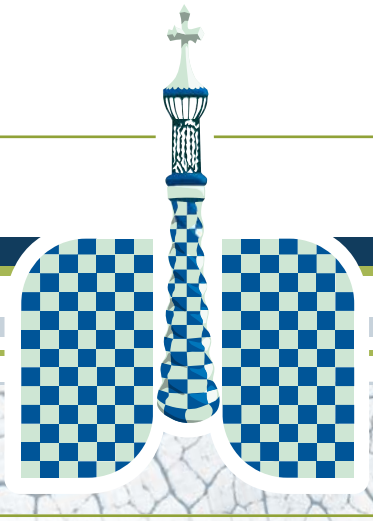
IASLC 20th World Conference on Lung Cancer

Industry Supported Symposium

Simplifying the sequencing of treatment in NSCLC patients with no actionable mutations



SCIENTIFIC SUMMARY

Chaired by Dr Corey Langer
With Dr Enriqueta Felip, Dr David Heigener and Dr Myung-Ju Ahn

Saturday 7th September, 2019
16:00–17:30
Barcelona, Spain

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CONTINUING MEDICAL INFORMATION

The live symposium titled: Simplifying the sequencing of non-small-cell lung cancer (NSCLC) with no actionable mutation, Barcelona, Spain, 07/09/2019-07/09/2019 was accredited by the European Accreditation Council for Continuing Medical Education (EACCME®) with 1 European CME credit (ECMEC®). Each medical specialist should claim only those hours of credit that they actually spent in the educational activity.

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If you attended the symposium and would like to apply for accreditation please fill out an evaluation form, where you can enter your email address, and provide valuable feedback on the event.

EDUCATIONAL GRANT

This program was made possible thanks to an independent educational grant from Eli Lilly and Company.

WELCOME MESSAGE

Dear Colleagues,

Thank you for downloading this report from our satellite symposium: "Simplifying the sequencing of treatment in NSCLC patients with no actionable mutations" which took place at the 20th IASLC World Conference on Lung Cancer in Barcelona, Spain.

The conference is a world-renowned platform for the presentation and discussion of new science in the field of lung cancer and thoracic oncology. It is also the largest international meeting of clinicians, researchers and scientists in this field, providing an ideal opportunity to learn about the latest research and network with colleagues from all over the world.

In this symposium we discussed treatment choices and shared a case study in the first-line setting, set against current standards in care and the latest clinical trial data. We also looked at a case study on how to treat patients in the complex second-line setting alongside the latest data, followed by a case on identifying and classifying hyperprogressive disease. Finally, we explored how to balance between promise and reality in order to overcome barriers for integration and uptake of suitable new treatments in different global regions.

We hope that your knowledge and understanding of this area will be enhanced by the information contained within this report and that you can utilise the learning in your daily practice.

Please also be aware of further enduring materials from this program, namely the Enriched Treatment Pathway Tool for Europe, Asia and the US regions, which will be presented by our expert faculty and published from November.

Yours faithfully,

Corey Langer, Chair

FACULTY BIOGRAPHIES

Corey Langer (Chair)

University of Pennsylvania, Philadelphia, USA

Corey Langer, MD, is a Professor of Medicine at the University of Pennsylvania, the Clinical Director of Thoracic Oncology at the Abramson Cancer Center and Chair of the Medical Oncology Committee for the Radiation Therapy Oncology Group (RTOG), now NRG Oncology.

Dr Langer received his medical degree from Boston University, Massachusetts, and completed his internship and residency in medicine at the Graduate Hospital of the University of Pennsylvania in Philadelphia. He is board certified in internal medicine and in hematology/oncology.

He is a Fellow of the American College of Physicians (ACP) and a member of the American Society of Clinical Oncology (ASCO), the American Association for Cancer Research (AACR), and the International Association for the Study of Lung Cancer (IASLC). He brings extensive clinical trial experience to research in the Cooperative Group system (RTOG and Eastern Cooperative Oncology Group [ECOG]), and is a core member of both the RTOG/NRG Oncology and ECOG Head and Neck Cancer and Thoracic Committees.

Over the past 29 years, he has led or co-led over 120 clinical trials in both small-cell and non-small-cell cell lung cancer, in the adjuvant, locally advanced and advanced disease setting, and at least 20 trials in head and neck cancer. His clinical research efforts include new drug combinations and special populations and, more recently, his focus has been on immuno-oncology trials. He is now very active in mentoring junior investigators as they launch their own clinical trials, and leads clinical research in thoracic malignancy as part of the Abramson Cancer Center's Interdisciplinary Thoracic Oncology Program (ITOP). He has authored or co-authored over 170 peer-reviewed papers, primarily focused on the treatment of smoking-related malignancies.

Enriqueta Felip

Vall d'Hebron University Hospital, Barcelona, Spain

Enriqueta Felip is the Head of the Thoracic Cancer Unit within the Oncology Department of Vall d'Hebron Hospital, Barcelona, Spain. Dr Felip is in charge of thoracic malignancy management, and is responsible for thoracic cancer trials undertaken by the Oncology Department. She is also Associate Professor at the Autonomous University of Barcelona (UAB). Dr Felip received her medical degree from the UAB, where she also completed her PhD studies in medical oncology. She is involved in the training of medical students, residents and particularly in mentoring fellows.

Dr Felip is currently a member of the Spanish Lung Cancer Group (SLCG), the Spanish Society of Medical Oncology, the European Society of Medical Oncology (ESMO), the ASCO, and the IASLC. Dr Felip has been involved in several initiatives with scientific organisations, among them, as Subject Editor of Guidelines Working group ESMO Minimum Clinical Recommendations in lung cancer and Coordinator of the 1st ESMO Consensus Conference in lung cancer. Dr Felip is at present a member of the scientific committee of the SLCG and coordinator of the European School of Oncology (ESO) lung cancer programme.

Dr Felip is also author of many peer-reviewed articles and book chapters relating to the field of thoracic malignancies.

David Heigener

Helios Klinik Schleswig, Schleswig, Germany

David Heigener is Head of the Department of Pulmonology at the Helios Klinik Schleswig, Germany. His main interest is medical treatment of lung cancer. He has participated in numerous trials in this field, with approximately 100 publications and book contributions. He is also a member of the palliative care task force in the German Respiratory Society (Deutsche Gesellschaft für Pneumologie; DGP).

Dr Heigener is member of IASLC, ESMO, DGP, German Cancer Society and the German Society for Palliative Medicine. He is on the editorial board of *Atemwegs- und Lungenkrankheiten* and a reviewer for *The Lancet, The Lancet Oncology, Lung Cancer, Respiratory Medicine, Annals of Oncology, British Medical Journal, Journal of Clinical Oncology* and *Journal of Thoracic Oncology*.

Myung-Ju Ahn

Sungkyunkwan University School of Medicine, Seoul, South Korea

Myung-Ju Ahn is Professor of Hemato-Oncology in the Department of Medicine at Sungkyunkwan University School of Medicine in Seoul, South Korea. She is a member of numerous associations and societies dedicated to cancer research, such as IASLC, AACR, ASCO, the Korean Society of Medical Oncology and the Korean Cancer Study Group, where she is also Chief of the executive committee and Chairperson of Lung Cancer Disease Committee. She was President of the Korean Society of Medical Oncology (2018–2019) and the President of the Multidisciplinary Immuno-oncology Study Group (2017–2018). Dr Ahn serves as a board member for the Korean Association of Cancer and the Korean Society of Medical Oncology, Korean Association for Lung Cancer, and Korean Association for Cancer, and also serves on the editorial board of *Journal of Thoracic Oncology*.

Dr Ahn received her education from Hanyang University College of Medicine in Seoul, where she earned her medical degree, as well as her doctorate. She completed her residency training in internal medicine at Hanyang University Hospital, and held numerous fellowships, including a postdoctoral research fellowship at the Memorial Sloan-Kettering Cancer Center in New York, USA.

Dr Ahn has authored or co-authored over 250 publications. Her research interests include the development of predictive and prognostic markers in lung cancer in terms of personalized therapy, and her recent research focuses on early clinical trials for the development of drug discovery and reposition of targeted drugs, as well as the development of a NSCLC genome atlas. In recognition of her dedication to cancer research, she has been awarded multiple honours, including the 2003 Best Researcher Award from the Korean Medical Women's Association, the 2015 Best Researcher Award from the Korean Association of Clinical Oncology, and the 2018 Boryoung Scientific Award from the Korean Cancer Research Foundation.

OPENING STATEMENT FROM THE CHAIR

Corey Langer

Corey Langer opened the symposium by acknowledging the recent changes in lung cancer treatment. "It's without question that the treatment landscape has irrevocably altered in the last 3 to 4 years with the introduction of immunotherapy in non-small-cell lung cancer," Dr Langer said, noting there "are a lot of open questions and unmet needs."

For patients without oncologic tumor driver mutations, the "treatment paradigm really hinges [...] on PD-L1 [programmed cell death ligand 1] testing," he explained, with the use of pembrolizumab alone or alongside histology-driven chemotherapy dependent on whether PD-L1 expression is above 50%, between 1% and 50%, or zero. For patients with inadequate tissue for analysis, the "default" is often pembrolizumab plus chemotherapy, he noted.

Other considerations may be the use of combination immunotherapy, such as ipilimumab plus nivolumab, for patients with a high tumor mutation burden (TMB) and some PD-L1 expression, Dr Langer said. Meanwhile patients with tyrosine kinase inhibitor (TKI)-refractory disease appear to benefit more from the use of atezolizumab alongside paclitaxel, carboplatin, and bevacizumab, he explained.

Langer's Current Paradigm in advanced NSCLC: 2019 (could change at any moment)

Tx Cohort	Non-Squamous	Squamous
PDL1 ≥ 50%	Pembro > Pem/Carbo/Pembro	Pembro > Taxane/Carbo/Pembro
PDL1 1-50%	Pem/Carbo/Pembro > Pembro	Taxane/Carbo/Pembro > Pembro
PDL1 < 1%	Pem/Carbo/Pembro	Taxane/Carbo/Pembro
PDL1 ≥ 1%, TMB > 10	Pem/Carbo/Pembro vs Ipi/Nivo	Taxane/Carbo/Pembro vs Ipi/Nivo
TKI-Refractory	Pac/Carbo/Bev/Atezo or Pem/Carbo +/- Bev	
Tissue QNS	Pem/Carbo/Pembro	Taxane/Carbo/Pembro

Click here to view a clip from Dr Langer's presentation

WHERE SHOULD WE BEGIN?

Enriqueta Felip

Enriqueta Felip opened her presentation on the first-line management of NSCLC with a patient case study of a 57-year-old female smoker without comorbidity who had presented with a cough and thoracic pain. Positron emission tomography–computed tomography (PET–CT) had revealed a 34 mm nodule in the right upper lobe, as well as an ipsilateral hilar lymph node mass, and multiple liver and bone metastases, but no brain involvement.

The optimal genetic testing approach

After biopsy confirmation of adenocarcinoma, Dr Felip asked the audience which biomarkers their institute would test for, with 43% recommending screening for genetic alterations in the epidermal growth factor receptor *(EGFR), ALK, ROS1*, or *BRAF*, and PD-L1 screening, and 33% advising next-generation sequencing (NGS) plus PD-L1.

Dr Felip noted that these responses are "very good" when considered against the 2018 ESMO clinical practice guidelines for metastatic NSCLC[1] which recommend PD-L1 assessment for all patients, as well as testing for all four of these mutations in patients with nonsquamous histology.

Furthermore, where available, both the ESMO guidelines and the ASCO Expert Consensus Opinion[2] recommend the use of multiplex NGS platforms over single gene assays, she said.

No mutation – which regimen?

The patient in the case study tested negative for genetic mutations but had a PD-L1 expression level of 70%, raising the possibility of immunotherapy and/or chemotherapy. When asked, the majority of the audience chose to give the programmed cell death protein 1 (PD-1) inhibitor pembrolizumab alone (45%) or in combination with platinum–pemetrexed (39%) for this patient.

Dr Felip reviewed the first-line chemotherapy options available before immunotherapy, noting that the ECOG 1594 trial[3] demonstrated equivalent median overall survival (OS) for paclitaxel, gemcitabine, or docetaxel given with cisplatin, and for paclitaxel plus carboplatin.

This was followed by the availability of the anti-angiogenic agent bevacizumab and improved OS for nonsquamous NSCLC patients using this alongside carboplatin–paclitaxel[4], as did use of cisplatin–pemetrexed for patients with nonsquamous histology compared with cisplatin–gemcitabine.[5] And the PARAMOUNT trial findings showed that maintenance pemetrexed in responding or stable patients increased OS compared with placebo.[6,7]

With the advent of immunotherapy, the KEYNOTE-024 trial demonstrated an improvement in both progression-free survival (PFS) and OS with pembrolizumab for patients with 50% or more PD-L1 expression when compared with platinum doublet chemotherapy.[8,9] The KEYNOTE-024 trial findings were updated for 3-year outcomes at WCLC 2019 by Martin Reck.[10]

A significant OS benefit has also been reported for nonsquamous NSCLC patients unselected by PD-L1 expression for use of chemotherapy plus immunotherapy with or without bevacizumab versus chemotherapy alone in the KEYNOTE-189[11], IMpower150[12], and IMpower130[13] trials. In addition, the IMpower132[14] findings were not statistically significant but showed "numerically superior" OS, Felip said.

PD-L1 expression of 50% or more – immunotherapy alone?

Returning to the case study, Dr Felip noted that there are no randomized trial findings to guide whether a patient with PD-L1 expression of 50% or more should receive immunotherapy alone or in combination with chemotherapy.

Nevertheless, 51% of participants in this PD-L1 group achieved 2-year OS in both the KEYNOTE-189 and KEYNOTE-024 trials, with the latter including both squamous and nonsquamous histologies, she said. Similarly, 1-year PFS was achieved by 47% of the KEYNOTE-189 and 48% of KEYNOTE-024 patients with PD-L1 of 50% or more.

"It is true that there is a difference in the toxicity," Dr Felip observed, with 50% of the KEYNOTE-189 patients experiencing toxicity from immunotherapy plus chemotherapy[15], compared with a smaller proportion of KEYNOTE-024 patients given pembrolizumab alone[16].

What about tumor burden? And tumor mutational burden?

Dr Felip asked whether the choice of treatment in her case study might be influenced by tumor burden, noting that the woman had a high tumor volume, extensive disease, and liver metastases. Close to three-quarters (71%) of delegates chose to use chemotherapy as well as immunotherapy, despite a lack of comparative data for patients with PD-L1 of 50% or above.

"I would agree with you – although there are no clinical trials – that probably patients with rapidly progressive disease or high tumor volume that could experience early progression may be candidates for [chemotherapy] plus immunotherapy," she said.

Furthermore, almost half (48%) of delegates voted that TMB is relevant in treatment decision-making, a result that Dr Felip described as an "interesting opinion because there is no correct answer."

CheckMate 227 trial findings[17] suggest that patients with a TMB of 10 mut/Mb or more have a significantly higher response to nivolumab plus ipilimumab than chemotherapy, with 1-year rates of 43% versus 13%.

And MYSTIC trial findings suggest that patients with blood TMB of 20 mut/Mb or above have 2-year OS rates of 48% with durvalumab plus tremelimumab, 33.8% for durvalumab alone, and 19.4% for chemotherapy, whereas the rates varied from 20.2 to 27.2% for those with a lower TMB[18].
Dr Felip highlighted that TMB findings would be reported at WCLC 2019 for the KEYNOTE-189[19], KEYNOTE-021[20] and MYSTIC[21] trials, noting that this information "could help us to define better the role of TMB in patients treated with chemo plus immunotherapy."

Optimal duration of immunotherapy

Returning to the case study, Dr Felip said that the patient received four cycles of pembrolizumab plus carboplatin–pemetrexed, followed by 1 year of pembrolizumab plus pemetrexed. This achieved a partial response with a 66% tumor reduction.

In the absence of toxicity, 40% of delegates chose to continue both treatments until disease progression, with 20% continuing with pembrolizumab only and 25% stopping pembrolizumab at 2 years and continuing with pemetrexed only.

Noting that the KEYNOTE-189 trial halted pembrolizumab therapy after 2 years and continued chemotherapy until disease progression, Dr Felip admitted that "we don't know for sure what could be the optimal treatment duration for immunotherapy."

However, she observed that the CheckMate 153[22] findings suggested that continuing nivolumab past 1 year may improve PFS, while KEYNOTE-010 indicated that 32% of patients who finished pembrolizumab at 2 years experienced disease progression, and that rechallenge achieved a partial response or stable disease in some of these patients.[23]

STK11/LKB1 mutation status

Finally, Dr Felip asked the audience whether they would recommend immunotherapy if the patient's NGS had shown a *STK11* or *LKB1* alteration, with 25% answering yes, 37% no, and 38% unsure. Data shows that patients with *KRAS*-mutated lung adenocarcinoma with these alterations had a low response to immunotherapy given alone[24], while a second analysis of patients with mutation, wild-type nonsquamous NSCLC indicated that 76.5% of patients' refractory to pembrolizumab

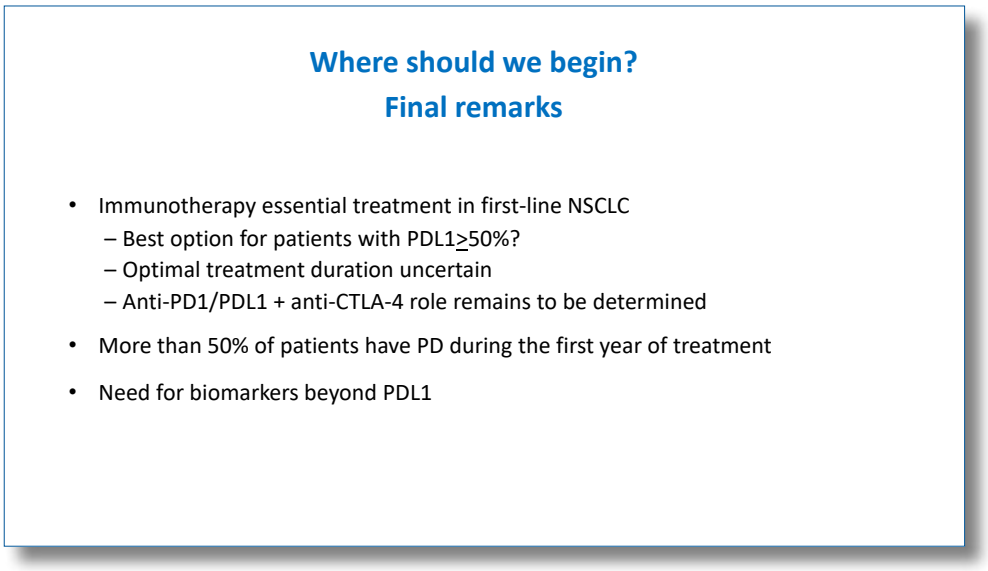
plus chemotherapy had a *STK11/LKB1* mutation[25]. An update on this study was also reported at the meeting[26].

Conclusions

Dr Felip concluded that "immunotherapy is essential in the treatment of first line" but we do not yet know what the best treatment option is for patients with PD-L1 of 50% or above, or the optimal duration of either chemotherapy or immunotherapy.

In addition, further research is needed to determine the role of PD-1/PD-L1 inhibitors in combination with cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitors.

"We have to admit that more than 50% of patients have progression during the first year of treatment so we need more biomarkers beyond PD-L1 and TMB," she said.



Click here to view a clip from Dr Felip's presentation

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NAVIGATING THE INCREASINGLY COMPLEX SECOND-LINE SETTING

David Heigener

David Heigener opened his presentation noting that the first-line treatment of NSCLC has "dramatically changed" in recent times with the "plethora of regimens" available that are guided by tumor biology, but what about the second-line approach?

He presented a case study of a 57-year-old man with hypertension and cough, dyspnea and pain; he was diagnosed with pleural effusion and stage IVa adenocarcinoma negative for *EGFR, ALK,* and *ROS1* mutations, and a PD-L1 tumor proportion score of 10%.

This patient was enrolled into the KEYNOTE-189 trial and achieved "impressive remission and complete resolution of his symptoms" with pembolizumab plus pemetrexed–carboplatin, Dr Heigener said.

But had this patient shown multifocal progression while maintaining his ECOG performance status of 1, what should the next treatment approach be?

The audience's most favored choice of regimen was docetaxel plus the vascular endothelial growth factor receptor (VEGFR)-2 antagonist ramucirumab (41%), followed by docetaxel plus the multi-targeted TKI nintedanib (30%), the PD-1 inhibitor nivolumab (15%), the PD-L1 inhibitor atezolizumab (12%), and best supportive care (2%).

Dr Heigener talked through these treatment options, noting that immune checkpoint inhibitor (ICI) monotherapy in the second line has been demonstrated to show a significant survival benefit in the CheckMate 017[1] and 057[2] trials of nivolumab, as well as the KEYNOTE-010[3] study of pembrolizumab and the OAK study of atezolizumab[4].

But he cautioned that with immunotherapy now used in first-line NSCLC, "I don't think that we will have many patients who will still get monotherapy with a PD-1 or PD-L1 inhibitor in the second line."

Back to 'good old chemotherapy'?

Two agents are approved in Europe, at least, for advanced NSCLC – pemetrexed and docetaxel – with a similar OS and identical 1-year survival of 29.7%[5], albeit this efficacy is only found among nonsquamous NSCLC histology[6].

Acknowledging that pemetrexed has a lower rate of both hematologic and nonhematologic toxicity than docetaxel[6], Dr Heigener described pemetrexed as the "drug of choice" for nonsquamous patients.

As pemetrexed is not approved for use in combination with anti-angiogenic agents, however, and as many patients will have received the antifolate drug in the first line, treatment therefore "comes back to docetaxel," he said.

The REVEL trial demonstrated an OS benefit for second-line docetaxel plus ramucircumab against docetaxel plus placebo in patients with stage IV NSCLC with squamous or nonsquamous histology.[7] "Although the difference is not that big, it is significant and I think this is an option for patients who have had [pemetrexed], as in my case," the presenter said.

In addition, European patients may be considered for treatment with nintedanib – targeting VEGFR, fibroblast growth factor receptor and platelet-derived fibroblast growth factor receptor – alongside docetaxel, with the LUME-Lung1 trial showing a significant PFS benefit with the TKI against stage IIIB/IV NSCLC.[8]

Dr Heigener described nintedanib as achieving "robust results" but noted that only the subgroup of adenocarcinoma patients experienced a significant OS benefit with nintedanib, restricting the agent's approval to this histology.

Finally, second-line therapy with the EGFR–TKI afatinib significantly improved OS compared with erlotinib for patients with squamous NSCLC in the LUX-Lung 8 study.[9] Dr Heigener observed that erlotinib was "not a good comparator" for afatinib but acknowledged that "it shows a survival benefit, and it is approved, and it is an option for patients with squamous cell lung cancer."

How best to sequence treatment?

Dr Heigener questioned whether it would be better to give an anti-angiogenic drug before or after ICI therapy, and reported findings from a small trial indicating that perhaps patients were more likely to achieve remission with ICI followed by ramucirumab than with the reverse order.[10] But he emphasized that the data are "very sparse."

The second case study described the order of treatment of a man with locally advanced squamous NSCLC who was initially treated with four courses of carboplatin–paclitaxel with consolidation radiotherapy. Although he initially achieved a minor response, he experienced progression with pulmonary metastases and began nivolumab therapy. This achieved a response but the patient chose to discontinue treatment because of fatigue and experienced primary tumor progression.

The patient subsequently achieved remission on platinum doublet chemotherapy but developed septic pneumonia requiring a long hospital stay. He switched to docetaxel plus ramucirumab, and achieved a 6-month remission with ramucirumab maintenance.

What next?

Dr Heigener introduced the possibility of combining anti-angiogenic therapy with PD-1 inhibition, citing some "sparse" results for pembrolizumab plus ramucirumab in a small clinical trial suggesting remission in around 80% of patients.[11]

Other combinations under investigation include first-line use of atezolizumab plus bevacizumab and chemotherapy, which he described as a "smart" concept on the basis that bevacizumab's normalization of tumor blood vessels might improve chemotherapy delivery.[12]

"VEGF produces a low immunogenic environment in the tumor by blocking the maturation of dendritic cells, by inhibiting infiltration of the tumor by CD8 cells, and by promoting immunosuppressive T regulatory cells. And if you block all these actions, you have some kind of immunotherapeutic effect," he continued.

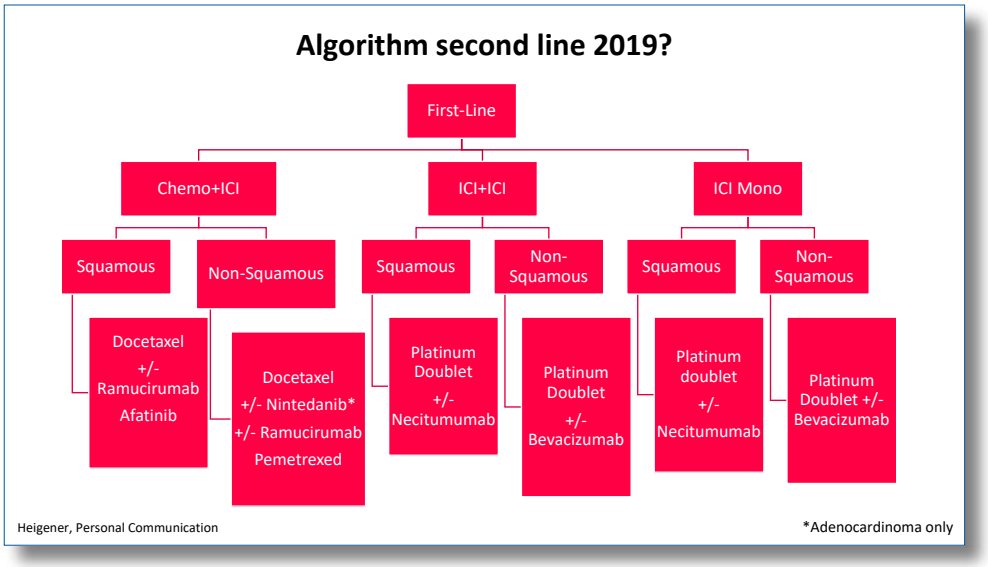
Conclusions

For most patients given a front-line ICI plus chemotherapy, second-line options are docetaxel plus ramucirumab, with an alternative of afatinib for squamous NSCLC patients. Meanwhile NSCLC nonsquamous patients may be considered for docetaxel plus nintedanib, or pemetrexed for those not previously given the agent.

For patients with first-line immunotherapy with a PD-1/PD-L1 inhibitor alone or alongside a CTLA-4 inhibitor, platinum doublet chemotherapy is an option, with or without the EGFR inhibitor necitumumab for squamous disease or bevacizumab for nonsquamous histology.

"I think docetaxel plus an anti-angiogenic agent is the new standard in second-line treatment of NSCLC after chemotherapy plus ICI, or ICI monotherapy," Heigener concluded.

"And I think we should pursue the concept of combining ICI and anti-angiogenics more in the future."



Click here to view a clip from Dr Heigener's presentation

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SPECIAL CONSIDERATIONS FOR HYPERPROGRESSIVE DISEASE

Myung-Ju Ahn

Myung-Ju Ahn opened her session with a case study of a male former smoker with an ECOG performance status of 1 who presented with back and shoulder pain, leading to a diagnosis of NSCLC adenocarcinoma in the right upper lobe and multiple bone metastases. He tested negative for *EGFR, ALK,* and *ROS1* mutations, and had PD-L1 expression of 60%.

The patient received palliative radiotherapy to his spine and Dr Ahn prompted the audience to choose which systemic regimen should be given, with a majority of 56% preferring pembrolizumab plus platinum–pemetrexed, and 36% pembrolizumab alone.

The patient began pembrolizumab monotherapy within a clinical trial but complained of neck mass after 1 week – a CT scan showed enlarged lymph nodes but the patient remained in good condition. Half the delegates recommended continuing with pembrolizumab and adding chemotherapy to the patient's regimen at this time, while 23% advised continuing pembrolizumab alone, and 21% recommended a switch to chemotherapy.

Dr Ahn explained that the patient continued with pembrolizumab as a further CT scan showed tumor shrinkage but he experienced rapid deterioration and a right pleural effusion, and died 2 months later.

Hyperprogression – 'a true phenomenon'

"The long-term follow-up data of the KEYNOTE-001 trial[1] demonstrated that the 5-year survival rate with pembrolizumab was 23% in treatment-naïve and 15% in previously treated patients, which is quite remarkable," the presenter said.

But since the introduction of ICIs, unconventional patterns of progression have been observed in some patients, namely hyperprogression and pseudoprogression.

"Hyperprogression is characterized by a rapid and unexpected rate and volume of tumor progression," explained Dr Ahn who said that debate continues on whether this is a "true phenomenon" or part of "natural tumor growth kinetics."[2]

More specifically, hyperprogression on ICI therapy has been defined as a two-fold or greater increase in the tumor growth rate between baseline and first evaluation, a calculation that requires pretreatment scans, she noted.[3]

Nevertheless, hyperprogression has been reported for solid tumor patients undergoing ICI therapy using different definitions, with rates varying from 4% to 29%.[2]

Dr Ahn told delegates that "hyperprogression has been observed in many clinical trials where the Kaplan-Meier curve of the PFS and OS has crossed over within 3 months, suggesting that some populations of the patients did worse with immunotherapy compared with chemotherapy." These include the first-line CheckMate 026[4] and 227[5], and KEYNOTE-042[6] trials, as well as the second-line setting CheckMate 057[7] and OAK[8] studies.

Thus, hyperprogression is associated with poor survival, Dr Ahn said, with further analysis of survival curves showing a significant OS difference between patients with hyperprogression and those with regular progression with the use of immunotherapy, whereas no such difference was found for chemotherapy.[9]

Hyperprogression – when and how?

Research suggests that hyperprogression may be associated with age over 65 years and female sex, as well as metastatic disease at more than two sites.[9,10,11] Other biomarkers may be recurrence within the radiation field[12], the density of tumor myeloperoxidase myeloid cells, and alterations in *EGFR, MDM2/4*, and *DNMT3A*.[13]

By contrast, hyperprogression appears to be independent of PD-L1 status, tumor burden, ECOG performance status, and type of ICI therapy[14], although Dr Ahn cautioned that as these studies are all retrospective, "we should be very careful to interpret the data."

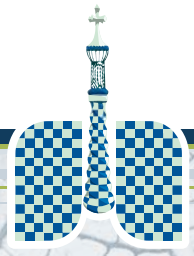
The biologic mechanisms behind hyperprogression are not yet fully determined, the presenter said, but hypotheses include a lack of tumor-infiltrating lymphocytes, the presence of immunosuppressive cells, and lack of T cell recognition of the tumor.[15]

Alternative mechanisms might be alterations in oncogenic pathways, such as the PI3K/AKT/mTOR[16] or WNT-β-catenin signaling[17], leading to immunosuppression. And recent findings have suggested that checkpoint blockade may lead to reprograming of M2-like macrophages leading to a pro-tumorigenic function, or proliferation of high expression PD-1-positive regulatory T cells.[18]

Second-line therapy after hyperprogression

Dr Ahn presented a second case study of a 52-year-old smoker without comorbidity who had been diagnosed with undifferentiated NSCLC and metastases to the left adrenal gland. The patient's tumor was wild-type for *EGFR* and *ALK*, and had an unknown PD-L1 status. The patient had begun palliative chemotherapy with carboplatin–paclitaxel but required a dose reduction after two cycles.

The presenter asked what the optimal systemic second-line treatment was in this scenario, with 56% of the audience recommending PD-1 or PD-L1 inhibitor monotherapy, 27% ramucirumab plus



docetaxel, and smaller proportions suggesting nivolumab and the CTLA-4 inhibitor ipilimumab (8%), or nintedanib plus docetaxel (7%).

Dr Ahn pointed out that, while the REVEL study was positive overall for second-line ramucirumab plus docetaxel, patients who had less than 9 months since their first-line therapy derived greater OS benefit from ramucircumab, as did those who previously achieved progressive disease as their best first-line response to platinum.[19]

Similarly, adenocarcinoma patients given nintedanib plus docetaxel in the LUME-Lung 1 trial achieved longer median OS than those using placebo plus docetaxel, with the greatest OS for patients with a duration of less than 9 months between first- and second-line therapy, and those with a prior best response of progressive disease.[20]

Returning to the case study, Dr Ahn said that the patient received docetaxel plus ramucirumab, but the tumor shrinkage did not meet the criteria for a partial response.

Dr Ahn observed that, following the use of first-line ICI therapy, the second-line treatment options are "quite challenging and we need more data." Nevertheless, she believes that chemotherapy with or without ramucircumab, afatinib, or a chemotherapy doublet regimen remain options.

Conclusions

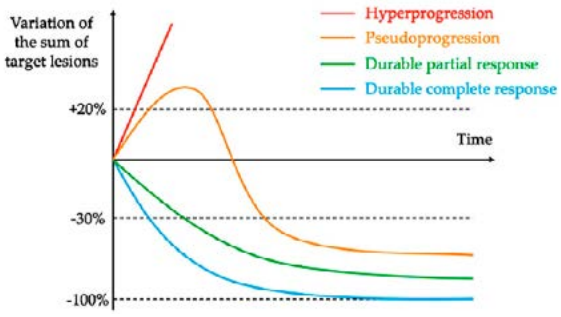
"Hyperprogression should be accepted as a real phenomenon with immune checkpoint [inhibitors]," Dr Ahn said, emphasizing that this affects between 4% and 9% of NSCLC patients and is therefore "not rare."

Moreover, the presenter told delegates that, although the definition of hyperprogression remains controversial, it is clear that affected patients have very poor OS. and thus patients with suspicion of hyperprogression should be reassessed quickly and immunotherapy stopped.

Dr Ahn concluded that while salvage chemotherapy is an option for patients with a good clinical condition, VEGF inhibitor therapy plus docetaxel might also play a role for those with early progression.

Hyperprogression

- In a subset of patients, ICI paradoxically accelerates tumor growth: hyperprogression (HP)
- Characterized by a rapid and unexpected rate and volume of progression
- Debate still exists whether HPD is a true phenomenon or simple natural tumor growth kinetics



Predictive factors associated with hyperprogression

Not fully determined yet,
but **may** be related to:

- Age > 65 year old
- > 2 metastatic sites
- Female gender
- Regional recurrence in the radiation field
- Density of myeloperoxidase myeloid cells within the tumor
- EGFR alterations, *MDM 2/4* and *DNMT3A* alterations

Not fully determined yet,
but **probably not** associated with:

- PDL1 status
- Tumor burden
- ECOG PS
- Type of ICI

Data from Champiat S, et al. *Clin Cancer Res* 2017; **23**(8):1920-1928; Ferrara R, et al. *JAMA Oncol* 2018; **4**: 1543-1552; Kanjanapan Y, et al. *Cancer* 2019; **125**(8):1218-1220; Saada-Bouzid E, et al. *Ann Oncol* 2017; **28**:1605-1611; Russo GL, et al. *Clin Cancer Res* 2018; DOI: 10.1158/1078-0432.CCR-18-1390. Kate S, et al. *Clin Cancer Res* 2017; **23**: 4242-4250; Matos I, et al. *J Clin Oncol* 2018: Abstract 3032.

Click here to view a clip from
Dr Myung-Ju's presentation

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BRIDGING THE GAP BETWEEN PROMISE AND REALITY
Panel and audience discussion

As immunotherapy antibodies have a duration of 3 or 4 months, does this mean that response to second-line chemotherapy with an anti-angiogenic agent is partly from the earlier treatment?

Dr Felip said this is "an excellent point," noting that retrospective analysis suggests that patients may do better with chemotherapy given after immunotherapy and that this should be addressed in clinical trials. Dr Ahn agreed and explained that her center is running a small randomized phase II trial comparing continuing ICI therapy plus chemotherapy after progression with chemotherapy alone.

Is the panel concerned about the risk of bleeding with second-line use of anti-angiogenic agents?

Dr Heigener replied that the risk of bleeding with ramucirumab and nintedanib has been shown as "extraordinarily low" without excessive severe bleeding and that bevacizumab is not approved in this setting.

"If someone has gross hemoptysis or severe cardiovascular disease, I would be reluctant to use anti-angiogenic agents but as long as these facts are not given, I would not be afraid to use them," he continued, even when considering that the REVEL trial occurred before the use of immunotherapy in the first line.

Would the panel consider using localized therapy to overcome resistance to immunotherapy?

The faculty members were in unanimous agreement on the use of localized radiotherapy to treat oligometastases at up to three sites during immunotherapy, with Dr Langer also reporting use of surgery to treat a solitary lung lesion during immunotherapy.

What is the optimal duration of immunotherapy and chemotherapy for a patient in remission?

Dr Langer reminded the panel of the split in audience opinion on the optimal regimen for a patient who has responded to the KEYNOTE-189 regimen of pembrolizumab and pemetrexed for 2 years, with 40% recommending continuing both agents, 25% continuing only pemetrexed, and 22% continuing instead with only pembrolizuamb.

Dr Felip said that her clinical practice halts pembrolizumab after 2 years, as per the trial protocol, but noted that KEYNOTE-010 results do suggest a risk of relapse after discontinuation of the PD-1 inhibitor. And Dr Ahn explained that Korean regulatory advice restricts pembrolizumab to 2 years but that she would consider restarting treatment if the patient progresses.

Dr Heigner told delegates that he would recommend stopping pemetrexed before 2 years, perhaps after 4–6 cycles, and continue with pembrolizuamb for 2 years. However, he observed that there is "a dilemma" as licensing in Germany recommends pembrolizumab use until disease progression. Dr Langer said he follows the KEYNOTE-189 approach but that ending pemetrexed before 2 years is becoming increasingly common in some clinics.

Regardless, all four clinicians agreed that duration of these treatments must be led by patient toxicity.

TMB, or not TMB, that is the question

Dr Langer noted that the audience response to use of TMB data agreed with his division of the community as falling into "TMB skeptics and TMB cultists," with just 15% unsure of its value.

Dr Felip said that the TMB results do not help her select specific treatments but are useful to know. While Dr Heigener said he is also keen to know TMB findings, he explained that he is a "TMB skeptic," believing the marker to be "prognostic not predictive" in the CheckMate 227 trial.

Dr Ahn also declared herself a skeptic based on the available results for TMB, noting that the MYSTIC study showed only a predictive effect with blood TMB rather than tumor assessment. This prompted Dr Langer to question whether "blood TMB is more reflective of the overall tumor as opposed to an isolated biopsy."

And *STK11/LKB1*?

Dr Langer asked the faculty whether they would be comfortable withholding immunotherapy on the basis of *STK11/LKB1* in patients with low or no PD-L1 expression, perhaps in a trial comparing chemotherapy alone or with bevacizumab versus immunotherapy.

Dr Felip agreed on the basis that "we have a feeling that patients with *STK11* will not benefit from immunotherapy," and Dr Ahn said that where *STK11* tests positive, she will not give immunotherapy.

By contrast, Dr Heigener said he would be "reluctant to preclude anyone" from ICI therapy on the basis of the available retrospective data on these mutations and Dr Langer said the marker was "incredibly intriguing" but the data needed to be verified.

He concluded the session, saying "I think we have an opening for other approaches, perhaps immuno combos, perhaps chemo in combination with other non-immune strategies, perhaps even going back to angiogenesis inhibitors."

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