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UV1 telomerase vaccine with ipilimumab and nivolumab as second line treatment for pleural mesothelioma – A phase II randomised trial

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ABSTRACT

Purpose: The NIPU-trial investigates the effect of adding the telomerase vaccine UV1 to treatment with ipilimumab and nivolumab for patients with pleural mesothelioma (PM).

Methods: In this phase 2 open-label trial, patients with PM progressing after first-line chemotherapy were randomised to receive ipilimumab and nivolumab alone (arm B) or combined with UV1 (arm A). The primary endpoint was progression-free survival (PFS) as determined by BICR. It was estimated that 69 PFS events were needed to detect a hazard ratio (HR) of 0.60 with 80% power and a one-sided alpha level of 0.10.

Results: 118 patients were randomised. The median PFS determined by blinded independent central review (BICR) was 4.2 months (95%CI 2.9–9.8) in arm A and 4.7 months (95%CI 3.9–7.0) in arm B (HR 1.01, 80%CI 0.75–1.36 P = 0.979), after a median follow-up of 12.5 months (95%CI 9.7–15.6). The investigator-determined median PFS was 4.3 months (95%CI 3.0–6.8) in arm A and 2.9 months (95%CI 2.4–5.5) in arm B (HR 0.60, 80% CI 0.45–0.81 P = 0.025). Confirmed objective response rate (ORR) by BICR was 31% in arm A and 16% in arm B (odds ratio 2.44 80%CI 1.35–4.49 P = 0.056). After a median follow-up time of 17.3 months (95%CI 15.8–22.9), the OS was 15.4 months (95%CI 11.1–22.6) in arm A and 11.1 months (95%CI 8.8–18.1) in arm B, (HR 0.73, 80%CI 0.53–1.0, P = 0.197).

Conclusion: The primary endpoint was not met. Predefined analyses of response rates are in favour of adding the vaccine.

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1. Introduction

There has until recently been few available treatment options after first-line platinum-based chemotherapy for patients with inoperable pleural mesothelioma (PM). Phase 2 studies testing the use of checkpoint inhibitors in second or later lines showed 8–29% objective response rates (ORR) and a median progression-free survival (PFS) of 2.1–6.2 months [1–3]. Improved overall survival (OS) has been observed in phase III trials for patients receiving first-line immunotherapy with or without chemotherapy, as compared to chemotherapy alone [4–6]. The CheckMate 743 trial demonstrated prolonged survival with ipilimumab and nivolumab compared to chemotherapy, but the median OS is still limited (18.1 months) and further improvements are warranted [4].

Cancer vaccines have been studied in many cancers showing minimal clinical effect as single agents [7]. Combining vaccines with checkpoint inhibitors to boost the immune response or with chemotherapy to reduce the effect of immunosuppressive myeloid cells have potential to improve clinical efficacy [8]. The UV1 vaccine is a peptide vaccine targeting telomerase. The expression of telomerase (hTERT) is upregulated in most human cancers including mesothelioma, in which it is overexpressed in 91–100% [9]. The UV1 vaccine has previously been tested in malignant melanoma, prostate, and lung cancer alone or in combination with checkpoint inhibitors. Durable vaccine-specific immune responses were observed in 78% of the patients included in three trials [10,11].

The randomised open label phase 2 NIPU trial investigated ipilimumab (IPI) and nivolumab (NIVO) with or without UV1 vaccination as second-line treatment in PM. The main objective was to evaluate and compare the efficacy of nivolumab and ipilimumab with or without UV1 vaccine in patients with inoperable pleural mesothelioma progressing after first-line platinum-based chemotherapy.

1.1. Materials and methods

1.1.1. Participants

Patients with histologically or cytologically confirmed PM progressing on or after first-line platinum-based chemotherapy were randomised 1:1 to ipilimumab and nivolumab (IPI-NIVO) alone (Arm B) or combined with UV1 (Arm A). Randomisation was performed automated in Viedoc version 4 and was done in blocks with block size 6 for the first 6 patients and with variable block sizes for patients included after that. The randomisation algorithm was created by the Clinical Trial Unit, investigators enrolled patients and study nurses at each centre performed the randomisation in the electronic case report software (Viedoc). Other inclusion and exclusion criteria have been previously described and include adequate organ function, measurable lesions according to RECIST and no immunological disease, active infections or immunosuppressive treatments [12]. Six sites in five countries participated in the trial with Oslo University Hospital as the sponsor. All participating centres were university hospitals. Patients were referred from other hospitals in the respective countries. All patients provided written informed consent. The study was performed in agreement with the Declaration of Helsinki and the protocol was approved by relevant ethics committees. The trial is registered in clinicaltrials.gov (NCT04300244) and EUDRACT (2019–002721-30).

1.1.2. Trial design and treatments

The NIPU-trial is a multicentre, open-label, randomised phase 2 trial. Patients were included from June 2020 to January 2023 and were randomly assigned 1:1 to receive intravenous ipilimumab (1 mg/kg Q6 weekly) and nivolumab (240 mg Q2 weekly) with or without the UV1 telomerase vaccine. UV1 was administered as eight 300 μg intradermal injections over 13 weeks together with 75 μg GM-CSF. The IPI-NIVO treatment was continued until radiological progression, unacceptable toxicity, patient withdrawal, or for a maximum of 2 years. Treatment could continue beyond progression when there was evidence of clinical benefit.

The primary endpoint was PFS evaluated by modified response evaluation criteria in solid tumours (mRECIST) [13] as determined by BICR, at the time of 69 PFS events. Secondary endpoints should be reported at the end of study and included OS, ORR, duration of response, time to response, safety, and patient reported outcomes as described earlier [12].

Safety assessments were performed on patients who had received at least one dose of study treatment. Adverse events were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Information on histological subtype was collected from the local pathology reports. Programmed death-ligand 1 (PD-L1) expression on tumour cells was evaluated by immunohistochemistry of archived formalin fixed paraffin embedded tumour tissue, using a PD-L1 mouse monoclonal antibody for staining (405.9A11, Cell Signaling Technology, Danvers, USA). This was performed centrally at the Department of Pathology at Oslo University Hospital, Norway.

1.1.3. Statistical analysis

It was estimated that 69 events in 118 patients were required to demonstrate a hazard ratio (HR) for PFS of 0.6 with a power of 80% and a one-sided alpha level of 0.10. PFS is defined as the time from randomisation to the first of progression or death of any cause. A Cox proportional hazards regression model was used to assess the PFS and OS, including covariates for randomised treatment and baseline histology. It was planned to include PD-L1 status in the model, but this variable was omitted because information on PD-L1 status was missing for 34% of the patients. Supportive analyses of PFS were performed using the Kaplan-Meier method with log-rank test, with censoring of patients who started any subsequent anticancer treatment without a prior reported progression, and using investigator determined progression. OS was analysed using the same methodology as for PFS. ORR was evaluated based on BICR according to mRECIST using the best response until data cut-off. ORR was analysed by logistic regression, including treatment arm and baseline histology in the model with a predefined 1-sided alpha of 0.1. The odds ratio was estimated from the model. Median follow-up was calculated from the survival data using the reversed Kaplan-Meier method. Further details on the statistical analyses are available in the Statistical Analysis Plan (Appendix A).

2. Results

2.1. Patient population

A total of 133 patients were screened and 118 patients were randomised in a 1:1 ratio from June 2020 to January 2023. Study consort diagram, listing of reasons for screening failures and protocol deviations are listed in Appendix B. The treatment arms were well balanced with regards to age, sex, ECOG performance status, histology, and PD-L1 expression on tumour cells (Table 1). PD-L1 status could not be analysed for one third of the patients and only 16 patients (13.6%) had a PD-L1 positive tumour (≥1%).

The median follow-up duration at assessment of the primary endpoint was 12.5 months (95% CI 9.7–15.6) (data cut-off date February 10, 2023). The data cut-off used to assess the secondary endpoints was August 28, 2023, after a median follow-up of 17.3 (95% CI 15.8–22.9) months.

2.1.1. Efficacy

The median PFS as determined by BICR was 4.2 months (95% CI 2.9–9.8) in arm A and 4.7 months (95% CI 3.9–7.0) in arm B (Figure 1B). The HR was 1.01 (80% CI 0.75–1.36) (Figure 1A). The investigator-evaluated median PFS was 4.3 months in arm A (95% CI 3.0–6.8) and 2.9 months (95% CI 2.4–5.5) in arm B (HR 0.60 80% CI 0.45–0.81)

Table 1
Baseline demographics and clinical characteristics for patients in treatment group A (IPI/NIVO + UV1 vaccine and arm B (IPI/NIVO alone). Number of patients (percentage of patients within each subgroup).

	Arm A (N = 59)	Arm B (N = 59)	Total (N = 118)
Sex			
Female	14 (23.7%)	12 (20.3%)	26 (22.0%)
Male	45 (76.3%)	47 (79.7%)	92 (78.0%)
Age			
Median	71.0	72.0	71.0
Range	39.0 - 79.0	42.0 - 83.0	39.0 - 83.0
ECOG			
0	17 (28.8%)	18 (30.5%)	35 (29.7%)
1	42 (71.2%)	41 (69.5%)	83 (70.3%)
Histology			
Epithelioid	44 (74.6%)	47 (79.7%)	91 (77.1%)
Sarcomatoid	5 (8.5%)	4 (6.8%)	9 (7.6%)
Biphasic	5 (8.5%)	7 (11.9%)	12 (10.2%)
Rhabdoid	1 (1.7%)	0 (0.0%)	1 (0.8%)
Unknown	4 (6.8%)	1 (1.7%)	5 (4.2%)
PD-L1(%)			
< 1	31 (52.5%)	32 (54.2%)	63 (53.4%)
1-49	6 (10.2%)	4 (6.8%)	10 (8.5%)
≥ 50	2 (3.4%)	4 (6.8%)	6 (5.1%)
Unknown	20 (33.9%)	19 (32.2%)	39 (33.1%)

(Figure 1 C+D). Further supportive analyses of the PFS are shown in Appendix B. Log-rank test of investigator-determined PFS for epithelioid tumours alone, shows a median PFS of 5.5 months (95% CI 4.1–10.1) in the vaccine arm A and 2.9 months (95% CI 1.8–5.5) in the standard arm, p = 0.005. For non-epithelioid tumours, there was no significant difference (see Appendix B for Kaplan-Meier plots). Confirmed ORR by BICR was 31% in arm A (IPI-NIVO + UV1 vaccine) compared to 16% in arm B (IPI-NIVO) (odds ratio 2.44 80% CI 1.35–4.49 P = 0.056). There were no complete responses. After an updated follow-up time of 17.3 months, 71 participants (60%) had died. The median OS was 15.4 months (95% CI 11.1–22.6) in arm A and 11.1 months (95% CI 8.8 −18.1) in arm B, with an HR of 0.73 (80% CI 0.53–1.0) (Figure 1E+F). The patients with epithelioid histology have a better prognosis than those with non-epithioid histology (Figure 1E). Kaplan-Meier plots for epithelioid patients only show significant difference in PFS determined by investigator (Supplementary data).

Fig. 1: Forest plots (A, C, E) from Cox regression models showing the effect of adding the vaccine (arm A) compared to the standard (Arm B) controlled for histology. A CI to the left of the vertical line indicates a benefit of adding the vaccine. Non-epithelioid tumours have a CI to the right of the vertical line, indicating worse prognosis compared with epithelioid tumours controlled for treatment arm. Kaplan-Meier plots (B, D, F) for PFS and OS. PFS was evaluated after a median of 12.5 months follow-up by (A,B) blinded independent review and (C,D) local investigators. OS (E,F) was evaluated after an updated follow-up time of 17.3 months.

2.1.2. Safety

The preliminary safety results after 17.3 months of median follow-up time were comparable in the two treatment arms (Table 2 and Appendix B). All patients but one experienced treatment-emergent adverse events (TEAEs) and 63 patients (53%) had at least one grade ≥ 3 TEAE. The most common TEAEs were fatigue / asthenia (33%), pruritus (31%), dyspnoea (30%), musculoskeletal pain (29%) and rash (28%). The most frequently reported TEAEs possibly related to the UV1 vaccine / GM-CSF were injection site reactions (14%), fatigue / asthenia (12%), pruritus (12%) and pyrexia (12%). There were 4 TEAEs leading to death (one pneumonia and one general physical health deterioration in arm A, and two completed suicides in arm B).

3. Discussion

This randomised phase 2 study did not meet its primary endpoint (improved PFS by BICR with an HR of 0.6). ORR (by BICR) showed a significant benefit of adding the UV1 vaccine (alpha level 0.1).

PD-L1 status was lacking for a large proportion of patients and was therefore omitted from the Cox regression model. Available archived tumour tissue was an inclusion criterion, but the tissue provided was not always enough or with a sufficient tumour percentage to determine PD-L1 status. PD-L1 status is not always assessed in routine clinical care. However, the arms were well balanced with respect to PD-L1 status, where known. In this cohort, few tumours were PD-L1 positive compared with previous studies [4]. This may be influenced by the use of different anti-PD-L1 antibodies in different studies.

While the primary endpoint was PFS by BICR, assessment by local radiologists was planned for secondary endpoints and supportive analyses. These analyses indicated an improved PFS among patients in the vaccine arm for all histologies combined and for the epithelioid subgroup alone, in contrary to the BICR-analyses. PM is radiologically difficult to assess, reflected in the need for a modified RECIST, which may explain the discrepancy [14]. Further, OS is therefore a more robust endpoint to determine the effect of adding UV1 to IPI-NIVO.

This randomised phase II study was powered to detect an HR for PFS of 0.60 with a one-sided alpha level of 0.10 and 80% power. The statistical design was chosen balancing between minimizing the exposure of a novel drug with uncertain efficacy and safety profile, while still enrolling enough patients to detect signals of meaningful clinical efficacy. It is increasingly acknowledged that PFS may be a negative endpoint for immunotherapy trials, where OS shows benefit, with the clearest example in mesothelioma being the CheckMate-743 study in which the HR for PFS was 1.00 whilst the HR for OS was 0.74 [4]. In CheckMate-743, the difference in OS was statistically significant. It is currently uncertain how a vaccine may affect surrogate efficacy endpoints (PFS and ORR) in PM, and for this reason, the assessment of OS is particularly important [15], and will be followed further as data matures. Pre-defined analyses of subtypes were performed, indicating a worse survival for patients with non-epithelioid histology compared with epithelioid subtype (Figure 1E).

IPI-NIVO is now approved as first-line treatment for PM. Durable responses have been observed, but the majority of patients do not respond or experience early progression, which may be due to an insufficient amount of tumour-specific T cells. There is a need for improvements to overcome the lack of immune response for these patients. Cancer vaccines may enhance the immune response to checkpoint inhibitors. The expression of telomerase is upregulated in most human cancers including 91–100% of mesotheliomas [9] and is therefore a putative target for a universal cancer vaccine. The NIPU trial tested the UV1 vaccine added to IPI/NIVO in the second line setting. There is no reason to believe that adding the UV1 vaccine would be less efficacious in the first-line than in the second-line setting.

4. Conclusion

Addition of the UV1 vaccine did not show significant improvement in PFS. Supportive analyses of ORR by BICR indicate a benefit of adding UV1 to ipilimumab and nivolumab for patients with PM. Further studies are warranted to explore the mechanisms of treatment effect and resistance.

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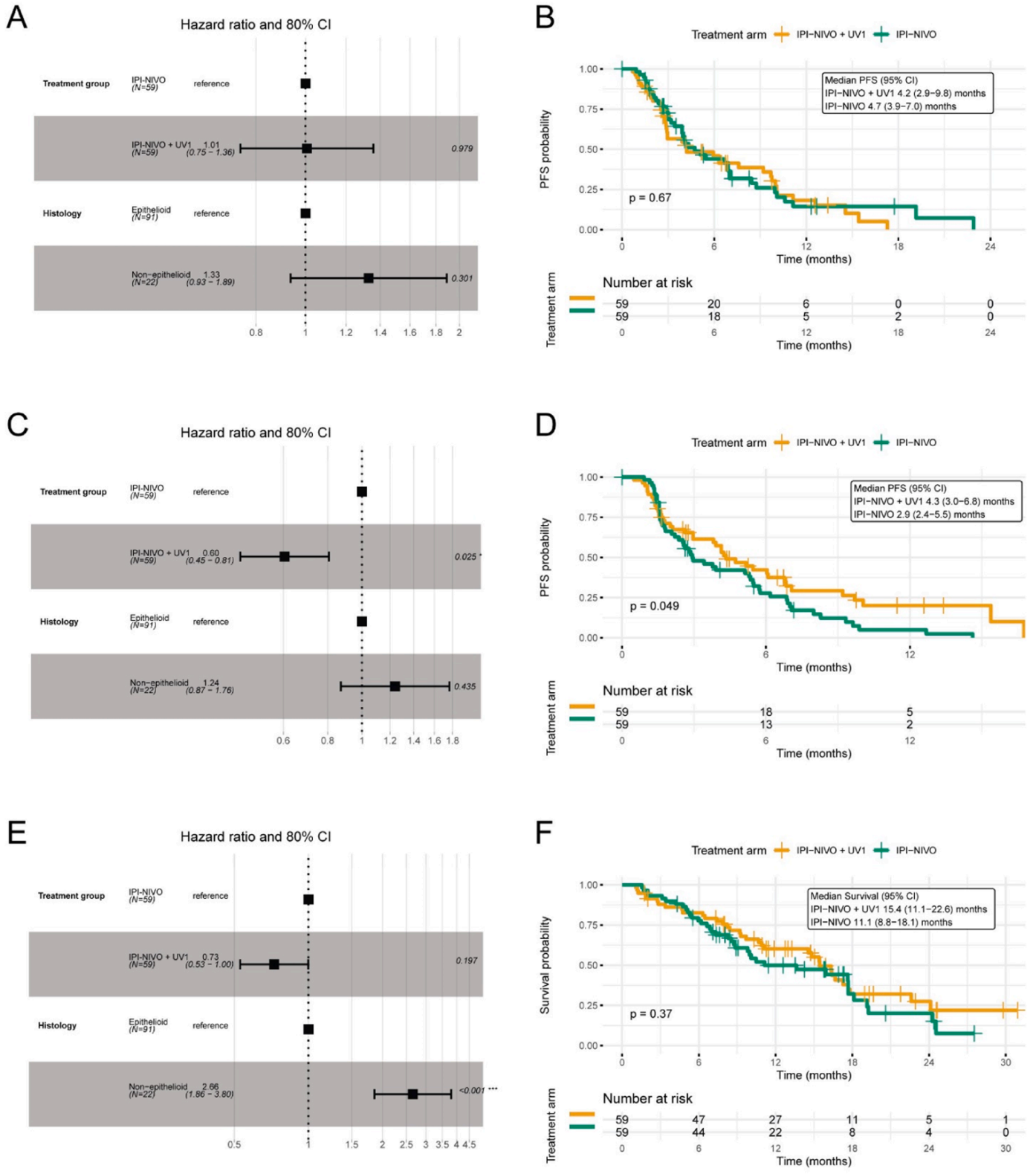

Fig. 1. Forest plots (A, C, E) from Cox regression models showing the effect of adding the vaccine (arm A) compared to the standard (Arm B) controlled for histology. A confidence interval (CI) to the left of the centre (vertical line) indicates a benefit of adding the vaccine. Kaplan-Meier plots (B, D, F) for PFS and OS. PFS was evaluated after a median of 12.5 months follow-up by (A,B) blinded independent review and (C,D) local investigators. OS (E,F) was evaluated after an updated follow-up time of 17.3 months. Investigator-evaluated RECIST display a CI to the left of the centre, indicating a benefit of adding the UV1 vaccine (C) corresponding to a log-rank test $p = 0.49$ (D). Non-epithelioid tumours have a CI to the right of the vertical line, indicating worse prognosis compared with epithelioid tumours controlled for treatment arm (E).

Table 2
Treatment-emergent adverse events (TEAEs) for patients in treatment group A (IPI/NIVO + UV1 vaccine and arm B (IPI/NIVO alone). Total number and percentage of patients experiencing a TEAE and a grade 3 or higher TEAE, by preferred term and system organ class. TEAEs that occurred in at least 10% of patients in at least one treatment arm are included.

Adverse Event	Arm A, **N = 59**		Arm B, **N = 59**	
	Any Grade Complication	Grade 3 + Complication	Any Grade Complication	Grade 3 + Complication
number of patients (percent)				
Endocrine disorders	3 (5.1)	—	7 (12)	—
Hypothyroidism	3 (5.1)	—	7 (12)	—
Gastrointestinal disorders	29 (49)	1 (1.7)	30 (51)	3 (5.1)
Constipation	11 (19)	—	10 (17)	—
Diarrhoea	13 (22)	1 (1.7)	20 (34)	2 (3.4)
Nausea	10 (17)	—	9 (15)	1 (1.7)
General disorders and administration site conditions	33 (56)	3 (5.1)	33 (56)	3 (5.1)
Fatigue / asthenia	19 (32)	1 (1.7)	20 (34)	1 (1.7)
Chest discomfort or pain	11 (19)	1 (1.7)	17 (29)	1 (1.7)
Injection site reaction	9 (15)	—	—	—
Pyrexia	10 (17)	1 (1.7)	9 (15)	1 (1.7)
Immune system disorders	7 (12)	1 (1.7)	2 (3.4)	—
Hypersensitivity	7 (12)	1 (1.7)	2 (3.4)	—
Infections and infestations	17 (29)	4 (6.8)	9 (15)	1 (1.7)
COVID-19	8 (14)	—	6 (10)	—
Pneumonia	9 (15)	4 (6.8)	3 (5.1)	1 (1.7)
Metabolism and nutrition disorders	11 (19)	—	14 (24)	2 (3.4)
Decreased appetite	11 (19)	—	14 (24)	2 (3.4)
Musculoskeletal and connective tissue disorders	19 (32)	3 (5.1)	24 (41)	1 (1.7)
Musculoskeletal pain	12 (20)	2 (3.4)	22 (37)	1 (1.7)
Back pain	10 (17)	1 (1.7)	7 (12)	—
Respiratory, thoracic and mediastinal disorders	22 (37)	4 (6.8)	25 (42)	3 (5.1)
Cough	9 (15)	—	13 (22)	—
Dyspnoea	18 (31)	4 (6.8)	17 (29)	3 (5.1)
Skin and subcutaneous tissue disorders	25 (42)	1 (1.7)	26 (44)	1 (1.7)
Rash	17 (29)	1 (1.7)	16 (27)	1 (1.7)
Pruritus	18 (31)	—	18 (31)	1 (1.7)

CRediT authorship contribution statement

Vilde Drageset Haakensen: Trial management, patient inclusion, interpretation, writing, reviewing and editing. Åsa Kristina Öjlert: Patient inclusion, data analysis, interpretation and writing, reviewing and editing. Solfrid Thunold: Trial management, patient inclusion, reviewing and editing. Anna K Nowak, Wee L Chin, Oscar Grundberg, Saima Farooqi, Weronika M. Szejniuk, Susana Cedres, Jens Benn Sørensen and Maria Bjaanæs: Patient inclusion, reviewing and editing. Tonje Sofie Dalen: Sample preparations, reviewing and editing. Marius Lund-Iversen: Assessment of H&E sections and PD-L1 staining, reviewing and editing. Åslaug Helland: Conceptualization, trial management, patient inclusion, data interpretation, writing, reviewing and editing.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: **Vilde Drageset Haakensen** - Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events: AstraZeneca, Roche, Takeda, Pfizer, BMS, MSD, Janssen. Participation on a Data Safety Monitoring Board or Advisory Board: Novartis, Astra Zeneca, BMS. Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid: Board member of lung cancer patient organization from 2022. Support from the South-Eastern Norway Regional Health Authorities, grant number 2021083. **Maria Bjaanæs** - Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events: AstraZeneca, Pfizer, BMS. **Weronika Maria Szejniuk** – none declared. **Solfrid Thunold** - Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events: BMS. **Susana Cedres** - Participation on a Data Safety Monitoring Board or Advisory Board: F. Hoffmann La Roche AG, MSD Oncology, Pfizer, Amphera, Boehringer Ingelheim, BMS **Wee L Chin** – none declared. **Tonje Sofie Dalen** – none declared. **Saima Farooqi** - Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events: Merck. **Oscar Grundberg** – none declared. **Åslaug Helland** - All support for the present manuscript (e.g., funding, provision of study materials, medical writing, article processing charges, etc.): South-Eastern Norway Regional Health Authorities, grant number 202007 and 2016056, Ultimovacs, BMS. Grants or contracts from any entity: Roche, InCyte, Astra Zeneca, Merck, Novartis, Eli Lilly, GSK, Illumina, Nanopore. Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events: AstraZeneca, Janssen, Medicovver, Bayer, Eli Lilly, MSD, BMS, Merck, Sanofi, Abbvie, Pfizer, Takeda, Novartis, Roche. Participation on a Data Safety Monitoring Board or Advisory Board: AMGEN (DSMC), AdBoard: Roche, AstraZeneca, Pfizer, Janssen, BMS, EliLilly, Abbvie, Bayer, Sanofi, Merck, Takeda. Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid: Board member of lung cancer patient organization until 2022 **Marius Lund Iversen** – none declared. **Anna K Nowak** - Grants or contracts from any entity: Astra Zeneca. Participation on a Data Safety Monitoring Board or Advisory Board: AstraZeneca, BMS, Douglas Pharmaceuticals **Åsa Kristina Öjlert** – none declared. **Jens Benn Sørensen** - Participation on a Data Safety Monitoring Board or Advisory Board: BMS, Merck, Astra Zeneca.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2024.113973.

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