# Supplementary Materials: New Generations of Tyrosine Kinase Inhibitors in Treating NSCLC with Oncogene Addiction: Strengths and Limitations

**Ilaria Attili, Carla Corvaja, Gianluca Spitaleri, Ester Del Signore, Pamela Trillo Aliaga, Antonio Passaro and Filippo de Marinis**

**Table S1.** 4th generation EGFR TKIs properties compared to those of osimertinib.

| Drug | $IC_{50}$ | CNS Penetrant | Clinical trial |
|---|---|---|---|
| Osimertinib | EGFR 19Del/C797S = 304.39 nM<br>EGFR 19Del/T790M/C797S =124.82nM<br>EGFR L858R/C797S = 573.72 nM | Y | FLAURA |
| EAI045 | EGFRC7697S = only when added cetuximab | - | Withdrawn |
| JBJ-04-125-02 | EGFRL858R/T790M= 0.26 nmol/l | - | Withdrawn |
| BLU-701 | EGFRex19del/C7697S = 0.5 nM<br>EGFRL858R/C797S= 1.5 nM | Y | None |
| BPI-361175 | No data available | Y | Phase I/II trial<br>Post-3rd TKI<br>NCT05393466 |
| QLH11811 | EGFRex19del/T790M/C7697S = 2.6 nM<br>EGFRL858R/T790M/C797S= 2.6 nM | - | Phase I trial<br>Either Tx naïve or post-TKIs<br>NCT05555212 |
| BDTX-1535 | EGFRC797S < 10nM | Y | Phase I EGFR+ NSCLC*<br>or glioblastoma<br>NCT05256290 |
| BBT-207 | EGFRex19del/T790M/C7697S <10nM<br>EGFRL858R/T790M/C797S < 10 nM | Y | Phase I/II trial<br>Post-3rd TKI<br>NCT05920135 |
| JIN-A02 | EGFRex19del/T790M/C7697S = 4.7nM<br>EGFRL858R/T790M/C797S= 12.8 nM | Y | Phase I/II trial<br>Post TKI and CT<br>NCT05394831 |
| HS-10375 | No data available | - | Phase I/II trial<br>Post-3rd TKI<br>NCT05435248 |
| TAS3351 | No data available | - | Phase I/II trial<br>Post-3rd TKI<br>NCT05765734 |
| BLU-945 | EGFRex19del/C7697S = 0.5 nM<br>EGFRL858R/T790M/C797S= 0.5 nM | - | Phase Ib/II<br>Post-3rd TKI<br>SYMPHONY<br>NCT04862780<br>(plus osimertinib) |
| BBT-176 | EGFR 19Del/C797S = 4.36 nM<br>EGFR 19Del/T790M/C797S = 1.79 nM<br>EGFR L858R/C797S = 5.35 nM | - | Phase I/II trial<br>Post-3rd TKI<br>NCT04820023 |
| H002 | EGFREx19del/T790M/C797S < 5 nM | Y | Phase I/II |

| | | | |
|---|---|---|---|
| | EGFRL858R/T790M/C797S < 5 nM | | Post-3rd TKI<br>NCT05519293 |
| WJ13404 | No data available | - | Phase I/II<br>**C797S+**<br>Post-3rd TKI<br>NCT05662670 |

**Abbreviations:** IC50 = Half-maximal inhibitory concentration CNS = central nervous system; Y = yes; EGFR = Epidermal Growth Factor Receptor; NSCLC = Non-Small-Cell Lung Cancer; TKI(s) = Tyrosine Kinase Inhibitor(s); CT = chemotherapy. *dose expansion catered for EGFR C797S+ NSCLC patients.

**Table S2.** Summary of EGFR Ex20ins TKi inhibitors.

| Drug | EGFRex20ins $IC_{50}$ | Clinical trial | Results | Ongoing CTs |
|---|---|---|---|---|
| Mobocertinib (TAK-788) 160 mg OD | 4.3-22.5 nM | EXCLAIM<br>NCT02716116<br>Zhou 2022[1] | ORR 28%<br>mPFS 7.3 months | NCT02716116<br>(w or wout BM+) |
| Poziotinib (HM781-36B) 16 mg OD | 1.0 nM | ZENITH20<br>[NCT03318939]<br>Le 2020[2] | ORR 14.8%<br>mPFS 4.2 months | NCT03318939<br>8 mg BID |
| TAS6417 (CLN-081) 100 mg BID | 3-21 nM | NCT04036682<br>Yu 2022[3] | ORR 41%<br>mPFS 12 months | NCT04036682<br>Ph II part<br>BM+ and prior TKIs |
| Sunvozertinib (DZD9008) 400 mg OD | 2.1 nM | WU-KONG1<br>[NCT03974022]<br>WU-KONG2 [CTR20192097]<br>Wang 2022[4] | ORR 37.5%<br>mPFS NR (> 4 months) | NCT05668988<br>Ph III S vs 1st line CT |
| Tuxobertinib (BDTX-189) 800 mg OD | 10-100 nM | Masterkey-01 NCT04209465 | 5 pts EGFREx20ins<br>5 pts HER2Ex20ins | NCT04209465<br>Enrollment is ongoing in non-fasting QD and BID cohorts, and the low fat food effect cohort |
| Furmonertinib 160 mg or 240 mg OD | 11-81 nM | FAVOUR<br>NCT04858958<br>Han 2021[5] | Pretreated<br>160 mg ORR 40%<br>240 mg ORR 50%<br>Tx naïve<br>ORR 80% | phase II trial NCT05466149<br>**Phase III trial**<br>**FURMO-004**<br>NCT to be determined<br>240 mg OD vs 160 mg OD<br>Vs CT<br>**Phase Ib trial**<br>**FURMO-002**<br>Dose escalation from 240 up to 320 mg OD |

**Abbreviations**: CTs = clinical trials; OD = once daily; nM = nanomole; ORR = overall response rate; mPFS = median progression-free survival; NR = not reached; pts = patients; Tx naïve = treatment naïve; w= with; wout= without; BM = brain metastases; BID = two times a day; NCT National = Cancer Center trial ID.

**Table S3.** Summary of HER2ex20 ins TKIs.

| Drug | HER2ex20ins $IC_{50}$ | Clinical trial | Results | Ongoing CTs |
|---|---|---|---|---|
| Mobocertinib[6] | YVMA = 70nM<br>G776->VC= 10 nM<br>GSP= 10 nM | - | - | NCT02716116<br>Cohort 2 HER2Ex20ins with no BM |
| Poziotinib (HM781-36B) | 1.9 nM | ZENITH20 [NCT03318939]<br>Le 2022[7] | ORR 28%<br>mPFS 5.1 months | NCT03318939<br>8 mg BID |
| Tarloxotinib | 0.15-4.34 nM | RAIN-701<br>Phase I/II trial<br>[NCT03805841]<br>Liu 2020[8] | ORR 22% | RAIN-701<br>[NCT03805841]<br>Phase II part |
| Pyrotinib | G776YVMA= 180 nM* | Phase II trial<br>NCT02834936<br>Zhou 2020[9] | ORR 30%<br>mPFS 6.9 months | PEER20 trial<br>Phase II trial<br>(NCT04063462)<br>PYRAMID-1 trial<br>Phase III trial<br>(vs docetaxel)<br>(NCT04447118)<br>Phase II<br>(pyrotinib + PD1 abs)<br>(NCT04144569) |
| Tuxobertinib (BDTX-189) | 13 nM^ | Masterkey-01<br>NCT04209465 | 5 pts EGFREx20ins<br>5 pts HER2Ex20ins | NCT04209465<br>Enrollment is ongoing in non-fasting QD and BID cohorts, and the low fat food effect cohort |
| TAS2940[10] | 1.54-3.28 nM | - | - | NCT04982926<br>Phase I trial |

**Abbreviations**: CTs = clinical trials; OD = once daily; nM = nanomole; ORR = overall response rate; mPFS = median progression-free survival; NR = not reached; pts = patients; BM = brain metastases; BID = two times a day. *refers to growth inhibition of patient-derived organoids and xenografts from a 42-year-old female with HER2-A775_G776YVMA-inserted advanced lung adenocarcinoma.

**Table S4.** Ongoing clinical trials of RAS inhibitors.

| Trial | Phase | Pt N | Drug | Disease | Key inclusion criteria | Location |
|---|---|---|---|---|---|---|
| CODEBREAK-IGR<br>NCT05631249 | II | 40 | Sotorasib | KRASG12C NSCLC | Post 1st line<br>No Prior KRAS-I | France |
| SOLUCOM<br>NCT05311709 | II | 100 | Sotorasib | KRASG12C NSCLC + comorbities | Post 1st line<br>60 pts ECOG PS2<br>No prior KRAS-I | Norway |
| ECOG-ACRIN LUNG-MAP<br>NCT04625647 | II | 116 | Sotorasib | KRASG12C NSCLC | No prior KRAS-I | USA |
| Breakthrough<br>NCT05451056 | II | 37 | Sotorasib | KRASG12C NSCLC | Post 1st line tx | Korea |
| LungKG12Ci<br>NCT05273047 | obs | 300 | Sotorasib | KRASG12C NSCLC | Real world data | France |
| MERIT-lung<br>NCT05398094 | II | 43 | Sotorasib | KRASG12C NSCLC | Stage III Ineligible for CRT | Spain |
| KRYSTAL12<br>NCT04685135 | III | 450 | Adagrasib Vs docetaxel | KRASG12C NSCLC | Post CT+ ICI<br>No prior RAS-I | Worldwide |
| ADEPPT<br>NCT05673187 | II | 68 | Adagrasib | KRASG12C NSCLC | Elderly<br>Post CT+/-ICI<br>No prior RAS-I | Europe |
| KRYSTAL 21 | II | 200 | Adagrasib | KRASG12C NSCLC | Post CT+/-ICI | USA |

| | | | | | | |
|---|---|---|---|---|---|---|
| NCT05853575 | | | 600 vs 400 mg BID | | No prior RAS-I | |
| NAUTIKA1 NCT04302025 | II | 85 | Divarasib | gene addicted NSCLC | Stage Ib-IIIB Neoadjuvant setting Biomarker-driven platform | USA |
| KontRASt-01 NCT04699188 | I/II | 475 | JDQ433 | KRASG12C solid tumours | No prior RAS-I | Worldwide |
| KontRASt-02 NCT05132075 | III | 360 | JDQ433 Vs docetaxel | KRASG12C NSCLC | Post CT+ ICI No prior RAS-I | Worldwide |
| STRIDER NCT05999357 | II | 42 | JDQ433 | KRASG12C NSCLC | BM+ No Prior RAS-I or at least after 1 year of interval | Nederland |
| KontRASt-06 NCT05445843 | II | 120 | JDQ433 | KRASG12C NSCLC | Tx naïve PD-L1 neg or PD-L1 +/SKT11+ | Worldwide |
| Neoadjuvant Platform NCT05714891 | II | 27 | JDQ433 | KRASG12C NSCLC | Neoadjuvant setting Stage IA2 to IIIA | Canada |
| NCT04956640 | I | 400 | LY3537982 | KRASG12C solid tumours | Post CT +ICI | Worldwide |
| NCT04973163 | I | 29 | BI 1823911 | KRASG12C solid tumours | No prior RAS-I allowed | USA, Europa |
| NCT05002270 | I/II | 124 | Glecirasib (JAB-21822) | KRASG12C solid tumours | Dose exp CRC drug + cetuximab | USA |
| NCT05737706 | I/II | 304 | MRTX1133 | KRASG12D solid tumours | Post standard tx | USA |

**Abbreviations:** Pt N = patient number; obs = observational; vs = versus; BID = two times a day; NSCLC = non-small-cell lung cancer; KRAS-I(s) = KRAS inhibitors; ECOG PS = Eastern Cooperative Oncology Group Performance Status; Tx = treatment; CT = chemotherapy; ICI = immune-checkpoint inhibitor; PD-L1 = Programmed Cell Death Ligand 1; CRT = chemo-radiotherapy; BM = brain metastases.

**Table S5.** Ongoing clinical trials of RAF inhibitors.

| Trial | Phase | Pt N | Drug(s) | Disease | K Inclusion criteria | Location |
|---|---|---|---|---|---|---|
| ENCO-BRAF NCT04526782 | II | 119 | Encorafenib + Binimetinib | BRAFV600E | Tx naïve or post CT+/-ICI No prior BRAF/MEK-I | France |
| OCEANII NCT05195632 | II | 55 | Encorafenib + Binimetinib | BRAFV600E | Tx naïve or post CT No prior BRAF/MEK-I | China |
| NCT05065398 | II | 20 | HLX208 (BRAF-I) | BRAFV600E | Post CT+/-ICI No prior BRAF/MEK-I | China, Taiwan |
| NCT05900219 | II | 75 | Vemurafenib+ HL-085 (MEK-I) | BRAFV600E | No prior BRAF/MEK-I | China |
| RAMP202 NCT04620330 | II | 100 | avutometinib (VS-6766) (RAF/MEK clamp) + Defactinib (FAK inhibitor) | KRASG12V/other BRAFV600E/other | Cht 1/2 KRASG12V Cht 3 KRAS other Cht 4 BRAFV600E Cht 5BRAFother No prior KRAS/BRAF/MEK-I | USA, Europe |
| NCT04913285 | I | 262 | Exarafenib (KIN-2787) panRAF-I+/- binimetinib | BRAF/NRAS+ solid tumours and NSCLC/Melanoma | Dose Exp No prior BRAF/MEK-I | USA, China, Taiwan, Korea, Australia, Europe |
| NCT05786924 | I | 140 | BDTX-4933 panRAF | BRAF/RAS/MAPK+ solid tumours | Dose Exp CHT1 NSCLC BRAF class II or KRAS NON G12C CHT3 BRAF class I | USA |
| NCT05668585 | I/II | 122 | CFT1946 (RAF-I) +/- Trametinib | BRAFV600E solid tumours | Prior or naïve RAF-I permitted | USA, France, Spain |
| ENHANCE NCT05275374 | I/II | 221 | XP-102 RAF-I) +/- Trametinib | BRAFV600E solid tumours | Prior RAF/MEK-I permitted | China |

| | | | | | | |
|---|---|---|---|---|---|---|
| NCT05501912 | I | 72 | ABM-1310<br>RAF-I | BRAFV600E solid tumours | Prior RAF/MEK-I permitted | China, Shanghai |
| NCT04190628 | I | 112 | ABM-1310<br>RAF-I<br>Cobimetinib<br>MEK-I | BRAFV600E/ or other solid tumours | Prior RAF/MEK-I permitted | USA |
| NCT05355701 | I | 174 | PF-07799933 (ARRY-440)<br>RAF-I-/+ binimetinib or cetuximab | BRAF class II/III solid tumours | BRAF class II/III | USA, Canada, Israel |
| NCT05538130 | I | 124 | Encorafenib +<br>PF-07799544<br>MEK-I | BRAF V600E or class II solid tumours | BRAF V600E or class II | USA, Canada |
| NCT04985604 | I/II | 168 | Tovorafenib<br>PanRAF-I+<br>Pimasertib<br>MEK1-2-I | MAPK Pathway Aberrations<br>Solid tumours | Pts must have<br>BRAF fusion,<br>CRAF/RAF1 fusion, or<br>CRAF/RAF1 amplification<br>No Prior RAF/MEK-I | USA, Australia, Europe, Korea |
| NCT04892017 | I/II | 323 | DCC-3116+/-<br>Trametinib, bimetinib or sotorasib | MAPK Pathway Aberrations<br>Solid tumours | RAS, NF1, or RAF mutations<br>No Prior RAS/RAF/MEK-I if discontinued due to safety | USA |
| NCT04800822 | I | 196 | PF-07284892<br>SHP2-I +<br>binimetinib | BRAF class III solid tumours | A/B ALK/ROS1 lorlatinib<br>C /D CRC BRAF<br>E BRAF Solid tumours | USA |

**Abbreviations:** Pt N = patient number; NSCLC = non-small-cell lung cancer; (B)RAF/MEK/KRAS/NF1-I(s) = KRAS inhibitors; ECOG PS = Eastern Cooperative Oncology Group Performance Status; Tx = treatment; CT = chemotherapy; ICI = immune-checkpoint inhibitor; Cht = cohort; Dose Exp= dose expansion. CFT1946 is an orally active and selective target ligand for BRAF kinase. CFT1946 is a degrader of mutant BRAFV600E, G469A, G466V and p61-BRAFV600E.

**Table S6.** Ongoing clinical trials of novel MET-inhibitors in MET dysregulated NSCLC or solid tumours.

| Trial | Phase | Pt N | Drug | Disease | Key inclusion criteria | Location |
|---|---|---|---|---|---|---|
| SPARTA<br>NCT03175224 | I/II | 344 | Bozitinib<br>(APL-101 or PLB1001) | MET+ solid tumours or NSCLC | Solid tumors or NSCLC harbouring MET alterations<br>MET-I naïve or refractory | Worldwide |
| KUNPENG<br>NCT04258033 | II | 185 | Bozitinib<br>(APL-101 or PLB1001) | MET+ | Must have c-Met dysregulation adv NSCLC<br>Not mentioned Prior MET-Is in the criteria | China |
| NCT04992858 | II | 80 | Ningetinib | METex14 NSCLC | METex14 in lx or tx<br>Prior therapies with MET-Is are not allowed | China (not yet recruiting) |
| SHIELD-1<br>NCT03993873 | I/II | 180 | TPX-0022<br>(elzovantinib) | MET+ NSCLC, gastric or solid tumours | METex14 or MET AMP<br>No restrictions on prior MET-Is | USA, Korea, France, Spain<br>**Enrollment completed** |
| NCT04270591 | I/II | 183 | Glumetinib (SCC244) | MET+/METex14 NSCLC | Cohort 1 (China):<br>MET OE, MET AMP, METex14<br>Cohort 2 (USA) METex14<br>Only in phase I Prior MET-Is allowed | China, Usa |
| NCT02929290 | Ib | 80 | BPI-9016M, a dual MET/Axl inhibitor | METex14 or MET OE NSCLC | MET OE or METex14<br>Adv NSCLC<br>Prior type I MET-Is are allowed | China |
| NCT04052971 | I/II | 78 | ABN401 (selective MET-I) | MET+ NSCLC or solid tumours | Phase I MET+<br>Phase II METex14 | Korea, Australia |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | Only in phase I Prior MET-Is allowed | |
| NCT05752552 | I | 15 | DO-2 (selective MET-I) | MET+ solid tumours | MET mut or MET AMP (≥10 copies)<br>No restrictions on prior MET-Is | Belgium, Netherlands |

**Abbreviations** = pt N = patient number; lx = liquid biopsy; tx = tissue biopsy; MET OE = MET overexpression; METex14 = MET exon 14 skipping mutations; MET AMP = MET amplification; MET-I(s) = MET inhibitor(s); NSCLC = Non-small-cell lung cancer. .

**Table S7.** Ongoing clinical trials of novel ALK TKIs.

| Trial | Phase | Pt N | Drug | Disease | Key inclusion criteria | Location |
|---|---|---|---|---|---|---|
| NCT03607188 | I | 18 | Alkotinib<br>(2nd ALK-I) | ALK+ NSCLC | Post-crizotinib | Shanghai |
| NCT04211922 | II | 104 | Alkotinib<br>2nd ALK-I | ALK+ NSCLC | Post-crizotinib | Shanghai |
| NCT05441956 | I | 100 | TGRX-326<br>(3rd ALK-I) | ALK+ or ROS1+ NSCLC | Post 1st/ 2nd ALK-I | China |
| NCT04237805 | I/II | 280 | Foritinib<br>(SAF-189s)<br>(3rd ALK-I/ROS-1) | ALK+ NSCLC | Tx naïve and Refractory | Shanghai |
| NCT05257512 | I/II | 70 | SY-3505<br>(3rd ALK-I) | ALK+ NSCLC | Refractory | China |
| NCT05055232 | I | 120 | XZP-3621<br>(3rd ALK-I) | ALK+ NSCLC | Naïve/refractory | China |
| NCT05482087 | II | 190 | XZP-3621<br>(3rd ALK-I) | ALK+/ROS1+ NSCLC | Naïve/refractory | China |
| NCT05204628 | RPIII | 238 | XZP-3621<br>Vs<br>crizotinib | ALK+ NSCLC | Tx Naive | China |
| NCT03917043 | I | 150 | APG-2449<br>FAK/ALK/ROS1 I | Solid tumours | Expansion phase<br>Tx naïve or pretreated ALK or ROS1+ NSCLC | China |
| NCT04849273 | I | 11 | TPX-0131<br>4th ALK-I | ALK+ NSCLC or solid tumours | Pretreated with up 3 ALK-Is | USA, Korea, Australia<br>Terminated (Adverse change in the risk/benefit) |
| ALKOVE-1<br>NCT05384626 | I/II | 214 | NVL-655<br>4th ALK-I | ALK+ NSCLC or solid tumours | Expansion Phase<br>Cohorts 2 A-C NSCLC<br>Cohorts 2D other solid tumours | USA, Europe |

**Abbreviations:** Pt N = patient number; ALK = Anaplastic Lymphoma Kinase; ALK-I(s) = ALK inhibitor(s); Tx = treatment; NSCLC = Non-small-cell-lung cancer.

**Table S8.** Ongoing clinical trials of novel ROS1 TKIs.

| Trial | Phase | Pt N | Drug | Disease | Key inclusion criteria | Location |
|---|---|---|---|---|---|---|
| NCT04603807 | III | 220 | Crizotinib<br>Vs<br>entrectinib | ROS1+ NSCLC | Tx naïve<br>With or without BM | Worldwide |
| BFAST<br>NCT03178552 | II | 1000 | entrectinib | ROS1+ NSCLC | Tx naïve<br>ctDNA+ for ROS1+ | Worldwide |
| NCT05170204 | III | 320 | Entrectinib<br>Vs durvalumab | ROS1+NSCLC | Stage III NSCLC<br>A1 ALK+ Alectinib<br>A2 ROS1+<br>A3 RET+ | Worldwide |
| TRIDENT-1<br>NCT03093116 | I/II | 500 | repotrectinib | ALK, ROS1, or NTRK solid tumours | EXP-1: ROS1 TKI-naïve ROS1+ NSCLC | Worldwide |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | EXP-2: 1 Prior ROS1 TKI and 1 Platinum based CT ROS1+ NSCLC<br>EXP-3: 2 Prior ROS1 TKIs ROS1+ NSCLC (No CT or ICI)<br>EXP-4: 1 Prior ROS1 TKI ROS1+ NSCLC (No CT or ICI)<br>EXP-5: TRK TKI-naïve NTRK+ solid tumors<br>EXP-6: TRK TKI-pretreated NTRK+ solid tumors | |
| NCT04395677 | II | 106 | taletrectinib | ROS1+ NSCLC | ROS1-I naïve or post-crizotinib | China |
| TRUST II<br>NCT04919811 | II | 154 | taletrectinib | ROS1+ NSCLC | TKI tx naïve or treated with prior ROS1-Is | Worldwide |
| ARROS-1<br>NCT05118789 | I/II | 359 | NVL-520 | ROS1+ solid tumours or NSCLC | 2a: ROS1 naïve/ up 1L CT<br>2b: 1L ROS1-I/ CT naïve<br>2c: 1L ROS1-I/ 1L CT<br>2d: ≥2L ROS-Is/1L CT<br>2e: solid tumours | Worldwide |
| NCT05765877 | II | 26 | Iruplinalkib WX-0593 | ALK or ROS1+ NSCLC | Stage IB-IIIA | China |
| NCT05351320 | II | 40 | Iruplinalkib WX-0593 plus CRT | ALK or ROS1+ NSCLC | Stage III | China |
| NCT04197076 | II | 200 | TKIs | NSCLC | IIB-IIIB stage<br>A: PD-L1 ≥ 50% ICI<br>B: EGFR/ALK or ROS1+<br>C: non-gene addicted | China |
| NCT03607188 | I | 18 | Alkotinib | ALK or ROS1+ NSCLC | Pretreated with CT or crito-tinib | China |
| NCT05441956 | I | 100 | TGRX-326 | ALK+ or ROS1+ NSCLC | Post 1st/ 2nd TKIs | China |
| NCT04237805 | I/II | 280 | Foritinib (SAF-189s) | ALK+ or ROS1+ NSCLC | Tx naïve and Refractory | Shanghai |
| NCT04996121 | I/II | 360 | XZP-5955 | NTRK+ or ROS1+ solid tumours | Dose exp<br>NTRK solid tumours<br>Tx naïve or post crizotinib<br>ROS1+ NSCLC | China |
| NCT03917043 | I | 150 | APG-2449 FAK/ALK/ROS1 I | Solid tumours | Expansion phase<br>Tx naïve or pretreated ALK or ROS1+ NSCLC | China |
| ALBATROS<br>NCT04621188 | II | 84 | lorlatinib | ROS1+ NSCLC | Post-crizotinib or entrectinib<br>Post-CT | France |
| NCT03612154 | II | 35 | lorlatinib | ROS1+ NSCLC | Tx naïve or post CT<br>**No prior ROS1-I** | Korea |
| NCT01639508 | II | 86 | cabozantinib | ROS1+ NSCLC | Group A RET+<br>Group B NTRK, AXL or MET<br>Group C ROS1<br>Group D RET+ prior RET-I | USA |

**Abbreviations:** Pt N= patient number; ROS1 = c-ros oncogene 1; ROS1-I(s) = ROS1 inhibitors ; Tx = treatment; NSCLC = Non-small-cell-lung cancer; BM = brain metastases; TKI(s) = tyrosine kinase inhibitor(s); TX = treatment; EXP = expansion; CT= chemotherapy; ICI = immunocheckpoint inhibitor.

**Table S9.** Ongoing clinical trials of novel NTRK-inhibitors.

| Trial | Phase | Pt N | Drug | Disease | Key inclusion criteria | Location |
|---|---|---|---|---|---|---|
| NAVIGATE NCT02576431 | II | 204 | Larotrectinib | NTRK+ solid tumours | 1: NSCLC<br>2: thyroid carcinoma<br>3: soft-tissue sarcoma<br>4: colorectal cancer<br>5 Salivary tumours<br>6: biliary tumours<br>7: Primary CNS<br>8: other solid tumours<br>9: solid tumours without confirmed NTRK gene fusions<br>10:melanoma/non secretary breast cancer/colorectal cancer<br>11: all tumour types without measurable disease | Worldwide |
| NCT05192642 | Obs. | 368 | larotrectinib | NTRK solid tumours | Real world data of larotrectinib outside clinical trials | USA |
| LAROTRACKING NCT04814667 | Obs | 27 | larotrectinib | NTRK solid tumours | Real world data of larotrectinib | France |
| ON-TRK NCT04142437 | Obs | 300 | larotrectinib | NTRK solid tumours | Real world data of larotrectinib | worldwide |
| NCT04945330 | Obs | 100 | larotrectinib | NTRK solid tumours | Real world data of larotrectinib | Japan |
| NCT04879121 | II | 13 | larotrectinib | NTRK AMP solid tumours | NTRK amplified<br>No prior treated with NTRK-Is | USA |
| TRUMP NCT03574402 | II | 400 | ensartinib | ROS1+ or NTRK+ NSCLC | Tx naïve<br>Arm 5 ROS1+<br>Arm 6 NTRK+ | China |
| TRIDENT-1 NCT03093116 | I/II | 500 | repotrectinib | ALK, ROS1, or NTRK solid tumours | EXP-1: ROS1 TKI-naïve ROS1+ NSCLC<br>EXP-2: 1 Prior ROS1 TKI and 1 Platinum based CT ROS1+ NSCLC<br>EXP-3: 2 Prior ROS1 TKIs ROS1+ NSCLC (No CT or ICI)<br>EXP-4: 1 Prior ROS1 TKI ROS1+ NSCLC (No CT or ICI)<br>EXP-5: TRK TKI-naïve **NTRK+ solid tumors**<br>EXP-6: TRK TKI-pretreated NTRK+ solid tumors | Worldwide |
| NCT03556228 | I | 74 | VMD-928 | NTRK1+ solid tumours or lymphoma | NTRK1+ solid tumours or lymphoma progressing on larotrectinib or entrectinib | USA |
| NCT04996121 | I/II | 360 | XZP-5955 | NTRK+ or ROS1+ solid tumours | Dose exp<br>NTRK solid tumours<br>Tx naïve or post crizotinib<br>ROS1+ NSCLC | China |

**Abbreviations:** Pt N= patient number; ROS1 = c-ros oncogene 1; NTRK = Neurotrophic tyrosine receptor kinase; NTRK-I(s)= NTRK inhibitor(s); ROS1-I(s) = ROS1 inhibitors ; Tx = treatment; NSCLC = Non-small-cell-lung cancer; BM = brain metastases; TKI(s) = tyrosine kinase inhibitor(s); TX = treatment; EXP = expansion; CT= chemotherapy; ICI = immunocheckpoint inhibitor.

**Table S10.** Ongoing clinical trials of novel RET TKIs.

| Trial | Phase | Pt N | Drug | Disease | Key inclusion criteria | Location |
|---|---|---|---|---|---|---|
| LIBRETTO-001 NCT03157128 | I/II | 875 | Selpercatinib | RET+ solid tumours | Tx naïve or pretreated RET+ solid tumours **Multitargeted inh allowed** | Worldwide |
| LIBRETTO-432 NCT04819100 | III | 170 | Selpercatinib after surgery or RT | RET+ NSCLC | IB-IIIA RET Fusion-Positive NSCLC Following definitive locoregional tx | Worldwide |
| LIBRETTO-431 NCT04194944 | III | 250 | Selpercatinib Vs CT +/-ICI | RET+NSCLC | Tx naïve RET fusion+ on tissue or lx | Worldwide |
| NCT05170204 | III | 320 | Pralsetinib Vs durvalumab | Stage III NSCLC | Stage III NSCLC After CRT Cohort A3 RET+ | Worldwide |
| acceleRET NCT04222972 | III | 226 | Pralsetinib Vs CT | RET+ NSCLC | **Tx naïve RET fusion+ on tissue** | worldwide |
| NCT01639508 | II | 86 | cabozantinib | RET+, ROS1+ or NTRK+ NSCLC | **A: RET+** B: NTRK+, MET+ or AXL+ C ROS1+ **D RET+ prior treated RET-Is** | USA |
| NCT05117658 | II | 83 | HA121-28 | RET+ NSCLC | After at least one CT line **No prior RET-Is** | China |
| MARGARET NCT04683250 | I/II | 202 | TAS0953/HM06 | RET+ solid tumours | RET+ solid tumours Progressing on standard tx **Prior RET-Is allowed** | USA, Japan |
| NCT05278364 | I/II | 184 | SY-5007 | RET+ solid tumours | RET+ solid tumours Progressing on standard tx No prior RET-Is | China |
| NCT06031558 | III | 120 | SY-5007 | RET+ NSCLC | Tx naïve RET fusion on tx or lx | Shanghai |
| NCT05675605 | I/II | 248 | TY-1091 | RET+ solid tumours | RET fusions solid tumours | China |
| NCT05451602 | I/II | 456 | HEC169096 | RET+ solid tumours | RET fusions solid tumours No restrictions on prior tx lines | China |

**Abbreviations:** Pt N= patient number; lx = liquid biopsy; inh = inhibitor; RET = rearranged during transfection; ROS1 = c-ros oncogene 1; NTRK = Neurotrophic tyrosine receptor kinase; RET-(S) = RET inhibitors; NTRK-I(s)= NTRK inhibitor(s); ROS1-I(s) = ROS1 inhibitors ; Tx = treatment; NSCLC = Non-small-cell-lung cancer; BM = brain metastases; TKI(s) = tyrosine kinase inhibitor(s); TX = treatment; EXP = expansion; CT= chemotherapy; ICI = immunocheckpoint inhibitor.

**Surufatinib** inhibits VEGFR1/2/3, FGFR1, and CSF-1R; **Sarilumab** is an IL6-receptor Antibody; **Dalpiciclib** (CDK4/6 inhibitor) already approved in China for breast cancer; **pelcitoclax (APG-1252)** is an anti-Bcl2; **pamiparib** is an investigational Poly (ADP-ribose) polymerase (PARP) inhibitor recently approved in China for the treatment of germline BRCA mutation-associated recurrent advanced ovarian, fallopian tube or primary peritoneal cancer previously treated with two or more lines of chemotherapy; **VIC-1911** is an Aurora A inhibitor; **Minnelide** is an oral anti-super-enhancer drug that inhibits MYC expression; **Telaglenastat** (CB-839) (glutaminase inhibitor)**envafolimab** is anti-PDL1 agent; LP300 is a TRX and GRX inhibitor; **patritumumab-deruxtecan** a new ADC anti-HER3 conjugated to deruxtecan; **Quaratusugene ozeplasmid** consists of non-viral lipid nanoparticles that encapsulate a DNA plasmid with the TUSC2 tumor suppressor gene; **PM8002** is a bifunctional antibody antiPDL1/VEGF

**Table S11.** Ongoing trials of TKI-based combinations in *EGFR* or *HER*2 Exon 20 insertions.

| Trial | Phase | Pt N | Drugs | Disease | Key inclusion criteria | Location |
|---|---|---|---|---|---|---|
| CONCERTO NCT05241873 | I/II | 322 | BLU-451+/-CT | EGFREx20ins | Several CTs All EGFREx20ins A CT ami or mobo B Post CT C BM D prior CT Ami and mobo E Tx naive F/G Uncommon | USA/Canada/Japan Taiwan |
| NCT04974879 | II | 20 | Osimertinib + bevacizumab | EGFREx20ins | Not indicated prior Tx | China |
| NCT05132777 | II | 155 | Osimertinib + JMT101 (ab antiEGFR) | EGFREx20ins | after CT | Shanghai |
| NCT05751187 | II | 54 | Pembrolizumab Plus Bevacizumab Plus CT | EGFREx20ins | Tx naive | Shanghai |
| NCT04144569 | II | 30 | Pyrotinib + PD1 | HER2Ex20ins | Post-CT | China |
| NCT05745740 | I/II | 26 | Pyrotinib + Disitamab Vedotin (RC48-ADC) | HER2Ex20ins | Post-CT and ICI | Shanghai |
| NCT05016544 | I/II | 48 | Pyrotinib + inetetamab (anti-HER2) | HER2 mut or AMP | Post-CT No prior HER2-Is | China |
| NCT05482568 | I/II | 324 | Pyrotinib + SHR-A1811+ SHR-1316 Anti-PDL1 | HER2 | Post CT Not specified HER2 alterations needed | China |
| NCT05847764 | II | 95 | Disitamab Vedotin + Furmonertinib or CT | HER2 alterations | Arm 1/2 HER2 alterations w or wout EGFR+ tx naïve Arm 3 pretreated HER2 mutated | China |
| NCT04324125 | Obs | 70 | CT+/-ICI | HER2ins or AMP | Tx naive | China |
| NCT05681780 | I/II | 20 | TILs +Nivolumab+ CTX+IL2 | EGFR, ALK, ROS1, or ERBB2 alterations | Post CT | USA Florida |
| NCT04042701 | Ib | 115 | T dxt + pembro | HER2 OE or mutated NSCLC or Breast | Post standard tx | USA, France, UK, Spain |
| COMBI-TED NCT04884282 | II | 105 | Tedopi + Nivo Tedopi + TXT TXT | NSCLC wout EGFR/ ALK/ROS1 | Tedopi vaccine against 5 antigenes CEA, p53, HER2, MAGE-2/3 | Italy |
| NCT04278144 | I/II | 390 | BDC-1001 (antiHER2 stimulating Ab) -/+ nivolumab | HER2 OE or AMP solitd tumours | Post CT | USA, Korea, Spain |
| NCT04143711 | I/II | 490 | DF1001 (target NK and Tcell)+ nivo Or PTX | Solid tumours | Dose esc HER2 OE AMP or mut Dose exp NSCLC HER2 low/high chts | USA, Europe |

**Abbreviations:** Pt N = patient number; EGFR = Epidermal Growth Factor Receptor; HER2 = human epidermal growth factor receptor 2; Ami = amivantamab; mobo = mobocertinib; wout = without; Tx

= treatment; CT = chemotherapy; TKI(s) = Tyrosine kinase inhibitor (s); NSCLC = Non-small-cell lung cancer.

**Table S12.** Ongoing clinical trials of KRAS inhibitor-based combinations.

| Trial | Phase | Pt N | Drugs | Disease | Key inclusion criteria | Location |
|---|---|---|---|---|---|---|
| CodebreaK202<br>NCT05920356 | III | 750 | Sotorasib+ CT<br>Vs<br>Pembro + CT | KRASG12G<br>NSCLC | Tx naïve<br>PDL-1 negative | Worldwide |
| NCT05118854 | II | 27 | Sotorasib + CT | KRASG12C NSCLC | Stage IIA-IIIB | USA |
| NCT05180422 | II | 43 | Sotorasib +<br>MVASI | KRASG12C NSCLC | BM+<br>No prior KRAS-I | USA |
| NCT05054725 | II | 47 | Sotorasib+<br>RMC-4630<br>(SHP2-inh) | KRASG12C NSCLC | No prior KRAS-I | Worldwide |
| RAMP203<br>NCT05074810 | Ib/II | 53 | Sotorasib +<br>Avutometinib (VS-6766)<br>(MEK-I) | KRASG12C NSCLC | Part 1 No prior KRAS-I<br>Part 2 Prior KRAS-I | USA |
| NCT04892017 | I/II | 323 | DCC-3116+/-<br>Trametinib, bimetinib or<br>sotorasib | MAPK Pathway Aberrations<br>Solid tumours | RAS, NF1, or RAF mutations<br>No Prior RAS/RAF/MEK-I | USA |
| Argonaut<br>NCT05480865 | Ib | 85 | Sotorasib +<br>BBP-398<br>(SHP2 inh) | KRASG12C<br>Solid tumours | Post standard tx | Australia, Spain, Italy, France |
| NCT04720976 | Ib | 200 | Sotorasib +<br>JAB-3312<br>(SHP2 inh) | KRASG12C<br>Solid tumours | Several combinations:<br>For KRASG12C + sotorasib | USA |
| NCT05374538 | Ib | 140 | VIC-1911<br>(aurora A inh)<br>-/+<br>sotorasib | KRASG12C NSCLC | Cohort RAS-Is naïve<br>Cohort RAS-Is refractory | USA |
| NCT05815173 | Ib | 40 | Sotorasib +<br>Ladarixin<br>(IL-8 rec Inh) | KRASG12C NSCLC | Post ICI +/-CT<br>No prior KRAS-I | USA |
| Neo-kan<br>NCT05472623 | II | 42 | Adagrasib +/-<br>nivolumab | KRASG12C NSCLC | stage IB-IIIA | USA |
| KRYSTAL-7<br>NCT04613596 | II/III | 950 | Adagrasib -/+<br>pembrolizumab<br>Vs CT + pembro | KRASG12C NSCLC | PDL1 <50%<br>Tx naive | Worldwide |
| NCT05609578 | II | 90 | Adagrasib +/-CT+/-<br>pembrolizumab | KRASG12C NSCLC | Tx naïve<br>PDL1+<br>PDL1 <50% | USA |
| RAMP204<br>NCT05375994 | I/II | 85 | Adagrasib +<br>Avutometinib (VS-6766)<br>(MEK-I) | KRASG12C NSCLC | Prior KRAS-I allowed | USA |
| KRYSTAL19<br>NCT05840510 | Ib/II | 79 | Adagrasib +<br>Nab-sirolimus | KRASG12G solid tumours | Part 2 NSCLC | USA |
| NCT05848843 | I | 44 | Adagrasib +<br>durvalumab | KRASG12G NSCLC and GI | Part 2 NSCLC and CRC<br>Prior RAS-I allowed | USA |
| NCT05578092 | Ib/II | 225 | MRTX0902<br>(SOS1 inh) -/+<br>adagrasib | MAPK alterations<br>NSCLC | Cohort 1 MAPK alterations<br>Cohort 2 KRAS G12C<br>No prior KRAS- | USA<br>I |
| NCT06024174 | I/II | 410 | Adagrasib<br>BMS-986406 (anti-LILRB2 ab)<br>-/+<br>cetuximab | G12C solid tumours | Part 2 NSCLC or CRC | USA, Europe, Argentina, Australia, Istrael |
| KontRASt-01<br>NCT04699188 | I/II | 475 | JDQ433+<br>TNO155 (SHP2-I)<br>tislelizumab | KRASG12C solid tumours | Prior RAS-I allowed | Worldwide |
| KontRASt-03<br>NCT05358249 | Ib/II | 346 | JDQ433 + trametinib<br>JDQ433 + ribociclib | KRASG12C solid tumours or NSCLC/CRC | Part 2 NSCLC or CRC<br>Post CT and ICI | USA, Europe, Korea, Singapore |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | JDQ433 + cetuximab | | | |
| KontRASt-04<br>JDQ433C12301<br>NCT TBD | III | 380 | JDQ433+TNO155<br>Vs<br>Pembro +CT | KRASG12C NSCLC | Tx naive<br>PDL1 three stratification<br>PDL1<1, 1-49%; >50% | Worldwide |
| NCT04956640 | I | 400 | LY3537982 in several combinations | KRASG12C solid tumours | Post CT +ICI<br>In the cohorts plus pembro or CT tx naïve NSCLC | Worldwide |
| NCT04973163 | I | 29 | BI 1823911 +<br>BI 1701963<br>(SOS1 inh)<br>Midazolam<br>(PK analysis) | KRASG12C solid tumours | Prior TKIs allowed | USA, Europa |
| NCT05288205 | I/II | 124 | Glecirasib<br>(JAB-21822) +<br>JAB-3312<br>(SHP2 inhibitor) | solid tumours | Post standard care<br>KRASG12C+ preferred | China |
| NCT05379946 | I/II | 92 | D-1553 +<br>IN10018<br>(FAK inh) | KRAS G12C solid tumours | - | China |
| MK-1084-001<br>NCT05067283 | I | 450 | MK-1084 +<br>Several combinations<br>Pembrolizumab<br>Cetuximab<br>CT according to tumour | KRAS G12C solid tumours | Arm2 (pembro)<br>tx naïve KRASG12C /PDL1 + NSCLC<br>Arm 4 (pembro +CT)<br>tx naïve KRASG12C nonsq NSCLC | Worldwide |

**Abbreviations:** Pt N = patient number; vs = versus; NSCLC = non-small-cell lung cancer; KRAS-I(s) = KRAS inhibitors; Tx = treatment; inh = inhibitory; CRC = colon rectal cancer; nonsq = Non squamous; CT = chemotherapy; ICI = immune-checkpoint inhibitor; PD-L1 = Programmed Cell Death Ligand 1; CRT = chemo-radiotherapy; BM = brain metastases; MVASI = bevacizumab biosimilar; TKI = tyrosine kinase inhibitor; MAPK = Mitogen-activated protein kinase.

**Table S13.** ICI-TKI based combinations in BRAF mutated NSCLC patients.

| Trial | Phase | Pt N | Drugs | Disease | Key inclusion criteria | Location |
|---|---|---|---|---|---|---|
| NCT03600701 | Ib/II | 48 | Atezolizumab + cobimetinib | NSCLC | Cohort 1 KRAS+<br>Cohort 2 No KRAS+ refractory to ICI | USA |
| BFAST<br>NCT03178552 | II/III | 1000 | Vemurafenib<br>Cobimetinib<br>atezolizumab | cfDNA BRAFV600E | A: ALK alectinib<br>B RET alectinib<br>C bTMB atezolizumab vs CT<br>D ROS1 entrectinib<br>E BRAFV600E<br>F EGFREx20ins<br>CT + beva + atezo<br>G KRASG12C<br>GDC-6036 or TXT | Worldwide |
| IM-BATTLE-2<br>NCT03225664 | Ib/II | 37 | Pembrolizumab + trametinib | NSCLC w/wout EGFR/ALK/ROS1 | Refractory to ICI and TKI if gene-addicted NSCLC | USA |
| NCT05988697 | II | 36 | Aspirin + dabrafenib+ trametinib | BRAFV600E<br>tx naive | No prior tx including BRAF/MEK-I | China |
| NCT05641493 | Ib/II | 49 | HLX208+<br>Serplulimab<br>(HLX10)<br>Anti-PD-1 | BRAFV600E<br>Solid tumours and NSCLC (ph II) | No prior BRAF/MEK-I | China |
| NCT04777175 | Obs | 186 | ICI | KRAS, BRAF, HER2, MET, ALK, RET | Retrospective study | China |

**Abbreviations:** Pt N = patient number; obs.= observational; NSCLC = non-small-cell lung cancer; KRAS = Ki-ras2 Kirsten rat sarcoma viral oncogene homolog; BRAF = v-raf murine sarcoma viral oncogene homolog B1 KRAS-I(s) = KRAS inhibitors; Tx = treatment; cfDNA circulating free DNA; ICI = immunecheckpoint inhibitor; w = with; wout = without; Tx = treatment naïve; atezo = atezolizumab.

**Table S14.** Ongoing clinical trials of TKI-based combination in MET dysregulated NSCLC patients.

| Trial | Phase | Pt N | Drugs | Disease | Key inclusion criteria | Location |
|---|---|---|---|---|---|---|
| METalmark NCT05488314 | Ib/II | 161 | Capmatinib plus amivantamab | MET+ NSCLC | Cohort 1A tx naïve METex14 NSCLC<br>Cohort 1B pretreated METex14 NSCLC<br>Cohort 1C pretreated MET AMP NSCLC | USA, Turkey, Korea |
| NCT05435846 | Ib | 33 | Capmatinib plus trametinib | METex14 NSCLC | METex14 on lx or tissue<br>Refractory to prior MET-I<br>Note MET-I is not mandatory to be the last line of treatment | USA |
| POTENT NCT05782361 | Ib | 38 | Tepotinib plus pembrolizumab | NSCLC with or without METex14 | METex14 on lx or tissue<br>Part A Tx Naïve or ICI refractory<br>Part B tx naïve METex14 | UK |
| SOUND NCT05374603 | II | 60 | Savolitinib plus durvalumab | MET+ NSCLC | MET OE, MET AMP or METex14<br>No prior MET-I or ICI | China |
| NCT05777278 | I/II | 29 | Savolitinib plus docetaxel | MET OE NSCLC | Second line setting<br>MET OE<br>(3+ in ≥50% of TC) | China |

**Abbreviations** = pt N = patient number; Lx = liquid biopsy; MET+ = MET dysregulated; MET OE = MET overexpression; METex14 = MET exon 14 skipping mutations; MET AMP = MET amplification; TC = tumor cells; Tx Naïve= treatment naïve; ICI = immune checkpoint inhibitors; MET-I(s) = MET inhibitor(s); NSCLC = Non-small-cell lung cancer.

**Table S15.** Ongoing clinical trials of TKI-based in ALK+ or ROS1+ NSCLC patients.

| Trial | Phase | Pt N | Drugs | Disease | Key inclusion Criteria | Location |
|---|---|---|---|---|---|---|
| **ALK-I based combo** | | | | | | |
| NCT04356118 | IV | 30 | RH endostatin+ intratecal MTX + ALKI | NSCLC | LMC+ | China |
| MASTER ALK NCT05200481 | RPII | 110 | Brigatinib +/- CT | ALK+ NSCLC | Tx naive | France |
| NCT05491811 | II | 77 | Ensartinib + bevacizumab | ALK+ NSCLC | Tx naïve<br>p53+ | China |
| NCT03202940 | Ib/II | 31 | Alectinib + cobimetinib | ALK+ NSCLC | Post-alectinib | USA |
| **Other Combo** | | | | | | |
| HARMONIC NCT05456256 | II | 90 | LP-300 + CT | Gene-addicted NSCLC | Post standard tx | USA |
| NCT05266846 | II | 30 | Pembrolizumab+ bevacizumab + CT | ALK+ NSCLC | Post alectinib | China |
| NCT03991403 | RPIII | 228 | CT + bevacizumab + atezolizumab | EGFR+ or ALK+ NSCLC | Post TKIs | Korea<br>Not recruiting |
| GFPC 06-2018 NCT04042558 | II | 149 | CT + atezolizumab+/- bevacizumab | EGFR+ or ALK+ ROS1+ NSCLC | Post TKIs | France |
| NCT04425135 | II | 59 | CT+ camrelizumab+ apatinib | ALK+ NSCLC | Post ALK-Is | China |
| NCT04989322 | II | 46 | Pembrolizumab + Lenvatinib + CT | EGFR+ or ALK+ ROS1+ NSCLC | Post TKis | Hong Kong |
| NCT05296278 | II | 80 | IBI-322 + Lenvatinib + CT | ALK+ NSCLC | Post alectinib | China |
| NCT04777084 | Ib | 100 | IBI-318+ Lenvatinib | NSCLC with or without EGFR/ALK | Post ICI<br>Post TKis | China |
| NCT05681780 | I/II | 20 | CD40L-Augmented TIL | EGFR, ALK, ROS1 or HER2 NSCLC | Post TKIs or standard tx | USA |
| PIKACHU | Obs. | 100 | Anti-PD1 plus CT | ALK+ ROS1+ | Post TKis | China |

| | | | | | | |
|---|---|---|---|---|---|---|
| NCT04322890 | | | | NSCLC | | |
| NCT05195619 | I | 16 | DC vaccines | NSCLC | Non-gene addicted NSCLC Or EGFR/ALK or ROS-1 post TKI | Switzerland |
| SNK_ASTER NCT04872634 | I/II | 24 | SNK01 NK + CT + /-cetuximab | EGFR+ or ALK+ ROS1+ NSCLC | Post-TKIs | Korea |
| NCT04880863 | II | 35 | NAP+ Docetaxel+ Obinutuzumab | NSCLC | NSCLC post ICI Gene addicted NSCLC post TKIs | USA Not recruiting |
| NCT03645928 | II | 178 | Autologous TILs | Solid tumours | NSCLC post ICI Gene addicted NSCLC post TKIs | USA, Europe |

**Abbreviations:** LMC = leptomeningeal carcinomatosis; ALK = Anaplastic Lymphoma Kinase; EGFR = Epidermal Growth Factor Receptor; ROS1 = c-ros oncogene 1; ALK-I(s) = ALK inhibitor(s); TKIs = tyrosine kinase inhibitor(s); MTX = methotrexate; CT = chemotherapy; PD1 = programmated death-1; DC vaccine = dendritic cell vaccine; TILs = tumor-infiltrating lymphocytes ICI = immune checkpoint inhibitor; Tx = treatment; NSCLC = Non-small-cell-lung cancer.

**Table S16.** Ongoing combinations in RET+ NSCLC.

| Trial | Phase | Pt N | Drugs | Disease | Key inclusion Criteria | Location |
|---|---|---|---|---|---|---|
| LungMAP NCT05364645 | II | 74 | Selpercatinib + CT | RET+ NSCLC | Progressing on RET-I as the most recent tx line | USA |
| NCT05845671 | I/II | 12 | Amivantamab + TKis | Gene addicted NSCLC | ALK+, ROS1+, or RET+ Post at least one TKI | USA |
| **Without TKI** | | | | | | |
| POSEIDON NCT04322591 | Obs | 70 | CT vs CT+ ICI | RET+ NSCLC | Tx naïve RET fusion+ | China |

Abbreviations Pt N = patient number; TKIs = tyrosine kinase inhibitors; NSCLC = Non-Small-Cell lung cancer; RET = rearranged during transfection; RET-I = RET inhibitors; tx = treatment; CT chemotherapy; ICI = immunocheckpoint.

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