

Supplementary Materials: Liquid Biopsies in Lung Cancer

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Table S1. Overview of studies, partly using liquid biopsy in mutational diagnostics, cited in this review.

| Study | Details | NCT Number | Status | n | Stages (UICC) | Histological Types | (Diagnostic) Result |
|-----------|---------------|-------------|------------------------|-----------------------------|---|---|--|
| LIQUIK | Observational | NCT04703153 | Active, recruiting | 200 (estimated enrollment) | IV | Non-squamous NSCLC | Ongoing, no update |
| AURA 3 | Phase III | NCT02151981 | Active, not recruiting | 419 | III, IV | NSCLC with EGFR mutation with prior EGFR-directed therapy | Superiority of osimertinib treatment compared to platinum-containing cytotoxic treatment after progression on first-line TKI therapy regarding PFS, ORR and adverse events |
| FLAURA2 | Phase III | NCT04035486 | Active, not recruiting | 556 | III B, IIIC, IV | NSCLC with EGFR mutation, no prior therapy | Superiority of osimertinib compared to comparator-TKI (gefitinib, erlotinib) regarding OS and exposure time |
| APPLE | Phase II | NCT02856893 | Active, not recruiting | 156 | IV | NSCLC (adenocarcinoma only) with plasma-confirmed EGFR mutations Del19 or L858R | Ongoing, no update |
| MELROSE | Phase II | NCT03865511 | Active, recruiting | 66 (estimated enrollment) | IIIB/IV | NSCLC (adenocarcinoma only), treatment-naïve with at least one of TKI-sensitivity-harboring EGFR mutations (Ex19 deletions or L858R) | Ongoing, no update |
| AURA | Phase II | NCT01802632 | terminated | 603 | IIIB/IV (advanced, non-operable) | EGFR mutated NSCLC with progression on single-agent TKI | Osimertinib shows efficacy (PFS 9.6 months) and high ORR (61%) in EGFR T790M mutated NSCLC |
| B-FAST | Phase II/III | NCT03178552 | Active, recruiting | 1000 (estimated enrollment) | III (advanced, not amenable to treatment with combined chemoradiation)/IV | NSCLC Cohort A: ALK pos Cohort B: RET pos Cohort C: bTMB pos. Cohort D: ROS1+ Cohort E: BRAF V600 Cohort F: Exon 20 + Cohort G: KRASG12C | For Cohort A: Clinical application of blood-based NGS as a method to inform clinical decision making in ALK-positive NSCLC |
| VISION | Phase II | NCT02864992 | Active, not recruiting | 337 | IIIB/IV | NSCLC (all types, including sarcomatoid and squamous) with METex14 skipping mutation | Tepotinib treatment in METex14 skipping: ORR 48% (liquid-based assessment) vs. 50% (tissue-based), mDOR 11.1 months independent from prior treatment |
| Lu et al. | Phase II | NCT02897479 | Active, not recruiting | 76 | IIIB/IV | Pulmonary sarcomatoid carcinoma and other NSLCL harboring | Savolitinib in METex14 skipping alterations leads to ORR to 49.2%, baseline positivity in |

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|-------------------|-------------|-------------|------------------------|--------------------------------------|---|--|--|
| | | | | | | METex14 skipping mutation | ctDNA sequencing had worse PFS and OS but higher ORR |
| LIBRETTO | Phase I/II | NCT03157128 | Active, recruiting | 875 (all arms, estimated enrollment) | Locally advanced or metastatic solid tumors | Medullary thyroid cancer, NSCLC, other solid tumors with RET mutation/fusion/alteration | Selpercatinib treatment in RET pos. NSCLC leads to an ORR of 64% (85% in untreated patients), mDOR 17.5 months; high activity in brain metastases (intracranial response rate 91%) |
| ARROW | Phase I/II | NCT03037385 | Active, not recruiting | 589 (all arms) | Locally advanced or metastatic solid tumors | Medullary thyroid cancer, NSCLC, other solid tumors with RET mutation/fusion/alteration | Praseltinib treatment in RET pos. NSCLC leads to an ORR of 53% (70% in untreated patients), 3 complete responses |
| CodeBreak | Phase I/II | NCT03600883 | Active, not recruiting | 713 (all arms) | Locally advanced or metastatic solid tumors | All entities with pathologically confirmed KRAS p.G12C mutation | Sotorastib treatment in NSCLC with KRAS p.G12C mutation leads to an ORR in 37.1% besides multi-lineage pre-treatment and disease control rate (DCR) in 80.6% of all patients, mPFS 6.8 months, mOS 12.5 months |
| Code-Break200 | Phase III | NCT04303780 | Active, not recruiting | 345 | Locally advanced and unresectable or metastatic NSCLC | Locally advanced and unresectable or metastatic NSCLC, pathologically confirmed KRAS p.G12C mutation | Sotorasib significantly improves PFS and has a more favorable safety profile vs. docetaxel |
| ClinCode-Break200 | Phase Ib/II | NCT04185883 | Active, recruiting | 1,143 (estimated enrollment) | Locally advanced or metastatic malignancies | All entities with pathologically confirmed KRAS p.G12C mutation | Higher rates of grade III and IV adverse events combining sotorasib and immunotherapeutics, dose escalation ongoing |
| MYSTIC | Phase III | NCT02453282 | Active, not recruiting | 1148 | IV | NSCLC, no sarcomatoid variant | no superiority of tremelimumab and durvalumab vs. cytotoxic treatment in first-line setting, optimal benefit at bTMB >20 mut/mb |
| POPLAR trial | Phase II | NCT01903993 | completed | 287 | IIIB, IV | NSCLC | Significant improvement of OS with atezolizumab treatment compared to docetaxel |
| OAK trial | Phase III | NCT02008227 | completed | 1,225 | IIIB, IV | NSCLC | Improvement of survival of atezolizumab vs. docetaxel after platinum-based chemotherapy bTMB ≥ 16 was associated with higher ORR and longer OS compared to bTMB <16 under atezolizumab treatment |
| B-F1RST | Phase II | NCT02848651 | completed | 153 | IIIB, IV | NSCLC | |

Table S2. Use of liquid biopsies in lung cancer screening, post-treatment surveillance and therapy response prediction.

| Study | Details | NCT number | Status | n | Subjects | Further Details | (Diagnostic) Result |
|----------|----------------------------|------------|-----------|--------|---------------|-----------------|--|
| DETECT-A | Prospective interventional | - | Completed | 10,006 | Healthy women | - | Screening via blood test revealed 26 cancer cases, confirmed by PET-CT |

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|-------------|----------------------------|-------------|------------------------|--------|--|--|---|
| SUMMIT | Observational | NCT03934866 | Active, not recruiting | 13,035 | Smoker/high lung cancer risk | 30 pack years (py) or lung cancer risk \geq 1.3% assessed by PLCOm2012 | Timely reporting of 645 (5.6%) LD-CT findings during 5 days is feasible |
| AIR | Prospective, observational | NCT02500693 | Active, not recruiting | 614 | Smokers and ex-smokers (\geq 30 py) | With COPD | 3% of patients were detected with prevalent lung cancer at first screening, and 4% with incident lung cancer during follow-up |
| SUPE_R | RCT | NCT03740126 | Active, not recruiting | 750 | NSCLC patients | I-III, eligible for definitive treatment | Surveillance with liquid biopsy and PET-CT after definitive treatment: Ongoing, no update |
| ORACLE | Prospective, observational | NCT05059444 | Active, recruiting | 1,000 | Patients with solid tumors | treatment in curative intent | Feasibility of ctDNA testing in observing residual tumor cells: Ongoing, no update |
| TRACERX | Prospective, observational | NCT01888601 | Active, not recruiting | 814 | NSCLC | Stage I-IIIa | Multi-regional exome and RNA-seq mapped with deep learning elucidates constraints that may shape the emerge of immune-evading subclones and aggressive phenotypes |
| LIBERTYLUNG | Prospective, observational | NCT04790682 | Active, recruiting | 300 | NSCLC | Stage IV | Feasibility of liquid biopsy to predict responses to first-line immunotherapy |