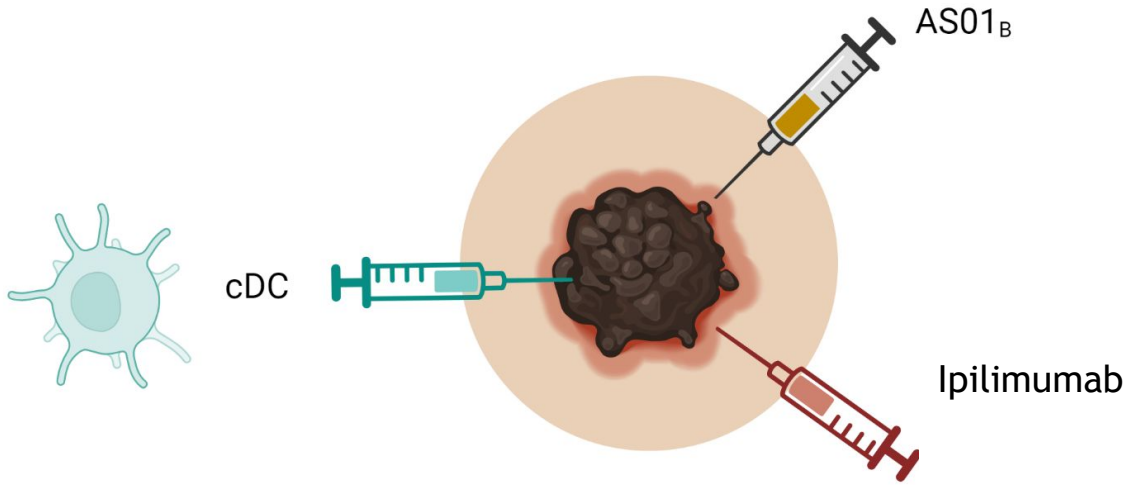
A PHASE I CLINICAL TRIAL

Intratumoral autologous myeloid **dendritic cells** with the immunologic adjuvant **AS01$_B$** in refractory advanced **melanoma**



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GENERAL AIM

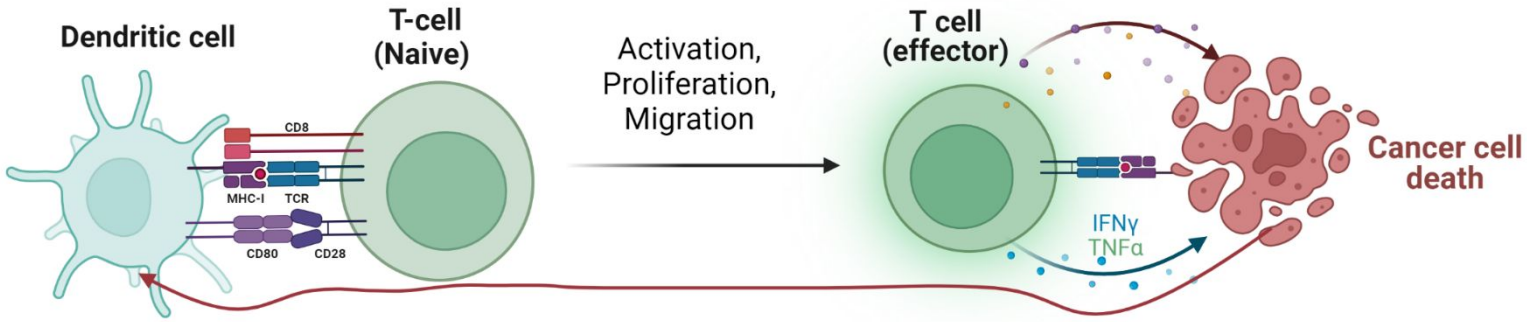
WHY?	To overcome **checkpoint refractory** (80%) cutaneous **melanoma** (4%)[1]
WHAT?	Combining autologous **myeloid dendritic cells**(cDC) with **AS01B**
HOW?	Develop a **novel enhanced intratumoral** combinatorial immunotherapy

Chillean Andes

Based on 3 principles

I. Cancer-immunity cycle

Myeloid dendritic cells initiate and intratumorally relicense T-cells yielding effective tumor eradication[1]



II. AS01B adjuvant

recruits cDC1 and cDC2 with enhanced antigen presentation to resp. $CD8^+$ and $CD4^+$ T-cells[2]

- Developed by GlaxoSmithKline®, used in the prophylactic vaccine Shingrix®
- First-in-human intratumoral application
- Induces a local and transient activation of the innate immune system:
  - MPL-A: Detoxified derivative of lipopolysaccharide from Salmonella minnesota. Signaling through TLR-4.
  - QS-21: presumably through NLRP3 inflammasome complex

1. Salmon, H. et al. Immunity 2016, 2. Bosteels, C.; Fierens, K.; De Prijck, S.; et al. Front Immunol, 2020

Methods

Inclusion: **Metastatic melanoma refractory** to **ICB** and **BRAF/MEK inhibitors** (in case of BRAF V600-mutant melanoma)

IV low-dose **nivolumab** (10mg) D1 and q2W

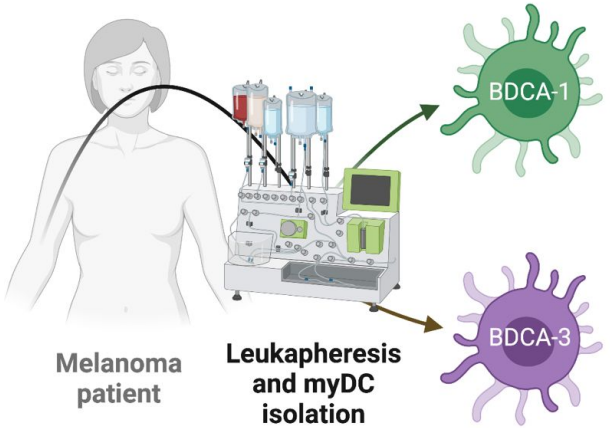
IT **ipilimumab** (10mg); D1 and q1W/q2W
IT **AS01$_B$** (0.5ml); D2 and q1W/q2W
IT **CD1c (BDCA-1)$^+$ / CD141 (BDCA-3)$^+$** myDC; D2

Response evaluation: PET/CT imaging q12W

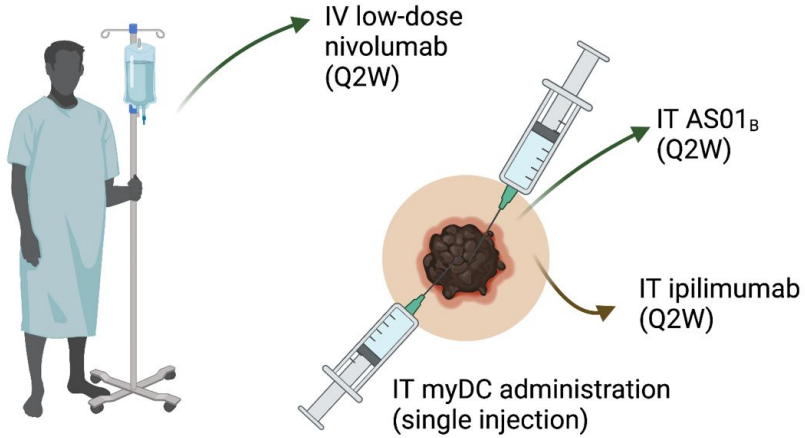
Safety (first-in-human IT application of AS01$_B$)
Feasibility
Early efficacy data: BOR (overall and injected lesion), PFS, OS

Methods

1 **Isolation of BDCA-1 (CD1c)⁺ and BDCA-3 (CD141)⁺ myDCs**

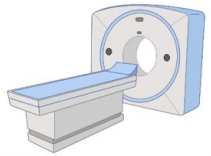


2 **Treatment administration**



3 **Clinical objectives**

Phase Ib



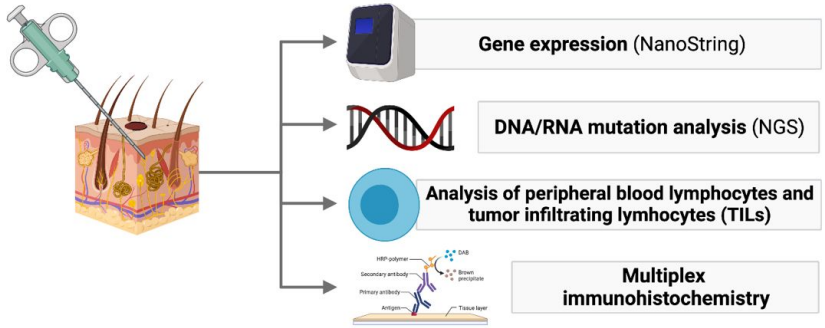
Phase II
Ongoing

- Dose escalation
- Safety (CTCAE v.5)
- Maximum tolerable dose
- Feasibility

→

- ORR (iRECIST)
- PFS
- OS
- Duration of response

4 **Molecular and cellular characterisation**



Results

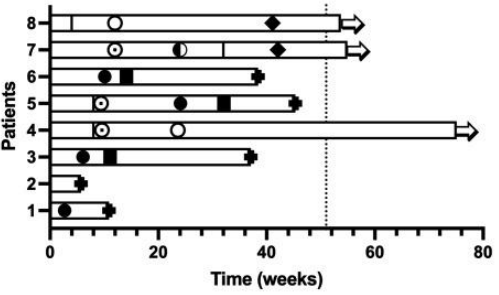
	2-weekly intratumoral therapy	Weekly intratumoral therapy
Baseline characteristics	n=8	n=6
Median age, years (range)	64 (33-83)	55 (35-60)
Female sex, n (%)	8 (100)	3 (50)
ECOG performance status, n (%) 0 - 1	6 (75) - 2 (25)	4 (66) - 2 (33)
Disease stage, n (%) Stage III Stage IV-M1a Stage IV-M1c	 0 4 (50) 4 (50)	 2 (33,3) 3 (50) 1 (16)
Treatment disposition		
Median # of IV treatments Median # of IT treatments	7.5 4.5	5 6

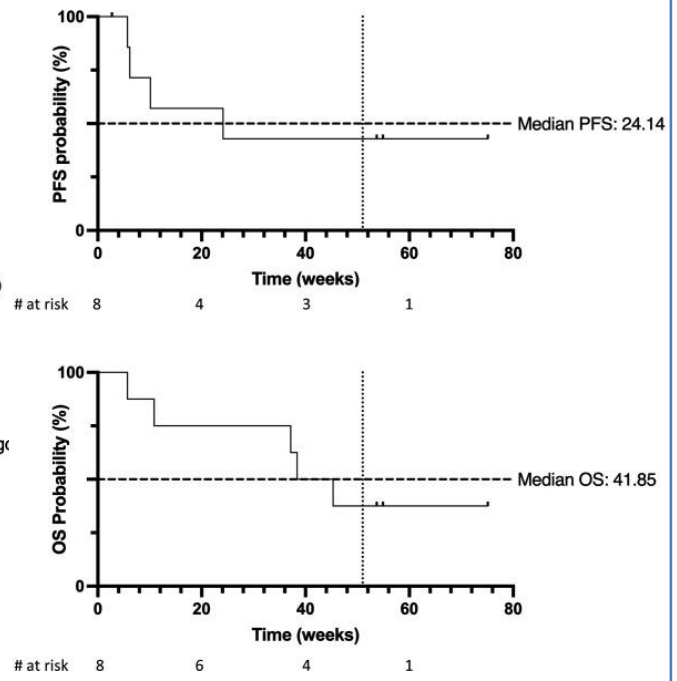
irAE n>1	2-Weekly		Weekly	
Adverse events (grade)	≤3	>3	≤3	>3
Arthralgia	2	0	0	0
Dyspepsia	2	0	0	0
Fatigue	7	0	5	0
Fever	1	0	2	0
Injection site reaction	5	0	10	0
Nausea	2	0	1	0
Pain	5	0	1	0
Intracranial hemorraghe	0	1	0	0
Muscle cramp	3	0	0	0
Ascites	0	0	0	1

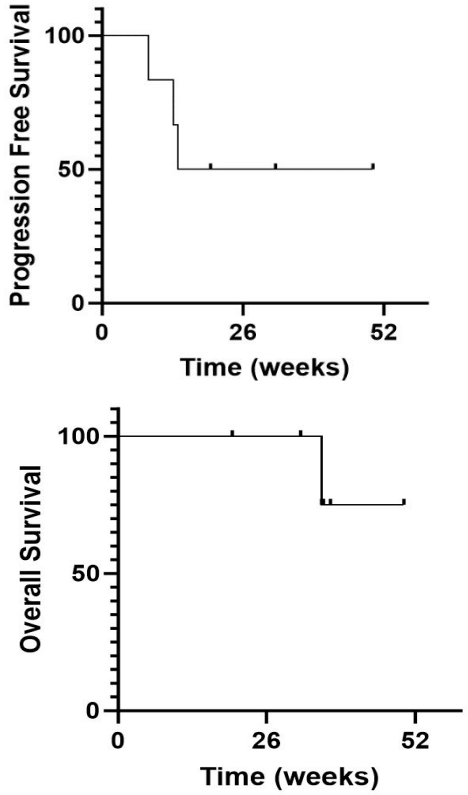
Treatment was **feasible and well-tolerated**,

no unexpected safety signals were observed

Response by iRECIST	2-weekly intratumoral therapy	Weekly intratumoral therapy
Evaluable for response	6	6
Complete response	2	2
Partial response	1	1
Stable Disease	1	0
Progressive disease	2	3 (1 unconfirmed progressive disease)
Disease control rate (CR+PR+SD), n (%)	3 (50)	3 (50)
Regression injected lesion, n patients (%)	4	3

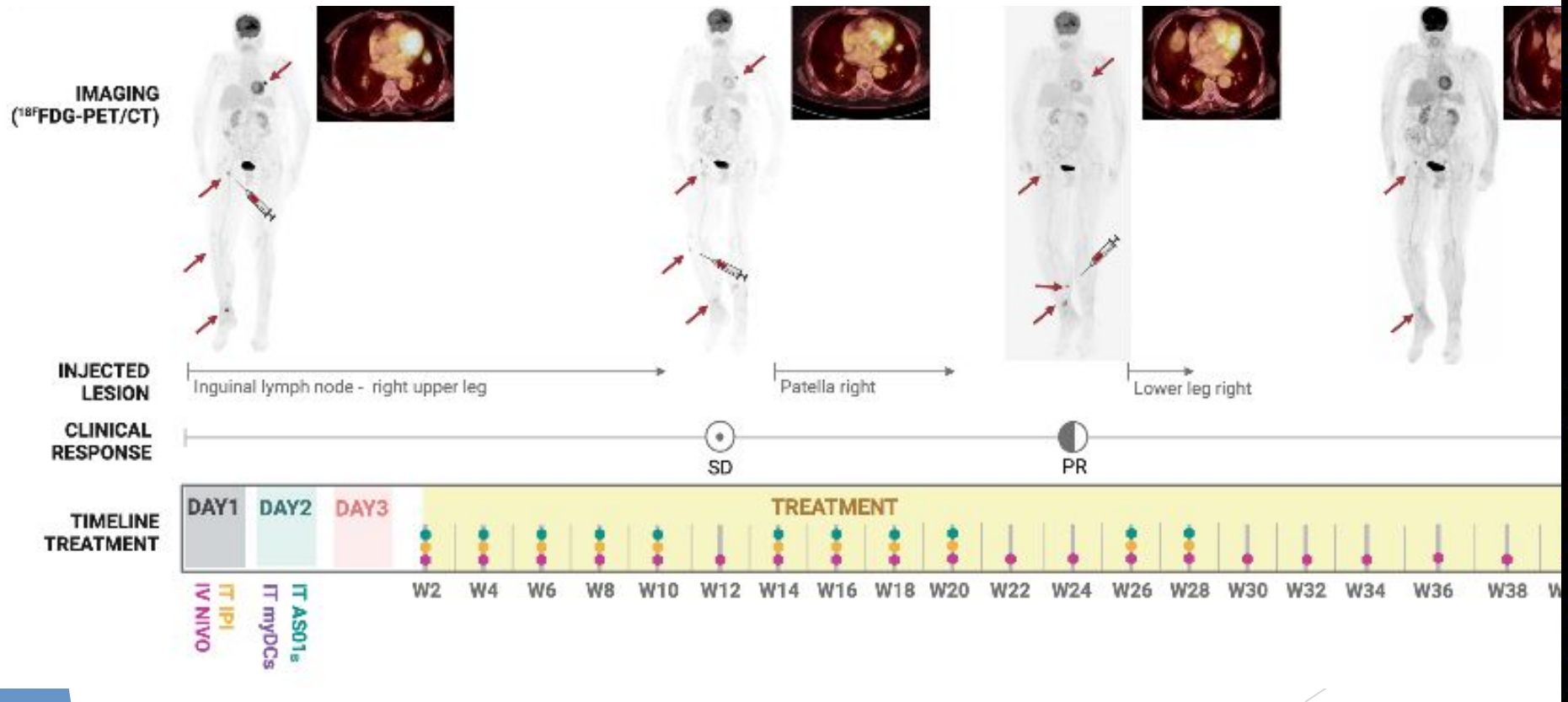


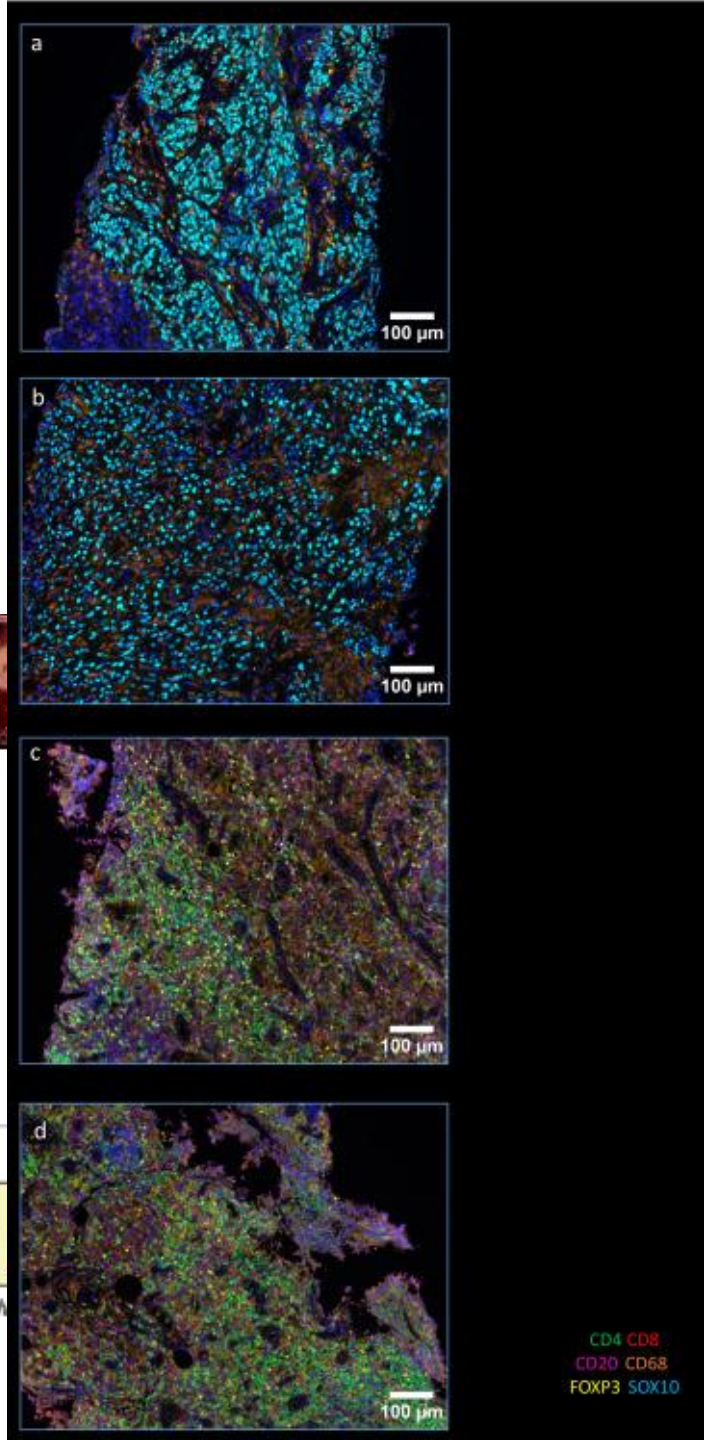




Case illustration

- 75y, Stage **IV - M1c melanoma (leg, lung, lymph node), refractory to ipilimumab, nivolumab, temozolomide**
- May 2022: Inclusion in trial, **injection of inguinal lymph node**
- July 2022: **Pathological CR** in inguinal **lymph node**





Conclusion

- Intratumoral myeloid dendritic cells combined with weekly IT IPI and AS01B, plus low-dose IV NIVO is tolerable and demonstrated a disease control rate of 50% in refractory advanced melanoma.
- The weekly administration regimen is considered the maximum tolerated treatment intensity.
- The trial continues as a randomized phase II trial

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Intratumoral administration of the immunologic adjuvant $AS01_B$ in combination with autologous CD1c $(BDCA-1)^+$/CD141 $(BDCA-3)^+$ myeloid dendritic cells plus ipilimumab and intravenous nivolumab in patients with refractory advanced melanoma

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Affiliations + expand

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