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

decelerated protons, or with carbon ions mimicking the tumor treatment situation. RBE values were determined relative to x-rays.
For protons a sharp increase in RBE was found only for the stopping particles at the very distal (decreasing) end of the dose deposition profile. For low energy carbon ions, the RBE is increased over a broader range of energies corresponding to the peak of dose deposition. Therefore, after therapy like irradiation, for carbon ions in contrast to protons a considerable fraction of the dose deposited will correspond to ions with a high RBE.
At the molecular level, the enhanced effectiveness is believed to be based on the production of complex DNA double-strand breaks (DSBs) that are difficult to repair. To study the induction and repair of DSBs under conditions mimicking therapeutical ion irradiation, stacks of cells grown on glass plates were exposed to high energy carbon ions in a water phantom. Immunostaining of phosphorylated histone H2AX was used for DSB detection. After post irradiation incubation, despite efficient repair even of ion-induced DSBs, the level of residual DSBs was slightly but consistently increased after exposure to ions in the tumor region compared to the entrance channel.
In summary, based on their physical properties both protons and heavier ions are advantageous to treat deep seated tumors. For carbon ions an increase of the RBE towards the end of the particle range, together with the concomitant increase in dose potentiates the inactivation effect in the tumor region. The molecular basis is the localized production of complex damage and the impaired repair.

80 INVITED

Particle therapy: Physical potential amid clinical realities

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Background: Proton radiation therapy has moved mainstream. Many new proton centers have recently been completed, or are under construction or at planning stage. The main physical advantage of both proton and heavier charged particle therapy is the finite range of the beam in the patient, which may be utilized to reduce the overall integral dose to healthy tissues and to improve local dose conformality. However, the range of a particle beam in a patient on a given day is often not exactly known. The range is therefore not used for tight dose conformation. Instead, dose shaping with the lateral dose fall-off is preferred, just as in the case of conventional photon therapy.
Materials and Methods: We will review the state of the art in proton therapy and focus on sources of range uncertainties, such as motion, imaging artifacts, and dose calculation errors. We will discuss how the impact of range uncertainties is limited in current clinical practice using methods such as field patching and feathering. We will also discuss methods for in-vivo dose measurements, either directly or indirectly through PET/CT imaging of the positron emitters activated by the particle beam. We will then review the potential of intensity modulated proton therapy (IMPT) to improve dose conformality and the robustness of the treatment plan.
Results: In some cases, especially in lung cancer treatments, the range of a particle beam can vary by several centimeters during the treatment course. Even in cases where motion and anatomic variations are not an issue, the range can be off by 5mm, for example due to metal artifacts. In-vivo dosimetry and PET imaging are two methods to substantially reduce range uncertainties. Unavoidable residual uncertainties can be taken into account by carefully designing IMPT treatments using robust optimization techniques.
Conclusions: Particle beams can produce highly conformal dose distributions, but, primarily due to range uncertainties, the dose in the patient may differ substantially from the treatment plan. Image guided radiation therapy and motion management are therefore more critically important in particle therapy than in photon therapy. Without them, the physical advantage of particle beams cannot be fully utilized for the benefit of the patient.

81 INVITED

Critical review of the clinical evidence

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Background: Protons and light ions (mainly Carbon), generate much excitement, for they exhibit a superior dose-distribution than the currently used photons. Light ions are on top of this biologically more active than photons and protons. We performed a systematic literature review of the clinical evidence.
Materials and Methods: Twelve databases were searched. No limit was applied to publication year, language or study design. Only studies with at least 20 patients and with a follow-up period of at least two years were included.
Results: *Prostate cancer*: Two phase III trials in locally advanced prostate cancer were identified (n=492). However, one used inadequate photon doses and techniques and the other used protons in both arms. From pro-and retrospective series, local tumor control, 5 year overall survival and late GI and GU toxicity were for protons 74%/89%/15%/7% and for C-ions 100%/89%/6%/<5%. The results with high dose photon therapy were similar
Ocular tumors: In the only phase III study, Helium ions were compared to brachytherapy. Tumor recurrences were more observed in the brachytherapy than in the He arm (13.3% vs. 0%, $p < 0.001$), with more side effects in the He group. From 9522 patients treated with protons, local tumor control and 5 year overall/cause specific survival were 97% and 85%/85% respectively. Eye retention was 90%, whereas neovascular glaucoma occurred in 12% of patients. Similar results were obtained with C-ions and in selected photon series. The latter were much smaller and with in general only short follow-up times.
Central nervous system: For common glioma's, no gain with protons or C-ions was observed. However, for chordomas of the skull base, the weighted local tumor control rate and 5 year overall survival treated with protons was 63% and 81% respectively and for C-ions 72% and 83%. With conventional photon therapy, local tumor control rates and 5 year survival were 25% and 44% respectively.
Head and neck cancer: For squamous cell carcinomas, the results of photon therapy were similar to protons or C-ions. However, for adenoid cystic carcinomas, local tumor control rates of over 75% as achieved with C-ions are much higher than reported with photons (approximately 25% local control).
Esophageal, hepatocellular, pancreatic, non-small cell lung, sarcomas, cervix and bladder cancer: no clear superiority of protons or C-ions was established, but all series were small.
Conclusions: Although most studies with protons and C-ions were performed in non-clinical research settings, the clinical results were superior to photons for tumors that are relatively radio-resistant (adenoid cystic carcinomas) or where normal tissues are critical (ocular tumors, base of skull chordoma's). For common malignancies, however, their superiority has not been established. The advent of multiple clinical facilities will enable to improve these new radiation qualities.

Special session (Tue, 25 Sep, 13:30−14:30)
Tumour responses – the contribute of targeting host cells versus tumour cells

82 INVITED

Radiation and endothelial cell damage

Z. Fuks. *USA*

Abstract not received.

83 INVITED

Pericytes and tumour cell metastases

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Tumour cells use two major routes to spread during metastasis, e.g. lymph vessels and blood vessels within or surrounding the primary tumour. The growth rate of the primary tumour often correlates with the quantity of new blood vessels that form within the tumour. However, recent studies directed our attention to the quality of tumour blood vessels, illustrating that the deficiency of the tumour environment to support or instruct a regular patterning and stabilization of blood vessels has profound effects on both perfusion of the primary tumour and escape of tumour cells into the circulation. Our recent evidence for a novel role of the supporting mural cells in limiting blood borne metastasis will be discussed.

84 INVITED

Gastrin – a pro-angiogenic factor and down stream target of HIF1a in gastro-intestinal malignancy

S. Watson, P.A. Clarke, R. Kumari, A.J. Tobias, E.L. Royal, A.M. Grabowska. *University of Nottingham, Academic Unit of Cancer StudiesD Floor West BlockQueen's Medical Centre, Nottingham, United Kingdom*

Background: The gut hormone gastrin is a transcriptional activator of a number of malignancy-associated genes including those involved in angiogenesis. The ability of gastrin to modulate endothelial cell activity via heparin-binding epidermal growth factor (HB-EGF) expression and shedding was assessed.