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Interim Analysis of GALAXIES Lung-201: Phase 2, Randomized, Open-label Platform Study of Belrestotug Plus Dostarlimab in Patients With Previously Untreated Locally Advanced/Metastatic PD-L1 High (TPS ≥50%) Non-Small Cell Lung Cancer

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DECLARATION OF INTERESTS

David R. Spigel

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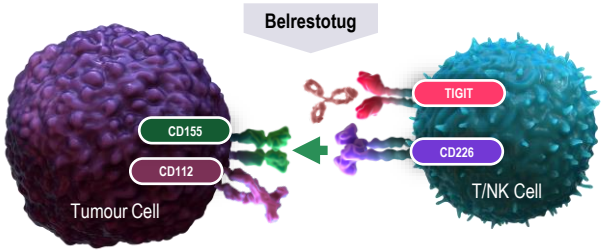
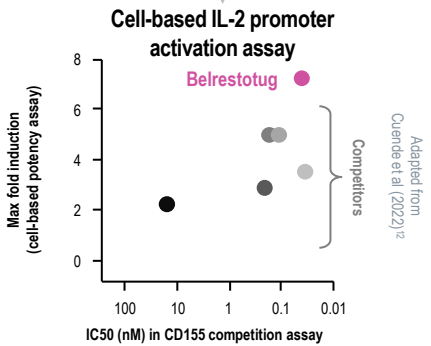
Background

- Current 1L treatment options for patients with PD-L1 high (expression ≥50%), locally advanced/metastatic NSCLC include single-agent immunotherapy; however, less than half of patients respond, necessitating new treatment approaches[1–3]
- Dostarlimab, an anti–PD-1 antibody approved for the treatment of endometrial cancer,[4,5] demonstrated comparable clinical activity to pembrolizumab in 1L NSCLC in the PERLA trial, a randomized, double-blind, head-to-head Phase 2 study of dostarlimab + chemotherapy vs standard of care pembrolizumab + chemotherapy[6]
- Anti-tumour activity with PD-(L)1 inhibitors may be further amplified through combination with novel anti-TIGIT inhibitory immune checkpoint agents, such as belrestotug[7–9]

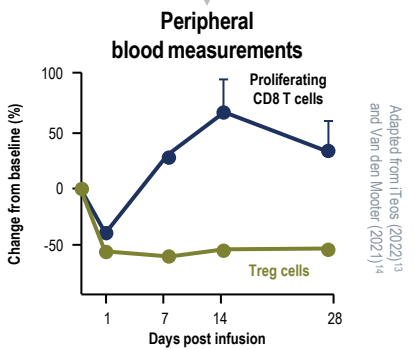
Belrestotug is an **Fcγ-receptor enabled mAb**[10,11] with two key mechanisms of action



Belrestotug demonstrated **higher potency** relative to other anti-TIGIT mAbs[12]



Belrestotug treatment leads to increases in proliferating CD8+ T-cells and a **marked reduction in Tregs** in patients[13,14]



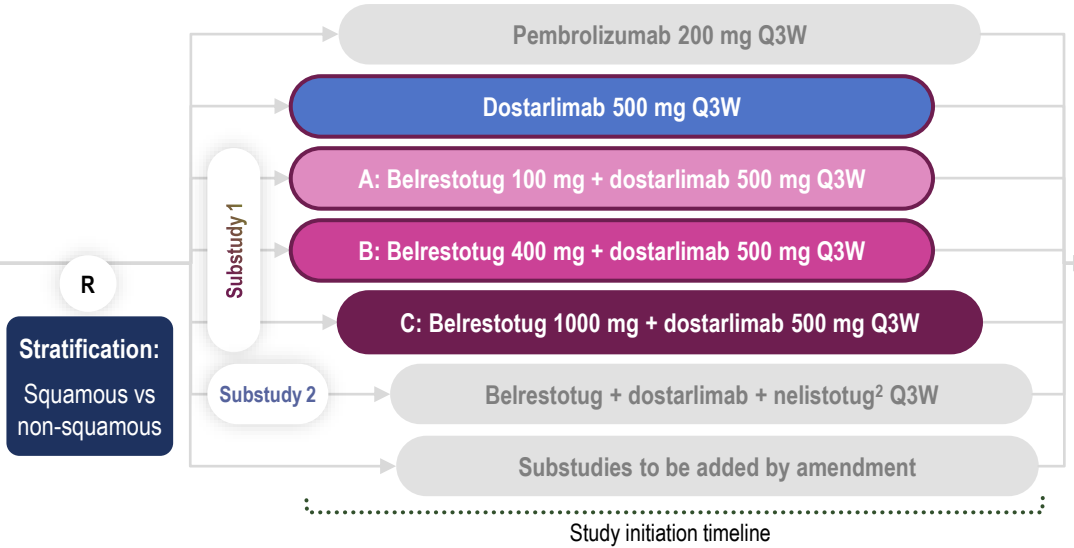
1L, first line; IC50, 50% inhibitory concentration; IL, interleukin; mAb, monoclonal antibody; NK, natural killer; NSCLC, non-small cell lung cancer; PD-(L)1, programmed cell death protein (ligand) 1; TIGIT, T-cell immunoreceptor with immunoglobulin and ITIM domain; Treg, regulatory T cell. 1. Reck, et al. J Clin Oncol 2021;39:2339–49; 2. Walsh, Soo. Ther Adv Med Oncol 2020;12:1–22; 3. Guo, et al. Medicine 2024;103:e36861; 4. GSK, Jemperli SmPC (2024) available from https://www.ema.europa.eu/en/documents/product-information/jemperli-epar-product-information_en.pdf; [accessed Aug 2024]; 5. GSK, JEMPERLI® (dostarlimab) US prescribing information (2024) available from https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761174s000lbl.pdf; [accessed Aug 2024]; 6. Lim, et al. Nat Commun 2023;14(1):7301; 7. Mittal, et al. Cancer Immunol Res 2019;7(4):559–71; 8. Sanchez-Correa, et al. Cancers (Basel) 2019;11(6):877; 9. Qin, et al. Mol Cancer 2019;18(1):155; 10. Preillon, et al. Mol Cancer Ther 2021;20(1):121–31; 11. Nguyen, et al. Presented at AACR 2020 (Abstract 3720), 22–24 Jun, online; 12. Cuende, et al. Poster #LB189 presented at: AACR; 8–13 Apr 2022; Philadelphia, PA; 13. iTeos corporate presentation (2022) available from https://investors.iteostherapeutics.com/static-files/f2ecce47-6d47-473c-93b3-7203f222af72 [accessed Aug 2024]; 14. Van den Mooter, et al. Presented at AACR (Poster CT118), 10–15 Apr and 17–21 May 2021, Philadelphia, PA.

GALAXIES Lung-201: A Phase 2, Open-label, Randomized Platform Study[1]

- This study is designed to assess the efficacy and safety of belrestotug + dostarlimab combinations in NSCLC
- Additional follow-up and recruitment will determine dose optimization, contribution of components, and comparisons to current standard of care (pembrolizumab monotherapy)

Key Eligibility Criteria:

- Previously untreated, unresectable, locally advanced/metastatic NSCLC
- PD-L1 high (TPS ≥50%; determined locally or centrally by DAKO 22C3 or VENTANA SP263 assay)
- EGFR/ALK wild-type, no actionable driver mutations
- Current or former smoker
- Asymptomatic and treated brain metastases are eligible



Primary Endpoint:

ORR per RECIST 1.1 by investigator assessment

Key Secondary Endpoints:

- PFS
- OS
- DoR
- Safety
- PK
- ADA

- **This follow-up interim analysis reports preliminary efficacy and safety (mITT ≥5.6 months follow-up)**
- **At data cut-off (7 June 2024), a total of 124 patients were included, with an overall median follow-up of 7.3 months**

[1]NCT05565378; EudraCT 2021-005115-32; [2]nelistotug is a CD96 mAb. ADA, antidrug antibodies; ALK, anaplastic lymphoma kinase; DoR, duration of response; EGFR; epidermal growth factor receptor; mAb, monoclonal antibody; mITT, modified intention-to-treat; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD-L1, programmed death ligand-1; PFS, progression-free survival; PK, pharmacokinetics; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumours; TPS, tumour positive score.

Baseline Demographics and Disease Characteristics

Characteristic, n (%)	Dostarlimab N=32	A: Belrestotug 100 mg + dostarlimab N=30	B: Belrestotug 400 mg + dostarlimab N=32	C: Belrestotug 1000 mg + dostarlimab N=30
Male	26 (81%)	18 (60%)	26 (81%)	16 (53%)
Years of age, median (range)	69.0 (37–86)	68.5 (45–79)	67.0 (50–78)	68.0 (47–83)
Race				
White	24 (75%)	17 (61%)	18 (58%)	19 (70%)
Asian	5 (16%)	7 (25%)	10 (32%)	6 (22%)
ECOG PS[1] 1, n (%)	11 (34%)	20 (67%)	16 (50%)	18 (60%)
Stage III[1]	4 (12.5%)	7 (23.3%)	5 (15.6%)	3 (10%)
Stage IVa[1]	18 (56%)	8 (27%)	12 (38%)	17 (57%)
Stage IVb[1]	10 (31%)	15 (50%)	15 (47%)	10 (33%)
Squamous[2]	11 (34%)	11 (37%)	13 (41%)	9 (30%)
PD-L1 TPS ≥50%[3]	32 (100%)	30 (100%)	32 (100%)	29 (97%)[4]
Central PD-L1 TPS ≥90%[5]	12 (38%)	11 (37%)	12 (38%)	11 (37%)
Metastases at baseline				
Bone	5 (16%)	7 (23%)	5 (16%)	4 (13%)
Brain	3 (9%)	4 (13%)	3 (9%)	3 (10%)
Liver	3 (9%)	6 (20%)	3 (9%)	0

[1]At screening; [2]stratification factor; [3]PD-L1 high (TPS ≥50%) was determined locally or centrally by DAKO 22C3 or VENTANA SP263 assay; [4]one patient was enrolled with a PD-L1 <50%, a protocol deviation was noted; [5]PD-L1 TPS ≥90% was determined centrally using the VENTANA SP263 assay. ECOG PS, Eastern Cooperative Oncology Group performance status; PD-L1, programmed death ligand-1; TPS, tumour positive score.

Primary Efficacy Endpoint: Investigator Assessment of ORR per RECIST 1.1

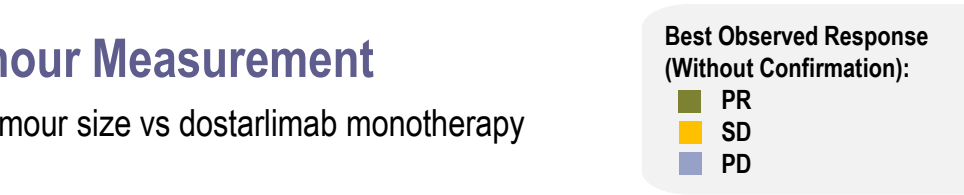
Belrestotug + dostarlimab combinations were associated with a clinically meaningful improvement in ORR vs dostarlimab monotherapy

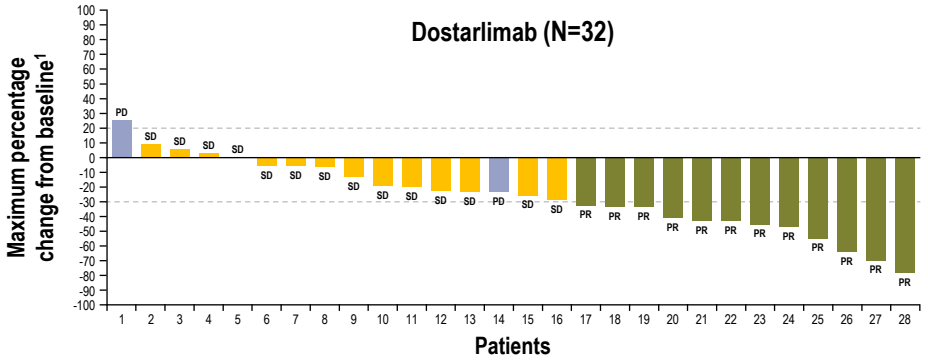
Response measure in mITT	Dostarlimab N=32	A: Belrestotug 100 mg + dostarlimab N=30	B: Belrestotug 400 mg + dostarlimab N=32	C: Belrestotug 1000 mg + dostarlimab N=30
Median follow-up, months (range)[1]	7.0 (0.2–16.6)	8.5 (0.3–14.3)	8.5 (0.4–16.2)	6.7 (2.4–9.7)
ORR,[2,3] **%** n (95% CI)	**37.5%** n=12 (21.1–56.3)	**63.3%** n=19 (43.9–80.1)	**65.6%** n=21 (46.8–81.4)	**76.7%** n=23 (57.7–90.1)
Complete response, n (%)	0	0	0	0
Partial response, n (%)	12 (37.5%)	19 (63.3%)	21 (65.6%)	23 (76.7%)
Stable disease, n (%)	14 (43.8%)	5 (16.7%)	4 (12.5%)	5 (16.7%)
Progressive disease, n (%)	2 (6.3%)	4 (13.3%)	3 (9.4%)	2 (6.7%)
Not evaluable/no assessment,[4] n (%)	4 (12.5%)	2 (6.7%)	4 (12.5%)	0
Confirmed ORR,[3,5] **%** n (95% CI)	**28.1%** n=9 (13.7–46.7)	**60.0%** n=18 (40.6–77.3)	**59.4%** n=19 (40.6–76.3)	**63.3%** n=19 (43.9–80.1)

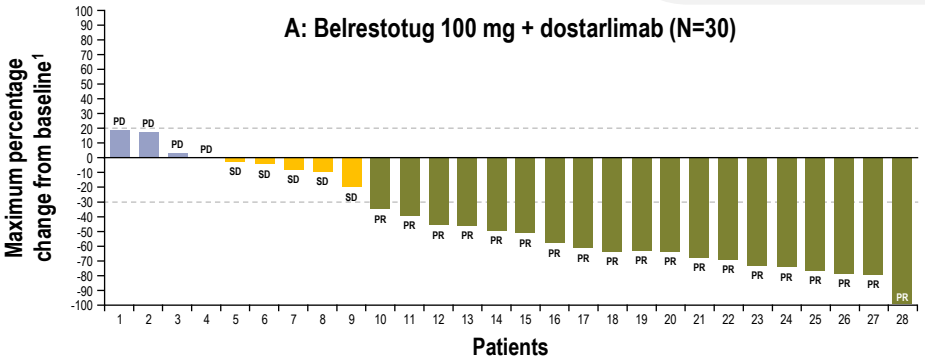
[1]As of data cut 7 Jun 2024, 65% of patients remained in ongoing follow-up and 33% of patients remained on study treatment; [2]unconfirmed ORR; [3]PD-L1 high (TPS ≥50%) was determined locally or centrally by DAKO 22C3 or VENTANA SP263 assay; [4]patients who only had "not evaluable" post-baseline assessments, those who had a best response of "not evaluable" per RECIST 1.1 by investigator assessment, or those where no post-baseline tumour assessment was performed; [5]complete or partial response confirmed by repeat imaging ≥4 weeks after response criteria first met. CI, confidence interval; mITT, modified intention-to-treat; ORR, objective response rate; PD-L1, programmed death ligand-1; RECIST, Response Evaluation Criteria in Solid Tumours; TPS, tumour positive score.

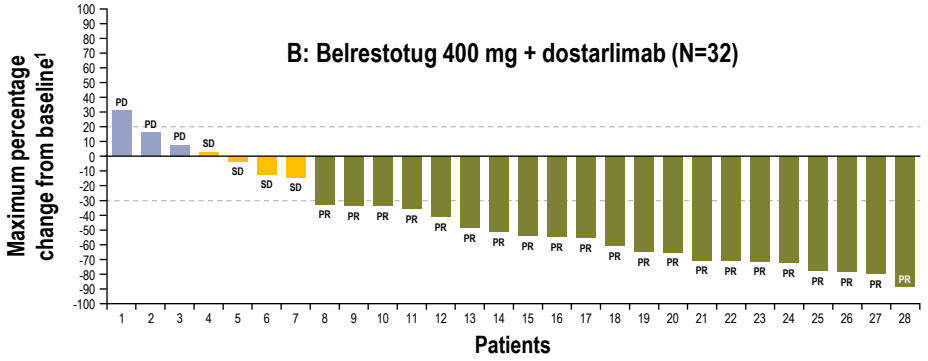
Best Percent Change From Baseline in Tumour Measurement

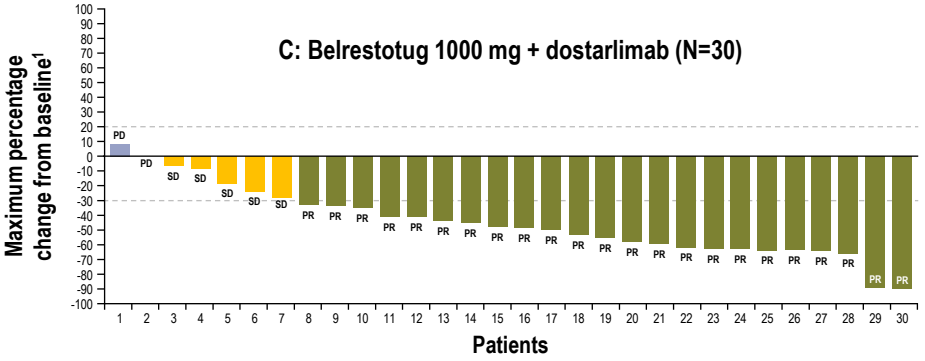
Combination therapy was associated with a greater reduction in tumour size vs dostarlimab monotherapy







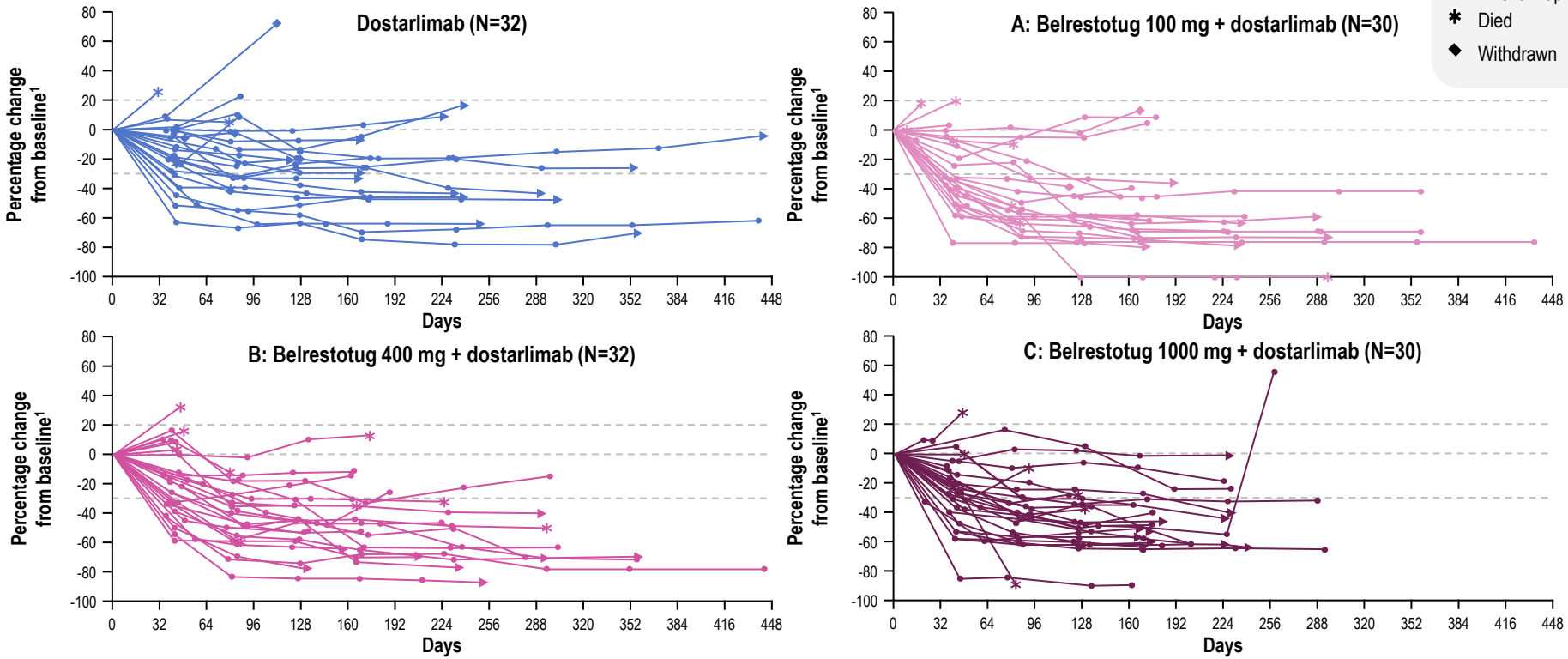




[1]Numerically lowest percent change from baseline that is on or prior to date of first radiological PD and start of follow-up anticancer therapy (excluding radiotherapy and surgery); patients without assessable post-baseline scans or where all baseline target lesions are not measured at subsequent visits are not included in figure; responses shown are per RECIST 1.1 by investigator assessment without confirmation. PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours; SD, stable disease.

Spider Plot of Percent Change From Baseline in Tumour Measurement

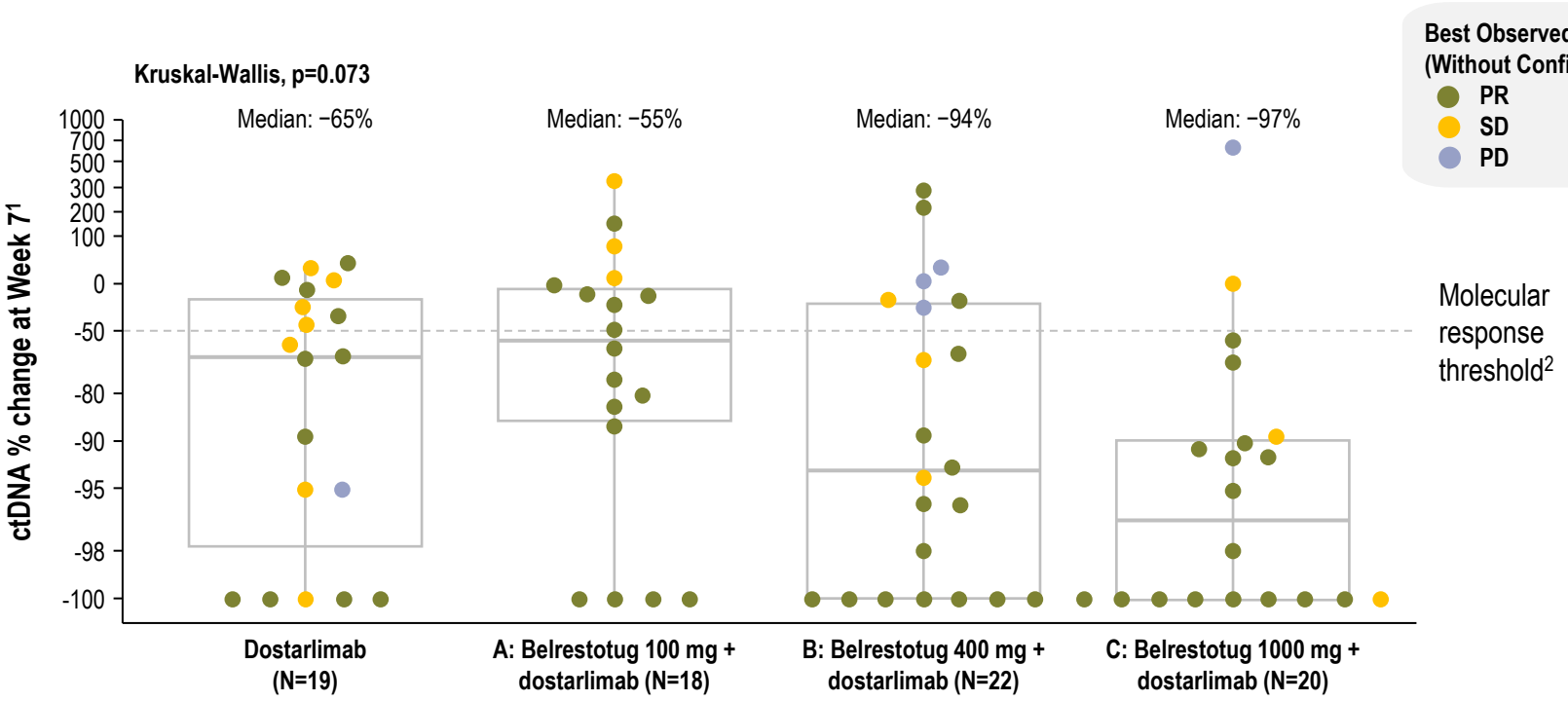
Depth of response was greater with belrestotug + dostarlimab vs dostarlimab monotherapy



[1]Investigator assessed percentage change from baseline per RECIST 1.1 by investigator assessment. RECIST, Response Evaluation Criteria in Solid Tumours.

Percentage Change of ctDNA From Baseline Across Dose Groups

There was a trend of numerically greater magnitude of ctDNA decrease associated with belrestotug dose



[1]Mean variant allele frequency change from baseline to Week 7; [2]molecular response threshold defined as having at least 50% reduction of ctDNA levels. Responses shown are per RECIST 1.1 by investigator assessment without confirmation. ctDNA, circulating tumour DNA; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours; SD, stable disease.

Overall Safety Profile

The combination regimen led to an increase in immune-related adverse events compared to dostarlimab monotherapy

Event, n (%)	Dostarlimab (N=32)	A: Belrestotug 100 mg + dostarlimab (N=30)	B: Belrestotug 400 mg + dostarlimab (N=32)	C: Belrestotug 1000 mg + dostarlimab (N=30)
TEAE	29 (91%)	29 (97%)	31 (97%)	30 (100%)
Grade 3+ TEAE	14 (44%)	19 (63%)	16 (50%)	16 (53%)
TRAE	19 (59%)	24 (80%)	27 (84%)	29 (97%)
Grade 3+ TRAE	5 (16%)	10 (33%)	7 (22%)	13 (43%)
Serious TRAE	3 (9%)	10 (33%)	8 (25%)	11 (37%)
Grade 5 serious TRAE	0	2 (7%)	1 (3%)	0
TRAE leading to discontinuation	2 (6%)	7 (23%)	5 (16%)	12 (40%)
TR-irAE[1]	6 (19%)	20 (67%)	18 (56%)	22 (73%)
Grade 3+ TR-irAE	4 (13%)	9 (30%)	5 (16%)	11 (37%)
Infusion-related reactions[2]	4 (13%)	8 (27%)	3 (9%)	7 (23%)

- The most common TRAEs overall (≥15%) were skin and subcutaneous tissue disorders (50%) and endocrine disorders (26%)
- The most common TEAEs leading to discontinuation were skin and subcutaneous tissue disorders (6%) and respiratory, thoracic and mediastinal disorders (6%)
- Fatal serious TRAEs include immune-mediated pneumonitis (N=1), immune-mediated hepatitis (N=1) and immune-mediated myocarditis (N=1)

[1]Immune-related AEs are events of potential immunologic aetiology, including irAEs; irAEs are identified as any Grade 2+ AEs (or AEs of unknown grade) based on a prespecified search list of preferred terms using the most recent MedDRA version identified by a custom MedDRA query (CMQ) using GSK Terms of Interest codes; [2]infusion-related reactions are drug component–related AEs which occurred ≤1 day after drug component infusion and are identified based on a prespecified search list of preferred terms and most recent MedDRA version. AE, adverse event; irAE, immune-related AE; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event; TR, treatment-related; TRAE, treatment-related treatment-emergent adverse event.

Immune-Mediated Adverse Events

The most common TR-irAE were skin and subcutaneous tissue disorders

Event, n (%)	Dostarlimab N=32	A: Belrestotug 100 mg + dostarlimab (N=30)	B: Belrestotug 400 mg + dostarlimab (N=32)	C: Belrestotug 1000 mg + dostarlimab (N=30)
TR-irAE[1] by preferred terms (≥10% incidence in any cohort[2]), Grade 2+ Grade 3+				
Immune-mediated dermatitis	0 0	5 (17%) 1 (3%)	0 0	6 (20%) 3 (10%)
Pruritus	0 0	3 (10%) 0	5 (16%) 0	4 (13%) 0
Rash	0 0	2 (7%) 0	4 (13%) 0	2 (7%) 1 (3%)
Immune-mediated hypothyroidism	1 (3%) 0	1 (3%) 0	3 (9%) 0	4 (13%) 0
ALT increase	1 (3%) 1 (3%)	3 (10%) 2 (7%)	0 0	1 (3%) 1 (3%)
Immune-mediated lung disease	0 0	1 (3%) 0	1 (3%) 0	3 (10%) 1 (3%)
Immune-mediated myocarditis	0 0	1 (3%) 1 (3%)	0 0	3 (10%) 1 (3%)

- The majority of Grade 2+ irAEs were skin and subcutaneous tissue disorders across all combination cohorts and were considered generally manageable with steroids (topical or oral). Adaptions to skin toxicity management are ongoing.
- Immune-mediated lung disease and myocarditis were more frequent in the belrestotug 1000 mg + dostarlimab cohort

[1]Immune-related AEs are events of potential immunologic aetiology, including irAEs; irAEs are identified as any Grade 2+ AEs (or AEs of unknown grade) based on a prespecified search list of preferred terms using the most recent MedDRA version identified by a custom MedDRA query (CMQ) using GSK Terms of Interest codes; [2]preferred terms selected based on a ≥10% incidence of Grade 2+ events in any cohort; data on infusion-related events are captured on a previous slide. AE, adverse event; ALT, alanine aminotransferase; irAE, immune-related adverse event; MedDRA, Medical Dictionary for Regulatory Activities; TR, treatment-related.

Conclusion

- GALAXIES Lung-201 is the largest presented prospectively designed, randomized, dose-ranging, Phase 2 study in patients with previously untreated, unresectable locally advanced/metastatic PD-L1 high NSCLC assessing anti-TIGIT + anti–PD-1 combinations
- Belrestotug is a differentiated anti-TIGIT mAb with multiple mechanisms of action
- A clinically meaningful improvement in ORR was observed in all combination cohorts compared with dostarlimab monotherapy
- The combination regimen had an increase in immune-related adverse events, which were manageable
- Ongoing recruitment in the reported arms and additional follow-up will better characterise the long-term efficacy and safety of belrestotug + dostarlimab. Follow-up of this study will inform the future development of belrestotug

Data support the ongoing **GALAXIES Lung-301 Phase 3 study** (NCT:06472076) of belrestotug + dostarlimab in patients with previously untreated, unresectable locally advanced/metastatic PD-L1 high NSCLC

mAb, monoclonal antibody; NSCLC, non-small cell lung cancer; ORR, objective response rate; PD-(L)1, programmed cell death protein (ligand) 1; TIGIT, T-cell immunoreceptor with immunoglobulin and ITIM domain.

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