

**NEET SS MEDICINE
HIGH YIELD TOPICS
VOLUME 2**

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ILD

★ 4.5 | 42 Min

PRQ

1082

MEDICAL GENETICS

145



Blood Disorders

★ 4.2 | 40 Min

PRQ

1097

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Genetics In Neurological Disorders

★ 4.4 | 51 Min

PRQ

1107

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Cardiology Genetics : I

★ 4.4 | 44 Min

PRQ

1117

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Cardiology Genetics : II

★ 4.3 | 28 Min

PRQ

1129

TARGETED AGENTS IN NSCLC

Introduction

00:01:06

Specific mutations :

- EGFR mutations :
 - most common.
 - Incidence : 15% in western population.
35 to 40% in Asian population.
- Anaplastic lymphoma kinase (ALK) rearrangements.
- ROS 1 rearrangements.
- MET exon 14 skipping mutations / MET amplifications.
- RET rearrangements.

Note : Above listed mutations are more commonly linked with adenocarcinoma, non-smokers, females > males.

- BRAF mutations : Seen in smokers.
- NTRK fusions.
- KRAS mutation.
- Her 2 mutation/over expression.

Detection of the mutations :

- Next generation sequencing (NGS).
- PCR : To detect EGFR mutations.
- IHC or FISH : ALK, ROS 1 rearrangements.
- If the biopsy is not available → Liquid biopsy (Blood) can be done.

Patients to be tested for the mutations :

- Adenocarcinoma patients.
- Non-smokers/ex-smokers.
- mixed histology.
- Small biopsy.

EGFR mutations

00:09:53

Exon 19 deletion, Exon 21 L858R mutation :

- Sensitive to anti-EGFR therapy.
- **IPASS trial** : Showed the benefit of TKIs (Tyrosine Kinase Inhibitors).

Treatment :

- EGFR inhibitors :
 - TKIs (Oral).
 - Early generation : Gefitinib, erlotinib, afatinib.
 - Recommended treatment now : **Osimertinib** (First line).
 - Osimertinib : Better tolerated, better blood-brain barrier penetration, good overall survival.
- TKI plus chemotherapy : Carboplatin + Pemetrexed + Gefitinib.
- Trials : Amivantamab (Bispecific monoclonal antibody against EGFR and MET) + Lazertinib (TKI-EGFR inhibitor).

Exon 20 insertions :

- Not sensitive to TKIs.
- Treatment : Chemotherapy + Amivantanab.

Uncommon mutations (Exon 18 mutation) :

- Afatanib or osimertinib can be tried.
- If there is no response : Chemotherapy.

Resistance mechanisms :

T790 mutation :

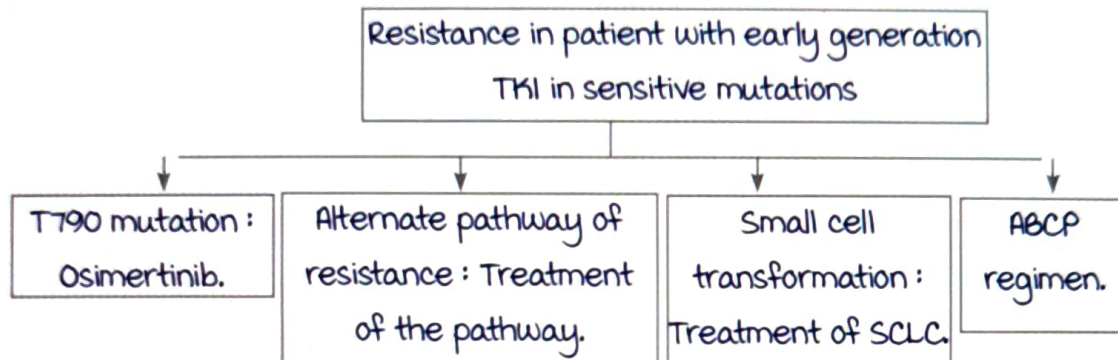
- most common mutation that leads to resistance.
- Occurs most commonly in exon 20.
- Treatment : **Osimertinib**.

Resistance in patients with early generation TKI in sensitive mutations :

Biopsy is sent again for NGS.

- If T790 mutation : Osimertinib.
- Look for alternate pathway of resistance (eg : MET mutation).
- Look for small cell transformation : Small cell lung CA regimens.

- If all the mechanisms are ruled out → ABCP regimen : Chemotherapy (Paclitaxel/ Carboplatin) + Immunotherapy (Atezolizumab) + VEGF inhibitors (Bevacizumab).
- Bevacizumab cannot be used in squamous cell carcinoma because of the risk of hemoptysis.



Resistance in patients with osimertinib in sensitive mutations :

- Small cell transformation or other pathway : Treat accordingly.
- ABCP regimen.

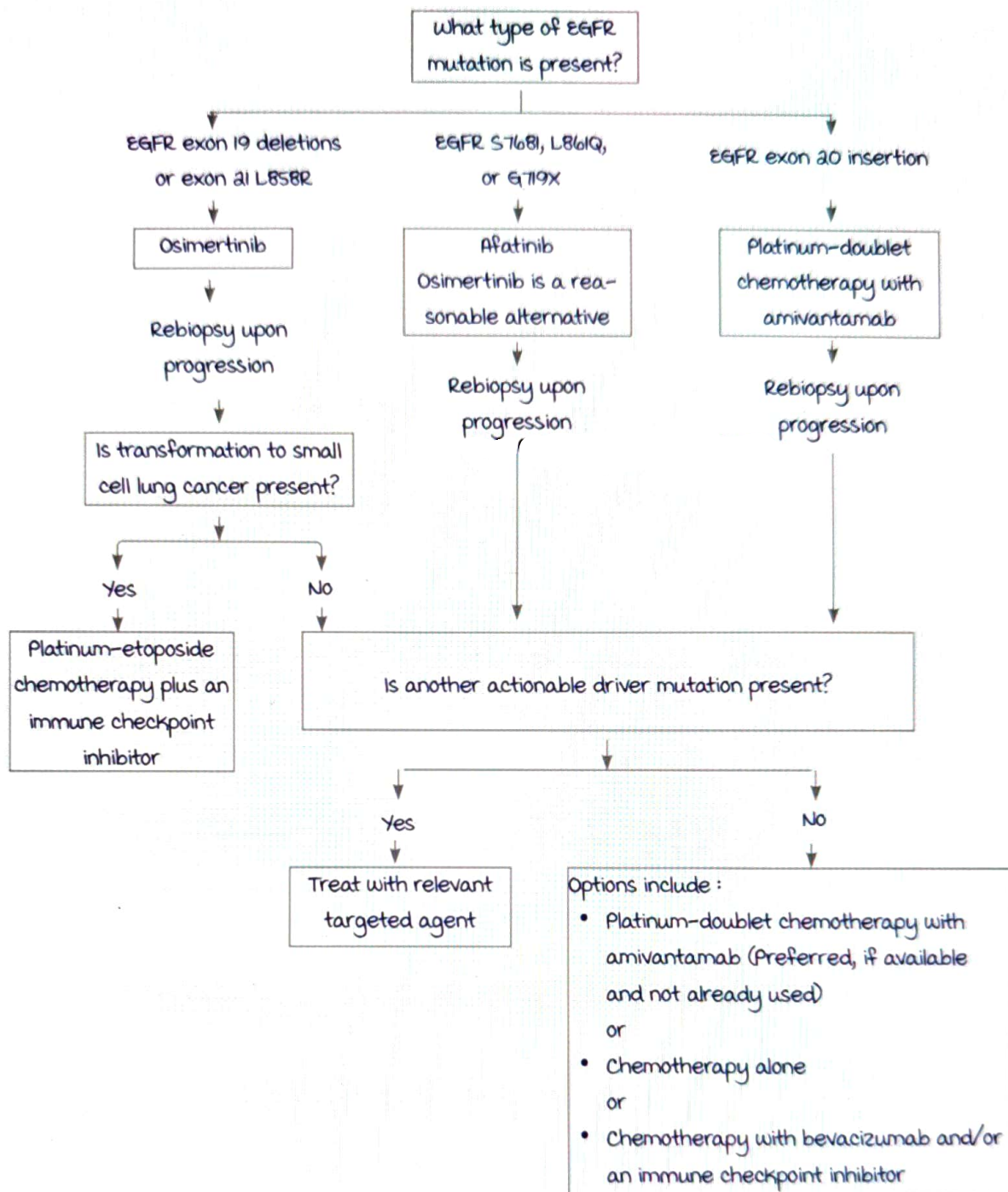
Patients with resistance in uncommon mutations :

- Same algorithm as above.
- ABCP.
- Chemotherapy + Amivantanab.

Patients with resistance in exon 20 :

- First line : Chemotherapy + Amivantanab.

management of EGFR-mutant adenocarcinoma of lung :



Amivantamab :

- Bispecific monoclonal antibody against EGFR/MET.
- Side effects : Infusion/hypersensitive reactions (Skin rashes), reduced albumin.

EGFR TKIs in adjuvant setting :

- Osimertinib can be used in advanced cases.

ALK rearrangements

00:36:47

ALK inhibitors :

- Alectinib :
 - CNS action ++
 - Well tolerated
- Brigatinib :
 - Commonly used
 - CNS action ++
- Lorlatinib : Latest ALK inhibitor.
- Ceritinib : CNS action +
- Crizotinib :
 - Earliest drug.
 - Poor CNS action.

First line : Alectinib/Brigatinib/Lorlatinib.

Resistance to crizotinib :

- m/c : L1196M mutation.
- G1202R mutation : Only Lorlatinib can be used
- Treatment :
 - Higher generation TKI (Alectinib/Brigatinib/Lorlatinib).
 - If no response after all the ALK inhibitors : ABCP regimen.

Side effects :

- musculoskeletal symptoms : Alectinib.
- CNS symptoms (Delirium, dementia, hallucinations) and dyslipidemia : Lorlatinib.
- male hypogonadism, visual toxicity, renal cyst : Crizotinib.
- Photosensitivity : Brigatinib.

ROS 1 rearrangements

00:47:38

Treatment :

First line :

- TKI > chemotherapy.
- Crizotinib : ROS1 - MET inhibitor).
- Entrectinib, riprosectinib :
 - Both have better CNS action.
 - ROS1 - nTRK blockers.

Second line :

- Lorlatinib.
- Ceritinib.

Other mutations

00:50:12

MET :

Features :

- Exon 14 skipping mutation :
 - Capmatinib, tepotinib.
 - If TKI not available : Chemotherapy.
- Particularly seen more in sarcomatoid histologies.
- Crizotinib has action, but no longer recommended.
- Amplification : Capmatinib or crizotinib.

RET rearrangements :

Features :

- Seen in medullary thyroid carcinomas (MEN syndrome).
- Anti RET agents : Selpercatinib/Pralsetinib.

BRAF mutations :

Features :

- V600E mutation : Type 1 (Sensitive to BRAF inhibitors).
- Non V600 E mutation : Type 2 and 3 (No response to BRAF inhibitors).
- Sensitive to immunotherapy.
- BRAF + MEK inhibitors : Dabrafenib + Trametinib; Encorafenib + Binimetinib.
- Single agents : Vemurafenib/Dabrafenib.

KRAS G12C inhibitors :

- TKI : Sotarasib/adagrasib.

Her 2 exon 20 insertion mutation :

- Anti Her 2 agents in later lines.
- Trastuzumab deruxtecan, TDM 1.

Her2 amplification :

- Trastuzumab deruxtecan.

SYSTEMIC THERAPY IN COLON CANCER

Staging of colon cancer :

Stage	
I	T1 NO MO T2 NO MO
II	T3 NO MO T4 NO MO
III	Any T, with positive N, MO
IV	M1

Stage I colon cancer :

- Treated with surgery alone followed by observation.
- No role of adjuvant chemotherapy.

Stage II colon cancer

00:02:03

Definition :

T3 NO MO and T4 NO MO.

Dilemma :

- First treated by surgery (Right or left hemicolectomy).
- Benefit of adjuvant chemotherapy is **limited**.
- Yet, there is a subset of high risk colon cancer patients in whom chemotherapy is beneficial.

microsatellite instability (MSI) testing :

- MSI high or dMMR (Deficient mismatch repair) :
 - Associated with HNPCC/Lynch syndrome.
 - Better prognosis.
 - With 5-FU or Capecetabine alone, response is less.
- MSI low or MSI stable (Proficient in MMR gene).

Risk factors :

- **T4** tumor.
- Poorly differentiated/undifferentiated histology (Not so if dMMR/MSI high).

- Lymphovascular invasion/perineural invasion.
- High tumour budding on biopsy.
- <12 lymph nodes.
- Clinical obstruction or perforation.
- High CEA levels.

Note :

MSI status is **not a risk factor**.

Treatment :

Low risk :

- Surgery alone followed by observation.
- Chemotherapy :
 - very less benefit.
 - 6 months of oral Capecetabine or 5-FU/Leucovorin chemotherapy IV.

High risk :

Chemotherapy beneficial.

i. pMMR/MSI stable :

- 3 months or 6 months of chemotherapy.
 - CAPOX regimen : Capecetabine (Oral but side effects $\uparrow$) + Oxaliplatin.
 - FOLFOX regimen : 5-FU/leucovorin + Oxaliplatin.
 - In a 3 months regimen, CAPOX is more effective than FOLFOX.
- 6 months of capecetabine alone or 5-FU/leucovorine alone if patient does not want to take Oxaliplatin.
- 3 months of therapy is equivalent to 6 months of therapy.

ii. dMMR or MSI high :

- Chemotherapy (CAPOX or FOLFOX) given if risk factors present.
- Observation alone if risk factors absent (Prognosis good).

iii. Circulating tumor DNA (ctDNA) :

- Upfront hemicolectomy done.
- If ctDNA in the blood is high : Chemotherapy given.
- ctDNA testing is **not part of conventional stratification system**.
- Helps make better informed decision about incorporating chemotherapy in the treatment protocol.

Stage III & IV colon cancer

00:25:22

Stage 3 colon cancer :

- Surgery → Followed by adjuvant chemotherapy.
- Regimen and duration :
 - CAPOX/FOLFOX for 6 months.
 - T3 N1 : Equivalent benefit with 3 months regime chemotherapy.

metastatic/stage 4 colon cancer :

First line treatment :

i. MSI high/dMMR :

Immunotherapy :

- 1st line treatment.
- Nivolumumab + Ipilimumab.
- Or Pembrolizumab alone or Dostarlimumab alone.

ii. MSI stable/pMMR :

Chemotherapy + biologicals.

- Chemotherapeutic agents : FOLFIRINOX (Best theoretically)/FOLFIRI/FOLFOX/CAPOX.
- Biologicals :
 - Right sided stage 4 : Bevacizumab (Anti VEGF agent).
 - Left sided tumors :
 - a. Assess KRAS, NRAS, BRAF mutation status.
 - b. Wild type (Not mutated) : Anti EGFR antibody (Cetuximab, Panitumumab).
 - c. mutated type : Bevacizumab.

Later line :

- RAS wild type, **BRAF V600E mutation** : Encorafenib + Cetuximab.
- RAS wild type, Her 2 over expression : Trastuzumab + Tucatinib.
- TRK fusion : Lorlatinib, Entrectinib, Repotrectinib.
- KRAS, G12C mutation :
 - Sotorasib + Panitumumab.
 - Adagrasib + Cetuximab.

TRIPLE NEGATIVE BREAST CANCER

IHC

00:00:30

Immunohistochemistry (IHC) panel helps in evaluation.

TNBC:

- Triple negative breast cancer.
- ER, PR, Her 2 : All three negative.

Her 2 grading :

- 0 : Negative.
- 1+ : Negative.
- 2+ : Depends on FISH results.
- 3+ : Positive.
- Low Her2 expressing tumors : 1+ and 2+ tumors that are FISH negative, have significance in medical management.

Etiology

00:03:38

Risk factors :

- TNBC accounts for 15% of all breast cancers.
- Age : more common in young individuals.
- Grade : Higher.
- more chemosensitive.
- Recurrence : Local recurrences as well as metastasis at visceral sites.
- metastasis : Bone metastases are rare, more common with hormonal cancers.
- Recurrence : maximum within 3 years.
- 20% have BRCA mutation, compared to other types which have <10%.

molecular classification :

- mostly basal type subtype, not synonymous.
- markers : Basal CK, Her 1 (EGFR), c-KIT, proliferation factor.
- P53 mutations more prevalent.

- Subtypes :
 - Basal like (1 & 2).
 - Immunomodulatory.
 - mesenchymal.
 - mesenchymal stem cell like.
 - Luminal androgen like.

Guidelines for gBRCA testing :

- All patients with TNBC < 60 years : mandatory.
- > 60 years :
 - unlikely to have germline BRCA mutation, no uniform guidelines.
 - metastatic/recurrent TNBC : All cases should undergo testing using next generation sequencing (NGS).

Staging :

Similar to other types of breast cancer.

Non metastatic disease management

00:10:52

Neoadjuvant chemotherapy (NACT) :

Indication : TNBC size > 0.5 cm

Reasons :

- Better control of micrometastasis.
- Better patient compliance to chemotherapy.
- Better surgery/potentially increased rates of BCS (Breast Conservation Surgery).
- Increased pathological complete response (PCR) : Better overall survival rate.
- Response adapted therapy : After neoadjuvant chemotherapy.

Regimens :

- Chemotherapy backbone : AC (Adriamycin, Cyclophosphamide) followed by Taxane (Paclitaxel/Docetaxel).
- Role of carboplatin : AC x 4 cycles, then Taxanes ± Carboplatin.
- Dose dense therapy : AC to be given once in 2 weeks + Paclitaxel weekly 80 mg/m² + Carboplatin (AUC2).
- Role of immunotherapy : Stage 2/3 TNBC benefit from Pembrolizumab every 3 weeks.

- Non anthracycline options :
 - Adriamycin : **Cardiac side effects**, hence avoided in heart failure.
 - Docetaxel + Cyclophosphamide can be used.

Adjuvant therapy :

After NACT :

- If Pembrolizumab is given pre operatively : Continue for 1 year.
- If patients do not achieve pathological complete response (PCR) :
Capcetabine x 6 months.
- Germ line BRCA mutation who do not achieve PCR : Olaparib (PARPi) x 1 year.

After upfront surgery :

- No role of immunotherapy.
- Role of PARPi :
 - Node positive/T2 or more.
 - If germline BRCA mutated : Olaparib is beneficial.

Metastatic management

00:30:02

Initial therapy :

Chemotherapy :

- Singlet : Taxanes.
- Doublet : Taxane + Carboplatin more commonly used.

Immunotherapy :

- Increase the survival rates.
- But not all patients benefit.
- **CPS score for PD-L1 expression** : $>10 \rightarrow$ Benefit from immunotherapy (Pembrolizumab).

Role of PARPi :

- maintenance therapy : Olaparib in germline BRCA mutation.
- Primary treatment : If already received chemotherapy.

Later line :

- Chemotherapy : Adriamycin, cyclophosphamide, **eribulin**, gemcitabine.
- Newer agents :
 - Trastuzumab deruxtecan, in Her 2 low cancers.

- Sacituzumab Govitecan.
- Pembrolizumab in high tumor mutational burden/micro satellite instability high tumors/tumors deficient in mismatch repair genes (MMR).

Drugs :

Trastuzumab deruxtecan (T-DXd) :

- Antibody drug conjugate.
- DXd :
 - Topoisomerase-I inhibitor.
 - 10 times more potent than SN38 (Pro drug of irinotecan).
- Side effects :
 - Risk of ILD : Grade 2 ILD → Withdraw drug.
 - monitor EF (Ejection fraction) : <40% → Discontinue.
 - Infusion reaction can occur.
 - Bone marrow suppression is reported.

Sacituzumab Govitecan :

- Antibody drug conjugate.
- hRS7 IgG directed against Trop 2 antigen, conjugated to SN-38.
- Side effects :
 - Infusion reaction can occur : Given over 3 hours.
 - myelosuppression.
 - **Diarrhea :**
 - Early (<24 hours) : Cholinergic action, treated by atropine.
 - Late (>24 hours) : Treated by loperamide, octreotide.