

Gender: Female | Birth year: 1975 | WHO: 1

Tumor: Lung adenocarcinoma | Lesions: Liver, Lung | Stage: IV

Summary

Clinical summary

| | | | |
|-------------------------------------|---|------------|--------------------------|
| Gender | Female | Birth year | 1975 |
| WHO | 1 | Tumor | Lung adenocarcinoma |
| Lesions | Liver, Lung | Stage | IV |
| Measurable disease (RECIST) | Yes | DPYD | *1_HOM (Normal function) |
| | | UGT1A1 | *1_HOM (Normal function) |
| Relevant systemic treatment history | 6/2023-1/2025 Osimertinib | | |
| Relevant other oncological history | None | | |
| Previous primary tumor | None | | |
| Relevant non-oncological history | 2023 Rheumatoid arthritis | | |
| Recent molecular results | KRAS G12C (0.3/2 copies)*, KRAS G12D (0.3/2 copies)*, NRAS: No reportable events, BRAF: No reportable events, HER2: No reportable events, MSS | | |

Recent molecular results

Hartwig WGS (22-Feb-2025)

| | |
|---|--|
| Biopsy location | Lung (purity 50%) |
| Molecular tissue of origin prediction | Lung: Non-small cell: LUAD (98%) |
| Tumor mutational load / burden | TML 160 / TMB 14 mut/Mb |
| Microsatellite (in)stability | Stable |
| HR status | Proficient (0) |
| Driver mutations | EGFR C797S, EGFR L858R, KRAS G12C, KRAS G12D |
| Amplified genes | None |
| Deleted genes | TP53 |
| Homozygously disrupted genes | None |
| Gene fusions | MET(exon13)::MET(exon15) fusion |
| Virus detection | None |
| Potential trial events, considered no high driver | None |

IHC results

| | |
|-------|-------------|
| PD-L1 | Score > 50% |
|-------|-------------|

Standard of care options considered potentially eligible

There are no standard of care treatment options for this patient

Trials in NL that are open and potentially eligible (4 cohorts from 4 trials)

| Trial | Cohort | Molecular | Sites | Warnings |
|----------------------------------|--------------------------------------|-------------------|--|---|
| METC 04 TEDR1 | Lung cancer C797S cohort | EGFR C797S | NKI-AvL | None |
| METC 02 KAYRAS | Dose expansion - monotherapy - NSCLC | KRAS G12D | Erasmus MC | Variant(s) G12D in KRAS but subclonal likelihood of > 50% |
| EGFR-C797S-TRIAL | <i>EGFR C797S</i> | <i>EGFR C797S</i> | <i>Elisabeth-TweeSteden Ziekenhuis</i> | |
| EGFR-L858R-TRIAL | <i>EGFR L858R</i> | <i>EGFR L858R</i> | <i>Elisabeth-TweeSteden Ziekenhuis</i> | |

Trials matched solely on molecular event and tumor type (no clinical data used) are shown in italicized, smaller font.

International trials that are open and potentially eligible (2 cohorts from 2 trials)

| Trial | Cohort | Molecular | Sites |
|------------------------------------|------------|------------|--------------------|
| EGFR-BE | EGFR L858R | EGFR L858R | Belgium: Brussels |
| KRAS-G12C-TRIAL-DE | KRAS G12C | KRAS G12C | Germany: Stuttgart |

International trials are matched solely on molecular event and tumor type (clinical data excluded).

Trials and cohorts that are considered ineligible (2)

| Trial | Cohort | Molecular | Ineligibility reasons |
|-------------------------------------|---|------------|---------------------------------------|
| METC 03 NO-SEE797ES | Dose escalation - monotherapy | EGFR C797S | C797S in EGFR in canonical transcript |
| METC 02 KAYRAS | Dose expansion - monotherapy - Colorectum | KRAS G12D | No colorectal cancer |

Resistance evidence

Resistance evidence

There are no standard of care treatment options for this patient

Molecular Details

Hartwig WGS (EXAMPLE-LUNG-01-T, 22-Feb-2025)

General

| Purity | Ploidy | TML Status | TMB Status | MS Stability | HR Status | DPYD | UGT1A1 |
|--------|--------|------------|------------|--------------|----------------|--------------------------|--------------------------|
| 50% | 2.3 | High (160) | High (14) | Stable | Proficient (0) | *1_HOM (Normal function) | *1_HOM (Normal function) |

Predicted tumor origin

| 1. Lung: Non-small cell: LUAD | |
|---|-----|
| Combined prediction score | 98% |
| This score is calculated by combining information on: | |
| (1) SNV types | 60% |
| (2) SNV genomic localisation distribution | 70% |
| (3) Driver genes and passenger characteristics | 80% |
| Other cohorts have a combined prediction of 2% or lower | |

Drivers

| Type | Driver | Trials (Locations) | Trials in Hartwig | Best evidence in External | Resistance in External |
|-----------------------------|---------------------------|---------------------|--------------------------|---------------------------|------------------------|
| Mutation (Gain of function) | EGFR C797S (1/4 copies) | TEDR1 (NKI-AvL) | NCT00000008 | Pre-clinical | |
| Mutation (Gain of function) | EGFR L858R (2/4 copies) | | NCT00000006, NCT00000007 | Approved | |
| Mutation (Gain of function) | KRAS G12C (0.3/2 copies)* | | NCT00000009 | | |
| Mutation (Gain of function) | KRAS G12D (0.3/2 copies)* | KAYRAS (Erasmus MC) | | | |

The table continues on the next page

PATIENT
EXAMPLE-LUNG-01
REPORT DATE
17-Apr-2025

| Type | Driver | Trials (Locations) | Trials in Hartwig | Best evidence in External | Resistance in External |
|--|---------------------------------|--------------------|-------------------|---------------------------|------------------------|
| Deletion | TP53 del, 0 copies | | | | |
| Known fusion (high driver) | MET(exon13)::MET(exon15) fusion | | | | |
| * Variant has > 50% likelihood of being sub-clonal | | | | | |

PD-L1 **Score > 50%**

Molecular History

Molecular history

| Event | Description | 2025-02-22 Hartwig WGS |
|---|--|---------------------------|
| EGFR L858R (Tier I) | Mutation (Gain of function) | VAF 0.5% |
| EGFR C797S (Tier II) | Mutation (Gain of function) | VAF 0.25% |
| KRAS G12C (Tier III) | Mutation (Gain of function) | VAF 0.15% |
| KRAS G12D (Tier III) | Mutation (Gain of function) | VAF 0.15% |
| MET(exon13)::MET(exon15) fusion (Tier III) | Known fusion (high driver) Gain of function | Detected |
| TP53 del (Tier III) | Deletion Unknown protein effect | Detected |
| TMB | | 14.0 |
| MSI | | Stable |

SOC literature efficacy evidence

Standard of care options considered potentially eligible

The following standard of care treatment(s) could be an option for this patient. For further details per study see 'SOC literature details' section in extended report.

There are no standard of care treatment options for this patient

Clinical Details

Clinical summary

| | | |
|-------------------------------------|---------------|----------------------|
| Relevant systemic treatment history | 6/2023-1/2025 | Osimertinib |
| Relevant other oncological history | None | |
| Previous primary tumor | None | |
| Relevant non-oncological history | 2023 | Rheumatoid arthritis |

Patient current details (20-Feb-2025)

| | |
|----------------------------------|-----------------------------|
| Unresolved toxicities grade => 2 | None |
| LVEF | 50% |
| Cancer-related complications | None |
| Known allergies | None |
| Recent surgeries | 01-Aug-2024 Cholecystectomy |

Tumor details (20-Feb-2025)

| | |
|---------------------|------------------------|
| Measurable disease | Yes |
| CNS lesion status | No known CNS lesions |
| Brain lesion status | No known brain lesions |

Active medication details

| Medication | Administration route | Start date | Stop date | Dosage | Frequency |
|-----------------|----------------------|-------------|-----------|----------------|------------|
| St. John's Wort | Oral | 01-Feb-2023 | | 300 MILLIGRAMS | 1 / 2 DAYS |

Blood transfusions

| Product | Date |
|----------------------|-------------|
| ERTHROCYTES_FILTERED | 20-Sep-2024 |

SOC literature details

There are no standard of care treatment options for this patient

Molecular Evidence

On label clinical evidence

| Event | CKB Event | Level A | Level B | Level C | Level D |
|------------|------------|---|---------|---------|---|
| EGFR C797S | EGFR C797S | | | | AFATINIB <i>Lung non-small cell carcinoma (2015)</i> |
| EGFR L858R | EGFR L858R | OSIMERTINIB <i>Lung non-small cell carcinoma (2016)</i> AFATINIB <i>Lung non-small cell carcinoma (2013)</i> | | | |

Off label clinical evidence

| Event | CKB Event | Level A | Level B | Level C | Level D |
|-------|-----------|---------|---------|---------|---------|
| None | | | | | |

Efficacy evidence description

| EGFR L858R | | | |
|---------------------|----------------|-------------------------------|---|
| <i>OSIMERTINIB:</i> | Level A (2016) | Lung non-small cell carcinoma | Osimertinib is effective in patients with EGFR L858R mutations |
| <i>AFATINIB:</i> | Level A (2013) | Lung non-small cell carcinoma | Afatinib is effective in patients with EGFR L858R mutations |
| EGFR C797S | | | |
| <i>AFATINIB:</i> | Level D (2015) | Lung non-small cell carcinoma | In a case-report, afatinib was effective against EGFR L858R/C797S positive lung cancer. |

Treatment ranking

| Treatment | Events | Score |
|-------------|--------------------------|-------|
| AFATINIB | EGFR L858R EGFR C797S | 2,150 |
| OSIMERTINIB | EGFR L858R | 1,900 |

Other Trial Matching Results

Trials in NL that are open and potentially eligible (2 cohorts from 2 trials)

| Trial | Cohort | Molecular | Sites | Warnings |
|----------------------------------|------------|------------|------------------------------------|----------|
| EGFR-C797S-TRIAL | EGFR C797S | EGFR C797S | Elisabeth-TweeSteden Ziekenhuis | |
| EGFR-L858R-TRIAL | EGFR L858R | EGFR L858R | Elisabeth-TweeSteden Ziekenhuis | |

Trials matched solely on molecular event and tumor type (no clinical data used) are shown in italicized, smaller font.

International trials that are open and potentially eligible (2 cohorts from 2 trials)

| Trial | Cohort | Molecular | Sites |
|------------------------------------|------------|------------|--------------------|
| EGFR-BE | EGFR L858R | EGFR L858R | Belgium: Brussels |
| KRAS-G12C-TRIAL-DE | KRAS G12C | KRAS G12C | Germany: Stuttgart |

International trials are matched solely on molecular event and tumor type (clinical data excluded).

Trial Matching Details

Potentially eligible open trials & cohorts

METC 01

| | |
|----------------------|---|
| Potentially eligible | Yes |
| Acronym | IEMOEN |
| Title | Phase I first-in-human study to evaluate safety of IEMOEN, a new PD-L1 inhibitor in advanced solid tumors |
| Reference | Evaluation |
| I-03 | <div>WARN</div> <div>Has not exhausted SOC (at least platinum doublet remaining)</div> |
| E-02 | <div>UNDETERMINED</div> <div>No measurement found for hemoglobin</div> |
| E-03 | <div>UNDETERMINED</div> <div>No measurement found for absolute neutrophil count</div> |
| E-01 | <div>PASS</div> <div>Has no other condition belonging to category autoimmune disease</div> |
| I-01 | <div>PASS</div> <div>Patient is at least 18 years old</div> |
| I-02 | <div>PASS</div> <div>Has solid primary tumor</div> <div>Stage IV is considered metastatic</div> |

METC 01 - Dose escalation - monotherapy

| | |
|-----------------------|-----|
| Cohort ID | A |
| Potentially eligible? | Yes |
| Open for inclusion? | Yes |
| Has slots available? | No |

METC 01 - Dose expansion - monotherapy

| | |
|-----------------------|-----|
| Cohort ID | B |
| Potentially eligible? | Yes |
| Open for inclusion? | No |
| Has slots available? | No |

METC 02

| | |
|----------------------|---|
| Potentially eligible | Yes |
| Acronym | KAYRAS |
| Title | A phase 1/2 trial for first in-human usage of KAYRAS, a new specific KRAS G12D inhibitor in NSCLC and colorectal cancer |
| Reference | Evaluation |
| I-04 | <div>WARN</div> <div>Variant(s) G12D in KRAS but subclonal likelihood of > 50%</div> |
| I-03 | <div>UNDETERMINED</div> <div>ASAT and ALAT are not present or cannot be evaluated</div> |
| I-01 | <div>PASS</div> <div>Patient is at least 18 years old</div> |
| I-02 | <div>PASS</div> <div>Stage IV is considered metastatic</div> |

METC 02 - Dose expansion - monotherapy - NSCLC

| | |
|-----------------------|--|
| Cohort ID | A |
| Potentially eligible? | Yes |
| Open for inclusion? | Yes |
| Has slots available? | Yes |
| Reference | Evaluation |
| I-02 | <div>PASS</div> <div>Tumor belongs to DOID term(s) lung non-small cell carcinoma</div> |

METC 02 - Dose expansion - monotherapy - Colorectum

| | |
|-----------------------|---|
| Cohort ID | B |
| Potentially eligible? | No |
| Open for inclusion? | Yes |
| Has slots available? | Yes |
| Reference | Evaluation |
| I-02 | <div>FAIL</div> <div>No colorectal cancer</div> |

METC 04

| | |
|----------------------|---|
| Potentially eligible | Yes |
| Acronym | TEDR1 |
| Title | TEDR1 Trial: A phase II trial to evaluate efficacy of specific EGFR inhibitors in lung cancer |
| Reference | Evaluation |
| I-1 | PASS Patient is at least 18 years old |
| I-2 | PASS Stage IV is considered metastatic Tumor belongs to DOID term(s) lung cancer |
| I-3 | PASS C797S in EGFR in canonical transcript |

METC 04 - Lung cancer C797S cohort

| | |
|-----------------------|-----|
| Cohort ID | A |
| Potentially eligible? | Yes |
| Open for inclusion? | Yes |
| Has slots available? | Yes |

Other trials & cohorts

METC 03

| | |
|----------------------|---|
| Potentially eligible | No |
| Acronym | NO-SEE797ES |
| Title | Phase I trial for development of NO-SEE797ES, a specific inhibitor for EGFR with C797 mutations but not C797S in solid tumors |
| Reference | Evaluation |
| I-03 | FAIL |
| | C797S in EGFR in canonical transcript |

METC 03 - Dose escalation - monotherapy

| | |
|-----------------------|-----|
| Cohort ID | A |
| Potentially eligible? | No |
| Open for inclusion? | Yes |
| Has slots available? | Yes |

METC 05

| | |
|----------------------|---|
| Potentially eligible | No |
| Acronym | PICKME3CA |
| Title | A phase 1/2 trial of ABC123 +/- platinum doublet in PIK3CA-mutated solid cancer |
| Reference | Evaluation |
| I-04 | FAIL |
| | No PIK3CA activating mutation(s) |

METC 05 - Dose expansion - monotherapy - NSCLC

| | |
|-----------------------|-----|
| Cohort ID | A |
| Potentially eligible? | No |
| Open for inclusion? | No |
| Has slots available? | Yes |

METC 05 - Dose expansion - monotherapy - Other cancer types

| | |
|-----------------------|---|
| Cohort ID | B |
| Potentially eligible? | No |
| Open for inclusion? | No |
| Has slots available? | Yes |
| Reference | Evaluation |
| I-03 | FAIL |
| | Tumor belongs to DOID term(s) lung non-small cell carcinoma |