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REVIEW ARTICLE

Treatment of advanced nonsmall cell lung cancer: First line, maintenance and second line – Indian consensus statement update

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[Under the aegis of Lung Cancer Consortium Asia (LCCA), Indian Cooperative Oncology Network (ICON), Indian Society of Medical & Pediatric Oncology (ISMPO), Molecular Oncology Society (MOS) and Association of Physicians of India API)]

Abstract

The management of advanced nonsmall cell lung cancer (NSCLC) patients is becoming increasingly complex with the identification of driver mutations/rearrangements and development/availability of appropriate targeted therapies. In 2017, an expert group of medical oncologists with expertise in treating lung cancer used data from published literature and experience to arrive at practical consensus recommendations on treatment of advanced NSCLC for use by the community oncologists. This was published subsequently in the Indian Journal of Cancer with a plan to be updated annually. The present document is an update to the 2017 document.

Key words: Consensus statement, driver mutations, nonsmall cell lung cancer, targeted therapies

Introduction

In the last decade, lung cancer treatment has changed from histology-based to target-based approach. Newer molecular alterations and driver mutations/rearrangements have been identified which can be targeted with appropriate therapeutic interventions. With the availability of newer targeted therapies, the treatment of advanced/metastatic nonsmall cell lung cancer (NSCLC) has become increasingly complex. In 2016, experts from the Indian Cooperative Oncology Network, Lung Cancer Consortium Asia, Indian Society of Medical and Pediatric Oncology, Molecular Oncology Society and Association of Physicians of India met to discuss and arrive at consensus statements to provide practical recommendations for the community oncologists for the treatment of this complex disease which was subsequently published in the Indian Journal of Cancer in 2017. The discussion was based on the review of the published evidence, subject expertise of the participating faculty and practical experience in real life management of lung cancer patients. The present document is an update to the previous consensus document and reflects changes in the evidence since the previous consensus.

Methods

A total of 55 lung cancer experts from all over India participated in the development of the consensus statement. As a part of the background work, the evidence supporting the answer to 18 clinically relevant questions (mentioned below) was compiled by lead discussants, and the review of the literature was presented to the panel. This was followed by a discussion on the consensus statements which were voted for by all the panellists using voting pads. The options for voting each consensus statement were "Agree," "Disagree," and "Not sure." The percentage of delegates "agreeing," "disagreeing," or "not sure" with each statement have been mentioned. For some statements, the consensus was unanimously passed by voice voting since there was 100% agreement among all the experts. The percentages for these statements have not been mentioned.

Members of the panel were also allowed to share their personal experiences, make comments, and record dissent while voting for the consensus statements. This manuscript is the outcome of the expert group discussion and consensus arrived in December 2017.

First-Line Therapy

Should programmed death ligand 1 testing be considered as a part of initial diagnostic workup for a patient diagnosed with lung cancer?

Understanding tumor-immune interactions and development of immune checkpoint inhibitors has changed the therapeutic landscape of NSCLC. The excitement about using immunotherapy has been primarily driven by the fact that antagonist antibodies to programmed death receptor 1 (PD-1) and PD ligand 1 (PD-L1) have prolonged tumor responses in patients with metastatic NSCLC progressing on the first-line chemotherapy.[1-4] Treatment with pembrolizumab (an anti-PD-1 antibody) in treatment naïve patients with least 50% tumor cell staining for PD-L1 as determined by the 22C3 pharmDx test, resulted in significant prolongation of progression-free survival (PFS) and overall survival (OS).[5] The median PFS was 10.3 months (95% confidence interval [CI]: 6.7–not reached) versus 6.0 months (95% CI: 4.2–6.2) for pembrolizumab compared with chemotherapy, respectively, (hazard ratio [HR] = 0.50; 95% CI: 0.37–0.68; $P < 0.001$). The 6-month OS rate was 80.2% in the pembrolizumab arm and 72.4% in the chemotherapy arm (HR = 0.60; 95% CI: 0.41–0.89; $P = 0.005$).

Consensus

- Inappropriate setting, PD L1 testing determined by the 22C3 pharmDx test may be included as a part of initial diagnostic workup for lung cancer patients, especially when planned to be treated with pembrolizumab in the first line.

Which patients of advanced stage nonsmall cell lung cancer should be treated with chemotherapy?

Literature review

Platinum-based doublet chemotherapy has shown to improve survival compared to best supportive care in patients with

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good performance status (PS) without impairing the quality of life.[6-12] Addition of a third cytotoxic agent improves the response rate (odds ratio [OR]: 0.66; 95% CI: 0.58–0.75; $P < 0.001$) and toxicity without an increase in 1 year survival (OR: 1.01; 95% CI: 0.85–1.21; $P = 0.88$).[13] Pooled analysis of six randomized trials has shown that platinum-based doublets improved objective response rate (ORR) (OR: 3.243; 95% CI: 1.883–5.583) and 1-year survival rate (OR: 1.743; 95% CI: 1.203–2.525) with increased hematological toxicities compared to single agent in patients with PS 2.[14] For patients who are the elderly or those with PS 2, single-agent vinorelbine and gemcitabine has shown to improve OS without compromising the quality of life.[15,16] In a phase III trial comparing docetaxel versus vinorelbine in elderly patients with PS ≥2, docetaxel improved PFS (median 5.5 months vs. 3.1 months; $P < 0.001$) and response rates (22.7% vs. 9.9%; $P = 0.019$) versus vinorelbine. The difference in the OS was not statistically significant (median 14.3 vs. 9.9 months, HR for death 0.78, 95% CI: 0.56–1.09). A French Intergroup study (IFCT-0501) compared monthly carboplatin plus weekly paclitaxel versus single-agent vinorelbine or gemcitabine in patients aged 70–89 years with PS 0–2 and reported a survival advantage for combination therapy (median OS 10.3 months for doublet vs. 6.2 months for monotherapy, HR = 0.64, 95% CI: 0.52–0.78; $P < 0.0001$).[17] Lower doses of paclitaxel administered weekly along with carboplatin resulted in similar efficacy and lesser neurotoxicity.[18] Cisplatin-containing regimens are associated with more nephrotoxicity, nausea, and vomiting and carboplatin combinations cause more severe thrombocytopenia.

An exploratory phase II study evaluated pembrolizumab in combination with chemotherapy versus chemotherapy alone in chemotherapy-naive, Stage IIIB or IV, non-squamous NSCLC without targetable epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genetic aberrations.[19] The combination of pembrolizumab and chemotherapy resulted in improved response rates (ORR 55% vs. 29%; $P = 0.0016$) and prolongation of PFS. An updated analysis has shown that the median OS was not reached (22.8–NR) for pembrolizumab + chemotherapy and 20.9 (14.9–NR) chemotherapy arm. The HR for OS was 0.59 (95% CI: 0.34–1.05; $P = 0.0344$).

Consensus

- All patients of advanced NSCLC with PS 0-2 without driver mutations/rearrangements and PD L1 <50% should be treated with upfront chemotherapy (agree– 100%, disagree– 0%)
- For patients with PS 0–1
  - 4–6 cycles of platinum-based doublet chemotherapy should be the standard of care (agree– 100%, disagree– 0%)
  - Carboplatin-based regimens should be used in patients in whom cisplatin is likely to be poorly tolerated. Weekly schedule of paclitaxel plus carboplatin may be considered (agree– 100%, disagree– 0%).
- For patients with PS ≥2 and for elderly patients
  - Single-agent chemotherapy (vinorelbine, gemcitabine, pemetrexed, or docetaxel) may be appropriate (agree– 100%, disagree– 0%)
  - Carboplatin-based combinations may be considered ineligible patients aged >70 years with PS 0–2 and adequate organ function (agree– 100%, disagree– 0%).
- Patients with PS 3–4 can be offered EGFR tyrosine kinase inhibitors (TKIs) (if EGFR wild-type) or best supportive care (in the absence of activating EGFR mutations or ALK/receptor tyrosine kinase gene (ROS 1 translocations) (agree – 100%, disagree – 0%)
- Currently, the evidence is not enough to make any recommendations on the use of a combination of pembrolizumab + chemotherapy in the upfront setting.

What should be the choice of therapy in patients of nonsmall cell lung cancer of non-squamous histology with no driver mutation/rearrangement?

Literature review

In a phase III trial cisplatin + pemetrexed conferred survival advantage compared to cisplatin + gemcitabine in patients with adenocarcinoma (median OS-12.6 months in cisplatin + pemetrexed arm vs. 10.9 months in cisplatin + gemcitabine arm).[10] A meta-analysis comparing the efficacy and toxicities of pemetrexed plus platinum with other platinum regimens in patients with previously untreated advanced NSCLC concluded that pemetrexed plus platinum chemotherapy in the first-line setting leads to a significant survival advantage with acceptable toxicities for advanced NSCLC patients, especially those with nonsquamous histology (HR = 0.87, 95% CI: 0.77–0.98, $P = 0.02$).[20] Addition of bevacizumab to carboplatin-paclitaxel regimen in patients of non-squamous histology offers high response rates, longer PFS (HR = 0.72; 95% CI: 0.66 and 0.79; $P < 0.001$), and improved OS compared (HR = 0.90; 95% CI: 0.81 and 0.99; $P = 0.03$) with carboplatin-paclitaxel alone in patients with non-squamous histology and PS 0–1 and significantly increased risk of Grade ≥3 proteinuria, hypertension, hemorrhagic events, neutropenia, and febrile neutropenia. These trials excluded patients with brain metastases or a history of hemoptysis.[21]

Recently, a phase III trial compared pembrolizumab to platinum doublet chemotherapy in 305 treatment naïve advanced NSCLC patients with at least 50% tumor cell staining for PD-L1. Patients with EGFR mutations or ALK translocations were not included in this study.[5] At a median follow-up of 11.2 months, pembrolizumab significantly prolonged the PFS compared with platinum-doublet chemotherapy. The median PFS was 10.3 in pembrolizumab versus 6 months with platinum-doublet chemotherapy (HR = 0.50, 95% CI: 0.37–0.68). ORRs and median duration of response for pembrolizumab and platinum-doublet chemotherapy were 45% and 28% and 12.1 and 5.7 months, respectively. OS was also prolonged with pembrolizumab compared with platinum-doublet chemotherapy (HR = 0.60, 95% CI: 0.41–0.89). About 81.2% of the patients treated with pembrolizumab in this trial had nonsquamous histology. The HR of disease progression or death in this subgroup was 0.55, 95% CI: 0.39–0.76. Severe (Grade 3–5) treatment-related adverse effects were seen in 27% of patients receiving pembrolizumab, compared with 53% in those treated with platinum-doublet chemotherapy.

Consensus

- NSCLC patients of nonsquamous histology without driver mutations/rearrangements and PD-L1 ≥50% may be treated

Table 1: Summary of recommendations

First line therapy

- Should PD L1 testing be considered as a part of initial diagnostic work up for a patient diagnosed with lung cancer?
  - In appropriate setting, PD L1 testing determined by the 22C3 pharmDx test may be included as a part of initial diagnostic work up for lung cancer patients especially when planned to be treated with pembrolizumab in the first line
- Which patients of advanced stage NSCLC should be treated with chemotherapy?
  - All patients of advanced NSCLC with PS 0-2 without driver mutations/rearrangements and PD L1 <50% should be treated with upfront chemotherapy
  - For patients with PS 0-1

    4-6 cycles of platinum based doublet chemotherapy should be the standard of care

    Carboplatin based regimens should be used in patients in whom cisplatin is likely to be poorly tolerated. Weekly schedule of paclitaxel plus carboplatin may be considered
  - For patients with PS ≥2 and for elderly patients

    Single agent chemotherapy (vinorelbine, gemcitabine, pemetrexed or docetaxel) may be appropriate

    Carboplatin based combinations may be considered in eligible patients aged >70 years with PS 0-2 and adequate organ function
  - Patients with PS 3-4 can be offered EGFR TKIs (if EGFR wild type) or best supportive care (in the absence of activating EGFR mutations or ALK/ROS1 translocations)
  - Currently evidence is not enough to make any recommendations on the use of combination of pembrolizumab + chemotherapy in the upfront setting
- What should be the choice of therapy in patients of NSCLC of nonsquamous histology with no driver mutation/rearrangement?
  - NSCLC patients of nonsquamous histology without driver mutations/rearrangements and PD-L1 ≥50% may be treated with pembrolizumab or pemetrexed and platinum agent in the first line
  - Pemetrexed and platinum agent should be considered as first line option for patients of nonsquamous histology without driver mutations/rearrangements and PD-L1 <50%
  - Bevacizumab in combination with paclitaxel-carboplatin may be offered to patients with nonsquamous histology, PD-L1 <50% and PS 0-1 after exclusion of contraindications
- What should be the choice of therapy in patients of nonsquamous histology with unknown mutation status?
  - All attempts should be made to test for driver mutations/rearrangements using biopsy or cell block (if biopsy specimen is not available) to guide the choice of therapy
  - At this moment there is not enough evidence to support the use of ctDNA for testing EGFR mutations in the upfront setting although it may be acceptable in cases where mutation status cannot be established either by biopsy or cell block
  - In case driver mutation/rearrangement testing is not feasible, chemotherapy should be first line treatment of choice for patients with good performance status
- What should be the choice of therapy in patients of NSCLC with activating mutations in the Epidermal Growth Factor Receptor (Del 19 and L858R)?
  - Patients with EGFR mutations should be treated with an EGFR TKI (afatinib, erlotinib, gefitinib, and osimertinib - all listed in alphabetical order) in the upfront setting
  - In case the chemotherapy is started before the mutation test results are available, chemotherapy may be continued for 4-6 cycles in responding patients. Switching to an EGFR TKI before completion of 4-6 cycles can also be a valid option
- What should be the treatment of choice in patients with uncommon EGFR mutations?
  - In addition to Del 19 and L858R mutations, the EGFR panel should include testing for uncommon mutations like denovo T790M, point mutations, duplications exons 18-21, exon 20 insertions etc
  - For specific point mutations like G719X, S768I and L861Q afatinib may be preferred. Erlotinib and gefitinib may also be reasonable
  - For exon 20 insertions and denovo T790M mutations, chemotherapy may be the preferred treatment of choice
- Should EGFR TKIs be continued beyond disease progression in first line?
  - Single agent continuation of EGFR TKI beyond PD may be beneficial in some patients (e.g., in patients with an isolated site of progression which can be treated with local therapy, those with mild and asymptomatic progression)
  - Addition of chemo to TKI after progression on first line TKI is not recommended. TKI should be discontinued and patients should be offered chemotherapy
- What should be the choice of therapy in patients of NSCLC with ALK rearrangements?
  - Patients with ALK rearrangements should be treated with alectinib, ceritinib or crizotinib (all listed in alphabetical order) in the upfront setting
  - In case the chemotherapy is started before ALK results are available, chemotherapy may be continued for 4-6 cycles in responding patients. Switching to alectinib, ceritinib or crizotinib before completion of 4-6 cycles is a valid option
  - In carefully selected patients (e.g., in patients with an isolated site of progression which can be treated with local therapy, those with mild and asymptomatic progression), alectinib, ceritinib or crizotinib may be continued beyond progression
- What should be the choice of therapy in patients of NSCLC with ROS1 rearrangements in first line?
  - Patients with ROS 1 rearrangements should be treated with ceritinib or crizotinib (listed in alphabetical order) in the upfront setting
  - In case the chemotherapy is started before ROS 1 results are available, chemotherapy may be continued for 4-6 cycles in responding patients. Switching to ceritinib or crizotinib before completion of 4-6 cycles is a valid option
- What should be the choice of therapy in patients of NSCLC of squamous histology?
  - 4-6 cycles of platinum doublet chemotherapy should be the standard of care for patients with squamous cell carcinoma of lung and PD L1 <50%
  - Patients of squamous histology with PD-L1 y should be the standard of care for patients with squamous cell carcinoma of lung and PD L
  - Platinum plus pemetrexed should not be used in patients with SqCC
  - Bevacizumab should not be used in patients with SqCC because of the risk of severe bleeding

Maintenance therapy

- Which patients should be offered maintenance therapy?

Contd...

Table 1: Contd...

- NSCLC patients of nonsquamous histology who have any response or stable disease after 4-6 cycles of first line chemotherapy are appropriate candidates for maintenance chemotherapy
- Maintenance should be continued until progression or unacceptable adverse events
- For patients whose initial regimen included bevacizumab, it may be continued as maintenance treatment in the absence of unacceptable toxicity or disease progression
- In NSCLC patients without driver mutations/rearrangements

  Maintenance therapy with pemetrexed is preferred

  EGFR TKIs should not be offered as maintenance therapy in patients who are EGFR wild type

  Pemetrexed or bevacizumab maintenance should not be used in patients with squamous histology
- In NSCLC patients with EGFR mutation or ALK/ROS1 translocation

  For patients with advanced NSCLC who were initially treated with chemotherapy but in whom EGFR mutation or ALK/ROS1 translocation has subsequently been identified, continuation of therapy is indicated with an appropriate targeted agent after the initial cycles of chemotherapy are complete

Second line therapy

- What should be the appropriate choice of therapy in patients of NSCLC of nonsquamous histology without driver mutations/rearrangements after progression on first line chemotherapy?

  Patients with good performance status should be offered second line therapy

  PD L1 testing is not required for atezolizumab and nivolumab. For pembrolizumab PD-L1 testing is required

  PD L1 testing should be done on the approved diagnostic kit.

  For patients who are PD L1 negative/unknown, atezolizumab or nivolumab may be considered. For those with PD-L1 >1%, atezolizumab or nivolumab or pembrolizumab may be considered. (Agree - 100%, Disagree - 0%)

  For those with rapid progression (<9 months from the start of first line therapy) and those with PD as the best response to first line therapy, docetaxel in combination with either nintedanib or ramucirumab are acceptable options

  For those who cannot afford the above treatments, single agent docetaxel or pemetrexed (if not used in the first line) are preferred options

  EGFR TKIs may be used as second line therapy in EGFR unknown status patients who are unwilling for chemotherapy/immunotherapy or in those with poor performance status who are not suitable for either chemotherapy or immunotherapy
- What should be the appropriate choice of therapy in NSCLC patients with EGFR mutations after progression on first line therapy?
  - EGFR mutated patients who were treated with combination chemotherapy in the first line should be offered EGFR TKIs (afatinib, erlotinib and gefitinib) in the second line if not already treated with EGFR TKIs in the maintenance setting
  - Patients who progress on first line EGFR TKI must be tested for the T790M mutation on either re-biopsy or cell block or ctDNA
  - In patients with documented T790M mutation after treatment with first/second generation TKIs, a third generation TKI like osimertinib should be considered. In case of nonavailability of osimertinib, chemotherapy is an acceptable option
  - Combination chemotherapy should be preferred as second line treatment option in patients who were treated with EGFR TKIs in the first line and who are T790M unknowm or T790M-ve
  - Patients who transition to small cell lung cancer should be treated with appropriate chemotherapy
- What should be the choice of therapy in NSCLC patients with ALK translocations after progression on first line ALK inhibitor?
  - Patients with ALK positive NSCLC who have progressed on crizotinib may be offered alectinib or ceritinib. Chemotherapy also remains an acceptable option for these patients
  - Chemotherapy is the treatment of choice in patients who progress on first line alectinib or ceritinib
- What should be the appropriate choice of therapy in patients of NSCLC of squamous histology after progression on first line chemotherapy?
  - Patients with good performance status should be offered second line therapy
  - Atezolizumab, nivolumab or pembrolizumab are preferred agents for the treatment of NSCLC of squamous histology after progression on first line chemotherapy

    For patients who are PD L1 negative/unknown, atezolizumab or nivolumab may be considered. For those with PD-L1 >1%, atezolizumab, nivolumab or pembrolizumab may be considered
  - PD L1 testing is not required for atezolizumab and nivolumab. For pembrolizumab PD-L1 testing is required. PD L1 testing should be done on the approved diagnostic kit
  - Single agent chemotherapy and TKIs are also acceptable options. Afatinib may be preferred over erlotinib based on superior OS data

NSCLC with brain metastases

- What should be the treatment of choice for NSCLC patients with brain metatases?
  - Treatment of patients with brain metastases depends on age and Karnofsky Index
  - RPA class I and II patients with >3 mets may be treated with WBRT
  - SRS may be a reasonable option in carefully selected patients with limited disease
  - In RPA class III patients, BSC is recommended
  - Patients with single brain metastases may be treated with either surgical resection or SRS/SRT

    Single large symptomatic metastases should be treated with surgery

    SRS/SRT is reasonable alternative to surgery for small (<3 cm) and inaccessible tumors
  - Patients of RPA class I and II with 1-3 small brain metastases (<3 cm) should be treated with SRS/SRT alone rather than SRS + WBRT
  - WBRT is reasonable option in patients who are not candidates of surgery or whose lesions are too large for radiosurgery
  - Patients treated with surgical resection or SRS should have follow-up MRI every 3 months
  - Dexamethasone is recommended for patients with symptomatic brain metastases

Contd...

Table 1: Contd...

- In patients with druggable oncogenic driver mutation and asymptomatic brain metastases, TKIs may control the brain disease and defer WBRT
- For patients with symptomatic metastases radiotherapy should be preferred
- ALK positive patients with brain metastases who progress on crizotinib may benefit from ceritinib
- Patients should have a follow up MRI/CT/imaging done every 3 months

Oligometastatic disease

- What are the recommendations for the treatment of NSCLC with oligometastatic disease?
  - Stage IV NSCLC patients with synchronous or metachronous oligometastasis may benefit from surgery and/or radiation therapy. Metachronous oligometastases has better prognosis than synchronous
  - Every attempt must be made to biopsy the second primary tumour in the lung and may be treated with radical intent if possible
  - For patients with oligometastatic recurrence or progression while on targeted therapy, SBRT may be offered to the progressing sites

What are the investigations recommended at the time of disease progression?

- Patient of nonsquamous histology has not been tested in the first line and treated with chemotherapy doublet
  - All attempts must be made to get tissue specimen in the form of biopsy or cell block (if biopsy is not possible)
  - All NSCLC patients of nonsquamous histology who progress on chemotherapy should be tested for EGFR, ALK, ROS1 and BRAF status if not tested previously
  - Biopsy or cell block (if biopsy specimen is not available) should be used for testing for EGFR, ALK, ROS1 and BRAF testing
  - ctDNA may be acceptable in cases where mutation status cannot be established either by biopsy or cell block
  - PD L1 testing on biopsy specimen should be done after progression on first line chemotherapy if the patient is planned to be treated with pembrolizumab
  - PD L1 testing is not required for atezolizumab or nivolumab
  - PD L1 testing should be done on the approved diagnostic kit
- Patient is EGFR mut +ve and treated with EGFR TKIs in the first line
  - In patients who have progressed on first line EGFR TKI, testing for exon 20 T790M mutation on either re-biopsy or cell block of FNAC specimen or ctDNA should be considered
  - An effort should be made to re-analyze the histology of the tumor on re-biopsy specimen for ruling out transition into small cell lung cancer
  - If feasible following additional analysis should be done on rebiopsy or cell block of FNAC specimen

    Her 2 mutation/amplification

    MET amplification
- What investigations should be performed in patients of squamous cell histology progressing on chemotherapy doublet?
  - EGFR testing may be done routinely in patients with squamous cell histology in the first line or on rebiopsy sample once patients progress on chemotherapy doublet
  - PD L1 testing should be done for second line SqCC before prescribing pembrolizumab
  - PD L1 testing is not required for nivolumab
  - PD L1 testing should be done on the approved diagnostic kit

NSCLC=Nonsmall cell lung cancer, EGFR=Epidermal growth factor receptor, TKI=Tyrosine kinase inhibitors, ALK=Anaplastic lymphoma kinase, MRI=Magnetic resonance imaging, CT=Computed tomography, FNAC=Fine needle aspiration cytology, SBRT=Stereotactic body radiation therapy, WBRT=Whole brain radiotherapy, SRT=Stereotactic radiotherapy, SRS=Stereotactic radiosurgery, SQCC=Squamous cell carcinoma, MET=MET proto-oncogene receptor tyrosine kinase, ROS1=c-ros oncogene 1, BRAF=v-raf murine sarcoma viral oncogene homolog B1

with pembrolizumab or pemetrexed and platinum agent in the first line.(agree – 100%, disagree – 0%)

- Pemetrexed and platinum agent should be considered as first-line option for patients of nonsquamous histology without driver mutations/rearrangements and PD-L1 <50% (agree – 100%, disagree – 0%)
- Bevacizumab in combination with paclitaxel-carboplatin may be offered to patients with nonsquamous histology, PD-L1 <50% and PS 0–1 after exclusion of contraindications (agree - 68% and disagree – 32%).

What should be the choice of therapy in patients of non-squamous histology with unknown mutation status?

Literature review

In a country like India, it is possible that the adequate tissue may not always be available for molecular testing at the time of diagnosis. Furthermore in certain circumstances, the general condition of the patient may warrant treatment before mutation results are available. There are limited clinical data which address the optimal approach in this situation. The choice of agent in such situations may be indirectly guided by the results of The Towards a Revolution in COPD Health trial which showed that OS was significantly longer in unselected patients assigned to initial chemotherapy followed by second-line erlotinib (median 11.6 vs. 8.7 months, HR = 1.24, 95% CI: 1.04–1.47). EGFR mutation status was analyzed in 64% of cases, 86% of whom were EGFR wild-type. For a small number of patients who were EGFR mutation negative, OS was significantly longer in patients with initial chemotherapy (median 9.6 vs. 6.5 months).[22]

The incidence of EGFR mutations in India is 25%–35%, which is higher compared to the western population.[23-26] In female and nonsmokers, this could be as high as 50%–55%. Recently, cell-free circulating tumor DNA (ctDNA) has been widely investigated as a potential surrogate for tissue biopsy for noninvasive assessment of tumor-related genomic alterations. In a study which assessed EGFR mutation status in 803 plasma samples, the concordance between baseline tumor and plasma samples was 94.3%, with a sensitivity of 65.7% and specificity of 99.8%.[27] A liquid biopsy may also be useful in detecting ALK rearrangements. In a study, echinoderm microtubule-associated protein-like 4 (EML4-ALK) rearrangements were analyzed by reverse transcription polymerase chain reaction (RT-PCR) in platelets and plasma isolated from blood obtained from 77 patients with nonsmall-cell lung cancer, 38 of whom had EML4-ALK-rearranged tumors.

RT-PCR demonstrated 65% sensitivity and 100% specificity for the detection of EML4-ALK rearrangements in platelets.[28]

Consensus

- All attempts should be made to test for driver mutations/rearrangements using biopsy or cell block (if biopsy specimen is not available) to guide the choice of therapy (agree – 100%, disagree – 0%)
- At this moment, there is not enough evidence to support the use of ctDNA for testing EGFR mutations in the upfront setting although it may be acceptable in cases where mutation status cannot be established either by biopsy or cell block. (agree – 100%, disagree – 0%)
- In case driver mutation/rearrangement testing is not feasible, chemotherapy should be first-line treatment of choice for patients with good PS. (agree– 100%, disagree – 0%).

What should be the choice of therapy in patients of nonsmall cell lung cancer with activating mutations in the epidermal growth factor receptor (Del 19 and L858R)?

Literature review

Six randomized clinical trials comparing the first generation EGFR TKIs (erlotinib and gefitinib) with platinum doublet in patients who are EGFR mutation positive have shown that EGFR TKIs significantly prolonged PFS. There was, however, no difference in the OS both in the overall patient population and subgroups of Del 19 and L858R mutations.[29-37]

Second generation EGFR TKI afatinib has also shown significant prolongation of PFS as compared to chemotherapy in patients with EGFR mutations in two separate head to head clinical trials.[38,39] In a preplanned analysis of patients with Del 19 mutation, afatinib has shown to prolong OS by additional 12.2 months in LUX-Lung 3 (33.3 months vs. 21.1 months, HR [95% CI] 0.54 [0.36–0.79] $P = 0.0015$) and 13 months in LUX-Lung 6 study (31.4 months vs. 18.4 months, HR [95% CI] 0.64 [0.44–0.94] $P = 0.0229$).[40]

Osimertinib is a third-generation, irreversible EGFR-TKI that selectively inhibits both EGFR sensitizing and EGFR T790M resistance mutations, with lower activity against wild-type EGFR.[41] Four head-to-head studies-WJOG 5108 L, CTONG 0901, Lux Lung 7, and FLAURA have compared the efficacy of EGFR TKIs.[42-45] In WJTOG 5108 L and CTONG 0901 studies, gefitinib demonstrated comparable efficacy with erlotinib. Median PFS and OS times for gefitinib and erlotinib were 6.5 and 7.5 months (HR = 1.125; 95% CI: 0.940–1.347; $P = 0$ 0.257) and 22.8 and 24.5 months (HR = 1.038; 95% CI: 0.833–1.294; $P = 0.768$), respectively, in WJTOG 5108 L trial. The response rates for gefitinib and erlotinib were 45.9% and 44.1%, respectively. Median PFS times in EGFR mutation-positive patients receiving gefitinib versus erlotinib were 8.3 and 10.0 months, respectively (HR = 1.093; 95% CI: 0.879–1.358; $P = 0.424$). In the Lux Lung 7 trial that compared afatinib with gefitinib, afatinib was superior to gefitinib in terms of PFS (median 11.0 months [95% CI: 10.6–12.9] with afatinib vs. 10.9 months [9.1–11.5] with gefitinib; HR = 0.73 [95% CI: 0.57–0.95], $P = 0.017$) and time to treatment failure (median 13.7 months [95% CI: 11.9–15.0] with afatinib vs. 11.5 months [10.1–13.1] with gefitinib; HR = 0.73 [95% CI: 0.58–0.92], $P = 0.0073$).[44] There was a trend toward improved OS with afatinib versus gefitinib (median 27.9 vs. 24.5 mos; HR = 0.86 [0.66–1.12], $P = 0.258$) but this did not reach statistical significance.[46] Although the incidence of Grade 3–4 adverse events were higher in the afatinib arm, the rate of adverse events related to treatment discontinuation was similar in both arms. FLAURA trial compared osimertinib with erlotinib and gefitinib (standard of care [SOC]) in treatment-naïve, EGFR-mutated advanced NSCLC patients. Osimertinib demonstrated improvement in PFS.[45] The median PFS was 18.9 months in osimertinib arm versus 10.2 months in SOC arm (HR = 0.46, 95% CI: 0.37–0.57). The PFS benefit was consistent across subgroups, including patients with or without brain metastases. There was a nonsignificant trend toward improvement in OS (HR = 0.63); however, OS results were immature, with only 25% of events collected. Response rates for osimertinib and SOC were 80% and 76%, respectively. Grade 3 or higher toxicities were lower for osimertinib versus SOC (34 vs. 45%).

Consensus

- Patients with EGFR mutations should be treated with an EGFR TKI (afatinib, erlotinib, gefitinib, and osimertinib – all listed in alphabetical order) in the upfront setting (agree – 100%, disagree – 0%)
- In case the chemotherapy is started before the mutation test results are available, chemotherapy may be continued for 4–6 cycles in responding patients. Switching to an EGFR TKI before completion of 4–6 cycles can also be a valid option (agree – 81.82%, disagree – 13.64%, not sure – 4.55%).

What should be the treatment of choice in patients with uncommon epidermal growth factor receptor mutations?

Most of the phase III studies with EGFR TKIs included patients with a deletion in exon 19 or the Leu858Arg mutation in exon 21 of EGFR. Retrospective data suggest that rare mutations except for Gly719Xaa and Leu861Gln point mutations have decreased responsiveness to erlotinib and gefitinib.[47-50] In an analysis from the NEJ002 trial, gefitinib was found to be ineffective against both Gly719Xaa and Leu861Gln mutations.[51] In a *post hoc* analysis from LUX-Lung 2, LUX-Lung 3, and LUX-Lung 6 trials high activity of afatinib was recorded in patients with Gly719Xaa, Leu861Gln and Ser768Ile mutations with a median PFS of 13.8 months (6·8–NE), 8·2 months (4·5–16·6), and 14·7 months (2·6–NE), respectively.[52] Objective response to EGFR TKIs in exon 20 insertions is poor.[52-55] Furthermore, patients with high allelic frequencies of Thr790Met mutations also do not respond to EGFR TKIs. In the *post hoc* analysis from LUX-Lung 2, LUX-Lung 3, and LUX-Lung 6 trials afatinib was ineffective in Thr790Met mutations.[52]

Consensus

- In addition to Del 19 and L858R mutations, the EGFR panel should include testing for uncommon mutations such as *de novo* T790M, point mutations, duplications exons 18-21, exon 20 insertions, etc. (Agree – 100%, Disagree – 0%, Not sure-0%)
- For specific point mutations such as G719X, S768I, and L861Q afatinib may be preferred. Erlotinib and

gefitinib may also be reasonable (Agree – 66.67%, Disagree – 12.5%, Not sure– 20.83%)
- For exon 20 insertions and *de novo* T790M mutations, chemotherapy may be the preferred treatment of choice (Agree – 90.91%, Disagree – 4.55%, Not sure – 4.55%).

Should epidermal growth factor receptor tyrosine kinase inhibitors be continued beyond disease progression in the first line?

Literature review

Some patients have rapid disease progression when an EGFR TKI is discontinued after a prolonged course of treatment. Therefore in certain situations, it may be reasonable to continue an EGFR TKI in the presence of RECIST defined progression. ASPIRATION trial evaluated the efficacy of first-line erlotinib therapy in patients with NSCLC with activating EGFR mutations and continuing erlotinib beyond progression. Out of the 208 patients enrolled, 176 had a PFS1 event, of these, 93 continued erlotinib therapy following progression. Median PFS1 and PFS2 in the 93 continuing patients was 11.0 (95% CI: 9.2–11.1) and 14.1 (95% CI: 12.2–15.9) months, respectively.[56]

IMPRESS trial enrolled 205 patients with activating EGFR mutations and compared chemotherapy plus gefitinib versus chemotherapy alone after radiological disease progression on first line gefitinib. Continuation of gefitinib did not prolong PFS. There was a trend toward shorter OS when gefitinib was continued in conjunction with chemotherapy.[57] In LUX-Lung 7 trial afatinib and gefitinib were continued beyond RECIST progression and median time to failure (TTF) was significantly prolonged in afatinib versus gefitinib (median TTF 13.7 months vs. 11.5 months HR = 0.73 95% CI: 0.58–0.92), $P = 0.0073$.[44]

Consensus

- Single-agent continuation of EGFR TKI beyond PD may be beneficial in some patients (e.g., in patients with an isolated site of progression which can be treated with local therapy, those with mild and asymptomatic progression) (Agree – 95.24%, Disagree – 4.76%, Not sure -%)
- Addition of chemo to TKI after progression on first-line TKI is not recommended. TKI should be discontinued, and patients should be offered chemotherapy (Agree – 85%, Disagree – 10%, Not sure-5%).

What should be the choice of therapy in patients of nonsmall cell lung cancer with anaplastic lymphoma kinase rearrangements?

Literature review

Results of a phase III trial comparing ALK inhibition using crizotinib with chemotherapy in treatment-naïve patients have demonstrated a prolongation in PFS (median, 10.9 months vs. 7.0 months; HR = 0.45; 95% CI: 0.35–0.60; $P < 0.001$) and improved response rate (ORR-74% and 45%, respectively, $P < 0.001$) and quality of life. Since crossover to crizotinib was permitted for those treated with chemotherapy, the majority of patients assigned to initial chemotherapy subsequently were treated with crizotinib. Because of the confounding effects of the crossover, no significant differences in OS were seen.[58] In a phase III trial comparing crizotinib in patients with ALK-positive lung cancer who had received one prior platinum-based regimen, crizotinib was superior to chemotherapy (pemetrexed or docetaxel) in delaying the risk of disease progression or death. The median PFS was 7.7 months in the crizotinib group and 3.0 months in the chemotherapy group (HR = 0.49; 95% CI: 0.37–0.64; $P < 0.001$).[59] In a retrospective analysis of two single-arm studies, it was shown that continuing ALK inhibition with crizotinib after PD may provide a survival benefit to patients with advanced ALK-positive NSCLC.[60] The median OS from the time of PD was 16.4 versus 3.9 months; HR = 0.27, 95% CI: 0.17–0.42; $P < 0.0001$, and from the time of initial crizotinib treatment was 29.6 versus 10.8 months; HR = 0.30, 95% CI: 0.19–0.46; $P < 0.0001$.

Second generation ALK inhibitors have shown promising efficacy in advanced ALK-positive NSCLC. In a global phase III study, 303 patients with ALK rearrangements were randomly assigned to the first-line alectinib versus crizotinib (ALEX trial). The rate of investigator-assessed PFS was significantly higher with alectinib than with crizotinib. 12-month event-free survival rate was 68.4% with alectinib versus 48.7% with crizotinib (HR = 0.46, 95% CI: 0.37–0.57).[61] The median PFS with alectinib was not reached versus 11.1 months in crizotinib arm. OS results are not yet mature. The time to central nervous system (CNS) progression in the overall population was improved with alectinib (HR = 0.16, 95% CI: 0.10–0.28). Grade 3–5 toxicities were less frequent with alectinib (41% vs. 50%). Ceritinib is another second generation which has demonstrated improved efficacy over combination chemotherapy in the front-line setting in ASCEND 4 trial.[62] The median PFS for patients treated with 750 mg ceritinib was 16.6 versus 8.1 months with pemetrexed and platinum (HR = 0.55, 95% CI: 0.42–0.73). The ORR (72.5% vs. 26.7%) and duration of response (23.9 vs. 11.1 months) were also higher with ceritinib.

Consensus

- Patients with ALK rearrangements should be treated with alectinib, ceritinib, or crizotinib (all listed in alphabetical order) in the upfront setting
- In case the chemotherapy is started before ALK results are available, chemotherapy may be continued for 4–6 cycles in responding patients. Switching to alectinib, ceritinib, or crizotinib before completion of 4–6 cycles is a valid option
- In carefully selected patients (e.g., in patients with an isolated site of progression which can be treated with local therapy, those with mild and asymptomatic progression), alectinib, ceritinib, or crizotinib may be continued beyond progression.

What should be the choice of therapy in patients of nonsmall cell lung cancer with receptor tyrosine kinase gene1 rearrangements in the first line?

Literature review

In an open-label, the study of crizotinib in 50 patients with ROS1 translocation, the ORR was 72% (3 complete and 33 partial responses). The median duration of response was 17.6 months, and the median PFS was 19.2 months.[63] Similar response rates were observed in another retrospective series of 32 patients treated with crizotinib with ROS1 rearrangement.[64]

Second generation inhibitor ceritinib was evaluated in a phase II trial of 28 with advanced ROS1-rearranged NSCLC.[65] The ORR with ceritinib was 62%, and duration of response was 21 months. The median PFS with ceritinib was 9.3 months in the overall population. For patients who were crizotinib-naïve, the median PFS was 19.3 months. The median OS was 24 months. Five of eight patients with brain metastases experienced disease control.

Consensus

- Patients with ROS 1 rearrangements should be treated with ceritinib or crizotinib (listed in alphabetical order) in the upfront setting
- In case the chemotherapy is started before ROS 1 results are available, chemotherapy may be continued for 4–6 cycles in responding patients. Switching to ceritinib or crizotinib before completion of 4–6 cycles is a valid option.

What should be the choice of therapy in patients of nonsmall cell lung cancer of squamous histology?

Literature review

Most of the studies evaluating chemotherapy regimens in the first-line setting did not report any differential efficacy in patients with squamous cell carcinoma (SCC). A retrospective analysis of four SWOG randomized studies did not show any correlation between histology and survival for the combination of platinum with paclitaxel, docetaxel, and vinorelbine.[66] Median OS in adenocarcinoma, SCC, large cell carcinoma and NSCLC not otherwise specified was 8.5, 8.4, 8.2, and 9.6 months, respectively. In a trial comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed, an improved OS was demonstrated for patients with SCC treated with cisplatin plus gemcitabine (median OS-10.8 vs. 9.4 months in cisplatin plus pemetrexed).[10]

Recently a phase III trial compared pembrolizumab to platinum doublet chemotherapy in 305 treatment naïve advanced NSCLC patients with at least 50% tumor cell staining for PD-L1.[5] Patients with EGFR mutations or ALK translocations were not included in this study. At a median follow-up of 11.2 months, pembrolizumab significantly prolonged the PFS compared with platinum-doublet chemotherapy. The median PFS was 10.3 months in pembrolizumab versus 6 months with platinum-doublet chemotherapy (HR = 0.50, 95% CI: 0.37–0.68). ORRs and median duration of response for pembrolizumab and platinum-doublet chemotherapy were 45% and 28% and 12.1 and 5.7 months, respectively. OS was also prolonged with pembrolizumab compared with platinum-doublet chemotherapy (HR = 0.60, 95% CI: 0.41–0.89). The benefit of pembrolizumab observed in the subgroup of patients with squamous histology (constituting 18.8% of overall population) was notable. The HR for disease progression or death in this subgroup was 0.35, 95% CI: 0.17–0.71. Severe (Grade 3–5) treatment-related adverse effects were seen in 27% of patients receiving pembrolizumab, compared with 53% in those treated with platinum-doublet chemotherapy.

Consensus

- 4–6 cycles of platinum doublet chemotherapy should be the SOC for patients with SCC of lung and PD L1 <50%. (Agree – 100%, Disagree – 0%, Not sure – 0%)
- Patients of squamous histology with PD-L1 -50% may be treated with pembrolizumab or platinum doublet chemotherapy in the first line (Agree – 100%, Disagree – 0%)
- Platinum plus pemetrexed should not be used in patients with SqCC (Agree – 85.71%, Disagree – 14.29%, Not Sure – 0%)
- Bevacizumab should not be used in patients with SqCC because of the risk of severe bleeding (Agree – 95.45%, Disagree – 4.55%, Not Sure – 0%).

Maintenance Therapy

Which patients should be offered maintenance therapy?

Literature review

In a large phase III trial, switch maintenance therapy with pemetrexed after four cycles of non pemetrexed containing platinum-based doublet (cisplatin or carboplatin plus gemcitabine, docetaxel, or paclitaxel) increased both median PFS (4.3 months vs. 2.6 months; HR = 0.50, 95% CI: 0.42–0.61, $P < 0.0001$) and OS (13.4 months vs. 10.6 months; HR = 0.79, 0.65–0.95, $P = 0.012$) compared with placebo. The benefits of pemetrexed were limited to patients with nonsquamous histology.[67] PARAMOUNT trial evaluated continuous maintenance with pemetrexed in nonsquamous NSCLC patients who had an objective response or stable disease after four cycles of cisplatin plus pemetrexed. PFS and OS were significantly increased in pemetrexed arm as compared to the placebo arm. The median PFS was 4.1 months for pemetrexed and 2.8 months for placebo (HR = 0.62, 95% CI: 0.49–0.79; $P < 0.0001$) and median OS was 13.9 months for pemetrexed and 11.0 months for placebo (HR = 0.78; 95% CI: 0.64–0.96; $P = 0.0195$).[68,69]

SATURN trial evaluated erlotinib as maintenance treatment in advanced NSCLC treated with four cycles of platinum-based doublet chemotherapy. There was a modest increase in the PFS (HR = 0·78, 95% CI: 0·63–0·96; $P = 0·0185$) and Os (HR = 0·77, 95% CI: 0·61–0·97; $P = 0·0243$) in the EGFR wild type patient population. Patients who harbored EGFR mutations had significant prolongation of PFS (HR = 0·10, 95% CI: 0·04–0·25; $P < 0·0001$).[70]

In a recent phase 3 study (IUNO) of erlotinib in EGFR wild patients, OS was not superior in patients who received maintenance erlotinib compared with patients randomized to receive erlotinib on progression. In view of this, the US prescribing information of erlotinib is being revised to limit NSCLC indications to patients with EGFR exon 19 deletions or exon 21 (L858R) substitutions.[71,72]

Consensus

- NSCLC patients of non-squamous histology who have any response or stable disease after 4–6 cycles of first-line chemotherapy are appropriate candidates for maintenance chemotherapy (Agree – 100%, Disagree – 0%)
- Maintenance should be continued until progression or unacceptable adverse events (Agree – 100%, Disagree – 0%)
- For patients whose initial regimen included bevacizumab, it may be continued as maintenance treatment in the absence of unacceptable toxicity or disease progression (Agree – 100%, Disagree – 0%)
- In NSCLC patients without driver mutations/rearrangements:

- Maintenance therapy with pemetrexed is preferred (Agree– 100%, Disagree– 0%)
- EGFR TKIs should not be offered as maintenance therapy in patients who are EGFR wild-type (Agree – 100%, Disagree – 0%)
- Pemetrexed or bevacizumab maintenance should not be used in patients with squamous histology (Agree – 100%, Disagree – 0%).

- In NSCLC patients with EGFR mutation or ALK/ROS1 translocation:
  - For patients with advanced NSCLC who were initially treated with chemotherapy but in whom EGFR mutation or ALK/ROS1 translocation has subsequently been identified, a continuation of therapy is indicated with an appropriate targeted agent after the initial cycles of chemotherapy are complete (Agree – 100%, Disagree – 0%).

Second Line Therapy

What should be the appropriate choice of therapy in patients of nonsmall cell lung cancer of non-squamous histology without driver mutations/rearrangements after progression on first-line chemotherapy?

Literature review

A phase III trial randomized previously treated NSCLC patients to docetaxel (100 mg/m^2 or 75 mg/m^2 every 3 weeks) or best supportive care. Patients assigned to docetaxel 75 mg/m^2 had significantly longer OS (7.5 vs. 4.6 months; log-rank test, P = 0.010), improved pain control and significantly less deterioration in the quality of life compared to best supportive care.[73,74] In a secondary analysis of head-to-head trials of pemetrexed vs docetaxel, the OS was significantly longer in patients randomized to pemetrexed in patients of non-squamous histology (median OS-9.3 months vs. 8.0 months, HR = 0.78, 95% CI: 0.61–1.00) with less Grade 3–4 adverse events.[75-77]

Addition of nintedanib (an oral triple angiokinase inhibitor) and ramucirumab to docetaxel has been shown to improve OS, particularly in patients who progress within 9 months and who have PD as the best response to first-line chemotherapy (refractory patients) from the start of first-line chemotherapy.[78,79]

Nivolumab compared to docetaxel significantly prolonged OS in NSCLC patients of non-squamous histology who progressed on first-line chemotherapy in CheckMate 057 trial.[2] The median OS was 12.2 months (95% CI: 9.7–15.0) in the nivolumab arm and 9.4 months (95% CI: 8.1–10.7) in the docetaxel arm (HR for death, 0.73; 96% CI, 0.59–0.89; P = 0.002). At 1 year and 18 months, the OS rate was 51% (95% CI: 45–56) and 39% (95% CI 34–45) with nivolumab versus 39% (95% CI: 33–45) and 23% (95% CI: 19–28) with docetaxel, respectively. However, patients with aggressive disease and with low PDL1 expression may be at risk of early deaths.[80] Treatment-related adverse events of Grade 3 or 4 were reported in 10% of the patients in the nivolumab group, as compared with 54% of those in the docetaxel group.

Another immune check point inhibitor pembrolizumab has also shown promising efficacy patients with ≥1% PD-L1 expression who progressed after first-line chemotherapy in two different clinical trials KEYNOTE-001 and KEYNOTE-010 study.[3,4] In KEYNOTE-010 study, previously treated NSCLC patients with PD-L1 expression on at least 1% of tumour cells were randomly assigned to pembrolizumab 2 mg/kg, pembrolizumab 10 mg/kg, or docetaxel 75 mg/m (2) every 3 weeks. OS was significantly longer for pembrolizumab 2 mg/kg versus docetaxel (HR 0.71, 95% CI: 0.58–0.88; P = 0.0008) and for pembrolizumab 10 mg/kg versus docetaxel (0.61, 0.49–0.75; P < 0.0001). Grade 3–5 treatment-related adverse events were 13% with 2 mg/kg and 16% with 10 mg/kg compared to 35% with docetaxel.

Atezolizumab, which is an immunoglobulin G1 antagonist antibody to PD-L1 was compared with docetaxel in a phase III trial which enrolled 1225 patients with advanced NSCLC who had already been treated with one or more platinum-based combination therapies. In this trial OS was prolonged in patients taking atezolizumab regardless of the PD-L1 expression.[1] The median OS was 13.8 months in atezolizumab arm versus 9.6 months in docetaxel arm. The 12 and 18 month OS rates were 55% and 40% in atezolizumab arm versus 41% and 27% in docetaxel arm. About 16% of enrolled patients had at least 50% of tumor cells or 10% of tumor area with immune cells staining for PD-L1. The median OS with atezolizumab versus docetaxel in this subgroup of patients was 20.5 versus 8.9 months (HR = 0.41, 95% CI: 0.27–0.64). OS was prolonged in atezolizumab arm regardless of NSCLC histology. Median OS with atezolizumab in patients with non-squamous histology was 15.6 months versus 11.2 months in docetaxel (HR = 0.73, 95% CI: 0.60–0.89).

In BR 21 trial, erlotinib improved OS versus placebo (6.7 months in erlotinib vs. 4.7 months in the placebo, HR = 0.70; P < 0.001) in the second line or in the third line in all NSCLC histological subtype patients not eligible for further chemotherapy, including patients with PS 3.[81] TITAN trial compared erlotinib to pemetrexed or docetaxel in NSCLC patients who progressed during or immediately after first-line chemotherapy.[82] There was no difference in OS in patients treated with erlotinib and those treated with docetaxel or pemetrexed. In the INTEREST trial, patients were treated with gefitinib or docetaxel, and there was no difference in OS.[83] DELTA trial compared erlotinib to docetaxel as second or third line therapy. There was no difference in the OS. However, for EGFR wild-type patients, PFS was significantly greater with docetaxel than erlotinib[84] In the TAILOR trial comparing erlotinib to docetaxel as second-line therapy, progression-free and OS durations were significantly better with docetaxel compared with erlotinib.[85]

Consensus

- Patients with good PS should be offered second-line therapy (Agree – 100%, Disagree– 0%)
- PD L1 testing is not required for atezolizumab and nivolumab. For pembrolizumab PD-L1 testing is required (Agree – 100%, Disagree – 0%)
- PD L1 testing should be done on the approved diagnostic kit (Agree – 100%, Disagree – 0%)
- For patients who are PD L1 negative/unknown, atezolizumab or nivolumab may be considered. For those with PD-L1 >1%, atezolizumab or nivolumab or pembrolizumab may be considered (Agree – 100%, Disagree – 0%)

- For those with rapid progression (<9 months from the start of first-line therapy) and those with PD as the best response to first-line therapy, docetaxel in combination with either nintedanib or ramucirumab is acceptable options (Agree– 100%, Disagree– 0%)
- For those who cannot afford the above treatments, single-agent docetaxel or pemetrexed (if not used in the first line) are preferred options (Agree– 100%, Disagree– 0%)
- EGFR TKIs may be used as second-line therapy in EGFR unknown status patients who are unwilling for chemotherapy/immunotherapy or in those with poor PS who are not suitable for either chemotherapy or immunotherapy (Agree– 100%, Disagree– 0%).

What should be the appropriate choice of therapy in nonsmall cell lung cancer patients with epidermal growth factor receptor mutations after progression on first-line therapy?

Literature review

Clinical trials evaluating first-generation EGFR TKIs in patients with EGFR mutation positive NSCLC have shown that whether EGFR TKIs are given in upfront setting or after progression on chemotherapy, the OS remains same.[14-21] Therefore in patients who are offered chemotherapy doublet in the first line must be treated with an EGFR TKI once their disease progress on first-line chemotherapy.

Almost all EGFR mutated patients who are treated with an EGFR TKI subsequently develop disease progression. T790M mutation in EGFR has been associated with acquired resistance to EGFR TKIs in up to 60% of these cases. Amplification of the mesenchymal-epithelial transition factor (MET) oncogene has been associated with resistance to EGFR TKIs in 5%–10% of cases. In addition, analyses of tumor tissue have observed the histologic transformation of EGFR mutation-positive NSCLC into small cell lung cancer in approximately 5% of cases.[86]

Osimertinib has shown activity in patients with acquired resistance to a prior EGFR inhibitor. In phase I/II study, osimertinib showed a response rate of 61% in patients with T790M mutation and median PFS of 10 months. For those whose tumors did not contain the T790M mutation, the response rate was 21%, and the median PFS was 3 months.[87]

Consensus

- EGFR mutated patients who were treated with combination chemotherapy in the first line should be offered EGFR TKIs (afatinib, erlotinib, and gefitinib) in the second line if not already treated with EGFR TKIs in the maintenance setting
- Patients who progress on first line EGFR TKI must be tested for the T790M mutation on either re-biopsy or cell block or ctDNA (Agree– 57.89%, Disagree– 21.05%, Not sure– 21.05%)
- In patients with documented T790M mutation after treatment with first/second generation TKIs, a third generation TKI like osimertinib should be considered. In case of nonavailability of osimertinib, chemotherapy is an acceptable option
- Combination chemotherapy should be preferred as second-line treatment option in patients who were treated with EGFR TKIs in the first line and who are T790M unknown or T790M-ve
- Patients who transition to small cell lung cancer should be treated with appropriate chemotherapy.

What should be the choice of therapy in nonsmall cell lung cancer patients with anaplastic lymphoma kinase translocations after progression on first line anaplastic lymphoma kinase inhibitor?

Literature Review

While ALK inhibitors are highly active in patients with ALK-positive NSCLC, the majority of the patients will develop resistance to the drug.[88] Various mechanisms of resistance vehave been reported in the literature. Patients who progress on first-generation ALK inhibitor may be responsive to second-generation ALK inhibitors such as ceritinib and alectinib.[89,90] ASCEND-5 study enrolled 231 ALK-positive patients who had been priorly treated with crizotinib. Patients were randomly assigned to ceritinib or chemotherapy. The median PFS was longer in the ceritinib arm than chemotherapy arm (5.4 vs. 1.6 months; HR = 0.49).[89] The OS analysis is currently immature. Alectinib was evaluated in two phase II studies performed in patients who had progressed after prior platinum-based chemotherapy or crizotinib.[91,92] In a combined analysis of these two studies, an ORR as assessed by the independent review committee was 51.3% (all PRs), the disease control rate (DCR) was 78.8%, and the median duration of response was 14.9 months.[90]

Consensus

- Patients with ALK-positive NSCLC who have progressed on crizotinib may be offered alectinib or ceritinib. Chemotherapy also remains an acceptable option for these patients
- Chemotherapy is the treatment of choice in patients who progress on first line alectinib or ceritinib.

What should be the appropriate choice of therapy in patients of nonsmall cell lung cancer of squamous histology after progression on first-line chemotherapy?

Literature review

Docetaxel 75 mg/m^2 significantly prolonged OS as second-line treatment of NSCLC with improved pain control and significantly less deterioration in the quality of life compared to best supportive care.[73,74] Ramucirumab added to docetaxel has shown to improve -PFS (4.5 vs. 3 months, $P < 0.0001$) and OS (median OS 10.5 vs. 9.1 months, HR = 0.86, 95% CI: 0.75–0.98, $P = 0.023$) compared to docetaxel alone regardless of the histology.[79] Erlotinib improved OS in the second line or in the third line in all NSCLC histological subtype patients not eligible for further chemotherapy, including patients with PS 3. The median OS in patients with squamous cell histology was 5.6 months with erlotinib versus 3.6 months with placebo HR = 0.67 (0.50–0.90).[81] In the TAILOR trial comparing erlotinib to docetaxel as second-line therapy, PFS and OS durations were significantly better with docetaxel compared with erlotinib in the overall population. However, in patients with squamous cell, histology OS was similar between erlotinib and docetaxel arm (HR for OS – 0.90, 95% CI: 0.49–1.65).[85] A meta-analysis of 8 randomized trials has shown that the

OS was similar between TKI and chemotherapy in unselected patient population in the second line.[93] In another meta-analysis carried out on six randomized controlled trials with a total of 990 patients with WT EGFR, PFS was significantly inferior in the EGFR TKI group versus the chemotherapy group (HR = 1.37, 95% CI: 1.20–1.56, $P < 0.00001$). However, this did not translate into an OS difference (HR = 1.02, 95% CI: 0.87–1.20, $P = 0.81$).[94] For those progressing on a platinum doublet, the II generation TKI, afatinib was found to be superior to erlotinib in terms of OS (7.9 vs. 6.8 months HR = 0.81, 95% CI: 0.69–0.95, $P = 0.0077$).[95]

In phase III (Check Mate 017) trial, nivolumab (3 mg/kg every 2 weeks) was shown to be superior to docetaxel in reducing the risk of death by 41% in patients previously treated for SCC. The median OS was 9.2 months (95% CI: 7.3–13.3) with nivolumab versus 6.0 months (95% CI: 5.1–7.3) with docetaxel. At 1 year, the OS rate was 42% (95% CI: 34–50) with nivolumab versus 24% (95% CI: 17–31) with docetaxel. The benefit of nivolumab was irrespective of PD L1 expression.[96] An updated follow-up reported an 18-month OS of 28% and 13% in the nivolumab and docetaxel arms.[97] In phase II/III KEYNOTE-010 trial, 1034 patients with previously treated NSCLC with PD-L1 expression on at least 1% of tumor cells were to randomized to receive pembrolizumab 2 mg/kg, pembrolizumab 10 mg/kg, or docetaxel 75 mg/m (2) every 3 weeks. Among patients with at least 50% of tumor cells expressing PD-L1, OS was significantly longer with pembrolizumab 2 mg/kg than with docetaxel (median 14.9 months vs 8.2 months; HR = 0.54, 95% CI: 0.38–0.77; $P = 0.0002$) and with pembrolizumab 10 mg/kg than with docetaxel (17.3 months vs. 8.2 months; 0.50, 0.36–0.70; $P < 0.0001$).[4]

In a phase III open-label, phase 3 trial (OAK), patients with advanced NSCLC who had already been treated with one or more platinum-based combination therapies, atezolizumab prolonged the OS compared with docetaxel in patients with squamous histology. The median OS in this population was 8.9 versus 7.1 months (HR = 0.73, 95% CI: 0.54–0.98).[1]

Consensus

- Patients with good PS should be offered second-line therapy
- Atezolizumab, nivolumab, or pembrolizumab are preferred agents for the treatment of NSCLC of squamous histology after progression on first line chemotherapy
    - For patients who are PD L1 negative/unknown, atezolizumab or nivolumab may be considered. For those with PD-L1 >1%, atezolizumab, nivolumab, or pembrolizumab may be considered
- PD L1 testing is not required for atezolizumab and nivolumab. For pembrolizumab PD-L1 testing is required. PD L1 testing should be done on the approved diagnostic kit
- Single-agent chemotherapy and TKIs are also acceptable options. Afatinib may be preferred over erlotinib based on superior OS data.

What should be the treatment of choice for nonsmall cell lung cancer patients with brain metastases?

Literature review

Conventional treatment of symptomatic brain metastatic has been whole brain radiotherapy along with supportive care including steroids. In routine clinical practice, the prognostic indices like RPA and GPA help to differentiate the patients groups in various survival cohorts. Patients with higher RPA class (Class III) has poor survival than in Class I patients. Their indices are based on performance score, age, number of brain metastasis, and presence of other extracranial disease. Whole brain radiotherapy traditionally is believed to improve quality of life, disease-free survival and OS. Contrary to popular practice recent trial of the whole-brain radiotherapy with steroids versus steroids alone did not demonstrate an improved survival benefit.[98] Apart from this, whole-brain radiotherapy demonstrated a short-term cognitive decline in comparisons to patients who were treated with focal treatment. However, these trial had a small number of patients and very small volume disease and <4 metastases.[99] These approaches require intensive imaging surveillance and fraught with an increased number of progression in brain other than the area treated in the brain.

In patients with solitary brain metastases where surgical resection is feasible surgery is advisable and if surgery is not feasible because the tumor is in the eloquent area, focal treatment alone or with WBRT has been recommended.[100,101] However, the addition of WBRT to focal treatment did not yield improved OS benefit.[102] To decrease local recurrences at resection cavities depending volume of the cavity and residual disease high dose focal radiotherapy has shown to decrease local recurrences at resection cavities.[103]

In patients with a druggable oncogene driver (EGFR, ALK), 45%–60% develop brain metastases in the course of their disease.[104] In such patients, treatment with targeted therapy has shown to improve the outcomes.[105-110] In a prespecified subgroup analyses of EGFR mutation-positive patients with brain metastases enrolled in two phase III studies, the magnitude of PFS improvement with afatinib was similar to that observed in patients without brain metastases.[107] The median PFS in patients with brain metastases treated with afatinib was 8.2 months versus 5.2 months with chemotherapy (HR = 0.50; $P = 0.0297$). Crizotinib has been shown to control intracranial disease in patients with ALK-rearranged NSCLC. The intracranial DCR was 56% and 62% in patients with previously untreated asymptomatic brain metastases and previously treated brain metastases, respectively.[108] In a retrospective review of 94 ALK-rearranged NSCLC patients with brain metastases in a phase, I expansion study of ceritinib, intracranial DCR was reported in 65.3% of crizotinib-pretreated patients and in 78.9% of ALK inhibitor-naive patients.[109]

Consensus

- Treatment of patients with brain metastases depends on age and Karnofsky Index
- RPA class I and II patients with >3 mets may be treated with WBRT
- Stereotactic radiosurgery (SRS) may be a reasonable option in carefully selected patients with limited disease
- In RPA class III patients, BSC is recommended (Agree – 35.29%, Disagree – 41.18%, Neutral – 25.53%)
- Patients with single brain metastases may be treated with either surgical resection or SRS/stereotactic radiotherapy (SRT)
    - Single large symptomatic metastases should be treated with surgery

  - SRS/SRT is a reasonable alternative to surgery for small (<3 cm) and inaccessible tumors.
- Patients of RPA class I and II with 1–3 small brain metastases (<3 cm) should be treated with SRS/SRT alone rather than SRS + WBRT (Agree – 76.47%, Disagree – 23.53%, Not Sure – 0%)
- WBRT is a reasonable option in patients who are not candidates of surgery or whose lesions are too large for radiosurgery (Agree – 94.44%, Disagree – 5.56%, Not sure – 0%)
- Patients treated with surgical resection or SRS should have follow-up magnetic reasoning imaging (MRI) every 3 months (Agree– 88.89%, Disagree – 11.11%, Not sure – 0%)
- Dexamethasone is recommended for patients with symptomatic brain metastases (Agree – 100%, Disagree – 0%, Not sure – 0%)
- In patients with druggable oncogenic driver mutation/rearrangement and asymptomatic brain metastases, TKIs may control the brain disease and defer WBRT (Agree– 58.82%, Disagree – 41.18%, Not sure – 0%)
- For patients with symptomatic metastases, radiotherapy should be preferred (Agree – 100%, Disagree – 0%, Not sure – 0%)
- ALK-positive patients with brain metastases who progress on crizotinib may benefit from alectinib or ceritinib (Agree – 94.12%, Disagree – 0%, Not sure– 5.88%)
- Patients should have follow-up MRI/CT/imaging done every 3 months.

What are the recommendations for the treatment of nonsmall cell lung cancer with the oligometastatic disease?

Oligometastatic disease in NSCLC refers to 1-5 disease sites separate from the primary.[111] Patients with oligometastatic NSCLC do not always progress to widespread metastases.[112] Appropriately selected patients can be treated with metastasis-directed surgical or ablative procedures. Identification of such patients is of utmost importance. Factors associated with improved OS in oligometastatic disease include metachronous metastases, better PS, limited nodal disease, the presence of EGFR mutation, metastases limited to one organ.[113-115] Surgical resection or definitive radiotherapy of intracranial and extracranial oligometastatic disease has been shown to have a positive effect on survival rates.[116-122]

In patients who have more than one pulmonary site of cancer, sometimes it can be difficult to distinguish between a second primary and metastasis. International Association for the Study of Lung Cancer Staging and Prognostic Factors Committee conducted a systematic review to develop clinical and pathologic criteria to identify two foci as separate primary lung cancers versus a metastasis. IASLC recommended a careful review by a multidisciplinary tumour board, and the pursuit of radical therapy, such as that for a synchronous secondary primary tumour, when possible.[123] SRS and surgery have been shown to result in long-term survivors in such patients.[122,124,125] Use of targeted agents combined with ablative doses of radiation in the oligometastatic setting has resulted in promising outcomes.[121,126]

Consensus

- Stage IV NSCLC patients with synchronous or metachronous oligometastasis may benefit from surgery and/or radiation therapy. Metachronous oligometastases has a better prognosis than synchronous
- Every attempt must be made to biopsy the second primary tumor in the lung and may be treated with radical intent if possible
- For patients with oligometastatic recurrence or progression while on targeted therapy, SBRT may be offered to the progressing sites (Agree – 42.86%, Disagree – 57.14%, Not sure – 0%).

What are the Investigations Recommended at the Time of Disease Progression?

Patient of non-squamous histology has not been tested in the first line and treated with chemotherapy doublet

Literature review

Literature suggests that the incidence of EGFR mutations in Indian population varies from 25% to 30% and that of ALK rearrangement varies from 2.5% to 9%.[23,25,127-129] Activating *BRAF* mutations have been observed in 2%–4% of NSCLC.[130] Data from the clinical trials of EGFR TKIs suggest that there is OS benefit even if the patients with EGFR mutations are treated with EGFR TKIs after progression on chemotherapy.[29-35,40,131] Same is true for patients with ALK or ROS1 rearrangements treated with TKIs.[59,64] In a phase II study of 57 patients with previously treated, advanced NSCLC with the BRAF V600E mutation, the combination of dabrafenib plus trametinib was associated with an ORR of 63% and the disease control rate of 79%.[132] The median PFS was 9.7 months in these patients.

PD-1 inhibitor nivolumab and PD-L1 inhibitor atezolizumab significantly prolonged OS in NSCLC patients of non-squamous histology, who progressed on first-line chemotherapy in CheckMate 057 and OAK trials, respectively.[1,2] Longer PFS and higher objective response rates were seen with both these drugs at higher levels of PD L1 expression. Pembrolizumab has also shown promising efficacy patients with ≥50% PD-L1 who progressed after first-line chemotherapy in two different clinical trials.[3,4]

Consensus

- All attempts must be made to get tissue specimen in the form of biopsy or cell block (if a biopsy is not possible)
- All NSCLC patients of non-squamous histology who progress on chemotherapy should be tested for EGFR, ALK, ROS1 and BRAF status if not tested previously
- Biopsy or cell block (if biopsy specimen is not available) should be used for testing for EGFR, ALK, ROS1 and BRAF testing
- ctDNA may be acceptable in cases where mutation status cannot be established either by biopsy or cell block
- PD L1 testing on biopsy specimen should be done after progression on first-line chemotherapy if the patient is planned to be treated with pembrolizumab
- PD L1 testing is not required for atezolizumab or nivolumab
- PD L1 testing should be done on the approved diagnostic kit.

Patient is epidermal growth factor receptor mutation positive and treated with epidermal growth factor receptor tyrosine kinase inhibitor in the first line

Almost all EGFR mutated patients who are treated with an EGFR TKI subsequently develop disease progression. T790M mutation in EGFR has been associated with acquired resistance to EGFR TKIs in up to 60% of the cases. Amplification of the MET oncogene has been been associated with resistance to EGFR TKIs in 5%–10% of cases. In addition, analyses of tumor tissue have observed the histologic transformation of EGFR mutation-positive NSCLC into small cell lung cancer in approximately 5% of cases. Some patients may develop resistance by human epidermal growth factor receptor 2 (Her 2) mutation/amplification.[86] Osimertinib has shown activity in patients with acquired resistance to a prior EGFR inhibitor. In a phase I/II study, osimertinib showed a response rate of 61% in patients with T790M mutation and median PFS of 10 months.[87] Afatinib, trastuzumab, and TD-M1 have shown to be effective in patients with mutations in the kinase domain of Her2/neu.[133-135] In patients with MET amplification, crizotinib has been found to be effective.[136,137]

Consensus

- In patients who have progressed on first line EGFR TKI, testing for exon 20 T790M mutation on either re-biopsy or cell block of fine needle aspiration cytology (FNAC) specimen or ctDNA should be considered
- An effort should be made to re-analyze the histology of the tumor on the re-biopsy specimen for ruling out transition into small cell lung cancer
- If feasible following additional analysis should be done on rebiopsy or cell block of FNAC specimen
  - Her 2 mutation/amplification
  - MET amplification.

What investigations should be performed in patients of squamous cell histology progressing on chemotherapy doublet?

In India, the data from Tata Memorial Hospital suggests that ~ 6% of patients of squamous histology may harbor EGFR mutations.[127] Data suggest that patients with EGFR mutations benefit from EGFR directed therapies. In phase III (Check Mate 017) trial, nivolumab (3 mg/kg every 2 weeks) was shown to be superior to docetaxel in reducing the risk of death irrespective of PD L1 expression.[96] In phase II/III KEYNOTE-010 trial, 1034 patients with previously treated NSCLC with PD-L1 expression on at least 1% of tumor cells were to randomized to receive pembrolizumab 2 mg/kg, pembrolizumab 10 mg/kg, or docetaxel 75 mg/m^2 every 3 weeks. Among patients with at least 50% of tumor cells expressing PD-L1, OS was significantly longer with pembrolizumab 2 mg/kg than with docetaxel (median 14.9 months vs. 8.2 months; HR = 0.54, 95% CI: 0.38–0.77; P = 0.0002) and with pembrolizumab 10 mg/kg than with docetaxel (17.3 months vs. 8.2 months; 0.50, 0.36–0.70; P < 0.0001).[4]

Consensus

- EGFR testing may be done routinely in patients with squamous cell histology in the first line or on rebiopsy sample once patients progress on chemotherapy doublet
- PD L1 testing should be done for second-line SqCC before prescribing pembrolizumab
- PD L1 testing is not required for nivolumab
- PD L1 testing should be done on the approved diagnostic kit.

All the consensus statements have been summarised in Table 1

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