Individualizing the treatment of advanced NSCLC

Chaired by Carlos Gil Ferreira

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Dear Colleagues,

Thank you for attending the satellite symposium entitled ‘Individualizing the treatment of advanced NSCLC’ at the IASLC 7th Latin American Conference on Lung Cancer (LALCA 2016).

Panama City provided a cosmopolitan and culturally vibrant host city for this conference that brought together a unique community of medical professionals from across the Latin–American region. The aim of the symposium was to facilitate the management of squamous and nonsquamous NSCLC, and the implementation of new discoveries in clinical practice. It also addressed the challenges facing clinicians in the Latin–American region in an increasingly complex treatment landscape.

During this session, the expert Faculty guided us through this complexity by placing the latest developments in advanced NSCLC into the context of treatment. They provided their insights into how we can use our biological knowledge not only to improve treatment pathways, but also to maximize treatment outcomes by understanding different approaches.

We hope that you found this symposium educational and that it has furthered your understanding of this evolving field.

Yours faithfully,

Carlos Gil Ferreira

Carlos Gil Ferreira
Chair
Faculty biographies

Carlos Gil Ferreira
(Symposium Chair)
D’Or Institute of Research and Education, Rio de Janeiro, Brazil

Carlos Gil Ferreira MD, PhD was trained as a medical oncologist at the Brazilian National Cancer Institute (INCA) back in 1997. He pursued a PhD program in molecular oncology and a Fellowship in thoracic oncology at the Free University in Amsterdam until 2001. Back in Brazil he was the Director of Clinical Research at INCA between 2001 and 2011, where he established the National Tumor and DNA Bank. Within the Ministry of Health he served as the founder and Chair of both the Brazilian Clinical Cancer Research Network (RNPCC) and the Brazilian Drug Discovery Network (REDEFAC) between 2012 and 2015.

Dr Ferreira is currently the CMO and Head of the Thoracic Division (Neotorax Program) of D’Or Oncology and Head of the Oncology Branch at D’Or Institute for Research and Education in Rio de Janeiro. Dr Ferreira is deeply involved in initiatives to increase access to molecular testing and cancer drugs for lung cancer patients in Brazil and Latin America, leading discussions within different stakeholders at a global level: government, diagnostic and pharmaceutical companies, regulatory agencies, payers, academia and venture capital players. Dr Ferreira is the co-chair of the IASLC Fellowship and Career Development Committee and member of the AACR International Affairs Committee. He has published over 120 papers and book chapters in peer-reviewed journals.
Mauricio Cuello  
Hospital de Clinicas–UdeLAR, Montevideo, Uruguay

Dr Mauricio Cuello became a Doctor in Medicine at the Universidad de la Republica, UdelaR, Montevideo-Uruguay in 2000. In 2004, he specialized in Medical Oncology at Hospital de Clinicas UdelaR.

He embarked on a Fellowship in Thoracic Oncology at the Hospital Germans trias i Pujol, Badalona, Barcelona, Spain from 2004–2009.

Now Dr Cuello is an Associate Professor at the Department of Oncology, Hospital de Clinicas, Montevideo, Uruguay and has been there since 2011.

His research activities include being the Coordinator of the Uruguayan Cooperative Oncology Group GOCUR and Director of the Oncology Respiratory Disease Unit at the Department of Oncology, Hospital de Clinicas, UdelaR from 2011 onwards. He has also been the Deputy Director at the National Cancer Institute since 2015.

In his professional career, Dr Cuello has been the Clinical Coordinator in the Department of Oncology, Institute Dexeus, Barcelona, Spain from 2007–2011 and the Trial Clinical Manager at Boehringer Ingelheim, Barcelona, Spain from 2009–2011.

Johan Vansteenkiste  
University Hospital Leuven, Belgium

Johan Vansteenkiste is Professor of Internal Medicine in the Faculty of Medicine at the Catholic University of Leuven, Belgium, and Head of Clinic in the Respiratory Oncology Unit and its Clinical Trial Unit at the Leuven University Hospital.

Professor Vansteenkiste studied Medicine at the University of Leuven before becoming a Board Certified Pulmonologist-Oncologist. He had additional training in Respiratory Oncology at the European School of Oncology in Milan, Italy, and in Respiratory Endoscopy at the Laser Centre in Marseille, France, before gaining his PhD at the University of Leuven in 1996.

Professor Vansteenkiste is an active member of different international societies such as ESMO, IASLC, ASCO, ERS and others. He was Secretary of the Thoracic Oncology Assembly of the ERS and member of the ERS School Board in 2009-2012. He was member of the Board of Directors of IASLC in 2009-2013. He is member of the ESMO Lung Educational Group and Guidelines Group, and chaired the European Lung Cancer Conference in April 2015.

He is the principal investigator or co-investigator in several clinical trials in the area of lung cancer. He is Associate Editor of the Annals of Oncology, member of the editorial board of several other journals, and author or co-author of more than 250 peer-reviewed papers and book chapters.
Management of nonsquamous NSCLC patients without EGFR/ALK alterations

Dr Mauricio Cuello opened the symposium with a discussion of treatment options for patients with nonsquamous non-small-cell lung cancer (NSCLC) not harbouring EGFR mutations or ALK translocations, with a special focus on the perspective of and contribution from Latin America.

Lung cancer is a “very important problem” in Latin America, he said. Among a population of 600 million in the Latin–American and Caribbean countries, 1 million new cases of cancer are diagnosed each year\(^1\). Of these, 85,000 are attributable to lung cancer, making it a “significant health problem” in these countries.

That said, Cuello believes that the incidence is underestimated due to the lack of good cancer registries in the region, and also because a significant portion of the population is excluded from healthcare systems.

NSCLC genetic landscape

Previous research has shown that Hispanic ethnicity is associated with good prognosis, and Saeed \(et\ al\) found that Hispanic individuals were more likely to harbour histological subtypes associated with a favourable prognosis – such as bronchioalveolar carcinoma – than those of non-Hispanic ethnicity\(^2\). The underlying explanation for this predilection is “very complex”, said Cuello, and potentially includes environment factors, such as smoking, and also genetic and epigenetic factors.

The genetic landscape of NSCLC in Latin America is heterogeneous, reflecting the heterogeneity of a population comprising individuals of American–Indian, European, African and mestizo descent. In the most up-to-date study\(^3\), Arrieta \(et\ al\) found that the frequency of EGFR mutations in Latin America was 26%, which is...
intermediate between the 40% rate reported for Asian populations and the 15% rate in Caucasians. However, the frequency across different countries ranged from 14% in Argentina to 51% in Peru.

Cuello drew attention to two posters presented at LALCA 2016, which report on EGFR mutation frequencies in Brazil and in Hispanic individuals living in the USA, with both finding a rate of around 25%, in line with the study by Arrieta and team.

Moreover, 4% of all nonsquamous cases in Latin America harbour ALK translocations.

But even though the rate of mutations is high, a large majority of patients are considered negative for targetable mutations, whether it is because they are indeed lacking these mutations or because we do not test for mutations as often as other populations is not known, the presenter observed.

First-line therapy

To review the treatment choices in the Latin–American population, Cuello presented a clinical case of a 67-year-old Caucasian man. The patient was a smoker who presented with persistent cough and weight loss, with a performance status (PS) of 0. A chest x-ray identified a left hilar mass and bronchoscopy confirmed an adenocarcinoma, with multiple liver metastases. The primary tumour was wild-type for EGFR and also lacked ALK or ROS1 rearrangements; furthermore, there was not enough tissue for additional testing, “a very common situation in my practice”, the presenter said.

On querying the audience on their choice of first-line therapy, the majority opted for cisplatin plus pemetrexed, either without (34%) or with (28%) bevacizumab. Around a fifth of the attendees chose carboplatin and pemetrexed (with or without bevacizumab; 21%) and a similar proportion (17%) thought they would prefer to include the patient in a clinical trial. There were no votes for the remaining options of cisplatin either alongside gemcitabine or vincristine and cetuximab.

The combination of cisplatin and pemetrexed was compared with cisplatin plus gemcitabine in a noninferiority study conducted by Scagliotti and co-investigators. They found a “very interesting difference” by histology, such that overall and progression-free survival (OS, PFS) were significantly longer for the pemetrexed versus cisplatin arm among patients with nonsquamous, but not squamous, histology.

But what makes cisplatin plus pemetrexed a particularly popular option in Latin America is that it is “very well tolerated”, remarked Cuello. For instance, the rates of several treatment-related grade 3 or 4 haematological (eg, neutropenia, anaemia and thrombocytopenia) and nonhaematological (eg, febrile neutropenia, alopecia and nausea) adverse events were significantly lower in patients given pemetrexed than gemcitabine. “In an environment with several economic limitations, it is important to have a drug that is well tolerated.”

Another challenge in Latin–American countries is that a large proportion (40%) of patients have a PS of 2. In order to identify the best regimen for these patients, Zukin et al randomly assigned 205 advanced NSCLC patients with PS 2 to receive first-line pemetrexed either with carboplatin or alone. Participants treated with combination therapy had significantly improved OS and PFS, with median times of 9.3 versus 5.3 months and 5.8 versus 2.8 months, respectively. Moreover, the safety profile of the combination was “excellent”, said Cuello.

He added that as the first clinical trial to originate in Latin America, it was particularly important as it showed the possibility of developing trials in “our continent”.

Maintenance therapy

The patient was treated with four cycles of cisplatin–pemetrexed, which led to disappearance of the hilar mass and reduction of the hepatic metastases. He did not experience any side effects of grade 3 or worse. What would be the next step for the patient, Cuello asked the audience.

By far the most popular option was continuing with pemetrexed, either as monotherapy or in combination with bevacizumab, securing 68% and 21% of the vote, respectively.

Maintenance therapy has several benefits – it has been shown to prolong not only the time to
disease progression but also OS. Treatment with a maintenance protocol can also increase the proportion of patients eligible for second-line therapy when they do progress. But what is the best regimen for nonsquamous NSCLC patients without targetable mutations?

A systematic review of 22 publications assessed various maintenance options, including chemotherapy and EGFR tyrosine kinase inhibitors (TKIs), but not bevacizumab as studies with appropriate controls were not available. The study showed a “clear benefit” favouring pemetrexed versus no pemetrexed in patients with stage IIIB or IV NSCLC, with improvements in both PFS and OS.

Cuello highlighted another poster presented at LALCA 2016 – a Bayesian meta-analysis by Gilberto Lopes – that “in a sense confirmed these results” as it found that optimal OS and PFS could be achieved in advanced nonsquamous NSCLC patients by either switching to or continuing with pemetrexed or switching to an EGFR TKI.

However, it is worth noting that the benefit of maintenance with EGFR TKIs is restricted to patients with mutations, and therefore, these agents would not be a good option for those lacking targetable EGFR mutations.

The speaker also pointed out that bevacizumab maintenance has been assessed in several trials, with “a very marginal benefit.” Nonetheless, the agent is used in clinical practice in some countries.

Another pressing question is whether we can select individuals who would benefit most from pemetrexed continuation? Most research thus far has shown OS benefits across all subgroups, and other than PS, there are no baseline or clinical factors that can be used as a marker.

That said, a recent study has pointed to the use of thymidylate synthase (TS) expression as a potential marker. A total of 144 Colombian patients were given first-line pemetrexed, carboplatin and bevacizumab, followed by maintenance with pemetrexed plus bevacizumab. Median OS in the overall study cohort was 21.4 months.

However, the researchers found that median OS times decreased in a stepwise fashion with an increase in TS protein levels, with significant differences between groups. Specifically, patients with TS protein expression below 10% had a median OS of 32.4 months while those with levels of 40% or more had a median OS of 13.2 months.

Second-line therapy

Going back to the case, the presenter explained that the patient received 8 cycles of maintenance pemetrexed, after which he experienced hepatic disease progression and his PS changed to 1. The patient refused to undergo another biopsy.

At this stage, 33% of the audience said that they would treat the patient with a checkpoint inhibitor, while 21% chose docetaxel plus ramucirumab. The remaining three options – single-agent TKI or docetaxel alone or with nintedanib – were each chosen by 15% of the attendees.

Discussing the second-line options in more detail, Cuello noted that docetaxel has been the gold standard for advanced NSCLC patients for over a decade since the landmark trial by Shepherd et al. But other therapeutic agents are now available for this patient population.

For instance, the LUME-Lung 1 trial showed that addition of nintedanib rather than placebo to docetaxel reduced the risk of mortality by a significant 25% in NSCLC patients with adenocarcinoma who had initiated first-line treatment less than 9 months previously. Nintedanib nearly doubled the 2-year OS rates, at 20.7% compared with 10.4% for the placebo arm.

The antiangiogenic agent ramucirumab, also given alongside docetaxel, had a “very superior” OS relative to the combination of placebo and docetaxel in nonsquamous NSCLC patients, at a median of 11.1 and 9.7 months, respectively.

And various PD-1 and PD-L1 inhibitors have led to an improvement in OS of around 3 months versus the control arms, but the problem in Latin America is access, said Cuello. He continued: “In light of the economic limitations, head-to-head trials of the available agents would be useful, as would real-world pharmacoeconomic data.”
Conclusions

For patients with nonsquamous NSCLC lacking targetable mutations, cisplatin remains the gold standard, with pemetrexed “the best partner”. This is also the only combination in the lung cancer setting for which data specific to Latin America are available. Cuello stressed the importance of local data and called for more clinical trials to be conducted in “our continent”.

“If we are convinced that the population is different, then we need to integrate this information into the design of clinical trials”, he concluded.

References

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Navigating the advanced squamous NSCLC pathway

Squamous cell carcinomas (SCCs) and adenocarcinomas are different histologically, the former are typically epithelial and the latter tend to be glandular. There are also immunohistochemical differences, such that SCCs express p63 and CK5/6 while adenocarcinomas are positive for TTF1 and CK7.

However, the differences go “beyond the microscope”, said Johan Vansteenkiste, as the patients also differ in a clinical sense. Adenocarcinoma patients tend to be young, nonsmokers and in good general condition; by contrast, individuals presenting with squamous histology are older, heavy smokers and often have major comorbidities. Until recently, SCC patients have also had fewer treatment options as they do not benefit from pemetrexed or bevacizumab, and there are currently no known targetable oncogenes.

New versions of NSCLC treatment guidelines have been issued over the years, but there has been very little difference with respect to the options for SCC patients, a situation that is “typical for a disease in which there has been very little progress up to now”, said Vansteenkiste. But he expects to see some changes in the latest version to be published in a couple of months, and he discussed some of the new options in the context of a patient case.

First-line pathway of the SCC patient

A 71-year-old male presented with dyspnoea, fatigue, anorexia and weight loss. The patient was an ex-smoker with diabetic neuropathy; a clinical examination established a PS of 1 and a chest x-ray showed a left hilar mass. Bronchoscopy detected the presence of a tumour in the left upper lobe and a molecular analysis favoured squamous histology (ie, TTF1-negative, p63-positive). The tumour had metastasized to the adrenal glands and liver, but not to the brain.

At the time – June 2013 – the patient was treated with carboplatin-based doublet chemotherapy. Single-agent chemotherapy was ruled out as individuals with PS 1 are generally not candidates for monotherapy, and triplet chemotherapy was disregarded as it does not provide a survival benefit beyond that afforded by doublet therapy. Moreover, carboplatin, rather than cisplatin, was the backbone of choice due to the presence of diabetic neuropathy.

However, Vansteenkiste asked the audience how they would choose to treat this patient at the present time – August 2016 – in “a wonderful world of universal reimbursement”. The audience were almost equally divided between four options, namely platinum-based doublet chemotherapy, carboplatin plus albumin-bound paclitaxel (nab-paclitaxel), cisplatin and gemcitabine alongside necitumumab, and enrolling the patient in a clinical trial with a targeted therapy. Only 4% of symposium attendees opted for single-agent chemotherapy.

Albumin-bound paclitaxel

Going through the options in detail, the presenter first talked about the phase III trial that pitted nab-paclitaxel against solvent-bound paclitaxel, both given alongside carboplatin, in patients with advanced NSCLC. The primary endpoint was improvement in objective response rate (ORR), which Vansteenkiste finds “remarkable” for such a large study, and although this was met, the difference between groups was driven mainly by the SCC subgroup (41 vs 24%). Furthermore, nab-paclitaxel had a better toxicity.
profile than the solvent-bound agent, with significantly less neuropathy and haematological side effects.

However, OS and PFS did not vary significantly between the treatment arms, either in the overall study cohort or the SCC subgroup, and the presenter highlighted a few key issues with the trial design and findings. For instance, three parameters differed between the arms – not only was the form of paclitaxel different, but so was the dose and dosing schedule of nab- and solvent-bound paclitaxel – which begs the question, “what exactly is being compared?” Furthermore, the ORR for the nab-paclitaxel arm was only 8% higher than for the solvent-bound group – is this difference clinically relevant in the absence of an OS or PFS benefit, asked Vansteenkiste. And how reliable are toxicity comparisons in an open-label trial?

**EGFR inhibitors**

Another therapeutic option assessed in the first-line NSCLC setting is the EGFR inhibitor cetuximab. The FLEX trial found that addition of cetuximab to cisplatin plus vinorelbine reduced the risk of death by a significant 13%, with the greatest benefit seen in participants with squamous histology\(^{9,10}\). However, the rate of febrile neutropenia was “very high” in the cetuximab arm, and owing to the unfavourable risk–benefit profile, the agent did not receive regulatory approval.

By contrast, necitumumab – also an EGFR inhibitor – has been approved for the treatment of chemotherapy-naive SCC patients, both in USA and Europe\(^{11,12}\). The approval was based on the phase III SQUIRE trial that recruited 1093 individuals with SCC and randomly assigned them to receive cisplatin plus gemcitabine either with or without necitumumab\(^{13}\). Necitumumab significantly improved OS, with a median of 11.5 versus 9.9 months, and a hazard ratio of 0.84.

The investigators noted some influence of EGFR expression – specifically, the hazard ratio for patients with high tumour EGFR levels was 0.75, compared with 0.90 for those with low levels, but this was not significant at the interaction level. Vansteenkiste highlighted that a similar effect of EGFR expression was also observed in the FLEX trial\(^{10}\).

In terms of toxicity, the problems with cetuximab were not seen with necitumumab – the incidence of grade 4 febrile neutropenia was less than 1%. And although there was an increase in grade 3–4 hypomagnesaemia, this was expected as a class effect, and can be managed with careful monitoring and supplementation as needed, the presenter observed. Necitumumab treatment was also associated with a “slightly” elevated incidence of grade 3 or 4 thromboembolic events, predominantly of the venous type\(^{13}\).

**Relapse pathway of the SCC patient**

Continuing with the case presentation, Vansteenkiste informed the audience that the patient showed good tolerance to first-line chemotherapy and his condition improved. However, after 10 months, his health deteriorated and a computed tomography scan showed progression in the liver, although the thoracic tumour remained stable.

As the patient had a PS of “1.5” and was in “reasonable condition”, best supportive care was not considered a viable option. And in light of ineligibility for a clinical trial and unavailability of immunotherapy, he was given docetaxel.

Once again, the presenter asked the audience to consider the therapeutic options for this patient in August 2016, with no economic limitations. The large majority of attendees (58%) chose immunotherapy, while 19% opted for docetaxel plus ramucirumab and around 8% each chose docetaxel monotherapy, clinical trial with a targeted agent and best supportive care. Vansteenkiste described the choices as “reasonable” and explained that the second-line setting is the time to consider a clinical trial with a molecularly targeted agent in SCC patients.

**Immune checkpoint inhibitors**

The first study to bring immunotherapy to the forefront was the phase III CheckMate 017 trial, which showed the superiority of nivolumab over docetaxel in relapsed patients with squamous NSCLC\(^{14}\). Although describing the OS findings as “impressive”, Vansteenkiste drew attention to the sharp drop-off in the PFS graph, with around 50% of patients not deriving any benefit, regardless of the treatment arm. He believes that even though immunotherapy is an important addition to the SCC armamentarium, “we should continue to investigate other possibilities”.

Another issue is the eligibility of patients for immunotherapy trials – for example, in the phase III trial investigating pembrolizumab\(^{15}\), of 2699 patients screened, 62% were ineligible for inclusion, as a result...
of missing PD-L1 assays, PD-L1–negative tumours or other reasons, and remained on chemotherapy. This proportion is "not trivial," observed Vansteenkiste, and these patients need options other than immunotherapy.

**Angiogenesis inhibitors**

Relapsed SCC patients have another new option – the angiogenesis inhibitor ramucirumab, which in combination with docetaxel improves survival in advanced NSCLC16, as discussed earlier by Dr Cuello. Unlike other antiangiogenesis agents assessed in SCC, which have "in general not been good friends", ramucirumab has a more favourable safety profile. Side effects related to bleeding and thrombosis have been problematic in the past, but in the REVEL trial16, most of these toxicities were balanced between the ramucirumab and placebo arms. Only the incidence of bleeding and haemorrhage was higher with ramucirumab, but this pertained to grade 1–2 events. The agent has since been approved by both the US Food and Drug Administration and the European Medicines Agency17,18.

**Conclusions**

Vansteenkiste commented that although the progress in the SCC setting has been slower than that for adenocarcinoma, several new therapeutic agents have recently become available for SCC patients.

And for the first time, median OS of first-line SCC has approached 1 year.

The presenter believes that "careful clinical judgement and appropriate use of these new agents will improve the prospect of these patients." However, there is a long way to go still with regard to making targeted therapy a reality for this patient population.

**References**

The Chair thanked the speakers for the comprehensive overview, but cautioned that the audience response to the questions put forward by Professor Vansteenkiste do not reflect the Latin–American setting as the attendees were asked to disregard economic limitations.

He queried Vansteenkiste on the second-line treatment options for a patient who is “rapidly progressing”. Vansteenkiste replied that in general, such rapid progression is “very bad news”, but luckily is not a common scenario; for such a patient, we would favour docetaxel over nivolumab or ramucirumab, he said.

Ferreira said that the take-home message of Dr Cuello’s talk is that we need local data from Latin America, especially health economics data, to enable us to incorporate the new diagnostic and therapeutic strategies.

And the key conclusion from Professor Vansteenkiste’s presentation is the hope that we are finally moving forward in the treatment of SCC, not as fast as we need, but “we can see some light at the end of the tunnel”, the Chair observed.