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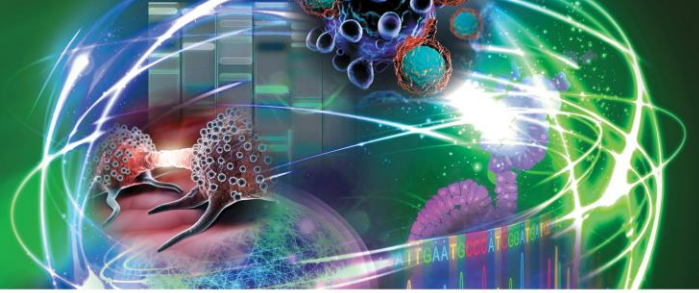

# Inducible T-cell co-stimulatory (ICOS) receptor agonist, feladilimab, alone and in combination with pembrolizumab: results from INDUCE-1 relapsed/refractory melanoma expansion cohorts

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# Disclosure Information



## Michele Maio

I have the following financial relationships to disclose:

Advisor/Consultant for: BMS, Roche, AZ, MSD, Merck, PierreFabre, and Alfasigma
Travel/Accommodations/Expenses: BMS, AZ, Roche, MSD, Merck, Amgen, Pierre Fabre, and Alfasigma
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Stocks/Shares held in: Theravance
Honoraria: BMS, AZ, Roche, MSD, Merck, Amgen, Pierre Fabre, and Alfasigma
Employee of: University Hospital of Siena

I will discuss the following off-label use and/or investigational use in my presentation:
*Inducible T-cell co-stimulatory (ICOS) receptor agonist, feladilimab, alone and in combination with pembrolizumab: results from INDUCE-1 relapsed/refractory melanoma expansion cohorts*

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# ICOS Agonist mAb Feladilimab

An investigational immunotherapy for R/R melanoma

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Inducible T-cell co-stimulator (ICOS) is a member of the CD28 Ig receptor superfamily, which includes CTLA-4 and PD-1 and has a pivotal role in stimulating T-cell survival and function[1–3]

Feladilimab is a first-in-class humanized IgG4 mAb selected for its agonist activity through the ICOS receptor, with low/no T-cell depleting effects[4]

Metastatic melanoma is an immunotherapy-responsive malignancy, with approved therapies including anti-PD-(L)1 and anti-CTLA-4 agents[5]

- Anti-CTLA-4 agents have been shown to increase ICOS expression; ICOS is a biomarker of increased response and survival in patients with unresectable melanoma and mesothelioma treated with anti-CTLA-4 agents[6,7] (**Table 1**)
- In nonclinical models, antitumor activity of ICOS agonists is enhanced in combination with CTLA-4/PD-1 blockade[4,8–13]

Table 1. $CD4^+$ $ICOS^+$ circulating T-cell count following ipilimumab treatment in advanced melanoma[6]

| $CD4^+$ $ICOS^+$ T cells, count/μL, mean (range) | Responders (N=6) | Non-responders (N=11) |
|---|---|---|
| Baseline | 6.7 (1.8–15) | 8.1 (0.9–24.0) |
| Week 7 | **50.6 (7.0–93.0)** | **28.6 (1.4–95.0)** |
| Week 12 | **72.6 (26.0–170)** | **26.7 (1.3–101.0)** |
| Week 24 | 17.2 (6.0–34.0) | 11.2 (6.0–19.0) |

CD, cluster of differentiation; CTLA-4, cytotoxic T-lymphocyte associated protein-4; ICOS, inducible T-cell co-stimulator; Ig, immunoglobulin; mAb, monoclonal antibody; PD-(L)1, programmed cell death protein 1/ligand 1; R/R, relapsed/refractory.

1. Hutloff A, et al. *Nature* 1999;397:263–6; 2. Sharpe AH, et al. *Nat Rev Immunol* 2002;2:116–26; 3. Simpson TR, et al. *Curr Opin Immunol* 2010;22:326–32; 4. Brett S, et al. ESMO 2018 poster presentation: Abstract 1840P; 5. Albittar A, et al. *Adv Exp Med Biol* 2020;1244:51–68; 6. Di Giacomo AM, et al. *Cancer Immunol Immunother* 2013;62:1021–8; 7. Calabrò L, et al. *Lancet Oncol* 2013;14:1104–11; 8. Yadavilli S, et al. AACR 2017 poster presentation: Abstract 1637; 9. Coutzac C, et al. AACR 2019 poster presentation: Abstract 2668; 10. Zamarin D, et al. *Nat Commun* 2017;8:14340; 11. Fan X, et al. *J Exp Med* 2014:211:715–25; 12. Waight JD, et al. AACR 2020 poster presentation: Abstract:2220; 13. Waight JD, et al. AACR 2021 poster presentation: Abstract:1849.

# INDUCE-1 Study Design

A phase I study of feladilimab ± pembrolizumab

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INDUCE-1 is an open-label, FIH study evaluating the safety, tolerability, pharmacokinetics, pharmacodynamics, and antitumor activity of feladilimab ± pembrolizumab in select advanced solid tumors

**Part 1A: Monotherapy dose escalation**

**Feladilimab** IV Q3W

Multiple selected solid tumors

**Part 1B: Monotherapy expansion†**

Randomized 1:1

**Feladilimab** 0.3 mg/kg (N=21) or
1 mg/kg (N=18) IV Q3W

Melanoma cohort

**Part 2A: Combination dose escalation***

**Feladilimab** IV Q3W +
**pembrolizumab** 200 mg IV Q3W

Multiple selected solid tumors

**Part 2B: Combination expansion**

Randomized 1:1

**Feladilimab** 0.3 mg/kg (N=6) or
1 mg/kg (N=11) IV Q3W +
**pembrolizumab** 200 mg IV Q3W

Melanoma cohort

## Melanoma population

- Non-uveal R/R melanoma
- ≤5 lines of systemic therapy
- Prior response or SD if PD-(L)1-experienced
- No prior immunotherapy-related Grade ≥3 toxicities leading to treatment discontinuation‡

## Study endpoints

- Safety: AEs/TRAEs/SAEs
- PK/PD
- Efficacy§: ORR, DoR, DCR, OS
- Exploratory biomarker analyses (e.g., ICOS IHC)

Here we report preliminary efficacy, safety, and PK data from the expansion cohorts of feladilimab ± pembrolizumab in R/R melanoma

*Starting dose of feladilimab two dose levels below Part 1A monotherapy dose deemed safe with PD activity; †for ≤2 years or until disease progression/unacceptable toxicity; ‡prior toxicity to checkpoint inhibitors was acceptable as long as no discontinuation from treatment; §irRECIST for response endpoints, RECISTv1.1 for disease assessments. AE, adverse event; DCR, disease control rate; DoR, duration of response; EC, expansion cohort; FIH, first-in-human; ICOS, inducible T-cell co-stimulator; IHC, immunohistochemistry; IV, intravenous; ORR, overall response rate; OS, overall survival; PD, pharmacodynamics; PD-(L)1, programmed cell death protein 1/ligand 1; PK, pharmacokinetics; Q3W, once every 3 weeks; (ir)RECIST, (immune-related) Response Evaluation Criteria in Solid Tumours; R/R, relapsed/refractory; SAE serious adverse event; SD, stable disease; TRAE, treatment-related adverse event

# Patient Baseline Characteristics

## All patients are immune checkpoint inhibitor-experienced



As of 6 November 2020, 39 and 17 patients were enrolled in the monotherapy and combination melanoma ECs, respectively

- mDoF was 8.5 months (range: 1.5–26.1) and 5.2 months (range: 1.5–27.2), respectively

| | Monotherapy EC (N=39) | Combination EC* (N=17) |
|---|---|---|
| Sex, n (%), female / male | 15 (38) / 24 (62) | 9 (53) / 8 (47) |
| Median age, years (range) | 52 (25–79) | 60 (32–78) |
| M stage at study entry, n (%) | | |
| M1a | 12 (31) | 4 (24) |
| M1b | 9 (23) | 5 (29) |
| M1c | 17 (44) | 7 (41) |
| M1d | 1 (3) | 1 (6) |
| Number of prior LOT in advanced/metastatic setting, n (%) | | |
| 0–1 | 14 (36) | 8 (47) |
| 2–3 | 18 (46) | 4 (24) |
| 4–5 | 7 (18) | 5 (29) |

| | Monotherapy EC (N=39) | Combination EC* (N=17) |
|---|---|---|
| Time since last progression, days, median (range)† | 50 (10–969)‡ | 55 (18–94)§ |
| Time since diagnosis, years, median (range)¶ | 3.2 (1.2–10.4)** | 3.9 (0.7–10.5)†† |
| Prior immunotherapy, n (%) | | |
| Anti-PD-(L)1 | **39 (100)** | **17 (100)** |
| Anti-CTLA-4 | **21 (54)** | **12 (71)** |
| Other‡‡ | 13 (33) | 3 (18) |
| Prior targeted therapy, n (%) | | |
| BRAF inhibitor | 7 (18) | 3 (17) |

*PD-(L)1-experienced efficacy analysis population N=17 excluded four PD-(L)1-naïve patients; safety population N=21; †first dose date to date of last progression + 1; ‡N=35; §N=13; ¶first dose start date to date of initial diagnosis + 1; **N=27; ††N=12; ‡‡includes cytokine therapy (i.e., interferon alpha), anti-LAG3, anti-4-IBB, epacadostat, tebentafusp, and T-VEC.

BRAF, B-raf proto-oncogene, serine/threonine kinase; CTLA-4, cytotoxic. T-lymphocyte associated protein-4; EC, expansion cohort; LOT, lines of therapy; mDoF, median duration of follow-up; PD-(L)1, programmed cell death protein 1/ligand 1

# Safety: AE Overview

## Safety profile is manageable



Feladilimab had a manageable safety profile in both monotherapy and combination ECs

- The majority of TRAEs were Grade 1 or 2
- No Grade 5 TRAEs, with one Grade 5 AE

| n, (%) | Monotherapy EC (N=39) | Combination EC* (N=21) |
|---|---|---|
| Any AE | 36 (92) | 21 (100) |
| TRAEs | 22 (56) | 15 (71) |
| Grade ≥3 TRAEs | 2 (5) | 3 (14) |
| AEs leading to permanent discontinuation of study treatment | 1 (3)† | 0 |
| AEs leading to dose interruption/delay | 10 (26) | 5 (24) |
| Any SAEs | 10 (26) | 11 (52) |
| Grade 5 TRAEs | 0 | 0 |

*N=21 all-treated safety analyses population, which included four PD-(L)1-naïve patients that were not included in the efficacy population (N=17); †AE leading to permanent discontinuation was fast progression and unrelated to study treatment.

AE, adverse event; EC, expansion cohort; SAE, serious adverse event; TRAE, treatment-related adverse event

# Safety: TRAEs Reported in ≥2 Patients

## No novel or unexpected toxicities observed



- No added toxicity was observed when feladilimab was used in combination with pembrolizumab
- No novel or unexpected TRAEs were observed
- The numbers of patients with TRAEs was similar between doses evaluated in both monotherapy and combination EC

| n, (%) | Monotherapy EC (N=39) | | | Combination EC* (N=21) | | |
|---|---|---|---|---|---|---|
| | Grade 1 | Grade 2 | Grade ≥3 | Grade 1 | Grade 2 | Grade ≥3† |
| Asthenia | 6 (15) | 4 (10) | 0 | 2 (10) | 1 (5) | 0 |
| Pruritus | 6 (15) | 0 | 0 | 2 (10) | 0 | 0 |
| Arthralgia | 2 (5) | 2 (5) | 0 | 1 (5) | 0 | 0 |
| Decreased appetite | 2 (5) | 1 (3) | 0 | 1 (5) | 0 | 0 |
| Nausea | 3 (8) | 1 (3) | 0 | 1 (5) | 0 | 0 |
| Diarrhea | 3 (8) | 0 | 0 | 2 (10) | 1 (5) | 0 |
| Fatigue | 1 (3) | 1 (3) | 0 | 2 (10) | 0 | 0 |
| Alanine aminotransferase increased | 0 | 2 (5) | 0 | 1 (5) | 1 (5) | 1 (5) |
| Aspartate aminotransferase increased | 1 (3) | 1 (3) | 0 | 2 (10) | 0 | 1 (5) |
| Vomiting | 2 (5) | 0 | 0 | 0 | 0 | 0 |
| Amylase increased | 0 | 0 | 0 | 1 (5) | 1 (5) | 0 |

*N=21 all-treated safety analyses population, which included four PD-(L)1-naïve patients that were not included in the efficacy population (N=17); †no Grade 5 TRAEs were reported; TRAEs reported in ≥2 patients shown.

EC, expansion cohort; TRAE, treatment-related adverse event

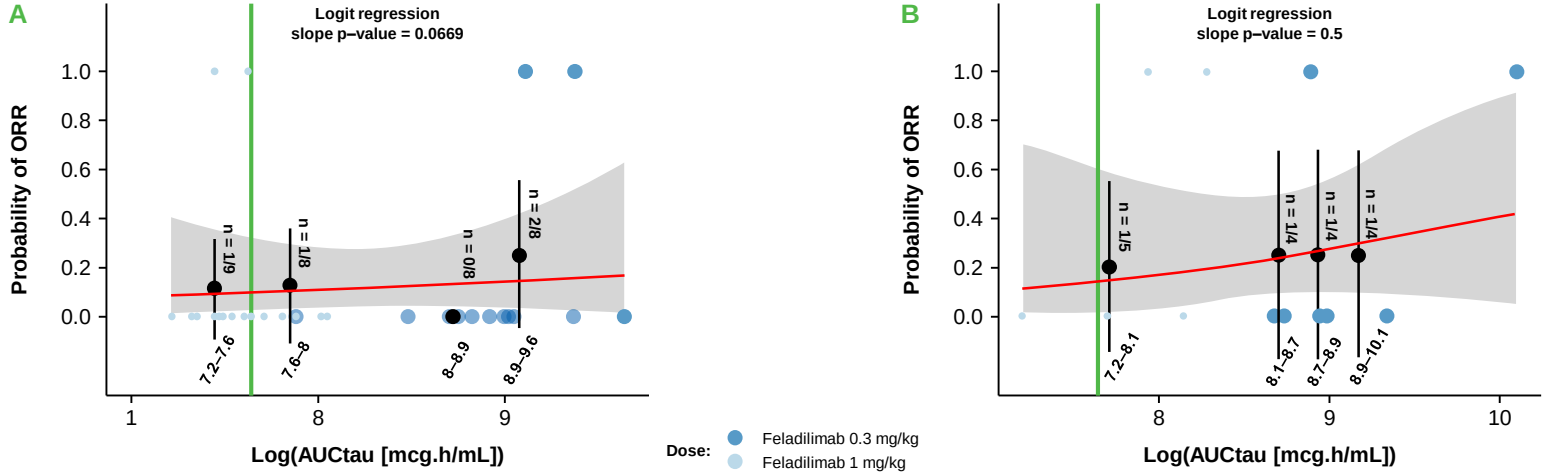
# Pharmacokinetics

Similarity of responses across doses



- PK of feladilimab was dose proportional between 0.01 to 10 mg/kg as monotherapy and 0.01 to 3 mg/kg as combination therapy, with no difference in PK between monotherapy and combination therapy
- Exposure-ORR relationship analysis confirmed similarity of responses at doses of 0.3 and 1 mg/kg for both monotherapy and combination therapy in the melanoma cohorts

## Regression analysis of exposure-ORR relationship for A) monotherapy EC and B) combination EC*




*N=33 for monotherapy EC, N=17 for combination EC (patients for whom a PK sample was available and analyzed); green vertical bars indicate typical value at 24 mg Q3W for an 80 kg patient. Data cutoff prior to that used for safety and efficacy analyses.

AUCtau, area under the curve over dosing interval; EC, expansion cohort; ORR, overall response rate; PK, pharmacokinetics; Q3W, once every 3 weeks

# Efficacy Results

## Clinical activity observed in PD-(L)1-experienced efficacy analysis population



| | Monotherapy EC (N=39) | Combination EC* (N=17) |
|---|---|---|
| **Best Overall Response, per irRECIST, n (%)†** | | |
| irCR | 1 (3) | 0 |
| irPR | 3 (8) | 3 (18) |
| irSD | 10 (26) | 6 (35) |
| irSD≥18 wks | 5 (13) | 3 (18) |
| irPD | 21 (54) | 5 (29) |
| NE‡ | 4 (10) | 3 (18) |
| **ORR, n (%)** | **4 (10)** | **3 (18)** |
| 95% CI | (2.9, 24.2) | (3.8, 43.4) |
| **DCR (irCR+irPR+irSD), n (%)** | **14 (36)** | **9 (53)** |
| 95% CI | (21.2, 52.8) | (27.8, 77.0) |
| **DCR (irCR+irPR+irSD ≥18 wks), n (%)** | 9 (23) | 6 (53) |
| 95% CI | (11.1, 39.3) | (14.2, 61.7) |
| **Median OS, months** | 10.6 | 10.8 |
| 95% CI | (6.5, 17.1) | (2.9, 24.1) |
| **OS at 6 months** | **76%** | **61%** |
| 95% CI | (59, 87) | (33, 81) |

*PD-(L)1-experienced efficacy analysis population N=17 excluded four PD-(L)1-naïve patients; safety population N=21; †unconfirmed responses per irRECIST (3/4 responses in monotherapy EC and 3/3 responses in combination EC were confirmed per both irRECIST and RECIST v1.1); ‡includes patients with no disease assessment post-baseline. **irCR**: disappearance of all lesions in 2 consecutive observations, at least 4 weeks apart. **irPR**: ≥30% decrease in tumor burden compared to baseline in 2 observations at least 4 weeks apart. **irSD**: 30% decrease in tumor burden compared to baseline, cannot be established nor 20% increased compared with nadir. **irPD**: ≥20% increase in tumor burden compared to nadir (at any single time point) in 2 consecutive observations at least 4 weeks apart. In addition, the sum must also demonstrate an absolute increase of at least 5 mm.

Duration of response for confirmed responders (months): monotherapy (N=3) **6.3, 10.4**, **8.9+;** combination (N=3) **8, 8.2, 13.3+**

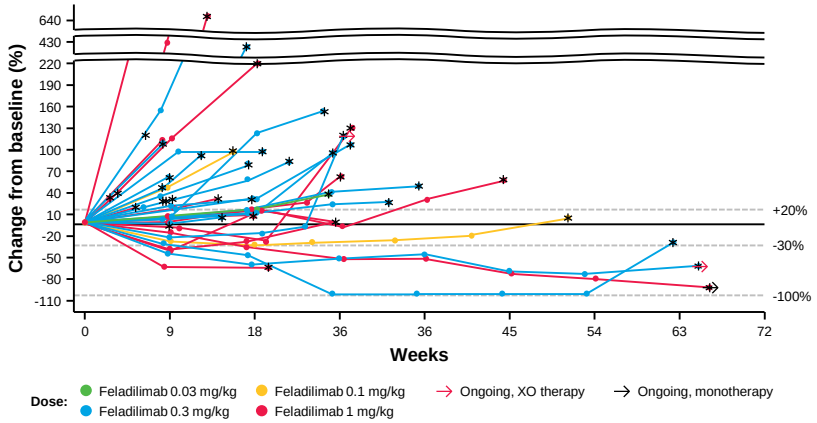
CI, confidence interval; CR, complete response; DCR, disease control rate; EC, expansion cohort; ir, immune-related; NE, non-evaluable; ORR, overall response rate; OS, overall survival; PD, progressive disease; PD-(L)1, programmed cell death protein 1/ligand 1; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors; SD, stable disease; wks, weeks

# Depth of Response

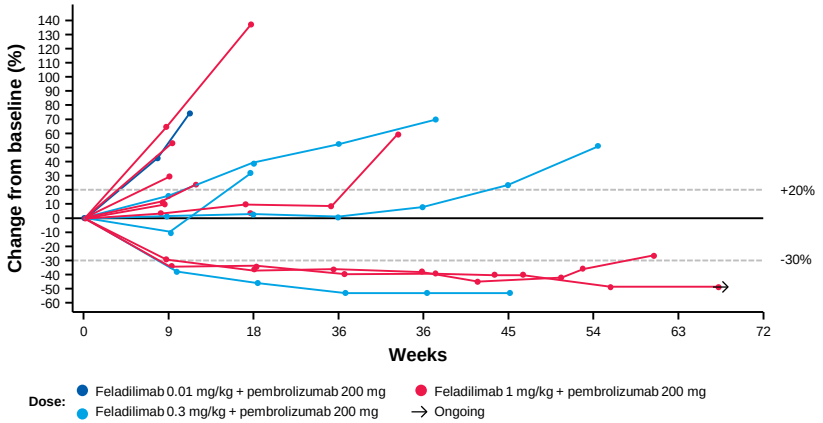
## Early, deep, and durable responses observed across doses



### Monotherapy cohort†




### Combination cohort†




∗Indicates PD-(L)1 experienced patients in the monotherapy cohort; all patients shown for the combination cohort were PD-(L)1-experienced; †patients from both dose escalation and EC phases included. Dashed lines are guidelines for determining level of response, breaks in y-axis inserted to facilitate data interpretation.

PD-(L)1-experienced patients demonstrated notable responses to feladilimab monotherapy, including

- One CR and three PRs
- 2/10 (20%) patients with stable disease had tumor size reductions (irRECIST) at ≥19%

PD-(L)1-experienced patients demonstrated notable responses to feladilimab + pembrolizumab, including

- Three PRs

CR, complete response; EC, expansion cohort; irRECIST, immune-related Response Evaluation Criteria In Solid Tumors; ORR, overall response rate; OS, overall survival; PD-(L)1, programmed cell death protein 1/ligand 1; PR, partial response; XO, crossover

# Response Rate Per irRECIST

## ORR by BRAF status and prior CTLA-4 experience



- Higher response rate in CTLA-4 treatment-experienced patients observed with feladilimab monotherapy, when compared to CTLA-4 treatment-naïve patients

| ORR, % (n/N) | BRAF mutation-positive | BRAF mutation-negative | CTLA-4 treatment-experienced | CTLA-4 treatment -naïve |
|---|---|---|---|---|
| Monotherapy EC (N=39) | 0 (0/9) | 14 (4/29) | 14 (3/21) | 6 (1/18) |
| Combination EC* (N=17) | 20 (1/5) | 17 (1/6) | 8 (1/12) | 40 (2/5) |

*PD-(L)1-experienced efficacy analysis population N=17 excluded four PD-(L)1-naïve patients; safety population N=21.

BRAF, B-raf proto-oncogene, serine/threonine kinase; CTLA-4, cytotoxic T-lymphocyte associated protein-4; EC, expansion cohort; irRECIST, immune-related Response Evaluation Criteria In Solid Tumors; ORR, overall response rate; PD-(L)1, programmed cell death protein 1/ligand 1

# Tumor Response in ICOS-enriched Subcohorts

Higher response rates observed in ICOS positive patients

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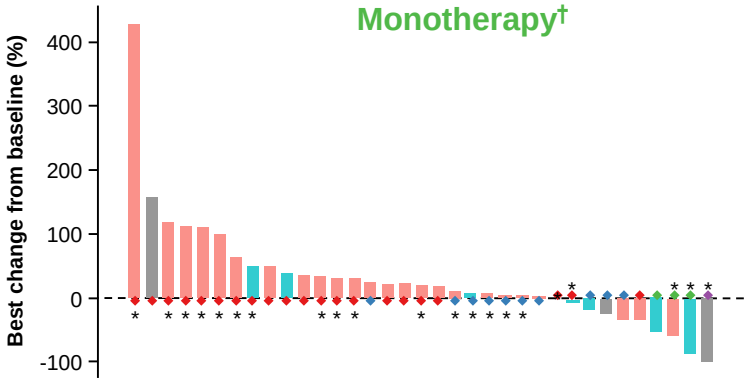
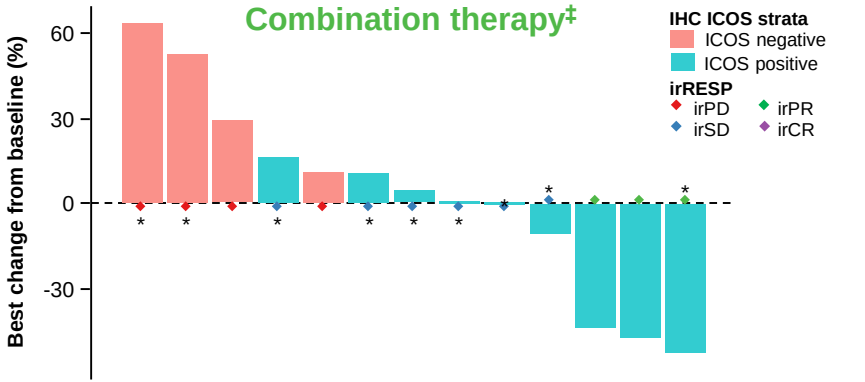



*Indicates patients with prior CTLA-4 treatment; †N=35 patients with available tumor change from baseline data; ‡N=13 patients with available tumor change from baseline data.

| | ICOS negative | ICOS positive |
|---|---|---|
| **ORR, % (n/N)** | 4 (1/27) | 29 (2/7) |
| **DCR, % (n/N)** | 22 (6/27) | 57 (4/7) |
| **DoR, range (mo)** | N/A | 6.3–8.9+ |

| | ICOS negative | ICOS positive |
|---|---|---|
| **ORR, % (n/N)** | 0 (0/7) | 30 (3/10) |
| **DCR, % (n/N)** | 14 (1/7) | 80 (8/10) |
| **DoR, range (mo)** | N/A | 8.0–13.3+ |

Monotherapy:

- **ORR of 29% and DCR of 57%** in ICOS positive patients
- ORR of 4% and DCR of 22% in ICOS negative patients

Combination therapy:

- **ORR of 30% and DCR of 80%** in ICOS positive patients
- ORR of 0% and DCR of 14% in ICOS negative expression patients

CTLA-4, cytotoxic T-lymphocyte associated protein-4; DCR, disease control rate; DoR, duration of response; ICOS, inducible T-cell co-stimulator; IHC, immunohistochemistry; irCR, immune-related complete response; irPD, immune-related progressive disease; irPR, immune-related partial response; irRESP, immune-related Response Evaluation Criteria In Solid Tumors response; irSD, immune-related stable disease; mo, months; N/A, not available; ORR, overall response rate; PD-(L)1, programmed cell death protein 1/ligand 1

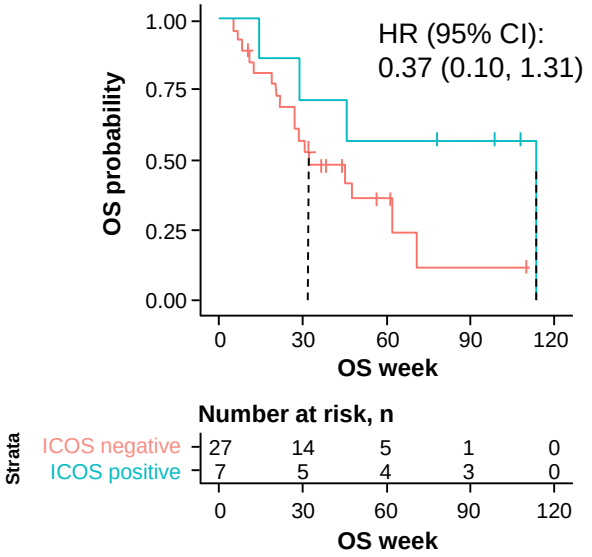
# Overall Survival in ICOS-enriched Subcohorts

Improved overall survival observed in ICOS positive patients

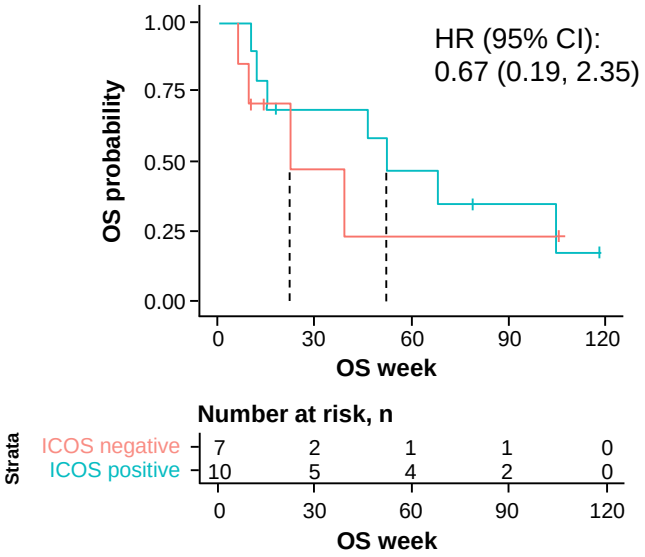


There were 63% and 33% reductions in risk of death in the ICOS positive expression population in the monotherapy and combination therapy cohorts, respectively, when compared to the ICOS negative population

## Monotherapy*




## Combination therapy†




*N=34 patients with available ICOS IHC data; †N=17 patients with available ICOS IHC data.

CI, confidence interval; HR, hazard ratio; ICOS, inducible T-cell co-stimulator; IHC, immunohistochemistry; OS, overall survival

# Patient Case Study

Patient achieved CR with feladilimab monotherapy

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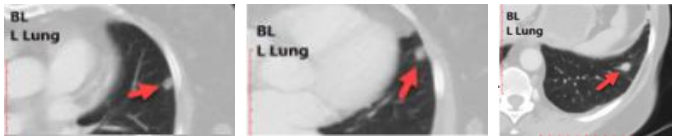
| 68-year-old female | |
|---|---|
| Disease | • Initial diagnosis (Apr 2017): Stage III melanoma; mutation (BRAF, K/NRAS, cKIT, EGFR) negative<br>• Metastatic diagnosis (Apr 2018)<br>• Last progression (Jan 2019) |
| Prior treatment | 1. Surgery (primary resection; May 2017; June 2017; Aug 2018)<br>2. Pembrolizumab (May–Oct 2018)<br>  • BOR of SD* prior to PD<br>3. Ipilimumab/nivolumab (Nov 2018–Jan 2019)<br>  • BOR of SD* prior to PD |
| Study treatment | Feladilimab 0.3 mg/kg: Mar 2019–Jul 2020 |
| Best overall response | Confirmed CR |

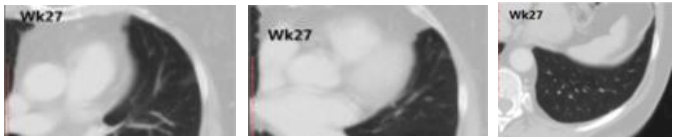
*Patient achieved PD per RECIST (v1.1).

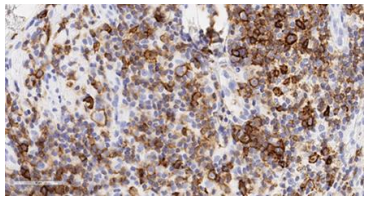
| $TL^{Wk1–54}$ | BL | Wk 9 | Wk 18 | Wk 27 | Wk 36–54 |
|---|---|---|---|---|---|
| Lung, left | 11 | 8 | 6 | 0 | 0 |
| SOD (mm) | 11 | 8 | 6 | 0 | 0 |
| % change from BL | N/A | −27 | −46 | −100 | −100 |

## BL




## Wk 27



**Representative example of stain showing positive expression of ICOS**

BOR, best overall response; BL, baseline; BRAF, B-raf proto-oncogene; CR, complete response; EGFR, epidermal growth factor receptor; ICOS, inducible T-cell co-stimulator; K/NRAS, kirsten/neuroblastoma rat sarcoma viral oncogene homolog; PD, progressive disease; RECIST, Response Evaluation Criteria In Solid Tumors; SD, stable disease; SOD, sum of diameters; $TL^{Wk1–54}$, target lesions for Wks 1 to 54; Wk, Week

# Conclusions



- Feladilimab monotherapy and feladilimab in combination with pembrolizumab, had a **manageable safety profile in R/R melanoma**
- **Responses at doses** of 0.3 and 1 mg/kg for both monotherapy and combination therapy **were comparable** as confirmed by exposure-ORR relationship analysis
- Feladilimab demonstrated clinical activity as both monotherapy and in combination with pembrolizumab in heavily pre-treated, PD-(L)1-experienced patients with R/R melanoma; there was **no apparent increase in overall survival** with combining feladilimab and pembrolizumab in a limited sample set
- **Feladilimab is the first ICOS agonist with reported single-agent activity in immune checkpoint inhibitor-experienced R/R melanoma, supporting ICOS as a therapeutic target**
  - **Early, deep, and durable responses** were observed **across doses** in both monotherapy and combination therapy cohorts
  - In a limited sample size, monotherapy **ORR** was **29%** in **biomarker-enriched (ICOS positive)** subcohorts, versus **10%** in **all-comers**
  - Feladilimab monotherapy in the biomarker-enriched subcohort is currently accruing and will be evaluated further
- Feladilimab is currently under evaluation for the treatment of advanced solid tumors in combination with other therapies in the ongoing pivotal adaptive phase 2/3 studies INDUCE-3 (NCT04128696) and INDUCE-4 (NCT04428333)

ICOS, inducible T-cell co-stimulator; ORR, overall response rate; PD-(L)1, programmed cell death protein 1/ligand 1; RR, relapsed/refractory

# Acknowledgements and QR code

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- **FLO** has no conflicts of interest to disclose.
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