Brain Radiotherapy Combined with Pyrotinib and Capecitabine in patients with HER2-positive Advanced Breast Cancer and Brain Metastases (BROPTIMA): A Prospective, Phase II, Single-arm Clinical Study

Clinical Study Protocol

Project No: NCT04582968

Sponsor: Fudan University Shanghai Cancer Center, China.

Principal Investigator: XiaoLi Yu

Version: 2.0

Date: December 28, 2019

Investigator Signature Page

As a participating doctor/statistical analyst, I have read this protocol and have fully discussed the purpose and content of this research with the research leader.

I agree to conduct the study following the current protocol and all stipulations of the protocol, including ethical standards. I agree to conduct the study in compliance with Good Clinical Practice (GCP) guidelines.

The signature below provides the necessary assurance that this trial will be conducted according to all statements regarding confidentiality. I agree not to disclose or otherwise make available any of the confidential information to anyone except those employees and agents of institution who need to know. I agree that this protocol is only used for this study.

I understand that if the trial is prematurely terminated or suspended for any reason at any time, I will be notified in written form. Similarly, if I decide to withdraw from this research, I will immediately notify the parties involved in the study in written form.

Investigator Signature:_____

Date:_____

Protocol Synopsis

Name	Brain Radiotherapy Combined with Pyrotinib and Capecitabine in patients with HER2-positive Advanced Breast Cancer and Brain Metastases (BROPTIMA): A Prospective, Phase II, Single-arm Clinical Study
Edition/date	Edition 2.0 / Dec.28.2019
Sponsor	Fudan University Shanghai Cancer Center, Professor XiaoLi Yu
Study type	Investigator-Initiated Exploratory Clinical Trials
Study Population	HER2-positive advanced breast cancer patients with brain metastases
Study Objective	To evaluate the efficacy and safety of stereotactic radiotherapy or whole brain radiotherapy combined with pyrotinib maleate tablets plus capecitabine therapy in HER2-positive advanced breast cancer patients with brain metastases
Study design	Prospective, single-arm, open label clinical study with a safety-run-in
Estimated Enrollment	39 patients
Inclusion criteria	Inclusion criteria 1. Female, ≥18 years of age 2. Karnofsky score (KPS)≥70 or KPS=60 mainly caused by neurologic symptoms (See Appendix1 KPS score) 3. The pathology performed by the Pathology Department of Fudan University Shang Cancer Center (FUSCC) clearly shows that HER2 is positive in primary breast lesions or metastatic lesions, and HER2 positivity is defined as HER2(3+) by immunohistochemistry or amplification by fluorescence in situ hybridization (FISH), and the specimens from external hospital must be consulted by the Pathology Department of Fudan University Shang Cancer Center (FUSCC) 4. Brain metastases confirmed by pre-treatment contrast-enhanced Magnetic

	Resonance Imaging (MRI). At least one measurable brain lesion is required as per RANO-BM criteria, and the measurability of extracranial lesions is not required 5. At least 2 weeks apart from previous treatment, and recovery of toxic side effects ≤ grade I (CTCAE 4.03) Concurrent use of bisphosphonates is allowed to be given at the same time. Mannitol and glucocorticoids is allowed, provided that the dosage (⩽16 mg dexamethasone (or equivalent) per day) of glucocorticoids was stable for at least one week before enrollment. 6. Expected life of survival ≥ 12 weeks 7. Patients must have adequate organ function, criteria as follows. Blood routine test：Absolute Neutrophil Count (ANC)≥1.5×109/L；PLT ≥90×109/L； Hb ≥90g/L Blood biochemical test：TBIL ≤1.5 times the upper limit of normal (ULN); ALT and AST≤2.5 times ULN; For patients with liver metastases, ALT and AST≤5×ULN; BUN and Cr≤1.5×ULN and creatinine clearance ≥50mL/min (CockcroftGault formula); Cardiac ultrasound: LVEF≥50% 12-lead ECG: The QT interval (QTcF) corrected by Fridericia's method is < 390 ms. 8. The patients voluntarily participated in the study and signed informed consent.

Exclusion criteria	Exclusion criteria 1. Patients with leptomeningeal metastasis or hemorrhagic metastases; 2. Patients with uncontrolled epilepsy. 3. There are serious and/or uncontrolled complications that may affect participation, including any of the following: 1) Dysphagia, chronic diarrhea and intestinal obstruction and factors that affect the administration and absorption of the drug; 2) Allergies to study drugs or auxiliary materials 3) History of immunodeficiency, including HIV positive, or other acquired or congenital immunodeficiency diseases; History of organ transplantation; 4) History of severe heart disease, including: myocardial infarction and heart failure; any other heart disease that is not suitable for participation (investigator assessment); 5) Infection; 6) Has a previous history of other malignancies, except for cured basal cell carcinoma of the skin or squamous cell carcinoma of the skin, and carcinoma in situ of the cervix; 4. Female patients during pregnancy and lactation; female patients of childbearing age who are unwilling to take effective contraceptive measures during the trial. 5. Patients unable to complete the enhanced-contrast MRI examination; 6. Patients unwilling or unable to undergo regular follow-up; 7. Patients who have previously received treatment with pyrotinib or capecitabine; 8. Any other circumstances in which the investigator concluded the patient was not eligible for participation in the study.
Study drug dose /route of administration	Radiotherapy regimens was delivered according to brain metastasis size, parenchymal brain location and number of metastases. Initiation of both pyrotinib and capecitabine therapy from day 1 to 1 week after the end of radiotherapy is permissible. An initial dose of pyrotinib 400 mg per day and capecitabine at 1000 mg/m2,

	twice daily for 1 cycle every 21 days on consecutive days 1 through 14 were administered until disease progression, unacceptable toxicity or death.
Study endpoint	Primary endpoint: CNS Progression Free Survival（CNS-PFS）rate at 12 months per RANO-BM criteria Secondary endpoint: 1. Progression Free Survival （PFS） 2. Objective response rate of Central Nervous System lesions (CNS-ORR) 3. Overall survival (OS) 4. Radiation and Drug safety 5. Neurocognitive function evaluated by Mini-mental State Examination （MMSE）
Sample size and statistical analysis	Our hypothesis was that the combination of radiotherapy with pyrotinib and capecitabine regimens would result in a further decrease in intracranial progression. Based on historical results, assuming that the CNS-PFS rate at 12 months would increase from 48% with the radiotherapy regimen to 70% with the combination regimen, a sample size of 39 subjects was required to accept the hypothesis with a one-sided α of 0.025 and a power of 80%. Continuous data were reported as median (IQR or range), and categorical data were reported as frequency (percentage). Survival was estimated using the Kaplan–Meier method, and the 95% confidence interval (CI) of survival was estimated using the Brookmeyer-Crowley method.

Content

Schedule of Events

Study staging	**Screening period**	**Treatment period[1]**										**End of study or early termination**	**Follow up**
	-2w	**1 w**	**2 w**	**3 w**	**2 m**	**4 m**	**6 m**	**8 m**	**10 m**	**12 m**	**15 m**	**18m and later**		
Interview	1	2	3	4	5	6	7	8	9	10	11	12…		
Collecting basic medical history														
Determining inclusion/exclusion criteria	√													
Signing informed consent	√													
Demographics [2]	√													
Previous medical history and treatment history [3]	√													
Combined medication and accompanying disease [4]	√	√	√	√	√	√	√	√	√	√	√	√	√	
Efficacy indicators														
Physical examination (blood pressure, heart rate, respiratory rate, breath sounds)	√	√	√	√	√	√	√	√	√	√	√	√	√	
Imaging examination of intracranial lesions（MRI）	√				√	√	√	√	√	√	√	√	√	

[5]													
Imaging examination of extracranial lesions（CT/MRI）[5]	√				√	√	√	√	√	√	√	√	
KPS score	√				√			√		√	once every 12 months	√	
Neurocognitive function evaluation [6]	√				√			√		√	once every 12 months	√	
Safety indicators													
Blood, urine routine examination, liver and kidney function and blood sugar examination7	√	√	√	√	√	√	√	√	√	√	√	√	
Electrocardiogram8	√				√	√	√	√	√	√	√	√	
Pregnancy test for women of childbearing age9	√											√	
Adverse event recording and assessment10		√	√	√	√	√	√	√	√	√	√	√	
Other													
Time to progress/death	√											√	√
Follow-up cancer care													√

A 3/7-day window is allowed for visits, and in the case of statutory holidays, the reason for the window can be advanced accordingly and recorded in the eCRF. Researchers can increase the number of

examination items or increase the rate of video visits according to the clinical situation of the subjects.

1. Radiotherapy program：Refer to Chapter 5
2. Systemic therapy dosing regimen: The dosing regimen for systemic therapy was as follows: Pyrotinib: 400 mg orally once daily within 30 minutes after breakfast, for 1 course of 21 days or until disease progression or intolerable toxicity reported by the patient. Capecitabine: 1000 mg/m2 orally within 30 minutes of a meal (morning and evening, approximately 12 hours apart, equal to a daily dose of 2000 mg/m2), continuous administration on days 1 to 14, for 1 course of 21 days. The above medication can be adjusted according to the adverse reactions of the subject. Participants continued to take the drug until disease progression, intolerable toxicity, withdrawal from the clinical trial, or termination as deemed necessary by the investigator. Initiation of both pyrotinib and capecitabine therapy from day 1 to 1 week after the end of radiotherapy is permissible.
3. Demographic: Initials, gender, ethnicity, marriage, date of birth, height, weight, and calculate the body surface area accordingly;
4. Medical history: Including past case history and treatment history (clinical/pathological diagnosis, diagnosis time, clinical/pathological stage, HER2/ER/PR expression; history of surgery, neoadjuvant therapy, adjuvant therapy, radiotherapy; time to progression and diagnosis basis; history of systemic treatment of advanced cancer; names, medication regimens, the treatment response to each line of drugs used in adjuvant therapy and advanced cancer systemic treatment, whether it is treated by other modalities (e.g., surgery), history of smoking and drinking (frequency, amount, duration), history of drug allergy (drug name, allergy symptoms), previous or concomitant diseases/symptoms (disease/symptom name, combined drug name, dose, usage, outcome);
5. Concomitant medications/treatments: Record the concomitant medications during the 14-day screening period and during the trial; once the subject discontinues treatment, only the concomitant medications and treatments used for the new or unresolved adverse events related to the trial treatment are recorded.
6. Tumor imaging: Intracranial lesions are examined with MRI. Extracranial lesions are examined with CT or MRI of the chest and abdomen, with neck, pelvic examination, bone scanning, etc. if necessary. Investigators can add scan sites to tumor evaluation at baseline or later as needed clinically. For the first 12 months, it is performed every 2 months, and then every 3 months.
7. Neurocognitive function evaluation: According to the patients' general situation and willingness, the MMSE evaluation results are collected for the patients who are physically permitted to fill in

the MMSE questionnaire.

8. Laboratory tests：Blood routine test including absolute counts of WBC, ANC, LC, RBC, Hb, PLT; Urinalysis: including urine protein, urine occult blood; Blood biochemical test: including alanine aminotransferase ALT, glutamyl aminotransferase AST, glutamyl transpeptidase GGT, alkaline phosphatase AKP, total protein TP, albumin ALB, total bilirubin TBIL, direct bilirubin DBIL, globulin GLU, indirect bilirubin IBIL, urea nitrogen BUN, creatinine Cr, blood electrolytes (K+, Na+, Cl-, Ca2+, Mg2+). Additional tests may be performed if necessary.
9. Electrocardiogram：QT, QTc, and P-R intervals should be noted. If the subject has chest pain, palpitations or other heart symptoms, a cardiac ultrasound may be added at any time.
9. Pregnancy test：Female participants of childbearing age were selected during the screening period to exclude pregnancy; During the study, investigators made their own decisions about testing based on clinical practice or as needed.
10. Adverse events ：Adverse events were monitored from the day of signing the informed consent form until at least 30 days after the last treatment. Adverse events, concomitant medications/treatments, and unscheduled investigations during the period should be documented in detail.

1. Background

1.1 Breast cancer brain metastases

Breast cancer is currently the most common malignant tumor with the highest incidence among Chinese women. According to data released by the National Cancer Center, the number of Chinese women diagnosed with breast cancer in 2013 was 278,000, with a mortality rate of 64,600 [1, 2]. It has become a major health concern that significantly impacts the well-being of Chinese women. Metastatic breast cancer is a significant contributor to breast cancer-related deaths. Recent literature reports indicate that the incidence of breast cancer brain metastases is as high as 24% [3], with the incidence of brain metastases in patients with HER2-overexpressing breast cancer exceeding 30% [4].

1.2 Radiation therapy for brain metastases

The treatment of brain metastases is divided into active treatment for metastatic lesions and supportive treatment to improve symptoms. Active treatments include surgery, radiotherapy, chemotherapy, and targeted therapy. Radiotherapy plays an important role in the local treatment of brain metastases and has a wide range of indications. WBRT improves neurological symptoms and quality of life in patients with brain metastases, and early studies indicate that WBRT extends the

median survival time of patients to 3-6 months[5]. However, the side effects of WBRT for patients with long survival times, such as irreversible cognitive function decline and memory function decline, are also obvious[6, 7]. WBRT can cause extensive alopecia and extensive white matter lesions on imaging.

Stereotactic radiotherapy (SRT) or stereotactic radiosurgery (SRS) can be performed with locally focused radiotherapy (stereotactic radiotherapy or radiosurgery, SRT or SRS) for metastases without affecting other intracranial sites. The SRS technique can be used alone or in combination with WBRT. Studies have demonstrated that the survival advantage of SRS alone is not inferior to that of SRS + WBRT[6, 7]. Patients treated with SRS alone have obvious advantages in the protection of cognitive function and memory. Moreover, the treatment time is short, which reduces the transportation and accommodation costs of patients. SRS can be the preferred treatment option for patients with 1-4 brain metastases. For patients with more than 5 lesions, the JLGK0901 study[8] found no difference in the median survival time between 2-4 metastases and 5-10 metastases.

Increasing evidence suggests that fractionated stereotactic radiation therapy (FSRT) is superior to single-shot SRS for local control of brain metastases. The Memorial Sloan Kettering Cancer Center (MSKCC) reported on 195 patients with 231 lesions treated with 30 Gy/5 Fx, with a median follow-up 1-year local control rate was 83%. Minniti et al. reported the treatment of 343 patients: 179 received a single SRS, 164 received FSRT (9 Gy*3 times), and the results indicated that better local control of FSRT than SRS. [9, 10].

However, available evidence shows that the recurrence rate of intracranial lesions exceeds 50% at 1 year after radiotherapy in both WBRT and SRS regimens[6, 11]. Reducing the risk of intracranial recurrence remains a key issue in the treatment of brain metastases.

1.3 HER2 positive breast cancer

The incidence of brain metastases in HER2-overexpressed metastatic breast cancer has been reported to be 30-50%. Despite the significant improvement in clinical outcomes owing to HER2-directed therapies, approximately half of patients with HER2-positive advanced breast cancer will develop brain metastases over time. Currrently, targeted systemic therapy against HER2 are divided into 2 main categories. The first category is macromolecular monoclonal antibodies, such as herceptin, pertuzumab, and T-DM1. The other type is small-molecule tyrosine kinase inhibitor (TKI) drugs, such as lapatinib, which can reversibly act on tyrosine kinases of HER1 and HER2 receptor cells, neratinib that irreversibly acts on tyrosine kinases of HER1, HER2, and HER4 receptor cells, and pyrotinib (Hengrui, Jiangsu, China) [12, 13]. Lapatinib is the first small-molecule TKI that has been shown to

penetrate the BBB and is effective against intracranial metastases. Preclinical studies have demonstrated that lapatinib can exert an antitumor effect through the BBB. LANDSCAPE[14] reported the results of a phase II clinical trial of oral capecitabine and lapatinib in 45 asymptomatic patients with brain metastases; 98% of the patients were evaluated as having received effective treatment, and the median follow-up was 21.2 months (range 2.2-27.6 months). The objective response rate (ORR) was 65.9% (29 cases), although all responses were partial responses. Although 82% of patients ultimately received radiation, anti-HER2 therapy delayed WBRT by 8 months, delaying the effects of WBRT on cognitive function. Neratinib, which targets the pan-HER receptor family, has also been shown to pass the BBB. The Breast Cancer Translational Research Collaborative (TBCRC)[15] reported that single-agent neratinib can achieve an ORR of 8% in patients with brain metastases that have progressed after previous cranial radiation therapy. If capecitabine is combined with neratinib, the ORR can be improved to 49%. Pyrotinib is also a small-molecule TKI drug targeting the pan-HER family. A prospective phase I dose escalation clinical trial[13] found that in 36 patients who progressed after multiple lines of chemotherapy containing Herceptin, pyrotinib 80-400 mg achieved a 50% ORR, and 8 patients in the 400 mg group achieved an ORR of 87.5%. The main dose-limiting toxicity (DLT) of pyrotinib was diarrhea. The incidence of Grade 3 diarrhea was 13.2%, which could be controlled by antidiarrheal treatment such as loperamide. In a phase II clinical trial, investigators randomly compared pyrotinib plus capecitabine to lapatinib plus capecitabine in patients with advanced HER2-positive receiving ≤2 lines of chemotherapy and found that regardless of treatment with Herceptin, the ORRs of the 2 groups were 87.5% and 57.1%, respectively, and the progression-free survival (PFS) times were 18.1 months and 7 months, respectively, which significantly reduced the risk of disease progression. The results of the interim analysis of the phase III pyrotinib clinical trial at ASCO in 2019 have indicated that the median PFS rates of the pyrotinib plus capecitabine group and the placebo plus capecitabine group were 11.4 months and 4.1 months, respectively (hazard ratio (HR) 0.18 (0.13-0.26), p<0.001). The study enrolled 31 patients with brain metastases and found that the median PFS rates were 6.9 months in the pyrotinib group and 4.2 months in the placebo group (HR 0.32 (0.13-0.77), p=0.011). The proportion of new-onset brain metastases was lower in the pyrotinib group (1.2% vs. 3.6%), and the times to new brain metastases were 397.5 days and 132 days, respectively. However, compared with those on TKIs that also target pan-HER receptors, studies on pyrotinib plus capecitabine in the treatment of brain metastases are limited, and relevant prospective studies focusing on combination of radiotherapy and TKI is still lacking.

1.4 Blood–brain barrier and radiotherapy

The blood–brain barrier (BBB) is composed of endothelial cells, pericytes, stellate cells, and the basement membrane and is a physiological and immune barrier that protects the brain. However, due to their low permeability, approximately 98% of small-molecule drugs and the vast majority of macromolecular drugs cannot effectively enter the brain. Although brain metastases are accompanied by local BBB damage, the existence of tight junctions that constitute the key structure with low permeability of the BBB still limits the delivery of therapeutic drugs into the brain to achieve effective therapeutic concentrations[16]. Animal research[17] indicated that the concentrations of the commonly used breast cancer drugs paclitaxel and doxorubicin in brain are only 15% of those in other parts of the extracranial region. Another recent pilot study[18] demonstrated that BBB permeability is significantly different in different metastases and between different breast cancer cell lines, which suggests heterogeneity and inhomogeneity in BBB permeability. Improving the permeability of the BBB effectively, thereby increasing the intracranial drug concentration for breast cancer and increasing the antitumor effect, is the key factor to improve the efficacy of breast cancer-associated brain metastasis treatment.

Radiation therapy is thought to increase BBB permeability, thereby increasing the permeability of the BBB to cytotoxic or targeted drugs. For example, T-DM1 is a conjugate of trastuzumab and the cytotoxic drug DM-1, and although trastuzumab cannot cross the BBB, a retrospective study[19] showed that T-DM1 treatment in patients who have progressed again after radiotherapy can achieve a 30-50% response rate, with a median intracranial progression-free survival of 5-7 months. This result suggests that the BBB of some patients was opened after radiotherapy, vascular permeability was increased, enabled DM1exert cytotoxic effect.

1.5 Summary

So far, there is a lack of prospective data to support the choice of combination of TKI in addition to local therapy. This phase 1b/2 study was designed to evaluate the efficacy and safety of combination between capectabine and pyrotinib with CNS SRT or whole brain irradiation in a population of HER2-positive breast cancer patients with brain metastases.

2. Research objective and endpoints

2.1 Study objective

To evaluate the efficacy and safety of stereotactic radiotherapy or whole brain radiotherapy combined with pyrotinib and capecitabine in the treatment of advanced breast cancer with HER-2 positive brain metastases.

2.2 Primary Endpoint

The primary endpoint was one-year CNS progression free survival (PFS) rate according to RANO-BM criteria, as determined by at least two experienced neuroradiologists.

2.3 Secondary Endpoints

CNS Progression Free Survival: CNS-PFS is defined as the time from the start of the subject receiving study treatment to the first imaging confirmed intracranial disease progression (PD) or death from any reason. RANO-BM criteria were used for intracranial lesions

Progression-free survival (PFS): PFS is defined as the time from the start of the subject receiving study treatment to the first imaging confirmed disease progression (PD) or death from any reason. RANO-BM criteria were used for intracranial lesions and Recist 1.1 criteria were used for extracranial lesions.

Overall survival (OS): Refers to the time period from the date of receiving study treatment to the date of death (any cause). Subjects without an observed death will be censored at the time of confirmed survival.

Central Nervous System objective response rate (CNS-ORR), CNS-ORR is defined as the percentage of participants that achieve CNS complete or partial response from the start of the subject receiving the treatment of this study to the period when the subject's out of the group. RANO-BM criteria is used for evaluation.

Drug safety indicators：KPS score, vital signs, Physical examination, laboratory tests (blood routine examination, routine urine and stool test), comprehensive metabolic panel, coagulation test), ECG, Cardiac ultrasound , adverse events (AEs), AEs is recorded based on NCI-CTC AE 4.03 criteria.

Neurocognitive function, evaluated by applying Mini-mental State Examination（MMSE）

3. Study design

This study is a single-center, open-label, prospective, single-arm phase 2 clinical study with a safety-run-in part. A total of 39 patients with advanced HER2-positive brain metastases who met the inclusion criteria were planned for enrollment.

After enrollment, according to the number of lesions and the size of the lesions, the investigator formulates a fractionated stereotactic radiosurgery regimens or a whole-brain radiotherapy regimens. The investigational drug pyrotinib plus capecitabine is started from day 1 to 1 week after completion

of radiotherapy. Treatment is continued until disease progression, toxicity intolerance, withdrawal of informed consent, or termination of medication is necessary at investigator determination.

In the safety run-in part, three patients will be enrolled and followed up for 8 weeks. If none of the first three patients, or none of the additional three patients, experienced dose-limiting toxicity (DLT), the study could proceed. If one of the first three patients experienced DLT, three additional patients would be enrolled. If two or more of the first three patients, or at least one of the additional three patients, experienced DLT, the study would be terminated. If patients experience suspected symptoms of radiation necrosis within an 8-week observation period, an immediate brain MRI examination should be conducted.

DLT was defined as the occurrence of the following adverse events (CTCAE v4.0.3 criteria (time window: 8 weeks)) related or possibly related to the combination of radiation therapy within 8 weeks. Definition of neurological DLT: symptomatic radiation necrosis, greater than or equal to Grade 3 headache, memory loss greater than or equal to Grade 3; and new-onset epilepsy greater than or equal to Grade 3.

Definitions of non-nervous system DLT:

1) Hematologic toxicity: Grade 4 neutropenia lasting ≥5 days; Grade 4 thrombocytopenia or Grade 3 thrombocytopenia with clinically significant bleeding; ≥Grade 3 neutropenia with fever (≥38.0 °C for 1 hour or >38.3 °C); and ≥Grade 4 anemia.
2) Nonhematologic toxicity: Any nonhematologic toxicity ≥Grade 3 other than neurological DLT, except for the following: Grade 3-4 nausea/vomiting and/or diarrhea and/or electrolyte disturbances; recovery within 72 hours to ≤ Grade 2 after best supportive care; and level 3-4 elevation of alkaline phosphatase and glutamyl transpeptidase clearly related to the tumor but not related to the drug.

4. Patient enrollment and exit

4.1 Inclusion Criteria

1. Female, ≥18 years of age
2. Karnofsky score (KPS)≥70 or KPS=60 mainly caused by neurologic symptoms (See Appendix1 KPS score)
3. The pathology performed by the Pathology Department of Fudan University Shang Cancer Center (FUSCC) clearly shows that HER2 is positive in primary breast lesions or metastatic lesions, and HER2 positivity is defined as HER2(3+) by immunohistochemistry or amplification by

fluorescence in situ hybridization (FISH), and the specimens from external hospital must be consulted by the Pathology Department of Fudan University Shang Cancer Center (FUSCC)

4. Brain metastases confirmed by pre-treatment contrast-enhanced Magnetic Resonance Imaging (MRI) At least one measurable brain lesion is required as per RANO-BM criteria, and the measurability of extracranial lesions is not required
5. At least 2 weeks apart from previous treatment, and recovery of toxic side effects ≤ grade I (CTCAE 4.03)
   a) Concurrent use of bisphosphonates is allowed to be given at the same time. Mannitol and glucocorticoids is allowed, provided that the dosage (⩽16 mg dexamethasone (or equivalent) per day) of glucocorticoids was stable for at least one week before enrollment.
6. Expected life of survival ≥ 12 weeks
7. Patients must have adequate organ function, criteria as follows.
   a) Blood routine test：Absolute Neutrophil Count (ANC)≥1.5×109/L；PLT ≥90×109/L； Hb ≥90g/L
   b) Blood biochemical test：TBIL ≤1.5 times the upper limit of normal (ULN);
   c) ALT and AST≤2.5 times ULN;
   d) For patients with liver metastases, ALT and AST≤5×ULN;
   e) BUN and Cr≤1.5×ULN and creatinine clearance ≥50mL/min (CockcroftGault formula);
   f) Cardiac ultrasound: LVEF≥50%
   g) 12-lead ECG: The QT interval (QTcF) corrected by Fridericia's method is < 390 ms.
8. The patients voluntarily participated in the study and signed informed consent.

4.2 Exclusion criteria

1. Patients with leptomeningeal metastasis or hemorrhagic metastases;
2. Patients with uncontrolled epilepsy.
3. There are serious and/or uncontrolled complications that may affect participation, including any of the following:

a) Dysphagia, chronic diarrhea and intestinal obstruction and factors that affect the administration and absorption of the drug;

b) Allergies to study drugs or auxiliary materials

c) History of immunodeficiency, including HIV positive, or other acquired or congenital immunodeficiency diseases; History of organ transplantation;

d) History of severe heart disease, including: myocardial infarction and heart failure; any other

heart disease that is not suitable for participation (investigator assessment);

e) Infection;

f) Has a previous history of other malignancies, except for cured basal cell carcinoma of the skin or squamous cell carcinoma of the skin, and carcinoma in situ of the cervix;

4. Female patients during pregnancy and lactation; female patients of childbearing age who are unwilling to take effective contraceptive measures during the trial.

5. Patients unable to complete the enhanced-contrast MRI examination;

6. Patients unwilling or unable to undergo regular follow-up;

7. Patients who have previously received treatment with pyrotinib or capecitabine;

8. Any other circumstances in which the investigator concluded the patient was not eligible for participation in the study.

4.3 Exit criteria

Subjects can withdraw their informed consent and exit the trial at any time. The investigator may decide to withdraw the subject from the study under the following circumstances:

1) Any clinical adverse event, laboratory abnormality, pregnancy event, or other medical condition that may no longer benefit the subject.

2) Subjects meet any exclusion criteria and may not be able to participate further in the trials (including newly developed clinical indications during the trial or persistent antiquated problems that could not be detected in time

3) From the perspective of medical ethics, it is deemed necessary to stop the test.

4) Subjects with poor compliance, no longer receiving medication or testing before completing all trials, or receiving other anti-tumor treatments at the same time before the completion of the trial, and unable to adhere to the completion of the trial as planned.

4.4 Elimination criteria

1) Non-compliance with the provisions of the plan(radiotherapy/medication) results in the inability to assess effectiveness and/or safety

2) Serious violation of the regimen, failure to take the drug in accordance with the prescribed dose, method and course of treatment.

4.5 Termination criteria

This study may be terminated or suspended early if there are sturdy reasons. Written notice setting out the reasons for the early termination or suspension will be provided by the deciding party and sent to the investigator, sponsor, ethics committee, and relevant departments.

The reasons for termination of this study include but are not limited to the following:

1) Major errors in the clinical trial protocol were found in the trial, making it difficult to evaluate the treatment results;

2) The sponsor requests termination;

3) The relevant department or the ethics committee ordered the termination of the trial for some reason.

5. Radiation therapy scheme

5.1 Immobilization

Patients will be positioned supine and immobilized with a thermoplastic mask and a vacuum cushion over and underneath the head-neck region. The head position should be stable, restricting rotational movements while maintaining reproducibility and comfort.

5.2 Simulation Imaging

The CT scans range from the top of the head to the C2 level with a 2-mm slice thickness. A contrast-enhanced MRI will be acquired within two weeks of the CT scan, with a 2-3 mm slice thickness. CT and MR images will be imported into the Varian Eclipse treatment planning system for fusion.

5.3 Structure Definition

5.3.1 Definition of Target Volumes and Margins: The Eclipse treatment planning system (Varian Medical Systems, Palo Alto, CA) will be used for image fusion and structure contouring. The gross tumor volume (GTV) will be delineated based on the contrast-enhancement T1-weighted MRI registered to the simulation CT. For intact tumors, the clinical target volume is identical to GTV and thus not required. For post-operative cases, the surgical cavity and corridor are defined as CTV. The entire brain and meninges are defined as CTV_brain for whole brain irradiation. The planning target volume (PTV) is defined as GTV or CTV plus 1-3mm based on the location and size of the tumor.

5.3.2 Critical Structures: The optic pathway (optic nerves and chiasm), normal brain tissue, the brain stem, the lens, the hippocampi, and the cochleas should be contoured. An additional 2mm margin will

be added to the optic pathway and the brain stem to generate the Planning organ at Risk Volume (PRV).

5.4 Prescription

Target dose (Rx):

RT Technique	number of lesions	Lesion size (cm)	Dose	Notes
SRT	1-4	<2	40Gy/5fx	
	1-4	2-4	32Gy/4fx	
	1-4	>4	24Gy/3fx	
	5-10	NA	32Gy/4fx	The prescription depends on the sizes and cumulative volume of lesions.
	5-10	NA	24Gy/3fx	
WBRT	5-10	NA	30Gy/10fx	
	>10	NA	30Gy/10fx	

5.5 Treatment Technology

In this protocol, all SRT treatments will be delivered on a linear accelerator-based platform (Varian Edge) with 6MV FFF (flattening filter free) photon beams, and non-coplanar volumetric modulated arc therapy (VMAT) will be employed. Intensity-modulated radiation therapy (IMRT) or three-dimensional conformal radiation therapy (3D-CRT) will be used for WBRT treatments.

5.6 Treatment Planning Priorities and Instructions

General considerations:

- Multiple non-coplanar arcs should be used for fast dose fall-off
- VMAT technology was employed for plan quality and delivery efficiency
- Higher isodoses (hotspots) must be manipulated to occur within the target and not in adjacent normal tissue

Dose calculation:

Dose distribution will be specified as dose-to-water and calculated using Anisotropic Analytical Algorithm (AAA) with tissue heterogeneity correction. The calculation grid size should be ≤ 1.5mm.

Clinically acceptable treatment plans should meet the following requirements:

1) Dose coverage: At least 95% of each PTV receives prescription dose, and at least 99% of each PTV

receives at least 90% of prescription dose. The volume receiving less than 95% of prescription dose should be located in the periphery of PTV. At least 95% of each GTV receives at least 110% of prescription dose. Prescribed dose coverage should be assessed individually for each metastasis (i.e., PTV_1, PTV_2 …) instead of evaluating all metastases as a whole.

2) Dose Uniformity: SRT plans should prioritize target coverage and dose fall-off outside target volume. Hotspots within target volume are generally acceptable. When organ at risk (OAR) overlaps the target, efforts should be made to keep the hotpots away from the OAR.

3) Normal Structure Dose Constraints: Dose constraints listed in the AAPM TG-101 report will be complied with [20].

4) Hotspot: This protocol has no specific constraint for maximum dose. Max dose as high as 150% of prescription dose is usually allowed. However, the location of the max dose must be manipulated to occur within the PTV.

5) High-Dose Spillage: The cumulative volume of the normal tissue outside the PTV receiving a dose >105% of prescription dose should not exceed 15% of the PTV volume. The ratio of the prescription isodose volume to the PTV should be <1.2.

6) Intermediate Dose Spillage: The dose outside the PTV must fall off rapidly in all directions. The distance between the 50% isodose and the edge of the PTV should be around 5 mm to 8 mm. Efforts should be made to avoid dose-bridging between adjacent targets.

7) Low-Dose Spillage: Low-dose exposure to normal brain tissue should be minimized.

Planning Priorities:

8) The dose constraints of the OARs should be met.

9) The conformity of prescription dose volume and the compactness of volume receiving 50% of prescription dose should be optimized. Dose-bridging should be avoided when possible.

10) Keeping dose to normal brain (brain – PTV) low. This protocol will use D_{mean} to monitor the dose to the normal brain. Attempts should be made to keep D_{mean} less than 6Gy.

11) PTV coverage can be compromised when critical structures are adjacent to or overlap with targets. At least 80% of prescription dose isodose line should cover the PTV when critical OARs are abutting. A minimum of 70% should encompass the PTV when critical OARs overlap with targets.

12) In WBRT, at least 95% of the target volume should receive 30Gy in 10fx.

5.7 Plan verification

The treatment plan approved by the corresponding physician will be scheduled for a dry run and patient-specific quality assurance (PSQA). If the plan fails the verification, the physics team will investigate the cause, and the treatment will be deferred.

5.8 Treatment Delivery

For SRT treatment, the attending physician and physicist must be present to oversee the first treatment. Pre-treatment Cone Beam CT (CBCT) imaging will be used to verify the target position. Automatic registration will be performed based on bony surrogate. Errors greater than 1 mm (translational) or 1° (rotational) will be corrected with 6-DoF couch. The attending physician will check and approve the result of the correction before proceeding to treatment. When the initial errors are greater than 3 mm or 3°, a confirmatory CBCT is required to verify the accuracy of the corrected position.

6. Drug therapy

6.1 Dosage regimen

Considering that brain radiation therapy may exacerbate patients' brain edema symptoms and that pyrotinib may cause severe diarrhea, leading to interruptions in radiation therapy and affecting treatment efficacy, the study protocol stipulates a permissible medication window for pyrotinib and capecitabine from the first day of radiation therapy until the seventh day after completion of radiation therapy. For patients scheduled to undergo fractionated stereotactic radiotherapy (FSRT) with a Karnofsky Performance Score (KPS) greater than 90, concurrent medication is allowed starting from the first day of radiation therapy. For patients with FSRT and KPS less than 90, as well as those scheduled for whole-brain radiation therapy (WBRT), sequential medication should commence from the first day to the seventh day after completion of radiation therapy.

Pyrotinib maleate tablets: 400 mg once a day, orally after breakfast, for 21 consecutive days as a cycle. Storage conditions: sealed and stored in a dry place below 25°C. After unsealing, it should not be stored for more than one month. validity period is 12 months.

Capecitabine: 1000 mg/m2, twice a day, orally after meals (1 time in the morning and evening, about 12 hours apart, equivalent to a daily dose of 2000 mg/m2, taken once in the morning together with pyrotinib), continue to take the medicine on days 1-14, a cycle of 21 days.

The dosage of the above-mentioned drugs can be adjusted according to the protocol and the adverse reactions of the subjects. The subject continues to take the drug until the disease progression or the intolerable toxicity, the informed consent is withdrawn or the investigators determines that the drug must be terminated withdrawal of informed consent, or termination was necessary at investigator's discretion. Detailed records should be made in the original data: if the drug is missed, it is necessary to record in detail the time when the missed drug should have been used and the reason

for the missed use; If there is a lack of use due to various reasons such as adverse drug reactions, it should be recorded in the subject's diary, original medical records, and eCRF.

6.2 Dose reduction

When an adverse event occurs during the study period, the investigator should take active symptomatic treatment, and record the combined treatment and drug treatment in detail during the course of the disease and the EDC system.

6.2.1 Dose interruption and dose adjustment of capecitabine:

Adverse reactions caused by capecitabine can be treated by symptomatic treatment, dose interruption and dose adjustment. If the adverse events during the experiment cannot be controlled after treatment or observation (≤14 days), according to the type and duration of the AEs, the investigator can make the following decision: stopping capecitabine is the first choice; or stopping capecitabine and applying targeted drug monotherapy. The dose of capecitabine is suspended and lowered according to the drug instructions. Once the dose of capecitabine is reduced, the dose cannot be increased afterwards. The dosage adjustment plan can refer to the table below.

Table2 Dose adjustment plan for capecitabine

NCI CTCAE 4.03*	Current Treatment	Dose adjustment for the next cycle of treatment
Grade 1	maintain the original dose	maintain the original dose
Grade 2		
First occurrence	Suspend medication until it returns to Grade	100%
Second occurrence	Suspend medication until it returns to Grade	75%
Third occurrence	Suspend medication until it returns to Grade	50%
Forth occurrence	Permanently discontinued	--
Grade 3		
First occurrence	Suspend medication until it returns to Grade	75%
Second occurrence	Suspend medication until it returns to Grade	50%
Third occurrence	Permanently discontinued	--
Grade 4		
First occurrence	Permanently discontinued or if the investigator believes that continuing treatment is beneficial to the patient, and then the treatment will be continued once	50%

6.2.2 Suspension and dose reduction of pyrotinib

Depending on the type of treatment related adverse events, investigators choose to discontinue pyrrotinib for adverse events that remain uncontrollable after stopping capecitabine.

According to the judgment of the investigator, pyrotinib can also be discontinued if necessary. During the trial, multiple suspensions or multiple adjustments of the dose of pyrotinib are allowed. The dose of pyrotinib was adjusted according to the gradient of 400 mg, 320 mg and 240 mg.

After the adjustment of administration, if the subject still has clinical uncontrollable (that is, clinical treatment or observation ≤ still exists after 14 days, ≥ 2 times) grade ≥ III. diarrhea or grade I ~ II diarrhea with complications, or other adverse events ≥ grade II., it is up to the investigator to judge that the dose is allowed to be reduced again by a gradient when resuming medication after suspension, and the dose is reduced to as low as 240mg of pyrotinib.

During the course of treatment, the drug is allowed to be suspended multiple times, and the drug should be resumed after the adverse event returns to grade 0 to 1 and the complications disappear. The cumulative suspension time of pyrotinib during each cycle should not exceed 14 days to ensure intensity of the drug that the subject received.

If the suspension of pyrotinib exceeds the above criteria due to adverse event, the subject will be withdrawn from the group.

Table 3: Principles of Dosage Adjustment of Pyrotinib/Capecitabine Recommended Based on Adverse Events

AE	**CTCAE GRADE**	**DOSE ADJUSTMENT**	**the dose adjustment of pyrotinib after the suspension**
Diarrhea	grade 3， Or grade 1-2 with complications (≥ Grade 2 nausea or vomiting, fever, neutropenia, hematochezia or dehydration)	Suspended capecitabine first. If the symptoms cannot be relieved 3 days after the capecitabine is suspended, pyrotinib can be suspended until the recovery to grade ≤1	first adjustment: 400mg second adjustment：320mg
	grade 4	Permanently discontinued	——
hand-foot syndrome	grade 2	Suspended capecitabine first. If the symptoms cannot be relieved 14 days after the capecitabine is suspended, pyrotinib can be suspended	first adjustment：400mg second adjustment：320mg

		until the recovery to grade ≤1	
	grade 3	Suspended capecitabine first. If the symptoms cannot be relieved 14 days after the capecitabine is suspended, pyrotinib can be suspended until the recovery to grade ≤1, If not relieved another 14 daysPermanently discontinued	320mg
	Severe progressive bullous rash or mucosal lesions	Permanently discontinued	——
decreased Left Ventricular Ejection Fractions	LVEF is lower than the lower limit of normal, or LVEF of grade ≥2 (at least 10-19% decrease from baseline) and related symptoms	Suspend pyrotinib until the LVEF returns to the normal range, and the decrease is less than 10% from the baseline, and the related symptoms are restored	320mg
Hepatobiliary disorders	≥ Grade 3 elevated ALT or AST (>5×ULN) with total bilirubin ≤2×ULN	Suspended pyrotinib until it returns to grade ≤1	first adjustment：400mg second adjustment：320mg
	≥ Grade 2 elevated ALT or AST (>3×ULN) with total bilirubin ≤2×ULN	Permanently discontinued	——
Other adverse events	≥ Grade 2 non-hematological adverse events and ≥ Grade 3 hematological adverse events	Suspended pyrotinib or capecitabine until it returns to grade ≤1	first adjustment：400mg second adjustment：320mg

6.3. Concomitant therapy

6.3.1 Prohibited Drugs during the study

During the treatment period, other anti-tumor drugs and adjuvant drugs related to tumor treatment other than the study drugs specified in this protocol should be stopped, including anti-tumor traditional Chinese medicines and immune preparations.

6.3.2 Drugs to be used with caution during the study

If the subjects have adverse reactions, they should be closely observed, and if necessary, actively treat the symptoms, and record and explain the drugs used on the eCRF form.

Subjects with adverse reactions should be closely observed. The symptoms associated with adverse effects should be treated actively, with medications used documented and described on the eCRF form.

The following drugs should be used with caution during the research:

1) Drugs and foods that interfere with Cytochrome P450 proteins, including：

a)CYP3A4 inducers (Dexamethasone, phenytoin sodium, carbamazepine, rifampicin, rifabutin, rifapentin) and inhibitors (ketoconazole, itraconazole, erythromycin, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole, citrus paradisi macf., etc.);

b)CYP3A4'substrates (Simvastatin, pimozide)

c)Other drugs metabolized by CYP3A4 (benzodiazepines, dihydropyridine, calcium ion antagonist HMG-COA reductase inhibitor);

d)CYP2C9" substrates (Diclofenac, phenytoin, piroxicam, S-warfarin and tolbutamide) and CYP2C19" substrates (Diazepam, Imipramine, Lansoprazole and S-Mephenytoin);

2) Drugs that prolong the QT interval： Including antibiotics, antiarrhythmic, antipsychotic, antifungal, antimalarial and antidepressant drugs (such as clarithromycin, quinidine, risperidone, fluconazole, mefloquine, amitriptyline, azithromycin, sotalol, fluphenazine, ketoconazole, chloroquine, imipramine, erythromycin, amiodarone, droperidol, clomipramine, roxithromycin, disopyramide, haloperidol, Dosulepin, metronidazole, procainamide, thioridazine, doxepin, moxifloxacin, pimozide, olanzapine and clozapine).

3) Coumarin anticoagulants: When phenytoin and coumarin derivative anticoagulants are used in combination with capecitabine, it may be necessary to reduce anticoagulants. For more information, see capecitabine instructions [drug interactions].

6.3.3 Drugs and treatments that can be used in combination during the study

Patients can receive the best supportive care, and clinical comorbidities and various AEs should be actively treated. Patients with bone metastases who have been started on bisphosphonates prior to enrollment are allowed to continue during the trial; During the study, the investigators used bisphosphonates as appropriate according to the patient's condition. All drugs used in combination should be recorded in the eCRF in strict accordance with the provisions of GCP. Concomitant

medications/treatments should be recorded from 4 weeks prior to study treatment until the end of safe follow-up.

7. Study procedures

Before starting the study, patients must read and sign the current ethics committee (EC) approved informed consent form.

7.1 Screening

After signing the informed consent form, the subjects entered the screening period. Unless otherwise indicated, the following screening steps must be completed within 28 days before starting study drug treatment.

[Demographics] Initials, gender, race, marital status, date of birth, height, weight;

[Medical history] Past medical history and treatment history (clinical/pathological diagnosis, diagnosis time, clinical/pathological stage, HER2/ER/PR expression, whether to surgery, neoadjuvant therapy, adjuvant therapy, radiotherapy, and when to progress recurring/metastatic breast Cancer, diagnosis progress basis, name, usage and dosage of each line of advanced systemic treatment, start and stop time of medication;

[KPS score] Refer to Appendix for the scoring criteria;

[Vital Signs] Body temperature, blood pressure, respiratory rate, pulse;

[Physical examination] General conditions, skin and mucous membranes, lymph nodes, head and neck, chest, abdomen, musculoskeletal, nerve reflexes, respiratory system, cardiovascular system, genitourinary system, mental status, etc.;

[Blood routine] White blood cell count (WBC), neutrophil count (ANC), red blood cell count (RBC), hemoglobin (Hb), platelet count (PLT);

[Blood biochemical test] Including alanine aminotransferase ALT, aspartate aminotransferase AST, glutamyl transpeptidase GGT, alkaline phosphatase AKP, total protein TP, albumin ALB, total bilirubin TBIL , Direct bilirubin DBIL, globulin GLU, indirect bilirubin IBIL, urea nitrogen BUN, blood electrolytes (K +, Na +, Cl-, Ca2 +, Mg2 +). If necessary, the investigator can conduct other tests;

[Urine routine] Urine protein, urine glucose, urine occult blood;

[Coagulation function] International standardized ratio INR, activated partial thromboplastin time APTT, prothrombin extended time PT, fibrinogen FIB, thrombin time TT;

[Pregnancy test] is only applicable to blood or urine tests for women of childbearing age;

[12-lead ECG] Must include QT, QTc and P-R interval. If there is an abnormality, the investigator can judge and perform other necessary inspections;

[Tumor imaging examination] Intracranial lesions: MRI is necessary. Extracranial lesions: CT or MRI of the chest and abdomen, neck and pelvic examinations, bone scans, etc. can be added if necessary. Investigators can add scan sites to tumor assessment during or after the baseline based on clinical needs. The report can be used within 14 days before registration.

[Combination medication/treatment] Participate in the combination medication part;

[Neurocognitive function evaluation] According to the patients' general situation and willingness, the MMSE evaluation results are collected for the patients who are physically permitted to fill in the MMSE questionnaire.

[Adverse events] From the day the subjects signed the informed consent form, it was recorded until 30 days after the last medication.

Subjects must meet all inclusion criteria to be included in the study

7.2 Trial period

After enrollment, the subjects received treatment according to the protocol. The treatment period visit will occur on the last day of each visit week (± 3) or the last day of the visit month (± 7), and the reason for the out of visit window was recorded in the eCRF. Investigators can add inspection items or increase the frequency of video visits based on the subject's clinical conditions, and the inspection results will be recorded in the eCRF "unscheduled visits".

[Vital signs] Heart rate, breathing rate, body temperature, blood pressure.

[Physical examination] General conditions, skin and mucous membranes, lymph nodes, head and neck, chest, abdomen, musculoskeletal, neural reflexes, respiratory system, cardiovascular system, genitourinary system, mental status, etc.;

[KPS score] Refer to the attachment for the scoring criteria;

[Coagulation test] Including the international standardized ratio INR, activated partial thromboplastin time APTT, prothrombin extension time PT, fibrinogen FIB, thrombin time TT;

[Blood routine] White blood cell count (WBC), neutrophil count (ANC), red blood cell count (RBC), hemoglobin (Hb), platelet count (PLT);

Blood biochemistry Including alanine aminotransferase ALT, aspartate aminotransferase AST, glutamyl transpeptidase GGT, alkaline phosphatase AKP, total protein TP, albumin ALB, total bilirubin TBIL, Direct bilirubin DBIL, globulin GLU, indirect bilirubin IBIL, urea nitrogen BUN, blood electrolytes (K +, Na +, Cl-, Ca2 +, Mg2 +). If necessary, the investigator can conduct other tests;

[Urine routine] Once every two cycles, urine protein, urine glucose, urine occult blood;

[12-lead ECG] Must include QT, QTc and P-R interval. If there is an abnormality, the investigator

can judge and perform other necessary inspections;

[Tumor imaging examination] Examinations were performed every two months for the first year and every three months thereafter, or as deemed necessary by the investigator. CT or MRI of the chest and abdomen, neck and pelvic examinations, bone scans, etc. can be added if necessary.

[Combination medication/treatment] Participate in the combination medication part;

[Neurocognitive function evaluation] According to the patients' general situation and willingness, the MMSE evaluation results are collected for the patients who are physically permitted to fill in the MMSE questionnaire.

[Adverse events] From the day the subjects signed the informed consent form, it was recorded until 30 days after the last medication.

7.3 End-of-treatment visit

At the end of study treatment or withdrawal from the study, if the patient has not been tested within 14 days prior to the end of the study, the following tests should be performed:

[Vital Signs] [Physical Examination] [KPS Score] [Coagulation Function] [Blood Routine] [Comprehensive metabolic panel] [Urine Routine] [12-lead ECG] [Combination medication/treatment] [Adverse events] [Imaging examination] [Neurocognitive function evaluation]

If imaging is not performed within 4 weeks prior to the end of treatment, imaging is required at the end of study treatment or at the end of study study.

7.4 FOLLOW-UP

For any reason, after discontinuing treatment, the subject will enter the follow-up period. Before completing the survival follow-up, the following follow-ups are required (enrolled subjects without study treatment do not need to be followed up).

Safety follow-up: For adverse events that have not recovered after stopping study treatment, follow-up and final evaluation should be carried out. All subjects received safety follow-up until 30 days after study treatment. A detailed record of the adverse events, combination medication/treatment and unplanned inspections during the period are needed.

Efficacy follow-up: For subjects who have discontinued drug treatment due to death of non-disease progression (such as intolerance, other conditions), tumor imaging will be performed every 3 months starting from the last tumor imaging evaluation until the subject' 's disease progresses, or start to use other anti-tumor drugs or death (whichever comes first); Detailed record of each follow-up during the period, tumor imaging evaluation results and other anti-tumor treatment information are needed.

Survival follow-up (OS data collection): All non-dead subjects who have completed safety

follow-up and efficacy follow-up (whichever is completed later) should receive survival follow-up. Starting from the date of completion of safety follow-up and efficacy follow-up (whichever is later), follow-up at clinics or telephone interviews with subjects, their family members or local doctors at least every 3 months, collecting survival rate (date of death and cause of death), and information from the end of the study treatment to death, and continue until the follow-up or termination of the trial (whichever comes first). It is necessary to record each survival follow-up in detail and record it into the corresponding eCRF form.

8. Efficacy Evaluation

8.1 Imaging evaluation

Intracranial lesions were evaluated using enhanced-contrast MRI, and extracranial lesions were evaluated using enhanced CT or enhanced MRI. The screening period should include at least chest and abdomen. If necessary, scan the neck, pelvis, bones, etc. According to clinical needs, investigators can scan additional body parts at baseline or subsequent tumor assessments.

Follow-up imaging evaluation should be conducted under the same conditions as baseline (layer thickness of scan, use of contrast agent, etc.). Imaging tests are performed every two months for first year and every three months thereafter. The researchers could also increase the visits according to the specific conditions

9 Safety Evaluation

During the trial period, the safety of the treatment methods will be evaluated based on adverse event records, laboratory examinations, vital signs, physical examination, KPS score, cardiac ultrasound, and electrocardiogram records. During the trial, the symptoms and signs of the subjects after receiving the drug should be closely observed. Adverse events/reactions should be addressed in a timely and effective manner to ensure the safety and interests of the subjects.

9.1 SRT therapy-related craniocerebral radiation necrosis (RN)

MRI will be used to evaluate RN: local enhancement, new nodular enhancing lesions with a soap bubble or Swiss cheese pattern, and enhancement with a shell-edge appearance on MRI images will be evaluated. At least two consecutive T1WI contrast-enhanced MRI sessions should show new enhancement in the area that has previously received high-dose radiotherapy. Since the imaging features of RN and tumor recurrence have a considerable degree of overlap, differential diagnosis will be performed based on the ratio of the largest mass to the largest background absorption rate

(SUVLmax/Bkgrmax) of FET PET-CT and the cerebral blood volume ratio (CBV) during the study.

9.2 Mini-mental State Examination (MMSE)

The scale includes the following seven aspects, namely, time orientation, location orientation, immediate memory, attention and calculation, delayed memory, language, and visual space, with a total of 30 questions, where each correct answer is scored 1 point, while an incorrect or unknown answer is scored 0 points. The total score range of the scale is 0-30 points.

9.3 Physical examination and vital signs

The physical examination is conducted by the study physician, includes: general conditions, skin and mucous membranes, lymph nodes, head and neck, chest, abdomen, musculoskeletal, nerve reflexes, respiratory system, cardiovascular system, genitourinary system, mental status, etc. Vital Signs includes: body temperature, blood pressure, respiratory rate, pulse;

9.4 Laboratory tests

Laboratory tests will be performed according to the time points specified in the "Clinical Trial Flow Chart". For subject safety reasons, unscheduled clinical laboratory tests may be performed at any time.

9.5 Grades of AE

Refer to the grading standard for adverse drug events in NCI-CTC AE 4.03version. Adverse events not listed in NCI-CTC AE 4.03 version can refer to the following standards:

Grade I: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade II: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL), which refer to preparing meals, shopping, using the telephone, managing money, etc.

Grade III: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL, which refer to bathing, dressing and undressing, feeding self, using the toilet, taking medication, and not bedridden.

Grade IV: Life-threatening consequences; urgent intervention indicated.

Grade V: Death related to AE.

10. Data analysis and statistical methods

10.1 Sample size calculation

The primary endpoint of this single-arm, historically controlled study is CNS-PFS rate. Combined with relevant studies and the investigator's clinical experience, the CNS PFS rate of HER2-positive breast cancer patients with brain metastases was 48% at one year after radiotherapy[11, 12]. The hypothetical PFS rate will increase to 70% after one year of combination therapy with radiotherapy, pyrotinib and capecitabine. A one-sided test will be used, α=0.025, the power will be 80%, and the sample size will be 39 cases.

10.2 Analysis Set

The analysis population includes the full analysis set (FAS), the per-protocol set (PPS), and the safety set (SS).

Full Analysis Set, FAS: Following the intent-to-treat (ITT) principle, all cases that have been enrolled and received treatment are analyzed for efficacy.

Per-Protocol Set, PPS: All patients who meet the trial protocol, have good compliance, have taken at least one cycle of study drugs (excluding patients who have experienced disease progression with substantial evidence after enrollment), have not received prohibited drugs during the trial period, and completed the CRF requirements. No filling is done for missing data. Efficacy results were statistically analyzed using both FAS and PPS.

Safety Analysis Set, SAS: All the enrolled cases receive treatment and all patients with safety records after radiotherapy or administration. This data set is used for safety analysis.

10.3 Treatment of missing values

Efficacy indicators: All main indicators missing due to early withdrawal of patients are recorded as "unassessable" in the analysis. When the calculation includes time variables (such as PFS), the censoring time is obtained by checking the subjects who have undergone imaging evaluation after discontinuity. No missing values are estimated for baseline and safety data.

For extreme values of laboratory data caused by improper sample processing, the corresponding unplanned visit data will be used in the analysis, or it will be considered missing data and not included in the analysis.

10.4 General principles of statistical analysis

Unless otherwise specified, the data in this study will be summarized as descriptive statistics in accordance with the following general principles.

Measurement data are summarized by means, standard deviation, median, maximum, and minimum; count data are summarized by frequency and percentage; time-to-event data are summarized by Kaplan-Meier method to estimate survival rate and draw survival curve; blood drug concentration data are summarized using mean, standard deviation, coefficient of variation, median, maximum, and minimum.

10.4.1 Patients distribution and dropouts

The number of cases (percentage) is used to describe the enrollment and completion of subjects. The distribution of cases in each data set. List the medications of dropouts and excluded patients and the reasons for early withdrawal. The distribution of cases in each analysis set.

10.4.2 Demographics and Baseline Characteristics

Compile statistics descriptively for demographic data and baseline characteristics. Measurement data needs to calculate the number of cases, mean, standard deviation, median, minimum and maximum; Calculate the frequency and composition ratio of count data and level.

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Appendix

Appendix 1 Karnofsky Performance Status

Percent	Performance Status
100	Normal no complaints; no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Normal activity with effort; some signs or symptoms of disease
70	Cares for self; unable to carry on normal activity or to do active work
60	Requires occasional assistance, but is able to care for most of personal needs
50	Requires considerable assistance and frequent medical care
40	Requires considerable assistance and frequent medical care
30	Severely disabled; hospital admission is indicated although death not imminent
20	Very sick; hospital admission necessary; active supportive treatment necessary
10	Moribund; fatal processes progressing rapidly
0	Deceased

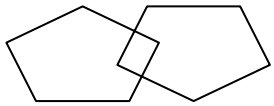
Appendix 2 MMSE

Mini-Mental State Examination (MMSE)

Patient's Name:_____ Date: _____

Instructions: Ask the questions in the order listed. Score one point for each correctresponse within each question or activity.

Maximum Score	Patient's Score	Questions
5		"What is the year? Season? Date? Day of the week? Month?"
5		"Where are we now: State? County? Town/city? Hospital? Floor?"
3		The examiner names three unrelated objects clearly and slowly, then asks the patient to name all three of them. The patient's response is used for scoring. The examiner repeats them until patient learns all of them, if possible. Number of trials: _____
5		"I would like you to count backward from 100 by sevens." (93, 86, 79, 72, 65, …) Stop after five answers. Alternative: "Spell WORLD backwards." (D-L-R-O-W)
3		"Earlier I told you the names of three things. Can you tell me what those were?"
2		Show the patient two simple objects, such as a wristwatch and a pencil, and ask the patient to name them.
1		"Repeat the phrase: 'No ifs, ands, or buts.'"

3		“Take the paper in your right hand, fold it in half, and put it on the floor.” (The examiner gives the patient a piece of blank paper.)
1		“Please read this and do what it says.” (Written instruction is “Close your eyes.”)
1		“Make up and write a sentence about anything.” (This sentence must contain a noun and a verb.)
1		“Please copy this picture.” (The examiner gives the patient a blank piece of paper and asks him/her to draw the symbol below. All 10 angles must be present and two must intersect.) 
30		TOTAL

(Adapted from Rovner & Folstein, 1987)

Instructions for administration and scoring of the MMSE

Orientation (10 points):

- Ask for the date. Then specifically ask for parts omitted (e.g., "Can you also tell me what season it is?"). One point for each correct answer.
- Ask in turn, "Can you tell me the name of this hospital (town, county, etc.)?" One point for each correct answer.

Registration (3 points):

- Say the names of three unrelated objects clearly and slowly, allowing approximately one second for each. After you have said all three, ask the patient to repeat them. The number of objects the patient names correctly upon the first repetition determines the score (0-3). If the patient does not repeat all three objects the first time, continue saying the names until the patient is able to repeat all three items, up to six trials. Record the number of trials it takes for the patient to learn the words. If the patient does not eventually learn all three, recall cannot be meaningfully tested.
- After completing this task, tell the patient, "Try to remember the words, as I will ask for

them in a little while."

Attention and Calculation (5 points):

- Ask the patient to begin with 100 and count backward by sevens. Stop after five subtractions (93, 86, 79, 72, 65). Score the total number of correct answers.
- If the patient cannot or will not perform the subtraction task, ask the patient to spell the word "world" backwards. The score is the number of letters in correct order (e.g., dlrow=5, dlorw=3).

Recall (3 points):

- Ask the patient if he or she can recall the three words you previously asked him or her to remember. Score the total number of correct answers (0-3).

Language and Praxis (9 points):

- Naming: Show the patient a wrist watch and ask the patient what it is. Repeat with a pencil. Score one point for each correct naming (0-2).
- Repetition: Ask the patient to repeat the sentence after you ("No ifs, ands, or buts."). Allow only one trial. Score 0 or 1.
- 3-Stage Command: Give the patient a piece of blank paper and say, "Take this paper in your right hand, fold it in half, and put it on the floor." Score one point for each part of the command correctly executed.
- Reading: On a blank piece of paper print the sentence, "Close your eyes," in letters large enough for the patient to see clearly. Ask the patient to read the sentence and do what it says. Score one point only if the patient actually closes his or her eyes. This is not a test of memory, so you may prompt the patient to "do what it says" after the patient reads the sentence.
- Writing: Give the patient a blank piece of paper and ask him or her to write a sentence for you. Do not dictate a sentence; it should be written spontaneously. The sentence must contain a subject and a verb and make sense. Correct grammar and punctuation are not necessary.
- Copying: Show the patient the picture of two intersecting pentagons and ask the patient to copy the figure exactly as it is. All ten angles must be present and two must intersect to score

one point. Ignore tremor and rotation.

Method	Score	Interpretation
Single Cutoff	<24	Abnormal
Range	<21	Increased odds of dementia
	>25	Decreased odds of dementia
Education	21	Abnormal for 8th grade education
	<23	Abnormal for high school education
	<24	Abnormal for college education
Severity	24-30	No cognitive impairment
	18-23	Mild cognitive impairment
	0-17	Severe cognitive impairment

Sources:

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Appendix 3 Response Assessment in Neuro-Oncology-Brain Metastases (RANO-BM) Criteria: Modified Excerpt from Original Publication

Definitions

Definition of Measurable Disease: Measurable disease is defined as a contrast enhancing lesion that can be accurately measured in at least one dimension with a minimum size of 10 mm, visible on two or more axial slices that are preferably≤ 5 mm apart with 0-mm skip (and ideally≤ 1.5 mm apart with 0-mm skip). In addition, although the longest diameter in the plane of measurement is to be recorded, the diameter perpendicular to the longest diameter in the plane of measurement should be at least 5 mm for the lesion to be considered measurable. In the event the MRI is performed with thicker slices, the size of the measurable lesion at baseline should be at least two times the slice thickness. If there are interslice gaps, this also needs to be considered in determining the minimum size of measurable lesions at baseline. Measurement of tumor around a cyst or surgical cavity represents a particularly difficult challenge. In general, such lesions should be considered non-measurable unless there is a nodular component measuring ≥10 mm in longest diameter and≥ 5 mm in the perpendicular plane. The cystic or surgical cavity should not be measured in determining response (Figure 1 in the original publication).

Definition of Non-measurable Disease: All other lesions, including lesions with longest dimension ＜10 mm, lesions with borders that cannot be reproducibly measured, dural metastases, bony skull metastases, cystic-only lesions, and leptomeningeal disease.

Specifications of Methods of Measurement

Method of Assessment: 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. It is important to use imaging techniques that are consistent across all imaging timepoints in order to ensure that the assessment of interval appearance or disappearance of lesions or of change in size is not affected by scan parameters such as slice thickness. Use of thin section imaging (for example, Appendix A of the original publication) is particularly important when evaluating lesions< 10 mm in LD and/or small changes in lesion size.

Imaging Modality: Gadolinium-enhanced MRI is the best currently available, sensitive, and reproducible method to measure CNS lesions selected for response assessment. Suggested brain MRI specifications are detailed in Appendix A of the original publication.

A sum of the diameters for all target lesions will be calculated and reported as the baseline sum of longest diameters (sum LD). All other CNS lesions should be identified

as non-target lesions and should also be recorded at baseline. Measurements are not

Definition of Best Overall CNS Response

Best overall CNS response represents a composite of radiographic CNS target and non-target response (see definitions above), corticosteroid use, and clinical status. In non-randomized trials where CNS response is the primary endpoint, confirmation of PR or CR at least 4 weeks later is required to deem either one the best overall response.

At each protocol-specified timepoint, a response assessment should occur and CNS assessments should be coincident with extra-CNS assessment. Table 1 shows the additional corticosteroid and clinical status requirements to deem a PR or CR.

Evaluation of Target Lesions

Complete response (CR): Disappearance of all CNS target lesions sustained for at least 4 weeks; no new lesions; no corticosteroids; stable or improved clinically.

Partial response (PR): At least a 30% decrease in the sum LD of CNS target lesions, taking as reference the baseline sum LD sustained for at least 4 weeks; no new lesions; stable to decreased corticosteroid dose; stable or improved clinically.

Progressive disease (PD): At least a 20% increase in the sum LD of CNS 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%, at least one lesion must increase by an absolute value of ≥5 mm to be 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 LD while on study.

Evaluation of Non-Target Lesions

Non-target lesions should be assessed qualitatively at each of the timepoints specified in the protocol.

CR: Requires all of the following: disappearance of all enhancing CNS non-target lesions, no new CNS lesions.

Non-CR/Non-PD: Persistence of one or more non-target CNS lesion(s).

PD: Any of the following: unequivocal progression of existing enhancing non-target CNS lesions, new lesion(s) (except while on immunotherapy-based treatment), or unequivocal progression of existing tumor-related non-enhancing (T2/FLAIR) CNS lesions. In the case of immunotherapy-based treatment, new lesions alone may not constitute progressive disease (see “Guidance in the case of new lesion(s) while on immunotherapy” below).

Special Notes on the Assessment of Target and Non-Target CNS Lesions:

a) Target lesions that become too small to measure: While on study, all CNS target lesions should have their actual measurement recorded, even when very small (e.g., 2 mm). If the lesion disappears, the value should be recorded as 0 mm. However, if the lesion is sufficiently small (but still present) that the radiologist does not feel comfortable assigning an exact measure, a default value of 5 mm should be recorded on the case report form.

b) Lesions that coalesce on treatment: As lesions coalesce, a plane between them may be maintained that would aid in obtaining maximum LD of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximum LD for the 'coalesced' lesion.

c) Definition of new lesion(s): The finding of a new CNS lesion should be unequivocal and not due to technique or slice variation. A new lesion is one that was not present on prior scans. If the MRI is obtained with ≤ 1.5 mm slice thickness, then the new lesion should also be visible in axial, coronal, and sagittal reconstructions of ≤ 1.5 mm projections. If a new lesion is equivocal, for example because of its small size (i.e., ≤ 5 mm), continued therapy may be considered, and follow up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan showing the new lesion. In the case of immunotherapy, new lesions alone may not constitute progressive disease (see "Guidance in the case of new lesion(s) while on immunotherapy" below).

d) Definition of Unequivocal Progression of Non-Target Lesion(s): When the patient also has measurable disease, to achieve 'unequivocal progression' on the basis of non-target disease alone, there must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. When the patient has only non-measurable disease, there must be an overall level of substantial worsening to merit discontinuation of therapy.

e) Guidance in the Case of Uncertain Attribution of Radiographic Findings and/or Equivocal Cases: The RANO-BM group acknowledges that in the case of patients followed after SRS or during immunotherapy-based approaches, there may be radiographic evidence of enlargement of target and non-target lesions which may not necessarily represent tumor progression. If there is evidence of radiographic progression but there is clinical evidence supporting the possibility that the radiological changes are due to treatment effect (and not to progression of cancer), additional evidence is required to distinguish true progression versus treatment effect as standard MRI alone is not sufficient. The methods used to distinguish between the two entities should be specified prospectively in the clinical protocol. Patients may be continued on protocol therapy pending further investigation with one or more of the following options: (1) Repeat the scan at the next protocol scheduled evaluation or sooner,

and generally within ~6 weeks. An investigator may choose a shorter time interval in the case of progressive symptoms or other clinically concerning findings. If there is continued increase in enhancement concerning for tumor growth, then this may be consistent with radiographic progression and the patient should be taken off study (Figure 2 in the original publication). If the lesion is stable or decreased in size, then this may be consistent

with treatment effect and the patient may remain on study (Figure 3 in the original publication). For patients with equivocal results even on the next restaging scan, the scan may be repeated again at a subsequent protocol scheduled evaluation or sooner although surgery and/or use of an advanced imaging modality (in the case of SRS) are strongly encouraged. (2) Surgical pathology obtained via biopsy or resection. (3) For SRS treated lesions, an advanced imaging modality such as perfusion MR imaging, MR spectroscopy, or 18FLT or 18FDG positron emission tomography (PET) may be used as additional evidence of tumor progression or treatment effect/radionecrosis. Upon review of the literature and extensive discussions by the Working Group, we were not able to conclude that any one modality or approach can be recommended across all patients to distinguish between radiation necrosis versus true progression, as the literature is not sufficiently robust, and recommend clinical judgment and involvement of a multidisciplinary team. We recognize this is less than satisfactory and agree that developing more sensitive and specific methods for distinguishing between treatment effect and tumor progression are needed. We should also note that these advanced imaging modalities have not been extensively studied with regards to immunotherapy-based approaches and therefore are cannot be recommended for distinguishing tumor progression versus immune-related changes at this time. Regardless of the additional testing obtained, if subsequent testing demonstrates that progression has occurred, the date of progression should be recorded as the date of the scan at which this issue was first raised. Patients may also have an equivocal finding on a scan (for example, a small lesion that is not clearly new). It is permissible to continue treatment until the next protocol scheduled evaluation. If the subsequent evaluation demonstrates that progression has indeed occurred, the date of progression should be recorded as the date of the initial scan where progression was suspected.

f) Guidance in the Case of New Lesion(s) while on Immunotherapy: For patients receiving immunotherapy-based approaches, an initial increase in the number and size of metastases may be followed by radiographic stabilization or regression. This may be related to the mechanism of action for immunotherapy, including immune infiltrates as well as the time required for development of an effective immune response. Thus, progressive disease will be defined not solely by the appearance of new lesions but by at least a 20% increase in the sum of the LD of CNS target lesions and the new lesion(s); or unequivocal progression of existing enhancing non-target CNS lesions; or unequivocal progression of existing non-enhancing (T2/FLAIR) CNS lesions; or clinical decline related to tumor.

If immune-related radiographic changes are suspected, we advise not changing treatment until a short interval scan is obtained. If the subsequent evaluation confirms that progression has indeed occurred, the date of progression should be recorded as the date of the initial scan where progression was suspected.

Notes Regarding Corticosteroid Use and Clinical Deterioration:

a) An increase in corticosteroid dose alone, in the absence of clinical deterioration related to tumor, will not be used as a sole determinant of progression. Patients with stable imaging studies whose corticosteroid dose was increased for reasons other than clinical deterioration related to tumor do not qualify for stable disease or progression. They should be observed closely. If their corticosteroid dose can be reduced back to baseline, they will be considered as having stable disease; if further clinical deterioration related to tumor becomes apparent, they will be considered to have progression. b) The definition of clinical deterioration is left to the discretion of the treating physician, but it is recommended that a decline in the KPS from 100 or 90 to 70 or less, a decline in KPS of at least 20 points from 80 or less, or a decline in KPS from any

baseline to 50 or less, for at least 7 days, be considered neurologic deterioration unless attributable to comorbid events, treatment-related toxicity, or changes in corticosteroid dose.

Table 1

Summary of the Proposed RANO Response Criteria for CNS Metastases

Criterion	**CR**	**PR**	**SD**	**PD**
Target lesions	None	□ 30% decrease in sum LD relative to baseline	□ 30% decrease relative to baseline but□ 20% increase in sum LD relative to nadir	□ 20% increase in sum LD relative to nadir*
Non-target lesions	None	Stable or improved	Stable or improved	Unequivocal PD*
New lesion(s)**	None	None	None	Present*
Corticosteroids	None	Stable or decreased	Stable or decreased	NA□

Clinical status	Stable or improved	Stable or improved	Stable or improved	Worse*
Requirement for response	All	All	All	Any

Abbreviations: CNS□ central nervous system; CR□ complete response; LD□ longest dimension; NA□ not applicable; PD□ progressive disease; PR□ partial response; RANO□ Response Assessment in Neuro-Oncology; SD□ stable disease. *Progression occurs when this criterion is met. **New lesion □ new lesion not present on prior scans and visible in at least 2 projections. If a new lesion is equivocal, for example because of its small size, continued therapy may be considered, and follow up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan showing the new lesion. For immunotherapy□based approaches, new lesions alone to do not define progression (See "Guidance in the Case of New Lesion(s) while on Immunotherapy"). □ Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration

Appendix4 Response evaluation criteria in solid tumours

（New Response Evaluation Criteria in Solid Tumors：Revised RECIST Version 1.1）。

Note: The appendix is internal translation materials for reference only. In actual operation, the English version shall prevail.

1. Background

Omitted

2. Purpose of this guideline

Omitted

1. Measurability of tumour at baseline

1.1. Definitions

At baseline, tumour lesions/lymph nodes will be categorized measurable or non-measurable as follows:

1.1.1. Measurable

Tumour lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
- 20 mm by chest X-ray.
- Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥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.

1.1.2. Non-measurable

All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal dis- ease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

1.1.3. Special considerations regarding lesion measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic lesions:

• 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.

Lesions with prior local treatment:

• Tumour lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

1.2. Specifications by methods of measurements

1.2.1. Measurement of lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

1.2.2. Method of assessment

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

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥10 mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions,

documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. As is described in Appendix II, when 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 (e.g. for body scans).

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 ad- vised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, laparoscopy: The utilization of these techniques for objective tumour evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Tumour markers: Tumour markers alone cannot be used to assess objective tumour response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in complete response. Because tumour markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer), have been published. In addition, the Gynecologic Cancer Intergroup has developed CA125 progression criteria which are to be integrated with objective tumour assessment for use in first-line trials in ovarian cancer.

Cytology, histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumour types such as germ cell tumours, where known residual benign tumours can remain). When effusions are known to be a potential adverse

effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumour has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

2. Tumour response evaluation

2.1. Assessment of overall tumour burden and measurable disease

To assess objective response or future progression, it is necessary to estimate the overall tumour burden at baseline and use this as a comparator for subsequent measurements. Only patients with measurable disease at baseline should be included in protocols where objective tumour response is the primary endpoint. Measurable disease is defined by the presence of at least one measurable lesion. In studies where the primary endpoint is tumour progression (either time to progression or proportion with progression at a fixed date), the protocol must specify if entry is restricted to those with measurable disease or whether patients having non-measurable disease only are also eligible.

2.2. Baseline documentation of 'target' and 'non-target' lesions

When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where patients have only one or two organ sites involved a maximum of two and four lesions respectively will be re- corded).

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.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumour. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumour. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, saggital or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those

with short axis ≥10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed.

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 as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterise any objective tumour regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression'. In addition, it is possible to record multiple non- target lesions involving the same organ as a single item on the case record form (e.g. 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

2.3. Response criteria

2.3.1. Evaluation of target lesion

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 diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of 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.

2.3.2. Special notes on the assessment of target lesions

Lymph nodes. Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of <10 mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis <10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that become 'too small to measure'. While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs, it is important that a value be recorded on the case report form. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

Lesions that split or coalesce on treatment. When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

2.3.3. Evaluation of non-target lesions

This section provides the definitions of the criteria used to determine the tumour response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumour 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 tumour marker level above the normal limits.

Progressive Disease (PD): Unequivocal progression of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

2.3.4. Special notes on assessment of progression of non- target disease

The concept of progression of non-target disease requires additional explanation as follows: When the patient also has measurable disease. In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumour burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to quality for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the patient has only non-measurable disease. This circumstance arises in some phase III trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e. an increase in tumour burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread, or may be described in protocols as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so, therefore the increase must be substantial.

2.3.5. New lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumour (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans con- firm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

No FDG-PET at baseline and a positive FDG-PET at follow-up:

If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.

If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan).

If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

2.4. Evaluation of best overall response

The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. On occasion a response may not be documented until after the end of therapy so protocols should be clear if post-treatment assessments are to be considered in determination of best overall response. Protocols must specify how any new therapy introduced before progression will affect best response designation. The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement. Specifically, in non-randomised trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the 'best overall response'.

2.4.1. Time point response

It is assumed that at each protocol specified time point, a response assessment occurs. Table 1 provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

Table 1 Time point response: patients with target (+/– non-target) disease.

Target lesion	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR=complete response, PR=partial response, SD=stable disease, PD=progression disease, NE=inevaluable

When patients have non-measurable (therefore non-target) disease only, Table 2 is to be used.

Table 2 Time point response: patients with non-target disease only.

Non-target lesion	New lesion	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD

Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	No	PD

a 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

2.4.2. Missing assessments and inevaluable designation

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements is made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and at follow-up only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

2.4.3. Best overall response: all time points

The best overall response is determined once all the data for the patient is known.

Best response determination in trials where confirmation of complete or partial response is not required: Best response in these trials is defined as the best response across all time points (for example, a patient who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the patient's best response depends on the subsequent assessments. For example, a patient who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same patient lost to follow-up after the first SD assessment would be considered inevaluable.

Best response determination in trials where confirmation of complete or partial response is required: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol (generally 4 weeks later). In this circumstance, the best overall response can be interpreted as in Table 3.

Table 3 Best overall response when confirmation of CR and PR required

Overall response First time point	Overall response Subsequent time point	Best overall response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE

CR=complete response, PR=partial response, SD=stable disease, PD=progression disease, NE=inevaluable

a: If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time

point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

2.4.4. Special notes on response assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of 'zero' on the case report form (CRF).

In trials where confirmation of response is required, repeated 'NE' time point assessments may complicate best response determination. The analysis plan for the trial must address how missing data/assessments will be addressed in determination of response and progression. For example, in most trials it is reasonable to consider a patient with time point responses of PR-NE-PR as a confirmed response.

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 'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in Tables 1–3.

Conditions that define 'early progression, early death and inevaluability' are study specific and should be clearly de- scribed in each protocol (depending on treatment duration, treatment periodicity).

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of complete response. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by dis- ease specific medical literature for the indication. However, it must be acknowledged that both

approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

For equivocal findings of progression (e.g. very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

2.5. Frequency of tumour re-evaluation

Frequency of tumour re-evaluation while on treatment should be protocol specific and adapted to the type and schedule of treatment. However, in the context of phase II studies where the beneficial effect of therapy is not known, follow-up every 6–8 weeks (timed to coincide with the end of a cycle) is reasonable. Smaller or greater time intervals than these could be justified in specific regimens or circumstances. The protocol should specify which organ sites are to be evaluated at baseline (usually those most likely to be involved with meta- static disease for the tumour type under study) and how often evaluations are repeated. Normally, all target and non-target sites are evaluated at each assessment. In selected circumstances certain non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected.

After the end of the treatment, the need for repetitive tumour evaluations depends on whether the trial has as a goal the response rate or the time to an event (progression/death). If ‘time to an event’ (e.g. time to progression, disease-free survival, progression-free survival) is the main endpoint of the study, then routine scheduled re-evaluation of protocol specified sites of disease is warranted. In randomised comparative trials in particular, the scheduled assessments should be performed as identified on a calendar schedule (for example: every 6–8 weeks on treatment or every 3–4 months after treatment) and should not be affected by delays in therapy, drug holidays or any other events that might lead to imbalance in a treatment arm in the timing of disease assessment.

2.6. Confirmatory measurement/duration of response

2.6.1. Confirmation

In non-randomised trials where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error. This will also permit appropriate interpretation of results in the context of historical data where response has traditionally required confirmation in such trials. However, in all other circumstances, i.e. in randomised trials (phase II or III) or studies where stable disease or progression are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of trial results. However,

elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in studies which are not blinded.

In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval (in general not less than 6–8 weeks) that is defined in the study protocol.

2.6.2. Duration of overall response

The duration of overall response is measured from the time measurement criteria are first met for CR/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 on study). The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

2.6.3. Duration of stable disease

Stable disease is measured from the start of the treatment (in randomised trials, from date of randomisation) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD). The clinical relevance of the duration of stable disease varies in different studies and diseases. If the proportion of patients achieving stable disease for a minimum period of time is an endpoint of importance in a particular trial, the protocol should specify the minimal time interval required between two measurements for determination of stable disease.

Note: The duration of response and stable disease as well as the progression-free survival are influenced by the frequency of follow-up after baseline evaluation. It is not in the scope of this guideline to define a standard follow-up frequency. The frequency should take into account many parameters including disease types and stages, treatment periodicity and standard practice. However, these limitations of the precision of the measured endpoint should be taken into account if comparisons between trials are to be made.

2.7. PFS/TTP

2.7.1. Phase II trials

This guideline is focused primarily on the use of objective response endpoints for phase II trials. In some circumstances, ‘response rate’ may not be the optimal method to assess the potential anticancer activity of new agents/regimens. In such cases ‘progression-free survival’ (PFS) or the ‘proportion progression-free’ at landmark time points, might be considered appropriate alternatives to provide an initial signal of biologic effect of new agents. It is clear, however, that in an uncontrolled trial, these measures are subject to criticism since an apparently promising observation may be related to

biological factors such as patient selection and not the impact of the intervention. Thus, phase II screening trials utilizing these endpoints are best designed with a randomised control. Exceptions may exist where the behavior patterns of certain cancers are so consistent (and usually consistently poor), that a non-randomised trial is justifiable. However, in these cases it will be essential to document with care the basis for estimating the expected PFS or proportion progression-free in the absence of a treatment effect.