In This Issue

Ceritinib plus Nivolumab in Patients with Advanced ALK-Rearranged NSCLC: Results of an Open-Label, Multicenter, Phase 1B Study

Tyrosine kinase inhibitors and immunotherapy have changed the spectrum of treatment in advanced NSCLC. ALK rearrangement is present in 3-7% of non-squamous NSCLC. Nivolumab, a programmed death-1 (PD-1) immune-checkpoint inhibitor is approved for advanced NSCLC progressed after platinum-based chemotherapy. This phase 1B study explored the role of combining ceritinib (ALK inhibitor [ALKi]) and nivolumab for the treatment of ALK-positive advanced NSCLC. It was an open-label, multi-center study with whose primary objective was to determine maximum tolerated dose and to assess anti-tumour activity. All patients had Fluorescent In-Situ Hybridisation (FISH) proven ALK rearrangement. Subjects received nivolumab 3mg/kg every two weeks and once-daily ceritinib for six weeks. Based on the dose of ceritinib, two group were tested (300 mg/day and 450 mg/day, while the 600 mg/day dose was not used due to safety concerns). Efficacy (overall response rates [ORR], duration of response [DOR] and progression-free survival [PFS]), safety and pharmacokinetics of both drugs was assessed. 36 patients were recruited, of which 16 were ALKi-naive. 14 received Ceritinib 450 mg daily dose and 22 received 300 mg per day. 4 patients in 450 mg group and 2 in 300 mg group experienced dose-limiting toxicity (DLT). The most common adverse event (AE) reported was diarrhea (69%). The proportion of grade 3 or 4 rash was higher in 450 mg arm, as compared to 300 mg one, while grade 3 or 4 AEs like increase in transaminases and amylase levels were equal in two arms. ORR was higher in 450 mg/day arm both for ALKi-naive as well as ALKi-pretreated patients. Although the sample size was small to derive conclusions, PFS and DOR favoured the 450 mg group. ORR was higher in patients with PD-L1 expression of $\geq 1\%$. Authors concluded that combining ceritinib and nivolumab has activity, but led to higher toxicity, especially rash, as compared to either single agent. Due to safety concerns, alternative dosing regimens are being investigated.
Evolution and Clinical Impact of EGFR Mutation in Circulating Free DNA in the BELIEF Trial

Circulating tumor DNA (ctDNA) and circulating free DNA (cfDNA) have proven to be useful for the diagnosis of EGFR mutations as well as for prognostic purposes. EGFR tyrosine kinase inhibitors (TKI) lead to shorter progression-free survival (PFS) in patients with blood-detected EGFR mutations as compared to those with negative results. This study was an exploratory analysis of preserved blood samples of patients recruited in BELIEF trial (a phase 2 multi-centric, single-arm study where tissue-detected EGFR-positive patients were treated with erlotinib and bevacizumab combination). 223 blood samples (collected at baseline, at response evaluation and at progression) were evaluated for the three most common EGFR mutations (exon 19 deletion, exon 21 L858R mutations, exon 20 T790M mutation) using peptide nucleic acid (PNA) probe-based 5'nuclease real-time quantitative PCR (PNA-Q-PCR) assay. As the overall mPFS was 13.3 months, patients with baseline T790M positivity had a mPFS 18.4 months, while for negative patients it was 10.9 months. Median overall survival (OS) was not different in the two groups. For cfDNA analysis, 60.4% samples out of 91 baseline samples were positive for EGFR mutations (exon 19/21). PFS was shorter for cfDNA EGFR positive patients as compared to those with negative ones (11.4 vs 22.9 months, respectively). At the first response evaluation only 4.1% of patients were cfDNA EGFR positive, whereas 50% of the patients were positive at the time of progression. Furthermore, cfDNA EGFR positivity was found to be an independent factor associated with poor OS. T790M positivity at progression was found in 33% in cfDNA but, in contrast to sensitizing mutations, it did not correlate with outcome. Longitudinal analysis also showed that cfDNA EGFR positivity at any time-point was associated with worse PFS and OS. Authors concluded that blood positivity of EGFR mutation and its longitudinal analysis can help in predicting progression.

LKB1 Deficiency Renders NSCLC Cells Sensitive to ERK Inhibitors

Serine-threonine kinase (STK11/LKB1) is a tumor suppressor gene that regulates cell metabolism and is mutated in approximately one-third of NSCLC cases. Currently, there is no specific treatment available to target LKB1 mutated NSCLC. The most well-known substrate of LKB1 is AMP-activated catalytic subunit alpha 2 (AMPK) that, together with LKB1, controls cell metabolism and growth. Activation of LKB1/AMPK leads to negative regulation of the phosphoinositide 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) pathway, inhibiting the cell cycle. Along with PI3K, extracellular signal-regulated kinase (ERK) also regulates mTOR by targeting mTOR complex 1 (mTORC1) activity. In this study, Caiola et al report the activity of 2 ERK inhibitors (ERKi), SCH772984 and ulixertinib, in NSCLC with different LKB1 and KRAS status. They show that SCH772984 successfully inhibited LKB1 deficient NSCLC cell lines by inhibiting P90 ribosomal S6 kinase (P90RSK), an ERK target, which impairs S6 ribosomal protein activation. These findings were then confirmed in P90RSK1 deficient clones. While ERKi activity in LKB1 deficient cell lines persisted, regardless of the KRAS mutation status, the same cell lines became insensitive to ERKis upon LKB1 reconstitution. Next, they showed that ERKi had no activity in phosphatidylinositol-4,5-biphosphate 3-kinase catalytic subunit alpha
(PIK3CA) mutated, LKB1 deficient cells; however, activity was restored upon combined treatment with PIK-75, a PI3K inhibitor, and SCH772984. These findings were corroborated by combining SCH772984 with ARQ 751, an AKT inhibitor. The authors confirmed their findings in-vivo in nude mice transfed with tumor cell lines, as well as in genetically engineered mouse models. Lastly, to generalize these findings, their experiments confirmed similar results when ulixertinib was used as the ERKi. In conclusion, this study provides evidence that LKB1 deficient NSCLC is susceptible to ERK inhibition and further clinical studies are warranted to test ERKis as monotherapy ERKis or in combinations with other agents in this sub-population.

Beyond Margin Status: Population-Based Validation of the Proposed International Association for the Study of Lung Cancer Residual Tumor Classification Re-Categorization

Current definition of incomplete NSCLC resection by the Union of International Cancer Control (UICC) ignores the recurrence-risk in cases of doubtful complete resection despite uninvolved margins, such as after suboptimal nodal resection. Hence, the IASLC proposed a more expansive definition of incomplete resection, creating a new category of ‘R-uncertain’ for cases with negative margins but high risk of residual disease. Osarogiagbon et al report the prognostic value of the new classification in a cohort of 3361 NSCLC resections from 2009-2019 in the United States. Using the UICC criteria, 95.3% resections were classified as R0, 4.3% as R1 (microscopic residual disease), and 0.4% as R2 (macroscopic residual disease), whereas, according to the IASLC R criteria, 33.3% were R-complete (R0), 60.8% R-uncertain, and 5.9% R-incomplete (R1/R2). 63.8% resections were reclassified from R0 in UICC classification to R-uncertain in IASLC criteria. Failure to achieve recommended nodal staging was the cause of R-uncertainty in 98% cases, followed by positive highest mediastinal node (5.8%). Using the IASLC criteria, median overall survival (mOS) was not reached for R0, while it was 69 and 25 months for R-uncertain and R1/R2, respectively. On the other hand, by using the UICC criteria, mOS was was 77, 25 and 39 months for R0, R1, and R2 resection, respectively. Compared to R0, R-uncertain resections with mediastinal nodes, no mediastinal nodes and no nodes had adjusted hazard ratios of 1.28 (CI, 1.10-1.48), 1.47 (CI, 1.24-1.74) and 1.74 (CI, 1.37-2.21), respectively. Interestingly, involvement of highest mediastinal node station was not an independent prognostic for survival. In conclusion, this study retrospectively validates the prognostic value of the IASLC resection criteria classification, except for the highest positive mediastinal node variable.
Research Watch

Long-Term Results of NRG Oncology RTOG 0617: Standard- Versus High-Dose Chemoradiotherapy With or Without Cetuximab for Unresectable Stage III NSCLC

The RTOG 0617 trial was a phase III randomized trial exploring comparing standard-dose (SD, 60 Gray) versus high-dose (HD, 74 Gray) conformal radiotherapy (CRT) with concurrent and consolidation chemotherapy (paclitaxel plus carboplatin), with or without the anti-EGFR monoclonal antibody cetuximab, in stage III NSCLC. The study had two co-primary end-points: overall survival (OS) of patients treated with HD-CRT versus SD-CRT and OS of patients treated with or without cetuximab. The trial was a 2 X 2 factorial design. At the first interim analysis the HD CRT arms were closed due to futility followed, after the third interim analysis, by the cetuximab arms. Bradley and colleagues reported the long-term results of this study, at a median follow-up of 2.7 years for all evaluable patients and 5.3 years for surviving ones. Comparing groups by radiation dose, 3 grade 5 treatment-related adverse events (TRAEs) were reported in the SD CRT and 9 in the HD CRT. While globally the incidence of grade ≥ 3 TRAEs were not different between the two radiation arms, by combining esophagitis and dysphagia, the HD CRT group developed significantly more events (20.8% vs 7.3%, p < 0.0001). When comparing patients treated with or without cetuximab, the addition of the monoclonal antibody led to a significantly higher incidence of grade ≥ 3 TRAEs (87.3% vs 71.2%, p < 0.0001). Compliance to protocol was similar between HD- and SD-CRT, even if the percent planning target volume (PTV) covered by 95% of the prescription dose as well as the 100% of the prescription dose was significantly better in the SD arms (p < 0.0001). The median (m)OS was 28.7 vs 20.3 months (2-sided p = 0.0072) for SD and HD-CRT, respectively, with a 5-year OS rates of 32.1% vs 23.0% (2-sided p = 0.007) favouring SD-CRT. The median progression-free survival (mPFS) was 1.0 year (95% CI, 0.8-1.2 year) versus 0.8 years (95% CI, 0.7-1.0 year) for SD- and HD-CRT, respectively (2-sided p = 0.055). The primary cause of death was lung cancer, independently of the radiation dose, and no significant differences were found in failure patterns. At the multivariable analysis, radiation dose, tumor location, institution accrual volume, esophagitis/dysphagia, PTV, and heart V5 were significantly associated with OS. The addition of cetuximab did not confer any survival benefit, beside being more toxic. To explain the inferior outcomes experienced by the HD-CRT, a separate analysis with regard to the impact of radiation dose to the heart is forthcoming.


Efficacy, Safety, and Biomarker Analysis of Ensartinib in Crizotinib-Resistant, ALK-Positive NSCLC: A Multicentre, Phase 2 Trial

Ensartinib is anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitor (TKI) with a ten-times greater potency than crizotinib. This agent is active against multiple crizotinib-resistant mutations such as F1174, C1156Y, G1269A, L1196M, S1206R, and T1151 and was already studied in Caucasian patients in a phase I/II trial. This phase 2 trial evaluated ensartinib 225 mg orally once daily in crizotinib-resistant ALK-positive NSCLC Chinese patients. The primary end-point was overall response rate (ORR) by independent review committee (IRC). The study enrolled 160 patients, with 156 eligible for efficacy analysis. Most patients received ensartinib as the first-treatment after crizotinib and 62% had brain metastases. Among 147 patients evaluable for response by IRC the ORR was 52%, while the disease control rate was 93%. The median progression-free survival (mPFS) was 9.6 months (95% CI, 7.4-11.6). The global intracranial response rate was 70% (41% among those patients evaluable by IRC). By analyzing cell-free DNA (cfDNA), the Authors had a baseline detection rate of 51% (with most patients carrying EML4-ALK variant 1 rearrangement), with 45 patients showing secondary ALK alterations and 5 putative bypass signaling pathways activation. ORR was 57% among patients with baseline detectable ALK fusion, 44% in those with secondary ALK alterations, and 57% in those without detectable resistance mechanisms. The most
common treatment related adverse events (TRAEs) were rash (56%) and increase alanine and aspartate aminotransferase elevation (46% and 41%, respectively). Grade 3 TRAEs were reported in 36 patients (23%), while no grade 4 and 5 TRAEs occurred.


The Impact of Gradual and Immediate Nicotine Reduction on Subjective Cigarette Ratings

A mandated reduction in the nicotine content of cigarettes may reduce the prevalence of smoking by reducing the addictiveness of combusted cigarettes. Recent studies have reported that cigarettes with very low nicotine content (VLNC; 0.04 mg nicotine/g tobacco) cigarettes reduce the number of cigarettes smoked per day, reduce toxicant exposure, decrease nicotine dependence, and increase the likelihood of making a quit attempt compared to normal nicotine content (NCC; 15.5 mg nicotine/g tobacco) cigarettes. However, it exists less compliance with the instruction to smoke only VLNC cigarettes in the immediate versus gradual reduction condition. The goal of this study was to test whether nicotine reduction method alters subjective ratings of VLNC cigarettes, and whether subjective ratings mediate effects of nicotine reduction method on smoking behavior, smoke exposure, dependence, and compliance. Across 10 sites in the United States, 1,250 smokers were randomized to either a control condition, or to have the nicotine content of their cigarettes reduced immediately or gradually to 0.04 mg nicotine/g of tobacco during a 20-week study period. Participants completed the modified Cigarette Evaluation Questionnaire (mCEQ). The Satisfaction subscale of the mCEQ mediated the impact of nicotine reduction method on smoke exposure, smoking behavior, dependence, compliance, and abstinence, and at week 20, the immediate reduction group scored significantly lower than the gradual reduction group on multiple subscales of the mCEQ (p < 0.001). These data endorse that an immediate reduction in nicotine content produces a more drastic change in the subjective effects of VLNC cigarettes than gradual reduction, which may have an impact in smoking behaviour and dependence, suggesting that immediate reduction further reduces cigarette reward value. This study will provide the Food and Drug Administration with information about the impact of nicotine reduction method on cigarette reward value.


Quasi-Experimentally Examining the Impact of Introducing Tobacco Pictorial Health Warnings: Findings from the International Tobacco Control (ITC) 4C and Netherlands Surveys in the Netherlands, Australia, Canada, United Kingdom, and the United States

Health warnings on the packet of tobacco products are a health communication strategy to inform the public about the health risks of smoking. In May 2016 all European member states were required to introduce pictorial health warnings (PHWs; on 65% of both sides of the packet; accompanied with textual health warnings, THWs on 50% of both sides). The current study evaluated the short-term impact of PHWs. To conduct this study, longitudinal data were collected at two time-points from 3,487 adult smokers, participating in the International Tobacco Control (ITC) surveys, conducted in the Netherlands, Australia, Canada, the United Kingdom and the United States. In the Netherlands, THWs were replaced by PHWs between both time-points. Health warning policies did not change in the other countries. Between both time-points, only Dutch smokers showed increases in noticing health warnings (β = 0.712, p < 0.001), self-reports of health warnings leading to a cognitive response such as thinking about smoking health-risks (SHRs) (OR = 1.834, p < 0.001), knowledge about SHRs (β = 0.369, p < 0.001), and avoiding health warnings (OR = 9.869, p < 0.001). However, Dutch smokers showed no changes in attitude towards smoking (β = 0.035, p = 0.518), intention to quit smoking (OR = 0.791, p = 0.157), self-efficacy to quit smoking (β = -0.072, p = 0.286), or reporting that health warnings helped them to resist having a cigarette (OR = 1.091, p = 0.714). The study endorses that European PHWs were effective in provoking changes closely related to health warnings, but did not impact in n variables more closely related to smoking cessation.

News in Brief

Two Seems Not to be Better Than One: Results From Two Randomized Phase III Trials on Maintenance Treatment in Advanced Non-Squamous NSCLC

Two randomized phase III clinical trials (ECOG-ACRIN5508 and COMPASS): have established that single-agent bevacizumab or pemetrexed is efficacious as maintenance therapy for advanced non-squamous NSCLC. In the ECOG-ACRIN trial, 1516 advanced NSCLC patients enrolled received four cycles carboplatin, paclitaxel and bevacizumab. Patients without progression after four cycles (N=874, 57%) were randomly assigned to maintenance therapy with bevacizumab (15 mg/kg), pemetrexed (500 mg/m²), or a combination of the two agents. The primary end point was overall survival, with bevacizumab serving as the control group. With a median follow-up of 50.6 months, median survival with pemetrexed was 15.9 months, compared with 14.4 months with bevacizumab (hazard ratio [HR], 0.86; P = 0.12); median survival with pemetrexed and bevacizumab was 16.4 months (HR, 0.9; P = 0.28). In the COMPASS trial, 907 advanced NSCLC received carboplatin, pemetrexed and bevacizumab. Out of all, 599 patients without progression after 4 cycles of induction chemotherapy were randomly assigned 1:1 for maintenance therapy with pemetrexed (500 mg/m²) plus bevacizumab (15 mg/kg) or bevacizumab (15 mg/kg) once every 3 weeks until disease progression or unacceptable toxicity. The median OS was 23.3 vs 19.6 months (hazard ratio [HR], 0.87; 95% CI, 0.73 to 1.05; 1-sided stratified log-rank P = .069). Both trials, endorse the current standard of single-agent as maintenance treatment for patients without progression after 4 cycles of induction chemotherapy.

Evaluating Unconscious Bias: Speaker Introductions at an International Oncology Conference

A well known issue in medicine is the gender gap in medical leadership, whose basis is not fully understood. Gender bias drives gender disparities in academic advancement, and may be reinforced through the use of gender-subordinating language, including variability in the level of formality in form of address. For this reason, the introduction of a female speaker without her occupational or professional title may have a direct impact on the public’s perception of the speaker herself. In their study, Duma and colleagues retrospectively reviewed the video archive of all oral presentations at the 2017 and 2018 American Society of Clinical Oncology (ASCO) Annual Meetings. The Authors codified the professional address of each speaker to identify any gender bias. Of 2,511 videos review, 781 met inclusion criteria, covering 89% and 91% of the session of 2017 and 2018 ASCO Annual Meetings, respectively. 322 speakers were female (41%), most from the United States (77%). Female speakers were less commonly introduced with their professional title as compared to males (62% vs 81%, p<0.001), and male moderators were less likely to use a professional address when introducing female speakers as compared to female moderators (53% vs 80%, p<0.01). Conversely, women introduced speakers without gender differences in professional address (75% vs 82%, p=0.13). At the multivariable analysis, male speakers were more likely to receive professional address as compared to female speakers (odds ratio, 2.43; 95% CI, 1.71-3.47; p<0.01).

Pembrolizumab Misses Overall Survival Mark in KEYNOTE-604 Study

Pembrolizumab, marketed as Merck’s Keytruda, in combination with chemotherapy was compared with chemotherapy alone as first line therapy for extensive stage small cell lung cancer (ES-SCLC) in KEYNOTE-604 study. Recently, the results of this phase 3 trial were announced by Merck & Co. It was found that combination therapy was successful in significantly improving progression free survival (HR= 0.75 [95% CI 0.61-0.91]) but did not lead to an improvement in overall survival as per pre-specified criteria’s. Overall survival is one of the important indicators, used by the FDA regulators for approval. This comes as a disappointment given the success of this anti-PD-1 therapy in the spectrum of non-small cell lung cancer.

US FDA Finalizes Enforcement Policy on Unauthorized Flavored Cartridge-Based E-Cigarettes

It is estimated that currently, over 5 million youth are using e-cigarettes in the United States, significantly higher from previous years. Therefore, on January 2, 2020, the US FDA issued an enforcement policy on the sale of certain unauthorized flavored electronic nicotine delivery system (ENDS) product. Accordingly, FDA intends to prioritize enforcement against all cartridge-based ENDS products other than tobacco or menthol flavored products. Amid the epidemic levels of youth e-cigarette use, this enforcement is formulated as an attempt to curb use of ENDS products in minors. Companies are required to cease manufacturing, distribution and sale of unauthorized products within 30 days. Notably, this policy only applies to cartridge-based e-cigarettes and not to liquids or tank-based devices.

**News from the IASLC Tobacco Control Committee**

**CDC Report on Post Hospital Care of EVALI Patients**

At the beginning of the new decade, the Centers for Disease Control (CDC) released a report advising on the care of EVALI patients after hospitalization. The CDC has rapidly collected data and reported on the EVALI epidemic as it has evolved. In November 2019 it observed that 95% of EVALI patients required hospitalization, with demographics and vaping similar as compared to those who were not admitted. As of November 2019, the CDC announced that it would no longer collect data on the non-hospitalized cohort. In the January 2020 report, the CDC described the rates of re-admission and death following initial discharge post-EVALI:

- by October 2019, 31/1139 (2.7%) patients were re-hospitalized after initial discharge with a median time to readmission of 4 days;
- 7 patients died following discharge (median time to death 3 days);
- these 2 groups have high rates of chronic medical conditions (70-80%) such as chronic obstructive pulmonary disease (COPD), obstructive sleep apnea (OSA) and diabetes compared with EVALI patients who have a less eventful post-discharge period (25%).

The CDC guidance report makes some specific recommendations about planning for and managing the discharge period after admissions for EVALI, specifically to avoid unexpected re-admission and death. These make intuitive sense for clinicians used to looking after patients with acute severe pulmonary illnesses (such as pneumonia, other inhalational injuries, severe exacerbations of chronic lung disease) and serve to highlight the danger of this new phenomenon:

- Wait 24-48 hours after reaching clinical stability before discharge;
- Put social, mental health and substance abuse supports in place;
- Optimize the likelihood of medication adherence (particularly for a steroid taper) with, for example, pharmacist counselling;
- Plan early medical follow-up (within 48 hours) plus other supports including home visits, phone or text checks and links to community services;
- Plan pulmonary specialist follow-up within 2-4 weeks.

This column had not started at the beginning of the last decade, but a look back to our first few months (early 2014) shows that the very first column included a piece on the European Tobacco Products directive, which among other things, introduced a maximum nicotine concentration for e-cigarettes, a move that may have saved the European region from this unexpected epidemic. An article in *The Guardian* from September 2019 highlights this as a major regulatory difference between the United Kingdom (where e-cigarettes have a nicotine level cap) and the United States (where they have not). Has this been a train-wreck in slow motion? First we saw the emergence of e-cigarettes, then (in some countries) the unfettered marketing, then the worries about rates of adolescent use, then (less than 6 months ago) the first reports of a strange respiratory illness affecting mainly young people, then the horror reports of deaths, intensive care admissions and transplantation, post-discharge reduction in lung function and now, the aftermath.

Not Even One Cigarette

For those of us who work in clinic and try to help our patients quit, it is a struggle. Often they cut down, sometimes to just a few cigarettes a day and then we all might relax. But low level smoking is not okay. In a meta-analysis published a couple of years ago, low cigarette consumption (1-5 cigarettes daily) was associated with a significant risk of vascular disease (around half the risk of those who smoke 20 cigarettes per day). A more recent study published in *Lancet Respiratory Medicine* examines lung function in several US population-based cohorts, all of whom had valid spirometry performed at least twice. The cohorts covered a range of ages (from young adulthood to the elderly) evaluated between 1984 and 2014. The degree of decline in FEV1 was compared between never smokers and former or current smokers and assessed according to duration of cessation, number of pack years and (in current smokers) cigarettes per day. The authors referred to previous evidence about lung function decline, in particular the famous Fletcher and Peto study entitled “The natural history of chronic airflow limitation.” This 1960s study, which is satisfying to quote in clinic, drawing Figure 1 for the patients, examines 800 fairly young working London men aged 30-59 and shows that rates of FEV1 decline slowed to normal after smoking cessation. Another, previously published meta-analysis of FEV1 decline showed no difference between never and former smokers in nearly 90,000 subjects, but the variability in data and the small size of many included studies weakened the findings. In the current study, based on over 23,000 participants followed for a mean of 7 years, the decline in FEV1 over time was greater in former smokers compared with never-smokers and this accelerated decline was apparent even decades after smoking cessation. Something similar was seen in low-intensity current smokers, defined in this study as those who smoked fewer than 5 cigarettes per day. Other factors that contributed to accelerated FEV1 decline included shorter times since cessation, the presence of underlying lung disease and a higher number of pack years. The rates and differences sound small (current smokers have a fall of FEV1 of just under 40ml/year compared with just under 35ml/year in former smokers and 31ml/year in never-smokers) although indicate ongoing biological effects of tobacco smoke exposure, even if the clinical impact may not be large. An accompanying editorial points out perhaps the major finding of the study — that ongoing low level smoking (< 5 cigarettes per day) had a rate of FEV1 decline (8ml/year more than never smokers) that was close to the excess rate of decline seen in smokers of more than 30 cigarettes per day (11ml/year more than never smokers). Bottom line — there is no safe level of smoking — not for hearts and not for lungs and it is this that should continue to guide our future tobacco control policy.

When it comes to understanding the tobacco epidemic, where it came from, how it started and what perpetuates tobacco’s strange and tragic grip, this column turns to the historians. We have read much of the Cigarette Century written by Allan M Brandt, Professor of the history of medicine at Harvard Medical School, which unpicks the corporate side of the epidemic, driven by industry’s suppression of damaging evidence about the risks and addictiveness of tobacco, hunger for profits and cynical manipulation of marketing strategies, even in the face of powerful scientific evidence for harms. The dramatically titled “Golden holocaust: origins of the cigarette catastrophe and the case for abolition” by Robert N Proctor, Professor of the history of science at Stanford University, calls for elimination and abolition of the cigarette. A thoughtful review published in BMJ Medical Humanities reflects on the methodology of this book noting that Proctor has acted as an expert witness in US legal cases against the tobacco industry and raises concerns about ignoring the “dangers and lessons of US alcohol prohibition.” The most recent addition to the inventory was published in October 2019 and approaches the epidemic with a clear-eyed view of the political, governmental and economic drivers behind it. Written by Sarah Milov, Assistant Professor of History at the University of Virginia, The Cigarette: A Political History has attracted much attention — there is an interview with the author conducted by David A. Kessler, former Commissioner of the FDA on C-Span and a plethora of internet options available through the Harvard University Press page. As reviewed in the The Lancet Respiratory Medicine, Milov points out how tobacco achieved a degree of “exceptionalism,” supported by an American president (Johnson) even as he prioritised public health. More than anything, the review underscores how the recent publication appreciates the complexity of the American tobacco epidemic in its evolution, emphasizing the risks faced by socio-economically deprived groups, the targeting of the poor and the “thicket of contradictions” inherent in a system that often stigmatises its victims and pits profit against health.