# OVERALL SURVIVAL AND BIOMARKER ANALYSIS OF NEOADJUVANT NIVOLUMAB PLUS CHEMOTHERAPY IN OPERABLE STAGE IIIA NON–SMALL-CELL LUNG CANCER (NADIM PHASE II TRIAL) MARIANO PROVENCIO, MD, PHD1 ; ROBERTO SERNA-BLASCO, MSC1

DR BHAVESH PAREKH

SHALBY HOSPITAL

AHMEDABAD

# 2 WHAT IS CONCLUDING REMARKS

- CONCLUSION

- The efficacy of neoadjuvant chemotherapy plus nivolumab in resectable NSCLC is supported by 3- year OS. ctDNA levels were significantly associated with OS and outperformed radiologic assessments in the prediction of survival

# 3 BACKGROUND

- Lung cancer is a devastating disease, being the leading cause of cancer deaths worldwide.1 Nevertheless, immunotherapy-based treatments have dramatically improved outcomes and become established as a major modality for the treatment of metastatic non–small-cell lung cancer (NSCLC).

- Yet, its role in earlier stages needs to be established.

# 4 STUDY DESIGN

- Patients were treated with neoadjuvant intravenous paclitaxel (200 mg/m2 once a day) and carboplatin (area under the curve 6; 6 mg/mL per min) plus nivolumab (360 mg) once on day 1 of each 21-day cycle, for three cycles before surgical resection, followed by adjuvant intravenous nivolumab monotherapy for 1 year (240 mg once every 2 weeks for 4 months, followed by 480 mg once every 4 weeks for 8 months).

# 5 END POINT

- The primary end point was PFS at 24 months and it has been previously published.

- Secondary end points included 3- year OS and the analysis of tissue and plasma biomarkers.

# 6 DEMOGRAPHIC DATA

- All patients (N = 46) were stage IIIA.

- Regarding nodal status, nine (19.6%) patients were N0, three (6.5%) patients were N1, and 34 (73.9%) were N2.
- The median follow-up time was 38.0 months (95% CI, 36.7 to 40.7), with 94% maturity at 36 months and 90% maturity at 42 months. There were no events (death or disease progression) during neoadjuvant treatment

# 7 BASELINE BIOMARKERS

- Of the 46 patients included in the trial, 35 (76.1%) had a biopsy sample available for next-generation sequencing analysis
- 29 (63.0%) had valid data for tumor mutation burden (TMB) assessment. Similarly, programmed cell death ligand-1 (PD-L1) data were available for 28 (60.9%) samples.

- In total, 43 pretreatment plasma samples were collected.

# TUMOR RESPONSE TO TREATMENT ASSESSMENT

- Tumor response to treatment was evaluated by CT scans in all patients (N 5 46), the pathologic response was assessed in all patients who underwent surgery (n 5 41), and a plasma sample collected after neoadjuvant treatment but before surgery was available in 40 cases
- Radiologic response according to CT scans did not show any association with PFS or OS (P 5 .698 for PFS and 0.848 for OS). Likewise, pCR was not significantly associated with survival (P 5 .111 for PFS and 0.102 for OS;
- Improved PFS and OS were observed for patients with undetectable ctDNA (limit of detection established at 0.1% MAF) after neoadjuvant treatment (adjusted HR, 0.26; 95% CI, 0.07 to 0.93; P 5 .038; and HR, 0.04; 95% CI, 0.00 to 0.55; P 5 .015 for PFS and OS, respectively)

# 9 DISCUSSION

- The main objective of any neoadjuvant study should be to contribute to the cure of the patients and increase their OS.18 Our study shows an OS of 81.9% at 3 years in the ITT population and 91.0% in the PP population
- The marked difference between the current standard of care and the NADIM-based treatments is shifting our perspective on stage IIIA NSCLC from being a lethal disease to one where it may be considered potentially curable. Accordingly, there are a significant number of ongoing clinical trials addressing the role of chemoimmunotherapy in the neoadjuvant setting.

# 10 DISCUSSION

- Currently, we continue to lack surrogate end points for immunotherapy-based treatment efficacy that accurately predict long-term survival.
- Although major pathologic response has been proposed as a surrogate end point in neoadjuvant trials for resectable NSCLC,23 the hitherto accepted definition of major pathologic response as <10% of residual viable tumor in NSCLC regardless of histologic subtype is under debate
- In this study, neither TMB nor PD-L1 staining predicted long-term survival.

# 11 DISCUSSION

- In our study, patients with low ctDNA levels (MAF , 1%) at baseline had significantly improved PFS and OS than patients with high pretreatment ctDNA levels. Currently, there is not a standardized methodology to quantify ctDNA. We hypothesize that the sum of MAFs from all detected mutations would better recapitulate the status of disease as different tumor lesions may harbor different somatic mutations.

# 12 DISCUSSION

- Tumor response to treatment according to RECIST criteria was not associated with survival questioning the usefulness of radiologic response as a survival surrogate or even PFS as a trial end point when evaluating the efficacy of immunotherapy-based treatments.

# 13 CONCLUSION

- In conclusion, here we report mature OS data, with more than 3 years of follow-up, in patients with resectable stage IIIA NSCLC treated with neoadjuvant chemoimmunotherapy.
- Survival time was almost three times that reported in the historical series, in which the 3-year OS did not exceed 30%.
- Pretreatment ctDNA levels were significantly associated with survival but not classical biomarkers such as TMB or PD-L1 staining.
- Finally, undetectable ctDNA levels after neoadjuvant treatment outperformed radiologic responses assessed according to RECIST criteria v 1.1 in the prediction of OS

# Summary

ROLE OF CHEMOIMMUNO IN NEOADJUVANT TREATMENT OF NSCLC STAGE IIIA

BIOMARKER PREDICTIVITY

# THANK YOU

DR BHAVESH PAREKH

bhaveshdm1@Hotmail.com