as a monotherapy. Remarkable activity has been observed in patients with BRCA1/2 mutations using Olaparib (AZD2281), an orally bioavailable PARP inhibitor, recently approved for refractory ovarian cancer with BRCA1/2 mutations. Toxicity with monotherapy has been remarkably low. Is the BRCA mutation story the only predictor of PARP inhibition (I) sensitivity? Perhaps other homologous and non-homologous repair defects may also contribute to PARP(I) sensitivity. Fanconi anemia phenotypes may also relate to sensitivity as well as pathways related to the SMAD family. We assessed the safety, toxicity and early response when combining escalating doses of Olaparib with fixed dose cetuximab and RT in heavy smoker HNSCC patients. We chose this group of patients due to their high local-regional failure rates and hypothesized amplified rates of HR defects that would lend itself to Olaparib sensitivity. We used a TITE-CRM model with a starting Olaparib dose of 50 mg po BID. The TITE-CRM algorithm uses both the length of observation and whether or not a DLT has occurred in each previous patient enrolled on the trial to estimate the probability of a DLT for each dose level, thereby optimizing subsequent dose assignment. We enrolled 13 patients to date. Among these patients, with a median follow-up of ~14 months, two failed distantly and one failed locally. Patients who experienced local/regional failures continued to smoke during treatment. Toxicity was primarily related to grade 3 dermatitis and acneiform rash. Skin toxicities resolved in all patients after treatment concluded; long-term follow up has revealed development of grade 2 fibrosis in the neck areas where dermatitis was most severe in four patients. The optimal timing of PARP inhibitors and radiation remains unknown and with dose enhancement factors seen pre-clinically, might it be possible to investigate radiation de-intensification or perhaps consider novel combinations with checkpoint inhibitors. This discussion will include a review of some of the pertinent pre-clinical studies with radiation, a review of toxicities and cautions as it relates to combinations with radiation and what are the possibilities for future approaches with DNA repair in locally advanced disease.

Symposium: Radiotherapy of prostate cancer: technical challenges

SP-0299
Extreme hypofractionation: indications and results

A. Widmark[1], L. Beckman[1,2], A. Gunnlaugsson[3,4], C. Thellenberg-Karlsson[1], M. Hoyer[5], M. Lagerlund[6], L. Franzen[1], P. Nilsson[3,4]
[1]*Umeå University, Department of Radiation Sciences, Oncology, Umeå, Sweden*
[2]*Sundsvall Hospital, Department of Oncology, Sundsvall, Sweden*
[3]*Skåne University Hospital, Department of Oncology, Lund, Sweden*
[4]*Lund Unversity, Department of Oncology, Lund Sweden*
[5]*Aarhus University Hospital, Department of Oncology, Aarhus, Denmark*
[6]*Kalmar Hospital, Department of Oncology, Kalmar, Sweden*

The α-ß ratio for prostate cancer (PCa) is postulated to be low; < 3 Gy, i.e. even lower than for late normal tissue reactions. Hence hypofractionated radiotherapy (RT) is hypothesized to be advantageous for treatment of localized PCa. Literature data indicating that this is the case for a moderately hypofractionated regimen was first reported from Italy by Arcangeli. This study was however quite small. At ECC 2015 Dearnaley presented the results from the UK three-armed CHHiP-trial comprising 3,200 patients. This three-armed trial showed non-inferiority between the 74 Gy conventional arm (37 fr; 2 Gy/fr) and the 60 Gy moderately hypofractionated arms (20 fr; 3 Gy/fr) while the experimental arm given 57 Gy arm (19 fr; 3Gy/fr.) had lower efficacy. Patients had predominately intermediate risk tumours and most patients received 6 month of neoadjuvant and concomitant castration treatment. Previously published toxicity data from the trial showed similar results for the trial arms. Results from other moderately hypofractionated schedules have also been reported recently. RTOG 0415 with only low-risk patients, showed that 70 Gy in 28 fr over 5.6 weeks is non-inferior to 73.8 Gy in 41 fr over 8.2 weeks for low risk PCa patients. The Dutch randomised phase III HYPRO trial with 804 evaluable patients with intermediate/high-risk PCa, comparing moderately hypofractionated RT (19 fr; 3.4 Gy/fr.) with conventional RT (39 fr; 2 Gy/fr), showed non-inferiority with comparable toxicity.
Some prospective results of Sterotactic Body RadioTherapy (SBRT) with 5 fractions and 7-8 Gy/fr suggest equal clinical outcome compared to conventional RT and with acceptable toxicity. The Scandinavian multicentre phase III trial "HYPO-RT-PC" was recently closed, with 1200 patients recruited during 2005-2015. All patients had intermediate risk PCa (PSA≤20; one or two of the risk factors; T3, Gleason≥7, PSA 10-20). No hormones were used. Patients were randomized to either conventionally fractionated RT (39 fr; 2.0 Gy/fr) over 7 weeks, or to a schedule with extreme hypofractionation (7 fr; 6.1 Gy/ fr) in 2.5 weeks (always including two weekends). The two treatment arms are designed to be equieffective for late normal tissue complications assuming α/ß=3 Gy. Primary endpoint will be mature within 2 years, and toxicity data will be reported by late this year.

SP-0300
Focal strategies: ready for prime time?

A. Bossi[1]
[1]*Institut Gustav Roussy, Radiation Oncology, Villejuif, France*

Abstract not received

SP-0301
Brachytherapy as a boost: the way to go?

P. Hoskin[1]
[1]*Mount Vernon Hospital, Northwood Middlesex, United Kingdom*

Brachytherapy has always represented the most focal means on delivering radiationh having the advantages of the inverse square law around the radiation source which ensures delivery of an intense high dose within the implant and a rapid fall dose outside. These characteristics mean that brachytherapy can deliver very high doses to the prostate gland with in the tolerance doses of bladder and rectum and that the characteristics of dose distribution with in the implant mean that the volume receiving 150% and 200% prescribed peripheral dose (the 150 and the 200) are considerably greater than can be achieved with any external beam technique.
Brachytherapy as a boost can be used in two distinct ways. First is as a boost to the whole gland following external beam radiotherapy. There is now grade a level I evidence from randomised controlled trials that both low dose rate and high dose rate brachytherapy achieve effective dose escalation and consequently better biochemical relapse free survival.
There is also increasing interest in the use of brachytherapy to deliver a focal boost to dominant lesions defined on multi-parametric MR scanning and mapping template biopsies. Thus within a whole gland brachytherapy volume sub volumes can be defined within which the dose can be further escalated. Planning studies have confirmed the feasibility of this approach with both low dose rate and high dose rate brachytherapy and the requirements for catheter or seed placement to achieve these endpoints has been described. The clinical application of this approach is still in its infancy although early results confirm its feasibility.
Summary: both low dose rate and high dose rate brachytherapy offer optimal means of focal dose delivery within the prostate gland. The use of this modality for whole gland treatment is now well established sound evidence base. Emerging application sub volume posts to dominant tumour volumes is under investigation.