Profile of Circulating Free DNA Using Targeted and Genome Wide Sequencing in the Patients with SCLC

SCLC is characterized by poor prognosis despite of therapy. Genomic analysis of SCLC has identified high mutation rates and copy number alterations (CNA). This study was conducted on blood samples in 32 non-cancer controls (NCC) and 69 SCLC patients. Circulating free DNA (cfDNA) and germline DNA were extracted after standard processing methods. Whole-genome libraries were generated, amplified and indexed. Targeted next-generation sequencing (NGS) of 110 cancer-associated genes was carried out in both cfDNA and germline DNA. Somatic mutations were also analyzed using two separate pipelines. Variant allele frequency of ≥3% was considered significant and recorded from cfDNA. Various readouts of CNA analysis like PGA, Z-score and Morgan’s I were calculated. The Authors found that reduced fragment size from cfDNA was significantly distinct between SCLC and NCC samples. Also, statistically significant association was seen in clinical stage and cfDNA CNA readouts. CNA, above the pre-specified threshold, was detectable in majority of SCLC samples, but in none of the control samples. Morgan’s I readout was shown to have highest sensitivity for detecting CAN readouts. For specific genes, copy number gains or losses were seen in 90% of extensive stage SCLC and 74% of limited stage SCLC. 94% of the patients were carrying at least one non-synonymous somatic mutation. TP53 and RB1 mutations were present in 78% and 34% of patient's samples, respectively. Other commonly mutated genes were COL22A1, KMT2D, NOTCH1 and MUC16. No difference in mutation profiles of extensive stage and limited stage SCLC was found. Circulating tumor cell number was increased in all SCLC patients’ samples. In conclusion, whole genome CNA changes (using three different readouts) are detectable in cfDNA of SCLC patients and can be used to pick up somatic mutations along with monitoring patients through treatment.
Phase II Trial of Concurrent Atezolizumab With Chemoradiation in Unresectable NSCLC

Current frontline treatment for unresectable non-metastatic NSCLC includes concurrent chemoradiation (CRT) followed by maintenance durvalumab for 1 year, based on the positive results of PACIFIC trial. The DETERRED trial was a two-part phase 2 trial: part 1 with CRT followed by consolidation chemotherapy and atezolizumab for 2 cycles and maintenance atezolizumab for 1 year; part 2 with CRT with atezolizumab, followed by consolidation and maintenance therapy as part 1. Primary endpoint was safety and tolerability. 10 patients were enrolled in part 1 and, upon meeting prespecified toxicity threshold, 30 patients were enrolled in part 2. Grade ≥ 3 AEs were seen in 80% in both parts. Immune related AEs grade ≥ 3 were seen in 30% and 20% patients in parts 1 and 2, respectively. These are higher than those observed in PACIFIC trial. In part 2, 13% grade 2 and 3% grade 3 pneumonitis were observed and 3%, which is similar to prior studies. Preliminary efficacy results showed a median PFS of 18.6 months and median OS of 22.8 months in part 1. In part 2, mPFS was 13.2 months, while mOS was not reached. Among 34 patients with tissue available for PD-L1 immunohistochemistry analysis, there was no statistically significant difference in rate of recurrence between tumor PD-L1 score, both using 1% cut-off for positivity (56.3% versus 38.9% for those with PD-L1 <1% and ≥1%, respectively; p=not significant) and 50% (53.8% versus 25% , for those with PD-L1 <50% and ≥50%, respectively; p=not significant). In conclusion, the DETERRED trial showed that atezolizumab with CRT followed by chemotherapy plus atezolizumab consolidation led to high rate of grade ≥3 adverse events (80%) possibly related to the addition of two cycles of consolidation chemotherapy after CRT. Preliminary efficacy results may warrant further studies.

Efficacy of Platinum/Pemetrexed Combination Chemo-therapy in ALK-Positive NSCLC Refractory to Second-Generation ALK Inhibitors

While second generation ALK tyrosine kinase inhibitors (TKIs) have high response rates and are preferred frontline agents for ALK positive metastatic NSCLC (mNSCLC), most patients develop eventual resistance to these agents. This retrospective cohort study enrolled 58 ALK positive mNSCLC patients (from 3 institutions), who were refractory to at least 1 second-generation ALK TKI and had received platinum plus pemetrexed chemotherapy (PT/pem), including PT/pem alone, PT/pem/bevacizumab, PT/pem/PD-1 inhibitor, PT/pem/TKI, PT/pem/TKI/bevacizumab, and PET/pem/TKI/PD-1 inhibitor. Among 37 evaluable patients, objective response rate (ORR) was 29.7% (partial responses: 11/37), similar to prior data reported for treatment-naïve patients, with a median duration of response of 6.4 months. 13 patients had stable disease and the remaining 13 had progressive disease. Median progression free survival (mPFS) was 4.3 months (95% CI 2.9 to 5.8 months), shorter than that reported for chemotherapy combination in treatment naïve ALK positive patients. Among 8 patients who received PT/pem/TKI, mPFS was significantly higher (6.8 versus 3.2 months) than for those who received PT/pem chemotherapy alone (n=32) (HR: 0.33, p=0.0245). There were no statistically significant differences in ORR or PFS according to ALK mutation status. In conclusion, platinum/pemetrexed based chemotherapy shows efficacy in ALK positive mNSCLC after resistance to second generation ALK TKIs. This study also suggests a potential role for continued ALK inhibition upon progression, based on improved PFS with the combination.
Research Watch

Osimertinib in Patients With Epidermal Growth Factor Receptor Mutation-Positive NSCLC and Leptomeningeal Metastases: The BLOOM Study

Approximately 9% of patients with EGFR mutation positive advanced NSCLC develop leptomeningeal metastases (LM). Such event is associated with a dismal prognosis accounting for a median overall survival (OS) of 3 to 10 months from diagnosis. The BLOOM study was a 2-part, phase I, open-label, multicenter study evaluating the safety and activity of osimertinib at 160 mg daily dose in patients with EGFR mutation positive advanced NSCLC and LM.1 In the present work, Yang and colleagues reported the results from the part B of the trial that included patients who have progressed on previous EGFR tyrosine kinase inhibitor (TKI) enrolled in 2 cohorts: unselected and those with T790M mutation.2 Treatment beyond progression was allowed as long as there was clinical benefit. Before the first dose of osimertinib, plasma and cerebrospinal fluid (CSF) were collected. The study enrolled 41 Asian patients, most female (71%) and never smokers (73%), 20 with known T790M mutation; the majority of patients had received first generation TKIs (93%), 85% had already been treated with chemotherapy, while 49% with brain radiotherapy. The confirmed LM overall response rate (ORR) by blinded central independent review (BICR) was 62% (95% CI, 45-78%) with 12 complete responses and a median LM duration of response (DoR) was 15.2 months (95% CI, 7.5-17.5 months). Such activity did not correlate with previous brain radiotherapy and was higher in the unselected population, probably due to selection biases. The confirmed central nervous systems (CNS) ORR was 58% (95% CI, 28-85%) while the confirmed ORR was 41% (95% CI, 26-58%). Confirmed CSF clearance was observed in 11 of 40 evaluable patients and treatment improved neurologic function 12 of the 21 impaired subjects. The median progression-free survival (PFS) and overall survival (OS) were 8.6 (95% CI, 5.4-13.7 months) and 11 (95% CI, 8.0-18.0 months) months, respectively. Safety was similar to that of the 80 mg daily dose, with 27 of patients experiencing a grade /C21 adverse events that was judged possibly related to osimertinib in 10 cases. None of these latter was fatal. BLOOM was the largest prospective study testing an EGFR TKI in patients with advanced NSCLC and LM, demonstrating meaningful efficacy and good tolerability. However, while retrospective analyses of trials investigating osimertinib at 80 mg daily dose suggest a similar activity even in patients with LM3,4, in the absence of a direct comparison, the 80 mg dose should still be considered the standard, even when LM are present.

1. Ahn MU, Kim DW, Cho BC, et al. Activity and safety of AZD3759 in EGFR-mutant non-small-cell lung cancer with CNS metastases (BLOOM): a phase 1, open-label, dose-escalation and dose-expansion study. Lancet Respir Med. 2017;5:891-902.
2. Yang JCH, Kim SW, Kim DW, et al. Osimertinib in patients with epidermal growth factor receptor mutation-positive non-small-cell lung cancer and leptomeningeal metastases: the BLOOM study [e-pub ahead of print]. J Clin Oncol. https://doi.org/10.1200/JCO.19.00457, accessed December 16, 2019.
3. Goss G, Tsai CM, Shepherd FA, et al. CNS response to osimertinib in patients with T790M-positive advanced NSCLC: pooled data form two phase II trials. Ann Oncol. 2018;29:687-693.
4. Reungwetwattana T, Nakagawa K, Cho BC, et al. CNS response to osimertinib versus standard epidermal growth factor receptor tyrosine kinase inhibitors in patients with untreated EGFR-mutated advanced non-small-cell lung cancer [e-pub ahead of print]. J Clin Oncol. https://doi.org/10.1200/JCO.2018.78.3118, accessed December 16, 2019.

Effect of Thoracoscopic Talc Poudrage Versus Talc Slurry via Chest Tube on Pleurodesis Failure Rate Among Patients With Malignant Pleural Effusions: A Randomized Clinical Trial

Malignant pleural effusion (MPE) is a common condition associated with many different neoplasms. Talc pleurodesis is the preferred treatment for many patients with MPE, with the goal to achieve the cessation of fluid production. However, such procedure may be done either through an intercostal chest tube in the form of a slurry or during a thoracoscopic procedure where talc is sprayed directly onto the pleural surface. The TAPPS trial was a randomized, open-label, parallel-group superiority study comparing thoracoscopy and talc poudrage versus pleurodesis using talc slurry with a 1:1 randomization. The trial was conducted in 17 hospitals in the United Kingdom, where a pulmonologist-led thoracoscopy service was present. Patients were defined to have MPE if cancer was histocytologically proven, unexplained pleural effusion appeared in the context of an already
known tumor, or pleural changes suggestive for malignancy were observed on cross-sectional imaging. At randomization, the imbalance was minimized using the underlying type of cancer and the performance status. All groups received 4 grams of sterile talc either during thoracoscopy with local anesthesia or through an ultrasonography-inserted 12-14 French chest tube. Patients were followed up until 180 days after randomization or death; chest X-rays were performed in any patients with worsening dyspnoea and further studied with ultrasonography and CT scans when fluid presence was suspected. The primary end-point was pleurodesis failure at 90 days after randomization, defined as: removal of $\geq$ 100 ml of fluid during thoracentesis, chest tube insertion for fluid management; insertion of an indwelling pleural catheter; thoracoscopy. Between August 2012 and April 2018, 330 patients were enrolled in the trial. Talc was received as intended in 97% and 89% of patients in the talc poudrage and talc slurry groups, respectively. Notably, fewer patients in the poudrage group were receiving chemotherapy as compared to the slurry group at the time of the procedure (9% versus 20%). The most frequent tumors were lung cancer, breast cancer and mesothelioma, accounting for 75% of patients. Fully lung expansion 18 to 24 hours after fluid drainage and at the time of tube removal was comparable between arms. The 90 days pleurodesis failure rate was 22% in the poudrage group and 24% in the talc slurry group (adjusted odds ratio 0.91, 95% CI 0.54-1.55, p=0.74). 27 and 34 patients died before pleurodesis failure in the poudrage and slurry groups, respectively. No differences in the failure rate were seen neither at 30 nor at 180 days, and there were no differences in time to pleurodesis failure. The two treatments did not differ even when analyzing hospital stay, chest pain, dyspnoea, post-tube chest opacification rate, or health-related quality of life. The most frequent adverse events, beside dyspnoea due to fluid re-accumulation, were pneumonia and pulmonary infections and pneumothorax unrelated to the intervention. In conclusion, the TAPPS trial did not demonstrate differences in pleurodesis failure rate between thoracosopic talc poudrage and talc slurry. As the Authors noted, the study has several limitations, as included only patients able to tolerate thoracoscopy, the intervention was not blinded, and was not powered to detect small differences that may be considered clinically relevant.

Bhatnagar R, Piotrowska HEG, Laskawiec-Szkonter M, et al. Effect of thoracoscopic talc poudrage versus talc slurry via chest tube on pleurodesis failure rate among patients with malignant pleural effusions: a randomized clinical trial [e-pub ahead of print]. JAMA. https://doi.org/10.1001/jama.2019.19997, accessed December 16, 2019.

An Analysis of E-cigarette Marketing in New Zealand Tobacco Retail Outlets Prior to Legislative Change

Use of electronic nicotine delivery systems (ENDS) has increased internationally, yet the public health community remains divided over the risks and benefits these devices offer. Indeed, not all smokers transition fully from smoking to ENDS use and point out high youth experimentation with ENDS. n 2017, the NZ Government announced that it would legalize sales of nicotine-delivering ENDS, a move that legitimized the status quo and recognized ENDS’ harm reduction potential. Liberalizing the sale and marketing of ENDS thus requires careful analysis to ensure policy changes do not place young people at risk of ENDS experimentation. After drawing a proportional random sample of 281 tobacco outlets from two NZ regions that included convenience stores, supermarkets and petrol stations, the authors conducted observational in-store assessments to record ENDS product ranges and promotions. Data were collected between October and December 2017 and analyzed using descriptive statistics and regression modelling. This research reported that of tobacco outlets sampled, 22% sold ENDS, mainly convenience stores (85%) and located in high deprivation areas (53%). Of stores selling ENDS, products were visible at point-of-sale (POS) in 89% of stores, including 15% with self-service displays and 15% with displays adjacent to children’s products. The ENDS advertising was present in 31% of the outlets and generally promoted ENDS as cheaper than smoked cigarettes. The NZ Government now views ENDS as part of a harm-reduction strategy; however, to reduce the harm posed by smoking, policy makers must ensure that regulatory changes target only current smokers and protect non-smokers, particularly children and young people, from ENDS promotions. Allowing ENDS marketing to include POS displays juxtaposed with children’s products may promote youth uptake.

Bateman J, Robertson J, Marsh L, Cameron C, Hoek J. An analysis of e-cigarette marketing in New Zealand tobacco retail outlets prior to legislative change [e-pub ahead of print]. Nicotine Tob Res https://doi.org/10.1093/ntr/ntz226, accessed December 16, 2019.
Real-World Effectiveness of Smoking Cessation Strategies for Young and Older Adults: Findings From A Nationally Representative Cohort

Young adults have high combustible cigarette and e-cigarette use rates, and low utilization of evidence-based smoking cessation strategies compared to older adults. It remains unknown whether evidence-based strategies for quitting smoking or with e-cigarettes also work in young adults compared to older adults. In this study two population samples were analyzed: young adult (aged 18-24, n = 745) and older adult (aged 25-64, n = 2,057) established cigarette smokers at Wave 1 (2013–2014) who reported having made a quit attempt at Wave 2 (2014–2015). Cessation strategies were: behavioral therapy, pharmacotherapy, product substitution, 2+ strategies, and unassisted. No cessation strategy (ref: unassisted) significantly predicted short-term cessation. No cessation strategy (ref: unassisted) significantly predicted long-term cessation patterns for young adults. Substitution with e-cigarettes predicted short-term cessation for older daily smokers of ≥5 cigarettes/day (AOR: 1.70; 95% CI: 1.08, 2.67), but did not predict long-term cessation patterns. Neither behavioral support, pharmacotherapy or product substitution was associated with short-term cessation for young or older adults compared to quitting unassisted. Cessation strategies were different between both samples and the effectiveness was short. Therefore, more effective interventions to quit smoking among young adult smokers are eagerly awaited.

Watkins SL, Thrul J, Max W, Ling PM. Real-world effectiveness of smoking cessation strategies for young and older adults: Findings from a nationally representative cohort [e-pub ahead of print]. Nicotine Tob Res. 2019 https://doi.org/10.1093/ntr/ntz223, accessed December 16, 2019.

Effectiveness of a Brief Self-determination Theory-Based Smoking Cessation Intervention for Smokers at Emergency Departments in Hong Kong: A Randomized Clinical Trial

The effectiveness of a brief intervention based on self-determination theory for smoking cessation in smokers, who present to emergency departments (EDs) remains unknown. The current single-blind, multicenter intent-to-treat randomized clinical trial was conducted at the EDs of 4 major acute care hospitals in different districts of Hong Kong. In total, 1571 smokers 18 years or older who presented at 4 major EDs between July 4, 2015, and March 17, 2017, were randomized into an intervention group (n = 787), who received brief advice (about 1 minute) and could choose their own quit schedules (immediate or progressive); and the control group (n = 784) who received a smoking cessation leaflet. Majority of participants were male (88%) and mean age was 47.4 years. Among those participants who self-reported abstinence at 6 months, 50.3% had biochemical validation by an exhaled carbon monoxide test and a saliva cotinine test. Compared with the control group, the interventional group had statistically higher biochemically validated abstinence at 6 months: 6.7% versus 2.8% (P < 0.001), with an adjusted relative risk of 3.21 (95% CI, 1.74-5.93; P < 0.001), and self-reported quit rates at 6- and 12-months were also higher (12.2% versus 9.3%, P = 0.04 and 13.0% versus 8.5%, P < 0.01, respectively). The additional cost for each intervention group participant was US $0.47, with an estimated gain of 0.0238 quality-adjusted life-year. The incremental cost per quality-adjusted life-year (US $19.53) fell within acceptable thresholds. This simple intervention may offer a cost-effective and sustainable approach to help many smokers to quit.

Li WHC, Ho KY, Wang MP et al. Effectiveness of a brief self-determination theory-based smoking cessation intervention for smokers at emergency departments in Hong Kong: a randomized clinical trial [e-pub ahead of print]. JAMA Intern Med. 2019 https://doi.org/10.1001/jamainternmed.2019.5176, accessed December 16, 2016.

News-in-Brief

Durvalumab Granted Priority Review by the FDA

On November 29, 2019, durvalumab was granted priority review by the US FDA for treatment of previously untreated extensive-stage small cell lung cancer. CASPIAN study is a phase III randomized trial of durvalumab plus platinum-etoposide versus durvalumab/tremilimumab plus platinum-etoposide versus platinum-etoposide alone in a 1:1:1 randomization. Results for durvalumab plus platinum-etoposide group showed prolonged overall survival compared to chemotherapy alone. Median OS was 13.0
months for chemotherapy-durvalumab combination, while it was 10.3 months for chemotherapy (HR 0.73; 95% CI 0.59–0.91; p=0.0047). Any-cause adverse events of grade 3 or 4 occurred in 62% patients in both groups.

Paz-Ares L, Dvorkin M, Chen Y et al. Durvalumab plus platinum-etoposide versus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial. Lancet. 2019;394:1929-1939.

FDA Approved Atezolizumab in Combination With Chemotherapy for First Line Treatment of Stage IV NSCLC

On December 3, 2019, the US FDA approved the combination of carboplatin, nab-paclitaxel and atezolizumab for the first-line treatment of adult patients with metastatic non-squamous NSCLC (mNSCLC) with no EGFR or ALK genomic tumor aberrations. This approval is based on results of IMpower130, a randomized (2:1) open label phase III study in 724 patients with mNSCLC. Patients received atezolizumab with carboplatin and nab-paclitaxel, followed by maintenance atezolizumab or carboplatin and nab-paclitaxel, followed by maintenance pemetrexed. The study met its primary outcomes of PFS and OS in patients with wild type EGFR or ALK alterations. The mPFS was 7.2 months for the atezolizumab arm compared to 6.5 months for the control arm (HR 0.75; 95% CI: 0.63, 0.91; p = 0.0024). Median OS were 18.6 months and 13.9 months for the atezolizumab and control arms, respectively (HR 0.80; 95% CI: 0.64, 0.99; p=0.0384).

FDA approves atezolizumab with nab-paclitaxel and carboplatin for metastatic NSCLC without EGFR/ALK aberrations. FDA, December 5, 2019. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-atezolizumab-nab-paclitaxel-and-carboplatin-metastatic-nsclc-without-egfralk. Accessed December 16, 2019.

Depression: A Common and Neglected Co-Morbidity in Newly Diagnosed Patients With NSCLC

A recent study evaluated the prevalence of major depression in newly diagnosed lung cancer patients. 186 patients who were treatment naive were subjected to screening measures for depression and 36% of the patients were found to be suffering from moderate to severe depression. Most of the patients reported symptoms of hopelessness, elevated anxiety levels and stress. Patients with severe depression were also found to be at higher risk of suicidal intentions. This group of patients reported increased incidence of physical symptoms like dyspnea, cough and pain. Depression was also found to be associated with low functionality and added to the morbidity of patients. This study re-emphasizes the importance of screening for depressive symptoms in newly diagnosed cases of lung cancer. It also provides highlights the need for appropriate referrals and care directed towards alleviating symptoms of depression.

Andersen BL, Valentine TR, Lo SB, Carbone DP, Presley CJ, Shields PG. Newly diagnosed patients with advanced non-small cell lung cancer: A clinical description of those with moderate to severe depressive symptoms [e-pub ahead of print]. Lung Cancer. https://doi.org/10.1016/j.lungcan.2019.11.015, accessed December 16, 2019.
Access to Novel Drugs for NSCLC in Central and South-Eastern Europe: A Central European Cooperative Oncology Group Analysis

Despite accelerated development and subsequent drug registrations by the European Medicinal Agency (EMA), novel drugs for NSCLC, mainly tyrosine kinase inhibitors and immune checkpoint inhibitors, are poorly accessible in Central and Eastern European (CEE) countries. In general, the availability of drugs is not in accordance with the Magnitude of Clinical Benefit Scale (MCBS), as defined by the European Society for Medical Oncology (ESMO). Time spans between drug registrations and national decisions on reimbursement vary greatly, from less than 3 months in one country to more than 1 year in the majority of countries. The access to novel drugs for NSCLC in CEE countries is suboptimal, introducing relevant treatment inequalities. Therefore, reimbursement decisions should be faster and ESMO MCBS should be incorporated into decision making. Cufer T, Guleanu TE, Berzinec P et al. Access to novel drugs for non-small cell lung cancer in Central and South-eastern Europe: a Central European cooperative oncology group analysis [e-pub ahead of print]. Oncologist. https://doi.org/10.1634/theoncologist.2019-0523, accessed December 16, 2019.

ESMO ASIA 2019

Overall Survival With Osimertinib in Untreated, EGFR-Mutated Advanced NSCLC

FLAURA trial compared osimertinib versus first generation EGFR tyrosine kinase inhibitors (erlotinib or gefitinib) as first-line treatment in advanced EGFR mutant NSCLC patients. Osimertinib had already reported benefit in PFS, and recently OS data has been presented and published. The median OS was 38.6 months in the osimertinib group and 31.8 months (95% CI, 26.6 to 36.0) in the comparator group (hazard ratio for death, 0.80; 95.05% CI, 0.64 to 1.00; \( P = 0.046 \)). At 3 years, 79 of 279 patients (28%) in the osimertinib group and 26 of 277 (9%) in the comparator group, without differences in the toxicity profile (adverse events of grade 3 or higher were reported in 42% of the patients in the osimertinib group and in 47% of those in the comparator group) despite a longer duration of exposure in the osimertinib group. Ramalingam SS, Vansteenkiste J, Planchard D, et al. Overall survival with osimertinib in untreated, EGFR-mutated, advanced NSCLC [e-pub ahead of print]. N Engl J Med. https://doi.org/10.1056/NEJMoa1913662, accessed December 16, 2019.

Overall Survival from the AURA3 Phase III Study: Osimertinib Versus Platinum-Pemetrexed in Patients with EGFR T790M Advanced NSCLC and Progression on a Prior EGFR-TKI

AURA3 Phase III trial compared osimertinib with platinum-based doublet chemotherapy (platinum-pemetrexed) in patients with EGFR T790M NSCLC and disease progression on a prior EGFR-TKI therapy. The results from the primary analysis (data cut-off 15 Apr 2016) demonstrated that osimertinib led to a statistically significant superior PFS as compared to platinum-pemetrexed. However, osimertinib did not improve OS compared with chemotherapy (26.8 months versus. 22.5 months, HR: 9.87; 95% CI: 0.67-1.12, \( p=0.277 \)). This lack of OS difference could be explained by the fact that 73% of patients in the control arm received osimertinib at the time of progression. Wu Y-L, Mok TSK, Han J, et al. Overall survival from the AURA3 phase III study: osimertinib versus platinum-pemetrexed in patients with EGFR T790M advanced NSCLC and progression on a prior EGFR-TKI. Ann Oncol. 2019;30(suppl_9):ix157-ix181. 10.1093/annonc/mdz437.
TATTON Expansion Cohorts: A Phase Ib Study of Osimertinib plus Savolitinib in Patients With EGFR-Mutant, MET-Positive NSCLC Following Disease Progression on Previous EGFR TKI

TATTON is a multi-arm, multi-drug combination study and one arm tested the combination of osimertinib and savolitinib (a highly selective MET TKI) in advanced/metastatic, MET-positive, EGFRm NSCLC patients, whose disease had progressed on prior therapy. Patients were enrolled based on MET status by local fluorescent in-situ hybridization (MET gene copy ≥5 or MET/CEP7 ratio ≥2), next-generation sequencing or immunohistochemistry (+3 in ≥50% of tumor cells), with retrospective central confirmation. At 2019 ESMO ASIA updated results from TATTON Part B and data from Part D were presented. Patients in Part B (N=138) received osimertinib 80 mg + savolitinib 600 mg or 300 mg orally (PO) once daily (QD) in 3 sub-parts: B1: previous 3rd generation EGFR TKI; B2: no previous 3rd generation EGFR TKI and T790M negative; B3: no previous 3rd generation EGFR TKI and T790M positive. Patients in Part D (N=42) received osimertinib 80 mg + savolitinib 300 mg PO QD, were T790M negative and did not received prior 3rd generation EGFR TKI. Primary endpoints were safety and tolerability; secondary endpoints included objective response rate (RR) and progression-free survival (PFS). The RR and PFS in B1, B2, B3 were: 30% and 5.4 months, 65% and 9.0 months, and 67% and 11.0 months, respectively, whereas in arm D were 64% and 9.1 months, respectively in Parts B and D. Grade ≥3 adverse events (AEs) were reported by 57% and 38% of patients in part B and D, respectively, while serious AEs by 45% and 26%, respectively.

Han J-Y, Sequist LV, Ahn M-J et al. TATTON expansion cohorts: A phase Ib study of osimertinib plus savolitinib in patients (pts) with EGFR-mutant, MET-positive NSCLC following disease progression on a prior EGFR-TKI. Ann Oncol. 2019;30(suppl_9):mdz446.001.

Brigatinib Versus Crizotinib in ALK Inhibitor–Naive Advanced ALK+ NSCLC: Updated Results From the Phase 3 ALTA-1L Trial

ALTA-1L trial compared brigatinib versus crizotinib in ALK-positive advanced NSCLC. One previous line of chemotherapy was allowed in the study. Updated PFS results were presented during the congress. Median PFS with brigatinib was 29.4 months versus 9.2 months with crizotinib, as assessed by investigators (HR 0.43, 95% CI 0.31-0.61, p < 0.0001), and benefit with brigatinib was more pronounced in patients with baseline brain metastases (HR 0.24, 95% CI 0.12-0.45, p < 0.0001). The BIRC-assessed median PFS was 24.0 months for brigatinib and 11.0 months for crizotinib (HR 0.49, 95% CI 0.35-0.68, p < 0.0001). The intracranial RR (78% versus 26%, p < 0.0001) and intracranial PFS assessed by BICR also favored to brigatinib instead of crizotinib (24 months versus 5.6 months, HR 0.31, 95% CI 0.17-0.56, p < 0.0001). Confirmed ORR was 74% for brigatinib compared with 62% with crizotinib as assessed by a BIRC (p = 0.0342).

Camidge DR, Kim HR, Ahn M-J et al. Brigatinib versus crizotinib in patients with ALK inhibitor-naive advanced ALK+ NSCLC: Updated results from the phase III ALTA-1L trial. Ann Oncol. 2019;30(suppl_9):ix183-ix202.

Updated Efficacy and Safety of Entrectinib in Patients With NTRK Fusion-Positive Tumors: Integrated Analysis of STARTRK-2, STARTRK-1 and ALKA-372-001

Entrectinib is a systemic and CNS-active, potent inhibitor of TRKA/B/C and ROS1. The updated results in 54 adult patients with advanced/metastatic NTRK+ solid tumors, including patients with baseline CNS metastases reported by blinded independent central review (BICR) an objective response rate (ORR) of 59.3% with median duration of response of 12.9 months and median OS of 23.9 months. Per baseline CNS status, BICR ORR was 58.3% and 59.5% and median DOR was NE (4.2–NE) and 12.9 months (7.9–NE) for patients with (n = 12) and without (n = 42) CNS disease, respectively. Intracranial ORR was 54.5% and median IC DOR by BICR was NE (6.7–NE). Entrectinib was well tolerated with a safety profile consistent with that previously reported; there were no new or unexpected safety findings.

Rolfo C, Dziadziuszko R, Doebele RC et al. Updated efficacy and safety of entrectinib in patients with NTRK fusion-positive tumours: Integrated analysis of STARTRK-2, STARTRK-1 and ALKA-372-001. Ann Oncol. 2019;30(suppl_9):ix22-ix29.
Entrectinib in Locally Advanced/Metastatic ROS1 and NTRK Fusion-Positive NSCLC: Updated Integrated Analysis of STARTRK-2, STARTRK-1 and ALKA-372-001

There were 53 efficacy-evaluable patients with treatment-naïve, ROS1-positive NSCLC and 10 patients with NTRK-positive NSCLC. The BICR ORR was 79.2% in ROS1+ and 70.0% in NTRK+, respectively. In ROS1+ NSCLC, median DOR was 24.6 months; in patients with and without baseline CNS disease, ORR was 73.9% and 83.3%, respectively; intracranial ORR was 55.0% and median IC DOR was 12.9 months. Entrectinib was well tolerated, with a safety profile consistent with that previously reported; there were no new or unexpected safety findings.

De Braud F, Siena S, Barlesi F et al. Entrectinib in locally advanced/metastatic ROS1 and NTRK fusion-positive non-small cell lung cancer (NSCLC): Updated integrated analysis of STARTRK-2, STARTRK-1 and ALKA-372-001. Ann Oncol. 2019;30(suppl_9):ix22-ix29.

News from the IASLC Tobacco Control Committee

Lung Transplant From the Vaping Epidemic

This story has yet to appear in the medical literature but there have been media reports that raise the seriousness of EVALI (e-cigarette or vaping associated lung injury) to a new level. At the time of writing, the CDC reports a total (in the United States) of 2409 cases of hospitalized EVALI with 52 deaths in 26 states with a mean age (for deceased patients) of 52y (17-75).1 In November, several media outlets reported a case of lung transplantation in a young man as a result of EVALI.2-5 The story emerged in mid-November: a 17 year-old student had received a lung transplant after falling ill a month beforehand as a result of vaping, although in the interests of privacy further details of devices, brands and whether nicotine or cannabis, had been withheld. At the time of reporting, the patient was evidently making good progress and was out of intensive care but, to quote the family, “our lives have been changed forever.”3(para.23) Relatively few medical details are given — he spent time on extracorporeal membrane oxygenation (ECMO) prior to transplant, required inter-hospital transfer and required urgent listing and priority for donor organs. A press conference video can be seen on the Washington Post report5 and images of his lungs, pre- and post-transplant, are presented with the media reports. Fortunately, the young man appears likely to recover, although the implications of transplantation last a lifetime and he will have to live with the permanent need for medication and close medical supervision. As the lead surgeon from the transplant team said, “this is a preventable tragedy”4(para.9), although prevention may require the kind of regulatory oversight of these products that appears impossible to introduce, at least at the speed required to stop this epidemic.

1. Latest outbreak information. CDC. https://www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-disease.html#latest-outbreak-information. Accessed December 16, 2019.
2. Shamus KJ. 17-year-old is first vape-injured patient in U.S. to undergo double lung transplant. USA Today, November 12, 2019. https://www.usatoday.com/story/news/nation/2019/11/12/teen-vaping-injuries-has-double-lung-transplant/2581217001/. Accessed December 16, 2019.
3. Grady D. Facing ‘certain death,’ teenager with vaping injury gets double lung transplant. NYTimes, November 12, 2019. https://www.nytimes.com/2019/11/12/health/vaping-double-lung-transplant.html. Accessed December 16, 2019.
4. Hawkins D. Doctors say they’ve performed the first double lung transplant due to vaping. Science Alert, November 14, 2019. https://www.sciencealert.com/vaping-injury-caused-this-young-athlete-to-need-a-double-lung-transplant. Accessed December 16, 2019.
5. Hawkins D. A young athlete just received what doctors say is first double-lung transplant due to vaping. The Washington Post, November 12, 2019. https://www.washingtonpost.com/health/2019/11/12/young-athlete-just-received-what-doctors-say-is-first-double-lung-transplant-due-vaping/. Accessed December 16, 2019.
Another Type of Lung Disease From Vaping

Lung injury from vaping can present with a range of findings. The American Thoracic Society lists vaping-associated disease patterns that may include acute eosinophilic pneumonia, lipoid pneumonia, acute lung injury and respiratory distress, hypersensitivity pneumonitis, organizing pneumonia, diffuse alveolar hemorrhage and respiratory bronchiolitis.1 A review of lung biopsies from 17 patients who were clinically suspected to have vaping-associated lung disease showed changes of acute lung injury, including diffuse alveolar damage.2 Many of the cases in the literature probably fit with acute lung injury and respiratory distress, including the case reported above. A recent case reported in the Canadian Medical Journal3 gives the details of a different lung injury, known as popcorn lung and thought to result from inhalation of diacetyl, the butter flavor agent in food. The injury includes intense inflammation of small airways and characteristic nodular infiltrates on chest CT. In this case report from the literature, another 17-year-old boy who had used vaping devices for five months (varying flavors and regularly adding THC) became unwell and, similar to above, required intensive care, ECMO support and was referred to the local transplant team. He survived with treatment however, avoided transplant and was eventually discharged home. Two things stand out from this case, especially for the pulmonologists on the Tobacco Control Committee. First, the type of injury — this varies somewhat from the bulk of cases reported so far and reminds us of the range of presentations possible. Secondly, the follow up information — in this case, the patient was left with impaired lung function at least in the short term. At one-month post-discharge the forced expiratory volume in one second (FEV1) measured 31% predicted, improving only partially at 3-months to 55% predicted, associated with a reduction in exercise tolerance, a worry in a young man. Follow up data like these will inform the long-term nature of this preventable tragedy and add to the urgent need for effective legislation and regulatory details.

1. Carlos WG, Crotty Alexander LE, Gross JE, et al. Vaping-associated pulmonary illness (VAPI). Am J Respir Crit Care Med. 2019;200:P13–P14.
2. Butt YM, Smith ML, Tazelaar HD, et al. Pathology of vaping-associated lung injury. N Engl J Med. 2019;381:1780-1781.
3. Landman ST, Dhaliwal I, Mackenzie CA, Martinu T, Steele A, Bosma KJ. Life-threatening bronchiolitis related to electronic cigarette use in a Canadian youth. CMAJ. 2019;191:E1321-E1331.

The Main Game

Plain packaging for tobacco cigarettes was introduced in Australia 7-8 years ago and represented a major change in the marketing and advertising of cigarettes, one of the key MPOWER measures recognized as crucial for good tobacco control.1 Once sold in glossy, coloured, brand-recognizable packs, cigarettes were subsequently sold in uniform, unattractive boxes with large font health warnings and daunting images of tobacco related disease. A quick search of the internet will find the Australian images, which we think are still fairly shocking even after the passage of time.2 The tobacco industry reacted strongly to the introduction of plain packaging, leaping in with legislative challenges even while laws were in the planning and prior to their enactment. A paper from Melbourne University Law School3 summarizes the efforts of the tobacco industry in its legislative opposition in Australia as follows:

- 2008: the industry objected to plain packaging,
- 2010: Australia announced its intention to pursue plain packaging,
- 2011: Australia passed the legislation,
- 2012: the tobacco industry loses a case in the High Court of Australia opposing plain packaging,
- 2015: Philip Morris Asia has a case against plain packaging rejected at an international tribunal,
- 2016: a Ukrainian claim against Australia lapses,
- 2018: a WTO Panel finds for Australia,
- 2019: Honduras and the Dominican Republic file appeals against Australia.

The details are often hidden, final decisions in some cases have yet to be released and there are suggestions that the tentacles of industry have reached to government levels — British American Tobacco has admitted supporting the Ukraine with legal costs here.4 The worries of the tobacco industry about plain packaging have been captured in a series of illuminating quotes5, recorded by Tobacco Tactics6, a project from the Tobacco Control Research Group at the University of Bath. The quotes are great; two of our favorites are:
Plain packaging is the "biggest regulatory threat to the industry, as packaging is the most important way tobacco companies have to communicate with the consumer and differentiate their products." Investment bank, Citigroup (April 2010)

"In the absence of any other Marketing messages, our packaging – comprised of the trademark, our design, color and information – is the sole communicator of our brand essence. Put another way – when you don’t have anything else – our packaging is our Marketing." Philip Morris (May 1994)

Plain packaging has continued a slow and steady march around the world with more than 20 countries at various stages of execution. Legislation has been passed in seven countries and implemented in five with a report from the Hürriyet Daily News, a major English language newspaper in Turkey, updating progress of plain packaging there. Turkey has become the 7th nation in the plain packaging line-up with legislation finalized in December 2018, supplementing the longstanding indoor smoking ban that dates from 2009. The plain packaging legislation will be implemented from December 5, 2019, with sales of branded packing to end on January 5, 2020 and will include pictorial warnings covering 85% of the pack. Smoking rates remain very high for Turkish men, with 41.4% of males over 15 smoking daily (compared with a rate of 16.3% in women) and a male mortality rate (for tobacco-related causes) of 26% (or over a 1000 men per week). It is too soon worldwide for a comprehensive review of the impact of plain packaging on smoking rates generally. But encouraging results have been summarized by the Cancer Council Victoria, on the website tobaccoinaustralia.org.au. Findings from research into the effects of plain packaging include negative views of the packs, less devotion to brand and greater perception of harms from smoking.

1. Tobacco Free Initiative. World Health Organization. https://www.who.int/tobacco/mpower/en/. Accessed December 16, 2019.
2. Choahan N. Update graphic images on cigarette packages to remind of health risks, experts say. RACGP, September 7, 2018. https://www1.racgp.org.au/newsgp/clinical/update-graphic-images-on-cigarette-packages-to-rem. Accessed December 16, 2019.
3. Voon T. Big tobacco vs Australia’s plain packaging. Pursuit, September 5, 2019. https://pursuit.unimelb.edu.au/articles/big-tobacco-versus-australia-s-plain-packaging. Accessed December 16, 2019.
4. Reuters. Ukraine drops lawsuit against Australia over plain-packaging tobacco laws, WTO says. ABC News, June 3, 2015. https://www.abc.net.au/news/2015-06-04/plain-packaging-tobacco-ukraine-drops-lawsuit-against-australia/6520160. Accessed December 16, 2019.
5. Good quotes on plain packaging. Tobacco Tactics. https://www.tobaccotactics.org/index.php?title=Good_Quotes_on_Plain_Packaging. Accessed December 16, 2019.
6. Welcome to Tobacco Tactics. Tobacco Tactics. https://www.tobaccotactics.org/index.php?title=Main_Page. Accessed December 16, 2019.
7. Plain packaging cigarettes. Cancer Institute NSW, September 10, 2019. https://www.cancer.nsw.gov.au/how-we-help/cancer-prevention/stopping-smoking/plain-packaging-cigarettes. Accessed December 16, 2019.
8. Plain tobacco packing hit shelves in Turkey to curb smoking. Hürriyet Daily News, December 8, 2019. http://www.hurriyetdailynews.com/plain-tobacco-packing-hit-shelves-in-turkey-to-curb-smoking-149592. Accessed December 16, 2019.
9. Turkey: new regulations on plain packaging. FCTC, March 5, 2019. https://untobaccocontrol.org/implldb/turkey-new-regulations-on-plain-packaging/. Accessed December 16, 2019.
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11. Turkey. The Tobacco Atlas. https://tobaccoatlas.org/country/turkey/. Accessed December 16, 2019.
12. Real-world research on the effects of plain packaging. Tobacco in Australia. https://www.tobaccoinaustralia.org.au/chapter-11-advertising/indepth-11a-packaging-as-promotion/11a-9-real-world-research-on-the-effects-of-plain-. Accessed December 16, 2019.