glucuronide by UGT1A1, the isoform catalyzing bilirubin glucuronidation. There is large interpatient variability in response to irinotecan, as well as severe side effects such as diarrhea and neutropenia, which might be explained in part by genetic variation in metabolic enzymes and transporters. Well-known variants are the promoter polymorphic repeat in UGT1A1 (UGT1A1*28) and the 1236C>T polymorphism in ABCB1. UGT1A1*28 genotype has been associated with toxicity and efficacy. The roles of ABCB1 variants and of variants the carboxylesterases continue to be elucidated. These polymorphisms and a systems biology approach evaluating variations in drug pharmacology as well as drug targets and host factors will be discussed.

**96** INVITED

**Predictive biomarkers for EGFR inhibitors in lung cancer**

R. Dziadziuszko. *USA*

Abstract not received.

## *Symposium* (Tue, 25 Sep, 14:45−16:45)
## What is new in cervical and endometrial cancer?

**97** INVITED

**Update on pathology and terminology of uterine cancers**

W. McCluggage. *Queen's University of Belfast, Department of Pathology, Belfast, United Kingdom*

A dualistic model of endometrial carcinogenesis is well established whereby the more common type 1 cancer (mostly endometrioid) develops from atypical hyperplasia under the influence of oestrogens while type 2 cancers (mostly serous) develop from an atrophic endometrium. In recent years, a presumed precursor lesion of type 2 cancer has been described, termed serous intraepithelial carcinoma (serous EIC). However, serous EIC may give rise to extrauterine disease, even in the absence of endometrial stromal or myometrial infiltration and, as such, may not represent a precursor lesion. In such cases, the term minimal uterine serous carcinoma may be more apt. Minimal uterine serous carcinoma has a marked propensity to arise in or involve endometrial polyps. Molecular alterations in both type 1 (PTEN, k-ras, β-catenin mutations and microsatellite instability) and type 2 (p53, p16, E-cadherin, Her2-neu mutations) cancers are now well described. It is also clear that mixed type 1 and type 2 cancers are not uncommon whereby the type 2 component develops from a type 1 cancer via a process of dedifferentiation secondary to p53 mutation. It is now clear that endometrial cancers are common in women with hereditary non-polyposis colorectal cancer (HNPCC) syndrome; the morphological types in women with HNPCC are not clear but surprisingly type 2 cancers may be more common than in the general population. The histogenesis of uterine carcinosarcomas has now been settled; most are, in reality, carcinomas with sarcomatous differentiation or metaplastic carcinomas, although a small number are true collision tumours. There has been a change in the terminology of malignant mesenchymal lesions derived from the endometrium with the terms high grade and low grade endometrial stromal sarcoma no longer used. Instead there is now a category of an indolent low grade malignant neoplasm composed of bland cells (endometrial stromal sarcoma) and an aggressive high grade malignant neoplasm composed of anaplastic cells (undifferentiated endometrial sarcoma).
In the cervix, adenocarcinomas appear to be increasing in incidence, especially in Western populations. Early invasive adenocarcinoma is now being diagnosed more commonly with refinement of the criteria for making this diagnosis. Neuroendocrine carcinomas in the cervix are also being diagnosed more frequently, especially large cell neuroendocrine carcinoma (LCNEC). This is in large due to the recognition that some undifferentiated carcinomas and poorly differentiated non small cell carcinomas in the cervix represent LCNEC.

**98** INVITED

**New molecular pathways in uterine cancers and their implications for new treatments**

A. Oza. *Canada*

Abstract not received.

**99** INVITED

**New drugs in cervix cancer treatment**

J.B. Vermorken. *University Hospital Antwerp, Department of Oncology, Edegem, Belgium*

The role of systemic treatment in cervical cancer has been changing over time. In the past chemotherapy has been considered appropriate only for patients with recurrent, metastatic or persistent disease for whom treatment with potentially curative intent is no longer amenable. Nowadays, chemotherapy is also often used in the treatment of primary disease for those who are at high risk for relapse. Cisplatin is considered to be the most active compound in all circumstances; it is mostly given alone when combined with radiotherapy, and given alone or combined with other agents when used for induction in the primary disease setting or applied for palliation. More and more patients in that latter setting will be offered chemotherapy after they have received cisplatin as part of primary chemoradiotherapy, and this will moderate the expected benefits. New drugs are more than ever needed. Taxanes, topo-I-inhibitors, vinca-alkaloids and gemcitabine have all been tested and suggested to be of benefit when used alone or in combination. Of these only paclitaxel, topotecan and irinotecan have been studied in combination with cisplatin in large randomized trials versus cisplatin alone. The greatest improvements in response, progression-free survival and median survival outcomes have been detected with the use of cisplatin plus topotecan. Targeted therapies alone, in combination with cisplatin or combined with (chemo)radiotherapy are under study. Recently, one of the prophylactic vaccines against HPV 6, 11, 16 and 18 (Gardasil) has been approved on the basis of several trials showing that CIN grades 2 and 3 and cervical adenocarcinoma in situ lesions were highly reduced by the use of this vaccine. Time will tell whether this will be the beginning of the end of cervical cancer.

**100** INVITED

**Progress with cervix cancer vaccines. The end in sight?**

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**Background:** HPV infection in the genital tract is common in young, sexually active individuals, the majority of whom clear the infection without clinical disease. In a minority of subjects the immune system fails to control the persistent virus and malignancies develop. The natural HPV specific E6 and E7 T cell immune response is found to be different in patients compared to healthy individuals. Antibody responses to the major virus capsid protein L1 accompany the induction of successful cell mediated immunity and these responses are protective against subsequent viral. Results from phase III trials of HPV VLP vaccines show efficacy against HPV 6, 11, 16 and 18 of which the latter two are high risk types for invasive lesions of the female genital tract.
Therapeutic vaccination, in cases with persistent HPV infection or (pre) invasive lesions, has the aim to enhance the HPV type specific cellular immune response. Several modalities have been tested in animal studies and are currently being tested in humans.
**Methods:** Previously, we demonstrated that long overlapping HPV16 E6 and E7 long peptide vaccine in Montanide ISA 51 was safe and able to elicit strong HPV16 specific T-cell response in end-stage cervical cancer patients. A phase II study is currently in progress in 20 patients with histologically proven HPV16+ vulvar intraepithelial neoplasia (VIN) grade III, who are vaccinated 4 times at a 3-week interval.
**Results:** IFN-gamma-ELISPOT analysis reveal that almost all patients mount a T-cell response to multiple regions of HPV16 E6 and 75% of the patients against HPV16 E7, already after 2 vaccinations. In proliferation assays we see that this T-cell reactivity is associated with the production of IFNä and IL-5 similar to the cytokine profile of the HPV16-specific memory T-cell responses observed in healthy individuals. Analysis of the local immune response demonstrates that after vaccination HPV16-specific Th1/Th2 cells infiltrate both the vaccination site and/or the VIN lesion. At this moment clinical efficacy at 3 month follow-up can be measured in a subgroup of the patients.
**Conclusion:** Prophylactic as well as therapeutic vaccination against HPV related disease in the female genital tract is showing potential efficacy.