10−23%. Prognosis may be positively influenced by a longer disease free interval of more than 6 months after initial lung resection.
Despite the lack of randomised studies as well as prospective phase II studies the current literature suggests that well selected patents with oligometastatic disease may profit from an individualised treatment including complete resection of the primary tumor as well as the metastases. Not only the indication for surgery is ill defined in the current literature also the role of adjuvant chemotherapy or radiotherapy is unclear despite it is often used in combination with surgery. Improvement in imaging modalities and minimal invasive staging techniques allow more reliably to define the macroscopic tumor extend.

**181** INVITED

**Which is the best treatment for non-small lung cancer patients with PS 2?**

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Patients with performance status of 2 (PS 2) usually account for a small proportion of patients enrolled in trials of first-line treatment for advanced disease but represent a significantly higher proportion (up to 30–40%) when population-based surveys are conducted. As in other types of cancer, PS has a clear prognostic role in advanced NSCLC. Median overall survival of patients with PS2, whatever the treatment under investigation, is always substantially shorter than that of PS0 or PS1 patients, and rarely exceeds 5 months, with 1-year survival rates <20%, and these unfit patients are at higher risk for severe toxicity.
For this sub-group of patients, there is no treatment widely accepted as standard and oncologists have to choose among several treatment options: best supportive care, single-agent chemotherapy, non-platinum-based combination chemotherapy and platinum-based combination chemotherapy.
It is still unclear if the benefit achieved with cisplatin-based chemotherapy is restricted only to PS0 and PS1 patients, or also applies to PS2 patients. In the meta-analysis published in 1995, although overall results were limited by statistical heterogeneity and evident outcome differences for the different chemotherapy categories, a significant benefit was demonstrated for cisplatin-based trials, and a sub-group analysis confirmed this benefit for both good and poorer PS patients. However, the outcome of 64 PS2 patients enrolled in the clinical trial ECOG 1594 comparing four platinum-based combinations has proven to be very poor. As for the role of carboplatin, the results of the CALGB 9730 study, comparing paclitaxel plus carboplatin versus paclitaxel alone, must be considered. In the sub-group of PS2 patients median survival in the group treated with combination chemotherapy was significantly longer than with paclitaxel alone. In a randomized phase II study carboplatin plus paclitaxel and cisplatin plus gemcitabine, administered at attenuated doses, proved to be feasible in PS 2 patients. After 1995, some advantage of chemotherapy versus supportive care alone has been shown also with many new cytotoxic agents as gemcitabine, vinorelbine, paclitaxel and docetaxel, administered as single agents. These drugs are usually characterised by a good tolerability, with a low incidence of severe adverse events. Most of the studies show some advantage of chemotherapy in terms of overall survival also in the sub-group of PS2 patients, although formal statistical comparisons are precluded by the low absolute number of patients. However, there is no consistent evidence that combination chemotherapy without platinum is better than third generation drugs given as single agents. An Italian randomised trial compared the combination of gemcitabine and vinorelbine to the two single drugs in patients >70 years of age, and the combination did not show advantage over mono-chemotherapy in terms of overall survival also in the sub-group of PS2 patients. The results of an European Experts Panel on the topic, indicate that single-agent chemotherapy could be the preferred option in the treatment of PS 2 patients, with carboplatin-based or low-dose cisplatin-based doublets representing alternative options. To date randomised trial in USA (carboplatin+ gemcitabine vs gemcitabine) and in Italy (cisplatin+gemcitabine vs gemcitabine) are ongoing. In the near future, the role of targeted agents with better safety profile than chemotherapy as the EGFR-TKI erlotinib, has to be explored in the first-line treatment of advanced NSCLC PS2 patients.

## *Special Session* (Tue, 22 Sep, 17:00−18:00)
## Deficient mismatch repair (dMMR) in colorectal cancer

**182** INVITED

**Defect Mismatch Repair System (dMMR): always genetic and sometimes hereditary**

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Lynch syndrome, also called Hereditary NonPolyposis Colorectal Cancer (HNPCC), accounts for about 5% of colorectal cancers and is caused by a germline mutation in one of the mismatch repair (MMR) genes. Colorectal cancer is the most common type of cancer in Lynch syndrome. Also, extra colonic carcinomas occur, i.e. carcinomas of the endometrial, ovaries, small bowel, stomach, sebaceous gland, biliary tract, and upper urinary tract. Typical Lynch syndrome families show an autosomal dominant predisposition of cancers associated with Lynch syndrome, and over 90% of colorectal cancers have a defect in the MMR system (dMMR). Germline mutations have been identified in the MMR genes MLH1, PMS2, MSH2 and MSH6.
Microsatellite instability (MSI) analysis and immunohistochemical (IHC) staining of MMR proteins can detect a defect in the MMR system (dMMR). This defect can be caused either by a germline mutation in the MMR system or by somatic hypermethylation of the promoter region of MLH1. A tumour that shows MSI without staining of MLH1 and PMS2 proteins and with somatic hypermethylation of the MLH1 promoter is characteristic for sporadic cancer, meaning not hereditary.
A disease causing germline mutation can be identified in 60% of patients suspected of Lynch syndrome with an MSI positive tumour (dMMR), 20% show hypermethylation of the MLH1 promoter and therefore do not have a hereditary but a sporadic type of cancer. Interestingly, the remaining 20% of patients, with an unexplained MSI positive tumour, had a less pronounced family history, but were diagnosed at an age comparable to that of proven Lynch syndrome patients.
Differentiation of sporadic CRC from Lynch syndrome-HNPCC is important as surveillance in the latter is more intensive and can reduce mortality from cancer in patients and their close relatives. The finding of a predisposing germline mutation will determine who is (and who is not!) a candidate for participation in surveillance programs. Identification of Lynch syndrome only by family history is insufficient and new strategies are needed to detect more patients at risk for Lynch syndrome.
To improve the identification of Lynch syndrome, we started to implement a new approach called MIPA (MSI indicated by a Pathologist): pathologists select newly diagnosed patients with colorectal cancer for MSI analysis based on one of the following criteria:

1. Colorectal cancer before the age of 50 years;
2. Second colorectal cancer before the age of 70 years;
3. Colorectal cancer and a Lynch associated cancer before the age of 70 years (Endometrial, ovarian, gastric, hepatobiliary, small bowel cancer or transitional cell carcinoma of the renal pelvis or ureter)

Next, the treating physician discusses referral to genetic counselling with patients who have a tumour with MSI indicating deficient MMR.
The newly proposed approach, in which pathologists select patients for MSI analyses, is found to be effective, efficient and feasible in daily practice. Deficient MMR is an excellent marker to distinguish sporadic CRC from patients at high risk for Lynch syndrome, but not all patients with dMMR have hereditary cancer. Therefore deficient MMR is always genetic and sometimes hereditary.

**183** INVITED

**Should patients with dMMR be treated with chemotherapy?**

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The selection of patients to treat with adjuvant chemotherapy for resected colorectal cancer is of outmost importance, in order to decrease the NNT (Number Needed to Treat), chiefly in stage II individuals, who have a relatively good prognosis after surgery alone. In the last few years, patients with colon cancer demonstrating Microsatellite instability (MSI-H) or defective DNA mismatch repair (dMMR) have been reported to have improved survival and to receive decreased or no benefit from 5-FU based adjuvant therapy as compared to patients with microsatellite-stable (MSS) tumors (Ribic C, JCO 2003).