



CAPITAL MARKETS DAY

Alpharadin Clinical development

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Objectives of Comprehensive Alpharadin Trial Program

PHASE 1

Establish safety of the new class – Alpha-pharmaceuticals

escalating dose study in patients with cancer

Establish distribution of alpha radiation within the body

dosimetry, to underpin safety data and define target organs

PHASE 2

Establish proof of concept – efficacy – in small phase 2 studies

usually with surrogate endpoints eg bone markers

Establish the dose range of activity and safety

to define the dose for definitive efficacy studies

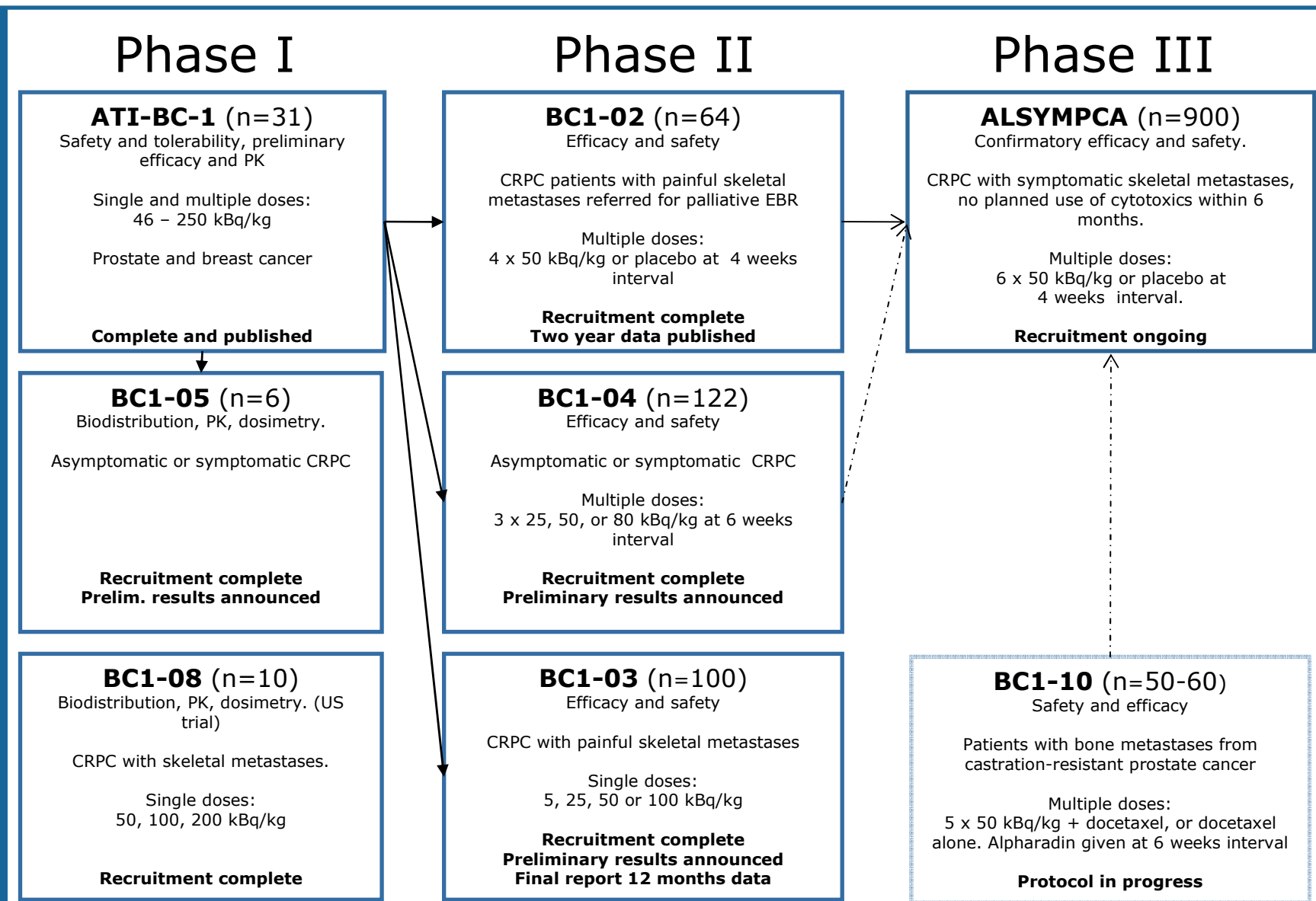
PHASE 3

Perform the pivotal efficacy study

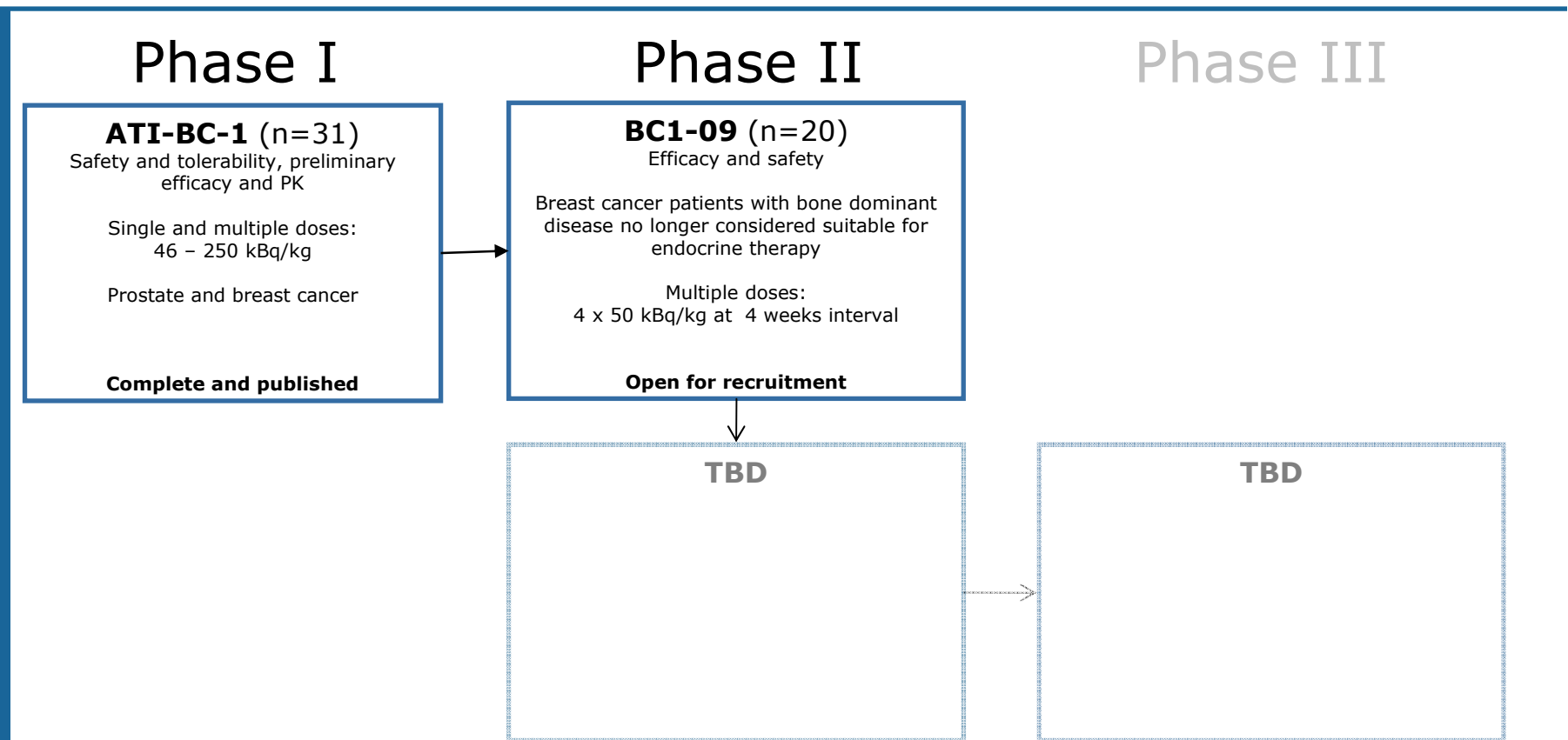
with hard clinical endpoints – survival

Extend into combinations and other indications

Clinical Development Program – Prostate



Clinical Development Program – Breast



Alpharadin Phase I–II - Principal Investigators

AT1-BC-1, -02, -03: Professor Sten Nilsson, Karolinska Institute, Stockholm

BC1-04, -05, -06: Dr Chris Parker, Royal Marsden Hospital, Surrey, UK

BC1-08, -10: Dr Michael Morris, Memorial Sloan-Kettering, NYC

BC1-09: Professor Robert Coleman, Sheffield, UK

Advisory Board members: well known opinion leaders in prostate and breast cancer including Ian Tannock, Howard Scher, Tia Higano, Martine Piccart and others

Phase I: Safety, Tolerability, Dosimetry

AT1-01

BC1-05

BC1-08

ATI-BC-01: Phase I – Prostate and Breast Cancer

Design

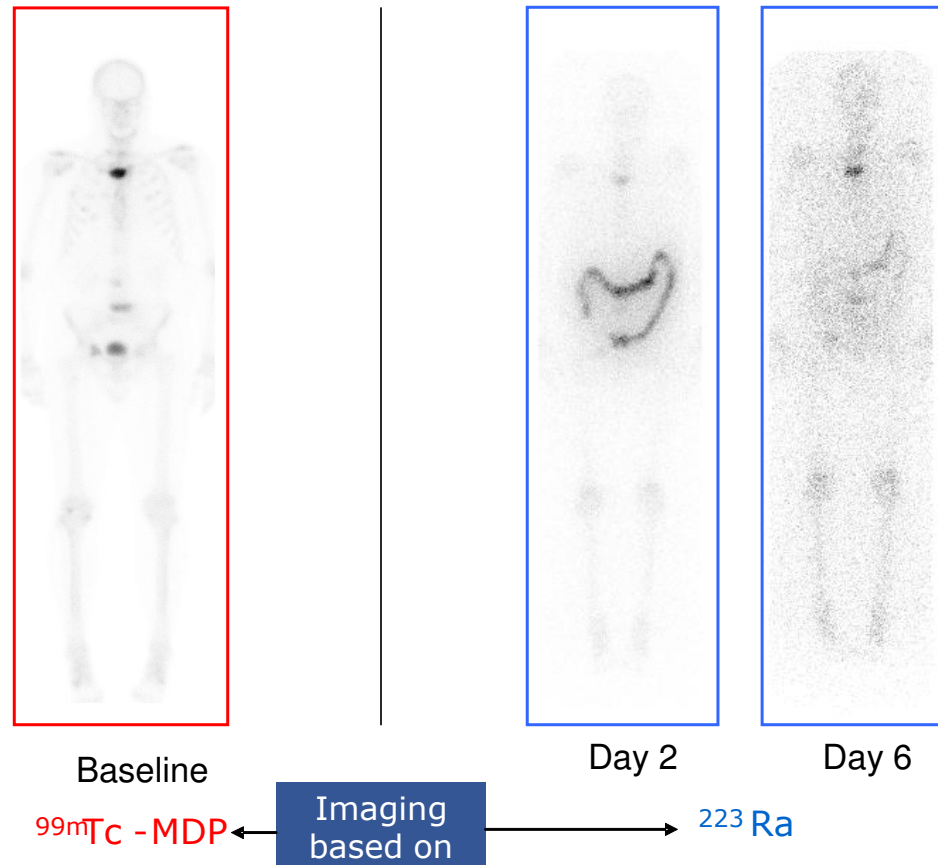
- Escalating dose study
- Prostate (n=15) and breast (n=10) cancer patients
- Dose range:
 - 46 - 250 kBq/kg, single dose
 - 50 kBq/kg, 5 times, 3 weeks apart
 - 125 KBq/kg, 2 times, 6 weeks apart

Results

- Well tolerated - no dose limiting toxicities
- Mild-to moderate reversible myelosuppression, lowest at 15 to 20 days
- Consistent reduction in total-ALP
- Pain relief in more than 50% of patients

Reported in: Nilsson S et al. First clinical experience with alpha-emitting radium-223 in the treatment of skeletal metastases. *Clin Cancer Res* 2005;11 (12) June 15, 2005

BC1-05: Advantageous Clearance Mechanism



- Clears blood rapidly, directly into gut (no apparent hepatobiliary excretion)
- Spares kidney – radiation dose low to all organs except bone

Phase II: Proof of Concept, Efficacy

BC1-02

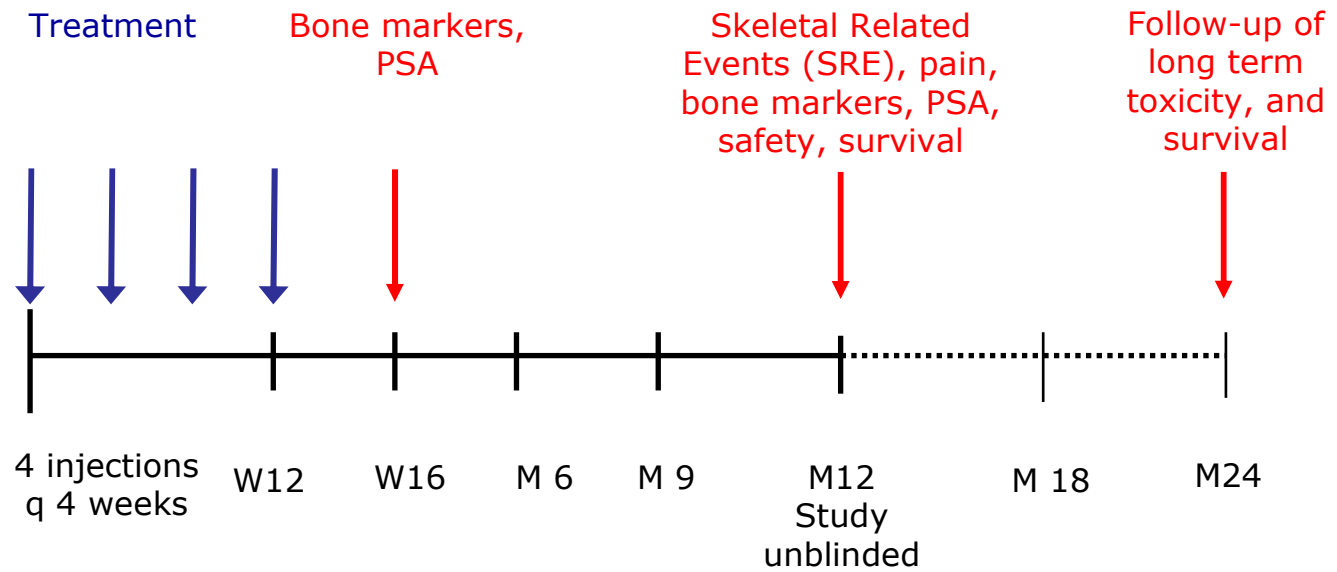
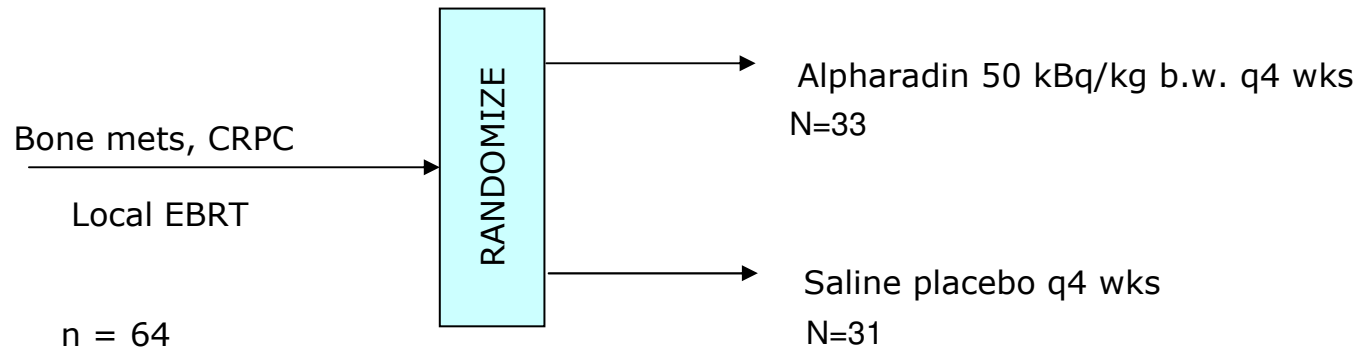
BC1-03

BC1-04

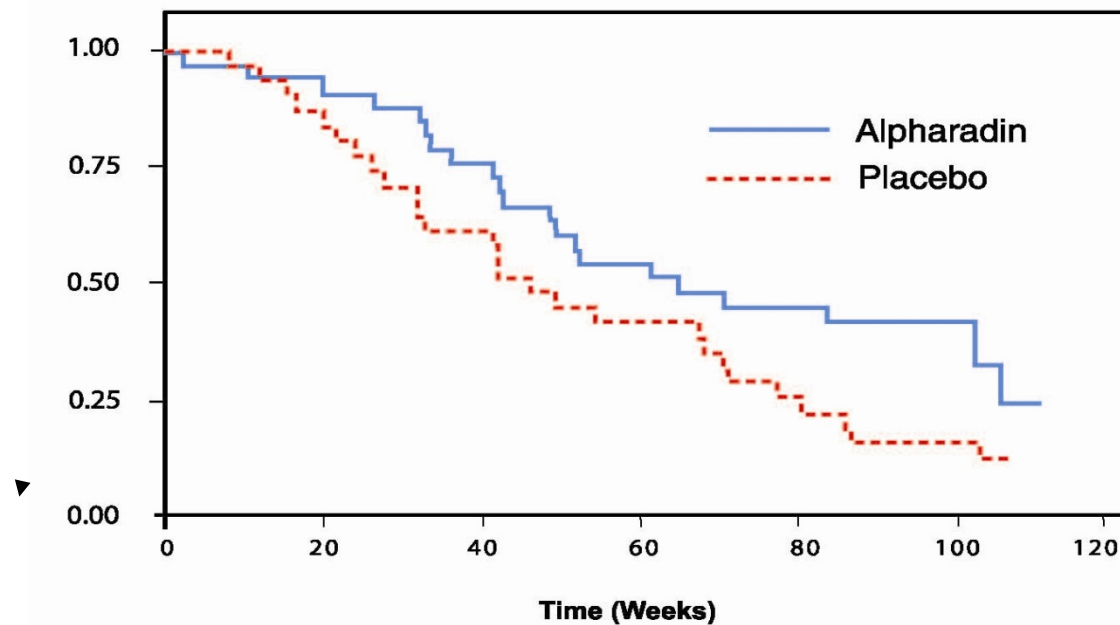
BC1-09

BC1-10

BC1-02 Phase II – Placebo Controlled Efficacy and Survival



BC1-02 Significant Increase in Survival



- Median survival 46.4 weeks in the placebo group and 65.3 weeks in the Alpharadin group; 4.5 months difference.
Hazard ratio 0.48, $p = 0.017$.
- 30% (10pts) of the patients were alive at 24 months in the Alpharadin group versus 13% (4 pts) in the placebo group

BC1-02 Significant Effects on All Relevant Biomarkers

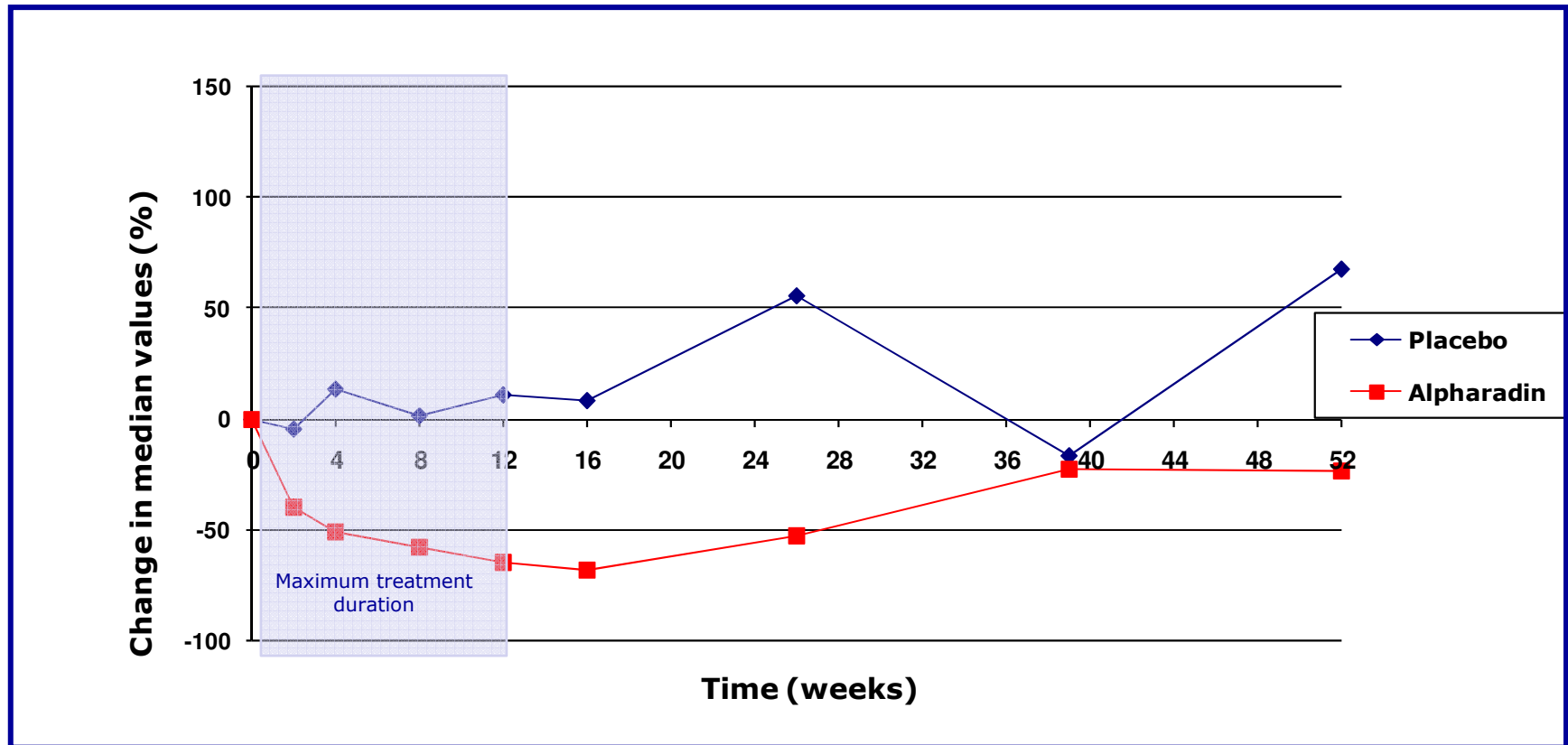
Relative change from baseline to 4 weeks after last injection

	Alpharadin ¹	Placebo ¹	P-value
Bone ALP (bone formation marker)	-66%	+9%	<0.0001
Total ALP (bone formation marker)	-46%	+31%	<0.0001
PINP (bone formation marker)	-63%	+38%	<0.0001
CTX-1 (bone resorption marker)	-31%	+32%	0.002
ICPT (bone resorption marker)	+15%	+43%	0.011
PSA (prostate tumor growth)	-24%	+45%	0.003

ALP = alkaline phosphatase
 PINP = amino-terminal procollagen propeptides of type I collagen
 CTXI = cross-linked C-terminal telopeptides of type I collagen
 ICTP = C-terminal telopeptides of type I collagen
 PSA = prostate specific antigen

¹ Data presented are median values, BC1-02 ITT population

BC1-02 Bone-ALP Relative Change (%) from Baseline



- Pronounced and rapid reduction of bone-ALP levels by Alfaradin even after one injection
- The reduction was sustained for at least 6 months
- Alfaradin treatment beyond 3 months may have prolonged effect

BC1-02 Minimal Haematological Toxicity

Worst grade for haematological toxic effects during treatment, 16 weeks, 4 injections of 50 kBq/kg with 4 weeks interval*

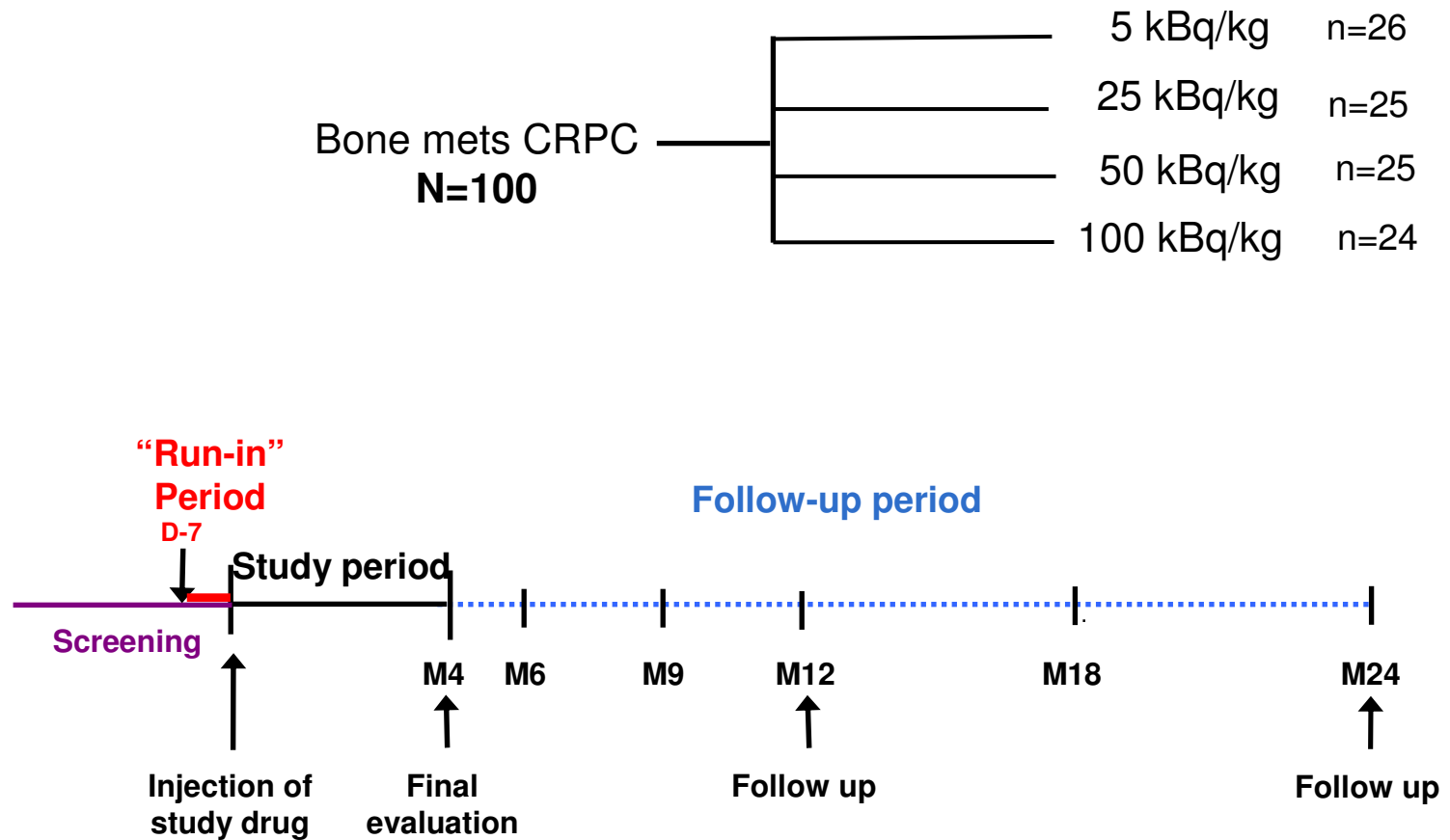
	Alpharadin (n=33)				Placebo (n=30)			
Grade	1	2	3	4	1	2	3	4
Platelets	6	0	0	0	4	0	1	0
Neutrophils	5	2	1	0	0	0	0	0
WBC	9	1	1	0	3	0	0	0
Haemoglobin	26	4	1	0	19	6	0	1

* Data are numbers of patients

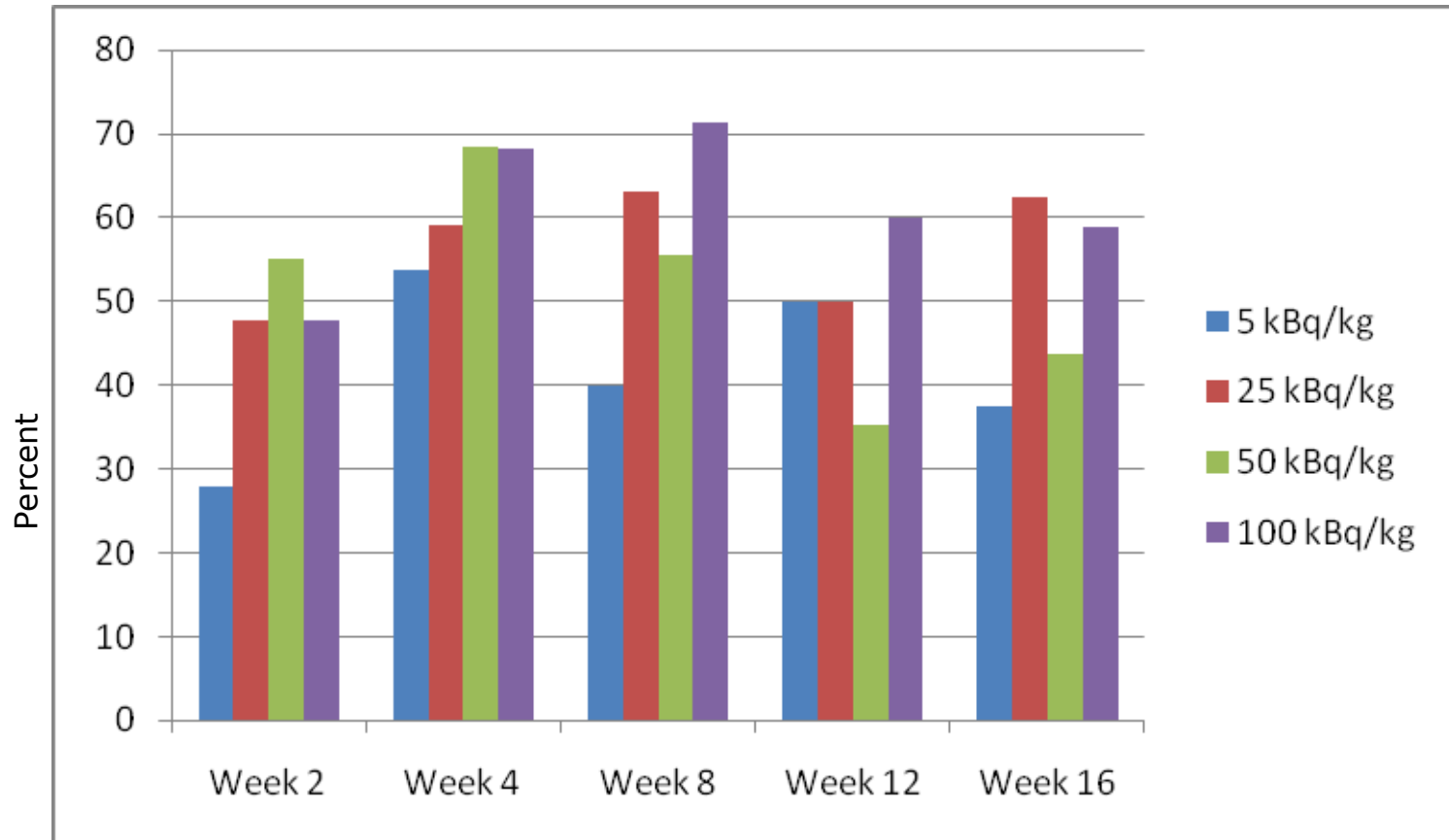
BC1-02 Adverse Events

	Alpharadin (n=33)	Placebo (n=31)
Number of adverse events	155	174
Number of SAEs	12	19
Number of patients with at least one SAE	8	14

BC1-03 Phase II - Dose Ranging Pain Study



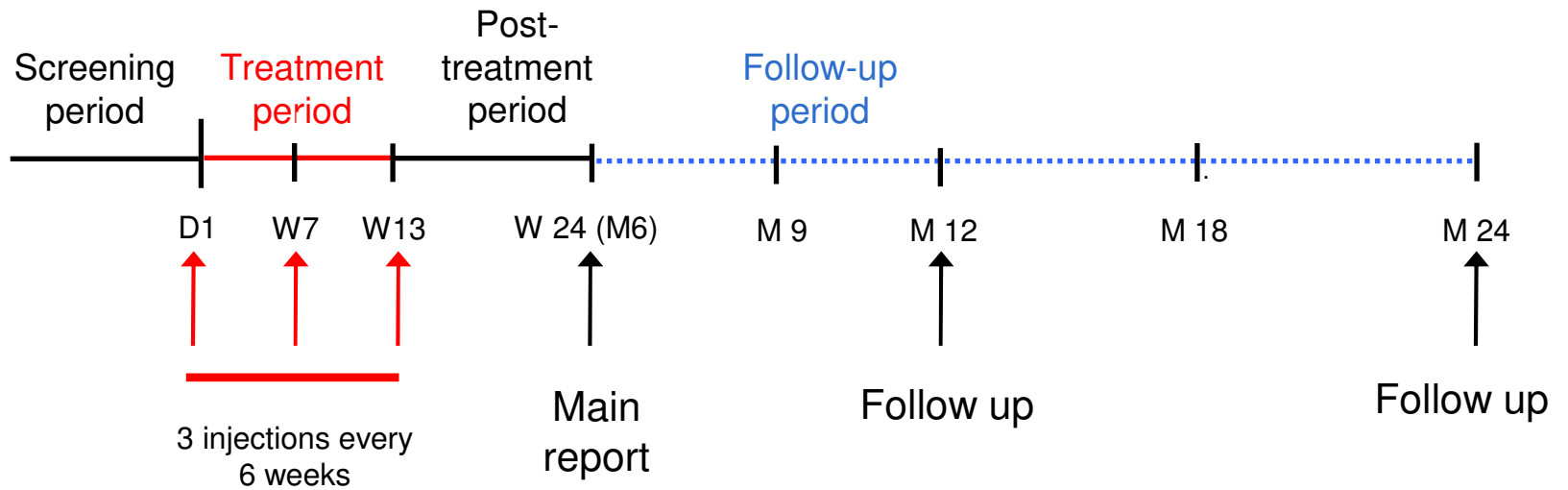
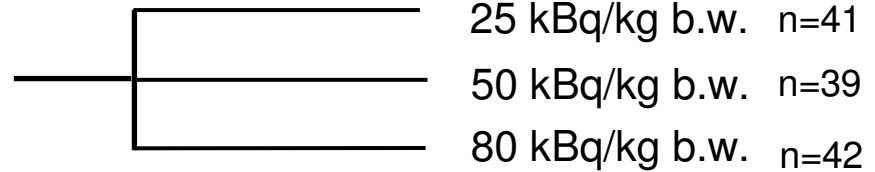
BC1-03 Percentage of Pain Responders



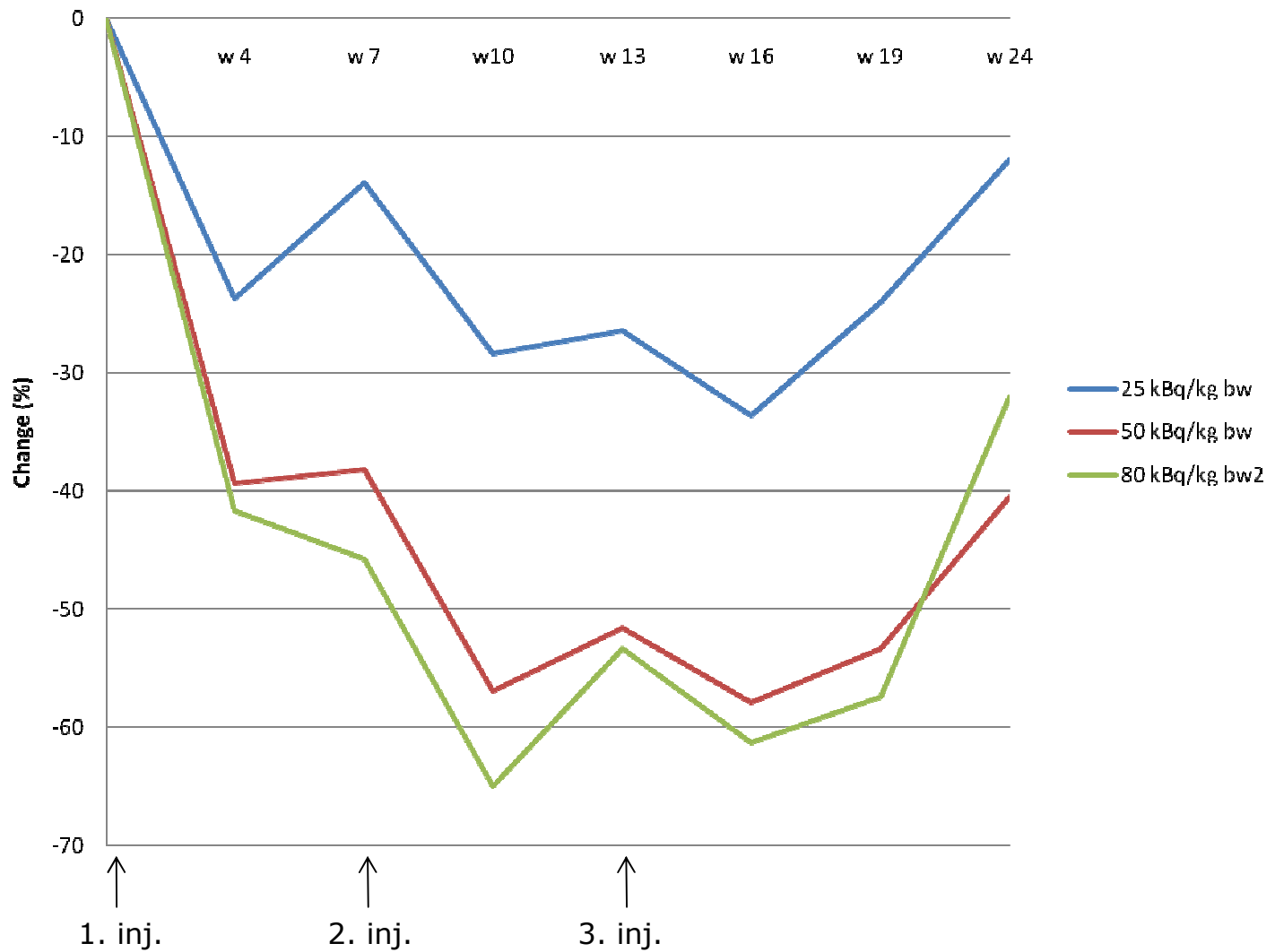
Sum of patients with minimal, moderate, marked and complete pain responders

BC1-04 Phase II – 6 Weekly Dose Ranging Efficacy

CRPC patients
Randomization
N=122



BC1-04 Median % Change in Bone ALP from Baseline



Conclusions Phase II Efficacy

- BC1-02 shows significant effect on survival
 - Hazard Ratio 0.48, $p = 0.017$
- All phase II studies showed profound, consistent and dose related effects on b-ALP and other bone markers
- Significant dose related effect on pain with single and multiple doses

Safety Profile Phase I-II Studies

Adverse events from 292 patients in Phase I and II (all patients receiving Alpharadin in any dose), compared with adverse events from patients in the placebo group in BC1-02 (31 pts)

<u>Preferred term</u>	<u>N (%) of patients</u>	
	Alpharadin (292 pts)	Placebo (31 pts)
Nausea	97 (33%)	10 (32%)
Bone Pain	89 (30%)	16 (52%)
Diarrhoea	77 (26%)	10 (32%)
Fatigue	76 (26%)	7 (23%)
Anaemia	71 (24%)	7 (23%)
Constipation	60 (21%)	2 (7%)
Vomiting	59 (20%)	6 (19%)

Presented at the ASCO Genitourinary Cancers Symposium (March 2010)
 Due to be presented at ASCO (June 2010)

Haematological Toxicity – Phase I-II Studies

In contrast to cytotoxics, low incidence of myelosuppression

	Alpharadin (n=292)* N (%)	
CTC Grade	3	4
Platelets	6 (2%)	3 (1%)
Neutrophils	5 (1.7%)	2 (0.7%)
WBC	8 (2.7%)	0
Haemoglobin	14 (4.8%)	3 (1%)

Highest grade for haematological effects, all patients receiving Alpharadin in any study at any dose

Safety Conclusions Alpharadin

Alpharadin has shown a highly tolerated safety profile

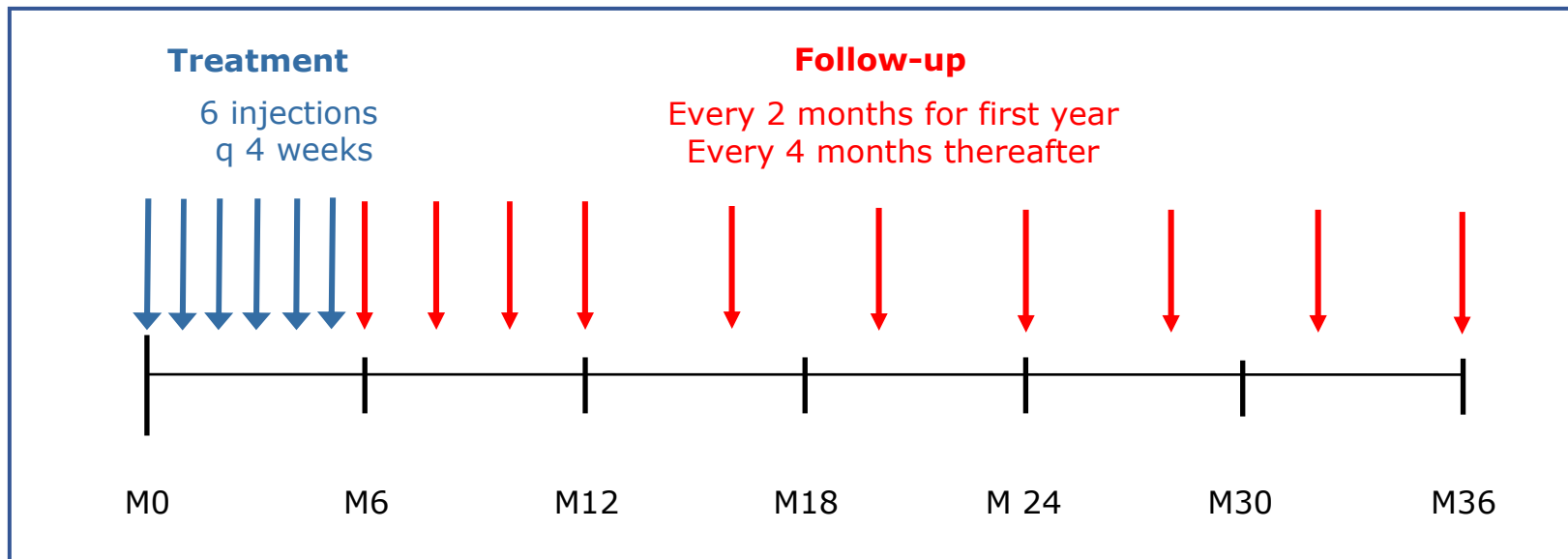
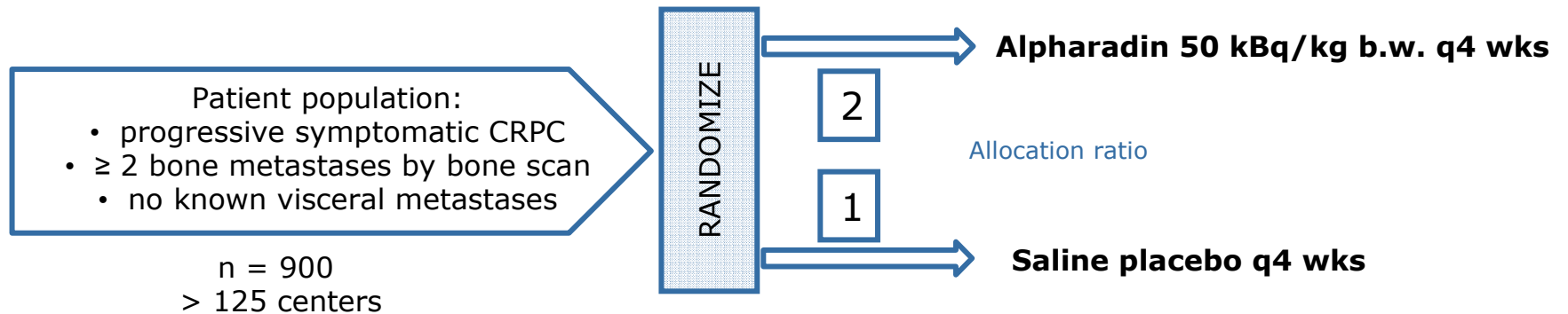
- Mild reversible myelosuppression
 - Mild reversible neutropenia
 - Mild anaemia
 - Minimal effect on platelets
- Mild to moderate gastrointestinal events
- No signs of kidney or liver toxicity
- Over 700 patients treated to date including Phase III

Phase III: Pivotal study

ALSYMPCA

ALpharadin in **SYM**ptomatic **P**rostate **CA**ncer

ALSYMPCA Phase III – Placebo Controlled Survival Study



ALSYMPCA Performance

- Enrolment has been brisk
 - Over 650 patients enrolled in over 125 centres
- Recruitment of 900 patients on track for year end
 - Sample size increased to improve power
 - Increases the probability of showing efficacy
 - Improves the dossier for submission, at no cost to timeline
- 640 events needed for trial completion
- Results anticipated 2012

Breast Cancer – New Indication, Proof of Concept

BC1-09 – bone metastases in breast cancer

Objective: Validation that Alphasaradin has broad potential in bone metastases of cancer

Patients: Bone dominant disease, endocrine refractory

Design: Single arm, open label

Endpoints: Bone markers and detailed imaging

Progress: Ongoing, first patient enrolled Q1 2010

Results: 2011

Combination with Taxotere: Safety, Efficacy in Bone Metastases

BC1-10 – bone metastases in prostate cancer

Objective: Show safety of combining Taxotere and Alpharadin; captures first line patients; pilot efficacy

Patients: Bone metastases, CRPC, being treated with Taxotere

Design: Rising dose tolerability, then randomised comparison of Alpharadin plus Taxotere vs Taxotere

Endpoints: Safety, bone markers, imaging

Progress: Ongoing, first patient enrolled 2010

Results: 2012

Summary

Comprehensive trial programme

3 phase I, 3 phase II, one large pivotal trial, and trials in new indications: total of 330 in phase II and 900 in phase III

Highly tolerable Safety Profile

Low incidence of haem tox and other tox

Dosimetry supports the highly tolerable safety profile – goes to bone and excreted in gut

Efficacy

Phase II shows improvement of survival and profound effects on bone markers

High unmet need in large markets

Current treatment for bone metastases is not targeted, or not effective