Advanced analytics identify a differential immune response to CAN-2409+valacyclovir in non-squamous vs squamous NSCLC, linked to improved survival in patients with progressive ICI-refractory NSCLC

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Abstract #513

CANDEL THERAPEUTICS

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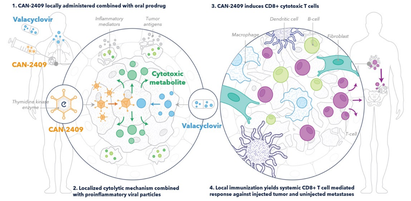
Background

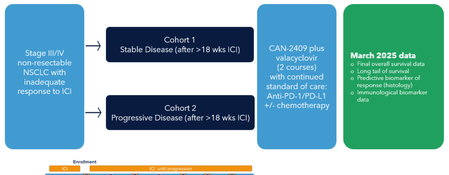
- Patients with unresectable, stage III/IV non-small cell lung cancer (NSCLC) with an inadequate response to immune checkpoint inhibitors (ICI) have very limited therapeutic options.
- We previously reported that two injections of CAN-2409+prodrug (valacyclovir) extended overall survival (OS) in patients with unresectable, stage III/IV NSCLC progressing under ICI treatment, nearly doubling median overall survival (OS) compared to historical standard of care second-line chemotherapy [1] .
- Survival post-CAN-2409 for patients inadequately responding to ICI was 24.5 months.
- We used an unbiased computational biology approach to identify associations between baseline clinical characteristics and biological features, biomarkers of immune response, and clinical outcomes.



Methods

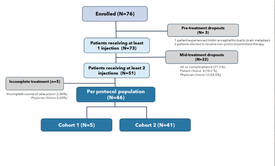
- NCT04495153 is an open-label, phase 2 clinical trial of CAN-2409+valacyclovir in combination with continued ICI in patients with non-resectable, stage III/IV NSCLC, refractory or resistant to anti-PD-(L)1.
- Patients were enrolled in 2 cohorts (C) depending on disease status at enrollment: C1 = stable disease or C2 = progressive disease after at least 18 weeks of ICI.
- Two doses of CAN-2409 (5x10[11]vp) were given 5-7w apart via bronchoscopic or percutaneous injection.
- A novel machine learning algorithm, Multi-Omics Factor Analysis (MOFA)[2], was applied to multimodal biomarker data including flow cytometry, CyTOF and blood proteomics based on analysis of biosamples from 42 NSCLC patients who received at least one injection of CAN-2409.
- MOFA results guided further analysis of the immunological response to CAN-2409 in patients with squamous versus non-squamous tumor histology.

Study schematic and biomarker analysis



Demographics and safety

Patients enrolled



Per protocol population: patients who received complete treatment consisting of 2 courses of CAN-2409 + prodrug (valacyclovir) and had a week 12 assessment.
Adverse events. Cohort 1(2inj): pneumonitis grade 3, possibly related to study drug; pulmonary embolism grade 3, unrelated to study drug. Cohort 2 (2inj): empyema grade 3, possibly related to study drug; pneumonia grade 3, pre-syncope grade 2, and bullous dermatitis grade 3, all unrelated to study drug.

Patient demographics

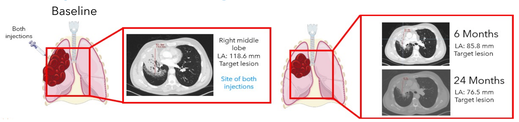
Age	Years
Median (Range)	67 (43-88)
Sex	**n (%)**
Female	32 (44)
Male	41 (56)
PD-L1 Expression	**n (%)**
<1%	35 (48)
1-49%	15 (21)
≥50%	19 (26)
Unknown	4 (5)
Histology	**n (%)**
Squamous	16 (22)
Non-Squamous	57 (78)
Treatment regimen at enrollment	**n (%)**
Single ICI	50 (68)
ICI plus pemetrexed	23 (32)

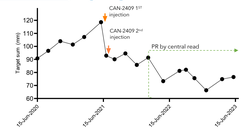
Safety

Most common treatment-emergent related adverse events occurring in ≥ 5% patients, n=73				
SOC/Adverse Event Term (v5.0)	**Grade 1**	**Grade 2**	**Grade 3**	**Total**
Gastrointestinal disorders	**n (%)**			
Diarrhoea	5 (7)	0 (0)	0 (0)	5 (7)
Nausea	11 (15)	4 (5)	0 (0)	15 (21)
Vomiting	4 (5)	2 (3)	0 (0)	6 (8)
General disorders and administration site conditions				
Chills	8 (11)	0 (0)	0 (0)	8 (11)
Fatigue	16 (22)	7 (10)	0 (0)	23 (32)
Influenza like illness	3 (4)	1 (1)	0 (0)	4 (5)
Pyrexia	12 (16)	1 (1)	1 (1)	14 (19)
Investigations				
Aspartate aminotransferase increased	4 (5)	0 (0)	0 (0)	4 (5)
Blood creatinine increased	4 (5)	3 (4)	0 (0)	7 (10)
Metabolism and nutrition disorders				
Decreased appetite	2 (3)	4 (5)	0 (0)	6 (8)
Nervous system disorders				
Headache	3 (4)	1 (1)	0 (0)	4 (5)
Respiratory, thoracic and mediastinal disorders				
Dyspnoea	2 (3)	4 (5)	0 (0)	6 (8)
Pneumonitis	0 (0)	2 (3)	2 (3)	4 (5)

Responses and long-term survival in patients treated with CAN-2409

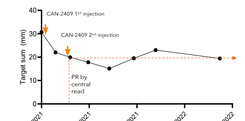
Durable post-treatment tumor regression after CAN-2409 treatment. Patient alive after 47.7 months (ongoing)





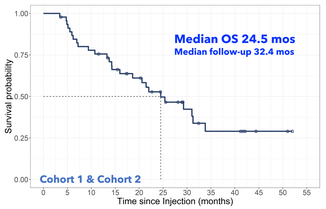
Evidence of abscopal effect with survival of more than 52.4 months (ongoing) after CAN-2409 treatment

Schematics to show general lesion injection orientation;not to scale

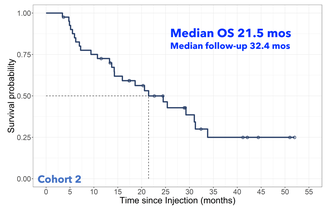


CAN-2409 improves overall survival in patients presenting with poor response to ICI

CAN-2409 improves overall survival in patients inadequately responding to ICI



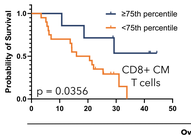
CAN-2409 improves overall survival in patients with progressive disease post ICI



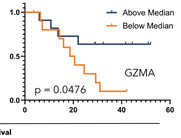
Kaplan Meier curves reporting survival in evaluable patients that received 2 injections and completed the 12-week treatment window, receiving a CT scan at week 12. Cohorts 1 & 2 safety population mOS is 14.3 mos (mFU 29.1 mos); cohort 2 safety population mOS is 13.7 mos (mFU 31.8 mos).

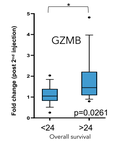
CAN-2409 treatment induces systemic increase in cytotoxic T cell response that correlates with improved patient survival

High post 2nd injection CD8+ CM T cells associate with long survival



High post 2nd injection granzyme A (left) and B (right) associate with long survival

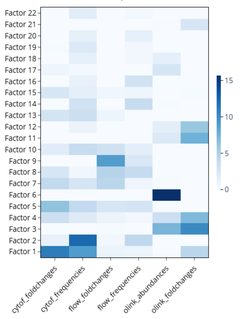




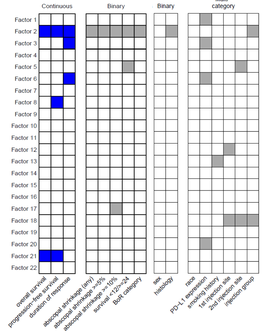
Flow cytometry and Olink proteomics data were generated longitudinally on peripheral blood. Post-second injection changes were analyzed individually, using log-rank and t-tests. This analysis revealed significant associations between survival and high post injection levels of cytotoxic T cells and granzymes.

Multi-Omic data integrated into distinct programs (factors) that are associated with clinical outcomes

Meaningful variations were captured up to Factor 22



MOFA factors associate with clinical features

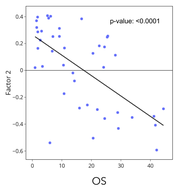


Using machine learning, MOFA integrated 3,097 features across CyTOF, Olink proteomics, and flow cytometry to identify latent immunological programs across the treatment window.

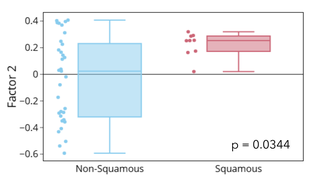
Across all factors, significant associations were found with key clinical outcomes and features. Factor 2 and 21 inversely correlated with overall survival. Variation in Factor 2 is driven by cell frequencies determined by CyTOF and flow cytometry.

MOFA identified factor 2 is significantly associated with overall survival and histologic subtype

Factor 2 levels by OS



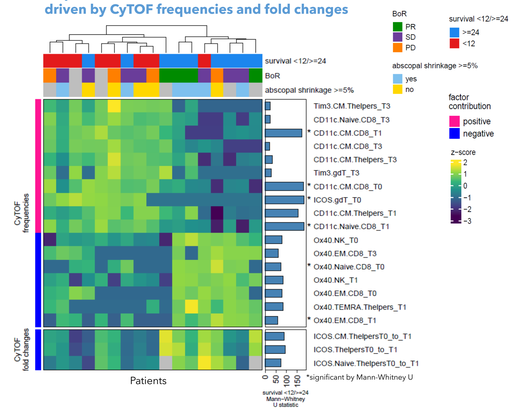
Factor 2 levels by histology



Patients with longer survival and non-squamous histology have lower levels of Factor 2 (spearman correlation and t-test p values shown), suggesting higher prevalence of an immune-resistant phenotype in patients with SQ histology.

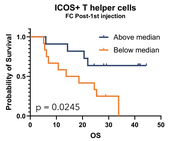
MOFA Factor 2 represents coordinated changes in the immune response independently associated with clinical outcomes

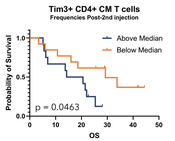
Top and Bottom 10 features from Factor 2 are driven by CyTOF frequencies and fold changes



High frequencies of Tim-3–expressing immune cells in <12 month surviving patients is consistent with T cell dysfunction. Patients surviving >24 months showed increased frequencies of activated lymphocytes expressing OX40 and ICOS, which are linked to enhanced T cell persistence and robust anti-tumor immune responses.

Some features are also individually associated with survival

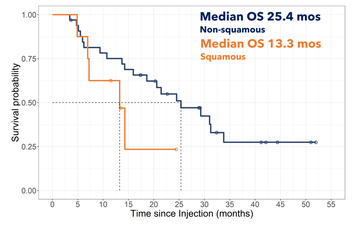




While some individual features with strong contribution to Factor 2 are independently associated with survival, not all are- and many would be missed by conventional analysis methods. MOFA identifies coordinated changes across immune functions.

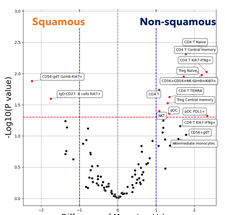
Improved survival and immune response in non-squamous patients treated with CAN-2409

Cohort 2 evaluable patients by histology



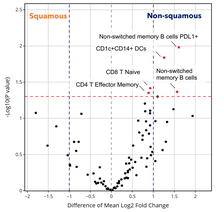
Kaplan-Meier curve demonstrating improved survival in patients with non-squamous histology as compared to squamous histology

Baseline differences in histology by flow cytometry



The immune state in non-squamous patients is more permissive to an immune response to CAN-2409+valacyclovir.

Post 2nd injection differences in histology by flow cytometry



Enhanced immune activation is observed following treatment in patients with NSQ tumors, which indicates a potentially greater therapeutic benefit in this histologic subgroup.

Conclusions

CAN-2409+valacyclovir administration is associated with enhanced survival in NSCLC patients with progressive disease despite ICI treatment. Unsupervised AI driven analysis identified distinct programs reflecting a favorable immune state before and after treatment in patients with longer survival. Patients with NSCLC with non-squamous histology exhibited enhanced immune activation after CAN-2409+valacyclovir treatment compared to patients with squamous histology, which was associated with improved survival.

References and Acknowledgements

References: ***1. Aggarwal C., et al. Overall survival after treatment with CAN-2409 plus valacyclovir in combination with continued ICI in patients with stage III/IV NSCLC with an inadequate response to ICI. J Clin Oncol 2024;42:8634.***
2. Argelaguet, R., et al. MOFA+: a statistical framework for comprehensive integration of multi-modal single-cell data. Genome Biol 2020;21:111.

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