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Platform study of genotyping-guided precision medicine for rare solid tumours: a study protocol for a phase II, non-randomised, 18-month, open-label, multiarm, single-centre clinical trial testing the safety and efficacy of multiple Chinese-approved targeted drugs and PD-1 inhibitors in the treatment of metastatic rare tumours

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ABSTRACT

Introduction Limited clinical studies have been conducted on rare solid tumours, and there are few guidelines on the diagnosis and treatment, including experiences with targeted therapy and immunotherapy, of rare solid tumours in China, resulting in limited treatment options and poor outcomes. This study first proposes a definition of rare tumours and is designed to test the preliminary efficacy of targeted and immunotherapy drugs for the treatment of rare tumours.

Methods and analysis This is a phase II, open-label, non-randomised, multiarm, single-centre clinical trial in patients with advanced rare solid tumours who failed standard treatment; the study aims to evaluate the safety and efficacy of targeted drugs in patients with advanced rare solid tumours with corresponding actionable alterations, as well as the safety and efficacy of immune checkpoint (programmed death receptor inhibitor 1, PD-1) inhibitors in patients with advanced rare solid tumours without actionable alterations. Patients with advanced rare tumours who fail standardised treatment and carry actionable alterations (Epidermal growth factor receptor (EGFR) mutations, ALK gene fusions, ROS-1 gene fusions, C-MET gene amplifications/mutations, BRAF mutations, CDKN2A mutations, BRCA1/2 mutations, HER-2 mutations/overexpressions/amplifications or C-KIT mutations) will be enrolled in the targeted therapy arm and be given the corresponding targeted drugs. Patients without actionable alterations will be enrolled in the PD-1 inhibitor arm and be treated with sintilimab. After the patients treated with vemurafenib, niraparib and palbociclib acquire resistance, they will receive combination treatment with sintilimab or atezolizumab. With the use of Simon's two-stage Minimax design, and the sample size was estimated to be 770. The primary endpoint of this study is the objective response rate. The secondary endpoints are progression-free survival in the targeted treatment group and single-agent immunotherapy group; the duration of response in the targeted therapy and single-agent immunotherapy groups;

Strengths and limitations of this study

- This is the first well-designed PLATFORM study to comprehensively evaluate the efficacy of multiple targeted therapy and immunotherapy drugs in the treatment of rare tumours.
- This study innovatively brings the definition of primary and acquired resistance into targeted therapy and immunotherapy in rare tumours.
- A novel strategy of targeted therapies combined with immunotherapy after the development of acquired resistance to original targeted drugs is introduced.
- Through the current study, a 'PLATFORM' will be built for novel agents or products to be investigated and submitted for 'fast-track' approval for the treatment of rare tumours.
- The limitation of this trial might be the comparatively small sample size of the single-agent targeted treatment subgroup, and there is heterogeneity among different subtypes of rare tumours regarding prognosis and responses to the investigated drugs.

durable clinical benefit in the single-agent immunotherapy group; and the incidence of adverse events.

Ethics and dissemination Ethics approval was obtained from the Chinese Academy of Medical Sciences (ID: 20/132-2328). The results from this study will be actively disseminated through manuscript publications and conference presentations.

Trial registration numbers NCT04423185; ChiCTR2000039310.

INTRODUCTION

Genotyping-guided precision targeted therapy and immune checkpoint inhibitors have brought significant treatment efficacy and improved survival for patients with metastatic solid tumours such as non-small-cell lung cancer (NSCLC) and melanoma. However, limited studies have been conducted on rare solid tumours, and there is a shortage of diagnostic and treatment guidelines, clinical trials and experiences with targeted therapy and immunotherapy for rare solid tumours in China, resulting in limited treatment options as well as relatively poorer outcomes compared with most common cancers.[1]

Since 2017, three drugs have been approved by the Food and Drug Administration (FDA) based on small-sample molecular-guided pan-tumour phase II clinical trials for the treatment of advanced pansolid tumours with specific molecular alterations: pembrolizumab (programmed death receptor inhibitor 1 (PD-1) blockade on solid tumours PD-L1 expression positive), larotrectinib (solid tumours with Neurotrophic tyrosine receptor kinase (NTRK) fusions) and entrectinib (solid tumours with NTRK fusions).[2 3] All of these drugs have substantially improved the treatment efficacy, including the objective response rate (ORR) and progression-free survival (PFS), in patients with corresponding actionable alterations. This led the current study to pursue efficacious treatment of rare tumours or common tumours with rare genetic alterations and obtain rapid approval by the government.

A type of study design known as pragmatic clinical trials (PCTs) overcomes the limitations of tumour types and solves the problem of difficulty in recruiting subjects for randomised clinical trials (RCTs). The PCT modality is well suited for clinical investigation of rare tumours. It combines the advantages of basket studies and umbrella studies for clinical trial investigations on rare tumours, which could help to improve the efficiency and solve the problems of clinical research on rare tumours. Therefore, it is important to conduct a real-world study based on molecular genotyping for rare tumours.

EVIDENCE FOR THIS STUDY

This study first proposes a definition of rare solid tumours

Based on the definition of rare tumours by the European Society for Medical Oncology (ESMO) and National Cancer Institute/WHO in the USA, combined with data from the National Cancer Registry Office of the National Cancer Center of China comprising the annual incidence of tumours and the characteristics of the patient population in China, this study first proposes a definition of rare tumours. We consulted the National Cancer Registry of the National Cancer Center and generated an estimation of the incidence of tumours in mainland China. Tumour types were classified according to the International Classification of Diseases (ICD), and we comprehensively synthesised the epidemiology data and availability of standard treatment as well as opinions of experts from the National Cancer Centre. We then defined rare tumours according to the following standards:

1. According to the statistics from the National Cancer Registry, a tumour with an annual incidence (classified by system, table 1) that is lower than 2.5 per 100 000 people, including advanced or metastatic malignant tumours with the following ICD codes: C3, C7, C8, C17, C23, C24, C26, C30, C31, C33, C37, C38, C39, C40, C41, C44, C45, C48, C49, C51, C52, C55, C57, C58, C60, C62, C63, C68, C69, C65, C70, C71, C72, C74, C75.
2. If the incidence of a tumour (classified by systems) was higher than 2.5 per 100 000 people (ICD code: C15, C16, C18, C20, C22, C25, C34, C47, C50, C54, C56, C61, C64, C67), pathological subtypes of the tumour with an incidence of less than 2.5 per 100 000 people were included in this study, according to the WHO pathological classification of rare tumours from the ESMO and the latest pathological classification of MSK OncoTree (http://oncotree.mskcc.org/) in 2020.
3. Primary unknown malignant tumours (ICD code: C76, C77, C80).

The above definitions and the list of rare tumours were formulated according to the current epidemiological situation and the diagnosis and treatment of malignant tumours in China and the world. They will be further clarified and improved during the course of clinical study.

The shortage of diagnostic and treatment guidelines for rare solid tumours

According to the above definition and the tumour incidence rate of the Cancer Registration Office of the National Cancer Centre and combined with ESMO and OncoTree's latest pathological classification in 2020, the final list of rare tumours in China is shown in table 1, including the first pathological subtype (by location), the second pathological subtype and the third pathological subtype. There were 133 s pathological subtypes and 316 specific third pathological subtypes. Through the search of international and domestic guidelines, there are only 65 tumour types with a first-line recommended treatment in the National Comprehensive Cancer Network (NCCN) guidelines. Twenty-five pathological subtypes had second-line recommended treatments, and nine had third-line recommended treatments. It is notable that there are only six rare tumours with a first-line recommendation in the Chinese Society of Clinical Oncology (CSCO) guidelines (pulmonary sarcomatoid carcinoma; pleural lung blastoma, recommended according to the treatment of NSCLC; breast salivary gland malignant tumours, recommended according to the treatment of breast cancer; soft

Table 1 Rare tumour types

Tier	System	Tumour types	ICD code
	1. Head and neck tumour		
1		Epithelial tumours of the eye and adnexa	C69
2		Epithelial tumours of the middle ear	C69
3		Squamous carcinoma	C69
3		Basal cell carcinoma	C69
2		Variants of adenocarcinoma of the eye and adnexa	C69
3		Adenocarcinoma, NOS	C69
3		Adenoid cystic carcinoma	C69
3		Mucoepidermoid carcinoma	C69
1		Epithelial tumours of the nasal cavity	CD30
1		Epithelial tumours of the sinuses	CD31
2		Lymphoepithelial carcinoma of the nasal cavity and sinuses	C30, C31
2		Undifferentiated carcinoma of the nasal cavity and sinuses	C30, C31
2		Intestinal type adenocarcinoma of the nasal cavity and sinuses	C30, C31
1		Epithelial tumours of the middle ear	C30
2		Variants of squamous cell carcinoma of the middle ear	C30
3		Squamous carcinoma	C30
2		Variants of adenocarcinoma of the middle ear	C30
3		Adenocarcinoma, NOS	C30
3		Adenoid cystic carcinoma	C30
1		Odontogenic malignant tumours	C03
2		Odontogenic malignant tumours	C03
3		Clear Cell Odontogenic Carcinoma	C03
1		Eepithelial tumours of major salivary glands and salivary-gland-type tumours	C00-C14, C30, C31, C32
2		Malignant tumour of the parotid gland	C07
3		Squamous carcinoma	C7, C8
3		Large cell carcinoma	C7, C8
3		Lymphoepithelial carcinoma	C7, C8
3		Carcinosarcoma, NOS	C7, C8
3		Adenocarcinoma, NOS	C7, C8
3		Clear cell adenocarcinoma, NOS	C7, C8
3		Mucinous adenocarcinoma	C7, C8
3		Ductal carcinoma	C7, C8
3		Oxyphilic adenocarcinoma	C7, C8
3		Papillary cystadenocarcinoma, NOS	C7, C8
3		Adenoid cystic carcinoma	C7, C8
3		Mucoepidermoid carcinoma	C7, C8
3		Acinar cell adenocarcinoma	C7, C8
3		Malignant myoepithelioma	C7, C8
3		Carcinoma in pleomorphic adenoma	C7, C8
3		Mixed tumour, malignant	C7, C8
3		Polymorphous low-grade adenocarcinoma	C7, C8
3		Basal cell adenocarcinoma	C7, C8
3		Epithelial-myoepithelial carcinoma	C7, C8
3		Sebaceous adenocarcinoma	C7, C8
3		Cystadenocarcinoma, NOS	C7, C8
3		Low-grade cribriform cystadenocarcinoma	C7, C8
3		Mammary Analogue Secretory Carcinoma of Salivary Gland Origin	C7, C8
3		Salivary Adenocarcinoma	C7, C8
2		Epithelial tumours of major salivary glands	C08
3		Mucoepidermoid carcinoma	C00–C06, C09–C14, C30, C31, C32
3		Adenocarcinoma, NOS	C00–C06, C09–C14, C30, C31, C32
3		Adenoid cystic carcinoma	C00–C06, C09–C14, C30, C31, C32
3		Acinar cell adenocarcinoma	C00–C06, C09–C14, C30, C31, C32
3		Ductal carcinoma	C00–C06, C09–C14, C30, C31, C32
3		Mucinous adenocarcinoma	C00–C06, C09–C14, C30, C31, C32
3		Basal cell adenocarcinoma	C00–C06, C09–C14, C30, C31, C32
3		Clear cell adenocarcinoma, NOS	C00–C06, C09–C14, C30, C31, C32
3		Epithelial-myoepithelial carcinoma	C00–C06, C09–C14, C30, C31, C32
3		Polymorphous low-grade adenocarcinoma	C00–C06, C09–C14, C30, C31, C32
3		Carcinoma in pleomorphic adenoma	C00–C06, C09–C14, C30, C31, C32
3		Malignant myoepithelioma	C00–C06, C09–C14, C30, C31, C32
3		Cystadenocarcinoma, NOS	C00–C06, C09–C14, C30, C31, C32
3		Oncocytic carcinoma	C00–C06, C09–C14, C30, C31, C32
3		Papillary cystadenocarcinoma, NOS	C00–C06, C09–C14, C30, C31, C32
2		Medullary thyroid carcinoma	
	2. Digestive system tumours		
2		Salivary-gland-type tumours of the oesophagus	C15
3		Mucoepidermoid carcinoma	C15
3		Adenoid cystic carcinoma	C15
2		Undifferentiated carcinoma of the oesophagus	C15
2		Salivary-gland-type tumours of the stomach	C16
3		Mucoepidermoid carcinoma	C16
3		Adenoid cystic carcinoma	C16
1		Epithelial tumours of the small intenstine	C17
2		Variants of adenocarcinoma of the small intestine	C17
3		Adenocarcinoma, NOS	C17
3		Mucinous adenocarcinoma	C17

Continued

Table 1 Continued

Tier	System	Tumour types	ICD code
3		Signet ring cell carcinoma	C17
3		Adenosquamous carcinoma	C17
3		Medullary carcinoma, NOS	C17
3		Undifferentiated carcinoma	C17
2		Variants of squamous cell carcinoma of the small intestine	C17
3		Squamous carcinoma	C17
3		Undifferentiated carcinoma	C20
3		Medullary carcinoma, NOS	C20
2		Serous cystadenocarcinoma of the pancreas	C25
2		Carcinoma with osteoclast-like giant cells of the pancreas	C25
2		Liver Angiosarcoma	C22
2		Malignant Rhabdoid Tumour of the Liver	C22
2		Undifferentiated Embryonal Sarcoma of the Liver	C22
2		Malignant Nonepithelial Tumour of the Liver	C22
1		Epithelial tumours of the gallbladder	C23
1		Epithelial tumours of the extrahepatic biliary tract (EBT) and unspecified regions	C24
2		Small Cell Gallbladder Carcinoma	C23
2		Variants of adenocarcinoma of the gallbladder	C23
3		Cholangiocarcinoma	C23
3		Papillary adenocarcinoma, NOS	C23
3		Adenocarcinoma intestinal type	C23
3		Mucinous adenocarcinoma	C23
3		Clear cell adenocarcinoma, NOS	C23
3		Signet ring cell carcinoma	C23
3		Adenosquamous carcinoma	C23
3		Undifferentiated carcinoma	C23
3		Bile duct cystadenocarcinoma	C23
2		Cholangiocarcinoma of IBT	C22
2		Variants of adenocarcinoma of EBT	C24
3		Cholangiocarcinoma	C24
3		Papillary adenocarcinoma, NOS	C24
3		Adenocarcinoma intestinal type	C24
3		Mucinous adenocarcinoma	C24
3		Clear cell adenocarcinoma, NOS	C24
3		Signet ring cell carcinoma	C24
3		Adenosquamous carcinoma	C24
3		Undifferentiated carcinoma	C24
3		Bile duct cystadenocarcinoma	C24
2		Squamous cell carcinoma of gallbladder and EBT	C23, C24
	3. Respiratory system tumours		
1		Epithelial tumour of the trachea	C33
2		Variants of squamous cell carcinoma of the trachea	C33
3		Squamous carcinoma	C33
3		Papillary squamous cell carcinoma	C33
3		Basaloid squamous cell carcinoma	C33
3		Squamous cell carcinoma clear cell type	C33
3		Verrucous carcinoma	C33
3		Squamous cell carcinoma, adenoid	C33
3		Spindle cell carcinoma	C33
3		Adenosquamous carcinoma	C33
3		Lymphoepithelial carcinoma	C33
3		Giant cell carcinoma	C33
3		Undifferentiated carcinoma	C33
2		Variants of adenocarcinoma of the trachea	C33
3		Adenocarcinoma, NOS	C33
3		Mucinous adenocarcinoma	C33
3		Papillary adenocarcinoma, NOS	C33
3		Solid carcinoma, NOS	C33
3		Clear cell adenocarcinoma, NOS	C33
3		Acinar cell adenocarcinoma	C33
3		Signet ring cell carcinoma	C33
3		Mucinous cystadenocarcinoma, NOS	C33
2		Salivary-gland-type tumours of the trachea	C33
3		Adenoid cystic carcinoma	C33
3		Mucoepidermoid carcinoma	C33
3		Myoepithelial carcinoma	C33
2		Typical and atypical carcinoid of the lung	C34
3		Well-differentiated endocrine tumours, carcinoid	All cancer sites except C15-C26, C34, C44, C48, C51, C60, C63.2, C73
3		Well-differentiated endocrine tumours, atypical carcinoid	All cancer sites except C15-C26, C34, C44, C48, C51, C60, C63.2, C73
3		Poorly differentiated endocrine carcinoma	All cancer sites except C15-C26, C34, C44, C48, C51, C60, C63.2, C73
2		Salivary-gland-type tumours of the lung	C34
2		Sarcomatoid carcinoma of the lung	C34
2		NUT Carcinoma of the Lung	C34
1		Epithelial tumours of the thymus	C37
2		Malignant thymoma	C37
3		Thymoma, malignant, NOS	C37
3		Malignant thymoma, type AB	C37
3		Malignant thymoma, type A	C37
3		Malignant thymoma, type B	C37
3		Malignant thymoma, type C	C37

Continued

Table 1 Continued

Tier	System	Tumour types	ICD code
2		Squamous cell carcinoma of the thymus	C37
2		Undifferentiated carcinoma of the thymus	C37
2		Lymphoepithelial carcinoma of the thymus	C37
2		Variants of adenocarcinoma of the thymus	C37
3		Adenocarcinoma, NOS	C37
3		Papillary adenocarcinoma, NOS	C37
	4. Reproductive system tumours		
3		Breast Invasive Carcinosarcoma, NOS	C50
3		Breast Carcinoma with Signet Ring	C50
3		Metaplastic Carcinosarcoma	C50
2		Salivary-gland-type tumours of the breast	C50
3		Mucoepidermoid carcinoma	C50
3		Adenoid cystic breast cancer	C50
3		Myoepithelial carcinoma	C50
3		Acinar cell adenocarcinoma	C50
1		Unspecified tumour of uteri	C55
2		Adenoid cystic carcinoma of corpus uteri	C54, C55
2		Clear cell adenocarcinoma, NOS	C54, C55
2		Small cell carcinoma ≠ NET	C54, C55
2		Gestational trophoblastic disease	C54, C55
1		Epithelial tumours of the ovary and fallopian tube	C57
2		Clear cell ovarian cancer	C56
2		Mullerian mixed tumour of the ovary	C56
2		Small cell ≠ NET	C56
2		Sex cord tumours of the ovary	C56
2		Malignant/Immature teratomas of the ovary	C56
2		Germ cell tumour of the ovary	C56
1		Eepithelial tumours of the vagina	C52
2		Squamous cell carcinoma of the vulva/vagina	C51
2		Variants of adenocarcinoma of the vulva and vagina	C51
2		Germ cell tumour of the vulva	C51
1		Eepithelial tumours of the vulva	C51
2		Paget's disease of vulva and vagina	C51
2		Poorly differentiated vaginal carcinoma	C52
1		Trophoblastic tumour of the placenta	C58
2		Choriocarcinoma of the placenta	C58
1		Other and unspecified male reproductive organs	C63
3		Adenoid cystic carcinoma	C61
2		Prostate Small Cell Carcinoma	C61
1		Tsticular and paratesticular cancers	C62
2		Variants of paratesticular adenocarcinoma	C62,C63
2		Non-seminomatous testicular cancer	C62
2		Seminomatous testicular cancer	C62
2		Spermatocytic seminoma	C62
2		Teratoma with malignant transformation	C62
2		Testicular sex cord cancer	C62
2		Testicular mesothelioma	C62
1		Epithelial tumours of the penis	C60
2		Variants of squamous cell carcinoma of the penis	C60
2		Variants of adenocarcinoma of the penis	C60
1		Extragonadal germ cell tumours	All sites
2		Non-seminomatous germ cell tumours	All cancers sites except C56, C58 and C62
3		Embryonal adenocarcinoma, NOS	All cancer sites except C56, C58, C62, C71–C72, C75.1, C75.3
3		Yolk sac tumour	All cancer sites except C56, C58, C62, C71–C72, C75.1, C75.3
3		Teratocarcinoma	All cancer sites except C56, C58, C62, C71–C72, C75.1, C75.3
3		Teratoma with malignant transformation	All cancer sites except C56, C58, C62, C71–C72, C75.1, C75.3
3		Germ cell tumour with somatic-type malignancy	All cancer sites except C56, C58, C62, C71–C72, C75.1, C75.3
3		Mixed germ cell tumour	All cancer sites except C56, C58, C62, C71–C72, C75.1, C75.3
3		Choriocarcinoma, NOS	All cancer sites except C56, C58, C62, C71–C72, C75.1, C75.3
3		Choriocarcinoma combined with other germ cell elements	All cancer sites except C56, C58, C62, C71–C72, C75.1, C75.3
2		Seminomatous germ cell tumours	All cancer sites except C56, C58, C62, C71–C72, C75.1, C75.3
3		Dysgerminoma	All cancer sites except C56, C58, C62, C71–C72, C75.1, C75.3
3		Seminoma, NOS	All cancer sites except C56, C58, C62, C71–C72, C75.1, C75.3
3		Seminoma, anaplastic	All cancer sites except C56, C58, C62, C71–C72, C75.1, C75.3

Continued

Table 1 Continued

Tier	System	Tumour types	ICD code
3		Spermatocytic seminoma	All cancer sites except C56, C58, C62, C71–C72, C75.1, C75.3
2		Germ cell tumours of central nervous system (CNS)	C71–C72, C75.1, C75.3
3		Dysgerminoma	C71–C72, C75.1, C75.3
3		Seminoma, NOS	C71–C72, C75.1, C75.3
3		Seminoma, anaplastic	C71–C72, C75.1, C75.3
3		Spermatocytic seminoma	C71–C72, C75.1, C75.3
3		Embryonal adenocarcinoma, NOS	C71–C72, C75.1, C75.3
3		Yolk sac tumour	C71–C72, C75.1, C75.3
3		Teratocarcinoma	C71–C72, C75.1, C75.3
3		Teratoma with malignant transformation	C71–C72, C75.1, C75.3
3		Mixed germ cell tumour	C71–C72, C75.1, C75.3
3		Choriocarcinoma, NOS	C71–C72, C75.1, C75.3
3		Choriocarcinoma combined with other germ cell elements	C71–C72, C75.1, C75.3
	5. Urinary system tumours		
3		Sarcomatoid renal cell carcinoma	C64
2		Rhabdoid cancer (MRT)	C64
2		Clear cell sarcoma of the kidney	C64
2		Variants of adenocarcinoma of the pelvis and ureter	C65, C66
1		Epithelial tumours of the urethra	C68
2		Transitional cell carcinoma of the urethra	C68
3		Undifferentiated carcinoma	C68
3		Transitional cell carcinoma, spindle cell	C68
3		Lymphoepithelioma-like carcinoma	C68
3		Transitional cell carcinoma, giant cell	C68
3		Transitional cell carcinoma, micropapillary	C68
2		Variants of squamous cell carcinoma of the urethra	C68
3		Basaloid carcinoma	C68
3		Verrucous carcinoma	C68
2		Variants of adenocarcinoma of the urethra	C68
3		Mucinous adenocarcinoma	C68
3		Clear cell adenocarcinoma, NOS	C68
3		Signet ring cell carcinoma	C68
3		Adenoid cystic carcinoma	C68
2		Urachal adenocarcinoma	C68
2		Salivary-gland-type tumours of the bladder	C67

Continued

Table 1 Continued

Tier	System	Tumour types	ICD code
3		Adenoid cystic carcinoma	C67
3		Mucoepidermoid carcinoma	C67
2		Sarcomatoid carcinoma of the urinary bladder	C67
2		Small cell bladder cancer	C67
2		Inflammatory myofibroblastic bladder tumour	C67
	6. Malignant tumours involving multiple systems		
1		Malignant mesothelioma	All cancer sites
2		Pleural mesothelioma	C45
2		Mesothelioma of pleura and pericardium	C38
3		Epithelioid malignant mesothelioma	C38
3		Sarcomatoid malignant mesothelioma	C38
2		Mesothelioma of peritoneum and tunica vaginalis	C48, C63
3		Epithelioid malignant mesothelioma	C48, C63
3		Sarcomatoid malignant mesothelioma	C48, C63
2		Primary peritoneal serous/papillary carcinoma	C48
2		Neuroendocrine carcinoma of other sites	All cancer sites except C15–C26, C34, C44, C48, C51, C60, C63.2, C73
3		Well-differentiated endocrine tumours, carcinoid	All cancer sites except C15–C26, C34, C44, C48, C51, C60, C63.2, C73
3		Well-differentiated endocrine tumours, atypical carcinoid	All cancer sites except C15–C26, C34, C44, C48, C51, C60, C63.2, C73
3		Poorly differentiated endocrine carcinoma	All cancer sites except C15–C26, C34, C44, C48, C51, C60, C63.2, C73
1		Neuroblastoma and ganglioneuroblastoma	All cancers sites, except CNS and Autonomic Nervous System and peripheral nerves
2		Neuroblastoma and ganglioneuroblastoma	All cancers sites, except CNS and Autonomic Nervous System and peripheral nerves
1		Nephroblastoma	C64
2		Nephroblastoma	C64
1		Retinoblastoma	C69
2		Retinoblastoma	C69
1		Hepatoblastoma	C22
2		Hepatoblastoma	C22
1		Pleuropulmonary blastoma	C34
2		Pleuropulmonary blastoma	C34

Continued

Table 1 Continued

Tier	System	Tumour types	ICD code
1		PANCREATOBLASTOMA	C25
2		Pancreatoblastoma	C25
1		Olfactory neuroblastoma	C30,C31
2		Olfactory neuroblastoma	C30,C31
	7. Cutaneous malignant tumour		
1		Epithelial tumours of the skin	C44
2		Neuroendocrine carcinoma of the skin	C44.0–C44.9, CC51.0–C51.9, C60.0,C60.9 C63.2
3		Merkel cell carcinoma	C44.0–C44.9, CC51.0–C51.9, C60.0,C60.9 C63.2
2		Basal cell carcinoma of the skin	C44
3		Basal cell carcinoma, NOS	C44
3		Basosquamous carcinoma	C44
3		Multifocal superficial basal cell carcinoma	C44
3		Basal cell carcinoma nodular	C44
3		Basal cell carcinoma fibroepithelial	C44
3		Adenoid basal carcinoma	C44
2		Variants of squamous cell carcinoma of the skin	C44
3		Squamous carcinoma	C44
3		Verrucous carcinoma	C44
3		Spindle cell carcinoma	C44
3		Pseudovascular/squamous cell carcinoma adenoid	C44
3		Adenosquamous carcinoma	C44
1		Adnexal carcinoma of the skin	C44
2		Adnexal carcinoma of the skin	C44
3		Nodular hidradenoma, malignant	C44
3		Sebaceous adenocarcinoma	C44
3		Adenoid cystic carcinoma	C44
3		Paget's disease extramammary	C44
3		Apocrine adenocarcinoma	C44
3		Mucinous adenocarcinoma	C44
3		Pilomatrix carcinoma	C44
3		Eccrine poroma, malignant	C44
3		Mixed tumour malignant, NOS	C44
3		Sclerosing sweat duct carcinoma	C44
3		Malignant eccrine spiradenoma	C44
3		Tubular adenocarcinoma	C44
3		Eccrine papillary adenocarcinoma	C44
	8. Malignant tumour of soft tissue		
1		Soft tissue sarcoma	C49
3		Aggressive angiomyxoma	All cancers sites except C40.0–C41.9
3		Alveolar soft part sarcoma	All cancers sites except C40.0–C41.9
3		Angiomatoid fibrous histiocytoma	All cancers sites except C40.0–C41.9
3		Angiosarcoma	All cancers sites except C40.0–C41.9
3		Clear cell sarcoma	All cancers sites except C40.0–C41.9
3		Dendritic cell sarcoma	All cancers sites except C40.0–C41.9
3		Desmoid/aggressive fibromatosis (DES)	All cancers sites except C40.0–C41.9
3		Desmoplastic small-round-cell tumour	All cancers sites except C40.0–C41.9
3		Epithelioid haemangioendothelioma	All cancers sites except C40.0–C41.9
3		Epithelioid sarcoma	All cancers sites except C40.0–C41.9
3		Fibrosarcoma	All cancers sites except C40.0–C41.9
3		Gastrointestinal stromal tumour	All cancers sites except C40.0–C41.9
3		Glomangiosarcoma	All cancers sites except C40.0–C41.9
3		Inflammatory Myofibroblastic Tumour	All cancers sites except C40.0–C41.9
3		Intimal Sarcoma	All cancers sites except C40.0–C41.9
3		Leiomyosarcoma	All cancers sites except C40.0–C41.9
3		Liposarcoma	All cancers sites except C40.0–C41.9
3		Dedifferentiated liposarcoma	All cancers sites except C40.0–C41.9
3		Myxoid/round-cell liposarcoma	All cancers sites except C40.0–C41.9
3		Pleomorphic liposarcoma	All cancers sites except C40.0–C41.9
3		Well-differentiated liposarcoma	All cancers sites except C40.0–C41.9
3		Low-grade fibromyxoid sarcoma	All cancers sites except C40.0–C41.9
3		Undifferentiated pleomorphic sarcoma/malignant fibrous histiocytoma/high-grade spindle cell sarcoma	All cancers sites except C40.0–C41.9
3		Myxofibrosarcoma	All cancers sites except C40.0–C41.9
3		Radiation-associated sarcoma	All cancers sites except C40.0–C41.9
3		Rhabdomyosarcoma	All cancers sites except C40.0–C41.9
3		Alveolar rhabdomyosarcoma	All cancers sites except C40.0–C41.9
3		Embryonal rhabdomyosarcoma	All cancers sites except C40.0–C41.9
3		Pleomorphic rhabdomyosarcoma	All cancers sites except C40.0–C41.9
3		Spindle cell rhabdomyosarcoma	All cancers sites except C40.0–C41.9
3		Spindle cell/sclerosing rhabdomyosarcoma	All cancers sites except C40.0–C41.9
3		Round cell sarcoma, NOS (RCSNOS)	All cancers sites except C40.0–C41.9
3		RCSNOS	All cancers sites except C40.0–C41.9

Continued

Table 1 Continued

Tier	System	Tumour types	ICD code
3		Sarcoma, NOS (SARCNOS)	All cancers sites except C40.0–C41.9
3		Solitary fibrous tumour/ haemangiopericytoma	All cancers sites except C40.0–C41.9
3		Soft tissue myoepithelial carcinoma	All cancers sites except C40.0–C41.9
3		Synovial sarcoma	All cancers sites except C40.0–C41.9
3		Ewing sarcoma of soft tissue	All cancers sites except C40.0–C41.9
3		Infantile fibrosarcoma	All cancers sites except C40.0–C41.9
3		Malignant glomus tumour	All cancers sites except C40.0–C41.9
2		Soft tissue sarcoma of the head and neck	C00.0–C14.8, C30.0–C32.9, C49.0, C73.9, C75.2, C75.4, C76.0
2		Soft tissue sarcoma of the limbs*	C49.1–C49.2, C76.4–C76.5
2		Soft tissue sarcoma of the superficial trunk*	C49.3–C49.4, C49.6, C76.1–C76.2, C76.7
2		Soft tissue sarcoma of the mediastinum*	C38.1–C38.3, C38.8
2		Soft tissue sarcoma of the heart*	C38.0
2		Soft tissue sarcoma of the breast*	C50.0–C50.9
2		Soft tissue sarcoma of the uterus*	C53.0–C55.9
3		Undifferentiated Uterine Sarcoma	C53.0–C55.9
3		Uterine Adenosarcoma	C53.0–C55.9
3		Endometrial stromal sarcoma (ESS)	C53.0–C55.9
3		High-grade ESS (HGESS)	C53.0–C55.9
3		Low-grade ESS	C53.0–C55.9
3		Uterine smooth muscle tumour	C53.0–C55.9
3		Uterine leiomyosarcoma	C53.0–C55.9
3		Uterine epithelioid leiomyosarcoma	C53.0–C55.9
3		Uterine myxoid leiomyosarcoma	C53.0–C55.9
2		Soft tissue sarcoma of the paratestis*	C63.0–C63.7
2		Soft tissue sarcomas of other genitourinary tract structures (vulva, vagina, ovary, penis, prostate, testis, kidney, renal pelvis, ureter, bladder, urethra)	C51.0–C52.9, C56.9–C57.9, C60.0–C62.9, C63.8–C63.9, C64.9–C68.9
3		Clear cell sarcoma of the kidney	64.9
3		Malignant rhabdoid tumour of the kidney	64.9
2		Soft tissue sarcoma of the viscera*	C15.0–C26.9, C33.9–C37.9, C38.4, C39.0–C39.9, C42.2
2		Soft tissue sarcoma of retroperitoneum and peritoneum*	C48.0–C48.8
2		Soft tissue sarcoma of the pelvis*	C49.5, C76.3
2		Soft tissue sarcoma of the skin*	C44.0–C44.9
2		Soft tissue sarcoma of the paraorbit*	C69.0–C69.9
2		Soft tissue sarcoma of brain and other parts of the nervous system*	C47.0–C47.9, C70.0–C72.9, C75.1, C75.3

Continued

Table 1 Continued

Tier	System	Tumour types	ICD code
2		Embryonal rhabdomyosarcoma of soft tissue	All cancers sites except C40.0–C41.9
2		Alveolar rhabdomyosarcoma of soft tissue	All cancers sites except C40.0–C41.9, C56 and C62
2		Ewing's sarcoma of soft tissue	All cancers sites except C40.0–C41.9, C56 and C62, C71, C72
3		Ewing sarcoma	All cancers sites except C40.0–C41.9, C56 and C62, C71, C72
3		Peripheral neuroectodermal tumour	All cancers sites except C40.0–C41.9, C56 and C62, C71, C72
3		Primitive neuroectodermal tumour, NOS	All cancers sites except C40.0–C41.9, C56 and C62, C71, C72
		9. Malignant tumour of bone and joint system	
1		Bone sarcoma	C40
1		Bone sarcoma	C41
2		Osteogenic sarcoma	C40–41
3		Conventional osteosarcoma	C40–41
3		Telangiectatic osteosarcoma	C40–41
3		Small cell osteosarcoma	C40–41
3		Paraosteal osteosarcoma	C40–41
3		High-grade surface osteosarcoma	C40–41
3		Low-grade central osteosarcoma	C40–41
3		Periosteal osteosarcoma	C40–41
3		Secondary osteosarcoma	C40–41
2		Chondrogenic sarcomas	C40–41
3		Chondrosarcoma	C40–41
3		Mesenchymal chondrosarcoma	C40–41
3		Clear cell chondrosarcoma	C40–41
3		Dedifferentiated chondrosarcoma	C40–41
2		Notochordal sarcomas, chordoma	C40–41
2		Vascular sarcomas	C40–41
3		Angiosarcoma	C40–41
2		Ewing's sarcoma	C40–41
3		Peripheral neuroectodermal tumour	C40–41
2		Epithelial tumours, adamantinoma	C40–41
2		Other high-grade sarcomas (fibrosarcoma, malignant fibrous histiocytoma)	C40–41
3		Fibrosarcoma	C40–41
3		Malignant fibrous histiocytoma	C40–41
		10. Malignant tumours of endocrine system	
1		Carcinomas of the parathyroid gland	C75
2		Carcinomas of the pituitary gland	C75
3		Pituitary carcinoma	C75
1		Carcinomas of the parathyroid gland	C75
2		Carcinomas of the parathyroid gland	C75
1		Carcinoma of the adrenal cortex	C74

Continued

Table 1 Continued

Tier	System	Tumour types	ICD code
2		Carcinoma of adrenal cortex	C74
3		Adrenal cortical carcinoma	C74
	11. Malignant tumour of nervous system		
1		Malignant tumour of cerebrospinal membrane	C70
1		Malignant tumours of the spinal cord, cranial nerves and other parts of the CNS	C72
2		Astrocytic tumours of the CNS	C71, C72
3		Astrocytoma, NOS	C71, C72
3		Astrocytoma, anaplastic	C71, C72
3		Glioblastoma	C71,
3		Gliosarcoma	C71, C72
3		Giant cell glioblastoma	C71, C72
3		Astroblastoma	C71, C72
3		Protoplasmic astrocytoma	C71, C72
3		Gliomatosis cerebri	C71, C72
3		Pleomorphic xanthoastrocytoma	C71, C72
3		Pilocytic and Pilomyxoid astrocytoma	C71, C72
3		Oligoastrocytoma	C71, C72
3		Anaplastic Oligoastrocytoma	C71, C72
3		Subependymal giant cell astrocytoma	C71, C72
2		Oligodendroglial tumours of the CNS	C71, C72
3		Oligodendroglioma	C71, C72
3		Oligodendroglioma, anaplastic	C71, C72
3		Anaplastic Oligodendroglioma	C71, C72
2		Ependymal tumours of the CNS	C71, C72
3		Ependymoma, NOS	C71, C72
3		Ependymoma, anaplastic	C71, C72
3		Clear Cell Ependymoma	C71, C72
3		Subependymoma	C71, C72
3		Myxopapillary ependymoma	C71, C72
2		Neuronal and mixed neuronal-glial tumours	C71, C72
2		Choroid plexus carcinoma of the CNS	C71
2		Malignant meningiomas	C70
3		Meningioma	C70
3		Anaplastic meningioma	C70
3		Atypical meningioma	C70
3		Chordoid meningioma	C70
3		Clear cell meningioma	C70
3		Haemangiopericytoma of the CNS	C70
3		Papillary Meningioma	C70
3		Rhabdoid Meningioma	C70
1		Embryonal tumours of the CNS	C71, C72, C75.3
2		Embryonal tumours of the CNS	C71, C72, C75.3
3		Medulloblastoma	C71, C72
3		Desmoplastic nodular medulloblastoma	C71, C72
3		CNS-PNET	C71, C72
3		Atypical teratoid/rhabdoid tumour	C71, C72
3		Medulloepithelioma, NOS	C71, C72
3		Pineoblastoma	C75.3
3		Ependymoblastoma	C71, C72
3		Neuroepithelioma, NOS	C71, C72
3		Atypical teratoid/rhabdoid tumour	C71, C72
3		Desmoplastic/nodular medulloblastoma	C71, C72
3		Embryonal tumour with abundant neuropil and true rosettes	C71, C72
3		Ganglioneuroblastoma	C71, C72
3		Large cell/anaplastic medulloblastoma	C71, C72
3		Medulloblastoma with extensive nodularity	C71, C72
3		Medullomyoblastoma	C71, C72
3		Melanotic medulloblastoma	C71, C72
3		Neuroblastoma	C71, C72
1	12. Cancer of unknown primary origin		
1		Cancer of unknown primary origin of other and unspecified sites	C76
1		Cancer of unknown primary origin of the lymph nodes	C77
1		Malignant tumour of unspecified sites	C80
2		Cancer of unknown primary origin in the digestive system	C26
2		Cancer of unknown primary origin in the respiratory and thoracic cavity	C39
3		Acinar cell carcinoma, NOS	C39, C26, C76, C77, C80
3		Adenocarcinoma, NOS	C39, C26, C76, C77, C80
3		Cancer of unknown primary origin, NOS	C39, C26, C76, C77, C80
3		Mixed cancer types (MIXED)	C39, C26, C76, C77, C80
3		Neuroendocrine carcinoma, NOS	C39, C26, C76, C77, C80
3		Neuroendocrine tumour, NOS	C39, C26, C76, C77, C80
3		Poorly differentiated carcinoma, NOS	C39, C26, C76, C77, C80
3		Small cell carcinoma of unknown primary origin	C39, C26, C76, C77, C80
3		Squamous cell carcinoma, NOS	C39, C26, C76, C77, C80
3		Undifferentiated malignant neoplasm	C39, C26, C76, C77, C80

*Head and neck, limbs, superficial trunk, mediastinum, heart, breast, uterus, paratestis, viscera, retroperitoneum and peritoneum, skin, paraorbit, brain and other parts of the nervous system.
DES, desmoid tumors; IBT, intrahepatic biliary tract; ICD, International Classification of Diseases; MRT, Malignant rhabdoid-tumor; NOS, not otherwise specified; PNET, primitive neurotodermal tumour.

tissue Ewing's sarcoma and soft-tissue sarcoma), seven rare tumours with second-line recommended regimens, and only two rare tumours with third-line recommended

treatment (pulmonary sarcomatoid carcinoma and pleural blastoma, also according to the treatment recommendation of NSCLC). In addition, there are six rare tumours that have recommendations for targeted therapy and five rare tumours that have recommendations for immunotherapy in the CSCO guidelines. Immunotherapy is approved for only two types of rare tumours, lung sarcomatoid carcinoma and pleural blastoma, in light of treatment recommendations for NSCLC.

High incidence of actionable gene alterations in rare tumours

Based on the analysis of results from next-generation sequencing (NGS) of genomic variations in 4901 patients with rare tumours in the international cBioPortal database, the mutation rate of therapeutic targets (ALK fusion, BRAF mutation, BRCA1/2 mutation, CDKN2A deletion, EGFR mutation, FGFR1/2/3 fusion/amplification, MET amplification, KIT mutation, NTRK fusion, RET fusion and ROS-1 fusion, etc) in 63 pathological subtypes is 20.40% (1000/4901). Additionally, the results from NGS testing of rare tumour samples (including 67 subtypes) in the Chinese patient population showed that the rate of actionable gene alterations (as defined above) was 53.43% (701/1312). Thus, the incidence of mutations in targeted genes included in this study (EGFR, ALK, BRAF, BRCA1/2, C-MET, ROS-1, C-KIT, CDKN2A) in the Chinese population is three times higher than the incidence rate in the world population according to cBioPortal. The incidence of actionable gene alterations covered by the current protocol was 32.4% among the 63 pathological subtypes, which suggests that studying these mutations in rare tumours in the Chinese patient population might help greatly improve patient outcomes.[4]

Limited exploration of targeted therapy of rare solid tumours with promising efficacy

Of the 133 s pathological subtypes of rare solid tumours, clinical investigations of targeted therapy cover only 11.9% (16/135) of rare solid tumours (except for all solid tumours similar to MSI-H/dMMR approved for treatment with pembrolizumab). However, notably, the ORR and disease control rate (DCR) of targeted therapy are superior to those of standard treatment in rare tumours with actionable alterations.

For example, among dermatofibrosarcoma patients with KIT mutations, the ORR of nilotinib (a TKI) was 26.2% (n=11/42; 95% CI 13.9% to 42.0%), and the median response duration time for patients with partial responses was 7.1 months.[5] The DCR of erlotinib (an EGFR tyrosine kinase inhibitor (TKI)) treatment in vulvar malignant tumours was 67.5%; however, molecular screening for EGFR mutations was not performed before treatment.[6] The FDA granted fast-track approval to infigratinib, a novel small-molecule inhibitor of FGFR 1–3, in January 2020 for the first-line treatment of cholangiocarcinoma with FGFR fusion or translocation. The ORR of infigratinib for the treatment of cholangiocarcinoma with FGFR2 fusion/translocation is 39.3%, the DCR is 83.6%, the median PFS is 6.8 months and the median overall survival (OS) is 12.5 months.[7] Additionally, pemigatinib, an oral small-molecule inhibitor of FGFR 1, 2, and 3, achieved a 40% ORR, 9.2-month PFS and 15.8-month OS[8] in a study of patients with gallbladder cancer. Limited data on targeted therapies in other rare tumours are available. Taken together, these results suggest that molecularly targeted therapy is a promising treatment strategy for rare tumours, and further investigation is warranted.

No indications for PD-1 inhibitors have been approved regarding rare tumours in China

Of the 135 rare solid tumours of the second pathological subtype, the study of immunotherapy covers only less than 12.6% (17/135) (pembrolizumab has been approved for all solid tumours with MSI-H/dMMR regardless of tumour type). Although some initial response has been observed, Libtayo (PD-1, cemiplimab-rwlc) has been indicated only for the treatment of skin squamous cell carcinoma.[9]

Several smaller studies investigating the use of immunotherapy in rare cancers have shown promising results. Among malignant tumours of the skin, only Merkel cell carcinoma has been recommended as an indication for first-line immune checkpoint inhibitor treatment according to the NCCN guidelines. The ORR of PD-1 monotherapy for the treatment of Merkel cell carcinoma is 56%–68%, and the ORR is 67%[10] when combined with the use of platinum-containing chemotherapy. However, only avelumab has been approved for Merkel cell by the FDA to date. Studies investigating the use of cemiplimab (a PD-1 inhibitor) in third-line or later-line therapy for the treatment of skin squamous cell carcinoma suggest that the ORR is 47.2%.[11] Cemiplimab has now been indicated for use in this setting by the FDA. The ORR of pembrolizumab monotherapy for the treatment of cholangiocarcinoma is 17.4%,[12] the ORR of lovastinib combined with a PD-1 inhibitor is 21.4%, and the DCR is 93%.[13] The ORR of SHR-1210 combined with GEMOX is 54%, and the DCR is 100%,[14] both of which were determined in small-sample studies. The ORR of pembrolizumab monotherapy in patients with MSI-H/dMMR gallbladder cancer is 40%, and the 3-month PFS rate is 78%[2] In patients with duodenal adenocarcinoma, the ORR of pembrolizumab as a single-agent second-line treatment is 40%.[2] In thymic malignancies, pembrolizumab had a complete remission (CR) rate of 3% in second-line and third-line treatment, a partial remission (PR) rate of 20%, a median PFS of 4.2 months (95% CI 2.9 to 10.3) and a median OS of 24.9 months (15.5–NR).[11] Pembrolizumab has been recommended as second-line therapy for the treatment of malignant mesothelioma, with an ORR of 20% (95% CI 6.8 to 40.7), a 12-month PFS rate of 20.8% (7.6–38.5) and a 12-month OS rate of 62.6% (40.4–78.5).[14] And lately it was reported that nivolumab plus ipilimumab improved the median OS with 18.1 months (95% CI 16.8 to 21.4), compared with 14.1 months (95% CI 12.4 to 16.2) in the chemotherapy arm (HR 0.74; 96.6% CI 0.60 to 0.91;

p=0.0020) in unresectable malignant pleural mesothelioma, with non-epithelioid patients deriving most benefit (OS median, 18.1 vs chemotherapy 8.8 months; HR 0.46; 95% CI 0.31 to 0.68).[15] Taken together, these studies suggest that immunotherapy is a promising treatment strategy for rare tumours. However, few of the above treatment strategies/regimens/modalities have been approved by the FDA or the National Medicine Products Administration. The exploration of immunotherapy in other rare tumours is extremely limited, and some of these studies are presented as case reports.

Definition of primary and secondary drug resistance in targeted therapy

TKIs targeting EGFR driver gene mutations, such as gefitinib, erlotinib, osimertinib and dacomitinib, currently play a leading role in precision medicine. Experiences from this field have provided direction for other targeted treatments, such as the concept of primary resistance and secondary resistance and the concept of slow progression and rapid progression. Resistance to EGFR-TKIs is currently subdivided into two categories: primary resistance and secondary resistance. Primary resistance to EGFR-TKIs is currently outlined as follows: patients have disease progression at the first response evaluation after receiving a single EGFR-TKI treatment, or patients achieve PR/CR/SD, but it does not last over 6 months. Secondary resistance is defined as follows: (1) patient achieves a PR/CR (response evaluation criteria in solid tumours, RECIST V.1.1) after single-agent EGFR-TKI treatment, (2) achieves a significant and long-lasting clinical benefit (stable disease ≥6 months), (c3) within 30 days after disease progression and (4) with no other treatment used after disease progression.[12]

In this study, the above criteria were used to define primary drug resistance and secondary drug resistance in the targeted therapy group. If a patient develops primary drug resistance, it suggests that the mutated gene is not a driver for that particular tumour, and they will be permitted to cross over to the immunotherapy group.

The current investigator-initiated study evaluated the efficacy and safety of targeted therapies and PD-1 inhibitors in the treatment of metastatic malignant solid rare tumours. At the same time, we also evaluated the driver gene status and resistance patterns of rare tumours with corresponding postprogression strategies.

METHODS AND ANALYSIS

Study design

This study is a phase II, open-label, non-randomised, multiarm, single-centre clinical study in patients with advanced rare solid tumours who have or have not previously received standard treatment. Detailed measures of this study are demonstrated in figure 1.

Study objectives

Primary objectives

To evaluate the safety and efficacy of drugs that have been approved by the Chinese Center for Drug Evaluation (CDE) for the treatment of rare tumours with specific indications:

- These drugs have been approved by the CDE for targeting specific tumour-driving gene alterations in

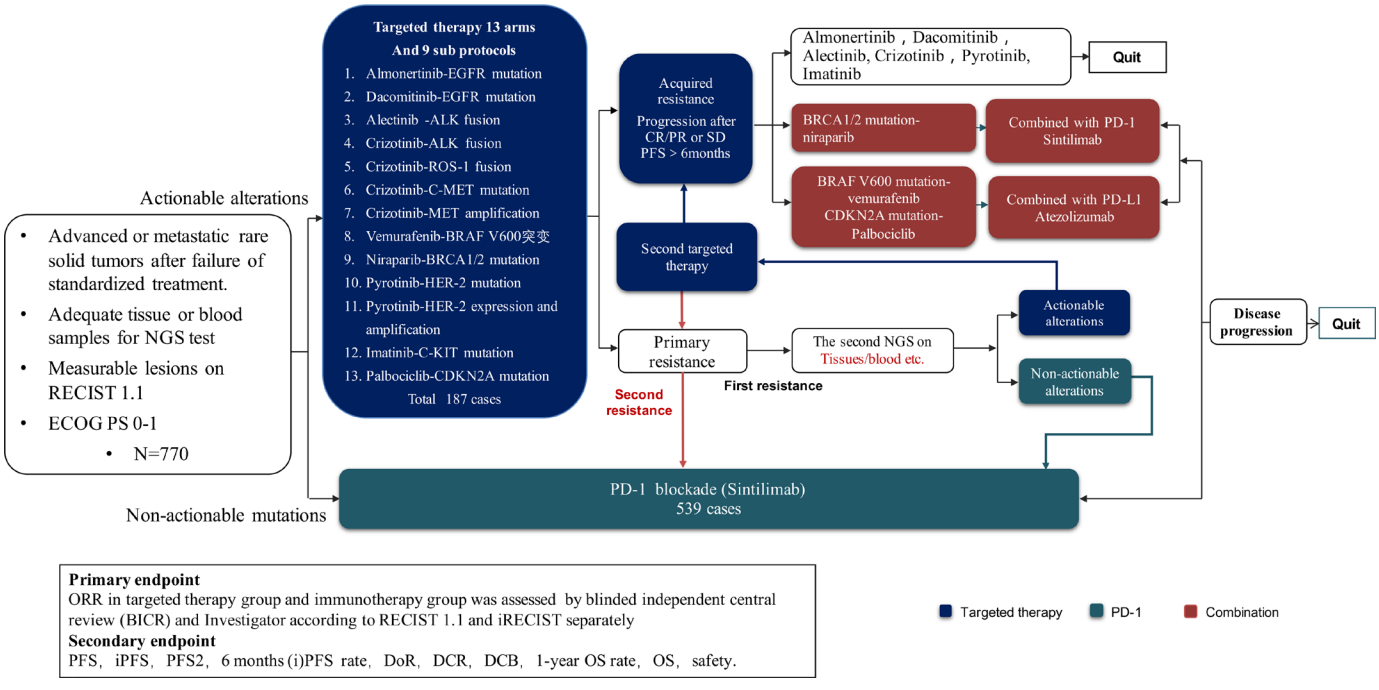

Figure 1 Flow chart of the study. Blue blocks: single-agent targeted therapy; green blocks: single-agent PD-1 inhibitor; red blocks: combination of targeted drugs with PD-1/PD-L1 inhibitors. DCB, durable clinical benefit; DCR, disease control rate; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; ORR, objective response rate; OS, overall survival; PD-1, programmed death receptor 1; PFS, progression-free survival; RECIST, response evaluation criteria in solid tumours.

patients with advanced rare solid tumours with the corresponding actionable alterations.
- To evaluate the safety and efficacy of immune checkpoint inhibitors (PD-1 antibodies) in patients with advanced rare solid tumours without actionable alterations.

Secondary objectives

- To evaluate the ORR of targeted therapeutic drugs in the treatment of advanced rare solid tumours with actionable alterations, DCRs, the duration of response (DoR), OS and PFS will be determined.
- To evaluate the ORR of immune checkpoint inhibitors in the treatment of advanced rare solid tumours without actionable alterations, the DCR, DoR, OS and PFS will be determined.
- To evaluate the PFS of the combined therapy with PD-1 inhibitor after the secondary resistance to single targeted agent, to see whether the combination with immunotherapy is able to reverse the resistance.
- To evaluate the improvement of disease-related symptoms and quality of life (QoL).
- To evaluate the adverse events (AEs) due to the study treatment regimens.

Exploratory objectives

- To explore biomarkers related to targeted therapy and immunotherapy based on the detection of the genome, transcriptome and proteome of tumour tissue specimens and peripheral blood samples.
- To evaluate the combination of spatiotemporal-specific therapeutic biomarkers of immunotherapy based on the identification and analysis of important components of the dynamic, stereoscopic and multi-spatial immune microenvironment.
- To develop diagnostic kits or detection technologies.

Study timetable and site

The programme commenced in September 2020, and accrual is planned to be completed in September 2022. The recruitment site is the Cancer Hospital of the Chinese Academy of Medical Sciences.

Target population

Patients with advanced or metastatic rare solid tumours who fail standard treatment or have no standard treatment are the target population. Additional eligibility criteria are listed in table 2. Specific criteria for each subprotocol are outlined in online supplemental table S1). Eligibility assessments and informed consent will be obtained before recruitment.

Statistical aspects

The sample size of each treatment group used in this study possesses great likelihood to determine whether the study drug has antitumour activity in statistics and the clinic. Designed for a single-centre multiarm study, the main purpose of this study is to evaluate the ORR of each group of patients with advanced rare tumours. The Simon two-stage minimax design will be applied, and the primary endpoint is the ORR evaluated by a BICR. On the basis of the research results of historical research data, only when the lower limit of the 95% CI of the ORR obtained by each group using the accurate method is greater than 5% can it be judged as valid. Assuming that the ORR of targeted therapy/immunotherapy for advanced rare tumours is 25%, the control type I error is 0.05, the power is 80%, the overall mutation rate is 30%, and the expulsion rate is 10%.

Adopting Simon's two-stage minimax design, in the first stage of clinical research, 12 subjects will be observed. If the number of patients with a CR and a PR is less than 1, the trial will be terminated; otherwise, the group will continue to expand to 16 subjects. Therefore, in the first stage, there will be 12*13/(1%–10%)=173 patients in the targeted treatment group and 405 patients in the immunotherapy group, for a total of 578 patients in the first stage. If all of these patients enter the second stage, there will be 16*13/(1%–10%)=231 patients in the final targeted treatment group and 539 patients in the immunotherapy group, for a total of 770 patients. The sample size of the study will be adjusted according to the interim analysis.

After disease progression, the patients will be followed for survival every 6 weeks (±7 days). Data collection will end at the time of final OS analysis.

Intervention

Patients will be separated into two treatment subgroups according to the results of genetic testing, and two types of treatments will be used differently for the two groups in this study.

Targeted group

After gene detection, after failure to standardised treatment, patients with advanced rare tumours who carry the actionable alterations (EGFR mutation (exon 19 deletion mutation, L858R replacement mutation or T790M mutation), ALK gene fusion, Ros-1 gene fusion, MET gene amplification or mutation, BRAF mutation (V600), BRCA1/2 mutation, HER-2 positive (mutation or overexpression or amplification), c-kit mutation, CDK4 amplification or CDKN2A mutation) will be separated into 13 study groups in which the corresponding target drugs (almonertinib, dacomitinib, alectinib, crizotinib, vemurafenib, niraparib, pyrotinib, imatinib, palbociclib) will be administered. The details of usage, dose adjustment principles and precautions of the abovementioned drugs will follow the individual drug instructions. Information on all AEs/serious AEs (SAEs) due to these drugs used in the treatment of advanced rare solid tumours will be collected as safety analysis data. After the subjects are enrolled in the corresponding targeted treatment groups, they will be treated according to the dose specified in the instructions until disease progression or intolerable side effects occur.

Table 2 Inclusion and exclusion criteria for main programme

Inclusion criteria	Exclusion criteria
Subjects will be required to meet all the following inclusion criteria:	Subjects meeting any of the following exclusion criteria will be excluded from the study:
1. Male or female, the age at the time of signing the informed consent is no less than 18 years old.	1. Other actionable alterations such as RET fusion, NTRK 1/2/3 fusion or FGFR amplification/fusion.
2. Advanced or metastatic rare solid tumour confirmed by histology or locally advanced rare tumours are not available to surgery and radiotherapy (table 1 rare solid tumour type).	2. A history of treatment with anti-PD-1/PD-L1.
3. An ECOG score of 0 or 1; the ECOG score needs to be evaluated 7 days before the first treatment.	3. A history of treatment with the targeted drug of this study.
4. Expected survival ≥12 weeks.	4. Allergies towards drug ingredients or excipients in this study.
5. According to RECIST V.1.1 evaluation standard of solid tumour efficacy, at least one imaging measurable lesion with obvious disease progression before radiotherapy or after radiotherapy.	5. A history of interstitial lung disease or radiation pneumonitis of any type.
6. Within the scope of CMPA approved drug indications, the disease has progressed after the standard treatment recommended by NCCN or CSCO guidelines (if there is standard treatment, the recommended level is IA–IIA), or there is no standard effective treatment plan, or the standard antitumour treatment is no longer suitable, or the patient refuses the standard treatment plan.	6.Central nervous system (CNS) metastases with brain metastases-related symptoms, which are not stable or need an increase in steroid dosage to control CNS disease. (Note: Patients with controlled CNS metastases are eligible to participate in this study. The subject must have completed radiotherapy or CNS tumour metastasis surgery for more than fourteen days before enrolling the study, and neurological function must be in a stable state, with no new neurological defects found in the clinical examination and no new problems found in the CNS imaging examination. If the need arises for subjects to use steroids for CNS metastasis treatment, the steroid treatment dose must have achieved stable treatment for ≥3 months at least 2 weeks before entering the study.
7. Fresh biopsy tissue samples (obtained within 12 weeks before the first use of the drug, 4 coarse needle biopsy specimens must be provided, and no other antitumur treatment, systemic anti-infection treatment, vaccination, etc) and peripheral blood samples must be provided for molecular typing.	7. Uncontrolled third cavity effusion as plural effusion or ascites, which grows fast and needs to be drained every week to relieve the symptoms or is newly detected compared with the last examination.
8. Paraffin tissue samples (15–20 specimens of 4–6 μm thick white films within 2 years) of primary or metastatic lesions (without radiotherapy), except for bone metastatic lesions, must be available before enrolment. If requirements are not met, investigators are allowed to enrol subjects on the basis of the specific situation for exploratory research.	8. A failure to meet the inclusion criteria of a substudy.
9. If there is pleural or peritoneal effusion, specimens must be taken for pathological cytological examination, of which ≥50 mL samples must be provided for exploratory study.	9. Major surgical operations or incomplete healing of injury within 28 days prior to study treatment's first administration.
10. If the primary lesions biopsy specimen has been provided and the metastasis is able to be biopsied, it is suggested to keep the specimen for pathological detection and to optionally obtain a fresh tissue specimen for exploratory research.	10. A history of receiving other investigational drugs within 14 days or five half-lives (whichever is longer) prior to the first administration.
11. After the progression of the subject's disease, if conditions permit, fresh tissue samples shall be obtained from the same biopsy lesions and the metastatic lesions of the previously obtained samples for exploratory study.	11. A history of receiving live vaccine within 30 days prior to the first administration. Seasonal influenza vaccines that do not contain live viruses are allowed.
12. Toxic and side effects caused by previous treatment need to be restored to ≤level one or returned to the baseline value (NCI-CTCAE V.5.0, except for hair loss).	12. A history of hypersensitivity to the active ingredients or nonactive excipients of the study drug, hypersensitivity to drugs with chemical structure similar to the study drug or hypersensitivity to similar drugs of the study drug.
13. Negative pregnancy test (only applicable for women with childbearing potential). No childbearing potential is defined as being postmenopausal for longer than 1 year or having undergone surgical sterilisation or hysterectomy. All patients (male and female) must agree to use an effective form of contraception and continue its use for the duration of treatment and within 8 weeks after the end of treatment.	1. Current active infection requiring systemic treatment (antibiotics) or any of the following: 1. HIV-positive status or known history of AIDS; 2. Hepatitis B virus (HBV) or hepatitis C virus (HCV) infection, defined as HBsAg positivity and a number of HBV DNA copies that exceeds the upper limit of normal value, or HCV AB positivity; 1. Active tuberculosis (with exposure history or a positive tuberculosis test; with clinical and/or imaging manifestations); or*Treponema pallidum* antibody positivity.

Continued

Table 2 Continued

Inclusion criteria	Exclusion criteria
14. Signed, written informed consent obtained from volunteers who join the study to follow the study treatment plan and the follow-up visit plan and to cooperate in observing the treatment adverse events and efficacy.	14. Current evidence of uncontrollable systemic diseases (such as severe mental or neurological disease; epilepsy or dementia; unstable or uncompensated respiratory, cardiovascular, liver or kidney diseases; uncontrolled hypertension (ie, still greater than or equal to CTCAE level three hypertension after drug treatment)).
	15. A history of myocardial infarction, coronary artery/peripheral artery bypass or cerebrovascular accident within 3 months.
	16. A history of other malignancy within the last 5 years, except for cured carcinoma in situ.
	17. A history of undergoing any organ transplantation, including allogeneic stem cell transplantation. Transplantations without immunosuppression (corneal transplantation, hair transplantation) are not included in this criterion.
	1. Cardiovascular disease or symptom, including any of the following: 1. A history of congestive heart failure requiring treatment and of New York Heart Association class III/IV CHF. 2. Current ventricular arrhythmia requiring antiarrhythmic drug treatment or uncontrollable or unstable arrhythmia. 3. Severe conduction disorder (such as grade II or III AV block). 4. Angina requiring treatment. 5. QT interval (QTC) of 12-lead ECG is ≥450 ms in males and ≥470 ms in females. 6. A history of congenital long QT syndrome, congenital short QT syndrome, torsade de pointe or pre-excitation syndrome. 1. A history of LVEF decline to below 50%, as determined by echocardiography or MUGA scan.A history of myocardial infarction in the past 6 months.
	1. Inadequate bone marrow reserve or organ function, as evidenced by the following laboratory results: 1. Absolute value of neutrophils <1.5×10^9/L. 2. Platelet count <100 × 10^9/L (transfusion-dependent patients should be excluded from this study). 3. Haemoglobin <90 g/L. 4. ALT >2.5 x the upper limit of normal (ULN) if there are no clear liver metastases or ALT >5 x ULN if there are liver metastases. 5. Aspartate aminotransferase (AST) >2.5 x ULN if there are no definite liver metastases or AST >5 x ULN if there are liver metastases. 6. Total bilirubin >1.5 x ULN if there are no liver metastases or total bilirubin >3 x ULN if there is definite Gilbert syndrome (unconjugated hyperbilirubinaemia) or liver metastases. 7. Creatinine >1.5 x ULN with creatinine clearance <50 mL/min (measured value, or calculated value by the Cockcroft-Gault formula; only when creatinine >1.5 x ULN does creatinine clearance need to be checked for confirmation). 8. If bone metastasis is present and investigator concludes that liver function is adequate, the increase in ALP alone will not be reason for study exclusion. 1. International normalised ratio and activated partial thromboplastin time or partial thromboplastin time (PTT or PTT) >1.5 x ULN (judgement will be made by an investigator on whether patients taking anticoagulants and those not taking anticoagulants are able to enter the group). 1. CK and CKMB are not in the normal range.The examination value of thyroid function is not within the normal range or it is slightly abnormal but does not need treatment.
	19. A history of swallowing dysfunction, active gastrointestinal disease or other diseases that significantly affect the absorption, distribution, metabolism and excretion of oral drugs. The patients with a history of subtotal gastrectomy. (Note: this standard is not applicable to the substudies in which the investigational drug is administered as an injection).
	20. Pregnancy or lactation.
	21. Serious medical or mental illness that may affect programme compliance and tolerance to treatment.
	22. Potential risks and inadequacies for the study as assessed by an investigator.

Continued

Table 2 Continued

Inclusion criteria	Exclusion criteria

ALP, Alkaline phosphatase; CHF, Congestive Heart Failure; CKMB, creatine kinase MB; CSCO, Chinese Society of Clinical Oncology; CTCAE, Common Terminology Criteria for Adverse Events; LVEF, Left ventricular ejection fraction; MUGA, A multigated acquisition; NCCN, National Comprehensive Cancer Network; NCI, National Cancer Institute; NMPA, National Medical Products Administration; PD-1, programmed death receptor 1; RECIST, response evaluation criteria in solid tumours.

Subjects with primary resistance to the single-agent targeted treatment group will be transferred to the single-agent immunotherapy group. The subjects in the almonertinib, dacomitinib, alectinib, crizotinib, pyrotinib and imatinib treatment group will be transferred out of the group if they develop secondary resistance. The subjects with secondary resistance in the vemurafenib, niraparib and palbociclib group will be treated with a combination of immune checkpoint inhibitors. The usages and dosages of the drug, the principles of dose adjustment and precautions will be conducted with reference to the drug instructions and the relevant early clinical research data. The specific and detailed targeted therapy drug plan is illustrated in figure 2.

Immunotherapy group

After failure of all the standardised treatment with approved drugs in China, patients with advanced rare tumours baring no actionable gene alterations after NGS testing will be treated with (PD-1 monoclonal antibody). The usages and dosages of the drug, the principles of dosage adjustment and precautions will be conducted with reference to the drug instructions. Concurrently, all the safety data for AEs/SAEs in late rare solid tumours will be recorded and analysed. PD-1 antibody treatment will be administered according to the dosage specified in the instructions until the disease progresses or intolerable side effects occur.

Outcomes

The primary endpoint is defined as follows:

- The clinical activity of treatments according to the ORR. The ORR in the targeted therapy group and immunotherapy group will be assessed by a BICR and an investigator according to RECIST V.1.1 and iRECIST, respectively.

The secondary endpoints are defined as follows:

- PFS in the targeted treatment group, as assessed by a BICR and an investigator.
- PFS (RECIST V.1.1) and iPFS (iRECIST) in the single-agent immunotherapy group, as assessed by a BICR and an investigator.
- A BICR and an investigator evaluated PFS2 of combined targeted agents with PD-1 therapy in the niraparib, palbociclib and vemurafenib groups, evaluated after primary resistance.
- A 6-month iPFS rate of PD-1 monotherapy, as assessed by a BICR and an investigator.
- The DoR in the targeted and single-agent immunotherapy groups, as assessed by an investigator.
- The DCR of the single-agent targeted and immunotherapy groups, as assessed by an investigator.
- The rate of durable clinical benefit in the single-agent immunotherapy group at different enrollment stages.
- A 1-year OS rate (1-year OS rate) in the single-agent targeted and immunotherapy groups.
- OS in the single-agent targeted and immunotherapy groups.
- The incidence of AEs in subjects (evaluated from the first study treatment administration to the 30th day and from 90 days after treatment with immunosuppressive drug regimens to approximately 5 years after the last treatment).

The efficacy evaluation criteria of the target group and immunotherapy group will be evaluated according to RECIST V.1.1 and iRECIST separately. Changes in vital signs, physical examination results and laboratory results before, during and after treatment will be recorded.

Exploratory endpoints are defined as follows:

- The relationship between actionable alterations and the efficacy of each targeted drug (ORR, PFS, DoR).
- The relationship between the expression of Programmed death-ligand 1 (PD-L1) (tumour and mesenchymal cells) and the tumour mutation burden within the immune microenvironment and its heterogeneous and dynamic changes and immunotherapy efficacy (ORR, PFS, DoR and OS) in the immunotherapy group.

Actionable alterations	Drugs	Dose
EGFR sensitive mutation/T790M mutation	Almonertinib	110mg qd
EGFR sensitive mutation	Dacomitinib	45mg qd
ALK gene fusion	Alectinib	600 mg bid
ALK/ROS-1 gene fusion MET amplification or exon 14 mutation	Crizotinib	250mg bid
BRAF mutation	Vemurafenib	960mg bid
BRCA1/2 mutation	Niraparib	200-300mg qd
HER-2 mutation/overexpression/amplification	Pyrotinib	400mg qd
C-KIT mutation	Imatinib	400mg qd/bid
CDKN2A mutation	Palbociclib	125mg qd 21d/q28d

Figure 2 Investigational drugs and applied dosages in the study.

Data statement

Clinical data will be collected for all patients, including those not eligible for participation in a clinical trial substudy. All patients will be followed up every 4–9 weeks, depending on the substudy regimen, for 48 weeks and

every 12 weeks beyond 48 weeks after entry into the molecular profiling phase to determine survival and disease status and whether they received matched molecular therapy on the basis of tumour profiling.

Patients enrolled in a substudy will be followed up every 4 weeks until progression or until the end of treatment and for at least 30 days after the end of treatment or 90 days after immunotherapy. After the end of treatment, patients will be followed up every 8 weeks until death or lost to follow-up. The date of death will be ascertained in medical records and appropriate registries.

Additional measures related to the assessment of clinical or biological activity of the study treatment collected as secondary outcomes will include associations of response, tolerability or resistance with biomarkers. The precise nature of any additional data to be collected will be specified in each subprotocol.

Health-related quality of life. Health-related quality of life will be measured by performance status assessments and with the The European Organization for Research and Treatment of Cancer, Quality of Life C30 (EORTC QLQ-C30) questionnaire[16] during the treatment phase. Validated patient-reported outcomes for assessing the patient's knowledge, values, attitudes, coping strategies, and decisional and psychosocial outcomes will be collected during the consent to molecular profiling, immediately after the return of profiling results and 2 months later. At these assessment points, patients will be invited to participate in an audiotaped interview to answer these questions.

PATIENT AND PUBLIC INVOLVEMENT STATEMENT

This PLATFORM study overcomes the limitations of tumour types and solves the problem of difficulty in recruiting subjects for RCTs and was designed for clinical investigation of rare tumours aim to help improve the efficiency and solve the problems of clinical research on rare tumours. No patients were involved in the design of this study. No patients were involved in the recruitment to and conduct of the study. Results of the study will be disseminated to patients after publication in peer-review journal. This is not an RCT.

ETHICS AND DISSEMINATION

The framework protocol and each substudy addendum have been reviewed in full and approved by the Cancer Hospital, Chinese Academy of Medical Sciences Ethics Committee (reference, 20/132–2328). The results from this study will be actively disseminated through manuscript publications and conference presentations.

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Contributors NL led the clinical implementation of the framework and main study as well as substudy protocols. SW contributed to the trial and protocol design. H-YH performed the statistical analysis, calculated the sample size and revised the protocol. DW and HF contributed to building the electric data collection system and protocol revision. JY contributed to the description of actionable alterations and the identification of genetic testing methods. YB, YY, YF, NJ, CS, AY, QF, SX, YN, WZ, CW, XJ, YG, QT, HW, YW and YT offered quality assessments of archival material and revised the protocol. All the authors involved in the manuscript writing and reviewed every version of the submitted protocol.

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