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SOT101, an IL-2/IL-15 Rβγ superagonist, in combination with pembrolizumab in patients with advanced solid tumors: interim safety and efficacy results from the AURELIO-03 dose escalation trial

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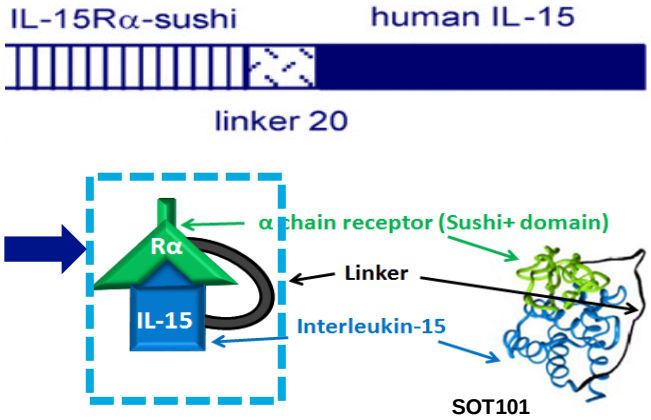
Disclosure Information

Stephane Champiat

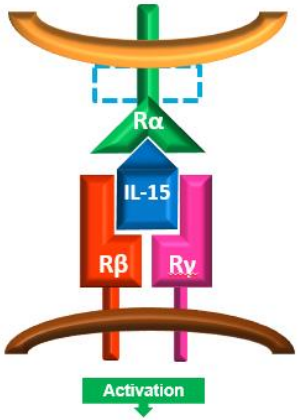
- I have the following relevant financial relationships to disclose:
  - Employee of: Institute Gustave Roussy, Villejuif, France
  - Consultant for: Alderaan Biotechnology, Amgen, AstraZeneca, Avacta, Ellipses Pharma, Oncovita, Seagen, UltraHuman
  - Research Grants from Astrazeneca, BMS, Boehringer Ingelheim, GSK, INCA, Janssen Cilag, Merck, Novartis, Pfizer, Roche, Sanofi
  - Principal Investigator of Clinical Trials for: Abbvie, Amgen, Cytovation, Eisai, Imcheck Therapeutics, Molecular Partners Ag, MSD, Ose Pharma, Pierre Fabre, Sanofi Aventis, SOTIO Biotech, Transgene
  - Honoraria from: Amgen, AstraZeneca, BMS, EISAI, Janssen, MSD, Novartis and Roche
  - Travel and congress: AstraZeneca, MSD, Ose Pharma, Roche, SOTIO
  - Non-financial support (drug supplied) from Astrazeneca, Bayer, BMS, Boringher Ingelheim, GSK, Medimmune, Merck, NH TherAGuiX, Pfizer, Roche
  - My additional disclosures are:
    - As part of the Drug Development Department (DITEP): Principal/sub-Investigator of Clinical Trials for Abbvie, Adaptimmune, Adlai Nortye USA Inc, Aduro Biotech, Agios Pharmaceuticals, Amgen, Argen-X Bvba, Arno Therapeutics, Astex Pharmaceuticals, Astra Zeneca Ab, Aveo, Basilea Pharmaceutica International Ltd, Bayer Healthcare Ag, Bbb Technologies Bv, Beigene, BicycleTx Ltd, Bioalliance Pharma, Blueprint Medicines, Boehringer Ingelheim, Boston Pharmaceuticals, Bristol Myers Squibb, Ca, Celgene Corporation, Chugai Pharmaceutical Co, Cullinan-Apollo, Curevarc, Daiichi Sankyo, Debiopharm, Eisai, Eisai Limited, Eli Lilly, Exelixis, Faron Pharmaceuticals Ltd, Forma Tharapeutics, Gamamabs, Genentech, Glaxosmithkline, H3 Biomedicine, Hoffmann La Roche Ag, Imcheck Therapeutics, Innate Pharma, Institut De Recherche Pierre Fabre, Iris Servier, Iteos Belgium SA, Janssen Cilag, Janssen Research Foundation, Kura Oncology, Kyowa Kirin Pharm. Dev, Lilly France, Loxo Oncology, Lytix Biopharma As, Medimmune, Menarini Ricerche, Merck Sharp & Dohme Chibret, Merus, Molecular Partners Ag, Nanobiotix, Nektar Therapeutics, Novartis Pharma, Octimet Oncology Nv, Oncoethix, Oncopeptides, Onyx Therapeutics, Orion Pharma, Oryzon Genomics, Ose Pharma, Pfizer, Pharma Mar, Pierre Fabre Medicament, Plexxikon, Roche, Sanofi Aventis, Seattle Genetics, SOTIO Biotech, Syros Pharmaceuticals, Taiho Pharma, Tesaro, Turning Point Therapeutics, Xencor

SOT101 Structure and binding

- SOT101 is a fusion protein containing IL-15 and the Sushi+ domain of IL-15Rα



- SOT101 mimics the high-affinity binding of IL-15 trans-presented to its βγ receptor at the synapse



Presenting cell, e.g., Dentritic cell

T or NK cell

SOT101 may have better efficacy than other IL2/IL-15 compounds because of a strong and well balanced induction of both innate and adaptive immunity

AURELIO-03 study

SOT101 dose escalation in combination with pembrolizumab

Main Objectives

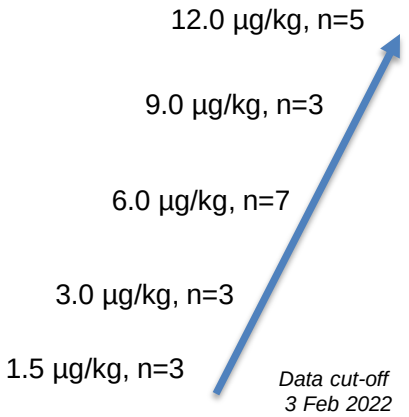
- Safety, tolerability, RP2D
- Preliminary efficacy
- PK, PD

Treatment

- SOT101, s.c. on days 1, 2, 8, and 9, in combination with Pembrolizumab 200 mg i.v., every 3 weeks until disease progression/unacceptable toxicity

Study design

- Standard 3+3 escalation



Inclusion criteria

- Age ≥ 18 y
- Confirmed, metastatic or unresectable solid tumor
- Refractory or intolerant to existing therapies
- Measurable disease according to RECIST 1.1
- ECOG PS 0-1
- Adequate renal, hepatic, haematological function

Patients and Disease Characteristics

Patients treated	**n = 21**
Median age (range)	62 (46–78)
Gender m/f, n	10 / 11
ECOG 0/1, n	14 / 7
Prior systemic therapies	
• Median lines (range), n	2 (1-6)
• ≥ 3 Lines, n (%)	10 (48%)
• Prior ICB, n (%)	11 (52%)

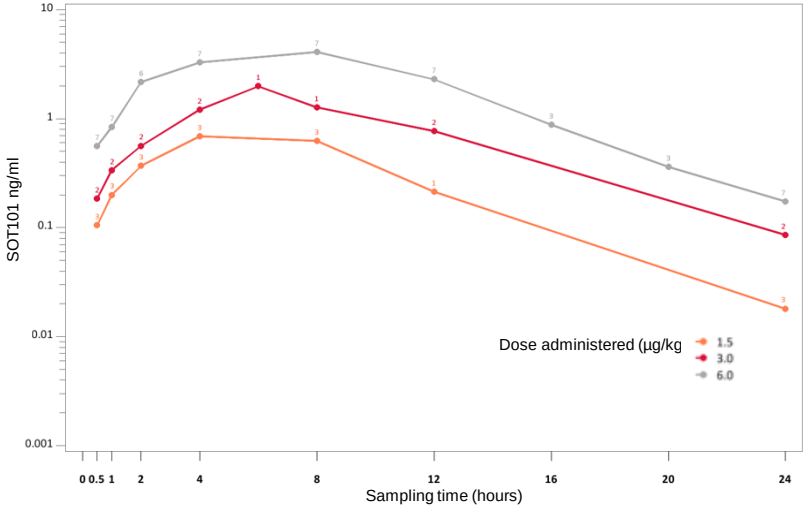
Tumor entities (n)	
Colorectal Cancer (MSI-H)	3 (2)
Melanoma	3
Gastric cancer	2
Anal squamous cancer	2
Mesothelioma	2
other: • ampullary adeno, ovarian sarcoma, thyroid medullary, cSCC, cervix adeno, bladder urothelial, liver cholangiocarcinoma, cervix squamous, biliary tract adeno	9

The majority of patients had received prior ICB anti-tumor treatment

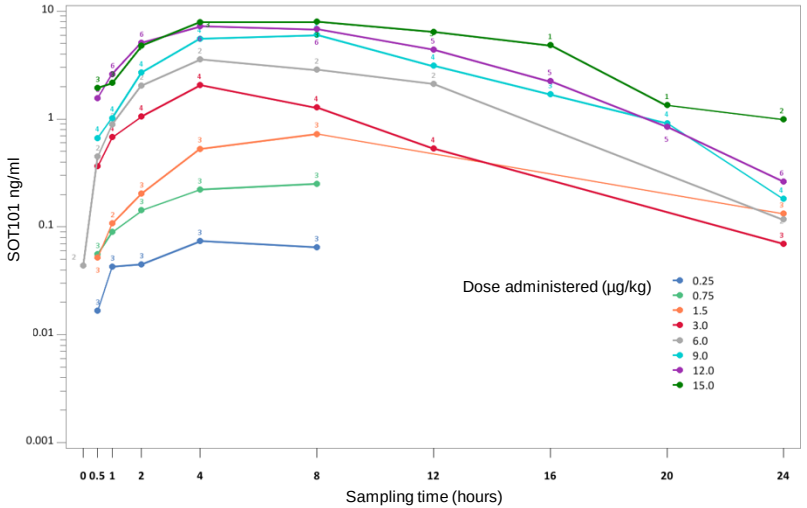
Pharmacokinetics

SOT101 dose levels over time

- Combination with pembrolizumab



- Monotherapy

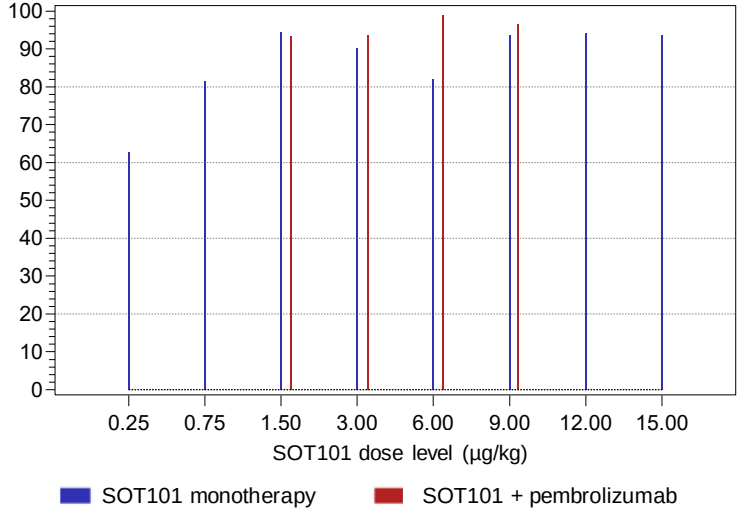


- Approximately dose proportional increase of exposure
- Time to maximum plasma concentration approx. 5-6 hours after administration; Terminal half-life in 4 hours range
- **Similar SOT101 PK profile for both mono- and combination therapy with pembrolizumab**

Dose dependent Pharmacodynamics

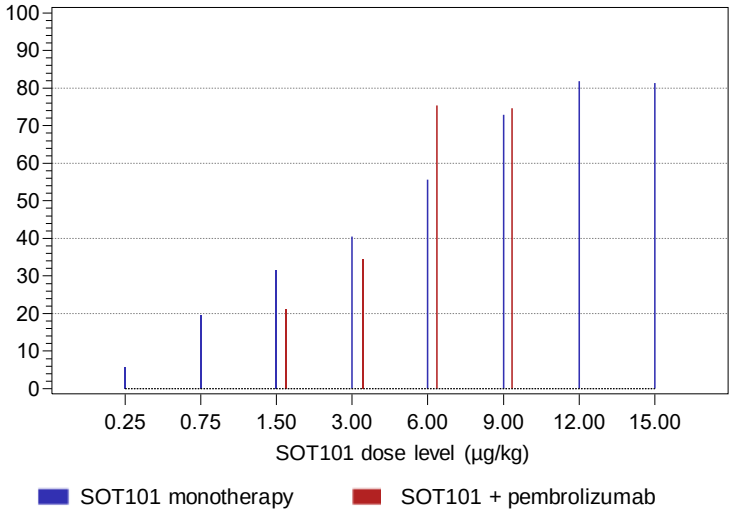
NK cell activation Ki-67 expression %

Maximum values per dose level



CD8+ T cells activation Ki-67 expression %

Maximum values per dose level



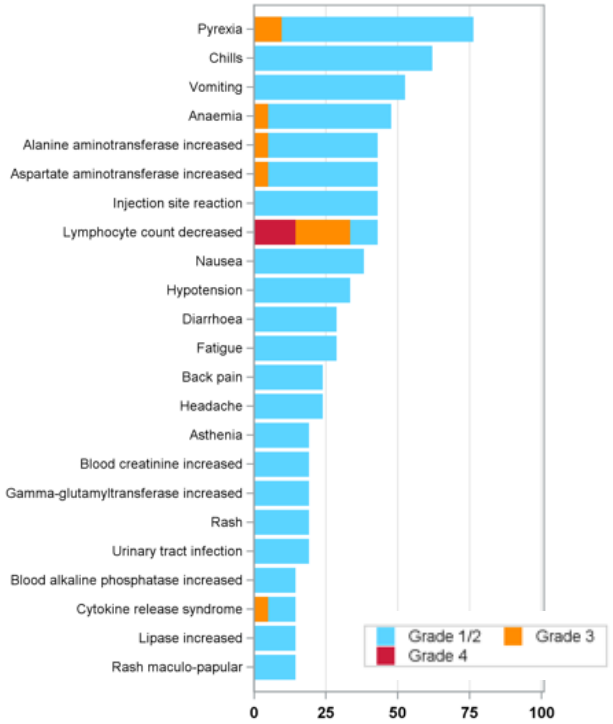
Maximum NK cell activation already reached at low dose levels

Maximum CD8+ T cell activation from 9 to 12 µg/kg

No relevant effect on T-regs

Adverse events: favourable safety profile

Percentage of TEAEs in ≥ 10% of patients and maximum severity



- Safety data from 21 patients at 5 SOT101 dose levels 1.5 to 12 µg/kg indicate that SOT101 + pembrolizumab is well tolerated
  - Most common adverse events were pyrexia, chills, vomiting, mainly Grade ≤ 2 and transient.
  - TEAEs G3/4 (n) assessed related to study treatment were Lymphopenia (7), ALT/AST increased (2), Neutropenia (1), Anemia (1), Pyrexia (2), CRS (1).
  - One DLT CRS G2 (hypotension G2, fever G2) at dose level 6.0 µg/kg after 1st administration, resolved within 6 days. Patient continued the study on a reduced dose (3 µg/kg). No DLT at higher dose level.
  - One patient at dose level 1.5 µg/kg has been discontinued study treatment due to AE ALT/AST G3 which resolved within 12 days after discontinuation.
  - No vascular leak syndrome. No treatment-related death.
- SOT101 RP2D determined to be 12 µg/kg (same as for monotherapy)

AE profile combination therapy in line with AE profile of either compound in monotherapy → no additive toxicity

Preliminary Efficacy

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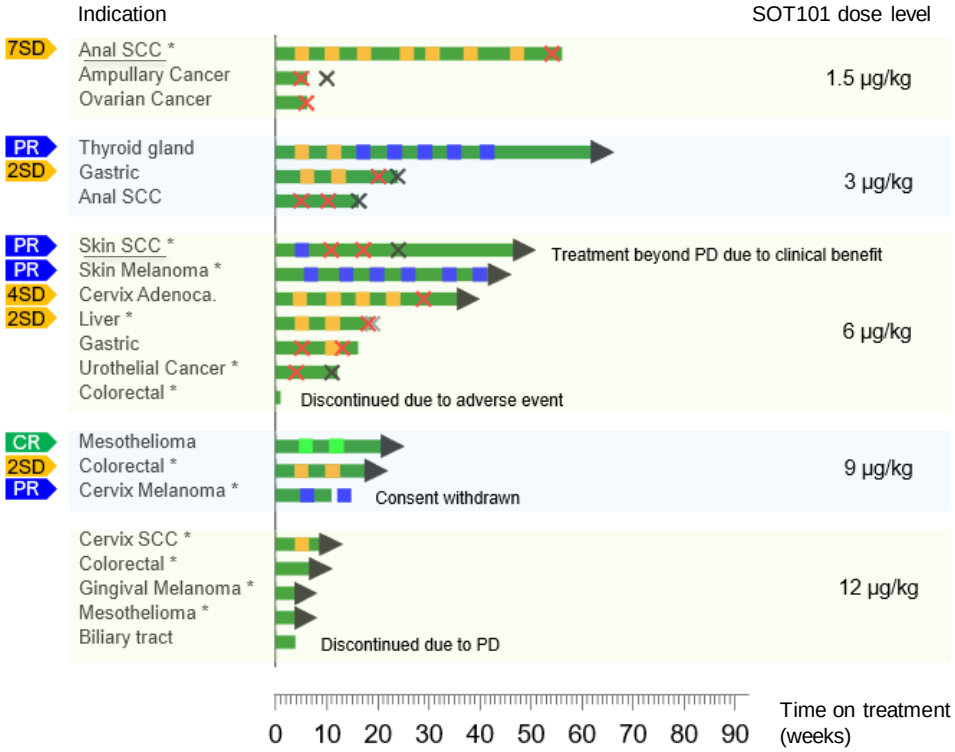


- 1 confirmed Complete Response
- 4 Partial Responses – 3 confirmed
- 7 Stable Diseases – 5 confirmed

Treatment duration
PR
CR
SD
Clinical progression
UPD
CPD
Treatment Ongoing

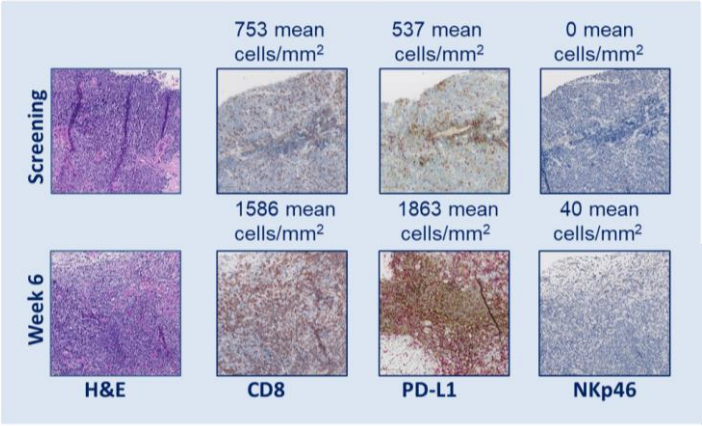
* ICB pre-treated (refractory)

Clinical benefit observed in 12 out of 16 pts with at least one tumor assessment

Case study 1: ICB-refractory patient

49 y female with anus squamous cell carcinoma; SD > 50 weeks

- Initial diagnosis: Aug 2019
- Previous therapies
  - 1L: 5-fluorouracil + leucovorin + oxaliplatin (Aug 2019 – Sep 2019); 2L: retifanlimab (Nov 2019 – Apr 2020) → ICB-refractory
- AURELIO-03 study: 3L SOT101 1.5 µg/kg in combination with pembrolizumab, C1D1 on 9 Jul 2020
- Stable disease for 52 weeks



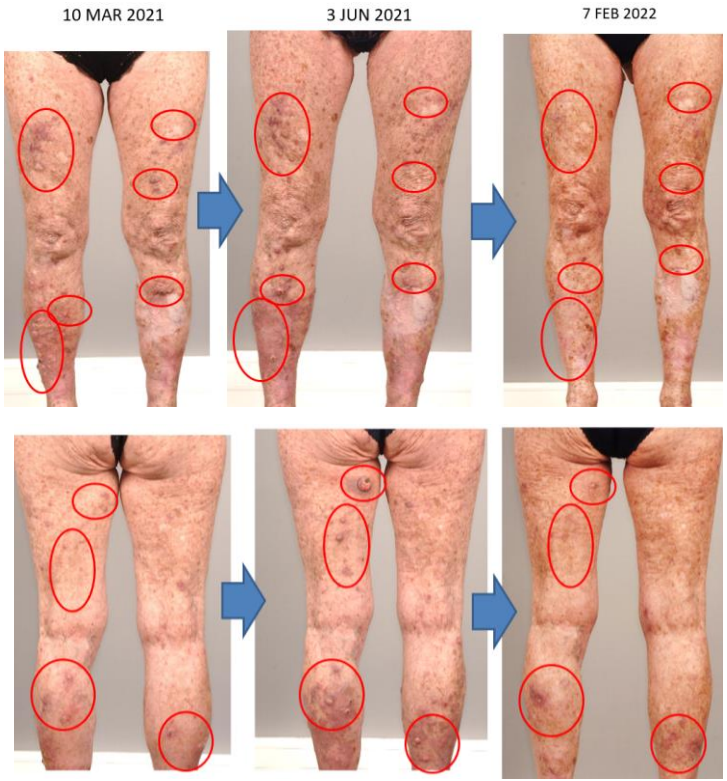
H&E-hematoxylin and eosin

Hot tumor microenvironment prior to SOT101 + Pembrolizumab treatment with a high immune CD8+ T cell infiltration and intra-tumoral PD-L1 expression

After the treatment with SOT101 + Pembrolizumab, markedly increased infiltration of CD8+ T cells and PD-L1+ cells was observed in tumor stroma as well as in tumor nests. NK cells were scattered throughout the intra-tumoral stroma and tumor nest

SOT101 + Pembrolizumab induced increased immune cell infiltration in an ICB-refractory tumor

Case study 2: Partial Response in SSCC



74 y female with skin squamous cell carcinoma, BOR: PR

- Initial diagnosis: 2016
- Previous therapies
  - 22 Surgeries
  - Systemic therapy
    - Cemiplimab (4 cycles) → primary resistence
- AURELIO-03 study
  - dose level 6 µg/kg; C1D1 March 11, 2021
- Partial response
  - Target lesion -100% after 4 cycles
  - Fluctuating new lesions coming and disappearing
- Status
  - Significant clinical response
  - On treatment for more than 50 weeks

Conclusions

- SOT101 in combination with pembrolizumab has a good tolerance profile; MTD not reached
- The RP2D was determined to be 12 µg/kg (same as for monotherapy)
- Clinical benefit was observed in the majority of patients (12 out of 16 patients with at least one tumor assessment), even in ICB relapsed/refractory tumors
  - Complete response in one patient with mesothelioma
  - Partial response in 4 patients
    - ICB refractory: squamous skin cell carcinoma
    - ICB relapsed: skin melanoma, cervix melanoma
    - not ICB pre-treated: medullary thyroid gland cancer
  - Longest duration of response observed was more than 40 weeks
  - Long lasting confirmed stable disease in 5 patients up to > 50 weeks

Conclusions (cont‘d)

- **Encouraging efficacy signals in this heavily pre-treated population will be further evaluated in AURELIO-04 “A phase 2, open-label, single-arm, multicenter study of SOT101 in combination with pembrolizumab to evaluate the efficacy and safety in patients with selected advanced/refractory solid tumors” (NCT05256381)**
  - Non-Small Cell Lung Cancer
    - with disease progression on or after an ICB-containing regimen and/or a platinum-containing regimen, with no EGFR or ALK genomic tumor aberrations
  - Colo-Rectal Cancer
    - MSI-H/dMMR that is unresectable or metastatic
  - Cutaneous Squamous Cell Carcinoma
    - first line cSCC that is recurrent or metastatic, and not curable by surgery or radiation, or second line cSCC that is refractory or has relapsed after an ICB-containing regimen
  - Hepato-Cellular Carcinoma
    - after recurrence or failure on an ICB-containing regimen
  - Metastatic Castrate-Resistant Prostate Cancer
    - that is treatment-refractory after recurrence or failure of docetaxel
  - Ovarian Cancer
    - after recurrence or failure on platinum-based therapy within 6 months

Thank you for your attention!