NYE METODER

# Anmodning om vurdering av legemiddel i Nye metoder

## Skjema for leverandører

En leverandør som ønsker offentlig finansiering av et legemiddel/legemiddelindikasjon i den norske spesialisthelsetjenesten, skal anmode om vurdering i Nye metoder ved å fylle ut dette skjemaet.

Utfylt anmodningsskjema sendes til Nye metoder: nyemetoder@helse-sorost.no

Leverandøren skal på anmodningstidspunktet både ha et forslag til type helseøkonomisk analyse og en plan for når de leverer dokumentasjonen. Merk at dokumentasjon i henhold til oppdraget fra Bestillerforum for nye metoder må leveres inn senest 12 måneder etter anmodningstidspunktet.

Hele anmodningsskjemaet skal fylles ut. Mer informasjon og veiledning finnes i artikkelen For leverandører (nyemetoder.no)

**Merk**: Skjemaet vil bli publisert i sin helhet på nyemetoder.no.

**Innsender er klar over at skjemaet vil bli publisert i sin helhet (må krysses av):** ☒

**Fyll ut dato for innsending av skjema**: 25.06.2026

| 1 Kontaktopplysninger | |
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| 1.1 Leverandør (innehaver/søker av markedsføringstillatelse i Norge) | Accord Healthcare AB |
| 1.2 Navn kontaktperson | Tomas Hallafors |
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| 2 Legemiddelinformasjon og indikasjon | |
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| 2.1 Hva gjelder anmodningen?<br><br>*Kryss av for hva anmodningen gjelder* | Et nytt virkestoff ☐<br>En indikasjonsutvidelse / ny indikasjon ☒<br>En ny styrke eller formulering ☐ |
| 2.2 Hvilken indikasjon gjelder anmodningen? | 1. Ikke-småcellet lungekreft (NSCLC)<br>HETRONIFLY i kombinasjon med karboplatin og pemetreksed er indisert til førstelinjebehandling |

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| *Indikasjonen skal oppgis på norsk. Hvis prosess for godkjenning pågår, oppgi også indikasjon på engelsk.*<br><br>*Merk: Leverandør skal anmode om vurdering av hele indikasjonen som de har fått godkjent eller søker om godkjenning for. Dersom leverandør foreslår en avgrensning til undergrupper, må dette begrunnes og leverandør må levere dokumentasjonen som trengs for å foreta en vurdering av undergruppen i tillegg til dokumentasjonen for hele indikasjonen.* | av voksne pasienter med ikke-plateepitel-NSCLC uten EGFR-, ALK- eller -positive mutasjoner, som har<br>- lokalavansert NSCLC som ikke er kandidater for kirurgi eller radioterapi, eller<br>- metastatisk NSCLC.<br><br>2. <u>Øsofagealt plateepitelkarsinom (OSCC)</u><br>HETRONIFLY i kombinasjon med fluoropyrimidin- og platinabasert kjemoterapi er indisert til førstelinjebehandling av voksne pasienter med ikke-resekterbart, lokalavansert, residiverende eller metastatisk øsofagealt plateepitelkarsinom med tumorer som uttrykker PD-L1 med en CPS ≥<br><br>Pending EC decision:<br>3. HETRONIFLY i kombinasjon med karboplatin og nab-paklitaksel er indisert til førstelinjebehandling av voksne pasienter med ikke-resekterbart, lokalavansert eller metastatisk ikke-småcellet plateepitelkarsinom i lungene (plateepitel-NSCLC).<br><br>We are applying for the reimbursement of Hetronifly (Serplulimab) for all the above indications. |
| 2.3 Handelsnavn | Hetronifly |
| 2.4 Generisk navn/virkestoff | Serplulimab |
| 2.5 ATC-kode | L01FF12 |
| 2.6 Administrasjonsform og styrke<br><br>*Oppgi også forventet dosering og behandlingslengde*<br><br>*Skriv kort* | Serplulimab is administered intravenously. The initial infusion rate should be set up to 100 mL per hour. If the first infusion is well tolerated, all subsequent infusions may be shortened to 30 minutes (± 10 minutes). Serplulimab must not be administered as an IV push or bolus injection. The total serplulimab dose required can be diluted with a sodium chloride 9 mg/mL (0.9%) solution for injection. When administered in combination with ChT, serplulimab should be given first, followed by ChT on the same day. Use separate infusion bags for each infusion.<br>The recommended dose is 4.5 mg/kg every 3 weeks until disease progression or unacceptable toxicity. Dose escalation or reduction of serplulimab is not recommended. Dose withholding or discontinuation may be required based on individual safety and tolerability. Dose withholding for up to 12 weeks for tolerability is acceptable. |
| 2.7 Farmakoterapeutisk gruppe og virkningsmekanisme. | Pharmacotherapeutic group: antineoplastic agents, monoclonal antibodies and antibody drug conjugates, |

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| *Skriv kort* | PD-1/PD-L1 (Programmed cell death-1/death ligand 1) inhibitors ATC code: L01FF12.<br><br>Therapeutic area: see example below<br><br>Small Cell Lung Carcinoma.<br><br>Serplulimab is a humanized monoclonal IgG4 antibody, which binds to the PD-1 receptor and blocks its interaction with ligands PD-L1 and programmed cell death-ligand 2 (PD-L2). The PD-1 receptor is a negative regulator of T-cell activity that has been shown to be involved in the control of T-cell immune responses. Engagement of PD-1 with the ligands PD-L1 and PD-L2, which are expressed in 16 antigen presenting cells and may be expressed by tumours or other cells in the tumour microenvironment, results in inhibition of T-cell proliferation and cytokine secretion. Serplulimab potentiates T-cell responses, including anti-tumour responses, through the blockade of PD-1 binding to PD-L1 and PD-L2. |

## 3 Historikk – virkestoff og indikasjon

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| 3.1 Har Nye metoder behandlet metoder med det aktuelle virkestoffet tidligere?<br><br>*Hvis ja, oppgi ID-nummer til metoden/metodene i Nye metoder* | Ja ☒ Nei ☐<br><br>ID-nummer:<br>ID2024_076 |
| 3.2 Er du kjent med om andre legemidler/virkestoff er vurdert i Nye metoder til samme indikasjon?<br><br>*Hvis ja, oppgi ID-nummer til metoden/metodene i Nye metoder* | Ja ☒ Nei ☐<br><br>ID-nummer:<br>1st line treatment nsNSCLC (metastatic or unresectable)<br>Atezolizumab (Tecentriq): ID2019_036<br>Cemiplimab (Libtayo): ID2021_007<br>Pembrolizumab (Keytruda): ID2016_067<br>Tislelizumab (Tevimbra): ID2022_127<br>Durvalumab (Imfinzi): ID2018_022<br><br>1st line treatment of squamous NSCLC (metastatic or unresectable)<br>Pembrolizumab (Keytruda): ID2018_125<br>Tislelizumab (Tevimbra): ID2022_151<br>Ipilimumab (Yervoy) og Nivolumab (Opdivo): ID2023_005<br>Nivolumab (Opdivo): ID2016_075<br><br>Oesophageal squamous cell carcinoma (OSCC):<br>Tislelizumab (Tevimbra): ID2024_081 |

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| | Nivolumab (Opdivo): ID2020_026 |
| 3.3 Er du kjent med om det er gjennomført en metodevurdering i et annet land som kan være relevant i norsk sammenheng?<br><br>*Hvis ja, oppgi referanse* | Ja ☐ Nei ☒<br><br>Referanse:<br>Klikk eller trykk her for å skrive inn tekst. |

## 4 Status for markedsføringstillatelse (MT) og markedsføring

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| 4.1 Har legemiddelet MT i Norge for en eller flere indikasjoner?<br><br>*Hvis ja - skriv inn dato for norsk MT for den første indikasjonen* | Ja ☒ Nei ☐<br><br>Dato for MT for første indikasjon:<br>02.03.2025 |
| 4.2 Markedsføres legemiddelet i Norge? | Ja ☐ Nei ☒ |
| 4.3 Har legemiddelet MT i Norge for anmodet indikasjon?<br><br>*For alle metoder: Fyll ut prosedyrenummer i EMA (det europeiske legemiddelbyrået)*<br><br>*Hvis metoden ikke har MT i Norge, fyll ut forventet tidspunkt (måned/år) for CHMP opinion i EMA.*<br><br>*Hvis metoden har MT i Norge, fyll ut dato for MT* | MT i Norge: Ja ☒ Nei ☒<br><br>Prosedyrenummer i EMA:<br>Nsq NSCLC, OSCC: EU/1/24/1870<br><br>On the market from 15.6.2026 |
| | **Hvis metoden ikke har MT**:<br><br>Forventet tidspunkt for CHMP opinion i EMA (måned/år):<br>Sq NSCLC: Positive opinion 21-05-2026<br><br>Forventet tidspunkt for markedsføringstillatelse (MT) for den aktuelle indikasjonen i Norge (måned/år):<br><br>Sq NSCLC: End of June 2026 |
| | **Hvis metoden har MT:**<br><br>Dato for MT i Norge for den aktuelle indikasjonen:<br><br>30.04.2026 |
| 4.4 Har legemiddelet en betinget markedsføringstillatelse for anmodet indikasjon?<br><br>*Hvis ja, fyll ut en beskrivelse av hva som skal leveres til EMA og når.* | Ja ☐ Nei ☒<br><br>Beskrivelse:<br>Klikk eller trykk her for å skrive inn tekst. |

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| 4.5 Har anmodet indikasjon vært i «accelerated assessment» hos EMA? | Ja ☐ Nei ☒ |
| 4.6 Har legemiddelet «orphan drug designation» i EMA?<br><br>*Hvis ja, fyll ut dato* | Ja ☐ Nei ☒<br><br>Dato for «orphan drug designation»:<br><br>Klikk eller trykk for å skrive inn en dato. |

## 5 Ordning for forenklet vurdering av PD-(L)1-legemidler

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| 5.1 Er legemiddelet registrert i Nye metoders ordning «Forenklet vurdering av PD-(L)1-legemidler"? | Ja ☒ Nei ☐ |

## 6 Sammenlignbarhet og anbud

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| 6.1 Finnes det andre legemidler med lignende virkningsmekanisme og /eller tilsvarende effekt til den aktuelle indikasjonen? | Ja ☒ Nei ☐<br><br>Kommentar:<br>Klikk eller trykk her for å skrive inn tekst. |
| 6.2 Vurderer leverandør at legemiddelet i anmodningen er sammenlignbart med et eller flere andre legemidler som Nye metoder har besluttet å innføre til den samme indikasjonen?<br><br>*Hvis ja, hvilke(t)? Oppgi ID-nummer på metoden/metodene i Nye metoder* | Ja ☒ Nei ☐<br><br>Legemiddel og ID-nummer:<br>Klikk eller trykk her for å skrive inn tekst. |
| 6.3 Er det eksisterende anbud på terapiområdet som kan være aktuelt for legemiddelet? | Ja ☒ Nei ☐<br><br>Kommentar:<br>Onkologitender start 1:a okt 2026. Nr 2607 |

## 7 Nordisk samarbeid JNHB (Joint Nordic HTA-bodies)

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| 7.1 Er anmodet indikasjon aktuell for utredning i det nordiske HTA-samarbeidet JNHB?<br><br>*Hvis nei, begrunn kort* | Ja ☐ Nei ☒<br><br>Begrunnelse:<br>This assessment could be a candidate for the fast-track procedure for PD-(L)1 inhibitors, “Forenklet vurdering av PD-(L)1 legemidler” |

| 8 Europeisk samarbeid om vurdering av relativ effekt og sikkerhet (HTAR) | |
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| 8.1 Er anmodet legemiddel/indikasjon omfattet av regelverket for utredning av relativ effekt og sikkerhet i europeisk prosess (HTAR)?<br><br>*Hvis ja, fyll ut dato for søknad om MT til EMA* | Ja ☐ Nei ☒<br><br>Dato for søknad til EMA:<br><br>Klikk eller trykk for å skrive inn en dato. |

| 9 Helseøkonomisk dokumentasjon og forslag til helseøkonomisk analyse | |
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| 9.1 Hvilken type helseøkonomisk analyse foreslår leverandøren?<br><br>*F.eks. kostnad-per-QALY analyse eller kostnadsminimeringsanalyse.*<br><br>*Begrunn forslaget* | Given the therapeutic comparability of PD-(L)1 inhibitors, in terms of effectiveness in within this indication, we propose a simplified health economic evaluation process based on cost-minimization analysis (CMA) versus atezolizumab (and potentially durvalumab) or Budget impact model (BIM), i.e., "forenklet metodevurdering (løp A)" as was decided previously by DMP in the assessment of the PD-(L)1 inhibitor Tislelizumab (ID2022_127)<br><br>https://www.nyemetoder.no/4a6aac/siteassets/documents/forslag/id2022_127-tislelizumab-nsclc-metodevarsel.pdf |
| 9.2 Pasientpopulasjonen som den helseøkonomiske analysen baseres på, herunder eventuelle undergrupper. | The population of interest in this analysis are the patients with nsNSCLC, squamous NSCLC and OSCC, aligned with the study population in ASTRUM-002, ASTRUM-004 and ASTRUM-007 respsectively.<br><br>https://clinicaltrials.gov/study/NCT03952403<br>https://clinicaltrials.gov/study/NCT04033354<br>https://clinicaltrials.gov/study/NCT03958890 |
| 9.3 Hvilken dokumentasjon skal ligge til grunn? (H2H studie, ITC, konstruert komparatorarm etc.)<br><br>*Angi det som er relevant med tanke på hvilken type analyse som foreslås.* | Relative efficacy of serplulimab (HLX10) is documented in:<br><br>Astrum-002:<br>- serplulimab + chemotherapy + HLX04 placebo (the approved indication) vs.<br>- serplulimab in combination with HLX04 (bevacizumab) and chemotherapy vs.<br>- chemotherapy + serplulimab placebo + HLX04 placebo<br><br>Astrum-004:<br>Serplulimab in combination with chemotherapy compared to chemotherapy in combination with HLX10 placebo |

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| | Astrum-007:<br>Serplulimab in combination with chemotherapy compared to chemotherapy and HLX10 placebo |
| 9.4 Forventet legemiddelbudsjett i det året med størst budsjettvirkning i de første fem år. | As in the metodevurdering for Tislelizumab (ID2022_127) for nsNSCLC and squamous NSCLC (ID2022_151), a price note was published 12. August 2024 where the budget consequences were not calculated. Similarly for Tislelizumab (ID2024_081) for OSCC where a price note was published 20. December 2024, where budget impact was also not calculated.<br><br>NSCLC:<br>There is a big uncertainty in how many patients would be elegible for these indications. As for Tislelizumab for the indications of nsNSCLC and squamous NSCLC, the patient population was estimated to be around 650. In the pricenote published the 12. August 2024 for nsNSCLC and squamous NSCLC, no significant budgetary consequences are expected since most of the expected patients are likely offered a treatment with PD(L1) drug already.<br><br>OSCC:<br>The patient population in question is not calculated in the pricenote published the 20. December 2024 for OSCC indication, however no expansion to the patient population elegible to PD(L1) drug in this indication is expected when introducing new PD(L1) drug into the indication.<br><br>In line with the above, 5 year-Budget impact is not provided due to the uncertainty in the eventual pricing for Hetronifly (serplulimab). |
| 9.5 Forventet tidspunkt (måned og år) for levering av dokumentasjon til Direktoratet for medisinske produkter og/eller Sykehusinnkjøp HF.<br><br>*Tidspunkt må oppgis* | Week 41 |

## 10 Sykdommen og eksisterende behandling

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| 10.1 Sykdomsbeskrivelse for aktuell indikasjon | Non-squamous and squamous NSCLC:<br><br>Lung cancer is one of the most common types of cancer and a leading cause of cancer-related deaths [Sung et al, 2020; WHO 2024; Bray 2024]. NSCLC |

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| *Kort beskrivelse av sykdommens patofysiologi og klinisk presentasjon / symptombilde, eventuelt inkl. referanser* | accounts for approximately 85% of all lung cancer cases and may be further subcategorized into either squamous (sq) or non-squamous (nsq) NSCLC. Within nsq NSCLC, adenocarcinoma is the most common histologic subtype, followed by large cell carcinoma (Hendriks et al, 2024, Paik et al, 2024). In the early stages, lung cancer is often asymptomatic, which is why the disease is often diagnosed only when it has reached the advanced stages, when symptoms, such as cough, haemoptysis (blood stained mucus), dyspnoea (shortness of breath) and weight loss may appear [Spiro 2007; Hendriks et al, 2024; Paik et al, 2024].<br><br>As mentioned, there are two main histological subtypes – squamous and non-squamous NSCLC. Squamous NSCLC could be characterised by keratinization areas, while non-squamous NSCLC is characterised mainly by gland formation. [icholson, 2015] There are also epidemiological differences between squamous and non-squamous NSCLC, where nonsquamous NSCLC is more common among women, while men are more at risk of developing squamous NSCLC. The proportion of women affected by non-squamous NSCLC has been increasing in past few decades, even without a clear presence of other risk factors. [Huang, 2019]<br><br>The treatment of squamous NSCLC is particularly challenging and therefore this disease is associated with a worse prognosis. [Socinski, 2016]<br><br>Sources:<br>Sung H., Ferlay J., Siegel RL. et al. (2020). Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J. Clin. 2021;71:209–249. doi: 10.3322/caac.21660.<br>WHO. (2024). "Cancer Today." available from https://gco.iarc.who.int/today/en/dataviz/bars?mode=cancer&key=total&group_populations=0&types=1&sort_by=value0&populations=900&multiple_populations=0&values_position=out&cancers_h=15.<br>Bray, F., Laversanne, M., Sung, H., et al. (2024). "Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries." CA Cancer J Clin 74(3): 229-263.<br>Hendriks LEL, Remon J, Faivre-Finn C et al. (2024). Non-small-cell lung cancer. Nat Rev Dis Primers. 2024 Sep 26;10(1):71. doi: 10.1038/s41572-024-00551-9. |

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| | Paik PK, Zhang J, West HJ, et al. (2026). Squamous Non-Small Cell Lung Cancer: Current and Emerging Treatment Options. Clin Lung Cancer. Apr;27(3):28-45. doi: 10.1016/j.cllc.2025.10.001. Epub 2025 Oct 6. PMID: 41253679.<br>Socinski, M.A. · Obasaju, C. · Gandara, D. ...<br>Clinicopathologic features of advanced squamous NSCLC J Thorac Oncol. 2016; 11:1411-1422<br>Huang, C. · Qu, X. · Du, J.<br>Proportion of lung adenocarcinoma in female never-smokers has increased dramatically over the past 28 years J Thorac Dis. 2019; 11:2685-2688<br>Nicholson, A.G. · Tsao, M.S. · Beasley, M.B. ...<br>The 2021 WHO Classification of lung tumors: impact of advances since 2015<br>J Thorac Oncol. 2022; 17:362-387<br><br>OSCC:<br><br>Esophageal squamous cell carcinoma is a malignancy arising from the flat epithelial cells lining the inner surface of the esophagus.<br>The esophagus is a muscular tube connecting the throat to the stomach, running through the chest cavity behind the heart and in front of the spine.<br>Squamous cell carcinoma typically develops in the upper and middle portions of the esophagus. It represents the most common histological subtype globally, although adenocarcinoma is more prevalent in Western countries. Key risk factors include long-term smoking, excessive alcohol consumption, poor diet, and chronic irritation of the esophageal lining.<br><br>Source: https://www.cancer.gov/types/esophageal |
| 10.2 Fagområde<br><br>*Angi hvilket fagområde som best beskriver metoden* | Velg fagområde fra menyen:<br><br>Kreftsykdommer |
| 10.3 Kreftområde<br><br>*Hvis metoden gjelder fagområdet Kreftsykdommer, angi hvilket kreftområde som er aktuelt* | Velg kreftområde fra menyen:<br><br>Lungekreft |
| 10.4 Dagens behandling | NSCLC: |

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| *Nåværende standardbehandling i Norge, inkl. referanse* | Non-squamous NSCLC:<br>For patients without driver mutations, the introduction of immunotherapy around ten years ago has led to a significant improvement in the survival prognosis [Yarchoan et al, 2019]. According to the ESMO 2023 guidelines, regardless of tumour PD-L1 status, for patients with newly diagnosed stage IV non-oncogene-addicted NSCLC (i.e., without EGFR-, ALK- or ROS1-positive driver mutations), with a PS of 0-1 and no contraindications for immunotherapy; a combination of platinum-based chemotherapy with an immunotherapy (namely an ICI such as an anti-PD-1/PDL1) represents the most common first-line treatment approach. (Hendriks et al, 2023; Hendriks et al, 2025)<br><br>Squamous NSCLC:<br>In the recent years, immunotherapy has been widely applicable as the first line treatment of squamous NSCLC. ICI with chemotherapy is a first line treatment of patients with advanced squamous NSCLC. [Henriks et al., 2025] As previously mentioned, squamous NSCLC has showever clearly lower survival rates among adult patients compared to non-squamous NSCLC.The combination of PD-1 blockade and VEGF(R) inhibition has been shown as a promising treatment opton for patients with squamous NSCLC. [Paik, 2025]<br><br>Source:<br>Yarchoan, M., Albacker, LA., Hopkins, AC., et al. (2019). PD-L1 expression and tumour mutational burden are independent biomarkers in most cancers. JCI Insight, 4.<br>Hendriks LE, Kerr KM, Menis J et al. (2023). ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org. Non-oncogene-addicted metastatic non-small-cell lung cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol. Apr;34(4):358-376. doi: 10.1016/j.annonc.2022.12.013.<br>Hendriks L, Cortiula F, Martins-Branco D et al. (2025). Updated treatment recommendations for systemic treatment: from the ESMO non-oncogene-addicted metastatic NSCLC Living Guideline. Annals of Oncology, 2025; 36, 1223-1227<br>Paik P, Zhang J, West H ...<br>Squamous Non-Small Cell Lung Cancer: Current and Emerging Treatment Options<br>Clinical Lung Cancer, 2025; 27, 28-45 |

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| | OSCC:<br><br>Immunotherapy has significantly improved outcomes in metastatic esophageal squamous cell carcinoma by enhancing the body's immune response against tumor cells. Unlike conventional therapies, it acts indirectly by activating immune-mediated tumor recognition and destruction.<br>Immune checkpoint inhibitors represent the main class of immunotherapies in this setting. These agents block inhibitory signals that suppress T-cell activity, thereby enhancing anti-tumor immunity. PD-1 inhibitors, including nivolumab and pembrolizumab, disrupt the PD-1/PD-L1 interaction, restoring T-cell function and promoting tumor cell elimination.<br><br>Source:<br>https://aoe.amegroups.org/article/view/8535/html |
| 10.5 Prognose<br><br>*Beskriv prognosen med nåværende behandlingstilbud, inkl. referanse* | Non-squamous and squamous NSCLC:<br><br>Non-squamous NSCLC:<br>With a low relative 5-year survival rate (25% for women and around 19% for men), the prognosis for patients with lung cancer is poor [Center for Cancer Registry Data 2024]. Although morbidity and death rates are higher among men than in women, for men, these rates have decreased and for women have increased over the recent decades; largely attributed to different smoking habits [AWMF Guideline 2025]. More than half of NSCLC patients have advanced disease at the time of initial diagnosis, with the probability of survival decreasing significantly as the disease progresses (i.e., a 5-year survival rate of 75% in stage I and 7.8% in stage IV) [Kraywinkel 2018; Tumour Registry Munich 2021]. In the advanced stage, there are differences in the probability of survival between sq NSCLC and nsq NSCLC.<br><br>Squamous NSCLC:<br><br>Compared to non-squamous NSCLC, patients with sq NSCLC have a worse prognosis, mainly because fewer targeted treatment options are available for this subtype [Center for Cancer Registry Data 2024].<br><br>Sources:<br><br>Center for Cancer Registry Data (2024). Database query with data up to 2022. Robert Koch Institute. |

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| | AWMF (Association of Scientific Medical Societies) Guideline (2025). S3 Guideline Prevention, Diagnosis, Therapy and Aftercare of Lung Carcinoma - Registration number 020-0070OL - Version 4.0 - Status: 02.04.2025 - Valid until 02.04.2030 - Long version.<br>Kraywinkel, K. & Schönfeld, I. (2018). Epidemiology of non-small cell lung cancer in Germany. The oncologist, 24, 946–51.<br>Munich Tumour Registry (TRM) (2022). ICD-10 C34: Non-small cell lung cancer – Survival. https://www.tumorregister-muenchen.de/facts/surv/sC34N_G-ICD-10-C34-Nicht-kleinzell.-BCSurvival.pdf.<br><br>OSCC:<br><br>Metastatic esophageal squamous cell carcinoma is associated with a poor prognosis, as curative treatment options are limited once the disease has disseminated. Treatment is therefore primarily aimed at controlling disease progression, extending survival, and maintaining quality of life.<br>Survival statistics should be interpreted with caution, as they reflect population averages and may not capture individual variability. Outcomes are influenced by patient- and disease-specific factors, and the introduction of new therapies such as immunotherapy provides optimism for improved future outcomes.<br><br>Sources:<br>https://www.cancerresearchuk.org/about-cancer/oesophageal-cancer/survival<br>https://cancer.ca/en/cancer-information/cancer-types/esophageal/treatment/stage-3 |
| 10.6 Det nye legemiddelets innplassering i behandlingsalgoritmen | First-line treatment of adult patients with locally advanced or metastatic or unresectable NSCLC or OSCC |

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| 10.7 Pasientgrunnlag<br><br>*Beskrivelse, insidens og prevalens av pasienter omfattet av aktuell indikasjon* i Norge, inkl. referanse.*<br><br>*Antall norske pasienter antatt aktuelle for behandling med legemiddelet til denne indikasjonen.*<br><br>** Hele pasientgruppen som omfattes av aktuell indikasjon skal beskrives* | Non-squamous and squamous NSCLC:<br><br>Lung cancer is one of the most common types of cancer in the world and is the leading cause of cancer mortality in Norway The disease is the second most common type of cancer among men and the third most common among women. Approximately 2,600 new cases of lung cancer are diagnosed in Norway each year, of which approximately 85% are classified as non-small cell lung cancer NSCLC. Of these, approximately 75 % have locally advanced or metastatic disease at the time of diagnosis. The main types of NSCLC are squamous cell carcinoma (squamous carcinoma). adenocarcinoma and large cell carcinoma. Adenocarcinomas adn large cell carcinomas together accont for approximately 50-55% of all lung cancer cases. Squamous cell carcinoma accounts for about 25-30%. Although NSCLC is associated with smoking in about 90% of cases, adenocarcinomas can be found in patients who have never smoked.<br><br>Source:<br>https://www.fhi.no/publ/2012/pemetrexed-som-vedlikeholdsbehandling-ved-avansert-ikke-plateepitel-ikke-sm/#bakgrunn<br>https://legehandboka.no/handboken/kliniske-kapitler/lunger/tilstander-og-sykdommer/svulster/lungekreft<br>Restrepo, J. C., Dueñas, D., Corredor, Z., & Liscano, Y. (2023). Advances in Genomic Data and Biomarkers: Revolutionizing NSCLC Diagnosis and Treatment. *Cancers*, *15*(13), 3474. https://doi.org/10.3390/cancers15133474<br><br>OSCC:<br><br>According to the Norwegian cancer Registry rapport from 2024, 325 persons were diagnosed with oesophagal squamous cell carcinoma in 2024. Although internationally cancers of oesophagus and stomach are among those most common ones, in Norway their incidence is relativelly low accounting for about 2% of all newly diagnosed cancer cases.<br><br>Source:<br>https://www.fhi.no/contentassets/e48ffae32c644d87b9cb28e636e5ddb0/rapport-kreft-i-spiseror-og-magesekk-2024.pdf |

| 11 Studiekarakteristika for relevante kliniske studier | | | |
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| | Studie 1 | Studie 2 | Studie 3 |
| 11.1 Studie-ID<br><br>*Studienavn, NCT-nummer, hyperlenke* | ASTRUM-002<br><br>NCT03952403<br><br>https://clinicaltrials.gov/study/NCT03952403 | ASTRUM-004<br><br>NCT04033354<br><br>https://clinicaltrials.gov/study/NCT04033354 | ASTRUM-007<br><br>NCT03958890<br><br>https://clinicaltrials.gov/study/NCT03958890 |
| 11.2 Studietype og -design | A Three Arm, Randomized, Double-blind, Multicenter, Phase III Clinical Study to Evaluate HLX10 (Recombinant Humanized Anti-PD-1 Monoclonal Antibody Injection) in Combination with Chemotherapy (Carboplatin-Pemetrexed) Versus HLX10 + HLX04 (Recombinant Humanized Anti-VEGF Monoclonal Antibody Injection) in Combination with Chemotherapy (Carboplatin-Pemetrexed) Versus Chemotherapy (Carboplatin-Pemetrexed) as First-line Therapy for Advanced Non-squamous Non-small Cell Lung Cancer (NSCLC) | A Randomized, Double-blind, Multi-center, Phase III Clinical Study of HLX10 (Recombinant Humanized Anti-PD-1 Monoclonal Antibody Injection) in Combination with Chemotherapy (Carboplatin and Nanoparticle Albumin-bound Paclitaxel) versus Chemotherapy (Carboplatin and Nanoparticle Albumin-bound Paclitaxel) as First-line Treatment for Locally Advanced or Metastatic Squamous Non-small Cell Lung Cancer (NSCLC) | A Randomized, Double-Blind, Multicenter, Phase Ⅲ Clinical Study to Evaluate HLX10 (Recombinant Humanized Anti-PD-1 Monoclonal Antibody Injection) versus Placebo in Combination with Chemotherapy (Cisplatin + 5-FU) as First-Line Therapy in Patients with Locally Advanced/Metastatic Esophageal Squamous Cell Carcinoma (ESCC) |
| 11.3 Formål | Primary Objective: | Primary Objective: | Primary objective: |

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| | • To evaluate the clinical efficacy of HLX10 in combination with chemotherapy, and HLX10 in combination with HLX04 and chemotherapy as first-line therapy in patients with advanced non-squamous NSCLC.<br><br>Secondary Objective:<br><br>• To evaluate the safety and tolerability of HLX10 in combination with chemotherapy, and HLX10 in combination with HLX04 and chemotherapy as first-line therapy in patients with advanced non-squamous NSCLC. | • To compare the clinical efficacy of HLX10 combined with chemotherapy versus placebo combined with chemotherapy as first-line therapy in patients with locally advanced or metastatic squamous NSCLC.<br><br>Secondary Objectives:<br><br>• To evaluate pharmacokinetics (PK), and immunogenicity profiles of HLX10, and to explore the biomarkers.<br><br>• To compare the safety of HLX10 combined with chemotherapy versus placebo combined with chemotherapy as first-line therapy in patients with locally advanced or metastatic squamous NSCLC. | • To evaluate the clinical efficacy of HLX10 versus placebo in combination with chemotherapy as first-line therapy in patients with locally advanced/metastatic ESCC.<br><br>Secondary objective:<br><br>• To evaluate the safety and tolerability of HLX10 versus placebo in combination with chemotherapy as first-line therapy in patients with locally advanced/metastatic ESCC. |
| 11.4 Populasjon<br><br>*Viktige inklusjons- og eksklusjonskriterier* | In the phase III study the actual enrollment was 643 subjects (HLX10 + HLX04 + chemotherapy group: 212 subjects; HLX10 + chemotherapy group: 214 subjects; placebo + chemotherapy group: 210 subjects).<br><br>Key inclusion criteria:<br>1. Histologically or cytologically confirmed, Stage IIIB/IIIC or IV non-squamous NSCLC<br>2. Participants with no EGFR, ALK | A total of 537 subjects were randomized and received the study drugs treatment.<br><br>Key inclusion criteria:<br><br>1. Patients with histologically or cytologically confirmed stage IIIB/IIIC and stage IV (AJCC Edition 8) squamous NSCLC where surgery or radiotherapy cannot be performed.<br>2. No known sensitizing EGFR | The number of subjects actually randomized was 551, including 368 subjects in the HLX10 group and 183 subjects in the control group.<br><br>Key inclusion criteria:<br><br>• Volunteer to participate in this clinical study; completely understand and know this study as well as sign the informed consent form (ICF); be willing to follow and be able to complete |

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| | and ROS1 mutation.<br>3. Participants with no prior treatment for Stage IIIB/IIIC or IV non-squamous NSCLC<br>4. Measurable disease as defined by RECIST v1.1<br>5. Eastern Cooperative Oncology Group performance status 0 or 1<br>6. Adequate hematologic and end organ function<br>7. 18 Years to 75 Years (Adult, Older Adult ), all sexes<br><br>Key exclusion criteria:<br><br>1. Malignancies other than NSCLC within 5 years prior to randomization, with the exception of those with a negligible risk of metastasis or death treated with expected curative outcome<br>2. Active central nervous system metastases<br>3. Prior treatment with cluster of differentiation immune checkpoint | mutations or ALK, ROS1 gene rearrangements.<br>3. Major organs are functioning well<br>4. Participant must keep contraception<br>5. Patients with prior denosumab use who can agree to switch to bisphosphonate therapy for bone metastases in the study.<br>6. 18 Years and older (Adult, Older Adult ), all sexes<br><br>Key exclusion criteria:<br><br>1. Patients with histologically non-squamous NSCLC. Mixed tumors will be classified according to the primary cell type. Patients do not meet the requirements for enrollment if small cell components and neuroendocrine carcinoma components are present. For non-small cell histology, patients meet the requirements for enrollment if squamous components (e.g., | all study procedures;<br>• Age ≥ 18 years and ≤ 75 years when ICF is signed;<br>• Never received systemic anti-tumor drug therapy before.Exception : for patients who have received neoadjuvant/adjuvant treatment, the time from the last treatment to recurrence or progression can be screened for more than 6 months;For patients who have received radical concurrent chemoradiotherapy or radiotherapy for esophageal cancer, the time from the last chemotherapy/radiotherapy to the recurrence or progression time is more than 12 months.<br>• According to the curative effect evaluation criteria in solid tumors (RECIST) v1.1, assessed by the center image with at least one measurable lesions (such as |

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| | blockade therapies or Bevacizumab<br>4. Has received a surgical operation within 4 weeks from the initial drug administration<br>5. Active or suspected autoimmune diseases. Subjects in a stable state with no need for systemic immunosuppressant therapy are allowed to enroll.<br>6. Currently having or have had interstitial pneumonia, pneumoconiosis, radiation pneumonitis, drug-related pneumonitis and severe impaired pulmonary function that may interfere with the detection and management of suspected drug-related pulmonary toxicity<br>7. Any active infection requiring systemic anti-infective therapy within 14 days prior to study drug administration | adenosquamous) are present.<br>2. Patients with known history of severe hypersensitivity to any monoclonal antibody.<br>3. Patients with known hypersensitivity to any compositions of carboplatin or nab-paclitaxel.<br>4. Pregnant or breastfeeding females.<br>5. Patients with a known history of psychotropic drug abuse or drug addiction; or a history of alcohol abuse.<br>6. Patients who have other factors that could lead to the early termination of this study based on the investigator's judgment. | esophageal cavity structure not as measurable lesions), measurable lesions should be not received radiotherapy, etc (lesions located in the usual radiation area, if confirm progress, can also be selected as the target lesion);<br>• PD-L1 positive subjects (CPS 1%).The subject must provide tumor tissue for pd-l1 expression level determination;<br>• Within 7 days before the first use of the study drug, ECOG: 0 ~ 1;<br>• Expected survival 12 weeks;<br>• The functions of the vital organs meet the following requirements (no blood transfusion, cytokine growth factor, or platelet raising drugs are allowed within 14 days before the first use of the study drugs); H. Absolute neutrophil count (ANC) ≥1.5 109/L |

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| | 8. Uncontrollable active infection(s)<br>9. History of immunodeficiency, including HIV antibody positive<br>10. active hepatitis B; or hepatitis C virus infections<br>11. Has bleeding tendency<br>12. History of severe cardiovascular diseases<br>13. Known gastrointestinal diseases as follows, Gastrointestinal perforation, abdominal fistula or abdominal abscess within 6 months before signing the informed consent; History of poorly controlled or recurrent inflammatory bowel disease; Active peptic ulcers, or > moderate esophageal varices<br>14. Pregnant or breastfeeding female | | I. platelet≥ 100 109/L; J. Hemoglobin≥ 9g/dL; K. Serum albumin≥ 3.0g/dL; L. Total bilirubin≤ 1.5 ULN, ALT, AST and/or ALP≤ 2.5 ULN;ALT and/or AST≤ 5 ULN in the presence of liver metastasis;If there is liver metastasis or bone metastasis ALP≤ 5 ULN; M. Serum creatinine ≤1.5 ULN or creatinine clearance > 60 mL/min (Cockcroft-Gault formula); N. APTT, INR and PT ≤1.5 ULN;<br>• For fertile female subjects, the serum pregnancy test must be negative within 7 days before the first dose.With fertile women subjects, and the partner for childbearing age women of male subjects, needs during the therapy, and after the last use HLX10 / placebo at least 3 months and the last time to use at least 6 months after |

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| | | | chemotherapy using an approved by the medical contraception (such as intrauterine device, the pill or condoms);<br>• Subjects voluntarily participated in this study and signed the informed consent, with good compliance and follow-up.<br><br>Key exclusion criteria:<br><br>• 1. BMI < 17.5kg /m2;<br>• 2. A history of gastrointestinal perforation and/or fistula within 6 months prior to the first administration;<br>• 3. Obvious invasion of tumor into adjacent organs (aorta or trachea) of esophageal lesions leads to high risk of bleeding or fistula;3. Subjects after endotracheal stent implantation;<br>• 4. Uncontrollable pleural effusion, pericardial effusion or |

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| | | | ascites requiring repeated drainage;<br>• 5. Previous allergies to monoclonal antibody, HLX10, 5-fu, cisplatin and other platinum drugs;<br>• 6.Have received any of the following treatments: A. Previous treatment with anti-pd-1 or anti-pd-L1 antibodies; B. Have received any research drugs within 4 weeks before the first use of the study drugs; C. Be enrolled in another clinical study at the same time, unless it is an observational (non-interventional) clinical study or a follow-up interventional clinical study; D. Receive the final anticancer treatment within 4 weeks before the first use of the study drug;Palliative radiotherapy for bone metastases was allowed and was completed 2 weeks before the first |

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| | | | dose.Radiotherapy covering more than 30% of the bone marrow area is not allowed within 28 days before the first dose.<br>• Subjects who require systemic treatment with corticosteroids (> 10 mg/ day prednisone therapeutic dose) or other immunosuppressive agents within 14 days prior to the first use of the study drug;In the absence of active autoimmune disease, inhalation or topical use of steroids is permitted, and the therapeutic dose of prednisone 10mg/ day is allowed.<br>• Those who have received the anti-tumor vaccine or the live vaccine within 4 weeks before the first dose of the study drug<br>• Have undergone major surgery within 28 days prior to the first use of the study drug. Major surgery in this |

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| | | | study is defined as requiring at least 3 weeks of postoperative recovery time before being able to receive the surgery treated in this study.Tumor puncture or lymph node biopsy were allowed. |
| 11.5 Intervensjon (n)<br><br>*Dosering, doseringsintervall, behandlingsvarighet* | HLX10, an engineered anti-PD-1 antibody<br>- HLX10 will be administered as IV infusion at a dose of 4.5mg/kg on Day 1 of each 21-day cycle until loss of clinical benefit or up to 2 year.<br>HLX04, a bevacizumab biosimilar<br>- HLX04 will be administered as IV infusion at a dose of 15 milligrams per kilogram (mg/kg) on Day 1 of each 21-day cycle until progressive disease, unacceptable toxicity, death or up to 2 year.<br>Carboplatin<br>- Carboplatin will be administered at area under the concentration-time curve (AUC) 5 on Day 1 of each 21-day | HLX10:<br>4.5 mg/kg, intravenous infusion, administered on Day 1 of each cycle, once every<br>3 weeks (21 days), for up to 2 years (up to 35 treatment cycles) or until loss of clinical benefit.<br><br>Placebo:<br>Intravenous infusion, administered on Day 1 of each cycle, once every 3 weeks (21 days), for up to 2 years (up to 35 treatment cycles) or until loss of clinical benefit.<br>The investigational products were infused within 30 to 90 minutes if no infusion reaction occurred.<br><br>Nab-paclitaxel:<br><br>100 mg/m2, intravenous infusion, administered on Day 1, 8, and 15 of each 3 week (21-day), for 4-6 treatment cycles.<br><br>Carboplatin: | Dosing sequence for combination therapy: HLX10/placebo, cisplatin, and 5-FU were administered sequentially, with 2 weeks (14 days) as a cycle.<br><br>HLX10:<br>3 mg/kg, intravenous infusion (IV), it was recommended to filter with 0.2–5 μm in-tube filter<br>before infusion; administered on Day 1 of each cycle, once every 2 weeks (14 days), with no<br>reduction in dose for up to 2 years or until loss of clinical benefit, intolerable toxicity, discontinuation decided by the subject or physician, death, withdrawal of informed consent,<br>pregnancy or other reasons specified in the protocol (whichever occurred first). |

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| | cycle for 4 cycles, or until loss of clinical benefit whichever occurs first.<br>Pemetrexed<br>- Pemetrexed will be administered as IV infusion at a dose of 500 milligrams per square meter (mg/m2) on Day 1 of each 21-day cycle until progressive disease, unacceptable toxicity, death or up to 2 year. | AUC = 5, maximum dose was not more than 750 mg, or AUC = 6, maximum dose was not more than 900 mg, intravenous infusion, administered on Day 1 of each cycle, once every 3 weeks (21 days), for 4-6 treatment cycles. The choice of AUC 5 or 6 was based on local guidance.<br><br>Subjects received HLX10 or placebo via intravenous infusion first and then nab-paclitaxel followed by carboplatin via intravenous infusion. HLX10 or placebo was given by infusion in a blinded state and nab-paclitaxel followed by carboplatin were given by open-label infusion | Cisplatin: 50 mg/m2, IV, once every 2 weeks (14 days), administered on Day 1 of each cycle, for up to 8 cycles.<br><br>5-FU: at a total dose of 2400 mg/m2, continuous IV for 44–48 hours in each cycle, once every 2 weeks (14 days), for up to 12 cycles |
| 11.6 Komparator (n)<br><br>*Dosering, doseringsintervall, behandlingsvarighet* | HLX10 Placebo<br>• Dosage and administration: 4.5 mg/kg, intravenous infusion, on Day 1 of each cycle (3 weeks, i.e., 21 days), continuous treatment until loss of clinical benefit or completion of 2 year treatment (35 cycles), after which Investigator assessed whether the subject should continue to receive the investigational product.<br><br>HLX04 Placebo<br>• Dosage and administration: 15 mg/kg, intravenous | Placebo:<br>Intravenous infusion, administered on Day 1 of each cycle, once every 3 weeks (21 days), for up to 2 years (up to 35 treatment cycles) or until loss of clinical benefit.<br>The investigational products were infused within 30 to 90 minutes if no infusion reaction occurred. | Placebo:<br>3 mg/kg, intravenous infusion (IV), it was recommended to filter with 0.2–5 μm in-tube filter before infusion; administered on Day 1 of each cycle, once every 2 weeks (14 days), with no reduction in dose for up to 2 years or until loss of clinical benefit, intolerable toxicity, discontinuation decided by the subject or physician, death, withdrawal of informed consent, |

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| | infusion, on Day 1 of each cycle (3 weeks, i.e., 21 days), continuous treatment until loss of clinical benefit or completion of 2 year treatment (35 cycles), after which Investigator assessed whether the subject should continue to receive the investigational product. | | pregnancy or other reasons specified in the protocol (whichever occurred first). |
| 11.7 Endepunkter<br><br>*Primære, sekundære og eksplorative endepunkter, herunder definisjon, målemetode og ev. tidspunkt for måling* | Primary Efficacy Endpoint:<br><br>Progression-free survival (PFS) assessed by IRRC per RECIST v1.1: the time from randomization to the first documented PD or death by any cause, whichever occurred first.<br><br>Key Secondary Efficacy Endpoint:<br><br>Overall survival (OS): the time from randomization to death by any cause.<br><br>Other Secondary Efficacy Endpoints<br>• PFS assessed by Investigator per RECIST v1.1: the time from randomization to the first documented PD or death by any cause, | Primary Efficacy Endpoint:<br><br>Progression-free survival (PFS) (assessed by independent radiology review committee [IRRC] based on Response Evaluation Criteria in Solid Tumors [RECIST] 1.1).<br><br>Secondary Efficacy Endpoints:<br><br>-Overall survival (OS);<br>- PFS (assessed by Investigator based on RECIST 1.1);<br>-PFS (assessed by IRRC and Investigator based on a modified RECIST 1.1 for immune based therapeutics [iRECIST]);<br>- Objective response rate (ORR) (assessed by IRRC and Investigator based on RECIST 1.1); | Primary endpoints:<br>• Progression-free survival (PFS) (assessed by Independent Radiology Review Committee [IRRC] as per RECIST v1.1);<br>• Overall survival (OS).<br><br>Secondary endpoints:<br>• PFS (assessed by IRRC as per iRECIST, and assessed by Investigator as per RECIST v1.1 and iRECIST);<br>• Objective response rate (ORR) (assessed by IRRC and Investigator as per RECIST v1.1 and iRECIST);<br>• Relationship between PD-L1 expression of tumor tissues and efficacy;<br>• Duration of response (DOR) (assessed by IRRC and Investigator as per RECIST v1.1 and iRECIST); |

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| | whichever occurred first.<br>• Objective response rate (ORR): the proportion of subjects whose best overall response (BOR) was evaluated as complete response (CR) or partial response (PR) by IRRC and Investigator, respectively, as per RECIST v1.1. Subjects without post-baseline tumor assessments were considered as non-responders.<br>• Duration of response (DOR): the time from the first documented response (CR or PR) to the first documented PD assessed by IRRC and Investigator per RECIST v1.1, or death (whichever occurred first).<br><br>Quality of Life:<br><br>• The EuroQol 5-dimension 5-level (EQ-5D-5L) questionnaire;<br>• European organization for research and treatment of cancer core quality of life (EORTC QLQ-C30) questionnaire;<br>• European organization for research and treatment of cancer quality of life 13-item lung cancer-specific questionnaire module (EORTC QLQ-LC13).<br><br>Pharmacokinetics :<br><br>Serum drug concentrations and PK | -Duration of response (DOR) (assessed by IRRC and Investigator based on RECIST 1.1);<br>- Quality of life assessment.<br><br>Safety Endpoints:<br>-Adverse events (AEs) (including serious adverse events [SAEs]), laboratory tests (hematology, blood chemistry, coagulation function, urinalysis, thyroid function, cardiac function), 12-lead electrocardiogram (12 lead ECG), vital signs, and physical examination,<br>etc.<br><br>Pharmacokinetic Endpoint:<br>- The concentration of HLX10 in serum.<br><br>Immunogenicity Endpoint:<br>- HLX10 anti-drug antibody/neutralizing antibody (ADA/NAb) positive rate.<br>Biomarker Endpoints:<br>- Relationship between PD-L1 expression, microsatellite instability (MSI), tumor mutation burden (TMB) in tumor tissue and efficacy. | • Incidence of adverse events (AEs) and serious adverse events (SAEs);<br>• Pharmacokinetics (PK): concentration of HLX10 in serum;<br>• Immunogenicity evaluation: positive rate of anti-drug antibody (ADA)/neutralizing antibody (NAb);<br>• Relationship between microsatellite instability (MSI), tumor mutational burden (TMB) and efficacy;<br>• Quality of life assessment. |

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| | parameters of HLX10 and HLX04, in which PK parameters included:<br>• Maximum concentration (Cmax): the concentration within 2 h after the administration in Cycle 1 and 8;<br>• Trough concentration (Ctrough): the concentration within 3 days before the administration in Cycle 2 and 8;<br>• Accumulation ratio (Rac_Cmax): the ratio of Cmax after the administration in cycle 8 to that in Cycle 1;<br>• Accumulation ratio (Rac_Ctrough): the ratio of Ctrough before the administration in Cycle 8 to that in Cycle 2.<br><br>Immunogenicity:<br><br>• Anti-drug antibody (ADA).<br><br>Biomarkers:<br><br>• PD-L1 expression level;<br>• Microsatellite instability (MSI);<br>• Tumor mutation burden (TMB).<br>Safety:<br>• Incidence of adverse events (AEs) and serious adverse events (SAEs). | | |

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| 11.8 Relevante subgruppeanalyser<br><br>*Beskrivelse av ev. subgruppeanalyser* | Subgroup analysis included the subgroups defined by stratification factors and biomarkers (if a subgroup population was less than 5% of the ITT set, only the number of subjects and events were summarized). The subgroup analysis results were used to plot forest plots. The subgroup analysis was performed in the ITT set. The subgroups planned for analysis included:<br>• Age: < 65 years vs. ≥ 65 years;<br>• ECOG score: 0 vs. 1;<br>• Gender: male vs. female;<br>• Smoking history: yes vs. no;<br>• Brain metastases: yes vs. no;<br>• PD-L1 expression level: negative (CPS < 1) vs. positive (CPS ≥ 1) vs. not evaluable;<br>• PD-L1 expression level: CPS < 1 vs. 1 ≤ CPS < 10 vs. CPS ≥ 10;<br>• PD-L1 expression level: TPS < 1% vs. 1% ≤ TPS < 50% vs. TPS ≥ 50%;<br>• Tumor status: locally advanced (stage IIIB/IIIC) vs. distant metastasis (stage IV);<br>• MSI: MSS/MSI-L vs. MSI-H;<br>• TMB: < 10 muts/Mb vs. ≥ 10 muts/Mb. | N/A | Age (< 65 years vs. ≥ 65 years):<br>- PFS assessed by IRRC based on RECIST v1.1:<br>- The subgroup analysis results of PFS assessed by IRRC and investigator based on RECIST v1.1 showed that subjects aged < 65 years and ≥ 65 years both could benefit from the treatment of HLX10.<br>ECOG Score (0 vs. 1):<br>- The subgroup analysis results of PFS assessed by IRRC and investigator based on RECIST v1.1 showed that subjects with ECOG scores of 0 and 1 both could benefit from the treatment of HLX10.<br>Gender (Male vs. Female):<br>- The subgroup analysis results of PFS assessed by IRRC and investigator based on RECIST v1.1 showed that subjects of different genders both could benefit from the treatment of HLX10. |

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| | | | PD-L1 Expression Level (1 ≤ CPS < 10 vs. CPS ≥ 10):<br>- The subgroup analysis results of PFS assessed by IRRC and investigator based on RECIST v1.1 showed that subjects with different PD-L1 expression levels both could benefit from the treatment of HLX10.<br>Tumor Status (Locally Advanced vs. Distant Metastasis):<br>- The subgroup analysis results of PFS assessed by IRRC and investigator based on RECIST v1.1 showed that subjects with different tumor status both could benefit from the treatment of HLX10.<br>MSI/MMR (MSS/MSI-L vs. MSI-H):<br>- There were no subjects with MSI-H in the HLX10 group, whereas two were observed in the control group. Due to the small number of subjects, the MSI-H subgroup could not be analyzed. |

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| | | | TMB (< 10 muts/Mb vs. ≥ 10 muts/Mb):<br>- The TMB ≥ 10 muts/Mb subgroup had 2 subjects from the HLX10 group and 1 subject from the control group. Due to the small number of subjects, the TMB ≥ 10 muts/Mb subgroup could not be analyzed.<br><br>In summary, in the ITT set, HLX10 group showed higher PFS benefit as compared to the control group in the subgroups of age (< 65 years vs. ≥ 65 years), ECOG score (0 vs. 1), gender (male vs. female), PD-L1 expression level (1 ≤ CPS < 10 vs. CPS ≥ 10), tumor status (distant metastasis vs. locally advanced), MSI/MMR (MSS/MSI-L), and TMB (< 10 muts/Mb). |
| 11.9 Oppfølgingstid<br><br>*Hvis pågående studie, angi oppfølgingstid for data som forventes å være tilgjengelige for vurderingen hos Direktoratet for medisinske produkter samt den forventede/planlagte samlede oppfølgingstid for studien* | All subjects should undergo safety follow-up visits by the study site within 30 days (± 7 days) after the last dose; if the end-of-treatment visit was delayed for any reason within 30 days (± 7 days) after the last dose, no additional safety follow-up visit was required. A safety follow-up telephone call was required within 90 days (± 7 days) after the | Safety follow-up by telephone was required 90 days (±7 days) after the final dose of study treatment, and AE, AE-related concomitant treatment, subsequent anti-cancer therapy, and survival status information of the subjects were collected. Subjects who discontinued the drug for reasons other than disease progression, | The follow-up period was defined as the period beyond 90 days after the last dose of study treatment.<br><br>As of April 15, 2022, the median duration of follow-up in the ITT set was 14.9 months. |

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| | last dose, only collecting the information of AEs and concomitant medications related to AE management. For subjects discontinuing treatment due to non-PD reasons, imaging assessment should be continued as scheduled until PD, initiation of a new anti-tumor therapy, withdrawal of ICF, death, or the end of the study (whichever occurred first). Subjects discontinuing treatment must undergo survival followed-up by telephone every 12 weeks (± 7 days); the frequency of survival follow-up might be increased as appropriate.<br><br>As of August 07, 2025, the median duration of follow-up in the HLX10 + HLX04 + chemotherapy group, HLX10 + chemotherapy group, and placebo + chemotherapy group were 48.4 months, 45.4 months, and 45.7 months, respectively. | where possible, continued the radiographic assessments in accordance with the stipulations on imaging tests in the protocol until disease progression (including first PD, second PD [if present]), initiation of new anti-cancer treatment, withdrawal of informed consent, death or end of study (whichever occurs first). A telephone follow-up for survival for the subjects were conducted every 12 weeks ± 7 days after the final dose of study drug; the frequency of survival follow-up was increased as appropriate.<br><br>As of 31 Jan 2023, the median duration of follow-up was 31.11 months. 229 (64.0%) subjects had PFS events in the HLX10 group, of which 177 (49.4%) subjects experienced disease progression and 52 (14.5%) subjects died. In the placebo group, 123 (68.7%) subjects had PFS events, of which 94 (52.5%) subjects experienced disease progression and 29 (16.2%) subjects died. | |
| 11.10 Tidsperspektiv resultater<br><br>*Pågående eller avsluttet studie? Tilgjengelige og fremtidige datakutt* | Study Initiation Date (first subject signed the informed consent form): November 25, 2019<br><br>Last Subject Enrolled Date: June 15, 2022 | First Patient Enrolled Date: 14 Aug 2019<br><br>Last Patient Enrolled Date: 25 Feb 2021 | Date of the first subject signed the informed consent form: June 19, 2019 |

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| | Data Cut-off Date: August 07, 2025<br><br>Database Lock Date: August 07, 2025<br><br>Status: Final | Data Cut-Off Date: 31 Jan 2023<br><br>Database Lock Date: 12 Apr 2023<br><br>Status: Final | Date of the last subject enrollment: December 17, 2021<br><br>Data cut-off date: January 09, 2023<br><br>Status: Final |
| 11.11 Publikasjoner<br><br>*Tittel, forfatter, tidsskrift og årstall. Ev. forventet tidspunkt for publikasjon* | https://pubmed.ncbi.nlm.nih.gov/41354044/<br><br>https://pubmed.ncbi.nlm.nih.gov/40932107/ | https://pubmed.ncbi.nlm.nih.gov/38181795/ | https://pubmed.ncbi.nlm.nih.gov/37215110/<br><br>https://pubmed.ncbi.nlm.nih.gov/36732627/ |

## 12 Igangsatte og planlagte studier

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| 12.1 Er det pågående eller planlagte studier for legemiddelet innenfor samme indikasjon som kan gi ytterligere informasjon i fremtiden?<br><br>*Hvis ja, oppgi forventet tidspunkt* | Ja ☐ Nei ☒<br><br>Klikk eller trykk her for å skrive inn tekst. |
| 12.2 Er det pågående eller planlagte studier for legemiddelet for andre indikasjoner? | Ja ☐ Nei ☒<br><br>Klikk eller trykk her for å skrive inn tekst. |

## 13 Diagnostikk

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|---|---|
| 13.1 Vil bruk av legemiddelet til anmodet indikasjon kreve diagnostisk test for analyse av biomarkør?<br><br>*Hvis ja, fyll ut de neste spørsmålene* | Ja ☐ Nei ☒ |
| 13.2 Er testen etablert i klinisk praksis?<br><br>*Hvis ja, testes pasientene rutinemessig i dag?* | Ja ☐ Nei ☒<br><br>Hvis ja, testes pasientene rutinemessig i dag?<br><br>Ja ☐ Nei ☐ |

| | |
|---|---|
| 13.3 Hvis det er behov for en test som ikke er etablert i klinisk praksis, beskriv behovet inkludert antatte kostnader/ressursbruk | Not applicable |

## 14 Andre relevante opplysninger

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|---|---|
| 14.1 Har dere vært i kontakt med fagpersoner (for eksempel klinikere) ved norske helseforetak om dette legemiddelet/indikasjonen?<br><br>*Hvis ja, hvem har dere vært i kontakt med og hva har de bidratt med?*<br><br>*(Relevant informasjon i forbindelse med rekruttering av fageksperter i Nye metoder)* | Ja ☐ Nei ☒<br><br>Klikk eller trykk her for å skrive inn tekst. |
| 14.2 Anser leverandør at det kan være spesielle forhold ved dette legemiddelet som gjør at en innkjøpsavtale ikke kan basere seg på flat rabatt for at legemiddelet skal kunne oppfylle prioriteringskriteriene?<br><br>*Hvis ja, begrunn kort.*<br><br>*Hvis ja, skal eget skjema fylles ut og sendes til Sykehusinnkjøp HF samtidig med at dokumentasjon til metodevurdering sendes til Direktoratet for medisinske produkter.*<br><br>*Nærmere informasjon og skjema:*<br>Informasjon og opplæring - Sykehusinnkjøp HF | Ja ☐ Nei ☒<br><br>Klikk eller trykk her for å skrive inn tekst. |
| 14.3 Andre relevante opplysninger? | This assessment could be a candidate for the fast-track procedure for PD-(L)1 inhibitors, “Forenklet vurdering av PD-(L)1 legemidler” |

Informasjon om Nye metoder finnes på nettsiden nyemetoder.no