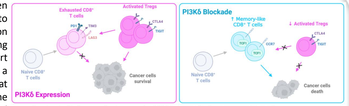
# #1181 - Roginolisib plus dostarlimab with or without docetaxel reverts immune suppression and shows clinical activity in immunotherapy-resistant non-small cell lung cancer (NSCLC)

Reinier Wener[1], Aitor Azkarate Martinez[2], Alessandra Bearz[3], Angelo Delmonte[4], Ernest Nadal[5], Ingel Demedts[6], Armando Santoro[7], Oscar Juan-Vidal[8], Amparo Sanchez-Gastaldo[9], **Michael Emig**[10], Mireille Cantarini[10], Giusy Di Conza[10], Alessio Bevilacqua[10], Nikita Janakarajan[10], Tracey Hammett[10], Paramjit Kaur[10], Karen Tonge[10], Lars van der Veen[10], Johanne Polasek[10] , Michael Lahn[10], and Michele Maio [11,12]

(1)Universitair Ziekenhuis Antwerpen,Antwerp, Belgium, (2)Hospital Universitari Son Espases, Palma, Spain, (3)CRO Aviano, National Cancer Institute, IRCCS, Aviano, Italy, (4)IRCCS Istituto Romagnolo per lo Studio dei Tumori "Dino Amadori" (IRST), Meldola, Italy, (5)Catalan Institute of Oncology, Bellvitge Biomedical Research Institute, L'Hospitalet de Llobregat, Barcelona, Spain, (6)AZ Delta Hospital, Roeselare, Belgium, (7) Department of Biomedical Sciences, Humanitas University, Milan, Italy, (8)Hospital Universitari i Politecnic la Fe, Valencia, Spain, (9)Hospital Universitario Virgen del Rocio, Seville, Spain, (10)iOnctura SA, Geneva, Switzerland, (11)University of Siena, Siena, Italy, (12)Center for Immuno-Oncology, Medical Oncology and Immunotherapy, Siena, Italy.

## 1. Introduction and methodology

**Background**. Accumulation of regulatory T cells (Tregs) has been identified as a mechanism of immune evasion and resistance to immune checkpoint inhibitors (ICIs), alongside increased exhaustion of CD8⁺ T cells. Phosphoinositide 3-kinase delta (PI3Kδ) signaling sustains this immune suppression, and its inhibition can revert resistance to ICIs in non-clinical tumor models [1]. Roginolisib is a novel conformation-selective, small molecule inhibitor of PI3Kδ, that inhibits Treg cells and increases memory-like CD8+ T cells [2,3]. The primary objectives of this study were to assess the safety and tolerability of roginolisib (R) in combination with dostarlimab (D) with or without docetaxel (T) and the reduction in peripheral blood Tregs.



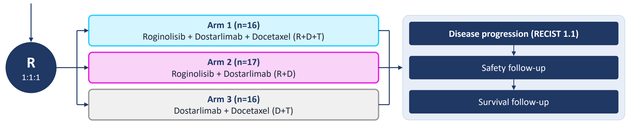

Created in BioRender. Bevilacqua, A. (2026) https://BioRender.com/tyfhdq7

**Methods:** PULMO-01 (NCT06879717) is a Phase I/IIa open-label, randomized, parallel-arm, multi-centre study

- Primary endpoints: number of adverse events (AEs) by CTCAE version 5.0; reduction in peripheral blood Tregs as assessed by mass cytometry (CyTOF)
- Secondary endpoints: evaluation of blood immune cell subsets such as naive, activated, memory and exhausted CD8⁺ and CD4⁺ T cells, B cells, and NK cells; objective response rate (ORR) by RECIST 1.1; clinical benefit rate (CBR=CR, PR, or SD for ≥ 6 months); progression-free survival (PFS); overall survival (OS)
- The TokuKit-fixed Whole Blood kit from Teiko was used to profile 41 immune markers in patient blood samples, enabling identification of 735 immune cell subsets (teiko-labs.com)
- Statistical analyses were performed in an unbiased manner; nominal and FDR-adjusted p-values are reported following multiple-testing correction

**Key eligibility**

- Adults (≥18 years)
- Advanced/metastatic non-squamous NSCLC
- Progression on ICI or ICI + platinum-based doublet
- Measurable disease (RECIST 1.1)




**Study treatment (21-day cycles):** Roginolisib 80 mg orally once daily; Dostarlimab 500 mg IV over 30 minutes on Day 1 of each cycle, to a maximum of 35 cycles; Docetaxel 75 mg/m² IV over 1 hour on Day 1 of each cycle

ICI, immune checkpoint inhibitor; NSCLC, non-small cell lung cancer; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors (version 1.1).

**Study status**

- Enrolment started in April 2025 and was completed in December 2025
- A total of 63 patients were enrolled at 10 sites across Italy, Spain and Belgium
- 51 patients were randomized and 49 were dosed

**NOTE: This trial is ongoing. Data are preliminary and subject to change**

## 2. PULMO-01 Baseline patient characteristics suggest a treatment refractory and ICI resistant study population

| | R+D+T | R+D | D+T |
|---|---|---|---|
| **N (treated)** | **16** | **17** | **16** |
| **Patient demographics** | | | |
| **Age, median (range) years** | 68 (61-78) | 62 (35-69) | 67 (44 -76) |
| **Gender, male, n (%)** | 11 (69) | 11 (65) | 12 (75) |
| **Race, White/Not Hispanic or Latino, n (%)** | 14 (88) | 16 (94) | 13 (81) |
| **ECOG PS (0/1) (%)** | 2/14 (13/87) | 5/12 (29/71) | 4/12 (25/75) |
| **No. of prior systemic treatment lines, n (%)** | | | |
| **1** | 12 (75) | 11 (65) | 12 (75) |
| **2** | 2 (13) | 5 (29) | 3 (19) |
| **3 or more** | 2 (13) | 1 (6) | 1 (6) |
| **Prior ICI monotherapy** | 0 | 1 (6) | 3 (19) |
| **BOR to prior ICI +/- Chemotherapy** | | | |
| **CR** | 1 (6) | 0 | 0 |
| **PR** | 2 (13) | 5 (29) | 7 (44) |
| **SD** | 4 (25) | 6 (35) | 3 (19) |
| **PD** | 5 (31) | 4 (24) | 6 (38) |
| **Not evaluable/Unknown** | 4 (25) | 2 (12) | 0 |
| **Resistance to prior ICI [4]** | | | |
| **Primary** | 7 (44) | 5 (29) | 4 (25) |
| **Secondary** | 7 (44) | 12 (71) | 9 (56) |
| **Unknown** | 2 (13) | 0 | 3 (19) |

**Acknowledgements**
The authors wish to thank the patients, families and investigator sites participating in this trial. We wish to also thank Simbec-Orion for managing the trial, Teiko-labs for performing the mass cytometry evaluation and GSK for its collaboration and provision of dostarlimab..

**REFERENCES**
[1] Spilopoulou et al. Cancer Drug Resist 2024;7:2.
[2] Vadas et al. Nat Commun. 17, 10220 (2026). https://doi.org/10.1038/s41467-026-77424-0
[3] Di Giacomo et al. Nat Commun 17, 10219 (2026). https://doi.org/10.1038/s41467-026-77358-7
[4] Rizvi et al. Journal for ImmunoTherapy of Cancer 2023; 11 (3): e007020

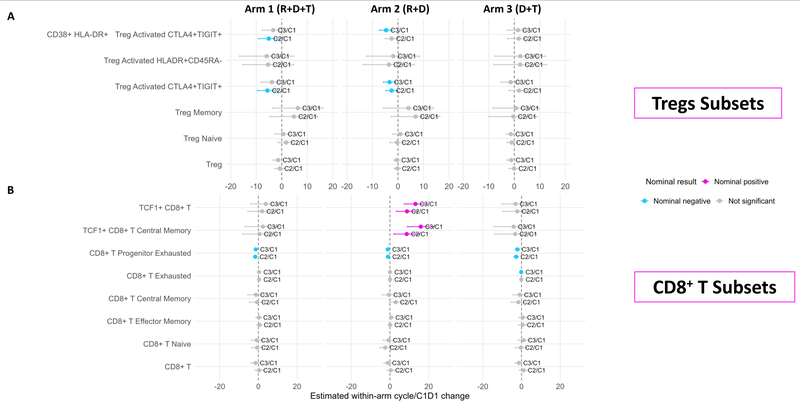
## 3. PULMO-01 Safety overview: Adding roginolisib to dostarlimab +/- docetaxel was tolerable with a manageable safety profile

| | R+D+T | R+D | D+T |
|---|---|---|---|
| **N (treated)** | **16** | **17** | **16** |
| **Any TEAE, n (%)** | 16 (100) | 16 (94) | 16 (100) |
| **TEAE ≥ Grade 3, n (%)** | 11 (69) | 6 (35) | 12 (75) |
| **Roginolisib-related** | 6 (38) | 2 (12) | NA |
| **Immune TEAE, n (%)** | 2 (13) | 2 (12) | 2 (13) |
| **Immune TEAE ≥ Grade 3, n (%)** | 0 | 2 (12) | 1 (6) |
| **Any SAE, n (%)** | 9 (56) | 9 (53) | 9 (56) |
| **Roginolisib-related** | 4 (25) | 2 (12) | NA |
| **TEAE leading to discontinuation, n (%)** | 2 (13) | 2 (12) | 1 (6) |
| **Any fatal TEAE n (%)** | 3 (19) | 1 (6) | 3 (19) |
| **Roginolisib-related** | 0 | 0 | NA |
| **Dostarlimab-related** | 0 | 0 | 0 |

Abbreviations: TEAE, Treatment Emergent Adverse Event; SAE, Serious Adverse Event. Data cut-off date Sep 10, 2026

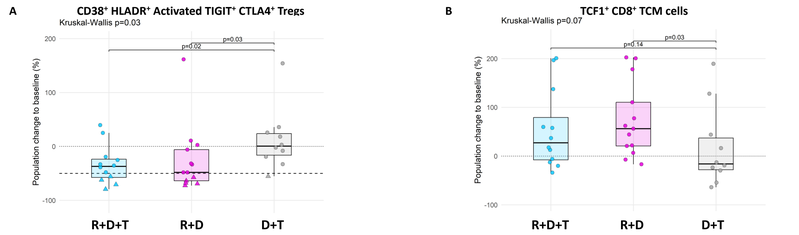
- The most common (in more than 2 patients) R-related TEAEs in the R+D+T arm were mild to moderate diarrhea (8/16), asthenia (4/16), and anemia (3/16); and in the R+D arm mild to moderate asthenia (4/17)
- The R+D arm showed the lowest rate of ≥ Grade 3 TEAEs.

## 4. Unbiased analysis of peripheral immunophenotyping shows a decrease of activated Tregs and increase of TCF1⁺ CD8⁺ (stem-like) T cells specifically in roginolisib-regimen arms



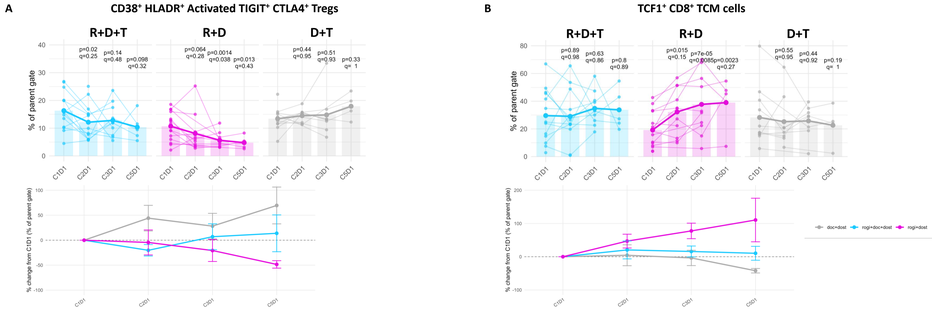

Within-arm changes from baseline for selected **A** Treg and **B** CD8⁺ subsets. Points represent model-estimated cycle-versus-baseline contrasts and horizontal bars indicate 95% confidence intervals. Estimates from LME models fitted separately for each CyTOF feature within each arm. (Arm 1 N= 14, Arm2 N= 15, Arm3 N= 12.)

## 5. The proportion of patients with any reduction of activated Tregs and an increase in stem-like CD8⁺ TCM cells is higher in roginolisib-regimen arms compared with control arm



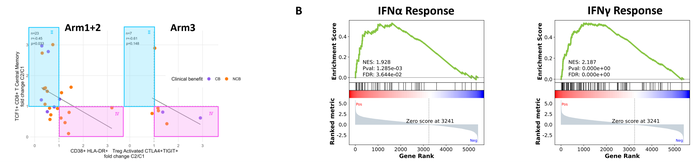

Patient-level percent change from baseline using the strongest change observed by C3D1 (day 42) for **A** CD38⁺HLADR⁺ activated Tregs and **B** TCF1⁺ CD8⁺ TCM. Arm differences were assessed by Kruskal–Wallis test with pairwise Wilcoxon rank-sum comparisons. (Arm1 N= 12, Arm2 N= 13, Arm3 N= 10).

## 6. Longitudinal analysis shows greater and more sustained modulation of activated Tregs and stem-like CD8⁺ TCM cells in the chemo-free arm versus triplet and the control arm




Longitudinal CyTOF changes for **A** CD38⁺HLADR⁺ activated Tregs and **B** TCF1⁺ CD8⁺ TCM. Within arm analysis using LME models with cycle as a categorical variable and patient as a random intercept. Model-based contrasts were used to compare each post-baseline cycle with C1D1, accounting for repeated measurements within patients.(Arm 1 N= 14, Arm2 N= 15, Arm3 N= 12).

## 7. Cycle 2 reduction in activated Tregs and expansion of stem-like TCF1⁺ CD8⁺ TCM cells are associated with clinical benefit and enhanced peripheral interferon responses




**A** Spearman correlation between the fold change of TCF1⁺CD8⁺ TCM C2/C1 and the fold change of CD38⁺HLADR⁺ Activated Tregs C2/C1. (Arm 1+Arm2 N= 23, Arm3 N= 7.) **B** Pre-ranked GSEA analysis performed on the Olink Proteomics HT panel analysis of the plasma of the patients. Only Arm 2 results are displayed.

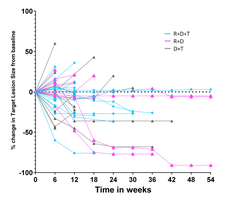
## 8. PULMO-01: Anti-tumor activity

**A**

| | R+D+T | R+D | D+T |
|---|---|---|---|
| **N (efficacy evaluable pop)** | **16** | **17** | **16** |
| **BOR** | | | |
| **cCR, n (%)** | 0 | 0 | 0 |
| **cPR, n (%)** | 1 (6) | 2 (12) | 2 (13) |
| **SD, n (%)** | 10 (63) | 4 (24) | 7 (44) |
| **PD, n (%)** | 5 (31) | 11 (65) | 6 (38) |
| **ORR, n (%)** | 1 (6) | 2 (12) | 2 (13) |
| **CBR, n (%)** | 5 (31) | 4 (24) | 3 (19) |

Abbreviations: BOR, Best Objective Response by RECIST 1.1, cCR, confirmed Complete Response; cPR, confirmed Partial Response; SD, Stable Disease, ORR, Objective Response Rate; CBR, Clinical Benefit Rate = CR, PR, or SD for ≥ 6 months.

**B**




- As expected in this treatment-refractory study population, ORRs were low across arms (Figure A). BOR was cPR in one patient in the R+D+T arm, and in 2 patients in the R+D and D+T arms, respectively
- Durable responses and deepening of responses were observed, including in the chemo-free R+D arm(Figure B)
- OS data is immature and continues to be tracked by treatment arm. As of September 30th, 2026, the median follow-up time was 6.4 months (range, 0.6-15.0). The 6-month OS rates (%, 95% CI) were 60.9% (32.7-80.3), 74.8% (45.8-89.7) and 43.8% (19.8-65.6) in the R+D+T arm, R+D arm, and D+T arm, respectively

## CONCLUSION

- This is the first clinical study of a conformation-selective PI3Kδ inhibitor demonstrating immune-cell changes consistent with biological activity and restored anti-tumor immunity, with a manageable safety profile and observed durable clinical benefit in the setting of treatment-refractory and ICI resistant NSCLC
- Fewer Grade ≥ 3 adverse events were reported in the R+D, chemo-free arm, while clinical benefit was comparable with T containing arms. In addition, immune-cell changes were more pronounced in the R+D arm
- The 6-months OS rate in patients receiving roginolisib (Arms 1 and 2) appeared favourable over patients not receiving roginolisib (Arm 3, dostarlimab + docetaxel). OS continues to be tracked by treatment arm
- These findings support further evaluation of PI3Kδ inhibition to overcome resistance to immune checkpoint blockade