VALO2 study
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Real-world outcomes of first-line PD-(L)1 inhibitor monotherapy in metastatic NSCLC across Nordic healthcare systems

Scientific briefing for Nordic Health Data Summit participants

Key scientific messages

- VALO2 evaluated site-specific outcomes after first-line PD-(L)1 inhibitor monotherapy in patients with PD-L1 ≥50% metastatic NSCLC and tested a federated Nordic research model.
- The Danish analysis compared policy-period groups, whereas the Finnish and Norwegian analyses compared treatments initiated. The estimates therefore do not represent one common Nordic treatment comparison.
- Observed associations were favourable for the Danish pembrolizumab policy-period group and for pembrolizumab in the Norwegian overall-survival analysis; Finnish estimates were inconclusive. None of these observational associations establishes causality.
- Federated analysis was operationally feasible, but a common data model and reusable code did not ensure comparable cohorts, variables, or adjustment opportunities across sites.

Background and rationale

Non-small cell lung cancer (NSCLC) accounts for approximately 85% of lung cancers. Many patients present with, or subsequently develop, metastatic disease, for which prognosis remains poor despite advances in systemic treatment. For patients without actionable oncogenic driver alterations and with tumour programmed death-ligand 1 (PD-L1) expression ≥50%, pembrolizumab, atezolizumab, and cemiplimab are established first-line immune checkpoint inhibitor options. Pivotal trials compared these agents with chemotherapy rather than directly with one another, leaving uncertainty about their relative performance in routine care.

Real-world evidence can complement trial findings by describing outcomes in patients encountered in everyday practice, including older adults and patients with comorbidity. However, non-random treatment allocation, calendar-time changes, incomplete clinical data, and differences between healthcare systems can distort comparisons. VALO2, part of the Value from Nordic Health Data initiative, therefore addressed two linked questions: how patients receiving first-line PD-(L)1 inhibitor monotherapy fared at participating Nordic institutions, and whether cross-border analysis could be performed within local Secure Processing Environments without transferring patient-level data.

Objectives

The primary objective was to compare overall survival (OS) among patients with PD-L1 ≥50% metastatic NSCLC receiving pembrolizumab, atezolizumab, or cemiplimab as first-line monotherapy. Secondary objectives covered patient characteristics, treatment patterns, treatment duration, time to next line of therapy or death (TTNT), and time to treatment discontinuation or death (TTD). Prespecified age analyses compared patients aged <75 and ≥75 years where event counts allowed. Exploratory analyses assessed the prognostic information provided by the Lung Immune Prognostic Index (LIPI) and Lung Immuno-Oncology Prognostic Score (LIPS-3). An infrastructure objective assessed cross-border use of local Secure Processing Environments (SPEs).

Study design and methods

Design and population

VALO2 was a retrospective, multisite observational cohort study using routinely collected electronic health record data. The observation period was 1 January 2018 to 31 December 2024; patients were identified through 30 June 2024 to provide at least six months of potential follow-up. Participating institutions were Rigshospitalet in Denmark, Helsinki University Hospital (HUS) in Finland, and Oslo University Hospital (OUS) in Norway. These institutional and regional cohorts should not be assumed to represent national populations.

Eligible patients were adults with histologically or cytologically confirmed metastatic NSCLC, PD-L1 expression ≥50%, and at least one administration of first-line pembrolizumab, atezolizumab, or cemiplimab monotherapy. Patients with documented EGFR, ALK, or ROS1 alterations or previous targeted therapy were excluded. Both de novo metastatic disease and progression from earlier-stage NSCLC were included.

Table 1. Final analytical cohorts and site-specific comparisons

Site	Final N	Exposure groups	Comparison
Rigshospitalet, Denmark	887	Pembrolizumab policy period: 694 (78.2%); atezolizumab policy period: 193 (21.8%)	Policy-period groups
HUS, Finland	91	Pembrolizumab: 74 (81.3%); cemiplimab: 17 (18.7%)	Treatment initiated
OUS, Norway	76	Pembrolizumab: 64 (84.2%); cemiplimab: 12 (15.8%)	Treatment initiated

Footnotes: Danish exposure-group assignment was based on predefined treatment-policy periods and did not necessarily correspond to the agent administered. HUS and OUS groups reflected treatment initiation. Atezolizumab at HUS was excluded from comparative analyses because the group was too small.

Figure 1. VALO2 study design and federated analytical framework. *The figure is adapted from Slide 13 of the VALO2 Consortium Meeting presentation. Patient-level data remained within participating institutions; standardized analyses were conducted in local secure environments, and only aggregate outputs were exported.*

Abbreviations: OMOP CDM, Observational Medical Outcomes Partnership Common Data Model; SPE, Secure Processing Environment. Note: the Danish analytical environment supported the local team but was not evaluated as an external researcher-facing SPE in the same manner as HUS and OUS.

Endpoints and statistical considerations

OS was defined from treatment initiation to death from any cause and was summarized using Kaplan-Meier methods and Cox proportional hazards models. TTNT was defined as time to a qualifying subsequent line of anticancer therapy or death. TTD was defined as time to permanent discontinuation of index treatment, treatment switch, treatment addition, or death; a 60-day allowable gap informed discontinuation. Because death formed part of TTNT and TTD, these composite endpoints reflect both treatment trajectory and mortality and should not be interpreted as direct measures of disease progression or treatment efficacy.

Cumulative-incidence methods and Fine-Gray regression were used for TTNT and TTD, with new primary malignancy treated as a competing event where identifiable. Adjustment depended on covariate availability, missingness, cohort size, and event counts. Multiple imputation and inverse probability of treatment weighting sensitivity analyses were performed for Denmark and Finland, but not Norway. No pooled estimate was produced because exposure definitions, cohort construction, variable availability, and analytical implementation were insufficiently comparable.

Results

Patient characteristics

Median age was 70 years at Rigshospitalet, 70 years at HUS, and 71 years at OUS. Approximately 29% to 36% of patients were in the oldest reported age category. Women accounted for 57% of the Danish cohort and 59% of the Finnish cohort; overall Norwegian sex counts were restricted by disclosure control. Smoking history, histology, Eastern Cooperative Oncology Group performance status, and prognostic-score components were not consistently available across sites, limiting common adjustment strategies.

Overall survival

At Rigshospitalet, assignment to the pembrolizumab policy-period group was associated with a lower adjusted hazard of death than assignment to the atezolizumab policy-period group (hazard ratio [HR] 0.72, 95% confidence interval [CI] 0.58–0.90; p=0.004). Unadjusted median OS was 566 and 401 days, respectively. The inverse probability-weighted sensitivity estimate was similar (HR 0.76, 95% CI 0.60–0.95).

At HUS, the adjusted association for pembrolizumab versus cemiplimab was not statistically significant (HR 1.48, 95% CI 0.60–3.67; p=0.391). Median OS was not reached in either group. Survival at 500 days was estimated at 55.4% with pembrolizumab and 57.4% with cemiplimab. The wide CI indicates substantial uncertainty and does not demonstrate equivalence.

At OUS, pembrolizumab initiation was associated with a lower adjusted hazard of death than cemiplimab initiation (HR 0.42, 95% CI 0.20–0.88; p=0.022). Median OS was not reached with pembrolizumab and was 192 days with cemiplimab. The comparator included only 12 patients and adjustment was restricted, so the magnitude of the association is uncertain.

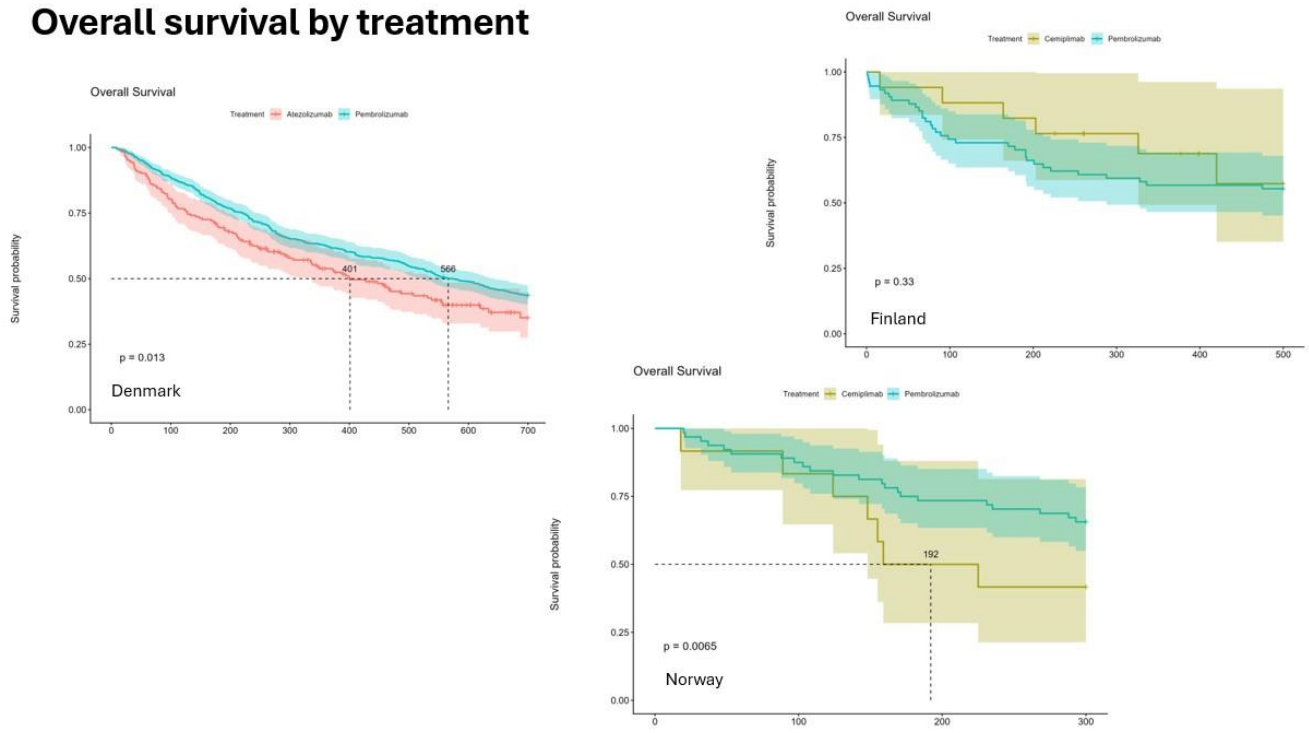

Figure 2. Country-specific Kaplan-Meier estimates of overall survival. *Reproduced from Slide 18 of the VALO2 Consortium Meeting presentation. The Danish analysis compared pembrolizumab and atezolizumab policy-period groups; the Finnish and Norwegian analyses compared treatment initiation. The plots must be interpreted separately because exposure definitions, cohort sizes, follow-up, covariate availability, and analytical implementation differed.*

Abbreviations: CI, confidence interval; KM, Kaplan-Meier; OS, overall survival. Notes: The HUS result is inconclusive rather than evidence of equivalence. The OUS cemiplimab group included 12 patients. Confirm before external distribution that the embedded plots are the latest approved versions and that Danish labels specify policy-period groups.

Table 2. Adjusted site-specific clinical outcome estimates

Site	Comparison	OS HR (95% CI); p	TTNT sHR (95% CI); p	TTD sHR (95% CI); p
Rigshospitalet	Pembro vs atezo policy period	0.72 (0.58–0.90); 0.004	0.71 (0.57–0.87); 0.001	0.79 (0.65–0.95); 0.012
HUS	Pembro vs cemi	1.48 (0.60–3.67); 0.391	1.45 (0.67–3.14); 0.346	1.06 (0.63–1.79); 0.817
OUS	Pembro vs cemi	0.42 (0.20–0.88); 0.022	0.65 (0.26–1.62); 0.360	0.97 (0.41–2.31); 0.950

Abbreviations: atezo, atezolizumab; cemi, cemiplimab; CI, confidence interval; HR, hazard ratio; OS, overall survival; pembro, pembrolizumab; sHR, subdistribution hazard ratio; TTD, time to treatment discontinuation or death; TTNT, time to next line of therapy or death.

Interpretation: Values below 1 indicate a lower estimated hazard of the corresponding outcome for pembrolizumab relative to the site-specific comparator. TTNT and TTD include death and are not isolated measures of treatment persistence. Models, adjustment sets, missing-data handling, follow-up, and sample sizes differed by site. Statistical significance does not establish causality; non-significance does not establish equivalence.

Secondary outcomes and treatment patterns

Chemotherapy was the most frequently reported subsequent treatment category. Median first-line treatment duration ranged from 2.44 to 4.88 months with pembrolizumab, was 2.55 months in the

Danish atezolizumab policy-period group, and ranged from 2.74 to 3.60 months with cemiplimab. At Rigshospitalet, the pembrolizumab policy-period group had lower cumulative incidence of the TTNT composite event (sHR 0.71, 95% CI 0.57–0.87; p=0.001) and TTD composite event (sHR 0.79, 95% CI 0.65–0.95; p=0.012). No statistically significant treatment-group associations were identified for TTNT or TTD at HUS or OUS. Because both composites included death, the Danish findings may partly reflect the OS difference rather than treatment transition or discontinuation alone.

Higher LIPI categories were associated with poorer outcomes where LIPI could be calculated. At Rigshospitalet, LIPI categories 1 and 2 were associated with higher hazards of death than category 0. These exploratory findings are hypothesis-generating because score availability and model implementation differed across sites. VALO2 did not include a dedicated comparative safety analysis; treatment discontinuation cannot substitute for adjudicated adverse-event evidence.

Treatment patterns and treatment sequences

Characteristic	Rigshospitalet (n=887)	HUS (n=91)	OUS (n=76)
First-line treatment distribution			
Pembrolizumab	694 (78.2%)	74 (81.3%)	64
Atezolizumab	193 (21.8%)	Not represented	Not represented
Cemiplimab	Not represented	17 (18.7%)	12
Second-line therapy after first-line pembrolizumab			
Platinum-based chemotherapy	186/694 (26.8%)	19/74 (25.7%)	11/64 (17.2%)
Non-platinum chemotherapy	79/694 (11.4%)	23/74 (31.1%)	13/64 (20.3%)
PD-L1 inhibitor	8	<5	<5
Other	8	<5	NA
Second-line therapy after first-line atezolizumab/cemiplimab			
Platinum-based chemotherapy	58/193 (30.1%)	6/17 (35.3%)	<5
Non-platinum chemotherapy	25/193 (13.0%)	6/17 (35.3%)	<5
PD-1 inhibitor	9	<5	<5
PD-L1 inhibitor	<5	<5	<5
Median duration of first-line therapy, months (IQR)			
Pembrolizumab	4.88 (1.52–13.41)	2.44 (0.70–6.84)	4.18 (1.63-17.78)
Atezolizumab	2.55 (1.00–7.37)	Not represented	Not represented
Cemiplimab	Not represented	3.60 (1.37–5.81)	2.74 (0.51-5.68)

Figure 3. First-line exposure groups, selected subsequent treatment categories, and median first-line treatment duration. *Adapted from Slide 19 of the VALO2 Consortium Meeting presentation. In Denmark, groups were defined by treatment-policy period; in Finland and Norway, groups reflected treatment initiation. Subsequent-treatment percentages use the relevant first-line group as denominator.*

Abbreviations: IQR, interquartile range; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1. Notes: OUS first-line values should read pembrolizumab 64 (84.2%) and cemiplimab 12 (15.8%). Values <5 reflect local disclosure-control suppression and are neither zero nor necessarily missing. Treatment distributions do not represent complete local prescribing practice.

Discussion and clinical interpretation

VALO2 provides site-specific observational evidence rather than a head-to-head Nordic comparison. The most consequential design difference is that the Danish groups represented treatment-policy periods, whereas the Finnish and Norwegian groups represented treatments initiated. Calendar time, evolving supportive care, implementation of new treatments, patient selection, and unmeasured prognostic factors could therefore contribute to the Danish associations. Consistency across OS, TTNT, TTD, and sensitivity analyses supports the presence of a difference between the Danish policy-period cohorts, but it does not identify the treatment itself as the cause.

The Finnish estimates were imprecise, particularly for cemiplimab, and should be considered inconclusive. The Norwegian OS estimate was statistically significant but derived from a small comparator group and limited prognostic adjustment. It should be interpreted as an exploratory association, especially because the estimated TTNT and TTD associations were not statistically significant.

Study limitations

- Non-random treatment allocation and potential residual or unmeasured confounding, despite multivariable adjustment and selected sensitivity analyses.
- Different exposure definitions, cohort-selection procedures, adjustment sets, missing-data methods, and follow-up across sites.
- Small cemiplimab groups at HUS (n=17) and OUS (n=12), producing wide confidence intervals and limited support for subgroup analyses.
- Inconsistent availability of smoking history, ECOG performance status, histology, quantitative PD-L1 values, biomarkers, and prognostic-score components.
- Use of routinely collected data not generated primarily for research, creating potential for incomplete capture and misclassification.
- Selected university-hospital and regional populations that may not represent national treatment practice or all eligible patients.
- Local disclosure-control suppression, which restricted reporting but should not be interpreted as missingness.
- Composite TTNT and TTD definitions that included death and may therefore be driven partly by mortality differences.

Conclusions and key scientific takeaways

VALO2 demonstrated the operational feasibility of federated cross-border research across participating Nordic institutions while keeping patient-level data local. Standardized analytical code was implemented in local secure environments, but common infrastructure did not automatically yield comparable cohorts, variables, or treatment definitions.

The Danish pembrolizumab policy-period group had more favourable OS, TTNT, and TTD outcomes than the atezolizumab policy-period group. No statistically significant treatment-group differences were identified at HUS. At OUS, pembrolizumab was associated with longer OS than cemiplimab, while TTNT and TTD did not differ significantly. These findings should be treated as site-specific observational associations rather than definitive comparative-effectiveness estimates.

Future Nordic studies would benefit from prospective feasibility assessment, transparent cohort derivation, harmonized exposure definitions, consistent capture of prognostic and biomarker variables, and demonstration of analytical comparability before pooling results.