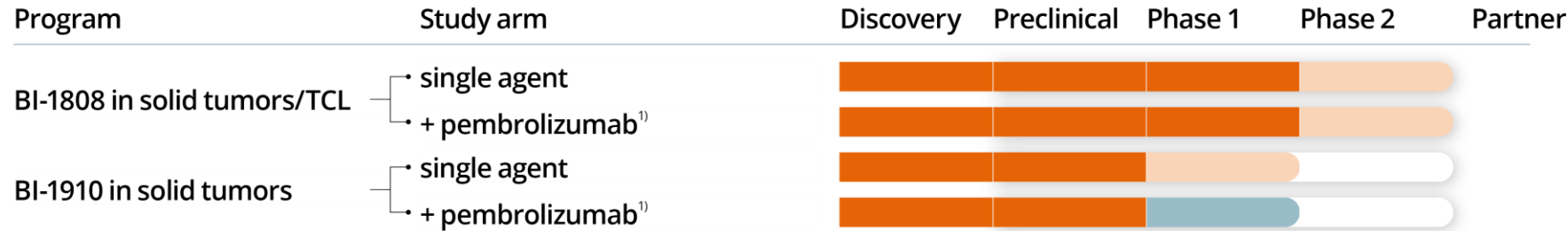


Proprietary **F.I.R.S.T.™** platform is the engine discovering novel cancer treatments

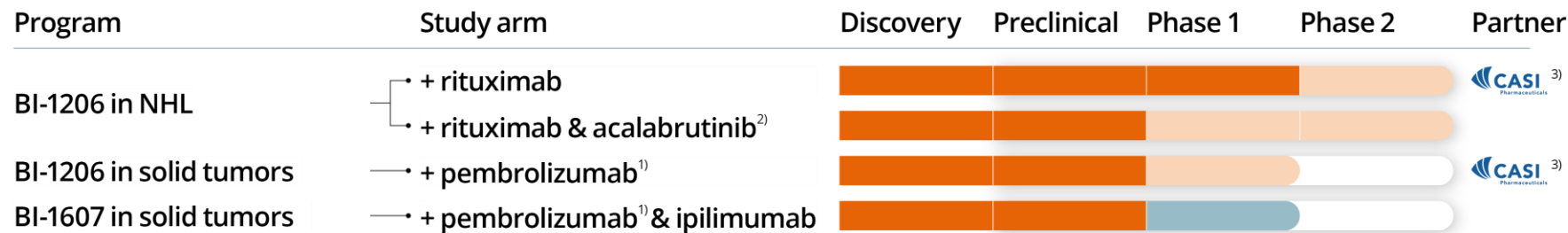
While others often focus on the targets and test function at the end, **we start from the function** (drug efficacy).

STRONG PROPRIETARY CLINICAL PIPELINE WITH MULTIPLE VALUE DRIVERS

TNFR2



FcyRIIB



CTLA-4



1) Supply agreement with MSD

2) Supply agreement with AZ

3) Licensed to CASI for China, Hong Kong, Macau and Taiwan

4) 50/50 co-development collaboration with Transgene

■ Completed
 ■ Ongoing
 ■ Upcoming



ANTI-TNFR2

BI-1808

BI-1910

BIOINVENT LEADS THE WAY IN TNFR2 BIOLOGY

- A New And Exciting Potential Treatment Opportunity

Out of hundreds of antibodies
two highly potent candidates with
different MoAs were selected:

BI-1808 - a ligand-blocking FcγR-engaging mAb

BI-1910 - an agonist mAb

Our focus is to pursue both MoA's to ensure patient benefit

Competitors are developing either agonists or antagonists

Drug Name	Company Name	Stage	Description
BI-1808	BioInvent	Phase 2	Human IgG1 Blocker/Depleter
BI-1910	BioInvent	Phase 1	Human antibody Agonist
LBL-019	Nanjing Leads Biolabs	Phase 1/2	Humanized IgG1 Blocker
SIM-0235	Simcere	Phase 1	Humanized IgG1 antibody Blocker/Depleter
HFB-200301	HiFiBiO	Phase 1	Humanized murine (IgG1) Agonist
NBL-020	NovaRock Biotherapeutics/ CSPC	Phase 1	Humanized IgG? Blocker
BIR-2101	BITT / BeiGene	IND-approved	Humanized IgG2 (variant) Antagonist
APX-601	Apexigen/Pyxis Oncology	IND ready	Humanized rabbit IgG1 Blocker/Antagonist
AN3025	Adlai Nortye/Biotime	IND-enabling	Humanized IgG1 (variant) Antagonist

BI-1808 **SINGLE AGENT** AND IN COMBINATION WITH **PEMBROLIZUMAB**

Strong BI-1808 single agent activity in CTCL

(September 2024)

- **3 partial responses (PR)**
- **1 patient with stable disease (SD)**
- **4 evaluable CTCL patients**
- **All of these patients had previously deteriorated** after standard treatment

Clinical Phase 1/2a study ongoing

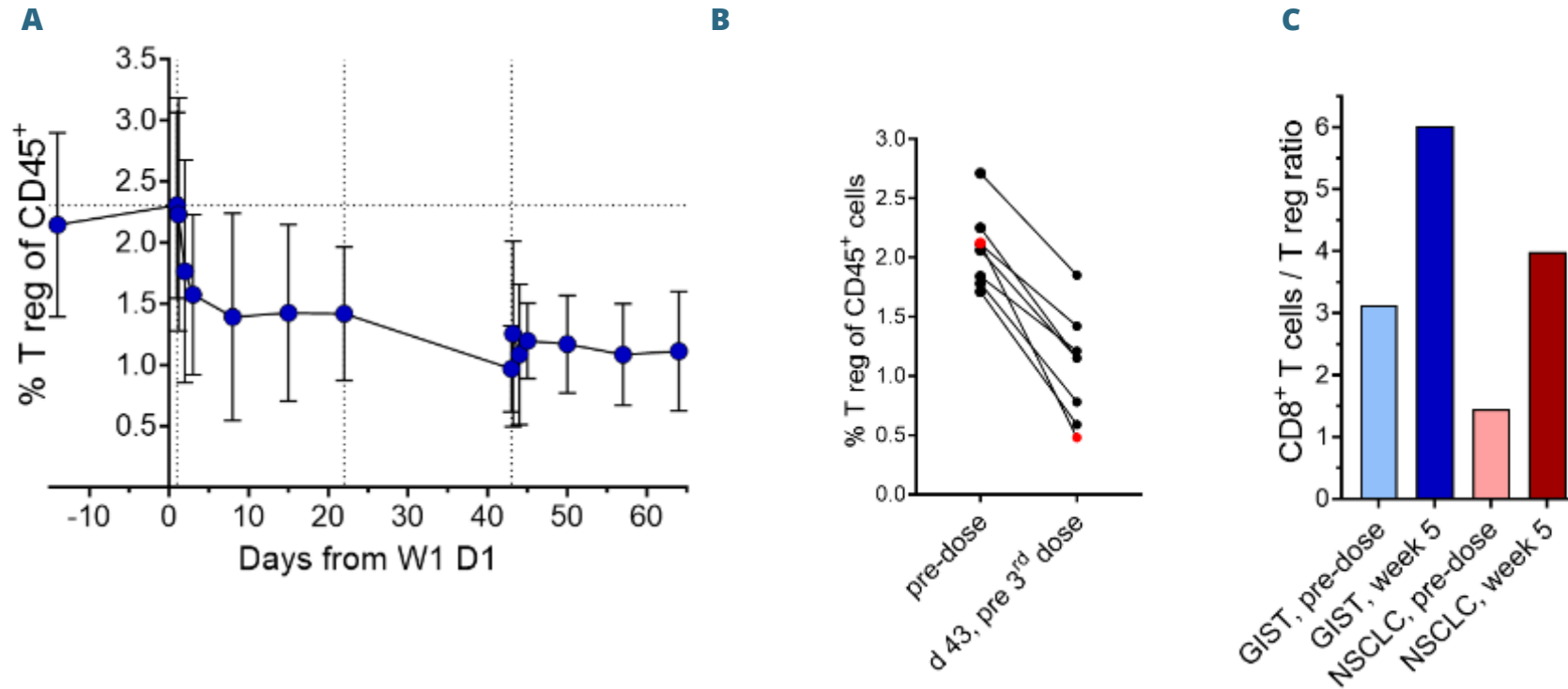
- CTCL data support earlier disclosed **single agent data** showing 1 complete response (CR), 1 PR and 9 patients with SD (ASCO June 2024)
- Promising signs of efficacy and favorable safety profile in Phase 1 dose escalation with **BI-1808 in combination with KEYTRUDA®** also presented at ASCO. Phase 2a dose expansion combination study with pembrolizumab has started enrollment. First Phase 2a combo data H225E.

WHAT'S NEXT?

Additional BI-1808 single agent Phase 2a data YE24E

BI-1808 SINGLE AGENT EFFICACY

Induces significant regulatory T-cell depletion and clear signs of CD8⁺ T-cell activation in responding patients



Data from the 1000 mg monotherapy cohort.

The data show substantial **T-reg depletion** compared to baseline. Panel B shows the individual patient drop in T-reg. Red dots indicate the drop in the GIST patient. (Dashed horizontal line = baseline. Dashed vertical lines = BI-1808 dosing occasions)

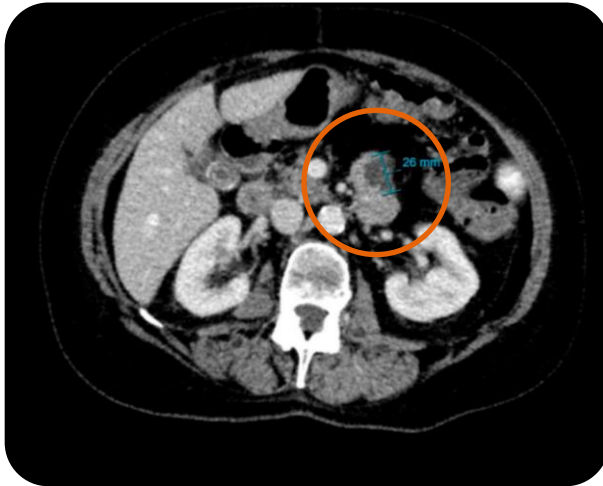
Tumor biopsies collected pre-, and 5 weeks post-treatment were stained for Foxp3⁺ CD4⁺ Treg cells and CD8⁺ T cells using immunofluorescence.

Percentages of stained area were quantified and a pre- and post-treatment CD8⁺/T reg ratio were calculated.

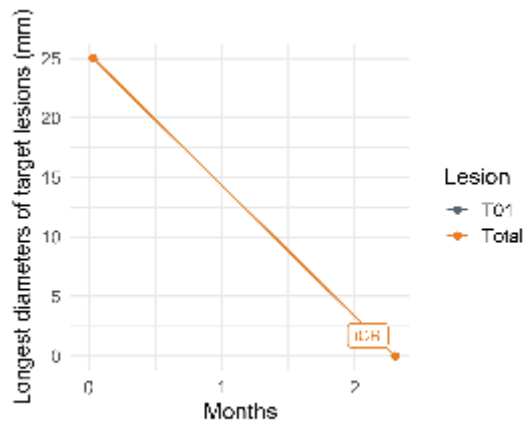
BI-1808 increases intratumoral CD8⁺/T reg ratio

ASCO CASE STUDY: COMPLETE RESPONSE IN OVARIAN CANCER

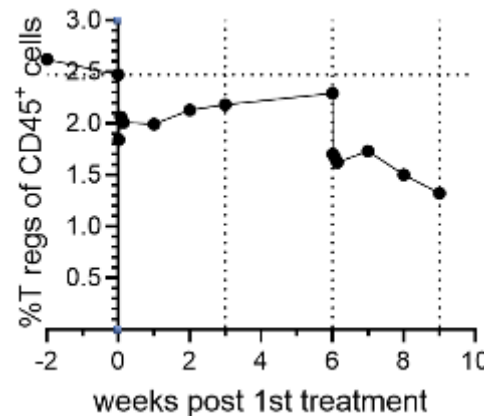
Baseline



2 months



Tumor assessment vs time on study



T reg levels vs time on study, dashed lines indicate administration of BI-1808

63-year-old patient with ovarian cancer, Stage IIIA at diagnosis, entered the study with PD.

Four previous lines of treatment:

- Paclitaxel/carboplatin
- Carboplatin/doxorubicin
- Olaparib
- Bevacizumab/topotecan

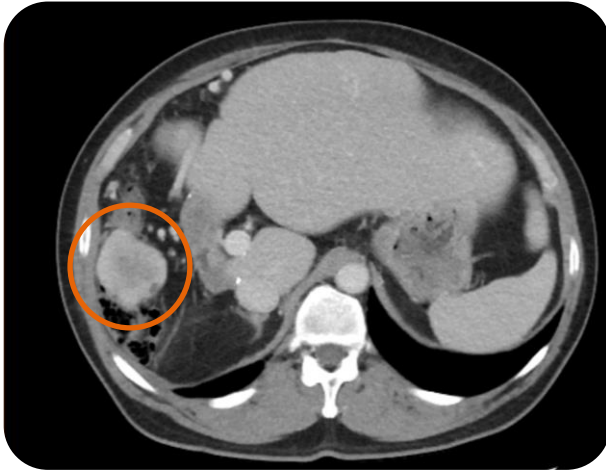
Patient had one target lesion of 25 mm and two larger non-target cystic lesions.

At first post-treatment scan, 9 weeks after the start of treatment, no quantifiable tumor mass could be measured.

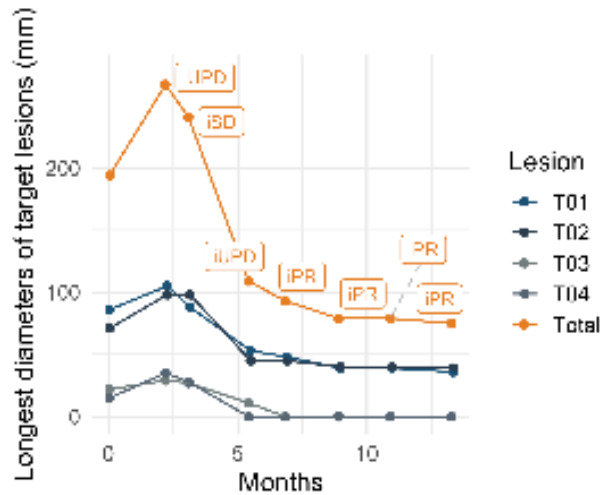
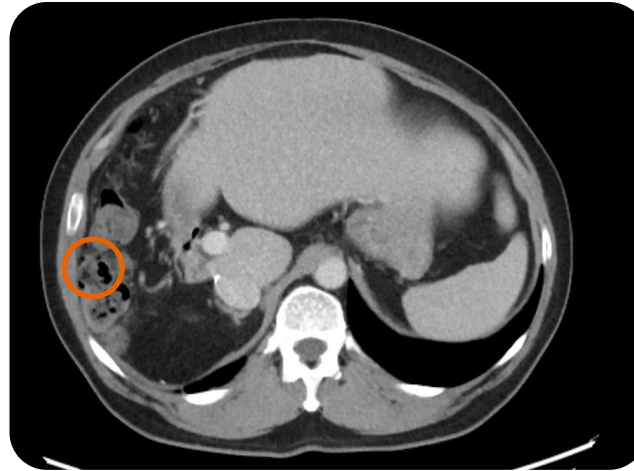
The response has been confirmed

ASCO CASE STUDY: ROBUST PR IN A PATIENT WITH GIST

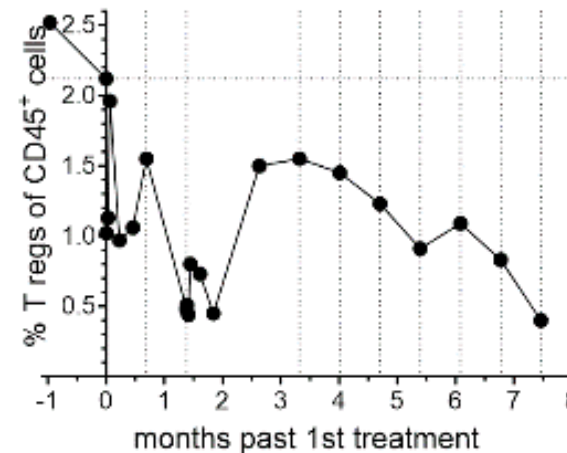
Baseline



Follow-up 13 months



Tumor assessment vs time on study



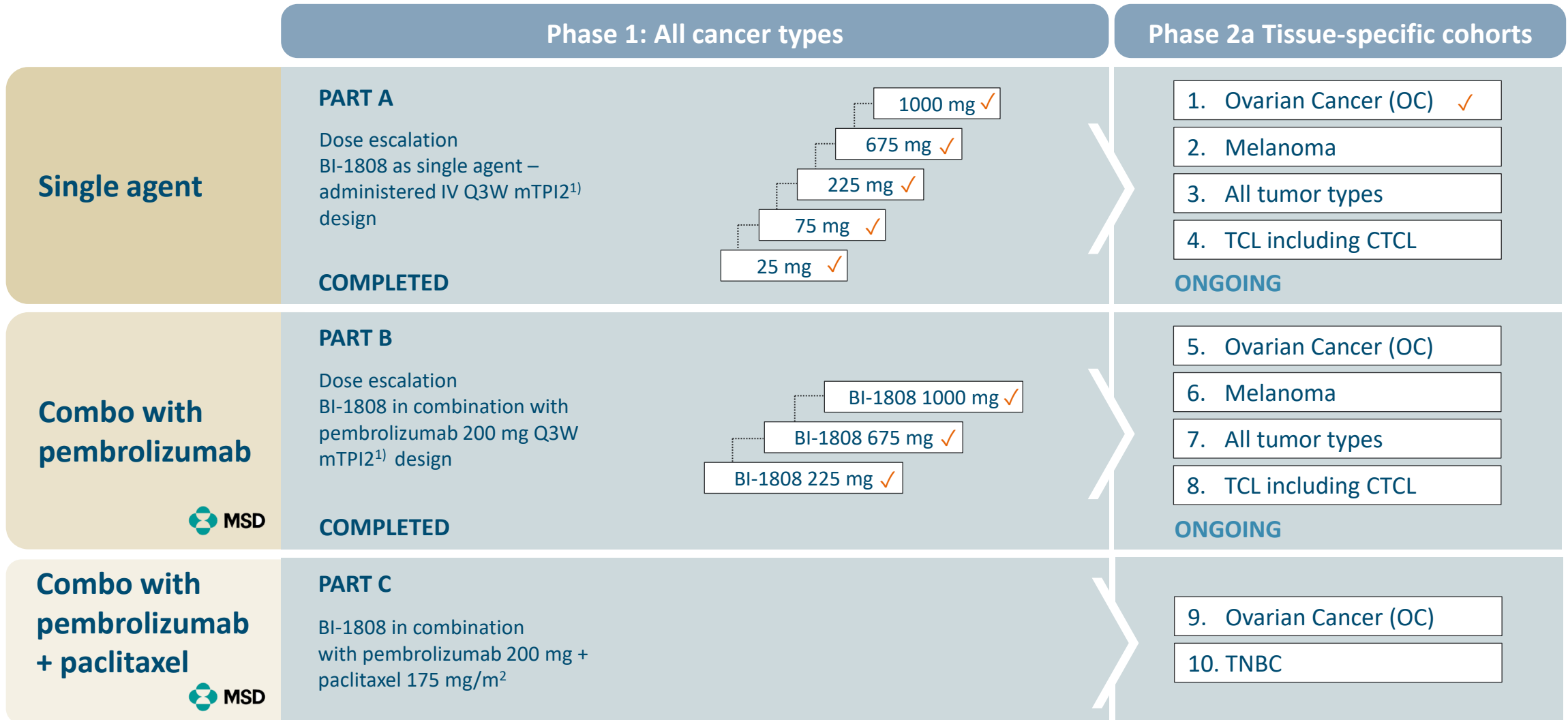
T reg levels vs time on study. Dashed lines indicate administration of BI-1808

55-year-old male patient with GIST, who presented with clinical PD for more than 6 months with multiple metastatic lesions. **12 previous lines of therapy.**

In the most recent scan, total tumor burden is **reduced by 61%** of baseline, with BI-1808 monotherapy for 13 months and ongoing.

GIST is a gastrointestinal tumor where current immune checkpoints inhibitors show very limited activity.

BI-1808: KEYNOTE-D20 PHASE 1/2A CLINICAL STUDY DESIGN



BI-1910: SINGLE AGENT AND IN COMBINATION WITH PEMBROLIZUMAB

Robust target occupancy reached, evidence of immune activation observed

(ESMO, September 2024):

Clinical Phase 1/2a study ongoing Part A dose escalation single agent BI-1910 at ESMO:

- Robust target occupancy in prespecified target dose range reached and evidence of immune activation observed
- Further exploration of the dose safety/tolerability margin expected to be completed before YE24



Trial-in-Progress 1073

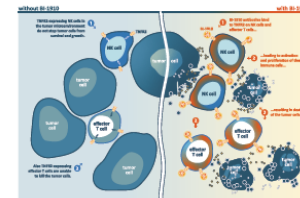
A phase 1/2a first in-human phase 1 study of BI-1910, a monoclonal antibody agonistic to TNFR2, as a single agent and in combination with pembrolizumab in subjects with advanced solid tumors

Rationale for Developing BI-1910

TNFR2 is a novel promising target for cancer immune therapy, and TNFR2 has been proposed as a costimulatory receptor for T cell activation. Early clinical development of ligand-blocking mAbs targeting TNFR2, such as BI-1808, indicate that modulating the pathway may lead to clinical responses with favourable tolerability.

We develop BI-1910, a TNFR2 targeting agonist. BI-1910 does not block the interaction between TNFR2 and its ligand TNF- α . Non-clinical in vivo data demonstrate enhancement of functional activity of TNFR2-expressing lymphocytes, including CD8⁺ and CD4⁺ T-cells, as well as NK cells, resulting in tumor regression and ultimately immune rejection.

Furthermore, BI-1910 show additive effects with anti-PD-1 therapy in several murine tumor models.



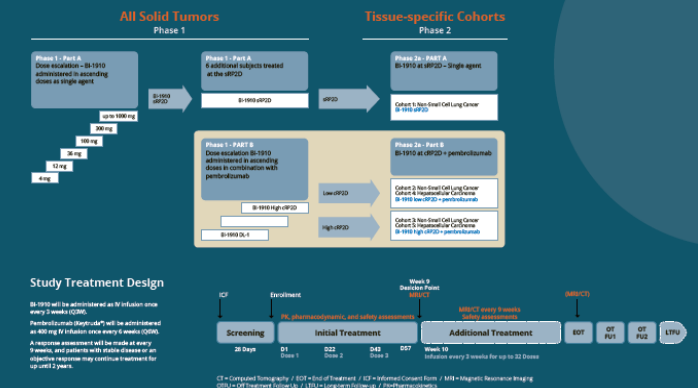
Background

Tumor necrosis factor (TNF) is a potent pro-inflammatory cytokine known to induce an inflammatory response and cell death, and anti-TNF drugs are used to treat autoimmune diseases. TNF has two receptors: TNFR1, which is broadly expressed on many different cell types, and TNFR2, with expression largely restricted to immune cells. TNFR2 is a type I transmembrane protein with typically high expression in myeloid cells and specific T cell subsets. Macrophages and Tregs constitutively express TNFR2. In effector T cells TNFR2 expression is upregulated after T cell receptor stimulation. The role of TNFR2 in inflammation is unclear, with both proinflammatory and immunoregulatory roles postulated.

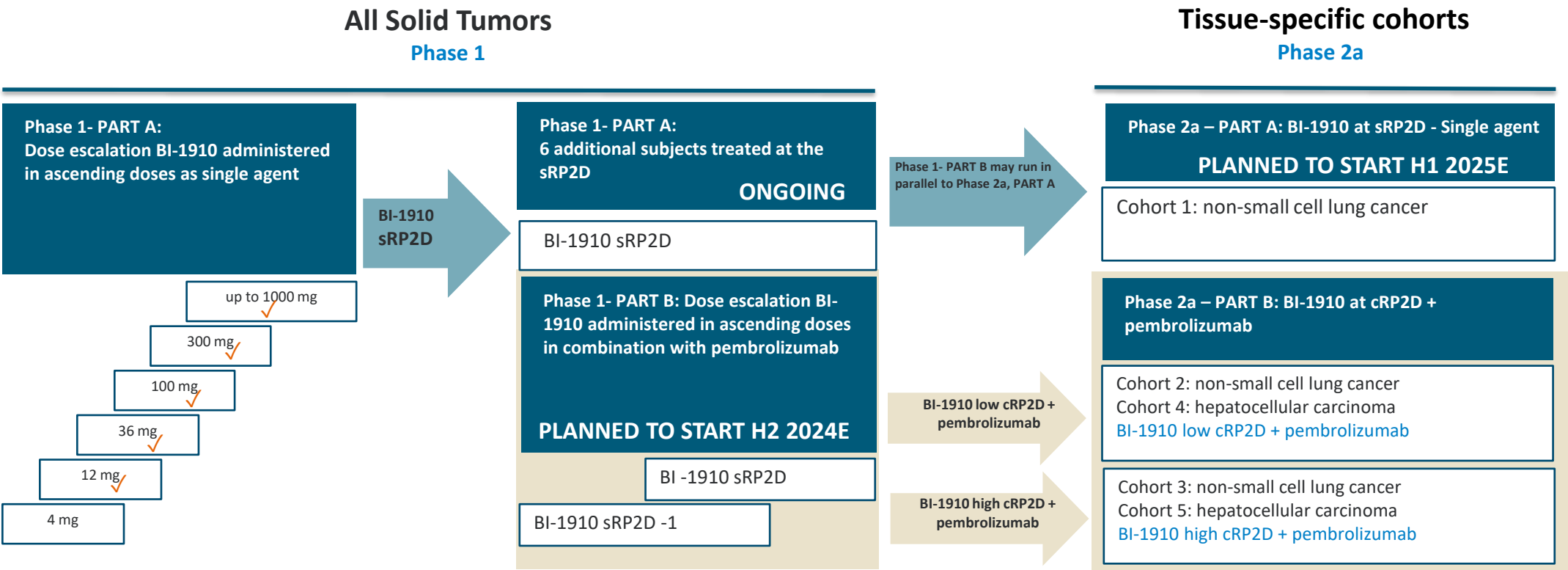
TNFR2 is important for Treg survival, while simultaneously acting as a potent costimulatory molecule on CD8⁺ T cells thereby promoting inflammatory activity. Given the costimulatory functions of TNFR2 in different immune cells, TNFR2 has in recent years been suggested as a promising novel target for anticancer treatment. We are developing BI-1910, an agonistic human IgG2 mAb targeting TNFR2. BI-1910 agonizes T cells and mediates CD4⁺ and CD8⁺ T cell activation. It binds human TNFR2 selectively but does not block the interaction between the receptor and its ligand, TNF- α . BI-1910 combined with anti-PD-1 showed additive and tumor effect in several murine tumor models including B16 melanoma cancer, MC38 colon cancer, and CT26 colon cancer, providing rationale to clinically evaluate this antibody in combination with pembrolizumab.

Study 22-BI-1910-01 explores the safety and preliminary antitumor activity of a novel agonist to TNFR2

BI-1910 has demonstrated robust T-cell mediated antitumor activity in the preclinical setting, with additive effects after combination with anti-PD-1 therapy. Monotherapy dose escalation started in December 2023, and enrollment into first cohort with pembrolizumab co-treatment is expected to start in Q4 2024.



BI-1910 STUDY DESIGN



RP2D=recommended phase 2 dose; cRP2D=combination RP2D; sRP2D= single agent RP2D

WHAT'S NEXT?

First Phase 1 single agent data YE 2024E

ANTI-Fc γ RIIB

BI-1206 + rituximab + acalabrutinib

BI-1206 + pembrolizumab

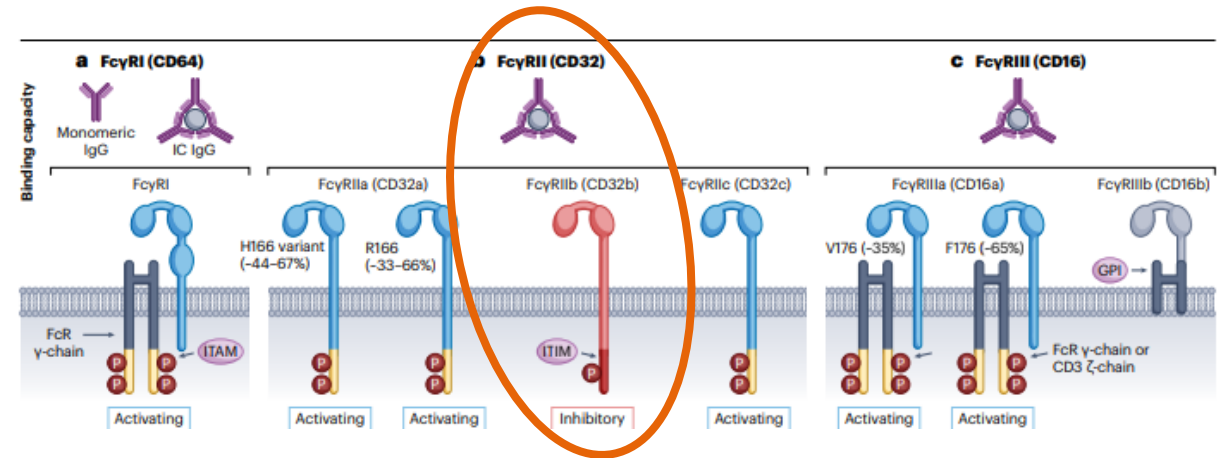
BI-1607

LEVERAGING OUR FcγRIIB TARGET EXPERTISE WITH A MULTI-PRONGED APPROACH

We have developed two antibodies with different mechanisms of action to tackle different needs

BI-1206 is an Fc-competent IgG1 antibody that enhances anti-CD20 and anti-PD-1 therapies. In **two separate programs**.

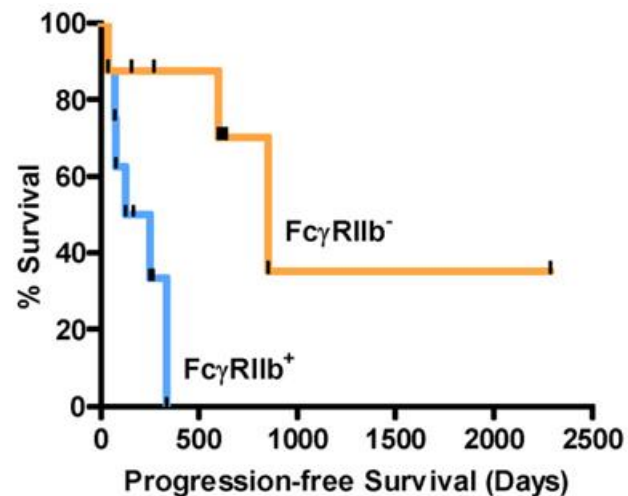
BI-1607 has a different MoA compared to BI-1206 having been engineered for reduced Fc-binding to FcγR.



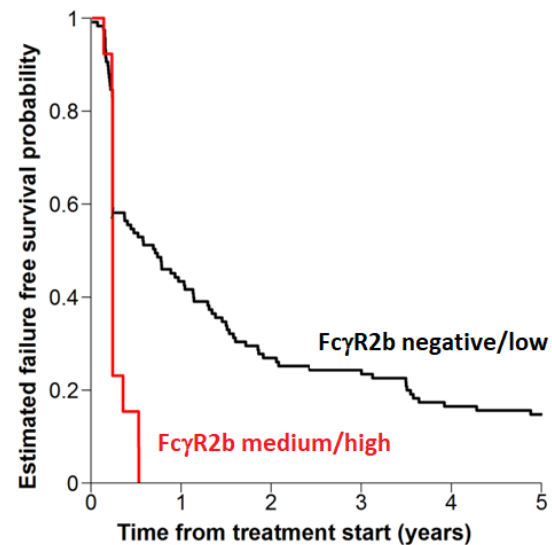
Galvez-Cancino, F., Simpson, A.P., Costoya, C. et al. Fcγ receptors and immunomodulatory antibodies in cancer. *Nat Rev Cancer* 24, 51–71 (2024). <https://doi.org/10.1038/s41568-023-00637-8>

FcγRIIB EXPRESSION CORRELATES INVERSELY WITH SURVIVAL

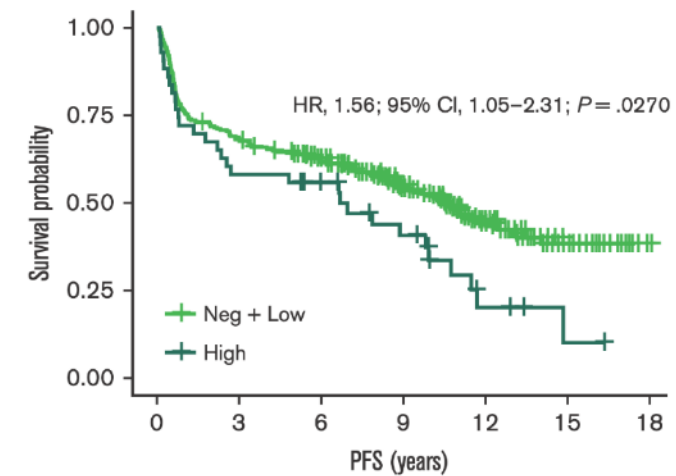
Mantle Cell Lymphoma



Follicular Lymphoma



Diffuse Large B-Cell Lymphoma



High FcγRIIB expression is associated with shorter survival in patients receiving rituximab therapy

BI-1206 IN NHL: DATA FROM PHASE 1 SC DOSE ESCALATION WITH RITUXIMAB

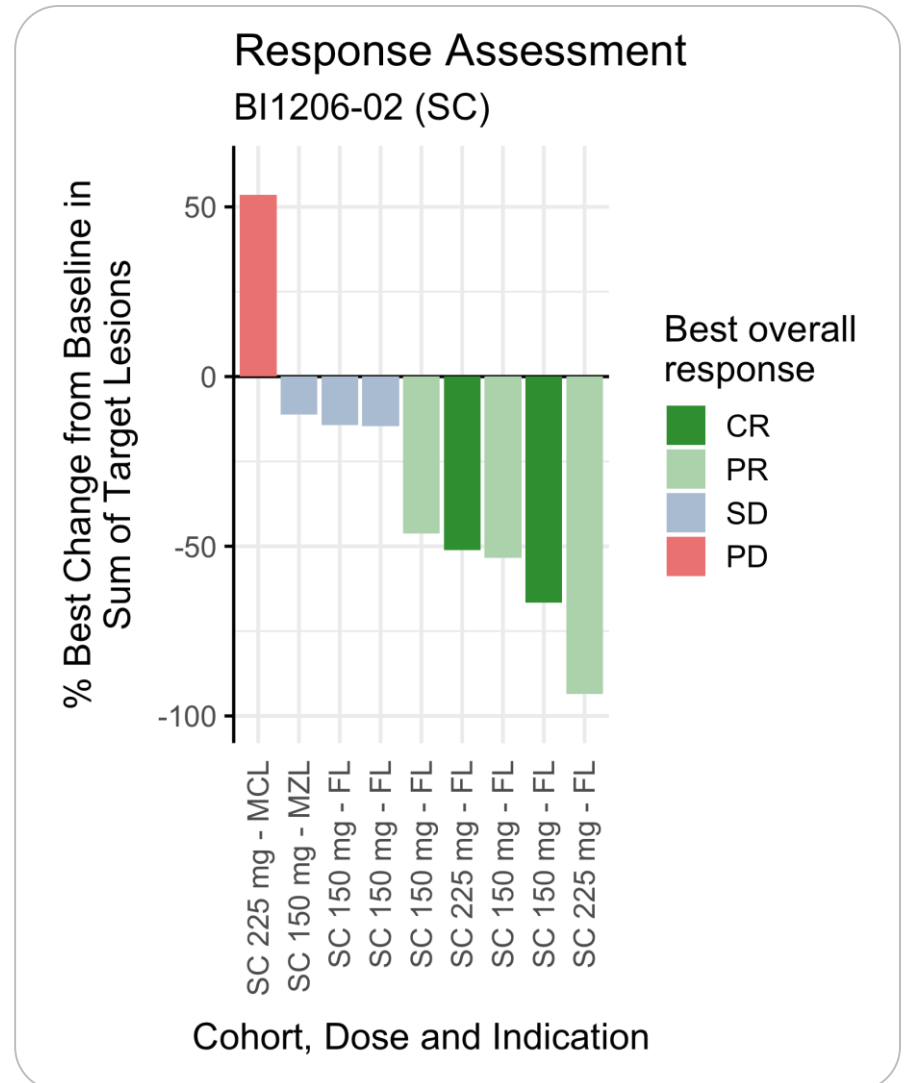
Impressive clinical efficacy data BI-1206 SC

(October 31, 2024)

- **1 additional complete response (CR)**
- **1 more partial response (PR)**
- **2 more patients with stable disease (SD)**

Together with the positive data reported at EHA 2024 (European Hematology Association) June 2024 it gives a total of:

- **2 CR**
- **3 PR**
- **3 SD**
- **Out of 9 evaluable patients**

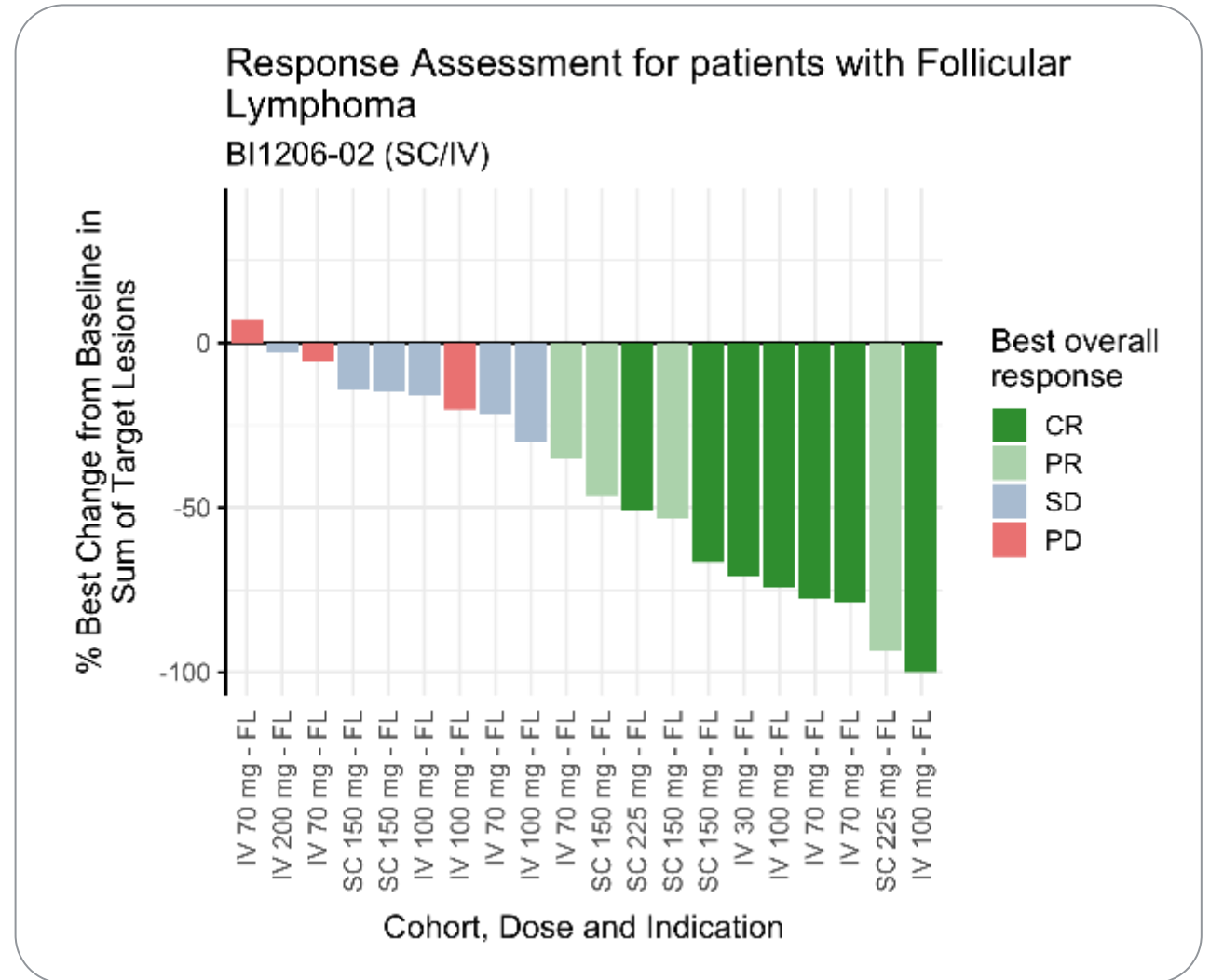


CO-ADMINISTRATION OF BI-1206 WITH RITUXIMAB LED TO HIGH RESPONSE RATES IN RELAPSED/REFRACTORY FL PATIENTS

Quality of responses particularly impressive

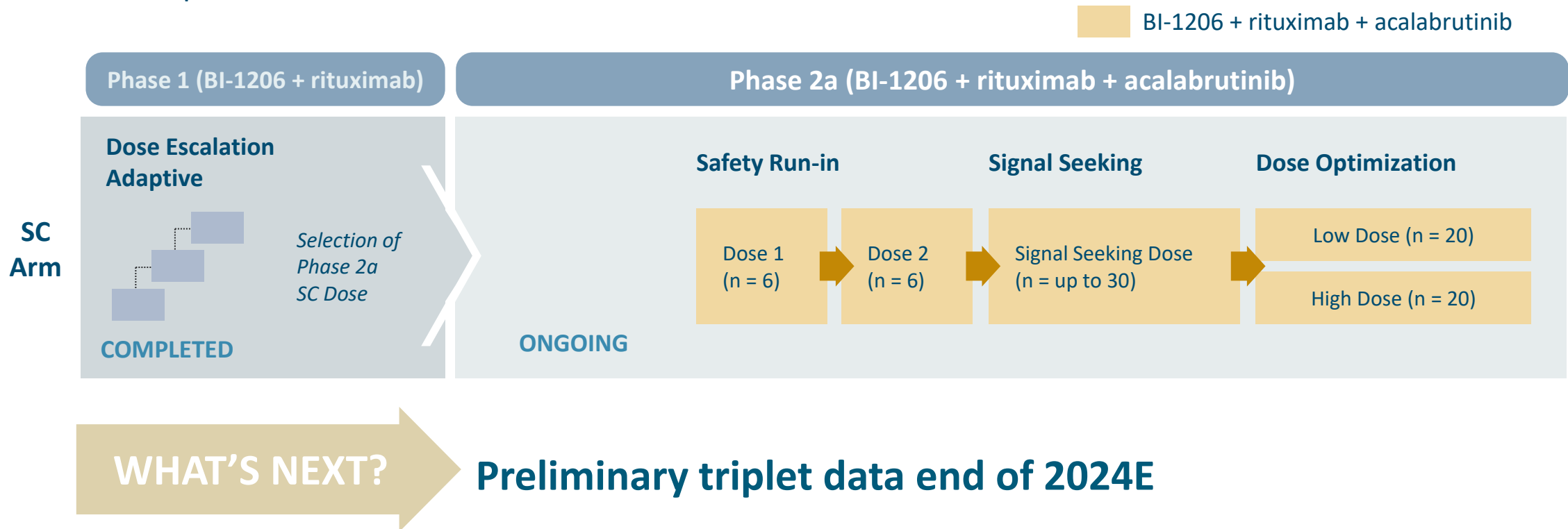
(October 2024, SC + IV):

- 7 complete responses (CR)
- 4 partial responses (PR)
- 6 patients with **stable disease** (SD)
- Out of 20 evaluable **FL patients**
- **ORR** of 55%, **CRR** of 35%, **DCR** 85%
- **CRs** have been **long-lasting**, three of them **lasting years after** end of treatment
- **No safety or tolerability concerns**

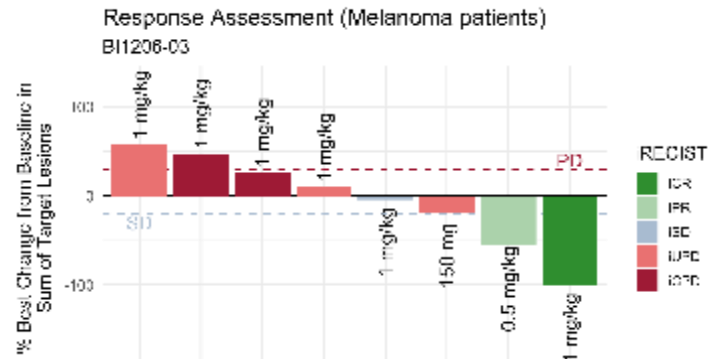


BI-1206 IN NHL: COMBINATION WITH **RITUXIMAB** AND **ACALABRUTINIB**

- **First patient enrolled** (Sep 2024) in **Phase 2a** study arm combining **BI-1206 with rituximab and acalabrutinib*** (BTK inhibitor)
- Approximately **30 patients** expected to be enrolled in Spain, Germany, the US, and Brazil
- Phase 1/2a clinical study in patients with NHL who have **progressed or are refractory to rituximab**
- The **conveniency and safety profile** of this **triplet** should be **very competitive** in the treatment landscape of NHL



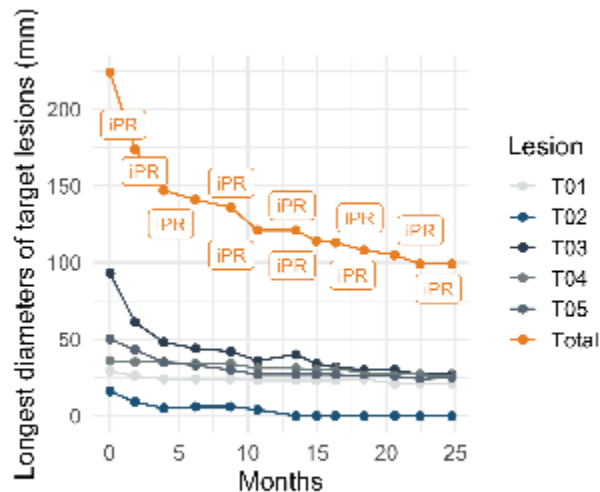
Co-administration of BI-1206 with pembrolizumab was well-tolerated in a heavily pretreated population, with promising responses observed in melanoma, and uveal melanoma, who previously failed anti-PD1 therapy.



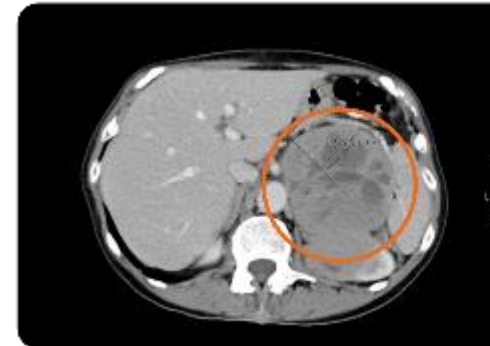
Case study: PR

69 YO female with **uveal melanoma**.

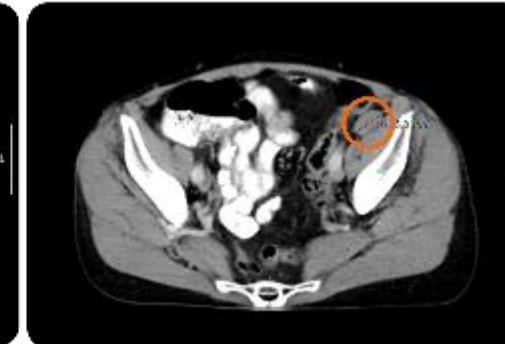
No response to prior immunotherapy or chemotherapy. Multiples lines of ICIs and Chemo. Progressing when entering study. Showed early partial response at first scan on BI-1206 + pembrolizumab, continued PR deepening during whole study duration (2years) with tumor burden reduced by 56% at end of trial.



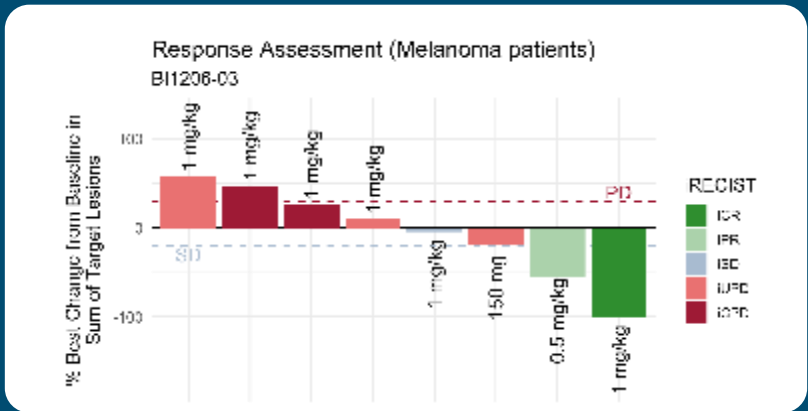
Baseline



End of treatment 2 years

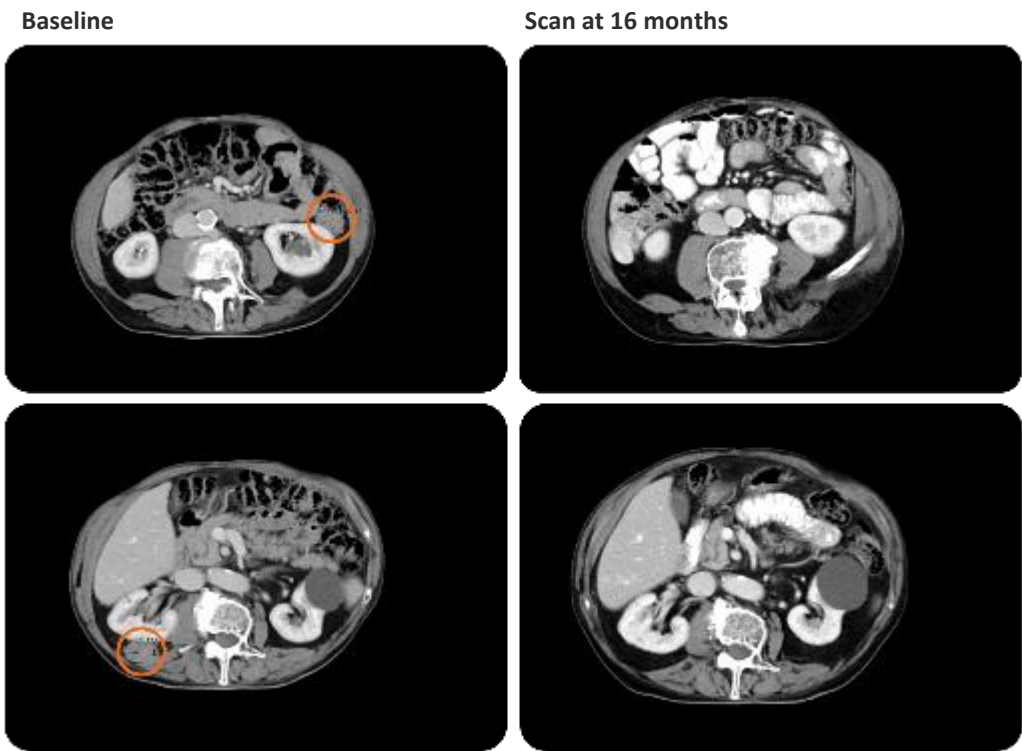
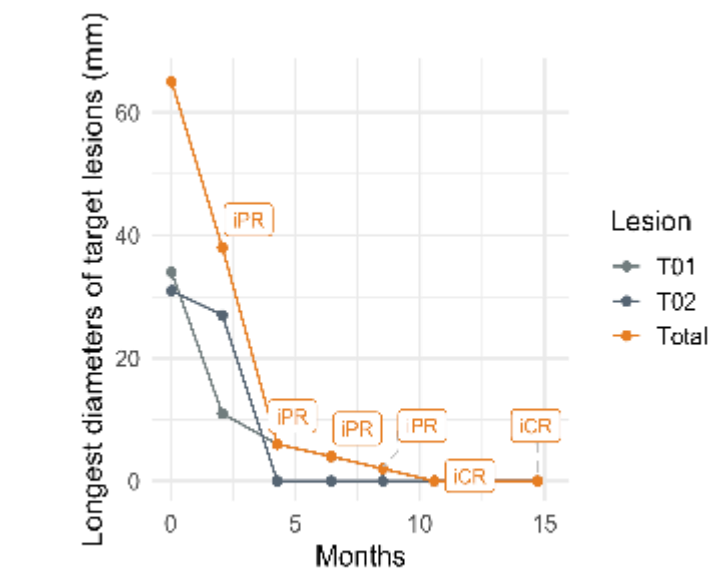


Co-administration of BI-1206 with pembrolizumab was well-tolerated in a heavily pretreated population, with promising responses to treatment observed in melanoma, including uveal melanoma, who previously failed anti-PD1 therapy.

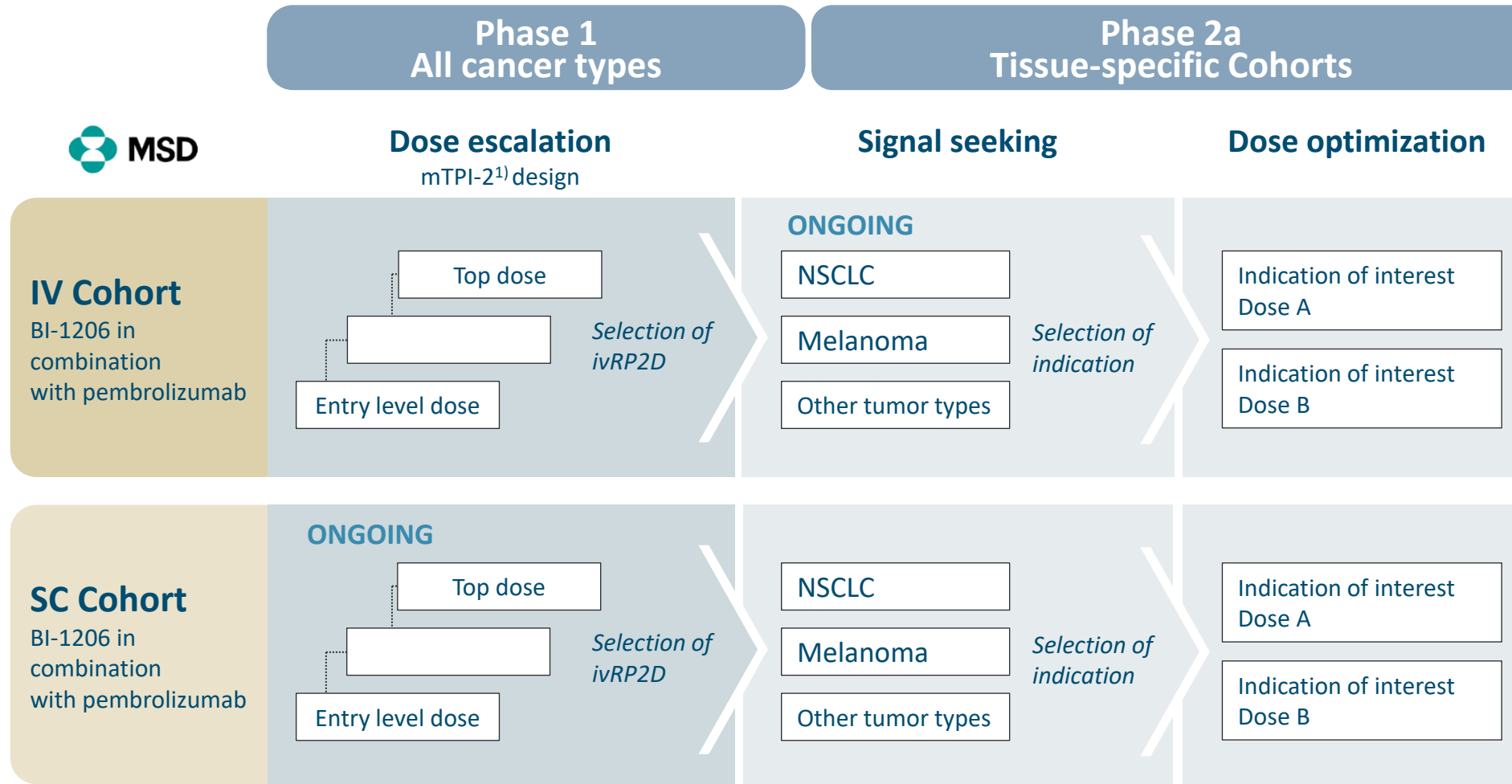


Case study: CR

77 YO male melanoma patient, stage IV.
Deep Partial Response at first scan at 2 months, evolving to CR at 10 months, still ongoing at 16 months. Three lines of previous ICI therapy, with PR as best prior response to ipilimumab + nivolumab.



PLANS FORWARD – STUDY DESIGN BI-1206 IN SOLID TUMORS (KEYNOTE-A04)

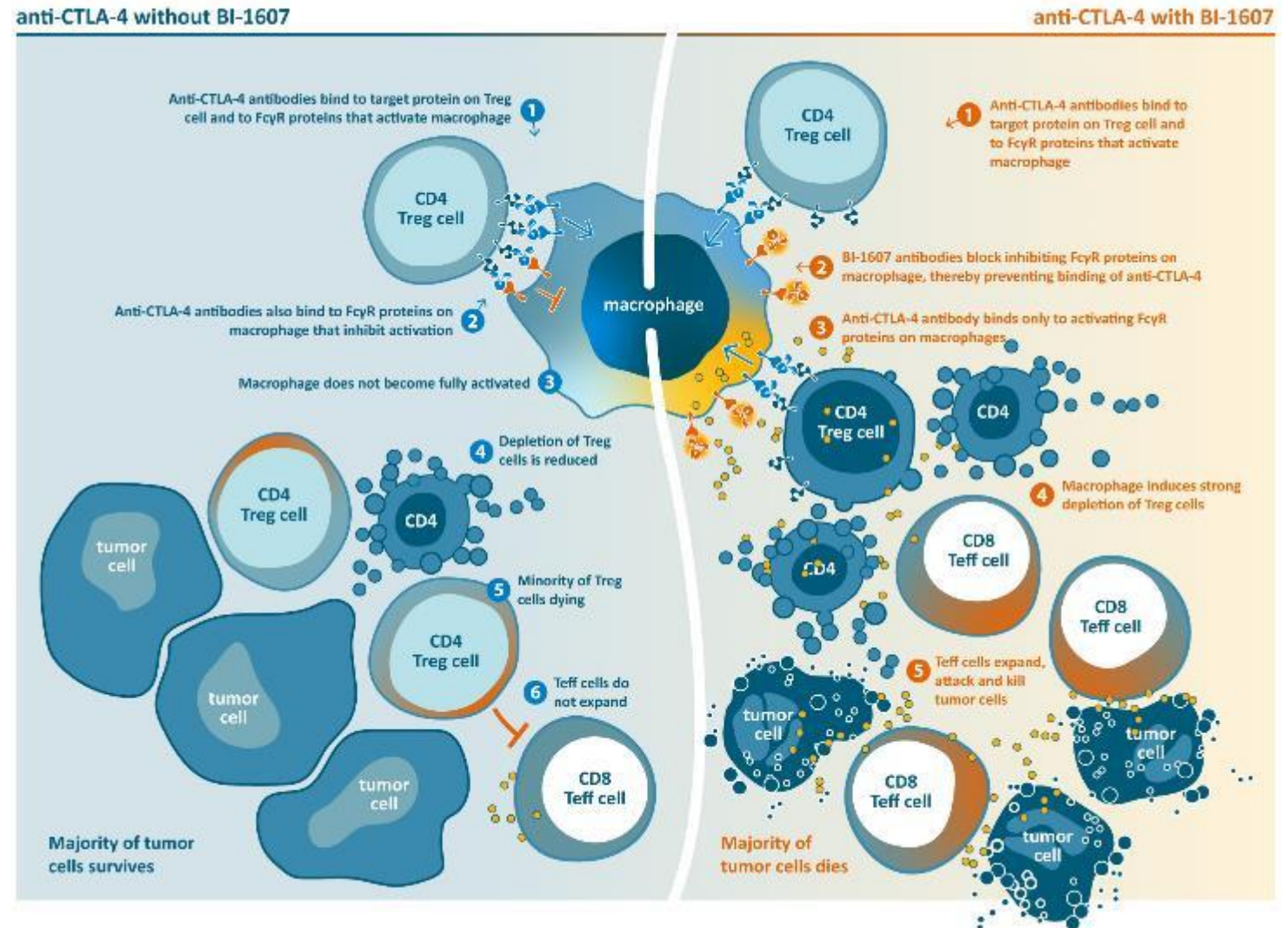


BI-1607 HAS THE POTENTIAL TO INCREASE EFFICACY OF OTHER ANTIBODY DRUGS

BI-1607 has an antagonistic function

Blocking the inhibitory function of immune effector cells

- Tumor-associated **macrophages** express **high levels of FcγRIIB** and a major target of BI-1607 in the tumor microenvironment
- Given its **high specificity and affinity** for FcγRIIB, BI-1607 blocks other antibodies' binding to FcγRIIB
- Engineered for reduced Fc-binding, resulting in a **differentiated mechanism of action** vs BI-1206



- To evaluate safety and anti-tumoral activity of **two different dose levels of BI-1607** with two different dose levels of **ipilimumab (anti-CTLA-4)** in combination with 200 mg flat dose of **pembrolizumab***
- Patients with unresectable or **metastatic melanoma**, previously treated with anti-PD-1/L1
- Includes an exploratory part assessing lower doses of anti-CTLA-4
- Preclinical studies indicate that a triple combination regimen including BI-1607 could allow the use of lower doses of ipilimumab, potentially achieving increased tolerability and higher efficacy.

Phase 1 data of BI-1607 + trastuzumab presented at the San Antonio Breast Cancer Symposium Dec 2023.

```

graph TD
    A[Phase 1  
B-1567 vaccine (102 patients  
50 males, 52 females)] --> B[10 patients  
ineligible]
    B --> C[92 patients]
    C --> D[10 patients  
ineligible]
    D --> E[82 patients]
    E --> F[10 patients  
ineligible]
    F --> G[72 patients]
    G --> H[10 patients  
ineligible]
    H --> I[62 patients]
    I --> J[10 patients  
ineligible]
    J --> K[52 patients]
    K --> L[10 patients  
ineligible]
    L --> M[42 patients]
    M --> N[10 patients  
ineligible]
    N --> O[32 patients]
    O --> P[10 patients  
ineligible]
    P --> Q[22 patients]
    Q --> R[10 patients  
ineligible]
    R --> S[12 patients]
    S --> T[10 patients  
ineligible]
    T --> U[2 patients]
    U --> V[0 patients]
  
```

At the time of the 2022.11 patients have been treated at doses ranging from 100 to 1000 µg with no serious adverse events from B-1567 observed (N=1424). No reactions (10% of dose group, in the 100 µg group), 2 patients experienced mild adverse events, 1 patient experienced 100 µg continued treatment at 500 µg and completed the trial, whereas all other patients have been seen at 100 µg. All patients had a B-1567 antibody titer at 14 evaluable patients, with disease control lasting up to 12 weeks.

B-1567 exhibit non-linear pharmacokinetics in line with expectations for a therapeutic antibody. Effective half-life in the therapeutic dose range is approximately 1 week. Doses rates of 500 µg and above are expected to achieve full target coverage throughout the five weeks dose interval, which was confirmed by observed antibody occupancy (98%).

As intracellular-combining therapies can cause a rapid rise for CD19⁺ progenitors, the potential for adverse effects of B-1567 was explored through a 14-week study. In this study, no positive correlation between B-1567 dose and CD19⁺ progenitors was observed. The study further validated the combination use of B-1567 and intracellular-combining therapies. The combination of B-1567 and intracellular-combining therapies was well tolerated. The overall exposure metric is 10% of any given treatment not statistically significant compared to dose, but a correlation to treatment duration, duration.

DOI: <https://doi.org/10.1016/j.xcrp.2023.101455>

WHAT'S NEXT?

Start patient recruitment for the triplet Phase 1b/2a study with first data H225E



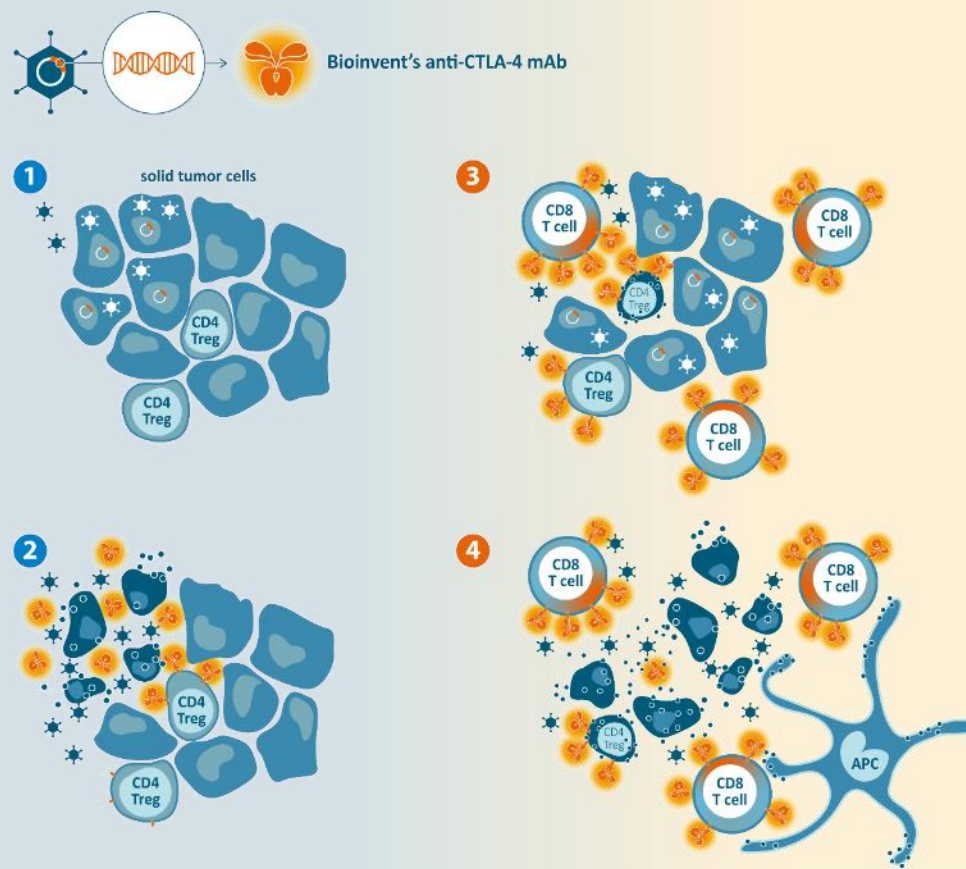
ANTI-CTLA-4

ONCOLYTIC VIRUS BT-001

BT-001: PHASE 1/2A ONGOING

50/50 PARTNERSHIP WITH TRANSGENE TO DEVELOP NEXT GENERATION ONCOLYTIC VIRUSES

mAbs and oncolytic virus attack the solid tumor together



Oncolytic virus & anti-CTLA-4 antibody combination elicits stronger antitumor response & targeted expression of anti-CTLA-4 antibody to improve safety profile

Journal for
Immunotherapy of Cancer

Vectorized Treg-depleting α CTLA-4 elicits antigen cross-presentation and CD8⁺ T cell immunity to reject 'cold' tumors

Monika Semmrich,¹ Jean-Baptiste Marchand,² Laetitia Fend,² Matilda Rehn,¹ Christelle Remy,² Petra Holmkvist,¹ Nathalie Silvestre,² Carolin Svensson,¹ Patricia Kleinpeter,² Jules Deforges,² Fred Junghus,¹ Kirstie L Cleary,³ Mimoza Bodén,¹ Linda Mårtensson,¹ Johann Foloppe,² Ingrid Teige,¹ Eric Quéméneur,² Björn Frenndéus^{1,3}

To cite: Semmrich M, Marchand J-B, Fend L, et al. Vectorized Treg-depleting α CTLA-4 elicits antigen cross-presentation and CD8⁺ T cell immunity to reject 'cold' tumors. *Journal for Immunotherapy*

ABSTRACT

Background Immune checkpoint blockade (ICB) is a clinically proven concept to treat cancer. Still, a majority of patients with cancer including those with poorly immune infiltrated 'cold' tumors are resistant to currently available ICB therapies. Cytotoxic T lymphocyte-

intratumoral VV_{car}- α CTLA-4 synergized with α PD-1 to reject cold tumors.

Conclusion Our findings demonstrate in vivo proof of concept for spatial restriction of Treg depletion-optimized immune checkpoint blocking, vectorized α CTLA-4 as a highly effective and safe strategy to target CTLA-4. A

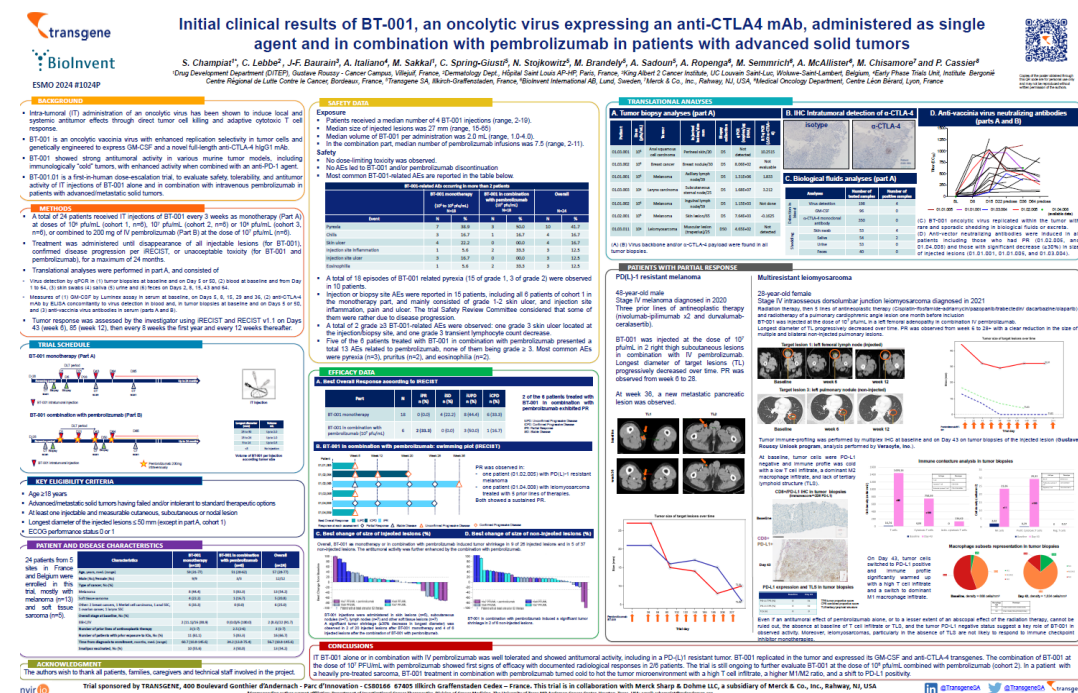
Winner of the 2022 JITC Best Oncolytic and Local Immunotherapy Paper Award



Clinical responses in 2/6 refractory patients when given in combination with pembrolizumab

Phase 1/2a open-label, multicenter, dose-escalation study of BT-001 Part B presented at ESMO September 2024

- **BT-001 induces tumor regression** in patients who **failed previous anti-PD(L)-1 treatment**
- In a patient with a **heavily pretreated leiomyosarcoma**, BT-001 was able to modulate the tumor microenvironment, turning a **“cold” tumor to “hot”**, enhancing the potential of T cell infiltration and a shift to PD(L)-1 positivity
- Early signs of efficacy with **clinical responses** observed with BT-001 in combination with KEYTRUDA® (pembrolizumab), in **2 of 6 patients** who failed previous treatment



BT-001:

PHASE 1/2A OPEN-LABEL, MULTICENTER, DOSE-ESCALATION STUDY

Ongoing phase

Phase 1A Dose Escalation

BT-001 IT (18 pts)
Metastatic/advanced solid tumors
 3 doses

COMPLETED

Phase 1B Dose Escalation

BT-001 IT + Pembrolizumab (12 pts)
Metastatic/advanced solid tumors
 RDPB

ONGOING

Phase 2a Expansion Cohorts

BT-001 IT + Pembrolizumab
Tbd: Soft tissue sarcoma, Merkel cell carcinoma, Melanoma, Triple negative breast cancer, Non-small cell lung cancer
 RDPB

PLANNED

Main Eligibility Criteria

- 1 injectable lesion 25-50mm in diameter
- ECOG 0-1
- Failed or not eligible for standard of care

Participating Countries

- France, Belgium
- IND approved in US





KEY CATALYSTS 2024 - 2025

Expected key clinical milestones 2024-2025

TNFR2 platform

BI-1808
single agent Ph 2a data

BI-1910 solid tumors
single agent Ph 1 data

BI-1808
further single agent Ph 2a data

BI-1808
pembro combo Ph 2a data

BI-1910 solid tumors
single agent Ph 2a data

BI-1910 solid tumors
pembro combo Ph 1 data

YE 2024

2025

**BI-1206 in NHL + ritux +
acalabrutinib Ph 2a data**

**BI-1206 in NHL + ritux +
acalabrutinib Ph 2a data**

BI-1206 (SC) solid tumors
pembro combo Ph 1 data

BI-1607 solid tumors
triplet Ph 1b data

FcyRIIB platform



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