

Lung cancer: targeted therapy, immunotherapy and side effects

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Updated 9 October 2026 · No doses · Verify current approvals and product information

A. Actionable alterations and targeted therapy

Alteration (how to find it)	Preferred first line	Alternatives and later lines	Key evidence	Brain activity	Signature side effects · what to monitor
EGFR exon 19 del / L858R ~25–35% of Indian adenocarcinoma · PCR or NGS · plasma OK	Osimertinib; osimertinib + platinum–pemetrexed; amivantamab + lazertinib	Gefitinib + pemetrexed–carboplatin (affordable); gefitinib, erlotinib, afatinib. After osimertinib: chemo ± amivantamab; re–biopsy for MET, C797S, SCLC transformation	FLAURA, FLAURA2, MARIPOSA, Tata Memorial	High (osimertinib, combinations)	Osimertinib: rash, paronychia, diarrhoea, dry skin, QTc prolongation, rare ILD and fall in LVEF · ECG, echo if cardiac risk. Amivantamab: infusion reactions, acneiform rash, paronychia, oedema, low albumin, venous thrombosis (prophylactic anticoagulation early)
EGFR uncommon (G719X, L861Q, S768I)	Afatinib or osimertinib	Chemo–immunotherapy at progression is of limited benefit	Pooled phase 2 and subgroup data	Moderate (osimertinib)	Afatinib: diarrhoea (often severe early), rash, stomatitis, paronychia
EGFR exon 20 insertion missed by many PCR kits · use NGS	Amivantamab + carboplatin–pemetrexed	Platinum–based chemotherapy; trials	PAPILLON	Limited	Infusion reactions (first dose), rash, paronychia, neutropenia, oedema, hypoalbuminaemia
ALK fusion ~5% · IHC (D5F3) or NGS/FISH	Alectinib, lorlatinib or brigatinib	After alectinib/brigatinib: lorlatinib (re–biopsy for G1202R); then chemotherapy (pemetrexed–based)	ALEX, CROWN; adjuvant ALINA	High (lorlatinib highest)	Alectinib: myalgia, raised CPK and bilirubin, oedema, weight gain, constipation, photosensitivity, bradycardia. Lorlatinib: high cholesterol and triglycerides, weight gain, oedema, neuropathy, mood, sleep and cognitive change · lipids, mood. Brigatinib: early pulmonary events in the first week (step–up start), hypertension, CPK, lipase
ROS1 fusion 1–2% · NGS (RNA) or IHC screen	Taletrectinib or repotrectinib (entrectinib acceptable; crizotinib less preferred)	Zidesamtinib after progression; chemotherapy	TRUST	High except crizotinib	Taletrectinib: raised liver enzymes, nausea, diarrhoea, QTc. Repotrectinib and entrectinib: dizziness, taste change, paraesthesia, ataxia, weight gain (TRK effects). Crizotinib: visual trails, oedema, nausea, liver enzymes, bradycardia
BRAF V600E ~1–2% · NGS or PCR	Dabrafenib + trametinib, or encorafenib + binimetinib	Chemo–immunotherapy (these tumours can respond to immunotherapy)	Phase 2 trials	Moderate	Dabrafenib + trametinib: fever (hold both until settled), rash, fatigue, fall in LVEF, serous retinopathy. Encorafenib + binimetinib: nausea, diarrhoea, fatigue, CPK rise, retinal effects · echo, eye review if visual change
MET exon 14 skipping ~2–3%, older patients · RNA NGS best	Capmatinib or tepotinib	Chemo–immunotherapy; crizotinib	Phase 2 trials	Moderate	Peripheral oedema (very common, slow to settle), nausea, low albumin, apparent creatinine rise (transporter effect, not true kidney injury), rare ILD, photosensitivity (capmatinib)

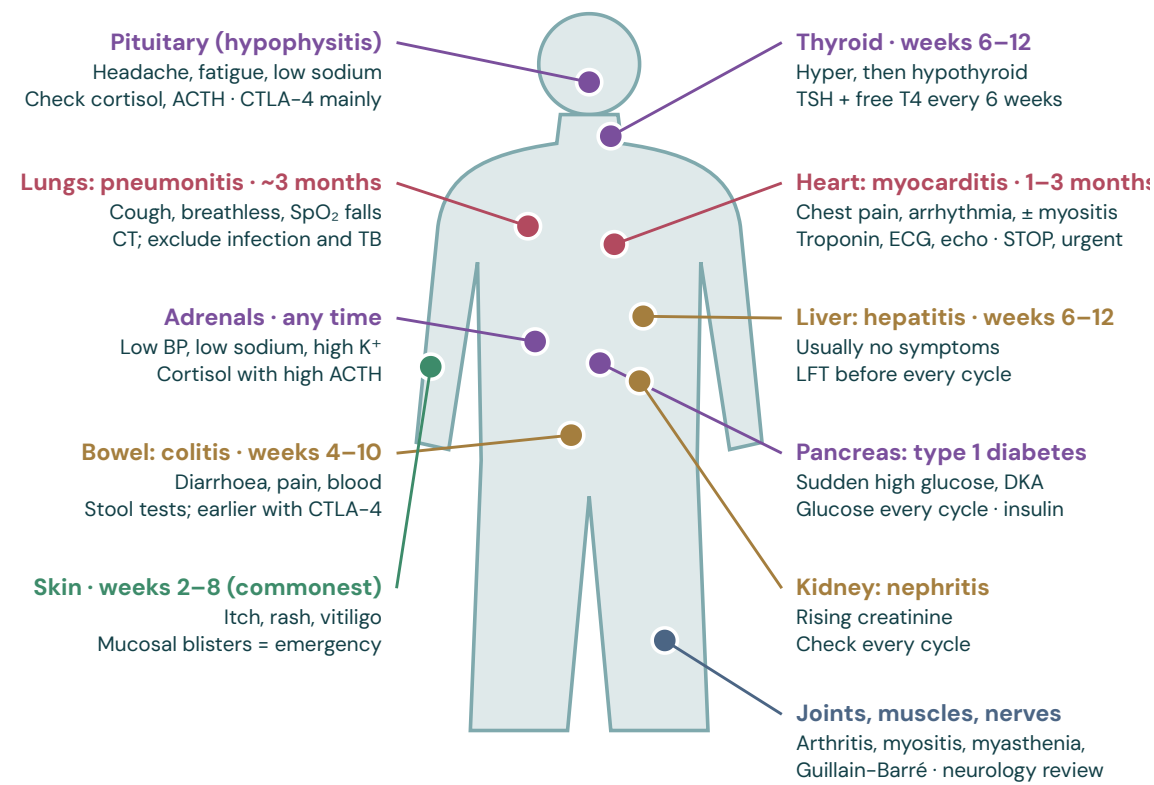
Alteration (how to find it)	Preferred first line	Alternatives and later lines	Key evidence	Brain activity	Signature side effects · what to monitor
c-MET protein overexpression IHC 3+ in ≥50% of cells, non-squamous, after first line	Telisotuzumab vedotin (where approved)	Docetaxel-based therapy	Phase 2 data	Unknown	Peripheral neuropathy, oedema, fatigue, ILD (antibody–drug conjugate)
RET fusion 1–2% · RNA NGS	Selpercatinib (pralsetinib alternative)	Adjuvant selpercatinib after resection; chemotherapy at progression	LIBRETTO–431 ; adjuvant LIBRETTO–432	High	Selpercatinib: hypertension, raised liver enzymes, QTc, dry mouth, diarrhoea, oedema, hypersensitivity, chylous effusions. Pralsetinib: cytopenias, hypertension, pneumonitis, infections · BP, LFT, ECG
NTRK1–3 fusion <1% · RNA NGS	Larotrectinib or entrectinib, or chemo-immunotherapy	Repotrectinib for resistance	Basket trials	High	Dizziness, weight gain, paraesthesia, liver enzymes; pain on stopping the drug (TRK withdrawal)
KRAS G12C ~1 in 3 KRAS mutations, smokers	Chemo-immunotherapy first	Sotorasib or adagrasib after progression	CodeBreak 200	Some (adagrasib)	Sotorasib: diarrhoea, nausea, hepatotoxicity (higher if started soon after immunotherapy). Adagrasib: nausea, vomiting, diarrhoea, QTc, liver enzymes
HER2 (ERBB2) mutation ~2–3% · NGS	Chemo-immunotherapy, or zongertinib where approved	Zongertinib or trastuzumab deruxtecan after first line	Beamion LUNG–1, DESTINY–Lung01	Moderate	Trastuzumab deruxtecan: ILD/pneumonitis (about 1 in 10; stop for any grade 2+), nausea, hair loss, neutropenia, fall in LVEF. Zongertinib: diarrhoea, rash, liver enzymes
NRG1 fusion rare · RNA NGS	Chemo ± immunotherapy (zenocutuzumab in selected patients)	Zenocutuzumab after first line	Phase 2 data	Unknown	Diarrhoea, infusion reactions, fatigue; check LVEF

B. When to use immunotherapy

Setting	Who	Immunotherapy used	Key evidence	Do not use, or use with caution
Metastatic NSCLC, no driver, PD-L1 ≥50%	PS 0–1 (PS 2 selected)	Pembrolizumab, atezolizumab or cemiplimab alone; chemo-immunotherapy if bulky or rapidly progressive	KEYNOTE-024, 5-year update	Any actionable driver (EGFR, ALK, ROS1, RET): targeted therapy first
Metastatic NSCLC, no driver, PD-L1 1–49%	PS 0–1	Platinum doublet + pembrolizumab (or other PD-(L)1 antibody); immunotherapy alone only if chemotherapy is impossible	KEYNOTE-189, KEYNOTE-407, KEYNOTE-042	Squamous: no pemetrexed
Metastatic NSCLC, no driver, PD-L1 <1%	PS 0–1	Chemo-immunotherapy; regimens adding CTLA-4 blockade (nivolumab + ipilimumab ± chemo, durvalumab + tremelimumab + chemo)	CheckMate 9LA, POSEIDON	More immune toxicity with CTLA-4; benefit smaller; chemotherapy alone acceptable if unaffordable
Second line, immunotherapy-naïve	After platinum doublet	Nivolumab, pembrolizumab (PD-L1 ≥1%) or atezolizumab	CheckMate 017, CheckMate 057, KEYNOTE-010, OAK	Re-using immunotherapy after progression on it is not standard (rechallenge only if ≥6 months off)
Resectable stage II–IIIB	EGFR/ALK negative, fit for surgery	Neoadjuvant chemo + nivolumab, pembrolizumab or durvalumab, then adjuvant antibody (perioperative)	CheckMate 816, KEYNOTE-671, AEGEAN, CheckMate 77T	EGFR- or ALK-positive tumours; ILD (excluded from trials)
Resected stage II–IIIA after adjuvant chemotherapy	No neoadjuvant therapy given	Atezolizumab (PD-L1 ≥1%, ≥5 cm or N+) or pembrolizumab (≥4 cm or N+)	IMpower010, PEARLS/KEYNOTE-091	Only after chemotherapy; EGFR/ALK-positive tumours get targeted therapy
Unresectable stage III after chemoradiation	No progression after concurrent CRT	Durvalumab for 12 months, started within about 6 weeks	PACIFIC	EGFR-positive (use osimertinib, LAURA); grade ≥2 radiation pneumonitis
Limited-stage SCLC after chemoradiation	No progression	Durvalumab for up to 2 years	ADRIATIC	Autoimmune disease, poor PS from comorbidity
Extensive-stage SCLC	First line	Atezolizumab or durvalumab with carboplatin–etoposide, then maintenance (± lurbinectedin with atezolizumab)	IMpower133, CASPIAN, IMforte	Not chosen by PD-L1; avoid if transplant recipient or active severe autoimmune disease

General cautions before any checkpoint inhibitor: active autoimmune disease needing systemic immunosuppression; organ transplant; ongoing high-dose steroids (short courses for brain oedema or nausea are acceptable); ECOG 3–4; interstitial lung disease (case by case); recent or planned EGFR TKI (pneumonitis); pregnancy. Controlled HIV, HBV and HCV are not contraindications. **Baseline:** TSH, free T4, morning cortisol, glucose, liver and kidney tests, blood count, HBV/HCV/HIV, symptom screen for TB (India: low threshold for testing latent or active TB), oxygen saturation; ECG and troponin if cardiac risk.

C. Immune-related side effects



Rose: can be life-threatening, act today · Gold: common, monitor blood tests · Purple: endocrine, often permanent, replace
Timing is typical, not fixed: side effects can appear months after the last dose. Give every patient an immunotherapy alert card.

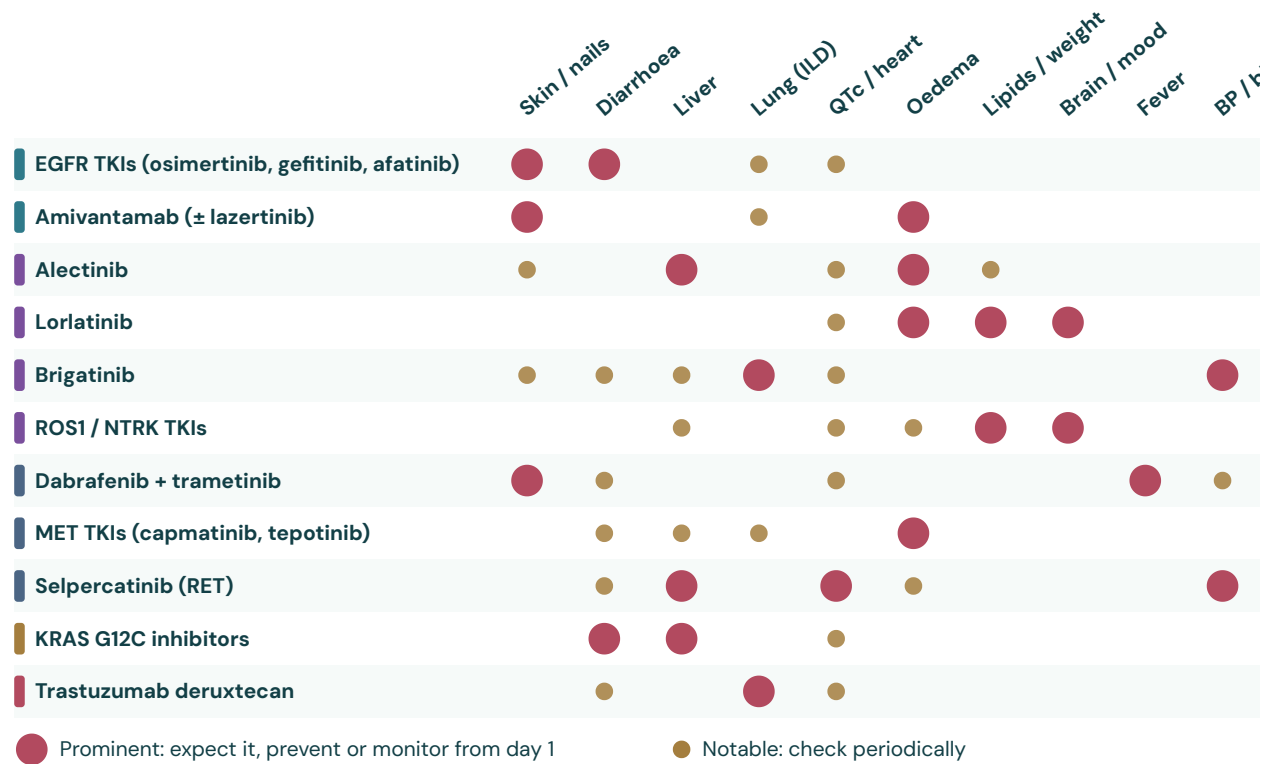
Immune-related side effects at a glance: where they occur, when they usually appear and the first test to order. Details and management are in Table C.

Immune-related side effect	How it presents · when	Check	Management principle (no doses)
Skin (commonest)	Itch, rash, vitiligo; rarely blistering (SJS/TEN) · weeks 2–8	Extent of body surface; mucosa	Emollients, topical steroids, antihistamines; hold for severe; stop permanently for SJS/TEN

Immune-related side effect	How it presents · when	Check	Management principle (no doses)
Colitis / diarrhoea	Diarrhoea, pain, blood · weeks 4–10 (earlier with CTLA-4)	Stool tests for infection (C. difficile), CT or colonoscopy if severe	Grade 1: fluids, continue. Grade 2: hold, oral steroids. Grade 3–4: IV steroids; infliximab or vedolizumab if no response in 2–3 days
Hepatitis	Raised ALT/AST, usually asymptomatic · weeks 6–12	LFT every cycle; exclude viral hepatitis, drugs, metastases	Hold for grade 2+; steroids; mycophenolate if refractory (avoid infliximab)
Pneumonitis	Cough, breathlessness, fall in saturation · any time, median ~3 months; higher after thoracic RT	CT chest; exclude infection (including TB) and progression; bronchoscopy if unclear	Grade 1: hold, monitor. Grade 2: hold, steroids. Grade 3–4: stop permanently, IV steroids, admit; add immunosuppressant if refractory
Thyroid	Thyroiditis: brief hyperthyroidism then hypothyroidism · weeks 6–12	TSH, free T4 every 6 weeks	Beta-blocker for the hyper phase; thyroxine replacement; immunotherapy usually continues
Hypophysitis (mainly CTLA-4)	Headache, fatigue, low sodium; low ACTH and cortisol, central hypothyroidism	Morning cortisol, ACTH, TSH/T4, MRI pituitary	Replace hydrocortisone first, then thyroxine; lifelong replacement often needed; sick-day rules
Primary adrenal insufficiency	Fatigue, hypotension, low sodium, high potassium	Cortisol with high ACTH	Hydrocortisone ± fludrocortisone; emergency IV steroids if in crisis
Type 1 diabetes	Sudden hyperglycaemia, diabetic ketoacidosis	Glucose every cycle; ketones, C-peptide	Insulin (steroids do not help); immunotherapy can continue when controlled
Myocarditis (rare, can be fatal)	Chest pain, breathlessness, arrhythmia, often with myositis or myasthenia · first 1–3 months	Troponin, ECG, echo, cardiac MRI; CK	Stop permanently; high-dose IV steroids urgently; cardiology; further immunosuppression if needed
Neurological	Myasthenia, Guillain-Barré, encephalitis, neuropathy	Neurology review, MRI, LP as needed	Hold or stop; steroids; IVIG or plasma exchange for myasthenia or Guillain-Barré
Kidney (nephritis)	Rising creatinine	Exclude other causes; urine	Hold for grade 2+; steroids
Joints, eyes, blood	Arthritis, uveitis, cytopenias	Rheumatology or ophthalmology review	NSAIDs or steroids for arthritis; urgent eye review for uveitis
T-cell engager (tarlatamab)	Cytokine release syndrome (fever, low BP, hypoxia) and neurotoxicity (confusion, dysphasia) · first doses	Temperature, BP, saturation, neurological checks during monitored doses	Supportive care, tocilizumab and steroids by grade; hold or stop by severity

Rules of thumb: grade 1 — usually continue and watch; grade 2 — hold until grade 1 or less, steroids for most organs; grade 3 — hold, high-dose steroids, consider stopping; grade 4 — stop permanently (except endocrine problems controlled by replacement). Taper steroids slowly over at least 4–6 weeks; give PJP prophylaxis and gastric protection on prolonged high-dose steroids; endocrine deficiencies are usually permanent. Side effects can appear months after the last dose: patients should carry an immunotherapy alert card.

D. Managing common targeted-therapy side effects



All TKIs: check drug interactions (rifampicin lowers levels; with lorlatinib it can cause severe liver injury), and ask about new cough or br

Which targeted drug causes what. Large rose dots are side effects to expect and plan for; small gold dots are worth periodic checks. Management is in Table D.

Side effect	Typical drugs	Practical management (no doses)
Acneiform rash, dry skin	EGFR TKIs, amivantamab	Start emollients and sunscreen from day 1; oral doxycycline or minocycline prophylaxis with amivantamab; topical steroid; dose interruption for severe
Paronychia	EGFR TKIs, amivantamab	Avoid nail trauma; antiseptic soaks; topical steroid–antibiotic; treat infection
Diarrhoea	Afatinib, other EGFR TKIs, adagrasib, sotorasib, zongertinib	Loperamide early, fluids; hold for grade 3; check for infection

Side effect	Typical drugs	Practical management (no doses)
Interstitial lung disease	Osimertinib, other EGFR TKIs, trastuzumab deruxtecan, telisotuzumab vedotin, brigatinib (early), MET TKIs	New cough or breathlessness → hold, CT, exclude infection; stop permanently if drug-induced and significant; steroids for moderate–severe
QTc prolongation	Osimertinib, adagrasib, selpercatinib, crizotinib, taletrectinib	Baseline and periodic ECG; correct potassium and magnesium; avoid other QT-prolonging drugs (some antiemetics, antibiotics, antifungals)
Hepatotoxicity	Selpercatinib, taletrectinib, sotorasib (especially after immunotherapy), crizotinib, gefitinib	LFT every 2 weeks for 2–3 months, then monthly; hold and resume at lower intensity
Oedema, low albumin	Capmatinib, tepotinib, amivantamab, alectinib, lorlatinib	Compression, leg elevation; diuretics help little; dose interruption
Lipids, weight, mood	Lorlatinib	Lipids at baseline and every few months; statin; ask about mood, sleep and cognition; dose reduction often resolves CNS effects
Raised CPK, myalgia	Alectinib, brigatinib, binimetinib	CK checks in the first months; hold for symptomatic or very high CK
Fever	Dabrafenib + trametinib	Hold both at the first fever and restart when settled; antipyretics; consider steroid prophylaxis for recurrent episodes
Hypertension, bleeding	Selpercatinib, pralsetinib, ramucirumab, bevacizumab	BP control before and during treatment; avoid anti-VEGF drugs with haemoptysis or central cavitating tumours
Venous thromboembolism	Amivantamab + lazertinib	Prophylactic anticoagulation for the first months
Vision changes	Crizotinib (light trails), MEK inhibitors (serous retinopathy), brigatinib	Usually mild; eye review for persistent changes
Drug interactions	Most TKIs (CYP3A metabolism)	Rifampicin (TB treatment) markedly lowers TKI levels and with lorlatinib can cause severe liver injury: discuss with the TB team (rifabutin-based or non-rifamycin regimens). Proton-pump inhibitors reduce absorption of gefitinib, erlotinib and some others. Check every new prescription, including herbal products.