Special session (Tue, 25 Sep, 13:00−14:30)
EMEA Special symposium 2007 – The development and approval of Erlotinib (Tarceva®) for the treatment of pancreatic cancer

75 INVITED

The EMEA review and outcome

F. Pignatti. *UK*

Abstract not received.

76 INVITED

Treatment of non-operable pancreatic cancer. The role of Tarceva

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More than 50% of pancreatic tumors overexpress epidermal growth factor receptor (EGFR), and the level of EGFR positivity was shown to have prognostic value in patients with pancreatic carcinomas forming the rationale for combining EGFR inhibitors with gemcitabine therapy. In a large, randomized, phase III study, the combination of gemcitabine with erlotinib, an EGFR tyrosine kinase inhibitor, was compared with gemcitabine plus placebo. EGFR status was not an inclusion criterion. A total of 569 patients were randomly assigned 1:1 to receive standard gemcitabine or gemcitabine plus erlotinib (100 or 150 mg/d orally). Overall survival based on an intent-to-treat was significantly prolonged on the erlotinib/gemcitabine arm with a hazard ration of 0.82 (95% CI, 0.69 to 0.99; p = 0.38), adjusted for stratification factors). One-year survival was also greater with erlotinib plus gemcitabine (23% vs 17%; p = 0.023). Progression-free survival was significantly longer with erlotinib plus gemcitabine with an estimated hazard ration of 0.77 (95% CI, 0.64 to 0.92; p = 0.004). Objective response rates were not significantly different between the arms, although more patients on erlotinib had disease stabilisation. There was a higher incidence of some adverse events with erlotinib plus gemcitabine, but most were grade 1 or 2.
Interestingly, the appearance of rash appeared to correlate with median and 1-year survivals. For example, median survival was 5.29 months and 1-year survival rate was16% in patients with no rash, compared with 10.51 months and 43% in patients with grade 2 or greater rash.
The clinical relevance of these results was questioned especially when the results were presented only in terms of response rates and median survival (6.24 months v 5.91 months).
For clinicians, it seems important to allow the use of erlotinib in the treatment of pancreatic cancer. The arguments in favour of the European approval were:

1. The consistent significant differences between the two arms: progression-free survival, overall survival, tumour growth control
2. The absence of major bias in this well-designed randomised trial
3. The favourable toxicity profile of the combination.
4. The clinically important benefits to patients with poor prognosis
5. The absence of other options for the treatment of pancreatic carcinoma. A lot of new or old agents have failed to demonstrate any advantage in the treatment of pancreatic carcinoma when combined to gemcitabine
6. The approval in the USA
7. The need for European clinical researchers to build clinical projects that could be considered all around the world on this new standard of care.
8. The risk that strong differences appear in handbooks of Oncology in Europe and the USA.

On the other hand, the fact that it is for the moment impossible to select patients who will respond to erlotinib has to be considered as a disadvantage and efforts should be made to define biological profile of responders. It could be recommended to cautiously evaluate the benefit risk ratio in patients who do not experience any cutaneous toxicity after two months of therapy.
Erlotinib is now a new standard of care for the treatment of metastatic pancreatic neoplasm in Europe. It is clearly not mandatory to give this combination therapy to all the patients with this disease but this option should be discussed in all of them.

77 INVITED

Challenges in the development and registration process: company perspective

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Pancreatic cancer is a disease with limited treatment options and dismal prognosis. The vast majority of patients diagnosed with this disease die within a relatively short time. Over a period of almost 40 years, only one drug, gemcitabine, showed a survival benefit for treating this disease, while every other drug tested failed to produce any significant benefit. Tarceva in combination with gemcitabine demonstrated a statistically significant survival benefit in a well designed and well-conducted phase III trial as compared to gemcitabine alone. This was a randomized, placebo controlled trial conducted by a reputable and experienced cooperative group, NCIC. In most situations, such a scenario would lead to an expeditious approval of the drug. However, this case provided major challenges for the regulators, the sponsor, clinical experts and the investigators. From the Company perspective, six major issues surfaced during the regulatory approval process which posed major challenges:

a. How does one define what degree of survival benefit is 'clinically significant' in a difficult to treat disease?
b. How can clinical benefit be assessed in a consistent, reliable, and transparent way that is acceptable to all the stakeholders and truly reflects the benefit of the drug for the patients?
c. Does 'median' survival always best reflects the magnitude of drug benefit?
d. In terms of methodology, what benefit-risk assessment models and methods are deemed reliable and acceptable from a regulatory authority viewpoint?
e. How does one discover and validate predictive biomarkers in view of the complexity of the biological pathways, putative resistance mechanisms, and limited feasibility of obtaining tissue from a large proportion of patients?
f. How can one bring the patient perspective into the EU drug approval process?
g. How can the drug approval process in EU be made more consistent and open? How can the regulators, investigators, sponsors, and patient advocates work together in EU to do the best for our patients who face very difficult choices in dealing with such difficult disease?

The perspectives of the sponsor, the reviewers and the members of the Scientific Advisory Group – Oncology differed in significant ways on many of the above issues and they reached different conclusions on the approvability of the drug for this indication at different points in time. This was not unexpected given the different needs of the various constituencies. Even though the procedure was complex, involving a new assessment as well as expanding the SAG-Oncology review to include additional experts, yet the process throughout was characterized by clear communications between all concerned and a sense of understanding of the contrarian viewpoint. In the final analysis, this sense of openness allowed a compromise to be reached that allowed the drug to be approved for the patient subpopulation which appeared to drive the greatest benefit and a further development strategy to address the next set of research questions was agreed between the sponsor and the EMEA.
In this presentation, the history of this approval process will be discussed from the sponsor's perspective and suggestions for how to improve this process for the future will be discussed.

78 INVITED

Critical review of development and approval

M. Marty. *France*

Abstract not received.

Special session (Tue, 25 Sep, 13:30−14:30)
Protons and light ions

79 INVITED

Physical and molecular basis of the biological effects of charged particle radiation

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The use of protons and heavier ions in radiation tumor therapy has increased considerably during the last years with very good clinical outcome. The most characteristic advantage of particle radiotherapy on the physical side is the inverse depth dose profile compared to photon beams, enabling to deliver high doses to the tumor while sparing normal tissues to a maximum extent. An additional biological benefit of heavier ions such as carbon is given by the increased biological effectiveness (RBE) of the ions in the tumor volume (at the end of the particle range).
The dependence of the RBE on the particle's energy was investigated for protons and carbon ions over a wide range of energies allowing comparison with the depth dose profiles. Cell survival was measured in human or hamster cell lines after irradiation with either monoenergetic or passively