

A Phase I/II Randomized Study of Debio 1143 Combined with Concurrent Chemo-Radiation Therapy (CCRT) in Patients with Locally Advanced Squamous Cell Carcinoma of the Head and Neck (LA-SCCHN)

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Background

Debio 1143 is a monovalent SMAC mimetic targeting IAPs to induce apoptosis

Drug resistance is a major problem in cancer therapy. The combination of drugs targeting simultaneously multiple critical sites of the signaling networks controlling growth and survival of cancer cells is necessary to achieve long-lasting responses (1, 2).

The members of the Inhibitor of Apoptosis Protein (IAP) family are key negative regulators of programmed cell death. Their frequent overexpression in most cancer types contributes to tumor cell survival and resistance to cancer therapy making IAPs attractive therapeutic targets (3).

The oral monovalent SMAC mimetic Debio 1143 (a.k.a. SM406 and AT406) functions as an antagonist of multiple IAPs thus facilitating cell death via both the intrinsic and extrinsic apoptosis pathways by interfering with X-linked IAP (XIAP) and cellular IAP1 and 2 (cIAP1/2), respectively.

Preclinical results show that Debio 1143 exhibits anti-tumoral activity as a single agent and potentiates chemo and radiation effects in SCCHN models [1].

Debio1143 monotherapy was well tolerated in cancer patients up to 900 mg OD, resulted in rapid and sustained cIAP1 suppression in patient peripheral blood mononuclear cells and in skin biopsies, and achieved exposures that were previously shown to be active in animal models [2].

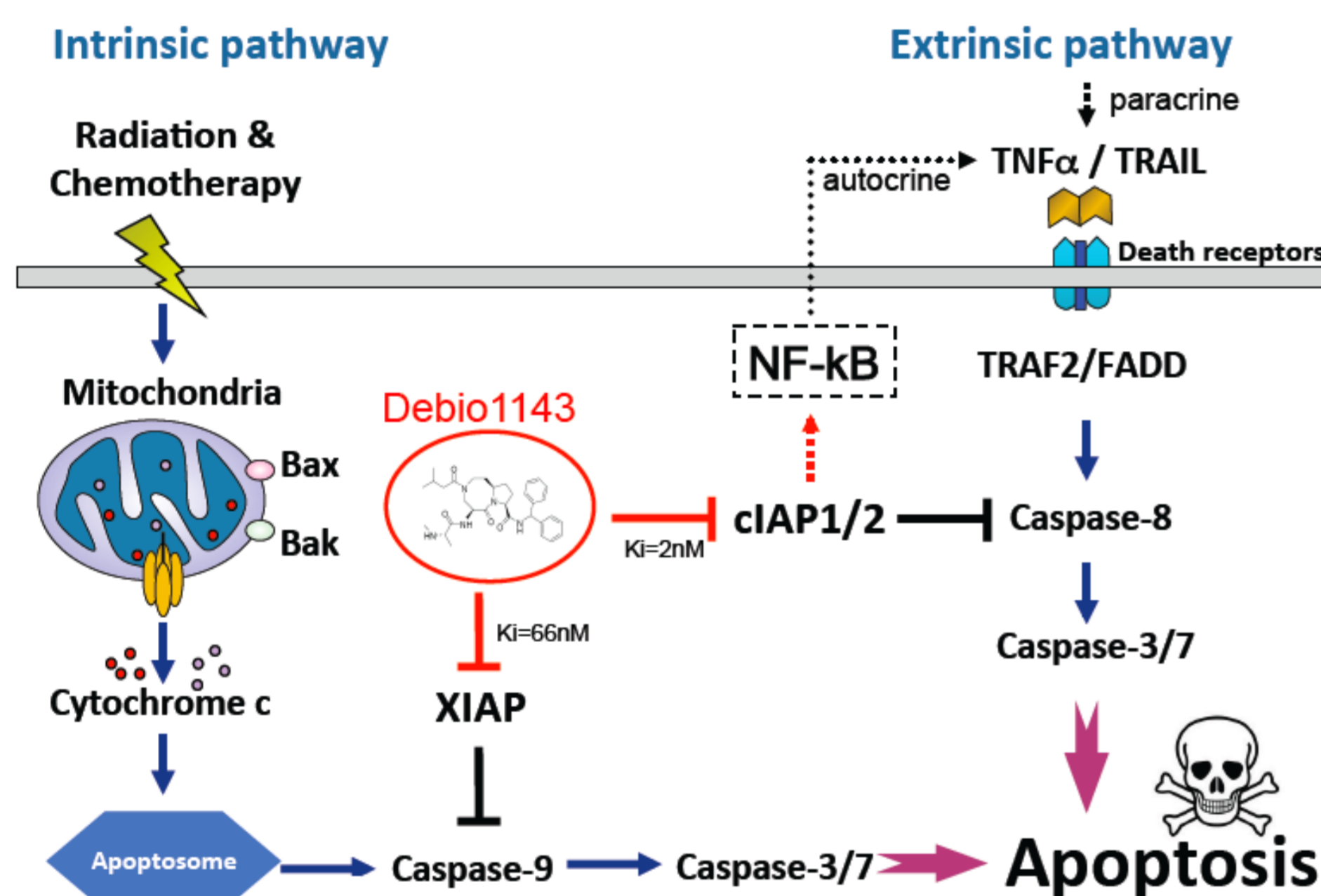
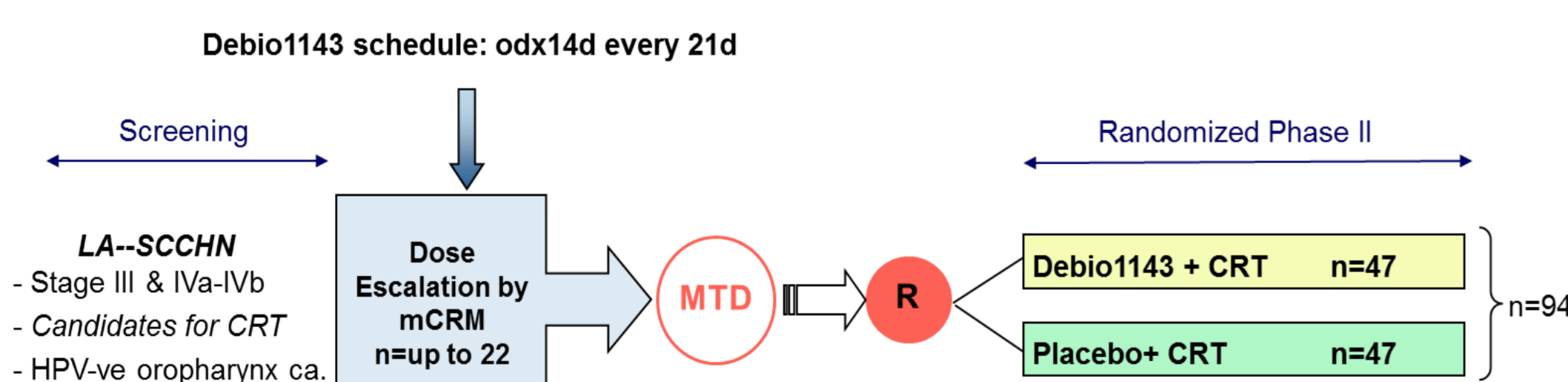


Fig. 1. Mechanism of action of Debio 1143. Debio 1143 facilitates cell death via both intrinsic and extrinsic apoptosis pathways by interfering with XIAP and c-IAP1/2, respectively.

Methods

Study scheme



Main Objectives
 • Feasibility of combination
 • PK and PD in plasma and tumor tissue

Main Endpoints
 • MTD
 • Hints of activity by RECIST

Methods

Primary objectives:

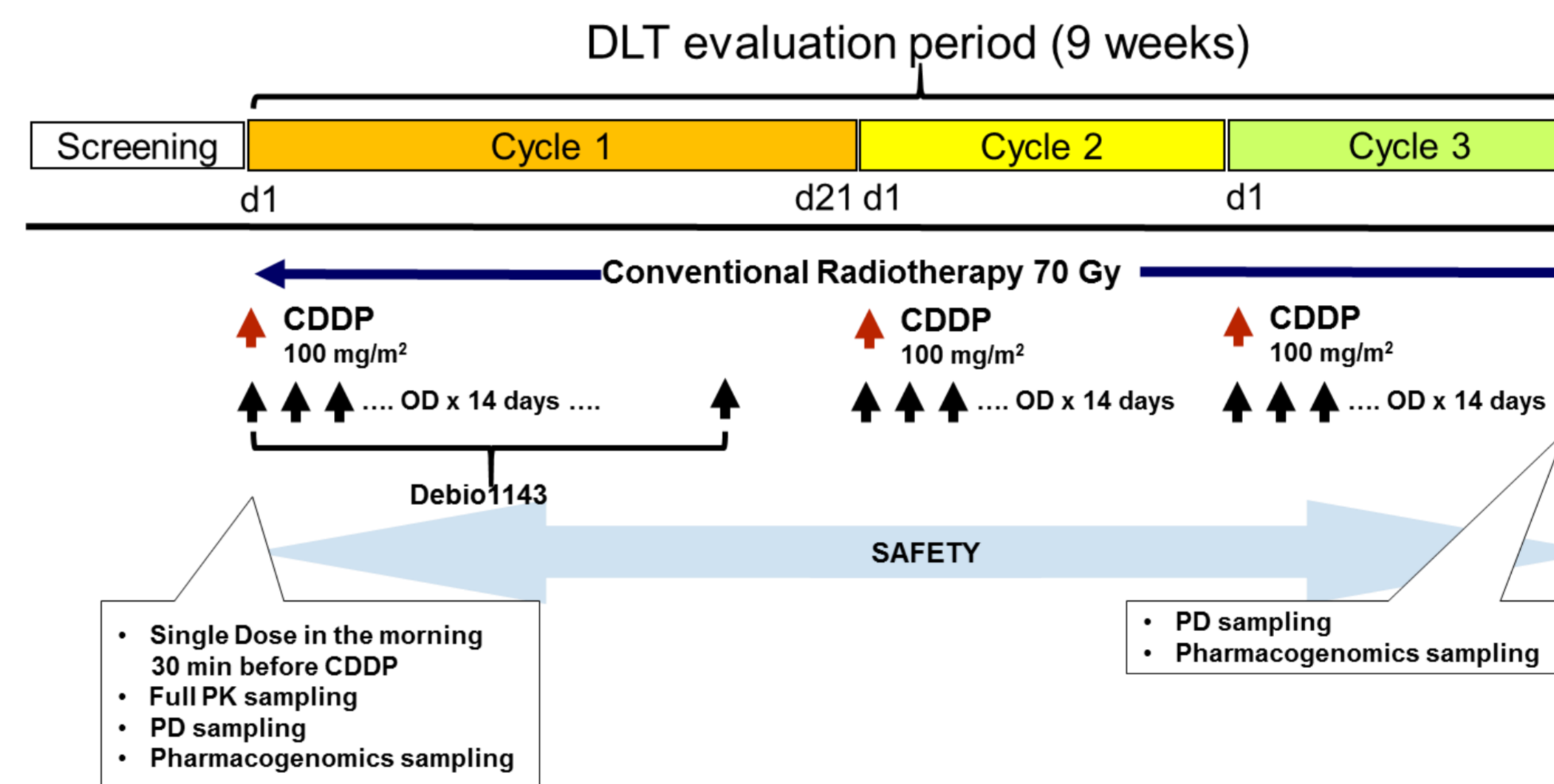
- To determine the maximum tolerated dose (MTD) of Debio1143 in combination with concurrent CRT in patients with LA-SCCHN.

Secondary objectives:

- To assess the safety profile of Debio1143 in combination with concurrent CRT.
- To evaluate the anti-tumor activity of the recommended dose of Debio1143 in combination with concurrent CRT in the study population.
- To explore the PK of Debio1143 and cisplatin when administered in combination with radiation therapy, and explore the potential for drug-drug interactions of Debio1143 in combination with cisplatin.
- To explore pharmacodynamic biomarkers of Debio1143 activity in combination with concurrent CRT.
- To explore pharmacogenomic, and tumor pharmacogenetic factors.
- To explore PK/PD, PK/efficacy, PK/safety PD/efficacy and PD/safety relationships and pharmacogenetic factors that may affect Debio1143 PK.

Phase I Dose Escalation

- Adaptive dose-escalation design using a modified Continual Reassessment Method (mCRM)
- Starting dose = 100 mg/day over 14 days every 21 days



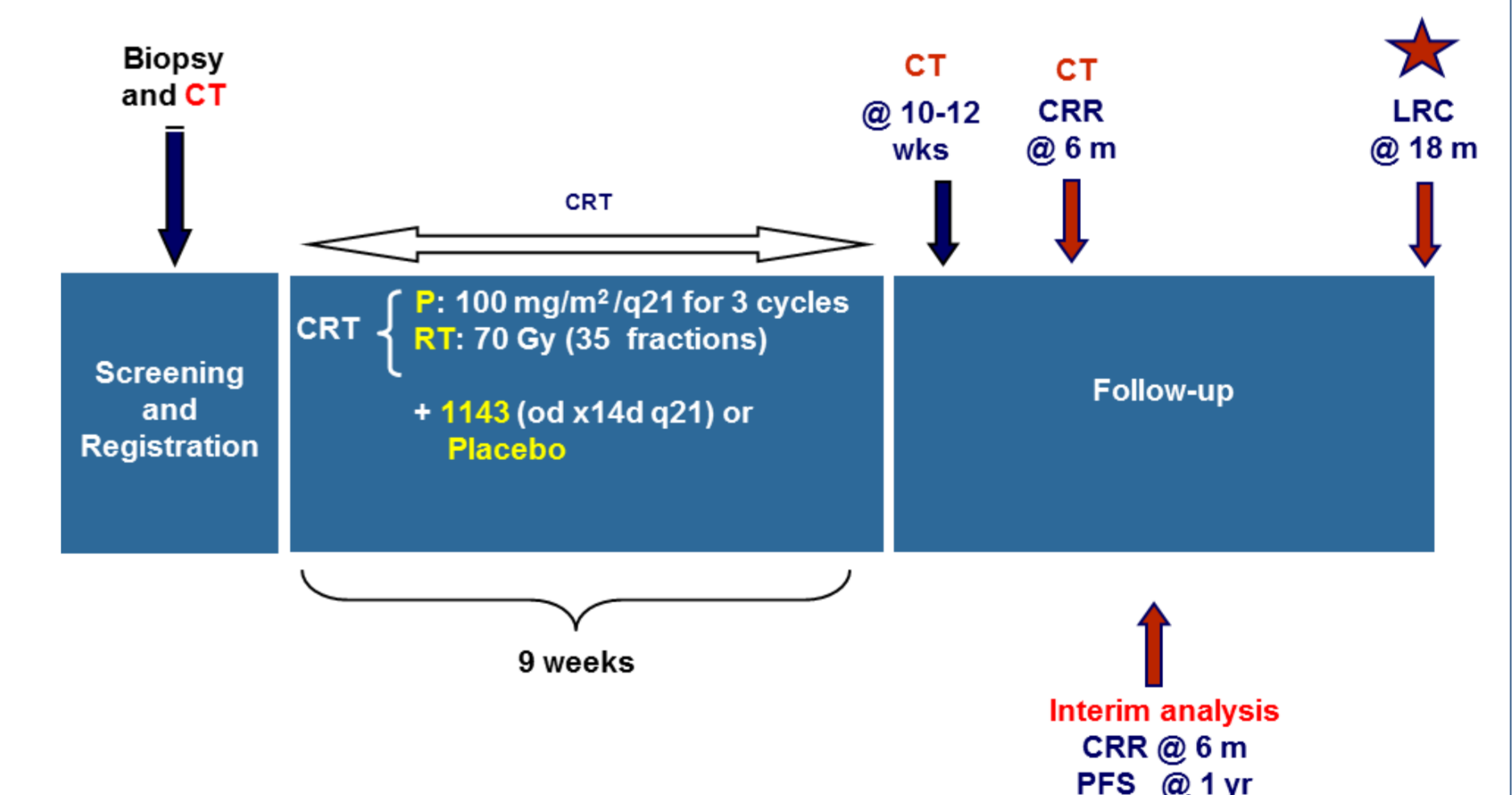
Phase II (randomized, double-blind at RD) – n = 94

Primary Endpoint

Proportion of patients achieving LRC @ 18 months from the end of CRT.

Secondary Endpoints

- CRR @ 6 months from the end of CRT;
- BORR, DCR and Response Rate after 10 weeks and 6 months from the end of CRT;
- Locoregional control @ 6 months and 1 year from the initiation of CRT;
- PFS @ 1 year and 2 years;
- Distant relapse @ 6 months, 1 year and 18 months from the end of CRT;
- Disease specific survival @ 1 year and 2 years;
- OS rate @ 1 year and 2 years;
- Change in vital signs and ECOG PS;
- Incidence and severity of AEs according to NCI-CTCAE toxicity criteria;
- Incidence of laboratory abnormalities according to NCI-CTCAE criteria;
- Incidence of treatment discontinuations due to AEs and SAEs;
- Incidence of late toxicity (as dysphagia, chronic swallowing dysfunction, speech problems, cervical fibrosis) @ 1 year and 2 years



Status

Recruitment started in September 2013 and it is in progress.

ClinicalTrials.gov identifier: NCT02022098

References

- Viertl et al. (2013). *Radiotherapy & Oncology* 106, Suppl. 1.
- Hurwitz et al. (2012). *Eur. J. Cancer* 48, Suppl. Abstract 76, p. 25.

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