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REVIEW ARTICLE

First-line management of metastatic non-small cell lung cancer: An Indian perspective

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Abstract

Lung cancer has been the most common cancer in the world for several decades. The non-small cell lung cancer (NSCLC) constitutes approximately about 80% of the total cases of lung cancer. Therapeutic interventions in NSCLC have shifted to the target-based approach from histology-based approach, and this has completely changed the face of the management of NSCLC. Developing countries, such as India, have very limited data compiled about the prevalence and treatment practices of lung cancer, despite a large burden of the disease. However, in recent times, there has been a lot of data generated in this regard. This article is an attempt to collate and shine light on the available data for the first-line treatment of NSCLC in India keeping in mind the current standards of care in this area.

Key words: Advanced non-small cell lung cancer, anaplastic lymphoma kinase, chemotherapy, epidermal growth factor receptor, tyrosine kinase inhibitor

Introduction

Lung cancer has been the most common cancer in the world for several decades of which histologically non-small cell lung cancer (NSCLC) constitutes approximately about 80% of the total cases.[1-3] Therapeutic interventions in NSCLC have changed drastically from chemotherapy to target-based approach following the detection of driver mutations and now including immunotherapy, rendering the treatments more complex, yet personalized than ever before.[4,5] Data available in India are very limited; here, we tried to compile the data available for the first-line treatment of advanced NSCLC in Indian patients.

First-Line Chemotherapy in Locally Advanced and Metastatic Non-small Cell Lung Cancer

Over the past three decades, a significant improvement in outcomes with advanced metastatic NSCLC has been demonstrated starting with doubling in survival with chemotherapy compared to only best supportive care.[6] This was followed by improvement in response rates with third-generation agents including paclitaxel, docetaxel, vinorelbine, gemcitabine compared to the second-generation ifosfamide, mitomycin, and vindesine along with standard platinum chemotherapy given in doublet.[7,8] With Indian patients, Shajeem *et al*. first demonstrated survival benefit with doubling of overall survival (OS) with combination platinum doublet compared to the best supportive care in metastatic NSCLC.[9] Data using the second-generation combination chemotherapy, ifosfamide, mitomycin, and cisplatin, Behera *et al*. demonstrated response rates of 45% but with median survival of 7 months.[10] A subsequent retrospective study comparing the second-generation cisplatin-etoposide with third-generation taxane, gemcitabine combination with platinum led to 3 months improvement in survival in paclitaxel-carboplatin cohort.[11] Similar to the above, another series using the second-generation chemotherapy in the majority of patients yielded median survival of 7 months.[12]

Compared to above older series, modern series of studies with third-generation combination platinum doublet yield superior response rates in the range of 30%–50% with average improvement in median survival by 3 months, i.e., from 7 to 10 months.[13-17] This improvement apart from the better selection of chemotherapeutic agents could also be because of stage migration due to the improved sensitivity of diagnosing metastatic disease using computerized tomography and positron-emission tomography compared to older generation chest X-ray and ultrasonographic techniques as part of adoption in routine clinical practice.

In landmark Phase III randomized multicentric international trial testing noninferiority of pemetrexed platinum compared to gemcitabine platinum, in which three major tertiary cancer centers of India were participants, demonstrated better survival benefit of pemetrexed-based combination in adenocarcinoma and large cell histology, while gemcitabine combination favored squamous histology in preplanned subset analysis.[18] This conclusion was adopted fairly across the majority of oncology centers worldwide with Indian studies using pemetrexed-platinum combination showing progression-free survival (PFS) ranging 4–7 months and OS extending to 10 months in epidermal growth factor receptor (EGFR) unmutated cohort of patients in retrospective studies.[19,20]

In Phase III randomized trial of East Asians, light/never smokers, unselected for EGFR mutation, and pemetrexed platinum followed by gefitinib maintenance was compared against upfront gefitinib use. This trial failed to show any difference in OS in any of the above groups. However, unplanned post hoc subset analysis favored upfront gefitinib in EGFR mutation NSCLC, while pemetrexed combination showed better survival in unmutated NSCLC [Table 1].[21-23]

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Maintenance Chemotherapy in Locally Advanced and Metastatic Non-small Cell Lung Cancer

The concept of continued treatment after the best response to achieve durable disease control was demonstrated in the PARAMOUNT trial. In this phase III placebo-controlled randomized, multicentric trial, having Indian patients as well from one major tertiary center showed not only progression-free but also OS benefit with 22% reduction in mortality with maintenance pemetrexed.[24,25] This benefit was seen across all subgroups with performance status (PS) 0 and 1, deriving maximum survival benefit.[26] Even, among the elderly population, the maintenance pemetrexed retained its survival benefit with acceptable toxicities.[27]

One of the major Indian studies exploring maintenance pemetrexed in patients achieving partial response (PR) or stable disease (SD) with induction pemetrexed-platinum doublet, Pandey *et al*. showed progression-free and OS of 8 and 20 months, respectively. Moreover, the patients with baseline pleural effusion had better PFS (9 vs. 7 months, $P = 0.02$) and OS (26 vs. 18 months, $P = 0.05$). The patients receiving more than six cycles of maintenance had improved PFS (12 vs. 7 months, $P = 0.002$) and OS (26 vs. 16 months, $P = 0.05$).[28] This benefit in OS with maintenance pemetrexed was similar compared to switch maintenance with tyrosine kinase inhibitors (TKIs) among patients having response to induction pemetrexed platin doublet and EGFR mutation positive.[29]

Another study by Pankaj *et al*., the maintenance pemetrexed was used in 60 patients who achieved PR/SD on induction pemetrexed doublet. The mean number of maintenance cycles was 8.3 (range 2–28). About 13 (21.6%) patients took >10 maintenance cycles. Pemetrexed maintenance therapy resulted in PFS of 5.4 months.[30] One of the two other smaller retrospective studies with 36 patients incorporating maintenance chemotherapy showed survival benefit over 6 months compared to no maintenance therapy.[20,31] The benefit may have been overestimated due to case selection bias of maintenance therapy in better PS and fewer number of patients in the above retrospective case audits [Table 2].

In summary, pemetrexed-based platinum treatment remained the first-line treatment in majority of the studies in the recent times with acceptable outcomes both in the frontline as well as maintenance treatment.

First-Line Treatment with Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors

EGFR mutation is often seen in patients diagnosed with NSCLC.[33] The discovery of EGFR mutation and other receptor tyrosine kinases and the directed therapies have completely changed the treatment landscape of NSCLC management. Molecular genotyping routinely involves testing for EGFR mutation studies, and other translocation studies since the outcomes are better with targeted therapies than the conventional therapies.[34,35] In the study presented by Mehta, EGFR mutation frequency was found to be higher in the Indian population (32%) as compared to Caucasian population; however, it was lower than that reported in the East-Asian population.[36]

Table 1: First-Line Chemotherapy in Locally Advanced and Metastatic Non-small Cell Lung Cancer

Author	Study details	Type	Response rate	Median PFS (months)	Median OS (months)
Shajeem O *et al*.[9]	Chemotherapy combination (38) vs.	Retrospective			5.8
	Best supportive care (40)				2.5
Behera *et al*.[10]	Ifosfamide, Cisplatin and Mitomycin	Retrospective	45%	-	5
Natukula *et al*.[11]	Gemcitabine+carboplatin (36)	Retrospective	-	-	7.5
	Carboplatin+Paclitaxel (27)				10.1
	Cisplatin+Etoposide (9)				7.1
Rajappa *et al*.[12]	Cisplatin doublet	Retrospective	35%	6	7
Pathak A. *et al*.[13]	Carboplatin+Paclitaxel (72)	Phase II randomized	ORR 33%	-	9
	Carboplatin+Paclitaxel+vitamin A, C, E (64)		ORR 37%	-	11
Bala *et al*.[14]	Platinum doublet (256)	Retrospective	52.3%	8	12
Hingmire *et al*.[15]	Platinum doublet (63)	Retrospective	38%	-	17
Doval *et al*.[16]	Platinum doublet (199/322)	Retrospective	45.7%	5	Not reached, 55% at 36 months
Babu G *et al*.[17]	Nimotuzumab+Docetaxel carboplatin (53)	Randomised Phase II trial	54%	4.9	10.1
	Docetaxel carboplatin (57)		34.5% (P=0.04)	4.8	10.4
Scagliotti *et al*.[18]	Cisplatin+Gemcitabine vs.	Phase III randomized	ORR 28.6%	4.8	10.3
	Cisplatin+Pemetrexed		ORR 30.2%	5.1	10.3
Louis *et al*.[19]	Gefitinib (47)	Retrospective	23%	10	10
	Platinum doublet (73)		6.8%	4	10
Paliwal *et al*.[20]	Pemetrexed platin (121/194)	Prospective non randomized	28.3%	7.4	11
Yang MD *et al*.[21,22]	Pemetrexed Cisplatin- gefitinib (118) vs.	Phase III randomized	23.7	8.38	26.9
	Gefitinib (118)		40.7	9.63	27.9
Murali AN *et al*.[31]	Platinum doublet (169)	Retrospective	-	5.7	6.5
	TKIs (179)			11.4	14.1
Mohan *et al*.[32]	Paclitaxel carboplatin (35)	Prospective, non randomized	35%	-	-

The data available with regard to EGFR mutation NSCLC patients and the management is very limited in the Indian context especially in the first-line management.

Parikh *et al*.[37] analyzed 77 Indian patients enrolled in the ISEL study. Specifically, in Indian patients, the median survival and objective response rates were better with TKI gefitinib as compared to placebo (6.4 vs. 5.1 months; 14 vs. 0%).

A study presented by Louis *et al*. without EGFR mutation testing showed modest benefit with first-generation TKI gefitinib with PFS and OS of 5 and 7.5 months, respectively. The PFS was better in females, nonsmokers, and those who received upfront gefitinib than those who did not receive the same.[38]

A study presented by Bhatt et al. was a retrospective analysis of 106 patients. In those patients where EGFR mutation was positive, the patients were treated with either upfront TKI n = 15 (14.15%) or if on chemotherapy arm finished six cycles and then given switch maintenance TKIs, n = 26 (24.52%). The median PFS for the patients with and without mutations was found to be 11 and 9 months, respectively. A median PFS of 14 months was demonstrated in patients with the mutation-positive group that received both chemotherapy followed by switch maintenance with TKIs versus 8 months in the group that received only TKI.[39]

Another retrospective analysis by Noronha *et al*. looked into the patients who were treated with EGFR TKI. The overall response rate was 30% in the entire study population, and in the patients with EGFR-activating mutations, the response rate was 74% whereas it was only 5% in EGFR wild-type cases. The PFS was 10 months in EGFR mutation-positive cases and 2 months without EGFR mutation. The OS was 19 versus 13 months in patients with or without EGFR mutations, respectively.[40]

More recent publication in a nontrial scenario, 225 patients with EGFR-activating mutation were treated with TKI. In the patients with good PS (0–2), the median OS was 18.17 months. In poor PS population (3–4), the OS was documented at 12.1 months. This study confirmed inferior outcomes in the patients with poor PS. Furthermore, in those patients who were ineligible for the trial, the outcomes were similar to many clinical trials reported earlier in this space.[41]

In the unpublished data presented in a review article by Malik *et al*., 50 patients who received upfront TKIs were analyzed. Median PFS and OS were 7.5 and 12.7 months, respectively. Interestingly, only seven patients underwent EGFR studies, and three cases were positive for EGFR-activating mutation.[42]

Joshi *et al*. looked into the outcomes of EGFR-mutant patients treated with gefitinib with respect to exon 19 and exon 21 analyses. The median PFS for exon 19 versus exon 21 status was 9.3 and 7.8 months. The median OS was 19.8 and 16.5 months, respectively, for exon 19 and 21 patients, respectively. Although numerically better outcomes were seen in exon 19 patients, there was no real difference between the two groups.[43]

Recently, Patil *et al*. presented the open-label randomized Phase III trial in the space of EGFR mutation patients in Indian patients. With 145 patients in each arm, the patients with activating EGFR mutation status were randomized to receive pemetrexed and carboplatin doublet followed by pemetrexed maintenance versus gefitinib. The median PFS was 5.6 months in chemotherapy arm and 8.4 months in gefitinib arm. There was no OS difference in the two arms. Grades 3–4 hematological toxicity was higher in chemotherapy arm whereas Grades 3–4 rash and diarrhea was reported higher in gefitinib arm.[23] This trial has pemetrexed platinum induction with maintenance pemetrexed in control arm which is the accepted gold standard, which none of the previous trial had explored in comparison to TKIs. Notably, OS in control chemotherapy arm was longer compared to gefitinib arm (26 vs. 18 months), though not significant.

Impact of exon 19 and exon 21 EGFR-activating mutations with first-line pemetrexed carboplatin was assessed by Noronha *et al*., and interestingly, found no differential impact. The patients with exon 19 population had better response outcome with gefitinib.[44]

Exon 20-mutated NSCLC is an uncommon variant.[45] Even though the numbers were limited, the study by Noronha *et al*. had exon 20 positive patients treated with pemetrexed platinum, paclitaxel platinum, or TKI. One patient did not receive any treatment. The OS for the exon 20-mutated patients was 5 months as compared to 16.1 months in other EGFR-activating mutations confirming the dismal outcome in this population.[46]

Indian consensus statement for advanced NSCLC treatment has recommend for (Del 19 and L858R mutation) patients in the first-line setting as that patients with EGFR mutations should be treated with an EGFR TKI (afatinib, gefitinib, and erlotinib) 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.[47]

Advanced Anaplastic Lymphoma Kinase-Positive Treatment in the First-Line Non-small Cell Lung Cancer

Standard practice in the treatment of metastatic NSCLC, is treatment based on anaplastic lymphoma kinase (ALK) TKI considered standard of care for ALK-positive patients proven by standard FISH (Fluorescence in situ hybridization) technique or ROS1 positive patients in advanced NSCLC.[35,48,49]

The preferred first-line agent now is alectinib as it has demonstrated superior PFS in head-to-head comparison with crizotinib.[50] In places where access to alectinib is limited options include crizotinib and ceritinib. An overview of the pivotal trials leading to the approval of these three drugs is given in Table 3.[35,50,51]

Indian Studies

A retrospective study by Dubey *et al*. done between September 2014 and 2016 to evaluate the epidemiological, clinicopathological profile, disease characteristics, and response to crizotinib in advanced echinoderm microtubule-associated protein-like 4-ALK-positive NSCLC patients.[52] The patients were started on either palliative chemotherapy or crizotinib. In this study, 20 patients were ALK positive. The median age was 43.9 years with an equal male-to-female ratio. About 80% of patients were nonsmokers. Adenocarcinoma and poorly differentiated carcinoma constituted 70% and 30% of cases,

Table 2: Maintenance chemotherapy in advanced

Author	Study details	Type	Response rate	Median PFS (months)	Median OS (months)
Paliwal *et al*.[20]	Maintenance Pemetrexed (36/99) Versus No maintenance (63/99)	Retrospective	-	8.5 6.5 (*P*=0.1613)	18.5 12.5 (*P*=0.0219)
Paz-Ares L *et al*.[24,25]	Maintenance Pemetrexed (359) Vs. Placebo (180)	Phase III randomized trial	3% 0.6%	4.1 2.8 (*P*=0.001)	13.9 11 (*P*=0.01)
Pandey A *et al*.[28]	Maintenace Pemetrexed (188)	Retrospective	-	8	20
Pankaj G *et al*.[30]	Maintenance Pemetrexed (60)	Retrospective	-	5.4	NR
Murali *et al*.[31]	Maintenance Pemetrexed (26)	Retrospective	-	9.6	24.6

Table 3: Pivotal anaplastic lymphoma kinase inhibitor studies

Drug	Trial	Comparison arm	No of patients	RR	PFS
Crizotinib	Profile-1014[35]	Pemetrexed/platinum combination	343	74% vs 45%	10.9 vs 7 motnhs
Alectinib	Alex[50]	Crizotinib	303		25.7 months vs. 10.4 months
Ceritinib	Ascend-4[51]	Pemetrexed/platinum combination	376	72.5% vs 26.7%	16.6 vs 8.1 months

respectively. Crizotinib was used in 18 of 20 patients. In ten patients, it was used as the first line, while in the rest it was used after cytotoxic chemotherapy. Eight out of ten patients receiving chemotherapy subsequently received crizotinib. PR in those on crizotinib was 89%. The median PFS for upfront and later line crizotinib was 9.2 and 8 months, respectively. Those, who were young and with good PS, had a better outcome with a superior PFS. Those with brain metastases also had a superior PFS than those without (10.5 vs. 6.5 months). The drug was reasonably well tolerated with Grades 3/4 gastrointestinal toxicity seen in one patient and symptomatic bradycardia in one patient.

In another study by Noronha *et al*., clinical profile and practice of treatment in ALK-positive NSCLC were analyzed in a retrospective analysis carried out at the Tata Memorial Hospital, Mumbai.[53] This study also looked at the limitations in using crizotinib in a real-world setting.

The median age in this study was 51 years, with a higher preponderance of males (56.4%). Close to 75% of patients had two or metastatic sites with three or more sites seen in 38% of cases which indicate the heavy tumor burden among this patient cohort. Brain metastases were observed in 22.3% of patients in this study.

Only 22.3% of ALK-positive patients received crizotinib upfront in this study. Reasons for not using crizotinib upfront included symptomatic patients needing chemotherapy (23.3%), ALK not being tested upfront (23.3%), and financial constraints (21.9%). However, 73.9% of patients received crizotinib at some point of their treatment course. In this study, 55% of patients received the drug through nongovernmental organization support, while 44.8% paid for the drug through credit or self-payment.

PR was seen in 37 patients (53.6%), while SD was observed in 13 patients (18.8%). The overall disease control rate (DCR = complete response [CR] + PR + SD) was 72.4%. The patients with an Eastern Cooperative Oncology Group (ECOG) PS 0–2 had a significantly better PFS than ECOG PS >2 (10 vs. 1.5 months, $P < 0.001$). Furthermore, exposure to crizotinib versus no exposure to crizotinib predicted for significantly longer PFS (10 vs. 2 months, $P = 0.028$). The median OS was not reached for the entire cohort, with estimated 1-year survival being 81.2% in this study. An ECOG PS 0–2 versus ECOG PS >2 (median OS not reached vs. 2.967 months, $P < 0.001$) and exposure to crizotinib versus nonexposure to crizotinib (median OS 39.86 vs. 11.2, $P < 0.001$) predicted for significantly longer OS.

Ceritinib use in Indian patients has been reported by Joshi *et al*.[54] This study included 13 patients for analysis. All had prior crizotinib exposure. The median age was 47 years (range 28–62 years), with a male:female ratio of 5 (39.2%):8 (60.8%). Almost half of the patients had an ECOG PS of ≥2. Furthermore, 50% of the patients had brain metastases. The patients were heavily pretreated with ceritinib given as the second-line therapy in 6 (46%) patients, third line in 5 (38%) patients, and as the fourth line in 2 (16%) patients.

Postceritinib two patients received pemetrexed platinum and two received taxanes. Both the patients who received pemetrexed-based regimen had SD as their best response. Among those who received taxanes, one had progressive disease, and the other had SD as their best response.

Median PFS and OS were not reached in this study. However, the mean PFS and OS of the entire population were 10.9 and 14.9 months, respectively. One-year PFS and OS were 56% and 78%, respectively. None of the patients, in this study, had disease progression in the brain even though approximately 50% of them had brain metastases. This highlights that the drug is active in the central nervous system. About 30% of the patients required dose interruptions with the median duration of cessation being 1 week. Twenty-two percent of them were started at reduced doses which they tolerated well.

Another study by Noronha *et al*. reported crizotinib use in advanced ROS-1 patients.[48] Eleven patients were evaluable in this study. Out of the 11 patients, five were exposed to crizotinib. The response rates for crizotinib-treated patients were 80%. With a median follow-up of 9 months, the median PFS and OS were 5.4 months and 8.5 months, respectively, for the entire population. Analyzing the outcomes separately, the median PFS and OS were not reached for those who received crizotinib compared to median PFS of 2.5 months and median OS of 4.2 months in those who were not exposed to crizotinib. The difference was statistically significant. Estimated 1-year OS was 80% for those who received crizotinib compared to 18% for who did not receive crizotinib.

Murthy *et al*. conducted a retrospective observational study on 341 Indian patients with lung adenocarcinoma to determine the clinical features and outcomes of *ALK*-positive patients.[55] Thirty-seven patients were *ALK*-positive by fluorescence *in situ* hybridization, of which 27 received crizotinib therapy. Of the 31 *ALK*-positive patients treated with crizotinib, ceritinib (n = 1), or chemotherapy (n = 3), the best response was one CR, 23 (74.2%) PR, and 5 (16.1%) SD. At the median follow-up of 12.5 months, the median PFS was not reached. In addition, a patient with ALK positivity detected by immunohistochemistry and presenting brain metastases received crizotinib after whole brain radiotherapy, reaching a PR.

Batra *et al*. conducted a study on the use of crizotinib in 25 Indian *ALK*-positive Stage IV lung adenocarcinoma patients.[56] The best response to crizotinib included one CR and 20 PR. The median PFS and OS were 11.8 (95% confidence interval [CI] 5.3–17.3) and 20.6 months (95% CI 12.8–34.1), respectively. The most commonly reported adverse events included vomiting (28%), anemia (28%), and cough (20%).

Bamania *et al*. described the use of crizotinib in a case series of 21 Indian *ALK*-positive NSCLC patients.[57] Most (87.5%) patients had a Stage IV disease and presented brain or bone metastases (44%, each). First-line crizotinib was given to three patients, and 12 patients received it in a second-line setting. The mean PFS was 6.96 and 8.9 months in patients treated with crizotinib in a first and second line, respectively. The respective mean OS was 13.6 and 8.3 months.

Bal *et al*. retrospectively analyzed a cohort of 240 lung adenocarcinoma patients from the North of India to determine the prevalence of *ALK*-rearrangement in this population.[58] Of the 17 *ALK*-positive patients, five were started on crizotinib, four of which were after one line of chemotherapy, and for one patient as the third-line therapy. PR and SD were reached by 60% and 40% of the patients under crizotinib therapy, respectively.

The Indian consensus statement for the treatment of advanced NSCLC: first line, maintenance, and second line published in January–March 2017 recommend the use of crizotinib as the first line in ALK/ROS-1-positive patients. Results of J-ALEX and ASCEND-4 were not available at the time of publication.[50,51]

Discussion

Lung cancer continues to pose challenges regarding the outcomes. It remains common cancer for urban India and remains the leading cause of mortality.[1,59] The treatment of advanced NSCLC indeed is a complex one especially in the era of newer chemotherapy, targeted therapy, and immunotherapy. It is prudent to individualize treatment for the patients considering the fact that NSCLC is no more a single disease entity. It is also useful to know the NSCLC treatment patterns in the country, such as India, which has vastly different patient population than the Western world.

In this review, we have compiled the relevant recent studies on the first-line NSCLC. In patients without an identifiable target, platinum-doublet chemotherapy is preferred treatment with third-generation agents and remains the first choice among locally advanced metastatic nonmutated NSCLC. Pemetrexed-platinum combination scores over other agents in adenocarcinoma histology. Maintenance pemetrexed in patients responding to induction doublet chemotherapy extends survival, and hence, recommended in suitable cohort. Second-line chemotherapy docetaxel produces modest but meaningful improvement in progression-free and OS. In treatment refractory, platinum ineligible patients, weekly metronomic paclitaxel may be attempted.

In EGFR-mutated patients, most of the studies published until date had first-generation EGFR TKI as the first-line therapy. In majority of the retrospective analyses as well as the randomized trial in these patients in the Indian context, the PFS was in the range of 8 months, which is similar to the published literature for first-generation EGFR TKIs.

The data on ALK inhibitors in the first line advanced NSCLC were found to be even more limited considering this to be newer treatment modality and the recent availability of ALK TKIs. With limited data, the PFS outcomes stood similar at approximate 10–11 months' duration, which was similar to the pivotal first-line study for crizotinib. The tolerance to crizotinib was excellent in Indian patients.

We could not identify or substantiate any relevant data with regard to immunotherapy in the first-line advanced NSCLC setting.

Conclusion

Advanced NSCLC management has evolved at breathtaking speed in the last decade and half. As of now, in India, majority of treatments are available and are administered as per the standard guidelines, and the outcomes are more or less comparable to the global studies published in the first-line space. The information on immunotherapy in the first line is still at a nascent stage but is expected to evolve in the near future. With higher burden of EGFR-activated tumors and substantial number of ALK patients, all patients should undergo baseline molecular studies to identify the targets as to streamline the treatment for the patients to maximize the outcomes in advanced NSCLC.

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Conflicts of interest

There are no conflicts of interest.

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