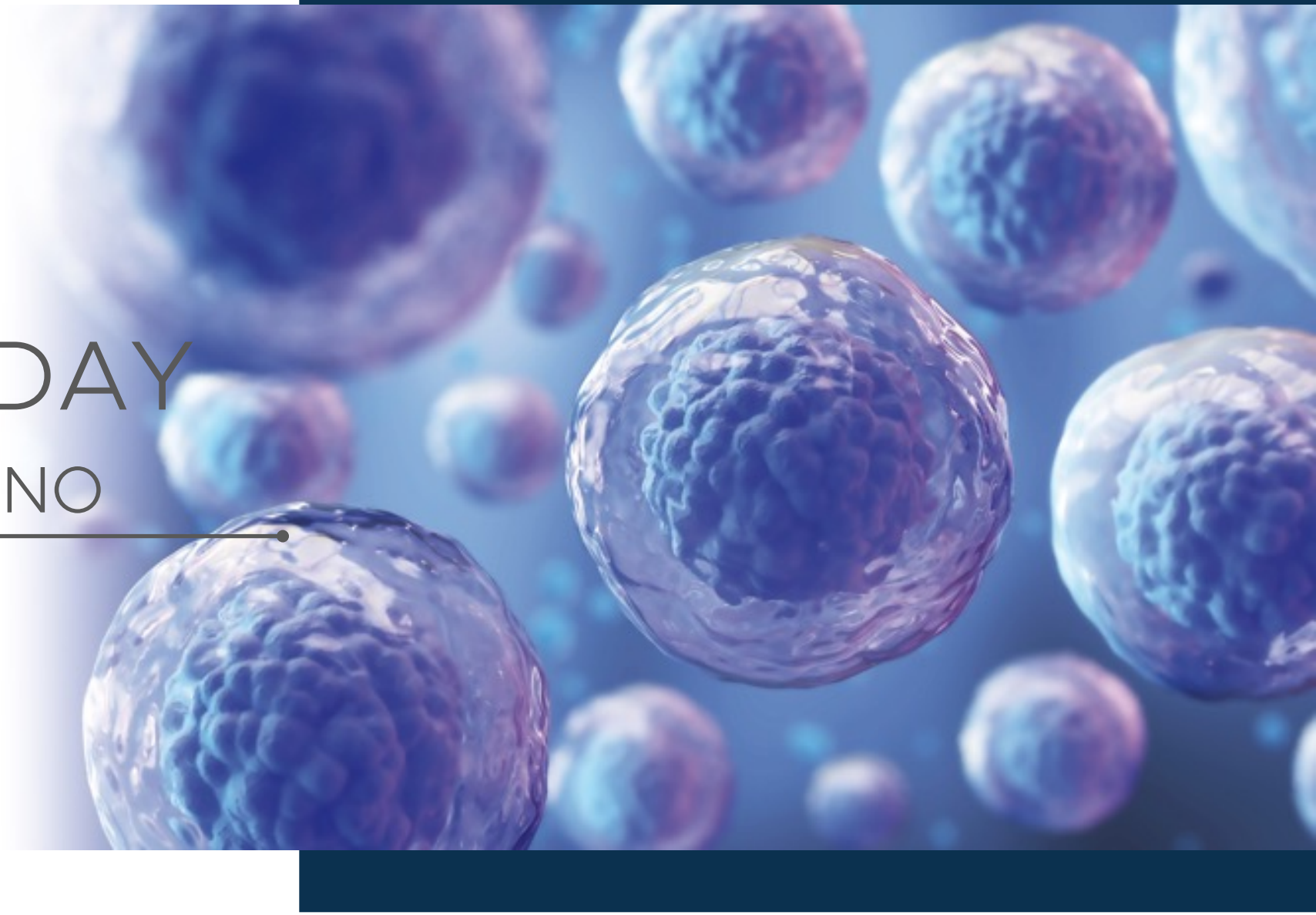
genenta science



INVESTOR DAY

PORTRAIT - MILANO

NASDAQ: GNTA

30 November 2023

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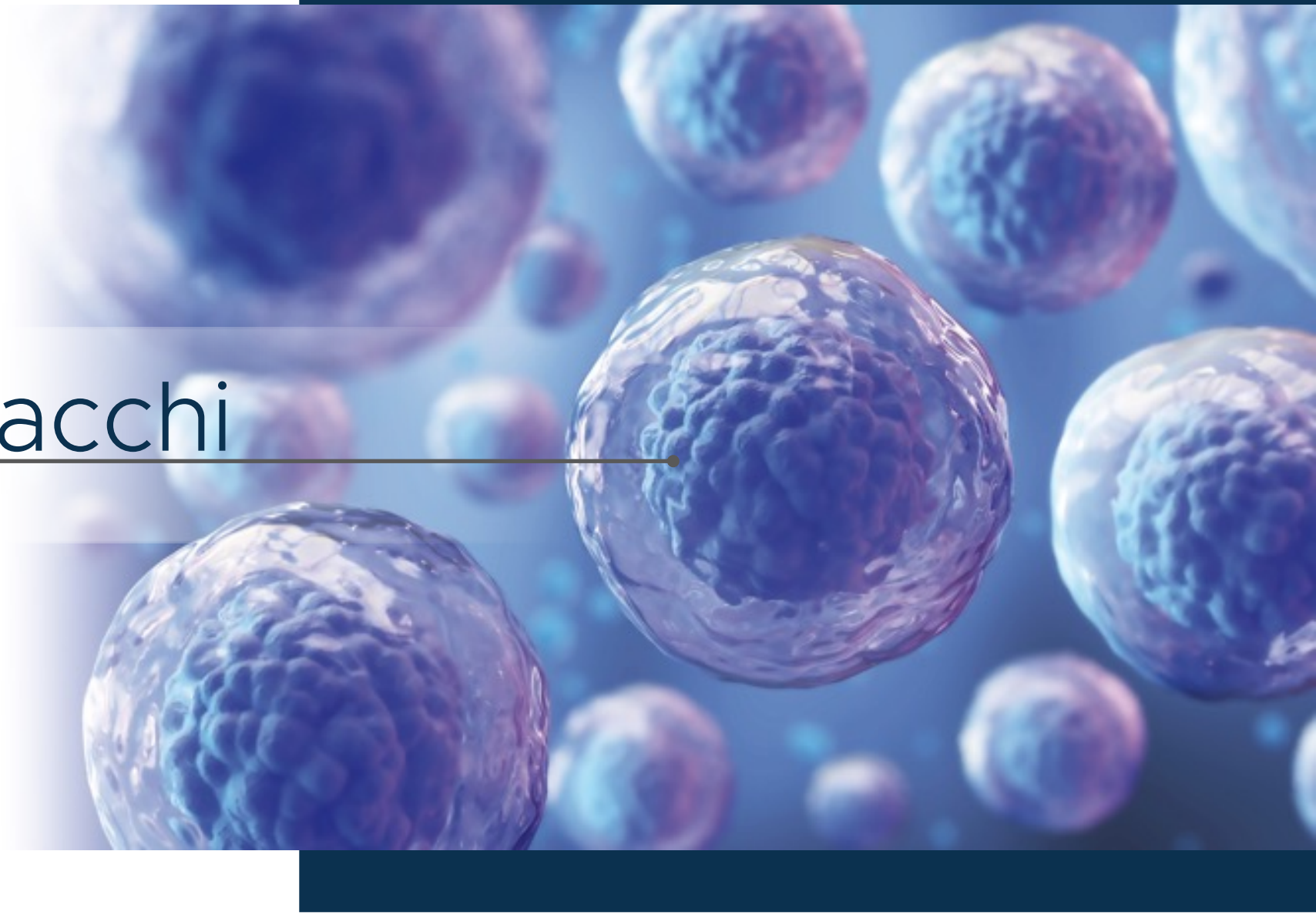
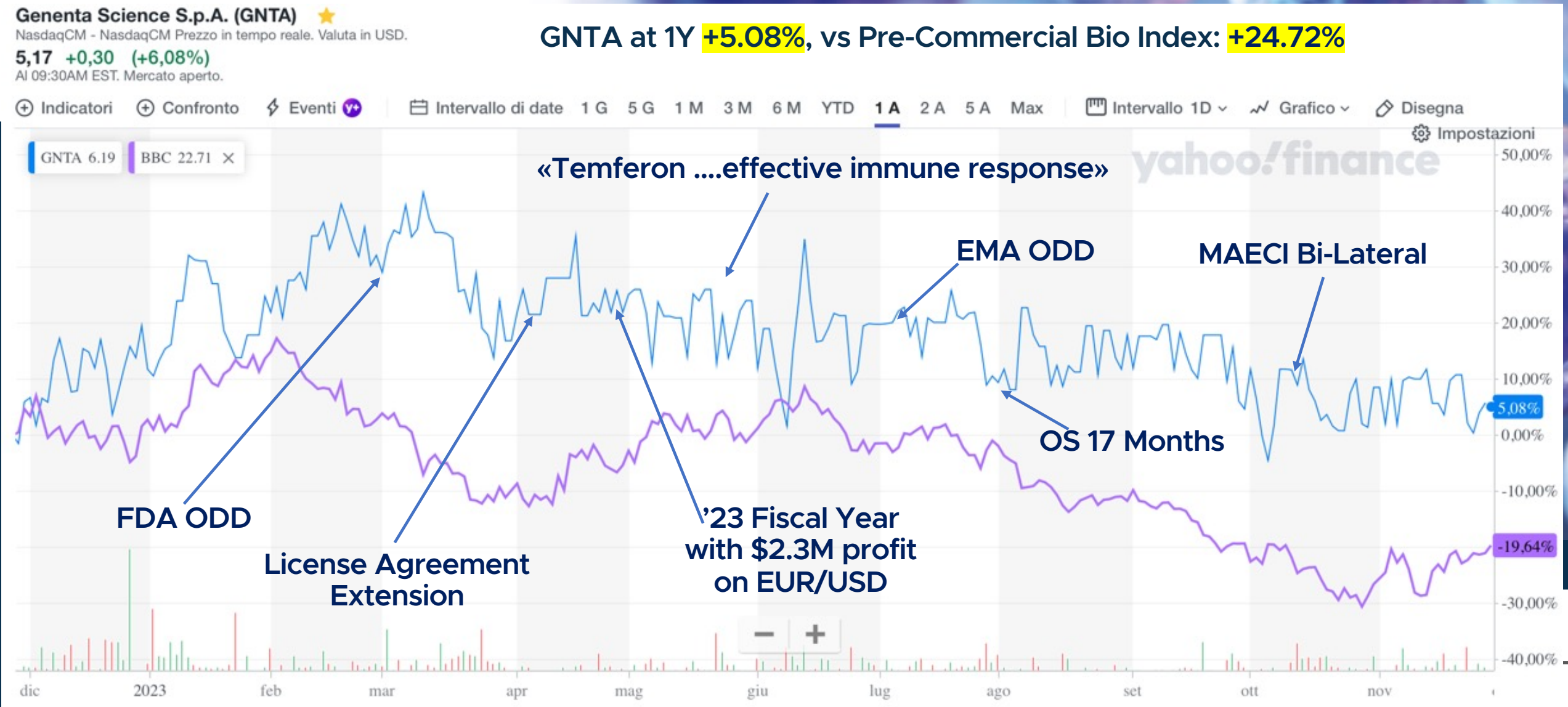


Pierluigi Paracchi

CEO and Co-Founder

Last Year in Review: Key Milestones and Achievements



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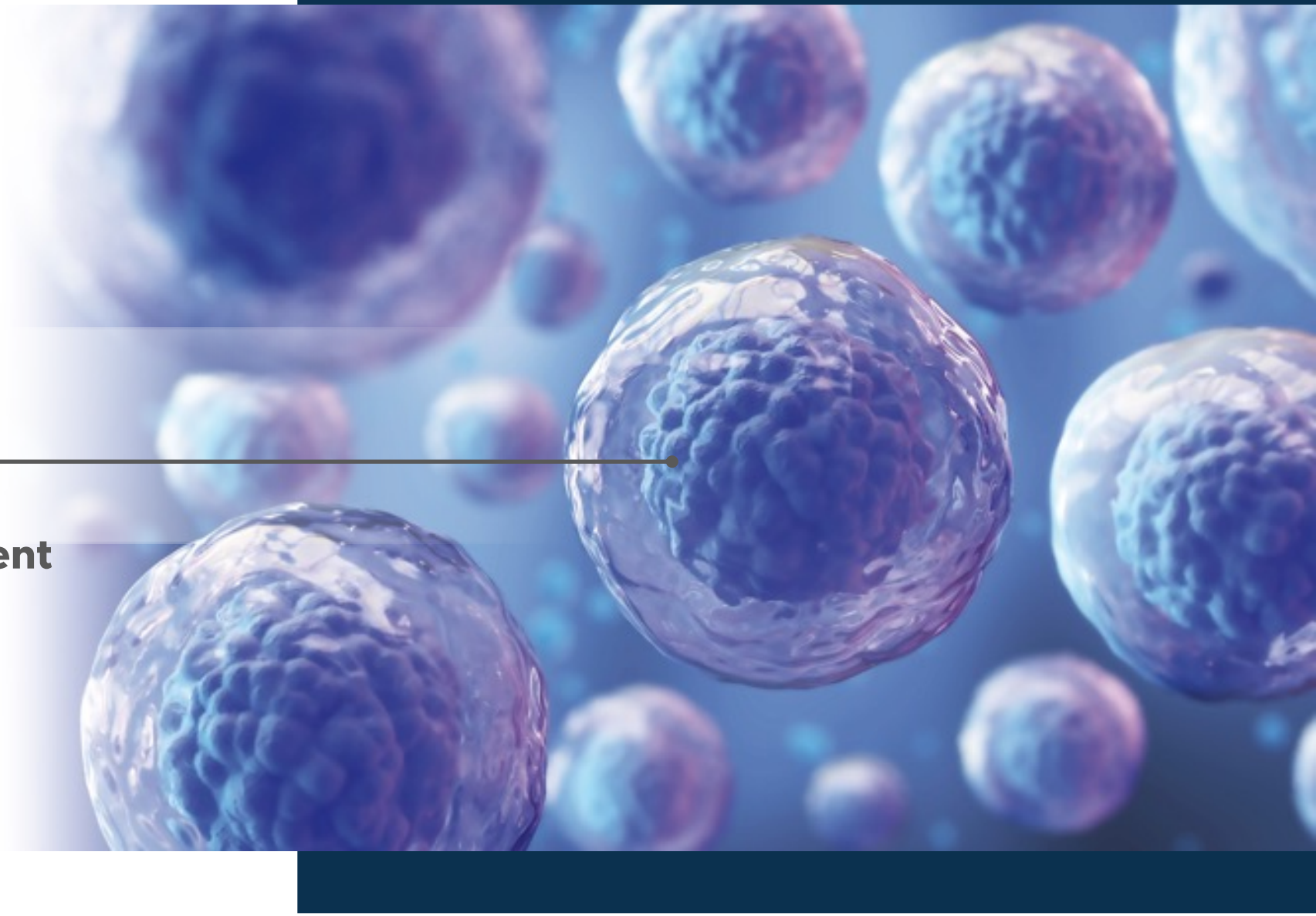
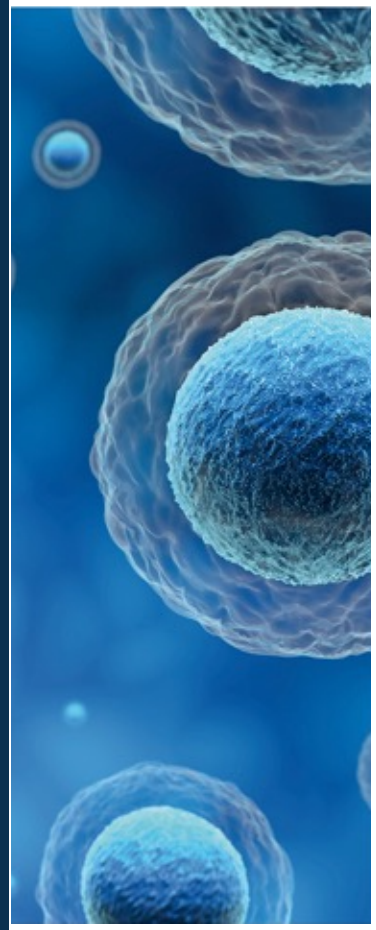


Carlo Russo

CMO & Head of Development

TEMFERON Clinical Programs



CLINICAL ACTIVITIES

REGULATORY ACTIVITIES

MANUFACTURING

TEM-GBM

- 21st patient dosed

2nd Indication GU Cancers

- Pre-CTA submitted – Meeting expected by the end of the year

TEM-GBM ODD granted by FDA & EMA

- FDA ODD granted on 1 March 2023
- EMA ODD granted on 20 June 2023

DP & LVV Manufacturing Processes

- Tech Transfer of DP to Bresso AGC facility - **COMPLETED**
- 48L LVV scale up – **COMPLETED**
  - Full scale Development batch manufactured and released

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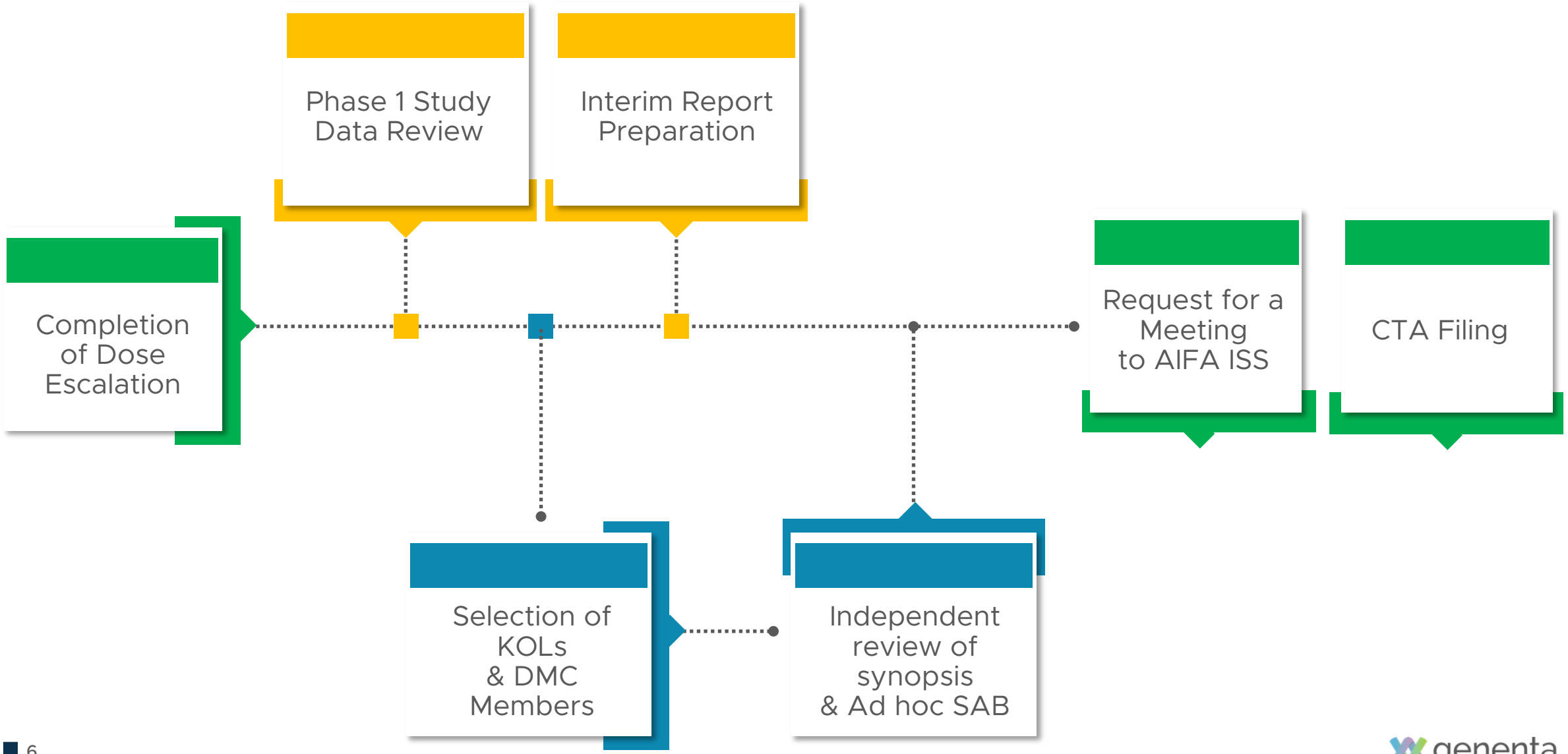
Phase 2 study in Glioblastoma Multiforme Timeline



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Phase 2 Identified Clinical Centers

SELECTED CLINICAL SITES	NEUROSURGERY UNIT	HAEMATOLOGY UNIT
Ospedale San Raffale - Milano*	✓	✓
Istituto Neurologico C. Besta - Milano	✓	
Humanitas – Milano	✓	✓
AOU Città della Salute e della Scienza - Torino*	✓	✓
Istituto Oncologico Veneto - Padova	✓	✓
Policlinico Gemelli - Roma*	✓	✓
Bologna - IRCCS Istituto delle Scienze Neurologiche	✓	

* CAR-T program

Centers engaged in Phase I

Centers identified for the Phase II (preliminary discussion performed)

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TEM-GBM STUDY

Interim Clinical Data

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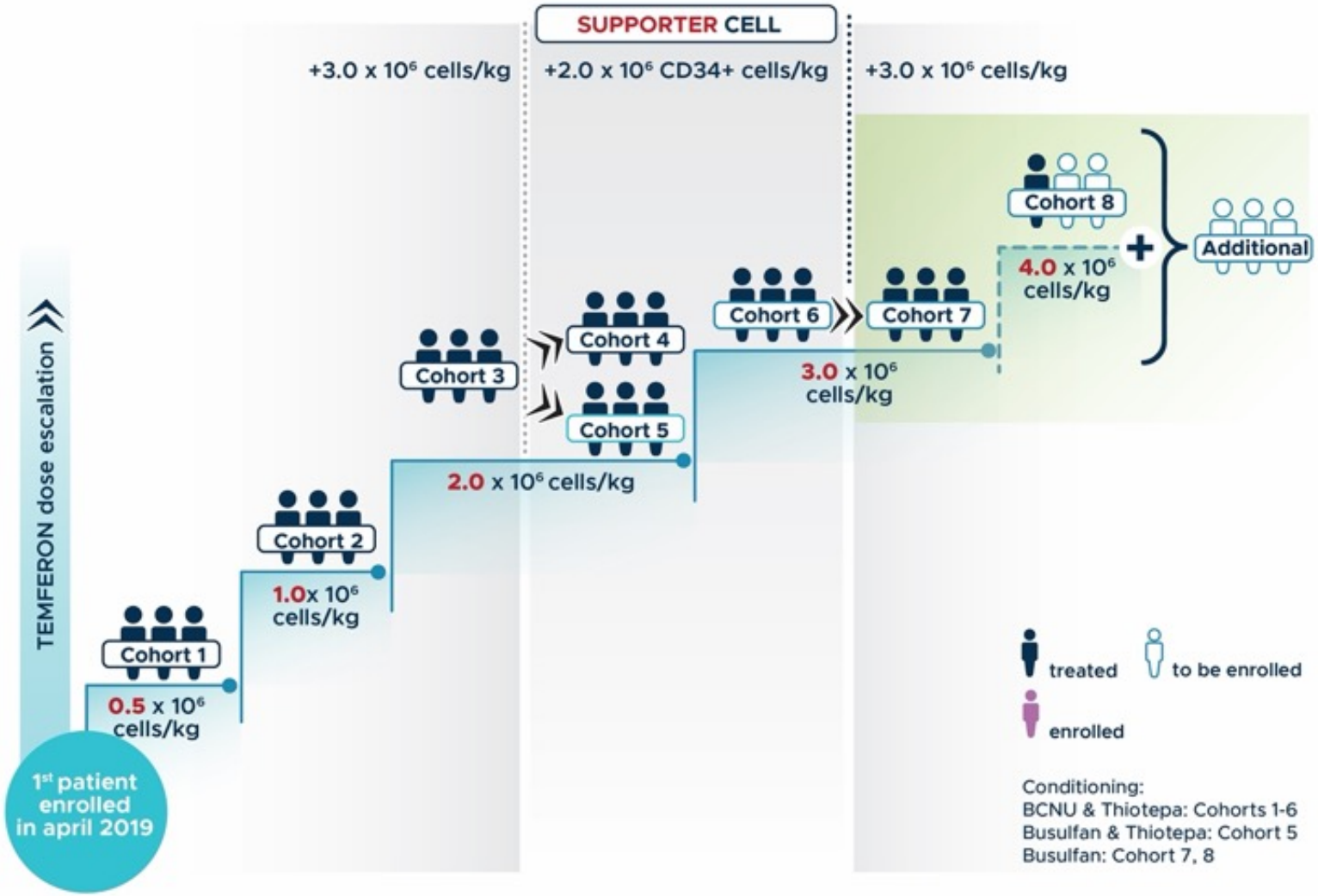
Temferon Phase 1/2a Design in Glioblastoma Multiforme

A multi-center, open-label, dose escalation & extension study in GBM patients with unmethylated MGMT promoter



KEY INCLUSION CRITERIA

- Histologically confirmed, **newly diagnosed supratentorial glioblastoma** with **unmethylated MGMT** gene promoter.
- Patients have undergone **complete** or **partial tumor resection** and are eligible for adjuvant radiotherapy.
- **18-70** years old, in **good clinical condition** (ECOG 0-1, KPS>70%), life expectancy >6mths, **adequate organ function.**

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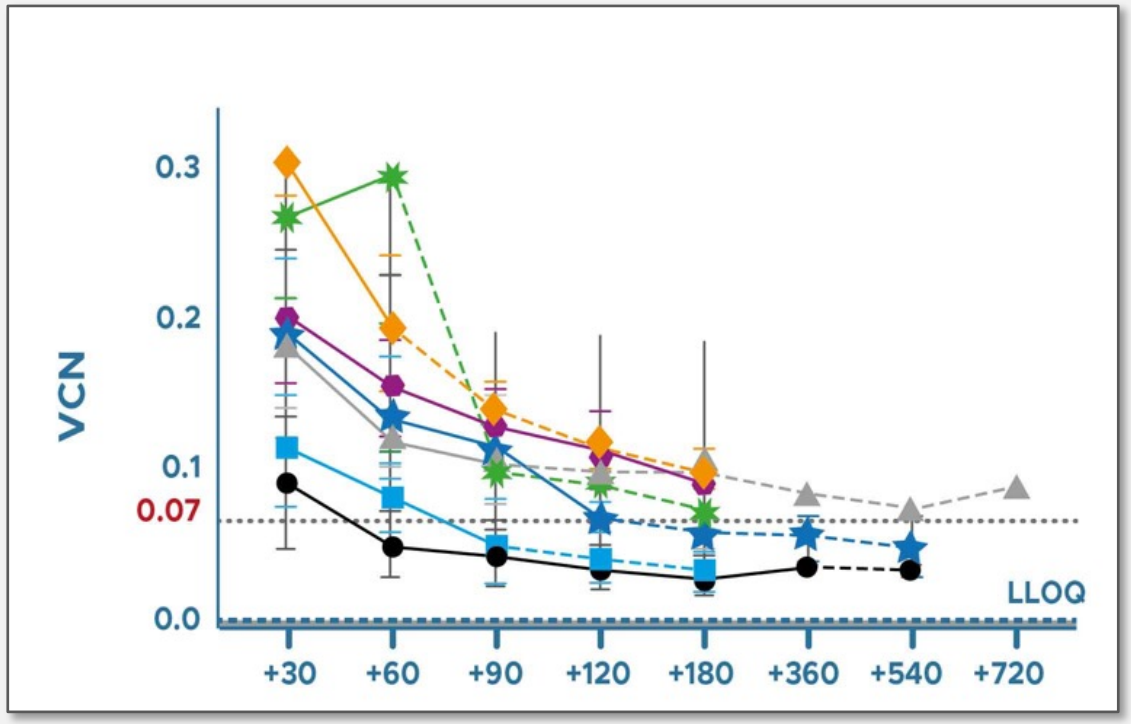
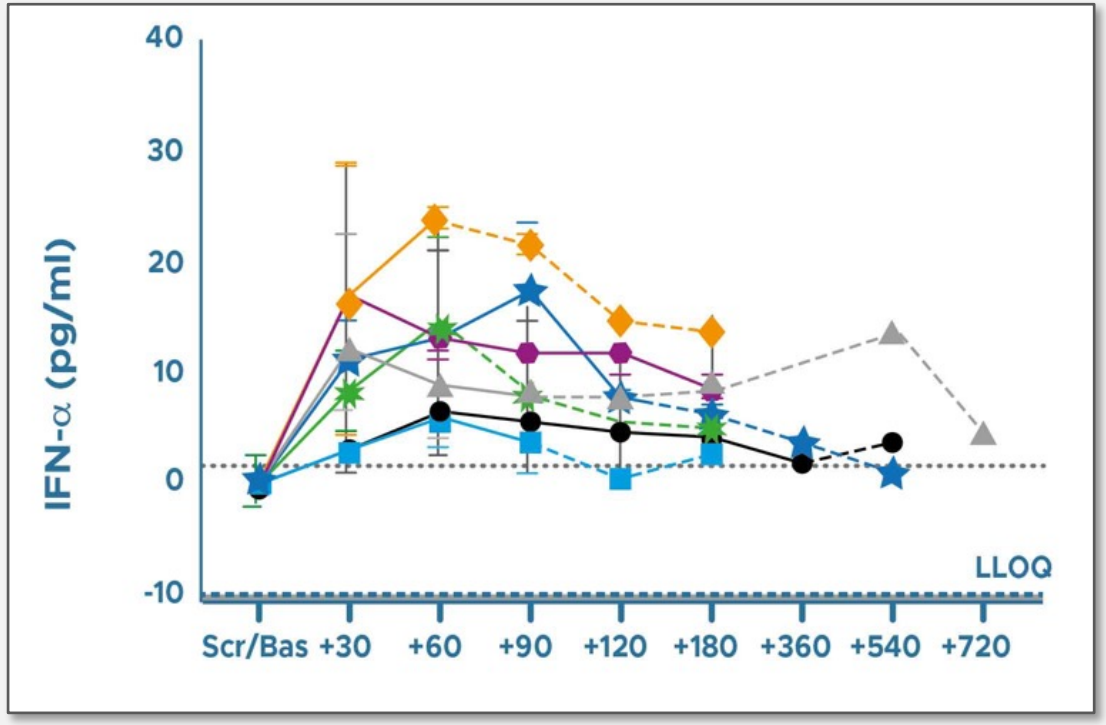
Single Temferon Dose: Durable and Below Tolerability Threshold

CD14



PLASMA



Dashes line connect timepoints with less than 3 measurements

Cohort 1 Cohort 2 Cohort 3 Cohort 4 Cohort 5 Cohort 6 Cohort 7

Engineered myeloid cells stabilize by day +90 and persist in blood with tightly regulated IFN-α expression (as shown by barely detectable IFN-α levels in the blood plasma in the pg/ml range)

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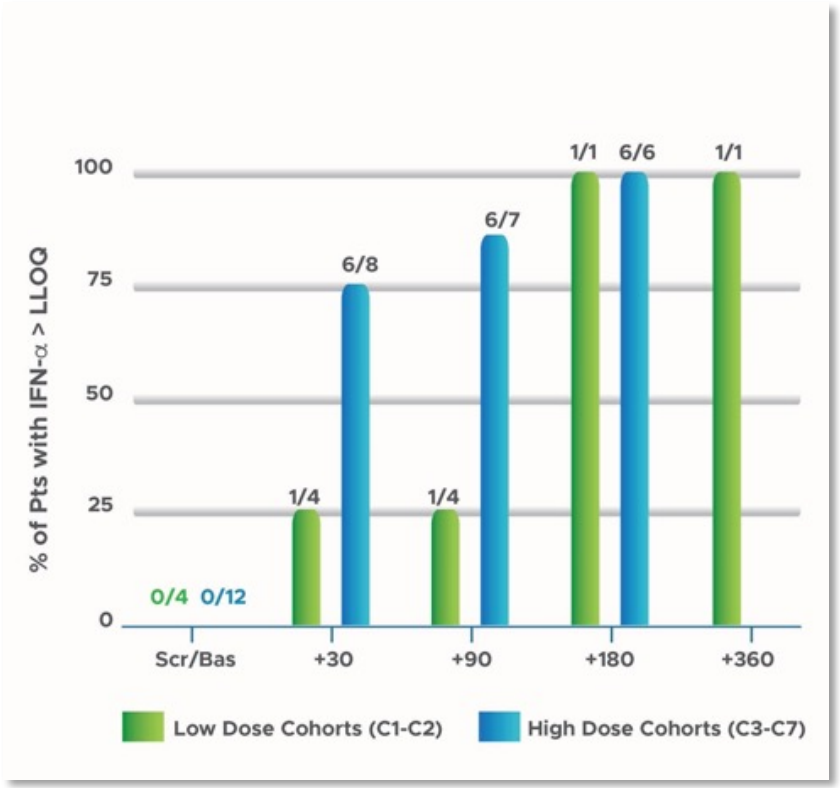
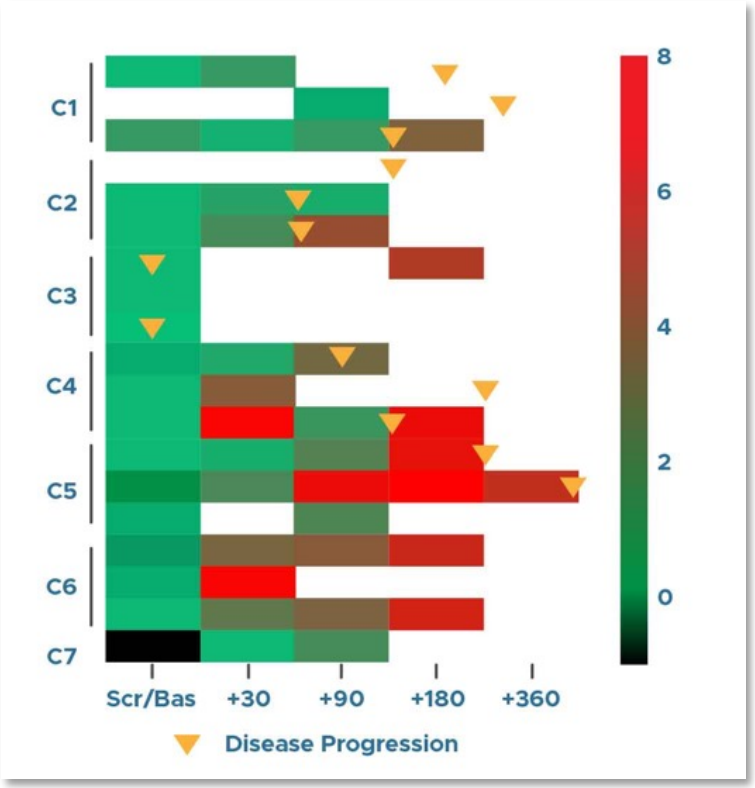
Raised IFN-α concentrations in the CSF are potentially related to TEMs Recruitment

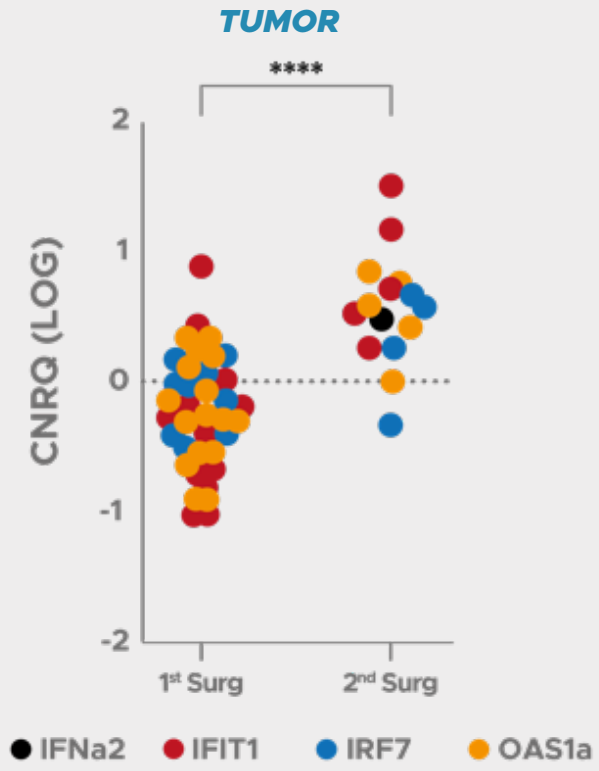
% of Pts with IFN-α > LLOQ



IFN-α concentration in CSF (pg/ml)



Interferon Stimulated Genes in Tumor Tissue



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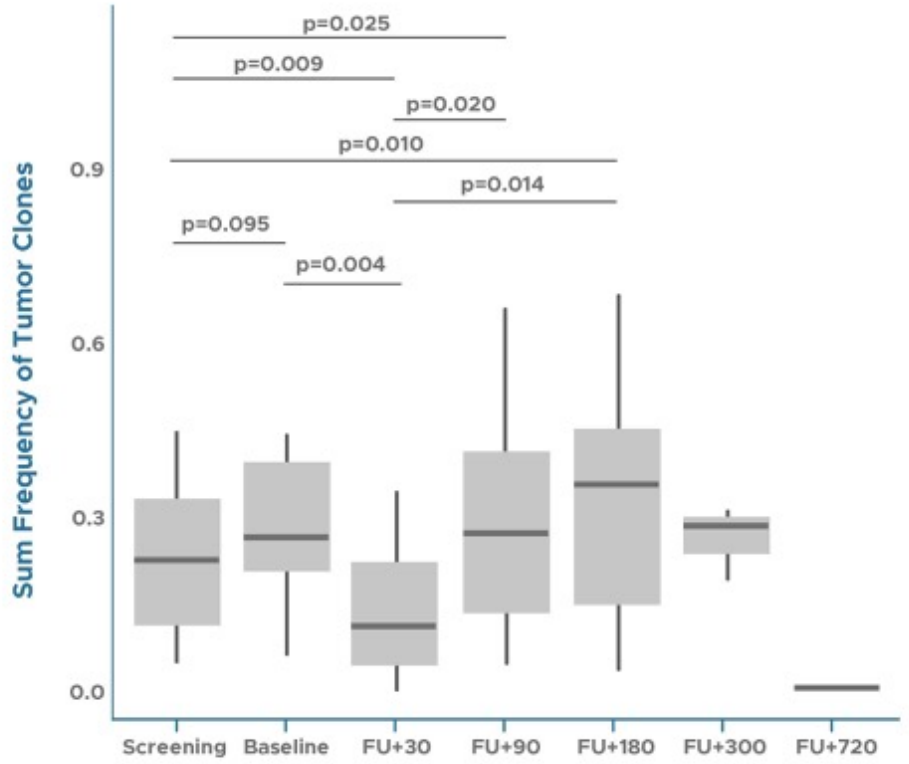
Induction of Potential Immune Response
T Cells Expand and Infiltrate GBM Tumor

T CELL CLONES FROM THE TUMOR CAN OFTEN BE DETECTED IN THE BLOOD

- Contraction at day +30 in the blood (ASCT conditioning)
- Rebound after 3-6 months

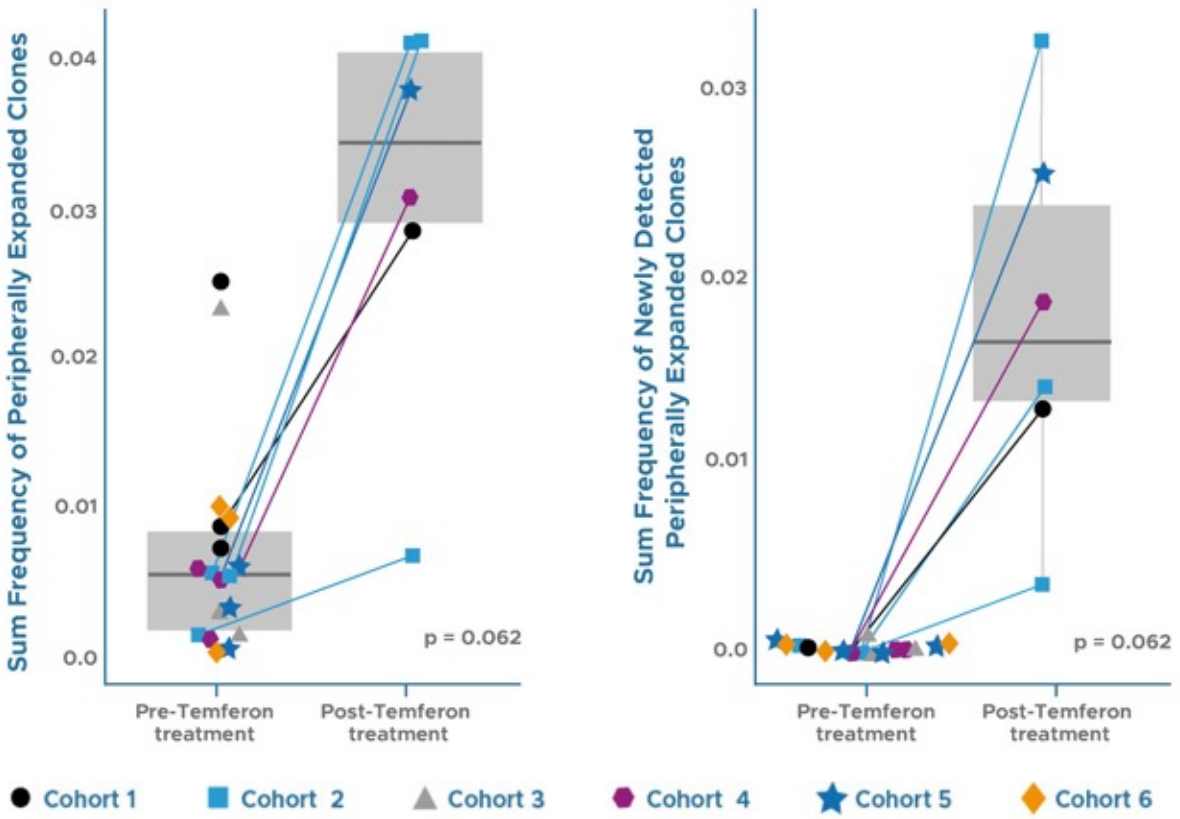


p-values from uncorrected paired Wilcox tests

EXPANDED PERIPHERAL T CELL CLONES ARE INCREASED AT 2nd SURGERY

Pre-existing peripheral T cells clones

Newly-detected peripheral T cells clones



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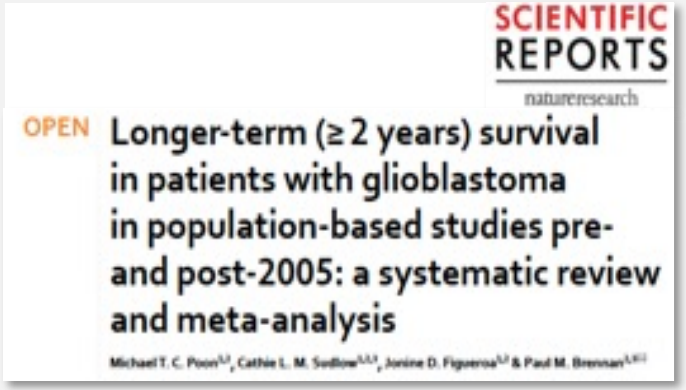
Survival rate at 2 Years in Temferon GBM Trial is Higher than in Published Reports


SCIENTIFIC REPORTS
nature research

OPEN **Longer-term (≥ 2 years) survival in patients with glioblastoma in population-based studies pre- and post-2005: a systematic review and meta-analysis**

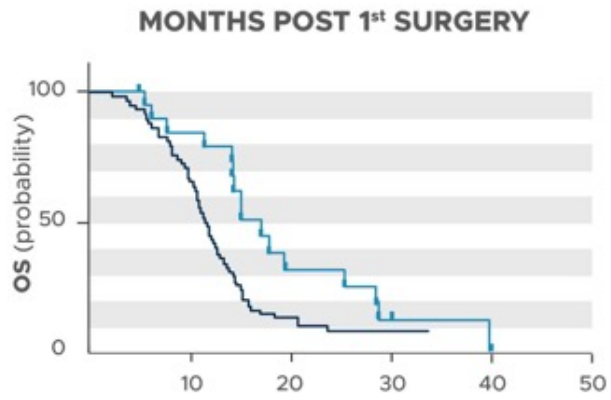
Michael T. C. Poon[1,2], Cathie L. M. Sudlow[1,2,3], Jonine D. Figueroa[1,2] & Paul M. Brennan[1,4]

§The study included all the all population-based studies reporting overall survival at ≥ 2 years in adults with glioblastoma without taking into consideration the methylation status.

	Deaths/ patients	Hazard ratio (95% CI)	Median (months; 95% CI)	2 years (%)	3 years (%)	4 years (%)	5 years (%)
MGMT unmethylated							
Radiotherapy	54/54	1·0	11·8 (10·0–14·4)	1·8 (0·1–8·6)	0	0	0
Combined	54/60	0·6 (0·4–0·8)	12·6 (11·6–14·4)	14·8 (7·2–25·0)	11·1 (4·7–20·7)	11·1 (4·7–20·7)	8·3 (2·7–18·0)
MGMT methylated*							
Radiotherapy	43/46	0·5 (0·3–0·7)	15·3 (13·0–20·9)	23·9 (12·9–36·9)	7·8 (2·2–18·3)	7·8 (2·2–18·3)	5·2 (1·0–15·0)
Combined	37/46	0·3 (0·2–0·4)	23·4 (18·6–32·8)	48·9 (33·7–62·4)	27·6 (15·4–41·4)	22·1 (11·0–35·7)	13·8 (4·5–28·2)

Data are percentage survival (95% CI) unless otherwise stated. *HR relative to radiotherapy unmethylated.

Stupp et al., 2009



	2 YEARS
Stupp, et al. Lancet Onc. 2009	14.8%
Poon et al., Scientific Reports 2020§	18%

TEM-GBM	2 YEARS
Patient number	5
% out of 18 pts*	28%

* 3 patients excluded – from Cohort 7 with insufficient follow-up

1 – Hegi et al., N Engl J Med. 2005;

Censored 30th June 2023

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BIOLOGICAL EVIDENCES OF TEMFERON EFFECT ON THE TUMOR MICROENVIRONMENT

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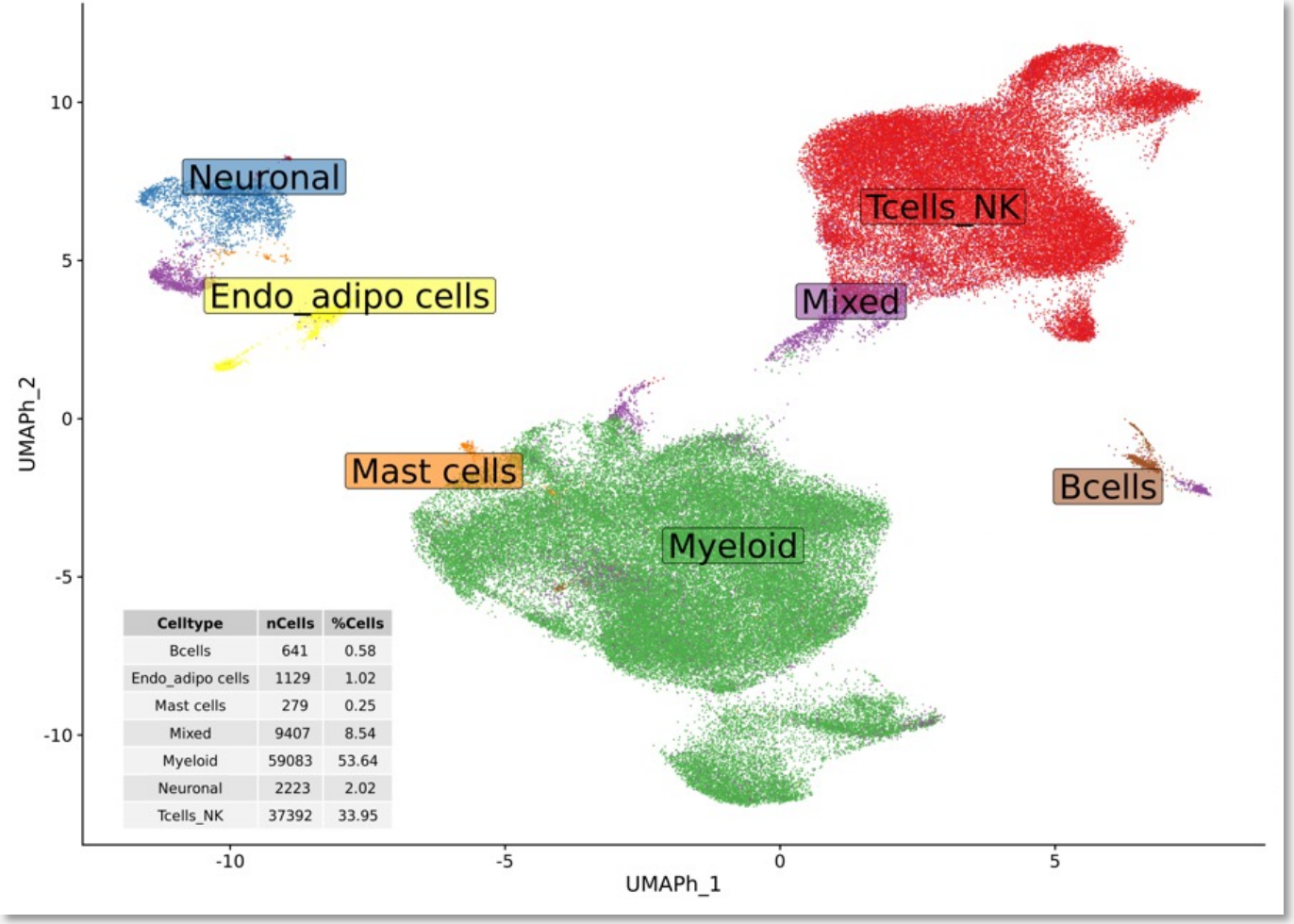
Analysis of the TME of Temferon and SOC treated patients by Single Cell RNA sequencing

Comparison of **5 Temferon patients** and **6 SOC control relapses pts**



Celltype	nCells	%Cells
Bcells	641	0.58
Endo_adipo cells	1129	1.02
Mast cells	279	0.25
Mixed	9407	8.54
Myeloid	59083	53.64
Neuronal	2223	2.02
Tcells_NK	37392	33.95

Identification of the major immune compartments, (myeloid and lymphoid), within the hematopoietic fraction

Collaboration with OSR Neurosurgery

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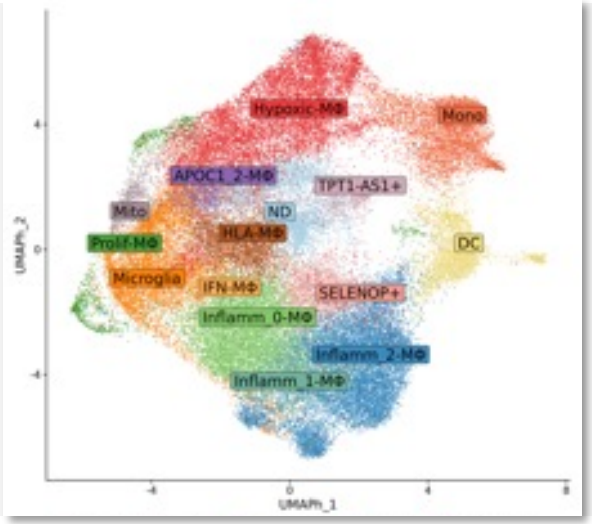
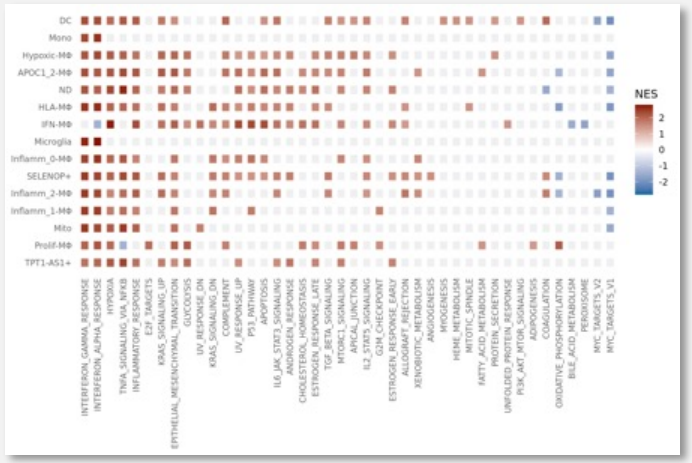
Temferon reprograms the myeloid and T cell compartment in the tumor microenvironment

scRNAseq of GBM TME: Comparison of **5 Temferon patients** and
6 Standard Of Care (SOC – Temozolomide + Radiotherapy) **control relapses pts**

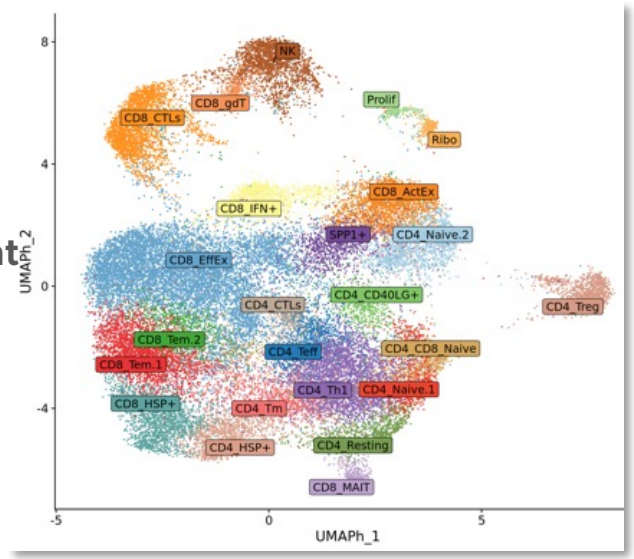
Myeloid compartment

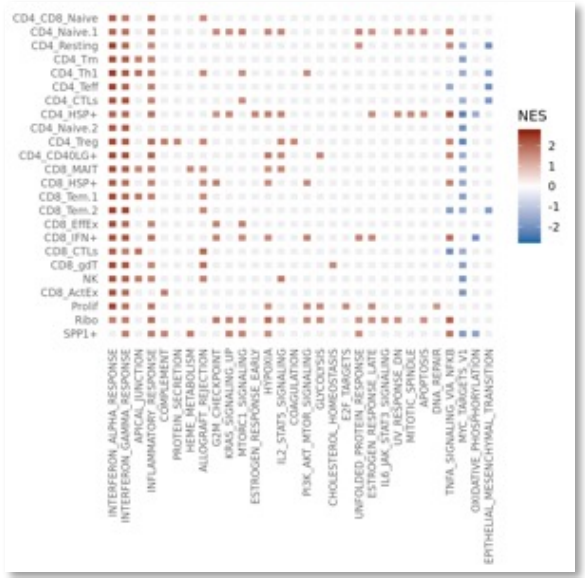




- Broad upregulation of
  - IFN and inflammation hallmarks
  - Hypoxia
  - Epithelial Mesenchymal Transition (EMT)
  - P53/apoptosis
- Limited changes in microglia and monocytes
  - Only IFN response
- General downregulation of MYC targets
  - Decreased proliferation

T cell compartment





- Broad upregulation of IFN and inflammatory responses across most T cell subsets
- Downregulation of proliferation signatures

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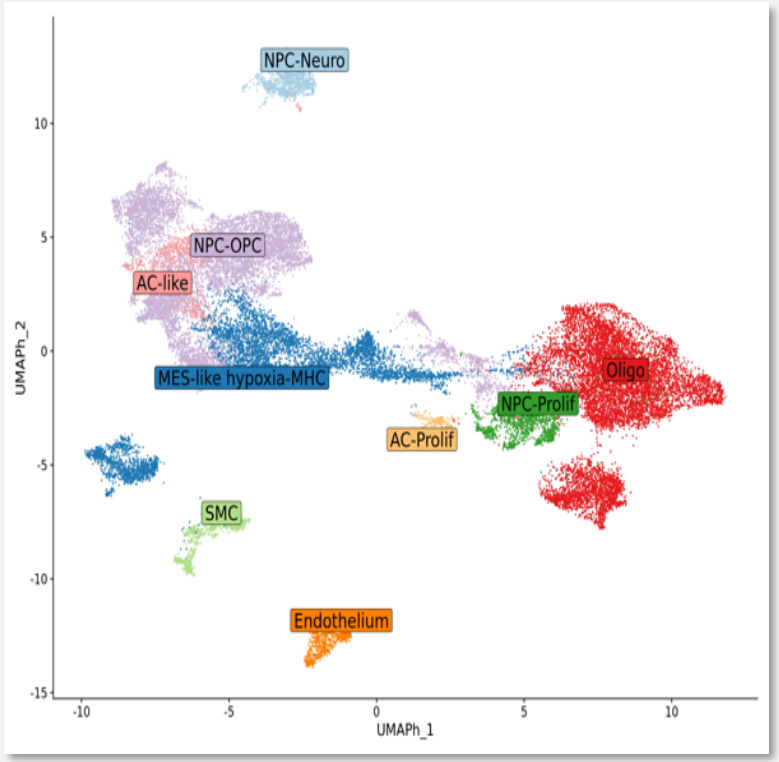
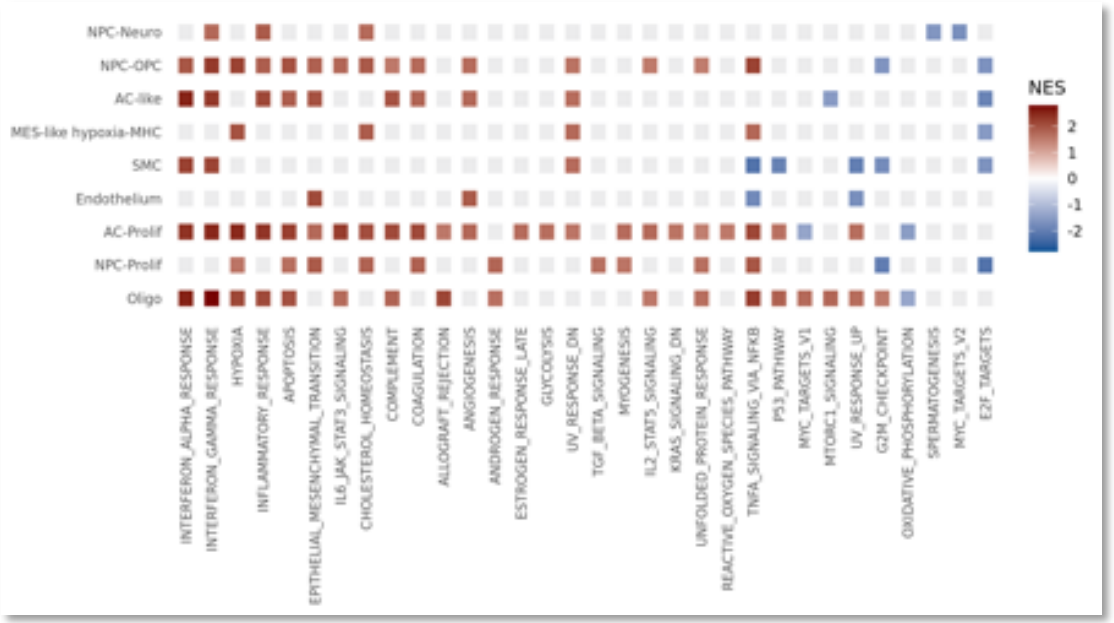
Temferon reaches and affects the CD45- tumor compartment

scRNAseq of GBM TME: Comparison of **5 Temferon patients** and **6 SOC control relapses pts**



AC = Astrocytes Cells;
NPC-OPC = Neuro Precursor Cells – Oligo Precursors Cells
MES = Mesenchymal
Oligo = Oligodendrocytes
Neuro = Neuron
SMC = Smooth Muscle Cells



- Downregulation of proliferation in AC, OPCs and MES-like
- Up-regulation of IFN response in all clusters except for endothelium, MES-like and proliferating NPCs.
- OPC, Oligo and proliferative astrocytes are the most sensitive populations to TEMFERON treatment

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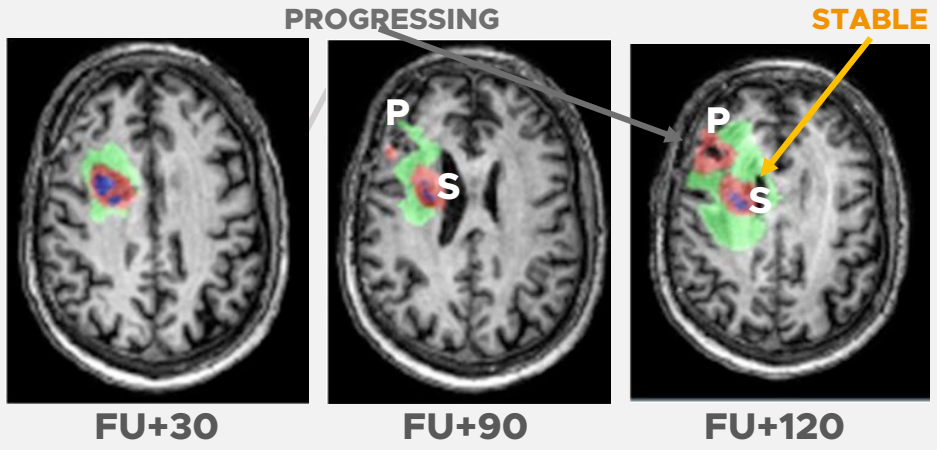
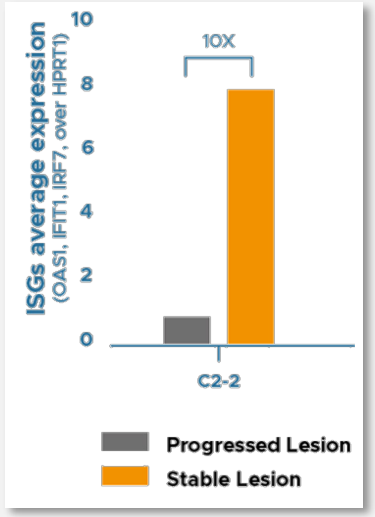
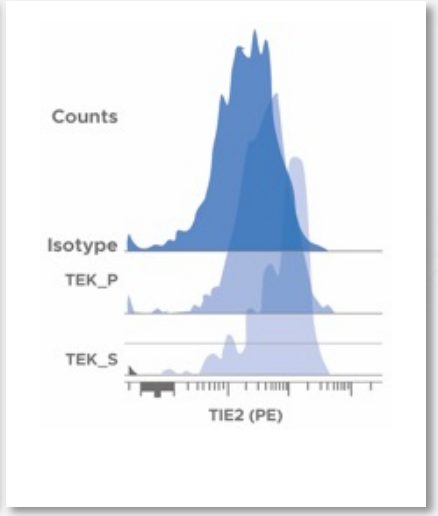
Striking Differences in TIM Landscape between Stable/Progressing Tumor

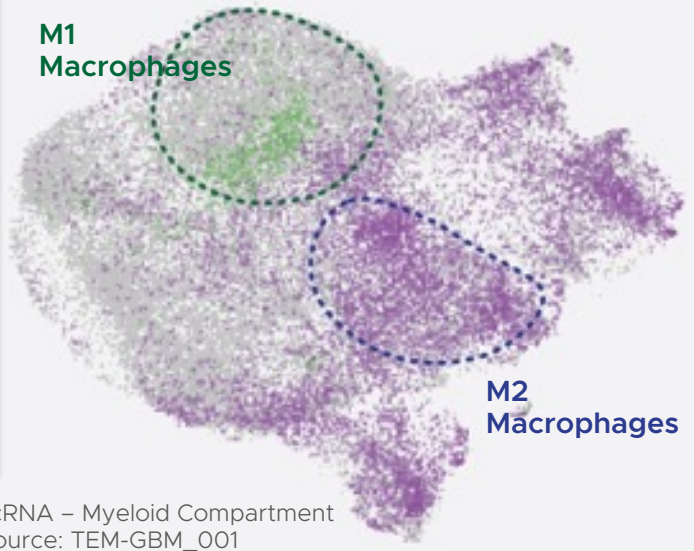
Differential biopises on day +205:







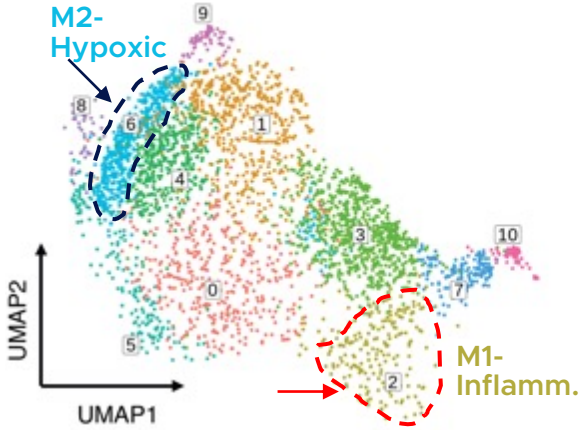
M1 macrophages *are the predominant population in the Stable lesion*



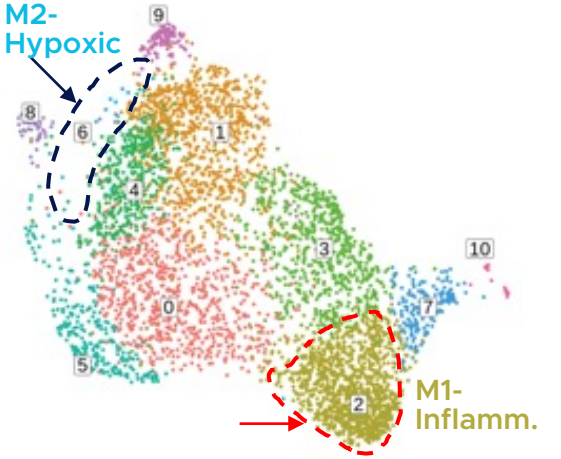
scRNA – Myeloid Compartment
Source: TEM-GBM_001

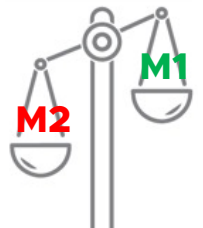
MYELOID GBM TME IN THE MOUSE MODEL

Control



Tie-IFNα (responder)





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Interim Clinical Data in uMGMT GBM: Temferon is Safe and Biologically Active

SAFETY

Detectable but very **low level of IFN-α** (pg/ml range) in the plasma.
Expected and **manageable** adverse events and serious adverse events[1,2] associated with autologous stem cell transplantation and glioblastoma.

TOLERABILITY

No dose limiting toxicities to date.
Rapid engraftment and **hematological recovery** observed in all patients treated (n=22).

BIOLOGICAL ACTIVITY

Current data shows median overall survival of 17 months[2] with a favorable survival rate at 2 years.
Temferon-derived differentiated cells were evident within the peripheral blood 14 days after infusion and were still **detectable at more than 24 months.**
Evidence of a **pro-inflammatory state** in patients that required a second surgery.

1 - The reported serious adverse events (SAEs) for Cohorts 1 to 7 were of the type typically associated with transplant procedures (pneumonia, pulmonary embolism, febrile neutropenia, fatigue, C.diff infection, CMV reactivation, septic shock, graft failure, anemia due to CMV reactivation) or underlying disease GBM (worsening left hemiparesis, seizure, brain abscess, hyperglycemia, sudden death). A suspected unexpected serious adverse reaction (SUSAR) of elevated gamma glutamyl transferase was also reported (spontaneously resolved).
2 - Cutoff date – June 30th, 2023

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IDENTIFICATION & SELECTION OF A 2nd SOLID TUMOR INDICATION

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Criteria for Selection of Temferon 2nd Indication

1. **Easy to biopsy**: potential for multiple samples preferred pre- and post-treatment
2. **Unmet need** even with available cellular therapies (CAR-T) and ICI
3. **IFNα evidence of anti-tumor activity**
4. **Monocyte rich tumour microenvironment**
5. **Rare cancer indication** to allow a potential faster route to registration
6. **Morbidity**
   Sustainability for autologous stem cell transplant (Auto-HSCT).
7. **Prognosis/progression free survival (PFS)**
   Temferon may require 3-6 months to mediate clinically efficacy (bone marrow engraftment > generation of transduced TEMs)
8. **Concomitant medications**
   - Efficacy assessment with multiple combinations of chemotherapy
   - Temferon synergy with other I/O treatments by reprograming TME
   - Need to avoid or reduce immunosuppressants eg steroids
   - Potential synergy with radiotherapy

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Tumor Targets*

	CANCER	STRENGTH	SOC/MEDICATIONS
1	**Renal cell carcinoma (RCC)**: Stage IV	Orphan disease, IFN well established, immunotherapy now well established and potential for combination, opportunity to perform biopsies, monocyte rich	Anti-PD-1 CTLA4 VEGFR
2	**Malignant melanoma**: Stage III-IV	IFNα well established, combo treatment approach, TAMs rich, biopsy feasible	Anti-PD-1 CTLA4 MEK1/2
3	**High grade osteosarcoma**	Orphan disease, limited treatment options after surgery and chemotherapy, biopsy feasible	No licensed, experimental only: VEGFR2 Other TKIs eg VEGFR2/TIE2
4	Non small cell lung cancer (NSCLC): Stage IV	Combo approach with EGFR mutation specific inhibitors or ICIs, high unmet need	Anti-PD-L1 EGFR inhibitors c-MET, RET, ROS-1, ALK inhibitor
5	Advanced Breast Cancer: Stage III-IV a)HER2-ve, ER +ve b)Triple –ve TNBC	Unmet need, preclinical data available with Temferon	Anti-PD-L1 CDK4/6
6	Squamous cell carcinoma (SCC) head and neck: (Stage IV)	Diverse range tumour types: potential for sub-group investigation. High potential for radiation synergy & native tissue biopsy.	Anti-PD-1 In clinical trials: PD-L1, CTLA4
7	Muscle Invasive Bladder cancer (Stage III-IV)	Temferon indicated after failed conventional chemotherapy: co-administration with immunotherapies	Anti-PD-1 Anti-PD-L1 FGFR

*Boyd's space review

Temferon 2nd Solid Tumor Indication
Urinary Cancers

Genenta selected **metastatic clear cell renal cell carcinoma** (mRCC) and **metastatic urothelial carcinoma** (mUC) as additional solid tumor indications for Temferon clinical development

RATIONALE

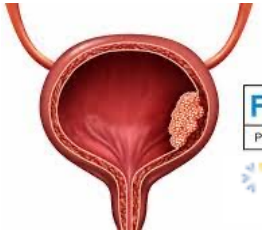
Strong historical evidence to support potential Temferon efficacy

- Until 2005, systemic administration of IFN-α and IL-2 were SOC treatment for mRCC.
- IFN-α in mRCC was associated with a survival benefit compared to controls [644 mRCC pts: OR for death at 1 year=0.56 (95%CI 0.40 to 0.77)[1]]
- Systemic IFN-α use limited in the past by the systemic toxicities
- IFN-α as an intravesical therapy for UC has been evaluated over many decades with variable results. Short drug exposure time rather than inherent lack of anti-tumour activity[2]

SOLUTION

Temferon has been designed to attenuate systemic toxicity associated with IFN-α and to achieve greater therapeutic benefit within the TME

Targeted IFN-α delivery as an innovative and clinically relevant approach



FERRING PHARMACEUTICALS

ADSTILADRIN (nadofaragene firadenovec-vncg)

BCG-unresponsive non-muscle invasive bladder

- CR in 51% of patients with *in situ* carcinoma by three months[3]

Temferon reprograms the TME and acts directly on tumors cells and neo-angiogenesis

1. Coppin et al. 2004; 2. Duplisea 2019; 3. Adstildarin USPI 2023

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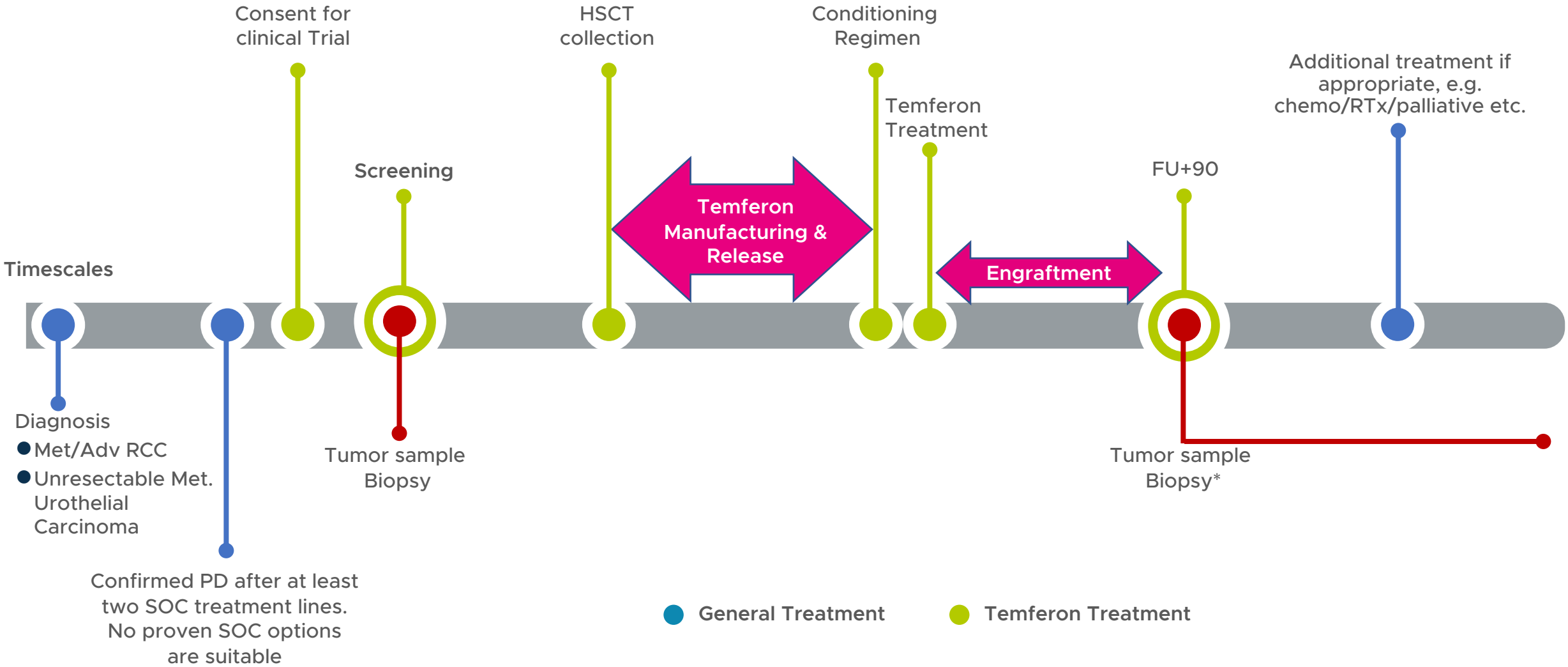
Temferon Study Design in Refractory Advanced Genitourinary Malignancies



* After FU+90 biopsy may be taken periodically at disease progression and as tolerated by the patient

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2nd Indication CTA Filing Process