1 TRIAL OVERVIEW "ONE SHOT

Sponsor:	**1**	Professor Miralbell
Trial Title:	**2**	ONE SHOT - Single shot radiotherapy for localized prostate cancer: A Multicenter, Single Arm, Phase I/II Trial
Short Title / Trial ID:	**3**	Single shot prostate SBRT
Protocol Version and Date:	4 **5**	Version 2.1 11th May 2018
Trial registration:	6 **7**	Swiss National Clinical Trials Portal (SNCTP) ClinicalTrial.gov (NCT03294889)
Trial category and Rationale	**8**	Study category B
Clinical Phase:	9 *10* *11* *12*	Phase I/II *Type:* Clinical trial. *Subtype and Category:* Category B. *Rationale for the risk category:* Stereotactic body radiation therapy (SBRT) is a currently used as treatment for localized prostate cancer. The interventions under investigation therefore involve no more than minimal additional risks and stress for the participating patients.

Background and Rationale:	Total dose and dose per fraction play an important role in the curative treatment of prostate cancer with radiotherapy (RT). Modern image guided external RT allows safe dose escalation of prostate cancer. Doses above 74 Gy with conventional fractionation (2 Gy/day) have been shown to be beneficial. There are strong radiobiological and clinical considerations that suggest that treatment with a small number of large fractions (hypofractionation) may increase the therapeutic ratio of RT for prostate cancer by increasing the tumor cell killing effect with relatively less toxic effect on the surrounding late responding normal tissues compared to conventional fractionation. Results on extreme hypofractionation with stereotactic body radiotherapy (SBRT) have been reported during the last few years. Most frequently, 5 fractions of 7.25 Gy have been delivered for a total equivalent dose to the tumor of 90 Gy in 2 Gy/fraction (LQ model) and a success rate of >95%, 5-year biochemical disease-free survival (bDFS) rates. The question of how far can the number of fractions with SBRT be reduced is an exciting research matter with an undoubtful goal, face the challenge of assessing the potential for cure of prostate cancer patients with a single and unique fraction of high dose irradiation similar to what is already undertaken with radiosurgery against brain, lung, and liver targets. Such type of effort has already been attempted with HDR-BT. Recently Prada *et al.,* reported a relatively disappointing 66% 5-year bDFS though a very good tolerance after a single interstitial application of 19 Gy to the prostate. Reasons for this suboptimal result may be related, for instance, to a suboptimal dose-distribution with HDR-BT compared to SBRT. However, Hoskin *et al.* have recently published the results on 49 patients treated with a single fraction of HDR-BT to 19/20 Gy. With 49 months median follow-up, the 4-year estimates of grade 3 genitourinary and gastrointestinal toxicities was 2% and 0%, respectively, with no grade 4 events. The 4-year bDFS was 94%. In conclusion, for the authors one single fraction is feasible, weakly toxic, and with promising preliminary results. Looking at SBRT series, biochemical disease-free survival rates of 97% and 96% at 5-years have been recently reported for patients with low- and intermediate risk disease, respectively, in a large study with 309 patients treated with 5 x 8 Gy (a dose equivalent to 19 Gy in a single fraction). Only 3% of the patients experienced grade 3 GU toxicity. Moreover, compared to HDR monotherapy (42 Gy in 6 fractions), SBRT (35 to 40 Gy in 4 to 5 fractions) provide a similar biochemical control in intermediate-risk prostate cancer, with a 96% rate at 4-years. Based on these data, we hypothesize that an ultra-hypofractionated single-dose SBRT employing state of the art of image-guided RT techniques may be feasible, with a safe toxicity profile and an optimal long-term tumor control. Hence, a prospective, multicenter international phase I/II clinical trial will be initiated in prostate cancer patients with a localized disease to validate internationally this treatment schedule as an alternative to normofractionated/moderate hypofractionated RT schedules to be tested in a second time in a phase III trial.
Objective(s):	The main objectives of this phase I/II trial is to determine the safety and efficacy of a single fraction SBRT at a dose of 19 Gy in patients with localized prostate cancer.

Endpoints:	**Primary endpoint (phase I)** - Safety will be evaluated using Grade ≥ 3 genitourinary and/or gastrointestinal acute adverse event (AE) during the first 3 month according to CTCAE classification v.4.03 **Primary endpoint (phase II)** - Efficacy will be evaluated using biochemical relapse-free survival (bRFS) at 3-years. **Secondary endpoints (phase II)** - Acute AE (during the first 3 months) according to CTCAE v4.03 - Late AE (after 3 months) according to CTCAE v4.03 - Progression free survival (PFS) - Clinical progression free survival - Local progression free survival - Time to further anti-cancer therapy - Prostate cancer-specific survival (PCSS) - Overall survival (OS) - Quality of life (QoL) evaluated using EPIC 26, IPSS, IIEF-5
Trial design:	This is a phase I/II, prospective, single-arm study