

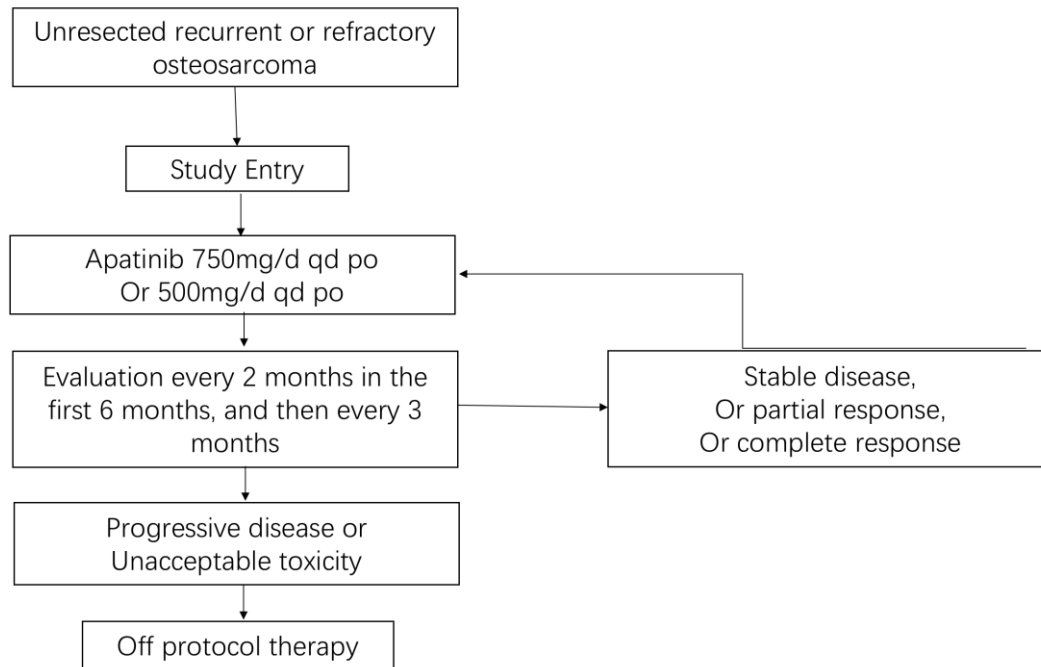
Protocol

**Apatinib for Advanced
Osteosarcoma after
Failure of Standard
Multimodal Therapy:
an open label phase 2
clinical trial**

1.0 Abstract

The prognosis of patients with recurrent or refractory osteosarcoma remains poor, with 5-year overall survival rates around 20%. Given the continued poor prognosis in this group of patients, novel treatment strategies are needed. There are no standard chemotherapeutic agents or targeted therapies proven to prolong survival in recurrent osteosarcoma. Apatinib, also known as YN968D1, is a tyrosine kinase inhibitor that selectively inhibits the vascular endothelial growth factor receptor-2 (VEGFR2, also known as KDR). It is an orally bioavailable, small molecule agent which is thought to inhibit angiogenesis in cancer cells; specifically, apatinib inhibits VEGF-mediated endothelial cell migration and proliferation thus blocking new blood vessel formation in tumor tissue. This agent also mildly inhibits c-Kit and c-SRC tyrosine kinases. Pre-clinical data suggest that apatinib may have anti-tumor activity in osteosarcoma. In this Phase 2 study, eligible patients between the ages of more than 16 years with unresected, recurrent or refractory osteosarcoma will receive apatinib tablets administered daily. Progression free survival and response to therapy will be assessed. In addition, the tolerability and quality of life will be evaluated.

2.0 Experimental Design Schema



3.0 Goals and Objectives (Scientific Aims)

3.1 Primary Aims

1.1.1 To estimate the objective response rate (ORR) at 3 month and progression free survival rate (PFS) at 4 month in patients with recurrent osteosarcoma who are administered apatinib therapy daily.

3.2 Secondary Aims

3.2.1 To estimate the overall survival rate (OS), clinical benefit rate (CBR) at 6 month, duration of response(DOR) in patients with recurrent osteosarcoma who are administered apatinib therapy daily.

3.2.2 To assess the feasibility and toxicity profile of apatinib in patients with recurrent or refractory osteosarcoma, pain improvement and life quality score.

4.0 Background

4.1 Introduction/Rationale for Development

The outcome of patients with newly diagnosed, localized osteosarcoma improved following the addition of multi-agent chemotherapy to complete surgical resection [1,2]. Current results in contemporary cooperative group studies reveal 5-year event-free survival (EFS) ranging between 50-75%. [1,2] Cisplatin and doxorubicin are the most active agents, and standard chemotherapy includes the use of these two agents alone or in combination with high-dose methotrexate and/or ifosfamide [2,3,6]. The prognosis is poor for the 30-40% of patients who develop recurrent disease [3]. as well as for those with clinically detectable metastases at the time of initial diagnosis with 2-year survival rates of 20-30% [6,10].

The aggregate EFS for patients with recurrent osteosarcoma enrolled on seven closed Phase 2 studies from the Children's Oncology Group (COG) or its predecessor groups is poor, with an overall 12% EFS at 4 months [5,7,8,9,10]. Due to the lack of progress seen in treatment of osteosarcoma over the past 25 years and overall poor prognosis for children, adolescents and young adults with recurrent or refractory osteosarcoma, novel treatment strategies are needed.

The study of oncogenesis and pathobiological behavior of osteosarcoma told us that new blood vessel formation (angiogenesis) is fundamental to tumor growth, invasion, and metastatic dissemination [23]. Several groups have evaluated tumor microvessel density and outcome in osteosarcoma. Expression of VEGF has been suggested as a means of evaluating the prognostic importance of angiogenesis in osteosarcoma [17,18,19]. Monotherapy with second-generation broad-spectrum VEGF receptor tyrosine kinase inhibitors (TKIs) in sarcoma has now become an area of active research and application beyond gastrointestinal stromal tumors (GISTs) [4,14]. Within all of those preclinical experiments and clinical trials [16,18,20], the

milestone of the treatment on advanced osteosarcoma should count on the application of anti-angiogenesis TKIs sorafenib on refractory cases from the Italian Sarcoma Group [20,22], which officially raised the 6-month progression-free survival (PFS) from <30-46% for the first time. However, things had seemed not to change as dramatically as was expected since then.

Apatinib, also known as YN968D1, is a tyrosine kinase inhibitor that selectively inhibits the vascular endothelial growth factor receptor-2 (VEGFR2, also known as KDR)(Fig. 4.1.1). It is an orally bioavailable, small molecule agent which is thought to inhibit angiogenesis in cancer cells; specifically apatinib inhibits VEGF-mediated endothelial cell migration and proliferation thus blocking new blood vessel formation in tumor tissue. This agent also mildly inhibits c-Kit and c-SRC tyrosine kinases.

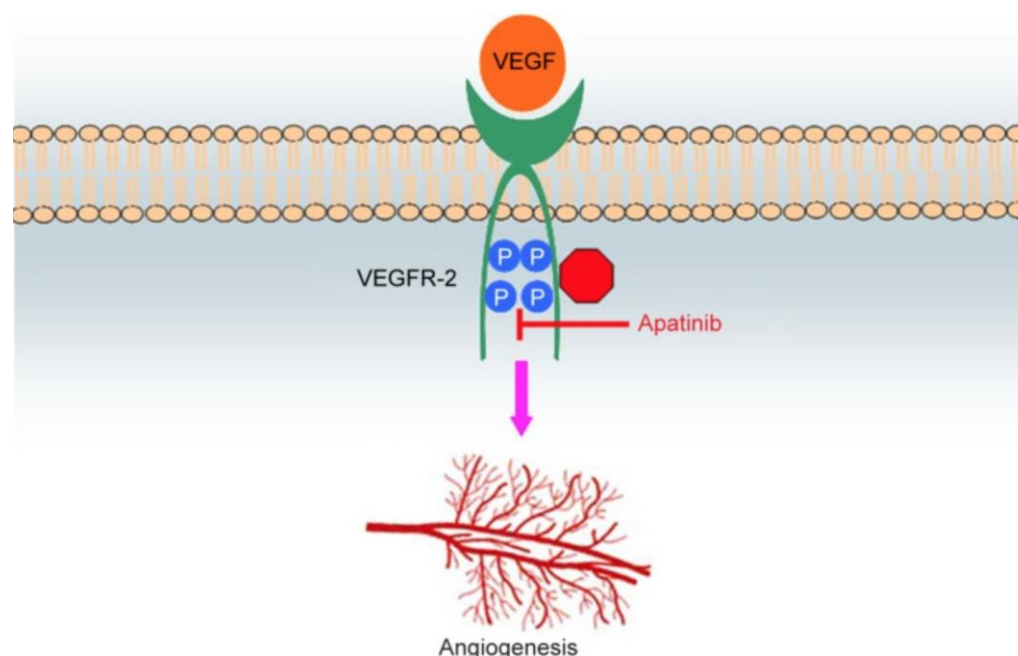


Fig.4.1.1 Schematic illustration of the possible mechanism of apatinib as the inhibitor of VEGFR-2.

Apatinib was approved and launched in People's Republic of China in 2014 as a subsequent-line treatment for patients with advanced gastric cancer (AGC). In addition, it is also currently undergoing Phase II/III clinical trials in People's Republic of China for the treatment of many cancer types, such as non-small-cell lung cancer (NSCLC) [24], breast cancer, and hepatocellular carcinoma. These clinical trials demonstrate that apatinib has potential antitumor activity across a broad range of advanced solid tumors. Compared with other TKIs focused on anti-angiogenesis, Apatinib is more effective on VEGFR2 (Table.4.1.1).

Table 4.1.1 Comparison of IC₅₀ in different TKIs

target	IC ₅₀ (nM)			
	Apatinib	Sorafenib	Sunitinib	Pazopanib
VEGFR-1	70	-	2	10
VEGFR-2	2	90	10	30
VEGFR-3	-	-	17	47
PDGFR-b	537	-	8	84
c-kit	420	68	-	74
FGFR-1	>10000	580	-	-
FLT-3	-	58	-	-

4.2 Preclinical Studies

Several basic studies have been dedicated to the antitumor activity of apatinib in vitro and in vivo. In vitro, apatinib potently suppressed the kinase activities of VEGFR-2, c-Kit, and c-Src, and inhibited cellular phosphorylation of VEGFR-2, c-Kit, and PDGFRb. Apatinib could also effectively inhibit proliferation, migration, and tube formation of human umbilical vein endothelial cells induced by fetal bovine serum, and block the budding of rat aortic ring. What's more, apatinib has also been demonstrated effective in several kinds of human cancers in vivo (Table 4.2.1).

Encouraged by the remarkable inhibitory activity against VEGFR-2 tyrosine kinase in vitro, they further performed the investigation of the potential antitumor effect of apatinib in vivo. The results demonstrated that apatinib showed antitumor efficacy in vivo when administrated alone or in combination with chemotherapy against a variety of established tumor xenografts with good tolerance [24]. To date, the outcome of cancer chemotherapy still encounters two major challenges: nonspecific targets and multidrug resistance (MDR). In fact, more than 90% of patients with malignant tumors die of MDR. Apatinib could also reverse cancer MDR mediated by MDR protein 1 (ABCB1), MDR-associated protein 1 (MDR1), and breast cancer resistant protein (BCRP) through inhibiting their transport function as well [24]. Thus, apatinib may be useful in overcoming MDR to other conventional antineoplastic drugs.

Table 4.2.1 Apatinib is effective in several kinds human cancers in mice.

pharmacodynamic model	Dose(mg/kg)	inhibitory effect(%)
Gastric cancer SCG-7901	50-200	39.3-80.7
Colon cancer Ls174t	50-200	20.3-83.7
Colon cancer HCT-116	50-200	41-81.2
Colon cancer HT-29	50-200	37.2-74.5
NSCLC A549	50-200	29.2-72.8
NSCLC NCI-H460	100, 200	43.1-78.8
Hepatic cancer H22	50-200	43.3-84.7
Sarcoma S180	50-200	60.3-69.9

4.3 Apatinib in Published Clinical Trials

Apatinib has been administered to a total of 338 patients with gastric cancer, non-small cell lung cancer or breast cancer in 3 clinical trials.

In a randomized, placebo-controlled, parallel-arm Phase III trial (NCT00970138), Li et al evaluated apatinib as a subsequent-line therapy for patients with histologically confirmed gastric cancer. In the trial, 144 enrolled patients were divided into three groups: placebo (group A), 850 mg of apatinib qd (group B), and apatinib 425 mg bid (group C). Progression-free survival (PFS) was the primary end point. Secondary end points included DCR, objective response rate, overall survival, and quality of life. The outcomes demonstrated that the median progression-free survival for groups A, B, and C was 1.40 months, 3.67 months, and 3.20 months, respectively. OS for groups A, B, and C was 2.50 months, 4.83 months, and 4.27 months, respectively. There were statistically significant differences between the apatinib groups and the placebo group in PFS and overall survival ($P < 0.001$). But, there was no significant difference between apatinib 425 mg bid vs 850 mg qd (hazard ratio [HR]:1.22, $P < 0.551$). These results illustrated that apatinib showed improved PFS and overall survival in heavily pretreated patients who had experienced treatment failure with two or more chemotherapy regimens.

A prospective, open-label, Phase II trial by Hu et al aimed to evaluate the efficacy and safety of apatinib in heavily pretreated patients with metastatic non-triple-negative breast cancer (TNBC) (NCT01176669). In the trial, after the

optimum dose level of 500 mg/day was recommended by Phase IIa, a Phase IIb study of 59 patients with metastatic TNBC was activated, with the endpoint PFS. The outcomes were reported that mPFS and mOS were 3.3 months and 10.6 months, respectively. In the 56 evaluable patients, overall response and clinical benefit rates were 10.7% and 25.0%, respectively. As for adverse events, the most common grade 3/4 hematologic toxicities were thrombocytopenia (13.6%), leukopenia (6.8%), neutropenia (3.4%), and anemia (1.7%). The most frequent grade 3/4 nonhematologic toxicities were hand–foot syndrome, proteinuria, hypertension, and increased alanine aminotransferase.

A multicenter, randomized, placebo-controlled, Phase II trial by Zhang et al was to determine whether apatinib could improve PFS compared with placebo in patients with advanced nonsquamous NSCLC who failed two lines of treatment (NCT01270386). In the study, 135 patients were randomized in a 2:1 fashion to apatinib 750 mg qd vs placebo until disease progression or unacceptable toxicity. As expected, mPFS was 4.7 months for apatinib group vs that of 1.9 months for placebo group with an HR of 0.278 ($P<0.0001$). The response rate and DCR were also significantly better in apatinib arm (12.2% and 68.9%) than in placebo arm (0% and 24.4%) ($P=0.0158$ and $P<0.0001$). Although hypertension, proteinuria, and hand–foot syndrome were the most frequent adverse events, they were generally mild or moderate in severity and were manageable.

4.4 Dose Rationale

Apatinib will be administered orally at a dose of 750mg/d for patients with body surface area (BSA) of more than 1.5m², and 500mg/d for patients with BSA of less than 1.5m². Pharmacokinetic analysis showed that the time to maximum plasma concentration level was ~4 hours after dose and the mean half-life was 9 hours. In three separate dosing groups, 500 mg (n=8), 750 mg (n=12), and 800 mg (n=8), of 28 patients enrolled into a single dose arm, the C_{max} and AUC₂₄ values were dose-dependent and demonstrated variability among patients with C_{max} of 1,521, 2,379, and 2,833 ng/mL and AUC₂₄ of 11,295, 18,172, and 21,975 ng·h/mL, respectively. Steady-state conditions analysis of eleven patients enrolled in the

multidose cohort suggested no accumulation during 56 days once a day administration of 750 mg apatinib.

5.0 Study Enrollment Procedures and Patient Eligibility

5.1 Study Enrollment Criteria

Patients must be enrolled before treatment begins. The date protocol therapy is projected to start must be no later than 7 business days after the date of study enrollment.

The eligibility criteria listed below are interpreted literally and cannot be waived. All clinical and laboratory data required for determining eligibility of a patient enrolled on this trial must be available in the patient's medical/research record which will serve as the source document for verification at the time of audit.

All clinical and laboratory studies to determine eligibility must be performed within 14 days prior to enrollment unless otherwise indicated. Laboratory values used to assess eligibility must be no older than 14 days at the start of therapy. Laboratory tests need not be repeated if therapy starts within 14 days of obtaining labs to assess eligibility. If a post-enrollment lab value is outside the limits of eligibility, or laboratory values are > 14 days old, then the following laboratory evaluations must be re-checked within 48 hours prior to initiating therapy: complete blood count (CBC) with differential, bilirubin, ALT and serum creatinine. If the recheck is outside the limits of eligibility, the patient may not receive protocol therapy and will be considered off protocol therapy. Imaging studies, if applicable, must be obtained within 2 weeks prior to start of protocol therapy (repeat the tumor imaging if necessary).

5.2 Patient Eligibility Criteria

5.2.1 Age

Patients must be equal to or greater than 16 years of age at the time of enrollment.

5.2.2 Diagnosis

5.2.2.1 Patients must have had histologic verification of high grade osteosarcoma at original diagnosis or relapse.

5.2.2.2 Patients must have measurable disease according to RECIST 1.1 (see Appendix 1), and have relapsed or become refractory to conventional therapy, unresectable.

5.2.3 Performance Level

Patients must have a performance status corresponding to ECOG scores (Appendix 2) of 0, 1 or 2, with a life expectancy >3 months.

5.2.4 Prior Therapy

Patients must have fully recovered from the acute toxic effects of all prior chemotherapy, immunotherapy, or radiotherapy prior to entering this study.

5.2.4.1 Myelosuppressive chemotherapy: Must not have received within 2 weeks of entry onto this study (4 weeks if prior nitrosourea).

5.2.4.2 Biologic (anti-neoplastic agent): At least 7 days since the completion of therapy with a biologic agent.

5.2.4.3 Radiation therapy (RT): ≥ 2 weeks for local palliative RT (small port); ≥ 6 months must have elapsed if prior craniospinal RT or if $\geq 50\%$ radiation of pelvis; ≥ 6 weeks must have elapsed if other substantial BM radiation.

5.2.4.4 Monoclonal antibodies: Must not have received any monoclonal based therapies within 4 weeks, and all other immunotherapy (tumor vaccine, cytokine, or growth factor given to control the cancer) within 2 weeks, prior to study enrollment.

5.2.4.5 surgery completion at least 4 weeks before enrollment.

5.2.4.6 Prior treatment (completed >2 weeks before trial entry) should include but not limited to standard high-grade osteosarcoma chemotherapy agents including doxorubicin, cisplatin, high-dose methotrexate, and ifosfamide.

5.2.5 Organ Function Requirements

5.2.5.1 Adequate Bone Marrow Function Defined As:

- Peripheral absolute neutrophil count (ANC) \geq 1500/ μ L
- Platelet count \geq 80,000/ μ L (transfusion independent)
- Hemoglobin \geq 8.0 g/dL (may receive RBC transfusions)

5.2.5.2 Adequate Renal Function Defined As:

- Creatinine clearance or radioisotope GFR \geq 70 mL/min/1.73 m² or
- A serum creatinine based on age/gender as follows (Table 5.2.6.2.1):

Table 5.2.6.2.1 Serum creatinine requirements

Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female
1 to < 2 years	0.6	0.6
2 to < 6 years	0.8	0.8
6 to < 10 years	1	1
10 to < 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
\geq 16 years	1.7	1.4

5.2.5.3 Adequate Liver Function Defined As:

- Total bilirubin \leq 2 x upper limit of normal (ULN) for age, and
- Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) < 135 U/L. For the purposes of this study the ULN is defined as 45 U/L.

5.2.5.4 Adequate Cardiac Function Defined As:

- Shortening fraction of \geq 27% by echocardiogram, or
- Ejection fraction of \geq 50% by radionuclide angiogram.

5.2.6 Exclusion Criteria:

- 5.2.6.1 Previously exposed to other TKIs;
- 5.2.6.2 Central nervous system metastasis;
- 5.2.6.3 Have had other kinds of malignant tumors at the same time;
- 5.2.6.4 Cardiac insufficiency or arrhythmia;
- 5.2.6.5 Uncontrolled complications, such as hypertension, diabetes mellitus and so on;
- 5.2.6.6 Coagulation disorders;
- 5.2.6.7 Urine protein \geq ++;
- 5.2.6.8 Pleural or peritoneal effusion that needs to be handled by surgical treatment;
- 5.2.6.9 Combined with other infections or wounds.
- 5.2.6.10 A history of allergic reactions attributed to compounds of similar composition to apatinib.
- 5.2.6.11 Pregnancy and Breast Feeding
 - 5.2.6.11.1 Female patients who are pregnant are ineligible since there is yet no available information regarding human fetal or teratogenic toxicities.
 - 5.2.6.11.2 Lactating females are not eligible unless they have agreed not to breastfeed their infants.
 - 5.2.6.11.3 Female patients of childbearing potential are not eligible unless a negative pregnancy test result has been obtained.
 - 5.2.6.11.4 Sexually active patients of reproductive potential are not eligible unless they have agreed to use an effective contraceptive method for the duration of their study participation.

6.0 Treatment Program

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or

on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable (except where explicitly prohibited within the protocol).

6.1 Overview of Treatment Plan

This is a single arm Phase 2 study to evaluate the use of apatinib, a small molecule TKI against VEGFR2. All subjects will receive apatinib 750 mg (BSA>1.5m²) or 500mg (BSA<1.5m²) orally once daily, given on the same time at half an hour after meal.

Treatment will be discontinued if there is evidence of progressive disease or drug related toxicity that requires removal from therapy, as defined in Section 7.0. Therapy may otherwise continue. Radiographic imaging assessments of disease status obtained every 2 months in the first 6 months, and then every 3 months, will be compared to imaging done just prior to initiating therapy.

Other therapy: Although not encouraged, subjects who achieve a partial response after 2 months that is confirmed after 6 months will be allowed to undergo resection of sites of disease or radiation and remain on protocol therapy. Apatinib therapy will be held 1 week before surgery and resumed when recovered from surgery but at least 2 weeks after surgery considering the time of wound healing. Apatinib therapy will be continued during radiation. If the patient has not recovered from surgery within 1.5 months the patient will go off protocol therapy. Surgery or radiation performed on any site of measurable disease before the end of the 6 months will render the patient inevaluable for disease control assessment and they will be removed from protocol therapy.

6.2 Concomitant Therapy

6.2.1 CYP3A4 inducers and inhibitors

The use of the following medications (Appendix 3) should be discontinued prior to initiation of protocol therapy and should be avoided during protocol therapy if reasonable alternatives exist. This is not an inclusive list; please refer to other resources such as <http://medicine.iupui.edu/clinpharm/ddis/table.aspx> or other frequently updated medical reference for additional information.

6.2.2 Allowed Therapy

6.2.2.1 No other antineoplastic agents may be given while the patient is receiving protocol therapy.

6.2.2.2 Permitted therapy during this study: Allow the use of diuretics (hydrochlorothiazide or furosemide), ACEI (captopril or enalapril) or ARB (Losartan or valsartan) and other drugs alone or in combination for the treatment of hypertension. Allow the use of calamine, antibiotic cream (e.g. mupirocin ointment), hormone cream (e.g. Hydrocortisone Butyrate or Pevisone Cream) and other drug for external use of skin rash, desquamation. Allow the use of Granulocyte colony stimulating factor (granulocyte colony, stimulating factor, G-CSF), erythropoietin (EPO), thrombopoietin (TPO) and interleukin -11 (IL-11) to treat leukopenia, anemia or thrombocytopenia for salvage therapy while prophylaxis is forbidden.

All drugs used concurrently with apatinib must be recorded in the CRF section, including blood transfusion, stem cell growth factors, antibiotics, analgesics and antidiarrheal drugs.

6.2.3 Criteria to Continue Apatinib Therapy

Patients are evaluated every 2 months in the first 6 months and then every 3 months for the ability to continue apatinib therapy. They must recover from toxicities

at least possibly related to apatinib therapy to \leq Grade 1 severity or baseline prior to beginning next cycle, including:

- ANC \geq 1500/ μ L
- Platelets \geq 80,000/ μ L (transfusion independent)
- Hemoglobin \geq 8.0 g/dL (may receive RBC transfusions)
- Creatinine clearance or radioisotope GFR \geq 70 mL/min/1.73 m² or a serum

creatinine based on age/gender as follows

Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female
1 to < 2 years	0.6	0.6
2 to < 6 years	0.8	0.8
6 to < 10 years	1	1
10 to < 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
\geq 16 years	1.7	1.4

- Total bilirubin \leq 2 x upper limit of normal (ULN) for age, and
- AST or ALT < 135 U/L for the purposes of this study the ULN is defined as 45 U/L.

7.0 Dose Modifications for Toxicities

7.1 Definition of Toxicities

NOTE: Any suspected or confirmed dose-limiting toxicity should be reported to the Study Chair within 24 hours of site knowledge of its occurrence. Dose modifications are carried out according to table 7.1.1.

Table 7.1.1 Dose modification criteria

Level of Dose	Group A (BSA>1.5m ²)	Group B (BSA<1.5m ²)
Initial Level	750mg	500mg
Level-1	500mg	250mg
Level-2	250mg*	0*

*The dose for each patient can be reduced no more than 2 times. If more dose reduction is needed, the patient should be dropped off from the study. Apatinib therapy will continue until disease progression is confirmed, or unacceptable toxicity occurs.

7.1.1 Definition of Dose-Limiting Toxicity (DLT)

DLT will be defined as any of the following events that are possibly, probably or definitely attributable to protocol therapy. Dose limiting hematological and non-hematological toxicities are defined differently.

7.1.1.1 Hematological Dose Limiting Toxicity

- Grade 4 neutropenia for > 7 days
- Grade 4 febrile neutropenia
- Platelet count < 25,000/ μ L
- Myelosuppression that causes a delay of > 14 days

7.1.1.2 Non-Hematological Dose-Limiting Toxicity

Any Grade 3 or greater non-hematological toxicity, except for the following:

- Grade 3 nausea and/or vomiting of < 3 days duration
- Grade 3 or 4 fever < 5 days duration
- Grade 3 infection < 5 days duration
- Grade 3 rash < 5 days duration
- Grade 3 pruritis < 5 days duration
- Grade 3 fatigue < 5 days duration
- Grade 3 non-hematologic laboratory abnormalities that resolve within 14 days to Grade 1, or to initial eligibility criteria, or to baseline (if the patient entered the study with existing toxicity).
- Grade 3 hypophosphatemia, hypokalemia, hypocalcemia, or hypomagnesemia responsive to oral supplementation.

Any Grade 2 non-hematological toxicity that persists for ≥ 7 days and is considered sufficiently medically significant or sufficiently intolerable by patients that it requires treatment interruption will also be considered a DLT.

7.2 Dose Modifications for Adverse Events

The Study Chair must be notified of any use of myeloid growth factor for hematologic toxicity and of any other dosage modification described below.

7.2.1 Dose Modifications for Hematological Toxicity

Factor	Hematologic Toxicity	Action
ANC ^a	<500/uL or <1000/uL with infection or fever for more than 5 days	Reduce to a lower level ^c
PLT ^b	< 75,000/ μ L	Reduce to a lower level ^c

^a G-CSF may be used before dose modification.

^b IL-11 or TPO may be used before dose modification.

^c Reduce to a lower level until removed from protocol therapy if dose-limiting toxicity recurs.

7.2.2 Dose Modifications for Non-hematological Toxicity

Toxity	Grade	Dose modification
Nausea and/or vomiting ^a	≥ 3	Reduce to a lower level
Elevations of serum AST and/or ALT	≥ 3	Reduce to a lower level if benefit from apatinib; otherwise removed from protocol therapy
Hypertension	$\leq 140/90$ mmHg	≥ 3 Continue at former dose
	$>140/90$ mmHg ^c	≥ 3 Reduce to a lower level if benefit from apatinib; otherwise removed from protocol therapy
Total bilirubin >ULN at any time	≥ 1	Reduce to a lower level
Others	≥ 3	Reduce to a lower level

a use antiemetic drugs, including serotonin/dexamethasone/lorazepam before reduction.

b after the use of medications to protect the liver.

c with the use of hypotensor.

8.0 Drug Information

8.1 Source and Pharmacology

Apatinib, also known as YN968D1, is a tyrosine kinase inhibitor that selectively inhibits VEGFR2. It is an orally bioavailable, small molecule agent which is thought to inhibit angiogenesis in cancer cells; specifically apatinib inhibits VEGF-mediated endothelial cell migration and proliferation thus blocking new blood vessel formation in tumor tissue. Apatinib was first synthesized by Advenchen Laboratories in California, USA and is being developed by Jiangsu Hengrui Medicine (China). Apatinib was approved by CFDA in December, 2014 for patients with late-stage gastric carcinoma in China. A phase IV study on safety of Apatinib started in April, 2015. The study aims to recruit 2,000 patients

8.2 Pharmacokinetics

Pharmacokinetic analysis showed that the time to maximum plasma concentration level was ~4 hours after dose and the mean half-life was 9 hours. In three separate dosing groups, 500 mg (n=8), 750 mg (n=12), and 800 mg (n=8), of 28 patients enrolled into a single dose arm, the C_{max} and AUC₂₄ values were dose-dependent and demonstrated variability among patients with C_{max} of 1,521, 2,379, and 2,833 ng/mL and AUC₂₄ of 11,295, 18,172, and 21,975 ng·h/mL, respectively. Steady-state conditions analysis of eleven patients enrolled in the multidose cohort suggested no accumulation during 56 days once a day administration of 750 mg apatinib. The primary routes of apatinib biotransformation include E- and Z-cyclopentyl-3-hydroxylation, N-dealkylation, pyridyl-25-N-oxidation, 16-hydroxylation, dioxygenation, and O-glucuronidation after 3-hydroxylation. Nine major metabolites were confirmed, of which E-3-hydroxy-apatinib-O-glucuronide (M9-2) was the major circulating metabolite. The total recovery of the administered dose was 76.8% within 96 hours postdose, with 69.8% and 7.02% of the administered dose excreted in feces and urine, respectively.

8.3 Adverse Effect

The incidence of all treatment-related AE in Phase III clinical trial in gastric cancer was listed in table 8.3.1.

Table 8.3.1 Incidence of Treatment-related Adverse Events

Adverse Event	No. (%)			
	Apatinib (n = 176)		Placebo (n = 91)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Hematologic				
Leukopenia	71 (40.3)	3 (1.7)	8 (8.8)	0 (0)
Neutropenia	66 (37.5)	10 (5.7)	9 (9.9)	1 (1.1)
Anemia	44 (25.0)	11 (6.3)	22 (24.2)	4 (4.4)
Thrombocytopenia	44 (25.0)	5 (2.8)	6 (6.6)	1 (1.1)
Nonhematologic				
Proteinuria	84 (47.7)	4 (2.3)	15 (16.5)	0 (0)
Hypertension	62 (35.2)	8 (4.5)	5 (5.5)	0 (0)
Hand-foot syndrome	49 (27.8)	15 (8.5)	2 (2.2)	0 (0)
Elevated transaminase	49 (27.8)	14 (8.0)	20 (22.0)	4 (4.4)
Hyperbilirubinemia	43 (24.4)	13 (7.4)	13 (14.3)	6 (6.6)
Bleeding	35 (19.9)	6 (3.4)	22 (24.2)	7 (7.7)
Fatigue	36 (20.5)	5 (2.8)	13 (14.3)	2 (2.2)
ALP increased	35 (19.9)	5 (2.8)	14 (15.4)	0 (0)
Elevated GGT	29 (16.5)	11 (6.3)	15 (16.5)	6 (6.6)
Abdominal pain	28 (15.9)	3 (1.7)	16 (17.6)	4 (4.4)
Decreased appetite	26 (14.8)	5 (2.8)	8 (8.8)	1 (1.1)
Hypoproteinemia	23 (13.1)	2 (1.1)	8 (8.8)	0 (0)
Diarrhea	20 (11.4)	2 (1.1)	3 (3.3)	1 (1.1)
Elevated LDH	18 (10.2)	0 (0)	12 (13.2)	2 (2.2)

NOTE. Adverse events are listed if they were reported in at least 10% of patients in either treatment group.

Abbreviations: ALP, alkaline phosphatase; GGT, γ -glutamyltransferase; LDH, lactate dehydrogenase.

8.4 Pregnancy and Lactation

Fertility and teratology studies have not been conducted with apatinib. It is not known if apatinib or its metabolites is excreted in milk or can cross the placenta. For this reason, pregnant and nursing women should not receive apatinib. Women of childbearing potential and their partners who are admitted to the clinical study must take adequate contraceptive measures.

8.5 Drug-drug Interactions

The effect of Apatinib on the absorption, metabolism, or excretion of other drugs has not been studied. To date, there have been no unexpected interactions observed between apatinib and other drugs.

In vitro data indicate that cytochrome P450 (CYP) 3A4 is the primary CYP isoenzyme involved in the metabolism of apatinib. The use of the following medications (Appendix 3) should be discontinued prior to initiation of protocol therapy and should be avoided during protocol therapy if reasonable alternatives exist. This is not an inclusive list; please refer to other resources such as <http://medicine.iupui.edu/clinpharm/ddis/table.aspx> or other frequently updated medical reference for additional information.

8.6 Guidelines for Administration

All patients will receive apatinib 750 mg (BSA > 1.5 m²) or 500 mg (BSA < 1.5 m²) orally once daily, given on the same time at half an hour after meal.

9.0 Criteria for Removal from Protocol Therapy and off Study Criteria

9.1 Criteria for Removal from Protocol Therapy

- Progressive disease.
- Unacceptable toxicity due to protocol therapy (see Section 7.0).
- Refusal of further protocol therapy by patient/parent/guardian.
- Completion of planned therapy.
- Physician determines it is in patient's best interest.
- Development of a second malignancy.

- Repeat eligibility studies are outside the parameters required for eligibility
- Surgery or radiation performed on any site of measurable disease before the end of the 6th months.
- Failure to recover from surgery within 6 weeks.
- Pregnancy.

Patients who are off protocol therapy are to be followed until they meet the criteria for Off Study (see below). Follow-up data will be required unless patient is taken off study.

9.2 Off Study Criteria

- Death.
- Lost to follow-up.
- Patient enrollment onto another study with tumor therapeutic intent.
- Withdrawal of consent for any further data submission.
- The fifth anniversary of the date the patient was enrolled on this study.

10.0 Statistical Considerations

10.1 Sample Size and Study Design

There is a surprising lack of published data for PFS of patients with high-grade osteosarcoma that have relapsed after standard treatments. At the same time, reported objective responses to chemotherapy after MAPI vary widely, making this endpoint unsuitable in the context of patients with advanced and unresectable high-grade osteosarcoma. Preclinical study on osteosarcoma specimens demonstrated that apatinib targets were expressed and effectively inhibited by this drug in xenografts, providing a rationale to explore apatinib in progressing osteosarcoma patients.

Therefore, we chose ORR at 3 month and PFS at 4 month as a primary endpoint rather than objective response recorded in previous trial as a point of reference. Thus, the trial was designed to discard a PFS at 4 month of 10% (null hypothesis) aiming to

reach a PFS at 4 month of 30% or higher (alternative hypothesis). Using Simon's optimum two-stage design and setting α -error at 0.05 and β -error at 0.10, the presence of at least six successes in the 17 patients enrolled in the first stage allowed the trial to proceed to the second stage in which 20 more patients were needed to be enrolled for the minimum total of 37 patients.

10.2 Statistical Analysis

The intention-to-treat analysis included all patients who received at least one dose of apatinib. The population assessable for treatment activity comprised all patients for whom at least one disease assessment (either clinical or radiological) was done. The primary endpoint was analysed in the intention-to-treat population. We estimated survival endpoints according to the Kaplan- Meier method, with 95% CIs. RECIST overall responses and disease control were calculated and reported with 95% CIs. We investigated the effect of P-ERK1/2 and P-RPS6 expression by comparing survival outcomes with the two-sided Mantle-Cox log-rank test, Fisher's exact test, and the Mantel-Haenszel odds ratio (OR) estimate. We compared baseline versus on-treatment PAS and BPI scores with a paired student's t test. We computed all statistics with IBM SPSS Statistics (version 20) and GraphPad Prism (version 5).

10.2.1 Evaluability for Disease Control and Response

10.2.1.1 Which Patients will be Considered Evaluable for RECIST Response:

Any eligible patient who receives at least one dose of apatinib will be considered evaluable for response with the following exception: if a patient receives non-protocol anti-cancer therapy during the response evaluation period after the patient is considered as having a partial or complete response but prior to confirmation of this status by tumor imaging and before progressive disease is noted, the individual will be considered inevaluable for the response endpoint. Further, patients who stop apatinib after the 1st evaluation because of toxicities or death will be considered evaluable for the response evaluation and will be counted as non-responders for the response endpoint.

10.2.2.2 Which Patients Will Be Considered Evaluable for Disease Control

Success:

Any eligible patient who receives at least one dose of apatinib will be considered evaluable for response with the following exception: if a patient receives non-protocol anti-cancer therapy during the first two months of therapy is considered as having a partial or complete response but prior to confirmation of this status by tumor imaging and before progressive disease is noted, the individual will be considered inevaluable for the disease control success endpoint.

10.2.2.3 Which Patients Will be Considered a Disease Control Success:

Any patient who is evaluated free of all detectable disease (complete response) or is considered as having a partial response after two months of therapy or is considered as having stable disease ('at least stable disease') after three months of therapy.

10.2.2.4 Which Patients Will be Considered Not a Disease Control Success:

Any evaluable patient who does not meet the criteria for disease control success (complete response, partial response or stable disease) will be considered to not have experienced disease control success.

In particular, any patient who dies because of treatment-related toxicity during the first three months since starting treatment will be considered not to have experienced disease control success. Also, any patient who is eligible, receives one dose of apatinib and is lost to follow-up at (for example) the end of the second (complete response, partial response) or third months will be considered not a disease control success (stable disease).

Patients who are not evaluable for both disease control and response evaluation may be replaced for the purposes of the statistical rule.

10.2.2 Evaluability for Toxicity

Tolerability of apatinib - An eligible patient will be considered for toxicity monitoring if one of the following occurs: (1) complete two months of apatinib prior to receiving non-protocol anticancer therapy; (2) die on protocol therapy for a reason considered possibly, probably or likely related to apatinib; or (3) are removed from

protocol therapy because of an adverse experience possibly, probably or likely related to apatinib. A toxicity- evaluable patient will be considered in the analysis during the interval from study enrollment until the termination of protocol therapy. A toxicity-evaluable patient will be considered to have experienced an excessive toxicity event if: (1) the patient dies on protocol therapy for a reason considered possibly, probably or likely related to; or (2) experiences a dose-limiting toxicity (DLT). DLTs will be as defined in Section 7.1.1 of the protocol:

The analytic unit for monitoring for excessive toxicity will be the patient-month: Each 2 months where the patient receives apatinib and does not receive non-protocol anticancer therapy will be considered in the analysis. If there is overwhelming evidence that the dose selected for this trial has a per-2 months-DLT probability of more than 30%, we will identify the regimen to a toxicity profile that may require modification of the regimen. We will use a Bayesian rule to monitor for excessive toxicity. We will assume a beta prior to distribution with $\alpha=0.6$ and $\beta=1.4$. If this posterior probability of the chance of DLT is at least 30% exceeds 80%, we will identify the regimen to a toxicity profile that may require modification of the regimen.

11.0 Evaluation Criteria

11.1 Common Terminology Criteria for Adverse Events (CTCAE)

This study will utilize version 4.0 of the CTCAE of the National Cancer Institute (NCI) for toxicity and performance reporting. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website

(http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm) or

Appendix 4. Additionally, toxicities are to be reported on the appropriate case report forms.

Please note: 'CTCAE v4.0' is understood to represent the most current version of CTCAE v4.0 as referenced on the CTEP website (ie, v4.02 and all subsequent iterations prior to version 5.0).

11.2 Response Criteria for Patients with Solid Tumors

For the purposes of this study, patients should be evaluated for response following Months 2, 4 and 6 and following every 3rd month thereafter. Patients who have a RECIST response (CR or PR) at Month 6 will have confirmatory imaging after Month 8.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) (Appendix 1). Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

11.2.1 Disease Parameters

11.2.1.1 Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as \geq 20 mm by chest x-ray, as \geq 10 mm with CT scan, or \geq 10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

11.2.1.2 Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be \geq 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

11.2.1.3 Non-measurable disease: All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with \geq 10 to <15mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis

cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

‘Cystic lesions’ thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

11.2.1.4 Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

11.2.1.5 Non-target lesions: All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

11.2.2 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the

beginning of treatment and never more than 2 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

11.2.2.1 Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (eg, skin nodules and palpable lymph nodes) and ≥ 10 mm diameter as assessed using calipers (eg, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

11.2.2.2 Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

11.2.2.3 Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (eg, for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

11.2.2.4 Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

11.2.2.5 Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

11.2.2.6 Cytology, Histology: These techniques can be used to differentiate between PR and CR in rare cases (eg, residual calcification in tumor types, where known residual benign calcifications can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

11.2.3 Response Criteria

11.2.3.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease: At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline

sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

11.2.3.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of “non-target” lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

11.2.3.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (ie, Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥ 4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥ 4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	documented at least once ≥ 4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	
<p>*See RECIST 1.1 manuscript for further details on what is evidence of a new lesion. **Only for non-randomized trials with response as primary endpoint. ***In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.</p> <p><u>Note:</u> Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as “<i>symptomatic deterioration.</i>” Every effort should be made to document the objective progression even after discontinuation of treatment.</p>				

11.2.4 Duration of Response

11.2.4.1 Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

11.2.4.2 Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

12.0 Appendix

Appendix 1 RECIST 1.1

Appendix 2 ECOG scores

Appendix 3 CYP3A4 inducers and inhibitors

Appendix 4 CTCAE version 4.0

Appendix 5 EORTC QLQ C-30

Adverse Effect of apatinib from company

13.0 References

1. Bernthal, N.M., et al., Long-term results (>25 years) of a randomized, prospective clinical trial evaluating chemotherapy in patients with high-grade, operable osteosarcoma. *Cancer*, 2012. 118(23): p. 5888-93.
2. Bielack, S., et al., Osteosarcoma: the COSS experience. *Cancer Treat Res*, 2009. 152: p. 289-308.
3. Kempf-Bielack, B., et al., Osteosarcoma relapse after combined modality therapy: an analysis of unselected patients in the Cooperative Osteosarcoma Study Group (COSS). *J Clin Oncol*, 2005. 23(3): p. 559-68.
4. Cheong, J.H., et al., Surgical management and outcome of metachronous Krukenberg tumors from gastric cancer. *J Surg Oncol*, 2004. 87(1): p. 39-45.
5. van Rijk-Zwikker, G.L., et al., Pulmonary metastasectomy in patients with osteosarcoma. *Eur J Cardiothorac Surg*, 1991. 5(8): p. 406-9.
6. Thompson, R.C., Jr., et al., Results of treatment for metastatic osteosarcoma with neoadjuvant chemotherapy and surgery. *Clin Orthop Relat Res*, 2002(397): p. 240-7.
7. Navid, F., et al., Combination of gemcitabine and docetaxel in the treatment of children and young adults with refractory bone sarcoma. *Cancer*, 2008. 113(2): p. 419-25.
8. Berger, M., et al., Phase 2 trial of two courses of cyclophosphamide and etoposide for relapsed high-risk osteosarcoma patients. *Cancer*, 2009. 115(13): p. 2980-7.
9. Saylor, R.L., 3rd, et al., Cyclophosphamide plus topotecan in children with recurrent or refractory solid tumors: a Pediatric Oncology Group phase II study. *J Clin Oncol*, 2001. 19(15): p. 3463-9.

10. Miser, J.S., et al., Ifosfamide with mesna uroprotection and etoposide: an effective regimen in the treatment of recurrent sarcomas and other tumors of children and young adults. *J Clin Oncol*, 1987. 5(8): p. 1191-8.
11. McNall-Knapp, R.Y., et al., Extended phase I evaluation of vincristine, irinotecan, temozolomide, and antibiotic in children with refractory solid tumors. *Pediatr Blood Cancer*, 2010. 54(7): p. 909-15.
12. Bomgaars, L.R., et al., Phase II trial of irinotecan in children with refractory solid tumors: a Children's Oncology Group Study. *J Clin Oncol*, 2007. 25(29): p. 4622-7.
13. Cosetti, M., et al., Irinotecan for pediatric solid tumors: the Memorial Sloan-Kettering experience. *J Pediatr Hematol Oncol*, 2002. 24(2): p. 101-5.
14. Debiec-Rychter, M., et al., KIT mutations and dose selection for imatinib in patients with advanced gastrointestinal stromal tumours. *Eur J Cancer*, 2006. 42(8): p. 1093-103.
15. Shepherd, F.A., et al., Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med*, 2005. 353(2): p. 123-32.
16. Sleijfer, S., et al., Pazopanib, a multikinase angiogenesis inhibitor, in patients with relapsed or refractory advanced soft tissue sarcoma: a phase II study from the European organisation for research and treatment of cancer-soft tissue and bone sarcoma group (EORTC study 62043). *J Clin Oncol*, 2009. 27(19): p. 3126-32.
17. Linch, M., et al., Systemic treatment of soft-tissue sarcoma-gold standard and novel therapies. *Nat Rev Clin Oncol*, 2014. 11(4): p. 187-202.
18. Schoffski, P., et al., Soft tissue sarcoma: an update on systemic treatment options for patients with advanced disease. *Oncol Res Treat*, 2014. 37(6): p. 355-62.
19. Xu, M., et al., Effects of endostar combined multidrug chemotherapy in osteosarcoma. *Bone*, 2013. 57(1): p. 111-5.
20. Grignani, G., et al., A phase II trial of sorafenib in relapsed and unresectable high-grade osteosarcoma after failure of standard multimodal therapy: an Italian Sarcoma Group study. *Ann Oncol*, 2012. 23(2): p. 508-16.
21. Yoo, C., et al., Multicenter phase II study of everolimus in patients with metastatic or recurrent bone and soft-tissue sarcomas after failure of anthracycline and ifosfamide. *Invest New Drugs*, 2013. 31(6): p. 1602-8.

22. Grignani, G., et al., Sorafenib and everolimus for patients with unresectable high-grade osteosarcoma progressing after standard treatment: a non-randomised phase 2 clinical trial. *Lancet Oncol*, 2015. 16(1): p. 98-107.
23. Lammler, J., et al., Expression of Vascular Endothelial Growth Factor correlates with the advance of clinical osteosarcoma. *Int Orthop*, 2012. 36(11): p. 2307-13.
24. Li, J., et al., Apatinib for chemotherapy-refractory advanced metastatic gastric cancer: results from a randomized, placebo-controlled, parallel-arm, phase II trial. *J Clin Oncol*, 2013. 31(26): p. 3219-25.
25. Aras, M., et al., Comparison of WHO, RECIST 1.1, EORTC, and PERCIST criteria in the evaluation of treatment response in malignant solid tumors. *Nucl Med Commun*, 2016. 37(1): p. 9-15.
26. Choi, H.C., et al., Comparison of the RECIST 1.0 and RECIST 1.1 in Non-Small Cell Lung Cancer Treated with Cytotoxic Chemotherapy. *J Cancer*, 2015. 6(7): p. 652-7.
27. Semiglazov, V., RECIST for Response (Clinical and Imaging) in Neoadjuvant Clinical Trials in Operable Breast Cancer. *J Natl Cancer Inst Monogr*, 2015. 2015(51): p. 21-3.
28. Young, J., et al., Comparison of ECOG/WHO performance status and ASA score as a measure of functional status. *J Pain Symptom Manage*, 2015. 49(2): p. 258-64.
29. Broderick, J.M., et al., Patients over 65 years are assigned lower ECOG PS scores than younger patients, although objectively measured physical activity is no different. *J Geriatr Oncol*, 2014. 5(1): p. 49-56.
30. de Kock, I., et al., Conversion of Karnofsky Performance Status (KPS) and Eastern Cooperative Oncology Group Performance Status (ECOG) to Palliative Performance Scale (PPS), and the interchangeability of PPS and KPS in prognostic tools. *J Palliat Care*, 2013. 29(3): p. 163-9.
31. Simon, R., Optimal two-stage designs for phase II clinical trials. *Control Clin Trials*, 1989. 10(1): p. 1-10.