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Update on research and management implications in NSCLC and SCLC

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As summer faded and autumn announced its presence, Stockholmers, not unlike their Canadian counterparts, were enjoying the last pleasures of balmy weather while anticipating an early start to what is forecast to be a long, cold winter. A brief glimpse at the geography of the Swedish capital reveals an unlikely location for a city, not to mention the seat of government. It consists of a system of islands, scattered in a mixture of sea and fresh water, all connected by a series of bridges to somehow create a cohesive, urban theme. From a lung cancer perspective, the 16th European CanCER Organization (ECCO)/36th European Society for Molecular Oncology (ESMO) European Cancer Congress, hosted by Stockholm for the second time in 4 years, will not go down in the annals as a meeting that rocked clinical practice in lung cancer to its core. Indeed, at times, the lung cancer program appeared to resemble Stockholm's own geography, an archipelago of seemingly unrelated trials, topics and presentations. Nevertheless, with some help from Swedish icons, it is possible to string some of these threads together to form cohesive commentary from the lung cancer presentations related to locally advanced Stage III non-small cell lung cancer (NSCLC), metastatic NSCLC, small cell lung cancer (SCLC), key trial data from AVAPER1, ECOG 5508, FLEX and BMS-099, as well as important findings regarding IHC and H scores.



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LOCALLY ADVANCED STAGE III NSCLC: RADIATION MAY BE KEY TO BETTER OUTCOME

Combination radical chemoradiation remains the mainstay of treatment for patients with locally advanced Stage III NSCLC, a paradigm based on research initiated in the 1990s. Long-term survival remains stubbornly steady at about 15-20%.

Changing this outcome has been challenging: newer agents are proving difficult to incorporate into this recipe, while the role of surgery as the third component of a trimodality approach remains controversial. In addition, increasing the dose of radiation seems unlikely to be the key to further improvements since, as pointed out by Senan et al,¹ even in countries such as the Netherlands, only about one-third of patients are candidates for radical treatment. Clearly, a concerted effort to make radical treatment more feasible to a larger proportion of patients is required.

So what can be done? A number of presentations at the 16th ECCO/36th ESMO European Cancer Congress by Senan,¹ Price² and Pastorani³ contributed to the impression that the key may lie in improving radiation approaches. Clearly, increasing what is already considered "a radical dose" is not generally feasible, but making minor adjustments to several other approaches may pay dividends. While we cannot improve one thing by 100%, it may be possible to improve 100 things by 1%. Better imaging allows for improved staging and better subclassification of what is a very heterogeneous group of patients. Radiating only positron emission tomography (PET)-positive disease may lead to improved targeting of active disease and a reduction in the volume of lung treated. Better tumour targeting using newer techniques such as intensity-modulated radiation therapy (IMRT) and image-guided radiation therapy (IGRT) may also play a substantial role. True, we may have heard this before, but a few tweaks here and there can, just as in a cover version of an ABBA song, make the sound a lot more palatable. In practical clinical terms, this will require (i) a more integrated multi-disciplinary approach, (ii) the willingness to apply more expensive technology to the cause of lung

cancer, and (iii) a willingness to design more Phase III trials for this heterogeneous category of NSCLC patients. Although the first two seem doable, the last, as alluded to by Dr. E Felip, the discussant, does not seem forthcoming at present.

METASTATIC NSCLC: MAINTENANCE TREATMENT UNDER DEBATE

There was more to digest in the world of metastatic NSCLC, which is still confronted by 2 main topics of interest: maintenance chemotherapy and the identification of predictive markers of response. The relentlessness of Swedish tennis star Bjorn Borg is echoed by attempts to demonstrate that treatment beyond the classic 4-6 cycles of first-line platin-based chemotherapy yields useful clinical benefits. This area of research is clouded by, among other things, matters of definition: Does “maintenance” constitute merely the continuation of one of the agents used in the initial therapeutic regimen — such as in the continuation of bevacizumab — to progression, or does it also include what may be termed “early second-line” treatment with a different agent, such as pemetrexed initiated immediately after completion of 4-6 cycles of platin-based treatment? An acknowledgement of the need for clarity here was reflected by Des Guetz⁴ in his presentation of the results of a meta-analysis of maintenance treatment in NSCLC. His findings pointed to a benefit of using maintenance treatment, but the magnitude of benefit seemed to depend on its specific nature. A hazard ratio (HR) of 0.93 was quoted for “continuation treatment,” 0.85 for “switch treatment” and 0.83 for “biologic treatment.” These benefits come at the expense of toxicity. However, given the inconsistency of trial design in this field to date, it was concluded that the jury is still out on this issue.

AVAPERL AND ECOG 5508 TRIALS — MAINTENANCE TREATMENT HERE TO STAY?

More light on the maintenance issue was provided by the presentation of the AVAPERL trial (AVAPERL: A Study of Avastin (Bevacizumab) With or Without Pemetrexed as Maintenance Therapy After Avastin in First Line in Patients With Non-Squamous Non-Small Cell Lung Cancer) by Barlesi.⁵ In this trial, patients with metastatic NSCLC were assessed for response after completing first-line chemotherapy.

Those who had progressed were excluded from the rest of the trial and those with either stable disease or partial responses and who had not experienced significant toxicity were then randomized to maintenance pemetrexed versus maintenance pemetrexed and bevacizumab. A total of 376 patients were enrolled. At the end of definitive first-line chemotherapy, the disease control rate was 62%, meaning that 253 patients were randomized to the maintenance arms. Analysis showed a significantly longer progression-free survival (PFS) (starting from the beginning of treatment) in the maintenance pemetrexed and bevacizumab combination arm, at 10.2 vs. 6.6 months (HR 0.50, $p < 0.001$).

There were a number of criticisms laid against this trial as outlined by the discussant R. Dziadziuszka: there was no non-maintenance arm for comparison. In addition, the design of the trial whereby those who progressed on chemotherapy were excluded made for a very select group of patients. Consequently, it is difficult to ascertain how much of the benefit was attributable to the nature of the enrolled patients. As was pointed out by the discussant, it is also difficult to know which of the agents is really responsible for the benefit seen. Additional, more meaningful information will come from the ECOG 5508 trial (a randomized Phase III study of maintenance therapy with bevacizumab, pemetrexed or a combination of bevacizumab and pemetrexed, following carboplatin, paclitaxel and bevacizumab for advanced NSCLC) currently ongoing in the US. We were left with the impression that this Borg-like relentlessness is paying off and that maintenance treatment will soon be here to stay, but that the concept does need one of those classic Borg winning passes from the baseline to secure its place in the lung cancer management paradigm.

Another Swedish icon, IKEA, has taught us that great things can be achieved in small spaces. It could be said that “IKEAfication” is the way we would like to go in NSCLC. Although we have recognized several histologic subtypes of NSCLC since pre-ABBA days, the management implications of that analysis was until recently non-existent. Over the last several years the need to distinguish squamous from non-squamous cancers has been highlighted by the need to avoid treating those tumours with anti-angiogenic agents and to reserve pemetrexed for the treatment of non squamous disease. However,

the most significant trend is that of the further subdivision of the broad swathe of NSCLC into several molecularly-defined subgroups. A vision exists for NSCLC to be divided into a range of smaller subgroups, each maybe making up no more than 5-7% of the total, whereby a more individualized approach to treatment can be made. Currently, this is most notable in the EGFR-activating mutation positive and the EML4 ALK translocation positive subgroup of NSCLC, where molecular classification is already directing treatment decisions.

FLEX TRIAL: POST HOC ANALYSIS

Recent experience has tempered some of this enthusiasm because of an inexplicable inability to put K-RAS into context in NSCLC in the way it has been placed in colorectal cancer. A very interesting and potentially management-changing series of presentations was made by O'Byrne,⁶ Lynch⁷ and Rüschoff⁸ regarding the post hoc analysis of the FLEX (First-Line Erbitux in Lung cancer) trial.

In this trial, Stage IV NSCLC patients were randomized to receive chemotherapy with or without the anti-epidermal growth factor receptor (EGFR) monoclonal antibody (mAb) cetuximab. Of note, a biopsy assessable for EGFR expression was a required for enrolment. O'Byrne explained how previous analysis using classic immunohistochemistry (IHC), with a 1+, 2+, 3+ scoring system, suggested that IHC-based assessment of EGFR was not a factor in determining the utility of cetuximab in this setting. However, a more quantitative IHC method, H analysis, whereby samples are given a score out of 300 based on both intensity of staining and the proportion of the sample that stains ($H\ score = 1 \times [\% \ 1+ \ cells] + 2 \times [\% \ 2+ \ cells] + 3 \times [\% \ 3+ \ cells]$), seemed to change this picture. Statistical analysis suggested that patients whose tumours scored 200 or more on this scale benefited from the addition of cetuximab, increasing the median overall survival from 8.9 to 11.2 months. While more pronounced in adenocarcinomas, this benefit was seen across all histologies.

BMS-099 TRIAL: IHC SCORES AND RESPONSE RATES

In light of the preliminary analysis presented at International Association for the Study of Lung Cancer (IASLC) earlier in Amsterdam, a similar analysis was carried out on the BMS-099 trial. In this trial,

cetuximab was added to carboplatin and paclitaxel in the same setting. Unlike the FLEX trial, tissue availability was not a prerequisite for enrolment and only 22% of patients had tissue available for IHC analysis, compared with 96% in FLEX. Despite this, a high IHC H score (>200) predicted for a better response rate to the cetuximab-containing regimen and showed a trend toward better survival. This was interpreted by Lynch⁷ as lending significant support to the finding in the FLEX trial and adds further weight to the utility of this quantitative IHC approach.

VALIDATION OF H SCORING

The final part in this series of presentations outlined how H scoring had been validated during its introduction into the trial and how interobserver variation was evaluated, then minimized. Rüschoff⁸ explained that 14 "blinded" pathologists had independently scored 30 NSCLC samples stained for EGFR using the same antibody. The importance of this approach was illustrated by showing 2 examples of IHC EGFR staining that would both have been assessed as 3+ on the classic scoring system, but which on H scoring differed dramatically, scoring 30 (10% of cells staining 3+) vs 270 (90% of cells scoring 3+). Pretraining concordance rate was 76% with a κ of 0.5 but a posttraining concordance rate of 90% and κ of 0.8 was achieved. As usual, the concordance rate was lowest in the mid-scoring range, between 150 and 200.

As summarized by the discussant Hirsch, it is difficult to be certain what the implications of these results will be, but there are grounds for thinking that they will soon affect clinical practice. First, these findings demonstrate that a methodologic approach to IHC can yield a more meaningful, less subjective scoring system. While not quite as quantitative a system as HistoRX AQUA,[®] the H system does account for both intensity and extent of expression within a given sample while still not requiring "fancy" equipment. Second, from a mechanistic angle, it makes sense that the efficacy of a therapeutic mAb is related to the density of the target in the tissue of interest. Whether the mAb is thought to exert its effect through modulation of the target in the cancer cell or by inducing an immune response against those cells, the target needs to be there for binding to occur. It would seem therefore that more quantitative assessment

of the presence of specific targets will become a watchword in this era of personalized medicine. Third, it helps put the role of K-RAS into context and suggests that at least in NSCLC, as long as there is enough EGFR expression, K-RAS status may not be important in determining the usefulness of anti-EGFR mAbs. Last, although it is a post hoc analysis, samples in the FLEX study were collected prospectively in 100% of the patients and so the quality of the data is high. There is no doubt that Sanofi-aventis will now file for an indication for use in NSCLC based on these data — probably the biggest clue that day-to-day oncology practice will be affected. The IKEAfication of NSCLC must continue.

PROGRESS IN LUNG CANCER EXCEPTIONAL IN NSCLC, NOT SCLC

From a lung cancer perspective, a striking feature of the 16th ECCO/36th ESMO European Cancer Congress was continued silence in the field of SCLC, an area of study that continues to be a graveyard for investigative treatments. Discouragingly, management of this disease remains remarkably similar to its management in the heyday of ABBA and when Borg last won Wimbledon. As reviewed later in this supplement, recurrent SCLC remains incurable and is an area of particular research and therapeutic need. SCLC represents one of the few areas of oncology where management is yet to be influenced by an improved understanding of its molecular basis.

However, in surveying the field of NSCLC in 2011, it is impossible not to marvel at the progress that has been made in 20 years: from no systemic treatment to the availability of third- and fourth-line options; from no molecular guidance to the acceptance of 2 predictive markers into current management paradigms; and from a culture of “no hope” to one of increasing possibilities and even an expectation that significant progress is just around the corner. One discussant from the 16th ECCO/36th ESMO European Cancer Congress commented that the fact that other tumour sites are trying to emulate the success of the adoption of multidisciplinary management in NSCLC is testament to how far things have come.

Equally noteworthy is that this remarkable progress has not come about as a result of one Nobel prize-worthy “eureka moment,” but rather as a consequence of a series of difficult small steps.

Each small step represents years of dedication by researchers, extensive and sometimes protracted clinical trials, the meticulous translation of new evidence into oncology practice and the time and energy of many thousands of patients who are rather anonymously represented on all those survival curves. While Alfred may be disappointed that there is no award to be given on his behalf in the field of lung cancer, he would be at least happy to think that the previous nihilism associated with lung cancer has been exploded: boom goes the dynamite.

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