

ACTIN Report (research use only)

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

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

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

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 |

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 | None |

Trial-relevant IHC results

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

Standard-of-care options considered potentially eligible

There are no standard of care treatment options for this patient

Phase 2/3+ trials in NL that are open and potentially eligible (1 trial)

| Trial | Cohort | Molecular | Sites | Warnings |
|---|--------------------------|------------|---------|----------|
| METC 04 TEDR1 (Phase 2) | Lung cancer C797S cohort | EGFR C797S | NKI-AvL | None |

Phase 1/2 (or unknown phase) trials in NL that are open and potentially eligible (4 trials)

| Trial | Cohort | Molecular | Sites | Warnings |
|--|---|-----------------------------|----------------------|---|
| METC 02 KAYRAS (Phase 1/2) | Dose expansion - monotherapy - NSCLC | KRAS G12D, PD-L1 >= 50.0 | Erasmus MC | Variant(s) G12D in KRAS but subclonal likelihood of > 50% |
| METC 01 IEMOEN (Phase 1) | Dose escalation - monotherapy (no slots) | None | | Has not exhausted SOC (at least platinum doublet remaining) |
| EGFR-C797S-TRIAL | EGFR C797S | EGFR C797S | Elisabeth-Tweesteden | |

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| Trial | Cohort | Molecular | Sites | Warnings |
|---|-------------------|-------------------|--|----------|
| <i>Ziekenhuis</i> | | | | |
| <u>EGFR-L858R-TRIAL</u> | <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 trials)

| Trial | Cohort | Molecular | Sites |
|---|-------------------|-------------------|---------------------------|
| <u>EGFR-BE</u> | <i>EGFR L858R</i> | <i>EGFR L858R</i> | <i>Belgium: Brussels</i> |
| <u>KRAS-G12C-TRIAL-DE</u> | <i>KRAS G12C</i> | <i>KRAS G12C</i> | <i>Germany: Stuttgart</i> |

Trials in this table are matched solely on molecular event and tumor type (clinical data excluded).

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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

Key drivers

| Type | Driver | Trials (Locations) | Trials in Hartwig | Best evidence in External | Resistance in External |
|-----------------------------|---------------------------|------------------------|-----------------------------|---------------------------|------------------------|
| Mutation (gain of function) | EGFR L858R (2/4 copies) | | NCT00000006, NCT00000007 | Approved | |
| Mutation (gain of function) | EGFR C797S (1/4 copies) | TEDR1 (NKI-AvL) | NCT00000008 | Pre-clinical | |
| Mutation (gain of function) | KRAS G12D (0.3/2 copies)* | KAYRAS (Erasmus MC) | | | |
| Mutation (gain of function) | KRAS G12C (0.3/2 copies)* | | NCT00000009 | | |
| Deletion | TP53 | | | | |

The table continues on the next page

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| Type | Driver | Trials (Locations) | Trials in Hartwig | Best evidence in External | Resistance in External |
|--------------|---------------------------------|--------------------|-------------------|---------------------------|------------------------|
| Known fusion | MET(exon13)::MET(exon15) fusion | | | | |

* Variant has > 50% likelihood of being sub-clonal

Other drivers or relevant events

| Type | Driver | Trials (Locations) | Trials in Hartwig | Best evidence in External | Resistance in External |
|------|--------|--------------------|-------------------|---------------------------|------------------------|
| None | | | | | |

IHC results

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

Molecular history

| Event | Description | Date |
|---|----------------------------------|-----------|
| 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 Gain of function | Detected |
| TP53 del | Deletion | Detected |

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| Event | Description | Date | Method |
|------------|------------------------|------------|-------------|
| (Tier III) | Unknown protein effect | 2025-02-22 | Hartwig WGS |
| TMB | | 14.0 | |
| MSI | | Stable | |

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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

There are no standard of care treatment options for this patient

Resistance evidence

There are no standard of care treatment options for this patient

Treatment ranking

| Event | Treatment | Score |
|------------|-------------|-------|
| EGFR L858R | | |
| EGFR C797S | | |
| | AFATINIB | 2,400 |
| EGFR L858R | | |
| | OSIMERTINIB | 1,900 |

On label clinical evidence

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

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Off label clinical evidence

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

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Clinical Details

Clinical summary

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|-------------------------------------|---------------|----------------------|
| 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% |
| Known allergies | None |
| Recent surgeries | 01-Aug-2024 Cholecystectomy |

Tumor details (20-Feb-2025)

| | |
|--------------------|------------------------------|
| Measurable disease | Yes |
| Known lesions | Liver, Lung |
| Unknown lesions | None |
| No lesions present | CNS, Brain, Bone, Lymph node |

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 |

Trial Matching Details

National trials that are open and potentially eligible (2 trials)

| Trial | Cohort | Molecular | Sites |
|----------------------------------|------------|------------|---------------------------------|
| EGFR-C797S-TRIAL | EGFR C797S | EGFR C797S | NL: Tilburg, Germany: Stuttgart |
| EGFR-L858R-TRIAL | EGFR L858R | EGFR L858R | NL: Tilburg, Germany: Stuttgart |

Trials in this table are matched solely on molecular event and tumor type (clinical data excluded).

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

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

Trials in this table are matched solely on molecular event and tumor type (clinical data excluded).

Trials and cohorts that are potentially eligible, but are closed (1 trial)

| Trial | Cohort | Molecular | Sites | Warnings |
|---------------------------------------|------------------------------|-----------|-------|---|
| METC 01 IEMOEN (Phase 1) | Dose expansion - monotherapy | None | | Has not exhausted SOC (at least platinum doublet remaining) |

Trials and cohorts that are considered ineligible (4 cohorts from 3 trials)

| Trial | Cohort | Molecular | Ineligibility reasons |
|---|--|-----------------------------|---|
| METC 02 KAYRAS (Phase 1/2) | Dose expansion - monotherapy - Colorectum | KRAS G12D, PD-L1 >= 50.0 | No colorectal cancer |
| METC 03 NO-SEE797ES | Dose escalation - monotherapy | EGFR C797S | C797S in EGFR in canonical transcript |
| METC 05 PICKME3CA | Applies to all cohorts below | None | No PIK3CA activating mutation(s) |
| | Dose expansion - monotherapy - NSCLC (closed) | | |
| | Dose expansion - monotherapy - Other cancer types (closed) | | Tumor belongs to DOID term(s) lung non-small cell carcinoma |

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Trials and cohorts that are not evaluable or ignored (0 trials)

| Trial | Cohort | Molecular | Sites | Configuration |
|-------|--------|-----------|-------|---------------|
| None | | | | |

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 | WARN Has not exhausted SOC (at least platinum doublet remaining) |
| E-02 | UNDETERMINED No measurement found for hemoglobin |
| E-03 | UNDETERMINED No measurement found for absolute neutrophil count |
| E-01 | PASS Has no other condition belonging to category autoimmune disease |
| I-01 | PASS Patient is at least 18 years old |
| I-02 | PASS Has solid primary tumor Stage IV is considered metastatic |

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10/16 Gene and variant annotations and related content are powered by Genomenon Cancer Knowledgebase (CKB).

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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**

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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 | WARN |
| | Variant(s) G12D in KRAS but subclonal likelihood of > 50% |
| I-03 | UNDETERMINED |
| | ASAT and ALAT are not present or cannot be evaluated |
| I-01 | PASS |
| | Patient is at least 18 years old |
| I-02 | PASS |
| | Stage IV is considered metastatic |
| I-05 | PASS |
| | PD-L1 expression above minimum of 50.0 |

METC 02 - Dose expansion - monotherapy - NSCLC

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

| Reference | Evaluation |
|-----------|---|
| I-02 | PASS |
| | Tumor belongs to DOID term(s) lung non-small cell carcinoma |

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METC 02 - Dose expansion - monotherapy - Colorectum

Cohort ID **B**

Potentially eligible? **No**

Open for inclusion? **Yes**

Has slots available? **Yes**

| Reference | Evaluation |
|-----------|------------|
|-----------|------------|

| | |
|------|------|
| I-02 | FAIL |
|------|------|

No colorectal cancer

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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 |

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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) |

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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 | |