cancers. Although the addition of concomitant chemotherapy has improved survival, therapeutic challenges remain, especially in locally advanced disease. Traditionally, prescription and treatment planning in intracavitary BT for cervix cancer have used either reference points (mainly points A and B) or reference isodoses (60 Gy according to ICRU recommendations). Up until recently, when point A was not used for prescription, target volume (CTV) was assessed mainly by clinical examination. Doses to critical organs were reported at bladder and rectum ICRU points. This practice has been supported by a long-standing clinical experience that has yielded an acceptable therapeutic ratio.

The recent development of imaging has contributed to the improvement in target and organs at risk knowledge. In 2005 and 2006, GEC-ESTRO recommendations publications on image guided adaptive BT (IGABT) have defined the different volumes of interest. These recommendations have been validated with intercomparison delineation studies. IGABT is based on an adaptive 4D target concept and requires the use of imaging (preferably MRI) with the BT applicator in place. With the concomitant development of remote after-loading projectors, provided with miniaturized sources, it is now possible to plan radiation doses by adjusting dwell positions and relative dwell time values. These procedures allow better coverage of the targets while sparing OAR. Tumour visualization has also led to the development of new applicators, allowing the combination of endocavitary and interstitial brachytherapy when the CTVs cannot be properly covered without a dose increase to organs at risk. The aim of these applicators is to performed interstitial brachytherapy with a limited number of needles, with a short distance between the needles and the CTVs.

Several teams have published a significant improvement in the HR-CTV coverage without increase in doses to the organs at risk. Some authors found a D2cc dose reduction of 7 ± 6 Gy$\alpha/\beta3$ for the bladder and 7 ± 6 Gy$\alpha/\beta3$ for the rectum. D2cc dose reduction was also observed in the sigmoid. The recent literature data evidenced a significant improvement in local control without increase in complications. This is particularly true for tumours larger than 5 cm at diagnosis with an improvement in overall survival as high as 30%. So far, the recommended doses to the HR-CTV have not clearly defined even if some teams have found a cut off level at 87 Gy$\alpha/\beta10$.

In France, between 2005 and 2007, 705 patients were included in the first prospective non-randomized multi-centre study based on a national grant: "Soutien aux Techniques Innovantes et Coûteuses" (STIC). The comparison was performed between 2D brachytherapy and IGABT. Local control at 2 years was improved from 74 to 79% and G3–4 morbidity reduced from 23 to 3% when comparing 2D brachytherapy and IGABT, without significant effect on disease free survival.

More recently, a prospective non randomized observational study, the so-called EMBRACE study registers IGABT since July 2008. So far, 20 centers have included 407 patients with cervix cancer. This study evidences the tendency to increase the indications of interstitial brachytherapy: 29% with the new applicators, allowing limited number of needles in the parametrium. The mean dose to the HR-CTV was 88.6 Gy$\alpha/\beta10$ $\pm$ 12.5 Gy$\alpha/\beta10$ and the mean dose to the IR-CTV was 68.7 Gy$\alpha/\beta10$ $\pm$ 6.8 Gy$\alpha/\beta10$. These very preliminary results evidence the attempt to increase the dose to the CTVs. This study is also a very appealing approach, as it will allow the comparison of all the biologically equivalent doses. All the different teams included in this prospective study will be able to compare their results according to the doses. This prospective study will help in better defining the dose recommended in both tumour and critical organs and will provide very important information in DVH parameters.

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Management Aimed at Fertility Preservation

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More than 25% of women with cervical cancer are under 40 years of age and the age of nulliparous women has increased in developed countries. Prior to assess the possibility to preserve fertility, the motivated patient should have realistic expectations. Fertility decreases with age and together with the availability of a partner, the chance to try to conceive should be part of the decision tree. A fertility sparing strategy is ideally executed in a motivated patient who is likely to try to conceive subsequently. Only few centers worldwide have sufficient experience to do these procedures on a regular basis. Most centers should call their approach experimental and time to seek for second opinion is available. Standard treatment of stage Ia1 cervical cancer (microinvasive) is treated by conisation and results in normal fertility. Standard treatment for higher stages is Wertheim-Meigs hysterectomy or radiochemotherapy. Tumour characteristics that allow consideration of fertility preservation include stage Ib1 smaller than 2 cm with negative pelvic lymph nodes. Magnetic resonance imaging enables adequate estimation of tumour diameter. When the decision is taken to try to preserve fertility, determination of lymph node status enables to identify high risk disease that needs standard treatment. When lymph nodes are negative two options exist. Firstly, radical trachelectomy which consists of removal of the cervix, parametria and vaginal cuff. This procedure requires sufficient surgical expertise in order to be executed radically and safe. Preliminary findings of less radical procedures (ie, deep cone and simple trachelectomy) in patients with tumours less than 2 cm are comparable with the results of radical trachelectomy. Secondly, neoadjuvant chemotherapy can be administered prior to surgery in order to reduce the amount of tissue (downstaging) that needs to be resected, by a less radical trachelectomy or conisation. It appears that chemotherapy does not affect fertility and chance to conceive. Although the experience is less well reported, this latter option results in a better obstetrical outcome, with less preterm delivery and more live births.

Special Session (Mon, 26 Sep, 13:15–14:15)
Hitting the Right Pathway: New Drugs for New Targets

299 INVITED

MET Inhibitors

Abstract not received

300 INVITED

RAF Inhibitors

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In the last decade, RAF kinases have emerged as valuable druggable targets, in particular after the discovery of the prevalence of oncogenic BRAF mutations in a number of solid tumours, including cutaneous melanoma, colorectal and papillary thyroid cancers. The BRAF V600E aminoacid substitution accounts for the majority of alterations and confers constitutive kinase activity. Among RAF inhibitors undergoing preclinical or clinical development, some display some preferential selectivity towards the mutant isoform (GSK2118436, vemurafenib), while others have similar activity on both mutated and wild type BRAF or other RAF isoforms.

The first targeted drug expected to reach clinical use is vemurafenib (known also as PLX4032, RO5185426, RG7204) that has demonstrated remarkable efficacy in melanoma patients carrying BRAF V600E mutated tumours. Initial enthusiasm has been dampened by the relatively short duration of clinical response. Indeed, secondary resistance to this drug emerges in patients who relapse after a median time of 6–7 months. Acquired resistance does not seem to be mediated by additional 'gatekeeper' mutations in the BRAF target gene itself. Rather, a number of studies on cell lines and melanoma samples indicate that tumours become resistant by modulating the expression or activity of other genes (such as NRAS, CRAF, COT, MEK1, PDGFR, IGF1R, PTEN) that compensate BRAF inhibition or obviate for the need of BRAF signaling. Consequently, combinatorial strategies with MEK or PI3K pathway targeted drugs or single molecule dual RAF/MEK inhibitors (such as RO5126766) are being evaluated to delay the onset of secondary resistance and improve patient survival.

Interestingly, not all BRAF V600E mutated tumours are sensitive to vemurafenib, with 15–20% melanoma cases and the vast majority of BRAF mutant colorectal cancer patients displaying intrinsic resistance to treatment with this inhibitor. The molecular bases of these partial failures represent an area of active research investigations.

Finally, newer compounds such as PLX-PB-4 and ARQ680 (and its prodrug ARQ736) are being developed to overcome the limitations of first-generation drugs, and, in particular, their ability to promote dimerization of RAF family members and paradoxical activation of MAPK pathway in treated cells bearing oncogenic or normally activated RAS. It is likely that this could be achieved by designing inhibitors with increased potency against CRAF and/or with the ability to block RAF dimerization.

301 INVITED

ALK in NSCLC – Paving the Way for Oncogene-directed Therapy

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The discovery of distinct subsets of non-small cell lung cancer (NSCLC) as defined by the presence of molecular oncogenes has greatly impacted oncogene-directed therapy for this disease. Gene fusions involving the kinase domain encoding region of the *ALK* gene were first reported in NSCLC in 2007 and displayed oncogenic properties. The tyrosine kinase inhibitor, crizotinib, has shown remarkable response rates and progression