

# **Guidelines for full-process pharmaceutical care for subcutaneous preparations of antitumor drugs**

## **1 Scope**

This document describes the clinical rational use and comprehensive management of adverse reactions of subcutaneous preparations of antitumor drugs and provides comprehensive guidance on pharmaceutical services and clinical application management.

This guideline applies to medical institutions at all levels and types that carry out subcutaneous administration of anti-tumor drugs.

## **2 Normative references**

There are no normative references in this document.

## **3 Terms and definitions**

The following terms and definitions apply to this document.

### 3.1

Subcutaneous injection

A method of administration in which a drug is injected between the skin and muscles.

### 3.2

Subcutaneous preparations

A preparation in which a small amount of drug can be injected into subcutaneous tissue via subcutaneous injection.

### 3.3

Adverse reactions

Harmful reactions unrelated to the purpose of treatment occur during the prevention, diagnosis, or treatment of diseases when drugs are applied according to normal usage and dosage.

### 3.4

Pharmacokinetics

The discipline describes the patterns of drug changes in the body over time. It mainly studies the process of how the body disposes of drugs, including the absorption, distribution, metabolism, and excretion of drugs.

## **4 Abbreviations**

The following abbreviations apply to this document.

ADA anti-drug antibodies

ADR Adverse drug reaction  
ALK anaplastic lymphoma kinase  
AUC area under the plasma concentration-time curve  
BID twice daily  
BIW twice weekly  
BSA body surface area  
CL clearance  
 $C_{\max}$  maximum plasma concentration  
CT computed tomography  
dMMR different mismatch repair  
EGFR epidermal growth factor receptor  
F bioavailability  
FDA Food and Drug Administration  
HER-2 human epidermal growth factor receptor-2  
IRRs infusion-related reactions  
JMML juvenile myelomonocytic leukemia  
MHRA medicines and healthcare products regulatory agency  
MRI magnetic resonance imaging  
MSI-H microsatellite instability-high  
NK-1 RA neurokinin-1 receptor antagonist  
NMPA National Medical Products Administration  
pCR pathologic complete response  
PD-L1 programmed cell death-ligand 1  
QD once a day  
Q12W every 12 weeks  
Q24W every 24 weeks  
Q2W every two weeks  
Q3W every three weeks  
Q4W every four weeks  
QW once a week  
RANKL receptor activator for nuclear factor- $\kappa$ B ligand  
 $T_{1/2}$  half life  
 $T_{\max}$  peak time  
Vd apparent volume of distribution  
5-HT<sub>3</sub>RA 5-hydroxytryptamine 3 receptor antagonists

## **5 Reasonable clinical use of subcutaneous preparations of antitumor drugs**

### **5.1 General explanation for the rational clinical use of subcutaneous preparations of antitumor drugs**

The antitumor drugs listed below refer to subcutaneous preparations that have been approved for marketing. As of April 2024, subcutaneous preparations of anti-tumor drugs that have been approved by both NMPA and FDA include trastuzumab, daratumumab, denosumab, rituximab, pertuzumab/trastuzumab (a fixed-dose combination of pertuzumab and trastuzumab), degarelix,

leuprorelin, bortezomib, cytarabine, azacitidine, and bleomycin; envafolimab has been approved by NMPA; omacetaxine mepesuccinate has been approved by the FDA; and atezolizumab has been approved for marketing by the MHRA.

The following points should be noted when using subcutaneous preparations of antitumor drugs in clinical practice. (1) The approved specifications, indications, and usage and dosage of subcutaneous preparations may be different from those of intravenous preparations and should be used according to the corresponding drug instructions. (2) While several subcutaneous formulations are licensed by both NMPA and FDA, their permitted indications differ. It's important to consider these discrepancies during clinical use. If off-label medicine is used, it must be properly followed in compliance with medical institutions' off-label drug management protocols. (3) Subcutaneous formulations may only be delivered subcutaneously and not intravenously, intramuscularly, or intradermally. (4) Anti-tumor drug preparations produced by some pharmaceutical companies can be administered intravenously and subcutaneously simultaneously, such as bortezomib (trade name: VELCADE), cytarabine (trade name: CYTOSAR), bleomycin (trade name: BLEOCIN). The final concentration and treatment plan of the same preparation may be different under different routes of administration. Clinical staff should reasonably choose the administration method based on the actual situation of the patient.

## **5.2 Conversion of intravenous and subcutaneous antitumor drugs**

Drugs approved for the marketing of intravenous and subcutaneous preparations with the same common name include trastuzumab, daratumumab, rituximab, pertuzumab/trastuzumab, atezolizumab, and omacetaxine mepesuccinate. In clinical practice, the conversion of intravenous preparations and subcutaneous preparations may be involved. Clinical trials have shown that the mutual conversion of intravenous preparations and subcutaneous preparations does not affect their efficacy, and the safety profile is similar <sup>[1-5]</sup>. Patients currently receiving intravenous preparations may be switched to subcutaneous preparations the next time they are scheduled to be administered. Both intravenous and subcutaneous preparations of daratumumab require pre-injection and post-injection medication to reduce the risk of infusion-related systemic or local reactions. Preventive drugs, such as antipyretic analgesics, antihistamines, and glucocorticoids, should be given before each administration of rituximab. Before starting subcutaneous rituximab treatment, all patients must first receive at least one full dose of intravenous rituximab without severe adverse reactions; if patients cannot receive the full dose of intravenous infusion, intravenous rituximab should continue to be infused in subsequent courses of treatment until the full dose of intravenous rituximab is successfully infused, and patients must not switch to subcutaneous rituximab until then. When patients receiving intravenous pertuzumab in combination with trastuzumab are switched to subcutaneous preparations if the last intravenous dose of pertuzumab and trastuzumab is less than 6 weeks, the subcutaneous formulation should be administered at the maintenance dose (pertuzumab 600 mg and trastuzumab 600 mg); if the last intravenous dose is  $\geq 6$  weeks, the subcutaneous formulation should be administered at a loading dose (pertuzumab 1200 mg and trastuzumab 600 mg), followed by maintenance doses every 3 weeks.

## **5.3 Indications for subcutaneous preparations of antitumor drugs**

### **5.3.1 Subcutaneous preparation of macromolecular antitumor drugs**

#### **5.3.1.1 Trastuzumab**

Trastuzumab is a humanized monoclonal antibody targeting the HER-2 protein, and its approved indications are shown in Table 1.

Table 1 Approval of trastuzumab indications

FDA		NMPA	
Tumor	Indications	Tumor	Indications
Metastatic breast cancer	This product is suitable for HER-2-positive metastatic breast cancer as a single drug to treat metastatic breast cancer that has received one or more chemotherapy regimens. In combination with paclitaxel or docetaxel, it is used for metastatic breast cancer patients who have not received chemotherapy.	Metastatic breast cancer	This product is suitable for HER-2-positive metastatic breast cancer as a single drug to treat metastatic breast cancer that has received one or more chemotherapy regimens. In combination with paclitaxel or docetaxel, it is used for metastatic breast cancer patients who have not received chemotherapy.
Adjuvant treatment of breast cancer	This product is suitable for adjuvant treatment of breast cancer with HER-2 positive, lymph node positive or negative (estrogen receptor/progesterone receptor negative or with 1 high-risk factor).	Early breast cancer	This product is indicated for early breast cancer with HER-2 positive and has been treated with single-agent adjuvant therapy after surgery, adjuvant chemotherapy containing anthracycline antibiotics, and radiotherapy.
Adjuvant treatment of breast cancer	Adjuvant therapy with doxorubicin, cyclophosphamide, and paclitaxel or docetaxel.	Early breast cancer	Combined adjuvant therapy with paclitaxel or docetaxel after doxorubicin and cyclophosphamide chemotherapy.
	Adjuvant therapy in combination with docetaxel and carboplatin		Adjuvant therapy in combination with docetaxel and carboplatin.
	Single-agent adjuvant therapy after anthracycline antibiotics chemotherapy.		Neoadjuvant therapy combined with chemotherapy, followed by adjuvant therapy, for locally advanced (including inflammatory) breast cancer or with tumor diameters > 2 cm

### 5.3.1.2 Envafolelimab

Envafolelimab is a humanized monoclonal antibody targeting PD-L1 that is used to treat adult advanced solid tumors with unresectable or metastatic MSI-H or dMMR, as well as in patients with advanced colorectal cancer who have progressed after previous treatment with fluorouracil, oxaliplatin, and irinotecan, and in patients with other advanced solid tumors who have progressed after previous treatment and have no satisfactory alternative treatment options.

### 5.3.1.3 Daratumumab

Daratumumab is a humanized, anti-CD38 IgG1 monoclonal antibody that binds to CD38 expressed by tumor cells and induces apoptosis in tumor cells through complement-dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity, and antibody-dependent cellular

phagocytosis, and various immune-related mechanisms such as Fcγ receptors. The approved indications for daratumumab are shown in Table 2.

Table 2 Approval of daratumumab indications

FDA		NMPA	
Tumor	Indications	Tumor	Indications
Multiple myeloma	Combination with bortezomib, melphalan, and prednisone for the treatment of newly diagnosed adult patients with multiple myeloma who are not candidates for autologous stem cell transplantation.	Multiple myeloma	Combination with lenalidomide and dexamethasone, or bortezomib, melphalan, and prednisone, for the treatment of newly diagnosed adult patients with multiple myeloma who are not candidates for autologous stem cell transplantation.
	Combination with lenalidomide and dexamethasone for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least front-line prior therapy.		Combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least front-line prior therapy.
	Combination with bortezomib and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least front-line prior therapy.		Monotherapy in adult patients with relapsed and refractory multiple myeloma who had received previous treatment including proteasome inhibitors and immunomodulators and had disease progression on their last treatment.
Multiple myeloma	Combination with pomalidomide and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least first-line prior therapy, including lenalidomide and proteasome inhibitors.	Multiple myeloma	Combination with pomalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least front-line therapy, including lenalidomide and proteasome inhibitors.
	Combination with carfilzomib and dexamethasone for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least first to third line therapy.		
	Single-agent use in adult patients with multiple myeloma (including those who are refractory to treatment) who		

	have received at least a previous third-line therapy, including proteasome inhibitors and immunomodulators.		
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#### 5.3.1.4 Denosumab

Denosumab is a human IgG2 monoclonal antibody targeting RANKL and is used for the prevention of bone-related events and the treatment of giant cell tumors of bone in patients with bone metastases from solid tumors and patients with multiple myeloma. The detailed indications are shown in Table 3.

Table 3 Approval of denosumab indications

FDA		NMPA	
Tumor	Indications	Tumor	Indications
Solid tumor bone metastases/multiple myeloma	For the prevention of bone-related events in patients with bone metastases from solid tumors and patients with multiple myeloma.	Solid tumor bone metastases/multiple myeloma	For the prevention of bone-related events in patients with bone metastases from solid tumors and patients with multiple myeloma.
Giant cell tumor of bone	Treatment of giant cell tumors of bone that are unresectable or surgically resectable may cause severe dysfunction.	Giant cell tumor of bone	For the treatment of giant cell tumors of bone that are not surgically resectable or that may cause severe dysfunction, including adults and adolescent patients with skeletal maturity (defined as at least one mature long bone with a body mass $\geq 45$ kg).
Hypercalcemia due to malignant tumor	For hypercalcemia caused by malignancies refractory to bisphosphonate therapy.		

#### 5.3.1.5 Rituximab

Rituximab is a humanized monoclonal antibody targeting CD20 protein and is used to treat lymphoma. Detailed indications are shown in Table 4.

Table 4 Approval of rituximab indications

FDA		NMPA	
Tumor	Indications	Tumor	Indications
Follicular lymphoma	Monotherapy for relapsed or refractory follicular lymphoma; Combination treatment with	Follicular lymphoma	Previously untreated patients with CD20-positive stage III-IV follicular non-Hodgkin

	first-line chemotherapy for previously untreated follicular lymphoma, and combination treatment with rituximab and chemotherapy for patients who achieve complete or partial remission with single-agent maintenance therapy; Non-progressive (including stable disease) follicular lymphoma treated with the single agent after first-line chemotherapy with cyclophosphamide, vincristine, and prednisone.		lymphoma, in combination with chemotherapy; Single-agent maintenance treatment for newly treated patients with follicular lymphoma who achieve complete or partial remission after receiving chemotherapy with this product; Recurrent or chemotherapy-resistant follicular lymphoma.
Diffuse large B-cell lymphoma	Previously untreated diffuse large B-cell lymphoma treated in combination with cyclophosphamide, doxorubicin, vincristine, prednisone, or other anthracycline-containing chemotherapy regimens.	Diffuse large B-cell lymphoma	CD20-positive diffuse large B-cell non-Hodgkin lymphoma should be treated in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone for 8 cycles.
Chronic lymphocytic leukemia	Previously untreated and previously treated chronic lymphocytic leukemia treated in combination with fludarabine and cyclophosphamide.		

### 5.3.1.6 Pertuzumab/trastuzumab

Both pertuzumab and trastuzumab are humanized monoclonal antibodies that target the HER-2 protein and are used for the treatment of breast cancer. Detailed indications are listed in Table 5.

Table 5 Approval of indications for pertuzumab/trastuzumab

FDA		NMPA	
Tumor	Indications	Tumor	Indications
Early-stage breast cancer	In combination with chemotherapy, used as part of a comprehensive treatment plan for early-stage breast cancer, neoadjuvant therapy for adult patients with HER-2 positive, locally advanced, inflammatory, or early-stage breast cancer (diameter > 2 cm or positive lymph nodes).	Early-stage breast cancer	In combination with chemotherapy, used as neoadjuvant therapy for HER-2 positive, locally advanced, inflammatory, or early-stage breast cancer patients (with a tumor diameter > 2 cm or positive lymph nodes), as part of a comprehensive treatment plan for early-stage breast cancer.

	Adjuvant therapy for adult patients with high recurrence risk of HER-2 positive early-stage breast cancer.		In combination with chemotherapy, used as adjuvant therapy for patients with HER-2 positive early-stage breast cancer who are at high risk of recurrence.
Metastatic breast cancer	In combination with docetaxel, for the treatment of adult patients with HER-2 positive, metastatic breast cancer who have not previously received anti-HER-2 treatment or chemotherapy.	Metastatic breast cancer	In combination with docetaxel, for the treatment of patients with HER-2 positive, metastatic, or inoperable locally recurrent breast cancer. Patients have not previously received anti-HER-2 treatment or chemotherapy for metastatic breast cancer.

### 5.3.1.7 Atezolizumab

Atezolizumab is a humanized monoclonal antibody targeting PD-L1, used for the treatment of urothelial carcinoma, lung cancer, breast cancer, and liver cancer. Detailed indications are listed in Table 6.

Table 6 Approval of atezolizumab indications

Tumor	Indications
Urothelial carcinoma	Used as a monotherapy for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma who have previously received platinum-based chemotherapy, or are not suitable for cisplatin treatment, and whose tumors express PD-L1 at $\geq 5\%$ .
Non-small cell lung cancer	Used as monotherapy for adult patients with non-small cell lung cancer at stages II to IIIA (7th edition UICC/AJCC-staging system) whose tumors express PD-L1 in $\geq 50\%$ of tumor cells and have not progressed after adjuvant chemotherapy with platinum-based treatment, as adjuvant therapy following complete resection.
	In combination with bevacizumab, paclitaxel, and carboplatin for first-line treatment of adult patients with metastatic non-squamous non-small cell lung cancer.
	In combination with bevacizumab, paclitaxel, and carboplatin, it is indicated only for treatment after appropriate targeted therapy has failed.
	In combination with albumin-bound paclitaxel and carboplatin, it is indicated for first-line treatment of adult patients with metastatic non-squamous non-small cell lung cancer that is EGFR mutation-negative or ALK-negative.
	Used as monotherapy for first-line treatment of adult patients with metastatic non-small cell lung cancer who have tumors with PD-L1 expression of $\geq 50\%$ in tumor cells or $\geq 10\%$ in tumor-infiltrating immune cells, and no EGFR mutations or ALK positivity.
	Used as a monotherapy for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer who have previously received

	chemotherapy.
Small cell lung cancer	In combination with carboplatin and etoposide, it is indicated as a first-line treatment for adult patients with extensive-stage small cell lung cancer.
Triple-negative breast cancer	In combination with albumin-bound paclitaxel, it is indicated for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer whose tumors express PD-L1 at $\geq 1\%$ and who have not previously received chemotherapy for metastatic disease.
Hepatocellular carcinoma	In combination with bevacizumab, it is indicated for the treatment of adult patients with advanced or unresectable hepatocellular carcinoma who have not previously received systemic therapy.

### 5.3.2 Subcutaneous formulations of small molecule antitumor drugs

#### 5.3.2.1 Degarelix

Degarelix is approved by the FDA for the treatment of patients with advanced prostate cancer and is approved in China for prostate cancer patients requiring androgen deprivation therapy.

#### 5.3.2.2 Leuprorelin

Leuprorelin is indicated for the treatment of endometriosis, uterine fibroids, prostate cancer, estrogen receptor-positive premenopausal breast cancer, and central precocious puberty.

#### 5.3.2.3 Bortezomib

Bortezomib is suitable for the treatment of the following patients. (1) In combination with melphalan and prednisone for the treatment of untreated multiple myeloma patients who are not eligible for high-dose chemotherapy and stem cell transplantation. (2) As a monotherapy for the treatment of relapsed multiple myeloma patients who have received at least one prior therapy. (3) In combination with rituximab, cyclophosphamide, doxorubicin, and prednisone for the treatment of untreated mantle cell lymphoma adult patients who are not eligible for stem cell transplantation or for the treatment of relapsed or refractory mantle cell lymphoma patients.

#### 5.3.2.4 Cytarabine

Cytarabine is primarily indicated for the induction of remission and maintenance therapy in adults and children with acute non-lymphocytic leukemia. It also has therapeutic effects on other types of leukemia, such as acute lymphocytic leukemia and chronic myeloid leukemia (blast crisis). There are many domestic varieties of cytarabine, suitable for the induction and consolidation phases of acute leukemia, with better effects on acute non-lymphocytic leukemia and also effective for the accelerated phase of chronic myeloid leukemia and malignant lymphomas.

#### 5.3.2.5 Azacitidine

Azacitidine is indicated for the following adult patients: intermediate-2 and high-risk myelodysplastic syndromes in the International Prognostic Scoring System, chronic myelomonocytic leukemia, and acute myeloid leukemia with 20%~30% bone marrow blasts accompanied by multilineage dysplasia according to the World Health Organization classification. The FDA approved it in 2022 for the treatment of newly diagnosed pediatric patients with JMML.

### 5.3.2.6 Bleomycin

Bleomycin is used for the treatment of malignant skin tumors, head and neck cancers (including maxillary sinus cancer, pharyngeal cancer, laryngeal cancer, oral cancers such as tongue and lip cancers), lung cancer (especially squamous cell carcinoma, both primary and metastatic), esophageal cancer, malignant lymphomas, cervical cancer, gliomas, and thyroid cancer. Domestically produced injectable bleomycin hydrochloride is used for the treatment of squamous cell carcinomas of the head and neck, esophagus, skin, cervix, vagina, vulva, and penis, Hodgkin's disease and malignant lymphomas, testicular cancer, and malignant pleural effusions.

### 5.3.2.7 Omacetaxine mepesuccinate

Omacetaxine mepesuccinate is indicated for the treatment of adult patients with chronic myeloid leukemia in the chronic or accelerated phase who are resistant to and/or intolerant of two or more tyrosine kinase inhibitors.

## 5.4 Usage and dosage of subcutaneous antitumor drugs

Table 7 and Table 8 present the usage and dosage of anti-cancer drugs administered via subcutaneous injection, with dosages primarily based on body weight per kilogram or as a fixed dose.

Table 7 Usage and dosage of subcutaneous formulations of large molecule anticancer drugs

Drugs	NMPA-approved usage and dosage	FDA-approved usage and dosage
Trastuzumab	The recommended dose is 600 mg, Q3W.	The recommended dose is 600 mg, Q3W.
Envafolimab	The recommended dose is 150 mg, QW.	/
Daratumumab	Recommended dose is 1800 mg, QW or Q2W or Q3W or Q4W.	Recommended dose is 1800 mg, QW or Q2W or Q3W or Q4W.
Denosumab	(1) Solid tumor bone metastasis and multiple myeloma: The recommended dosage is 120 mg, Q4W. (2) Giant cell tumor of bone: The recommended dosage is 120 mg, Q4W, with an additional 120 mg dose on the 8th and 15th day of the first month of treatment.	(1) Metastatic bone disease from solid tumors and multiple myeloma: The recommended dose is 120 mg, Q4W. (2) Giant cell tumor of bone and hypercalcemia due to malignancy: The recommended dose is 120 mg, Q4W; an additional 120 mg dose is given on the 8th and 15th day of the first month of treatment.
Rituximab	Follicular Lymphoma and Diffuse	Follicular Lymphoma and

	Large B-Cell Lymphoma: The recommended dosage is 1400 mg, with the treatment cycle determined according to the specific treatment plan.	Diffuse Large B-Cell Lymphoma: The recommended dose is 1400 mg, with the treatment cycle based on the specific treatment regimen. Chronic Lymphocytic Leukemia: The recommended dose is 1600 mg, with the treatment cycle based on the specific treatment regimen.
Pertuzumab/trastuzumab	Loading dose (15 mL): pertuzumab 1200 mg and trastuzumab 600 mg for the first administration. Maintenance dose (10 mL): pertuzumab 600 mg and trastuzumab 600 mg, Q3W.	Initial dose (15 mL): 1200 mg pertuzumab and 600 mg trastuzumab for the first administration. Maintenance dose (10 mL): 600 mg pertuzumab and 600 mg trastuzumab, Q3W.
Atezolizumab	The recommended dosage is 1875 mg, Q3W (approved usage and dosage by the MHRA).	

Table 8 Usage and dosage of small molecule anticancer drugs for subcutaneous formulations

Drugs	NMPA-approved usage and dosage	FDA-approved usage and dosage
Degarelix	Initial dose: 240 mg, administered as two consecutive subcutaneous injections, each 120 mg. Maintenance dose: 80 mg, Q4W.	Initial dose: 240 mg, divided into two consecutive subcutaneous injections, each 120 mg. Maintenance dose: 80 mg, Q4W.
Leuprorelin	Endometriosis: 3.75 mg, Q4W. Uterine fibroids: 1.88 mg, Q4W. Prostate cancer: 3.75 mg, Q4W. Breast cancer: 3.75 mg, Q4W.	Prostate cancer: 1 mg, QD; 7.5 mg, Q4W; 42 mg, Q4W. Breast cancer: 11.25 mg, Q12W.
Bortezomib	The recommended starting dose is 1.3 mg/m <sup>2</sup> , BIW, with a 10-day break after two weeks of continuous infusion. For patients with liver impairment, the initial dose will be 0.7mg/m <sup>2</sup> .	The recommended starting dose is 1.3 mg/m <sup>2</sup> . For patients with moderate or severe hepatic impairment, a lower starting dose should be used (the starting dose should be reduced to 0.7mg/m <sup>2</sup> ).
Cytarabine	Induction of remission (low dose): 100~200 mg/m <sup>2</sup> , QD, for 5~10 days. Maintenance dose: 70~200 mg/m <sup>2</sup> , administered continuously for 5 days, Q4W (only the maintenance treatment	Induction of remission: 2 mg/kg (or 1~3 mg/kg), QD, for 10~14 consecutive days. Maintenance therapy: 1 mg/kg, administered 1~2 times daily, for 7~10

	can be administered subcutaneously according to the instructions).	consecutive days.
Azacitidine	The recommended starting dose for the first treatment cycle is 75 mg/m <sup>2</sup> , QD, for a total of 7 days. Subsequent treatment cycles: 75 mg/m <sup>2</sup> , with a treatment cycle every 4 weeks. It is recommended that patients receive at least 6 cycles of treatment. Pediatric patient dosage: The dosage should be adjusted based on factors such as the child's age, body weight, or body surface area.	Adult initial treatment cycle: 75 mg/m <sup>2</sup> , QD, for 7 days. Adult subsequent treatment cycles: Q4W. For children with JMML, the recommended dose is 2.5 mg/kg for children aged 1 month to 1 year or with a body weight less than 10 kg; for children older than 1 year and with a body weight of 10 kg or more, the recommended dose is 75mg/m <sup>2</sup> .
Bleomycin	15~30 mg, Q2W, with the option to adjust to QD or QW based on the condition, aiming for tumor disappearance, with a total dose of 300 mg (potency) or less.	0.25~0.5 U/kg (10~20 U/m <sup>2</sup> ), QW or BIW, with a total dose not exceeding 400 U.
Omacetaxine mepesuccinate	/	Induction dose: 1.25 mg/m <sup>2</sup> , BID, for 14 consecutive days, with a 28-day cycle. Maintenance dose: 1.25 mg/m <sup>2</sup> , BID, for 7 consecutive days, with a 28-day cycle.
Note: the "/" indicates that the usage and dosage have not been approved by NMPA.		

### 5.5 Preparation and administration of subcutaneous antitumor drug formulations

Anti-cancer drugs in subcutaneous formulations are best prepared and used immediately. Most of these drugs do not contain antimicrobial preservatives, so an aseptic technique must be followed during preparation. The standard preparation methods and specific operational steps for different drugs are detailed in Tables 9 and 10. Subcutaneous injections should be regularly changed to different injection sites within the specified area. Other subcutaneous drugs are best injected in different areas. Do not inject in areas with tough or fibrous subcutaneous tissue, areas with tenderness/bruising/erythema/swelling/pain, areas with moles or scars, or areas that may be rubbed or compressed (such as areas affected by a belt or clothing).

Table 9 Key points and procedures for the preparation of large molecule anti-cancer drug subcutaneous formulations

Generic name	Trastuzumab	Envafohimab	Daratumumab	Denosumab	Rituximab	Pertuzumab/trastuzumab	Atezolizumab
Trade name	Herceptin® SC	恩维达®	DARZALEX FASPRO®	Xgeva®	MabThera® SC	Phesgo®	Tecentriq Hybreza™
Specification	5 mL:600 mg	1 mL:200 mg	15 mL:1800 mg	1.7 mL:120 mg	11.7 mL:1400 mg 13.4 mL:1600 mg	15 mL: 1200 mg pertuzumab and 600 mg trastuzumab 10 mL: 600 mg pertuzumab and 600 mg trastuzumab	15 mL:875 mg
Composition	Active ingredient: trastuzumab Excipients: recombinant human hyaluronidase, L-histidine, L-histidine hydrochloride monohydrate, α,α-trehalose dihydrate, L-methionine, polysorbate 20, sterile water for injection.	Active ingredient: envafolimab Excipients: sodium acetate, proline, polysorbate 20, glacial acetic acid.	Active ingredient: daratumumab Excipients: recombinant human hyaluronidase, L-histidine, L-histidine hydrochloride monohydrate, L-methionine, polysorbate 20, sorbitol (E420), sterile water for injection.	Active ingredient: denosumab Excipients: sodium acetate (18 mM), polysorbate 20, sorbitol, sterile water for injection, sodium hydroxide.	Active ingredient: rituximab Excipients: recombinant human hyaluronidase, L-histidine, monohydrate L-histidine, trehalose dihydrate, methionine, polysorbate 80, water.	Active ingredients: pertuzumab, trastuzumab Excipients for the 15 mL specification: recombinant human hyaluronidase, trehalose, L-histidine, monohydrate L-histidine, L-methionine, polysorbate 20, sucrose. Excipients for the 10 mL specification: recombinant human hyaluronidase, trehalose, L-histidine, monohydrate L-histidine, L-methionine, polysorbate 20, sucrose.	Active ingredient: atezolizumab Excipients: recombinant human hyaluronidase, L-histidine, methionine acetate, L-polysorbate 20, sucrose, sterile water for injection.
Rewarming before	No need for rewarming	No need for rewarming	Remove this product from	Remove this product from	No need for rewarming	No need for rewarming	Remove this product from

preparation			2°C~8°C and allow it to equilibrate to room temperature ( $\leq 30^\circ\text{C}$ ).	2°C~8°C and allow it to equilibrate to room temperature ( $\leq 25^\circ\text{C}$ ), for approximately 15~30 minutes.			2°C~8°C and allow it to equilibrate to room temperature.
Visual inspection before and after solution preparation	Colorless to light yellow, clear to opalescent solution.	Transparent solution	Clear to opalescent and colorless to yellow solution.	A clear, colorless light yellow solution, may contain trace amounts of translucent to white protein particles.	Clear to opalescent, colorless to light yellow liquid.	Clear to opalescent, colorless to light brown solution	Colorless to slightly yellowish liquid.
Prepare the solvent	/	/	/	/	/	/	/
Procedure	Draw up the product into a syringe in preparation for injection.	Draw up the product into a 1 mL syringe in preparation for injection.	Draw up this product into a syringe and prepare for injection."	Use a No. 4 needle to aspirate and inject this product.	Use a 20 mL syringe to draw up the required volume and prepare for injection.	Use a No. 4 to No. 5 needle to aspirate and inject this product.	Draw the product into a syringe in preparation for injection.
Final concentration	120 mg/mL	200 mg/mL	120 mg/mL	70.6 mg/mL	119.7 mg/mL 119.4 mg/mL	/	125 mg/mL
Storage time after preparation	Under 2~8°C, store for less than 24 hours; Under 20°C~25°C with lighting conditions, store for less than 4 hours.	/	Under refrigerated conditions, store for less than 24 hours; under ambient temperature of 15°C~25°C with light exposure,	Store at room temperature ( $< 25^\circ\text{C}$ ) for less than 14 days, avoiding direct sunlight.	Under 2°C~8°C, store for less than 48 hours; At room temperature ( $< 30^\circ\text{C}$ ) for less than 8 hours.	Under 2°C~8°C, store for less than 24 hours; Under 20°C~25°C, store for less than 4 hours.	/

			store for less than 12 hours.				
Injection Site	Select the injection site by alternating between the left and right thighs, and ensure that new injection sites are at least 2.5 cm away from previous ones. During treatment with this product, other subcutaneously administered medications should be injected in different areas.	It is recommended to administer the medication subcutaneously in the upper arm, specifically in the area between the elbow and the midline of the shoulder. When injecting, gently pinch the skin of the upper arm between the thumb and the index and middle fingers, holding 2.5~5 cm of skin taut.	Administer 15 mL of this product subcutaneously within 3~5 minutes into the abdominal subcutaneous tissue approximately 7.5 cm to the right or left of the navel.	Administer subcutaneously in the upper arm, upper thigh, or abdominal area.	Administer this product into the abdominal subcutaneous tissue within approximately 5~7 minutes.	Administer injections alternately between the left and right thighs only, with new injection sites being at least 2.5 cm away from previous ones. Do not divide the administration between two syringes or two injection sites.	Administer this product into the thigh within approximately 7 minutes, alternating between the left and right thighs as the injection site, with each new injection site being at least 2.5 cm away from the previous one.
Note: the "/" indicates that the information is not mentioned in the instructions; the storage time after preparation includes both the time for storing the medication and the time for administration.							

Table 10 Key points and process for the preparation of subcutaneous preparations of small molecule antitumor drugs

Generic name	Degarelix	Leuprorelin	Bortezomib	Cytarabine	Azacitidine	Bleomycin	Omacetaxine mepesuccinate
Product Name	FIRMAGON®	ENANTONE®	VELCADE®	CYTOSAR®	VIDAZA®	BLEOCIN®	SYNRIBO®
Specification	80 mg;120 mg	1.88 mg;3.75 mg	3.5 mg	0.1 g;0.5 g	100 mg	15 mg	3.5 mg

Element	Active ingredient: degarelix Excipients: (1) Powder injection: mannitol; (2) Solvent: Water for injection	Active ingredient: leuprorelin Excipients: (1) Sterile powder for injection: copolymer (DL-lactic acid/glycolic acid) (3:1) and D-mannitol; (2) Injection solvent: D-mannitol, sodium carboxymethyl cellulose, Tween 80, water for injection	Active ingredient: bortezomib Excipients: mannitol	Active ingredient: cytarabine Excipients: hydrochloric acid, sodium hydroxide	Active ingredient: azacitidine Excipients: mannitol	Active ingredient: bleomycinA <sub>2</sub> Excipients: None	Active ingredient: omacetaxine mepesuccinate Excipients: hydrochloric acid, mannitol, sodium bicarbonate
Rewarming before configuration	No rewarming required	No rewarming required	No rewarming required	No rewarming required	No rewarming required	Return the vial to room temperature	No rewarming required
Visual inspection before and after solution preparation	The powder injection is a white to off-white freeze-dried block; the solution is a colorless clear liquid	The powder injection is a white powder; the solution is an off-white to light yellow emulsion	The powder injection is white or off-white lumps or powder; the solution is a clear colorless solution	The powder injection is white or off-white lumps or powder; the solution is a clear colorless solution	Powder injection is a white loose mass or powder; the suspension is uniform and turbid	The powder injection is white to light yellow loose lumps; the solution is a clear colorless solution	The powder injection is a white to off-white freeze-dried powder, and the solution is a colorless clear solution
Placement Solvent	Sterile water for injection	Additional solvent composition: D-mannitol, sodium carboxymethyl cellulose, Tween 80,	0.9% NaCl	Sterile water for injection, 0.9% NaCl, 5% GS	Sterile Water for Injection	Sterile water for injection, 0.9% NaCl, 5% GS	0.9% NaCl

		water for injection					
Step	(1) Connect the vial adapter to the vial and assemble the syringe. (2) Inject sterile water for injection into the vial from the syringe and gently swirl to reconstitute the injection. (3) Transfer the liquid to the syringe and prepare for injection.	(1) Use a syringe with a No. 7 needle to extract 1 mL of the solution and inject it into the vial. (2) Shake the vial thoroughly to mix it into a uniform suspension. The liquid will become emulsified. (3) Transfer the liquid to the syringe and prepare for injection.	(1) Take an appropriate amount of 0.9% NaCl and inject it into the vial. Let it stand for 1 minute. (2) Gently vortex the vial in a circular motion for 30 seconds. Place the vial upright for 30 seconds. (3) If undissolved powder is observed, repeat step 2 until the powder is completely dissolved.	Take an appropriate amount of solvent and slowly inject it into the vial, rotating the vial until a homogeneous solution is obtained.	Reconstitute each vial with 4mL of sterile water for injection. Slowly inject the diluent into the vial. Shake or rotate the vial vigorously until a homogenous suspension is obtained.	Use 1~5 mL of solvent to reconstitute. Slowly inject the diluent into the vial. Rotate the vial until a homogeneous solution is obtained.	Reconstitute with 1 mL of 0.9% NaCl. After adding the diluent, vortex gently until a clear solution is obtained. The lyophilized powder should be completely dissolved within 1 minute.
Final concentration	Starting dose:40 mg/mL Maintenance dose:20 mg/mL	/	2.5 mg/mL	/	25 mg/mL	/	3.5 mg/mL
Storage	At room	Give medication	At room	At room	(1) At room	After dissolving in	2°C~8°C<144 h;

time after configuration	temperature <1 h	immediately	temperature <8 h	temperature <24 h	temperature <1 h (2) Reconstitution with unrefrigerated water for injection: 2°C~8°C <8 h (3) Reconstitution with refrigerated water for injection: 2°C~8°C <22 h	0.9%NaCl at room temperature <24h	at room temperature <12 h
Injection site	Abdomen	Upper arms, abdomen, buttocks	The injection site should be rotated each time (thigh or abdomen) /		The injection site should be rotated (thigh, abdomen or upper arm) each time. The new injection should be made at least 2.5cm away from the old site.	When injected subcutaneously around the lesion, the dose should not exceed 1 mg/mL.	The injection site should be rotated each time (thigh, abdomen or upper arm). The new injection should be at least 2.5 cm away from the old site.
Note: “/” means not mentioned in the instructions; storage time after preparation includes storage time of drug solution and administration time.							

## 6 Use of subcutaneous preparations of antitumor drugs in special populations

The incidence and severity of various events in clinical trials of anticancer drugs may not reflect the incidence and occurrence observed in clinical practice. At the same time, due to limited pre-market clinical data, some potential rare or serious safety issues of anticancer drugs cannot be fully exposed, especially the safety of special populations. Special populations have potential risks of adverse events or other unexpected adverse reactions, and the pros and cons should be weighed and selected carefully before taking the drug. The use of subcutaneous preparations of anticancer drugs in special populations is detailed in Tables 11 and 12.

Table 11 Usage of subcutaneous preparations of macromolecular antitumor drugs in special populations

Special populations	Usage
Child	<ul style="list-style-type: none"> <li>●Trastuzumab, envafolimab, daratumumab, rituximab, pertuzumab/trastuzumab, and atezolizumab: safety and efficacy in children under 18 years of age have not been established.</li> <li>●Denosumab: its safety and efficacy have not been established in children other than skeletally mature adolescents with giant cell tumors of bone. Denosumab may inhibit bone growth in children with open growth plates and inhibit tooth eruption.</li> </ul>
Elder	<ul style="list-style-type: none"> <li>●Trastuzumab, daratumumab, denosumab, rituximab, atezolizumab: no dose adjustment is required.</li> <li>●Envafolimab: should be used with caution under the guidance of a physician. If used, no dose adjustment is required.</li> <li>●Pertuzumab/trastuzumab: the increased adverse reaction rate in some elderly patients is based on intravenous administration studies, and no relevant studies have been conducted on subcutaneous injection preparations.</li> </ul>
Renal insufficiency	<ul style="list-style-type: none"> <li>●Trastuzumab, daratumumab: no dose adjustment is required.</li> <li>●Envafolimab: not recommended for patients with moderate or severe renal impairment. Patients with mild renal impairment should use this product with caution under the guidance of a doctor. If it is used, no dose adjustment is required.</li> <li>●Denosumab, pertuzumab/trastuzumab: not mentioned in the instructions.</li> <li>●Rituximab: severe (including fatal) renal toxicity may occur after administration. Closely monitor for signs of renal failure and discontinue use in patients with elevated serum creatinine or oliguria.</li> <li>●Atezolizumab: no dose adjustment is required for patients with mild or moderate renal impairment. Data on patients with severe renal impairment are limited and no conclusions can be drawn for this population.</li> </ul>
Hepatic insufficiency	<ul style="list-style-type: none"> <li>●Trastuzumab, atezolizumab: no dose adjustment is required for patients with mild or moderate liver impairment, and there is no research data on the use of Envafolimab in patients with severe liver impairment.</li> <li>●Envafolimab: not recommended for patients with moderate or severe liver impairment. Patients with mild liver impairment should use this product with caution under the guidance of a doctor. If it is necessary to use it, no dose adjustment is required.</li> <li>●Daratumumab: no dose adjustment is required. Denosumab, rituximab, Pertuzumab/trastuzumab: not mentioned in the instructions.</li> </ul>
Pregnancy	<ul style="list-style-type: none"> <li>●Trastuzumab: contraindicated. Women of childbearing potential are advised to use effective contraceptive measures during treatment and within 7 months after the last dose.</li> </ul>

	<ul style="list-style-type: none"> <li>●Envafolelimab: contraindicated. Women of childbearing potential are advised to use effective contraceptive measures during treatment and within 5 months after the last dose.</li> <li>●Daratumumab: contraindicated. Women of childbearing potential are advised to use effective contraceptive measures during treatment and within 3 months after the last dose.</li> <li>●Denosumab: the use of denosumab by pregnant women may cause fetal harm. Pregnant women should be informed of the potential risks to the fetus.</li> <li>●Rituximab: contraindicated. Women of childbearing potential are advised to use effective contraceptive measures during treatment and within 12 months after the last dose.</li> <li>●Pertuzumab/trastuzumab: contraindicated. Women of childbearing potential are advised to use effective contraceptive measures during treatment and within 7 months after the last dose.</li> <li>●Atezolizumab: based on its mechanism, its use during pregnancy may cause fetal harm, including the potential risk of increased miscarriage or stillbirth rate.</li> </ul>
Lactation	<ul style="list-style-type: none"> <li>●Trastuzumab: it is recommended to stop breastfeeding during medication.</li> <li>●Envafolelimab: it is recommended that breastfeeding women stop breastfeeding during treatment with this product and for at least 5 months after the last dose.</li> <li>●Daratumumab, denosumab, atezolizumab: the benefits of breastfeeding to the infant and the benefits of treatment to the mother should be weighed before deciding to stop breastfeeding or terminating treatment with this product.</li> <li>●Rituximab: it is recommended that breastfeeding women stop breastfeeding during treatment with this product and for at least 6 months after the last dose.</li> <li>●Pertuzumab/trastuzumab: the benefits of breastfeeding to the infant and the benefits of treatment to the mother should be weighed before deciding to stop breastfeeding or terminate treatment with this product. The elimination half-life and 7-month washout period of pertuzumab should also be considered.</li> </ul>
Infected	<ul style="list-style-type: none"> <li>●Trastuzumab, envafolimab, daratumumab, denosumab, pertuzumab/trastuzumab, atezolizumab: not mentioned in the instructions.</li> <li>●Rituximab: should not be used to treat patients with concurrent severe active infection.</li> </ul>
Severely impaired immune response	Trastuzumab, envafolimab, daratumumab, denosumab, rituximab, pertuzumab/trastuzumab, atezolizumab: not mentioned in the instructions.
Patients with cardiovascular disease	<ul style="list-style-type: none"> <li>●Trastuzumab: use with caution in patients with high cardiac risks (e.g., hypertension, coronary artery disease, heart failure, diastolic dysfunction, the elderly).</li> <li>●Envafolelimab, denosumab, atezolizumab: not mentioned in the instructions.</li> <li>●Daratumumab: this drug combined with bortezomib, cyclophosphamide, and dexamethasone is not suitable and is not recommended for patients with NYHA class IIIB or IV heart disease or Mayo stage IIIB primary light-chain amyloidosis.</li> <li>●Rituximab: closely monitor patients with a history of heart disease.</li> <li>●Pertuzumab/trastuzumab: may cause subclinical and clinical heart failure, with the incidence and severity being greatest in patients receiving it in combination with anthracycline-containing chemotherapy. Periodically assess cardiac function before and during pertuzumab/trastuzumab treatment and discontinue pertuzumab/trastuzumab in patients who develop clinically significant left ventricular dysfunction.</li> </ul>

Table 12 Usage of subcutaneous preparations of small molecule antitumor drugs in special populations

Special populations	Usage
Child	<ul style="list-style-type: none"> <li>●Cytarabine: the use of this product in children is the same as that in adults, but adjustments should be made based on age, weight, body surface area, and other factors.</li> <li>●Degarelix, leuprolide, bortezomib, bleomycin, omacetaxine mepesuccinate: the safety and efficacy of azacitidine in children under 18 years of age have not been established.</li> <li>●Azacitidine: the safety and efficacy of azacitidine in children with myelodysplastic syndrome and newly diagnosed juvenile myelomonocytic leukemia under 1 month have not been determined.</li> </ul>
Elder	<ul style="list-style-type: none"> <li>●Degarelix, leuprolide, bortezomib, azacitidine: no dose adjustment required.</li> <li>●Cytarabine, bleomycin: use with caution in patients aged <math>\geq 60</math> years.</li> <li>●Omacetaxine mepesuccinate: patients aged <math>\geq 65</math> years are more likely to experience toxicity, especially hematologic toxicity.</li> </ul>
Renal insufficiency	<ul style="list-style-type: none"> <li>●Degarelix: pharmacokinetic studies have not been conducted in patients with impaired renal function. Degarelix should be used with caution in patients with creatinine clearance <math>&lt; 50</math> mL/min.</li> <li>●Leuprorelin, cytarabine, bleomycin, omacetaxine mepesuccinate: use with caution.</li> <li>●Bortezomib: it is not recommended to adjust the starting dose.</li> <li>●Azacitidine: the risk of renal toxicity may be increased in patients with renal impairment and should be closely monitored. The safety and efficacy of azacitidine have not been studied in patients with myelodysplastic syndrome with renal impairment.</li> </ul>
Hepatic insufficiency	<ul style="list-style-type: none"> <li>●Degarelix: no dose adjustment is required for patients with mild or moderate hepatic impairment; use with caution in patients with severe hepatic impairment.</li> <li>●Bortezomib: a lower starting dose is recommended for patients with moderate or severe hepatic impairment.</li> <li>●Leuprorelin, cytarabine, bleomycin, omacetaxine mepesuccinate: use with caution.</li> <li>●Azacitidine: azacitidine has the potential to be hepatotoxic in patients with a history of severe hepatic impairment and should be used with caution. The safety and efficacy of azacitidine has not been studied in patients with myelodysplastic syndrome and hepatic impairment.</li> </ul>
Pregnancy	<ul style="list-style-type: none"> <li>●Degarelix, leuprolide, cytarabine: contraindicated. Women of childbearing potential must take effective contraceptive measures during treatment.</li> <li>●Bortezomib: contraindicated. Women of childbearing potential are advised to take effective contraceptive measures during treatment and within 7 months after</li> </ul>

	<p>the last dose.</p> <ul style="list-style-type: none"> <li>●Azacitidine, bleomycin: women of childbearing potential are advised to avoid pregnancy during treatment.</li> <li>●Omacetaxine mepesuccinate: contraindicated. Women of childbearing potential are advised to use effective contraceptive measures during treatment and within 6 months after the last dose.</li> </ul>
Lactation	<ul style="list-style-type: none"> <li>●Degarelix, leuprolide, cytarabine, bleomycin: it is recommended to stop breastfeeding during medication.</li> <li>●Bortezomib: it is recommended that breastfeeding women do not breastfeed during treatment and within 2 months after treatment.</li> <li>●Azacitidine: it is recommended not to breastfeed during treatment and within 1 week after the last dose.</li> <li>●Omacetaxine mepesuccinate: it is recommended not to breastfeed during treatment and within 2 weeks after the last dose.</li> </ul>
Infected	<p>Degarelix, leuprolide, bortezomib, cytarabine, azacitidine, bleomycin, omacetaxine mepesuccinate: not mentioned in the instructions.</p>
Severely impaired immune response	<ul style="list-style-type: none"> <li>●Degarelix, leuprolide, azacitidine, bleomycin, omacetaxine mepesuccinate: not mentioned in the instructions.</li> <li>●Bortezomib: it is recommended that patients with severely impaired immune response should not use it.</li> <li>●Cytarabine: in patients who are immunosuppressed by chemotherapy drugs including cytarabine, administration of live or live-attenuated vaccines may result in serious or fatal infections. It is recommended to avoid live vaccines.</li> </ul>
Patients with cardiovascular disease	<ul style="list-style-type: none"> <li>●Cytarabine, azacitidine: not mentioned in the instructions.</li> <li>●Degarelix, leuprorelin, bortezomib: use with caution.</li> <li>●Omacetaxine mepesuccinate: patients with existing arrhythmias and various organic cardiovascular diseases should use it with caution or not use it. Patients with severe or frequent arrhythmias and organic cardiovascular diseases should not use it.</li> <li>●Bleomycin: contraindicated in patients with severe heart disease.</li> </ul>

## 7 Comprehensive management of ADRs to subcutaneous anticancer agents

### 7.1 Full-course evaluation and close monitoring of drug-related ADRs

This involves three stages: pre-treatment, during treatment, and post-treatment.

Pre-treatment: patients must be assessed for susceptibility to ADRs, encompassing disease history and family history, general condition, autoimmune diseases, baseline laboratory tests, and imaging studies (mostly chest, abdomen, and pelvic CT scans, and cranial MRI), as well as residual ADR symptoms from prior treatments.

During treatment: close monitoring is essential to promptly evaluate any emerging symptoms. Adverse events occurring during treatment should be considered in three possible contexts: disease progression, coincidental events, or ADRs. Attention should also be given to differentiating ADRs arising from combination therapies with other drugs or symptoms inherent to the disease itself.

Post-treatment: even when the disease is stable, ADRs must still be taken into account.

Monitoring of ADRs related to subcutaneous anticancer agents includes monitoring during treatment and follow-up after treatment. Monitoring during treatment refers to the regular or irregular detection of certain laboratory parameters and organ functions while the patient is undergoing drug therapy, enabling early and timely identification of ADRs. Follow-up after treatment involves the periodic or irregular assessment of these same parameters and functions within a certain period following the completion of drug therapy, allowing for the early and timely detection of any delayed ADRs. Detailed items for monitoring ADRs to anticancer drugs are presented in Table 13.

Table 13 Monitoring of ADRs for anticancer agents

Monitoring item	Specific content
General situation	At each follow-up visit, an assessment of clinical symptoms and adverse events should be conducted, including physical examination (including neurological examination) and evaluation of bowel habits.
Imaging examination	During treatment, chest, abdomen, and pelvic CT scans should be repeated every 4 to 6 weeks. Based on specific symptoms, irregular CT scans of particular areas should be performed. Brain MRI and whole-body scans should be repeated every six months to one year.
General hematological examination	During treatment, blood routine tests and blood biochemistry (comprehensive panel) should be reviewed every 2 to 3 weeks or as indicated. If indicated, irregular tests for glycated hemoglobin, HBsAg, anti-HBs, anti-HBc, anti-HCV, cytomegalovirus antibody, and HIV antigen (p24) should be conducted. If indicated, irregular monitoring of hepatitis B DNA and hepatitis C RNA should also be performed.
Skin and mucosa	Skin and mucous membrane examinations should be conducted during each patient round, particularly for patients with a history of autoimmune skin diseases. The affected body surface area and lesion types should be monitored and photographed for records. If indicated, a skin biopsy should be performed.

Pancreas	Routine monitoring is not necessary in the absence of symptoms. For symptomatic patients, prompt blood and urine amylase tests as well as pancreatic imaging should be conducted.
Thyroid	During treatment, thyroid function should be reassessed every 4 to 6 weeks, and every 12 weeks based on symptoms. If thyroid-stimulating hormone levels are high, irregular testing for thyroid peroxidase antibodies should be performed. If thyroid-stimulating hormone levels are low, irregular testing for thyroid-stimulating hormone receptor antibodies should be conducted.
Lungs	During treatment, resting or exertional oxygen saturation should be reassessed every 4 to 6 weeks, along with routine lung imaging. For patients with a history of lung diseases (such as chronic obstructive pulmonary disease, nonspecific interstitial pneumonia, sarcoidosis, or pulmonary fibrosis), irregular pulmonary function tests and 6-minute walk tests should be performed. A lung biopsy should be conducted if necessary.
Cardiovascular system	During treatment with small-molecule drugs, electrocardiograms, and myocardial enzyme spectrums should be reassessed every 2 to 4 weeks. Irregular reassessments of myocardial infarction markers (such as troponin I or T, etc.), brain natriuretic peptide (BNP), or pro-BNP should be conducted. If necessary, 24-hour ambulatory electrocardiography should be repeated.
Rheumatoid/musculoskeletal	Routine monitoring is not necessary in the absence of symptoms. For patients with preexisting conditions, irregular joint examinations/functional assessments should be conducted.

## 7.2 Understanding the spectrum of ADRs and basic management principles

The safety profile of subcutaneous formulations of antineoplastic agents is generally comparable to that of their intravenous counterparts, although they may exhibit specific injection site reactions such as pain, erythema, swelling, and pruritus. Most of these reactions are graded as 1-2 and tend to resolve spontaneously. Different classes of subcutaneous antineoplastic agents exhibit distinct spectra of adverse reactions (Table 14). The management principles should be based on the corresponding type and severity of adverse reactions, with rational treatment and comprehensive assessment leading to appropriate adjustments in the antineoplastic therapy regimen, cycle, and dosage (Table 15). A tiered management approach is adopted for common skin adverse reactions,

gastrointestinal adverse reactions, and thrombocytopenia associated with antineoplastic agents (Tables 16-18).

Table 14 Summary of ADRs to subcutaneous formulations of anticancer agents

Drugs	Classification	Major adverse reactions
Trastuzumab	Anti-HER-2 monoclonal antibody	Cardiac dysfunction, administration-related reactions, hematological toxicity (particularly neutropenia), infections, pulmonary adverse reactions.
Pertuzumab	Anti-HER-2 monoclonal antibody	
Envafolimab	Anti-PD-L1 monoclonal antibody	Liver function abnormalities, bone marrow suppression, rash, weight loss, fatigue, hypothyroidism, decreased appetite.
Atezolizumab	Anti-PD-L1 monoclonal antibody	Fatigue, decreased appetite, rash, nausea, diarrhea, fever, cough, arthralgia, dyspnea, pruritus, asthenia, back pain, vomiting, urinary tract infection, headache.
Daratumumab	Anti-CD38 monoclonal antibody	Bone marrow suppression, upper respiratory tract infection, diarrhea, constipation, fatigue.
Denosumab	RANKL inhibitor	Patients with bone metastases from solid tumors: fatigue/asthenia, hypophosphatemia, nausea. Patients with multiple myeloma: diarrhea, nausea, anemia, back pain, thrombocytopenia, peripheral edema, hypocalcemia, upper respiratory tract infection, rash, headache.
Rituximab	Anti-CD20 monoclonal antibody	Infections, neutropenia, nausea, constipation, cough, alopecia, anemia, fever, fatigue.
Degarelix	GnRH antagonist	Injection site reactions, hot flashes, weight gain, fatigue, elevated serum transaminases, elevated gamma-glutamyltransferase.
Leuprolide	GnRH antagonist	Hot flashes, hypertension, injection site reactions, upper respiratory tract infection, pain, fatigue.
Bortezomib	26S proteasome inhibitor	Nausea, diarrhea, bone marrow suppression, peripheral neuropathy, fatigue, neuralgia, constipation, vomiting, rash, fever, anorexia.
Cytarabine	Pyrimidine antimetabolite	Bone marrow suppression, infections, oral mucositis, nausea and vomiting, diarrhea,

		abdominal pain, liver function abnormalities, alopecia, rash, cytarabine syndrome, fever.
Azacitidine	Pyrimidine antimetabolite	Nausea and vomiting, bone marrow suppression, fever, diarrhea, constipation, injection site erythema.
Bleomycin	Cytotoxic drug	Pulmonary fibrosis or interstitial pneumonia, skin sclerosis or pigmentation, fever and chills, alopecia, anorexia and weight loss, asthenia, nausea and vomiting, stomatitis, and nail changes.
Omacetaxine mepesuccinate	Cell cycle-specific drug	Bone marrow suppression, diarrhea, nausea, fatigue, injection site reactions, fever, infections.

Table 15. Dose adjustments based on ADRs to subcutaneous formulations of anticancer agents

Drugs	Adverse reaction	Treatment measure
Trastuzumab	For clinically significant left ventricular dysfunction, anaphylactic reactions, angioedema, interstitial pneumonia, or acute respiratory distress syndrome	Suspend administration
Envafolelimab	For Grade 2 pneumonia, Grade 2 or 3 diarrhea and colitis, Grade 2 hepatitis, Grade 2 nephritis and renal dysfunction, Grade $\geq 2$ hyperthyroidism, Grade $\geq 2$ hyperglycemia or type 1 diabetes mellitus, Grade $\geq 2$ hypophysitis, Grade $\geq 2$ adrenal insufficiency, Grade 3 or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN), Grade 1 myocarditis, Grade 3 thrombocytopenia, Grade 1 encephalitis, Grade 2 or 3 pancreatitis, Grade 2 myasthenia gravis, Grade 3 or 4 elevated blood amylase or lipase, Grade 2 or 3 first occurrence of other immune-related adverse reactions, Grade 2 hypersensitivity reactions	Suspend administration
	For Grade 3 or 4 or recurrent Grade 2 pneumonia, Grade 4 diarrhea and colitis, Grade $\geq 3$ hepatitis, Grade $\geq 3$ nephritis and renal dysfunction, Grade 4 skin adverse reactions or confirmed SJS or TEN, Grade $\geq 2$ myocarditis, Grade 4 thrombocytopenia,	Permanently discontinue treatment

	Grade $\geq$ 2 encephalitis, Grade 4 pancreatitis, Grade 3 or 4 myasthenia gravis, Guillain-Barré syndrome, Grade 4 first occurrence of other immune-related adverse reactions, recurrent Grade 3 or 4 (excluding endocrine disorders), Grade 3-4 injection site reactions, Grade 3-4 hypersensitivity reactions	
Daratumumab	For Grade 4 hematological toxicity (anemia, neutropenia, or thrombocytopenia), Grade 3 or higher thrombocytopenia with bleeding, febrile neutropenia of any grade, neutropenia with infection of any grade, and Grade 3 or 4 toxicities assessed to pose an increased risk to the patient	Suspend administration
	For immediate allergic reactions or life-threatening (Grade 4) administration-related reactions	Permanently discontinue treatment
Denosumab	For immediate allergic reactions or other clinically significant severe allergic reactions	Permanently discontinue treatment
Rituximab	For hepatitis B virus reactivation, progressive multifocal leukoencephalopathy, hypersensitivity reactions, severe or life-threatening cardiac arrhythmias, increased serum creatinine, or oliguria	Suspend administration
Pertuzumab/trastuzumab	For injection-related reactions, left ventricular dysfunction	Suspend administration
	For severe hypersensitivity reactions	Permanently discontinue treatment
Atezolizumab	For Grade 2 pneumonia, Grade 2 or 3 diarrhea and colitis, Grade 2 hepatitis, symptomatic hypothyroidism or hyperthyroidism, symptomatic adrenal insufficiency, Grade 2 or 3 hypophysitis, Grade 3 or 4 hyperglycemia in patients with type 1 diabetes, Grade 3 or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN), Grade 1 or 2 facial palsy, Grade 3 or 4 elevated serum amylase or lipase levels or Grade 2 or 3 pancreatitis, Grade 2 nephritis, Grade 2 or 3 myositis, Grade 1 pericarditis, Grade 2 or 3 immune-mediated adverse	Suspend administration

	reactions, Grade 1 or 2 infusion-related reactions	
	For Grade 3 or 4 pneumonia, Grade 4 diarrhea and colitis, Grade 3 or 4 hepatitis, Grade 4 hypophysitis, Grade 4 skin adverse reactions or confirmed SJS or TEN, myasthenia gravis/severe myasthenia gravis or Guillain-Barré syndrome and meningoencephalitis of any grade or Grade 3 or 4 facial palsy, Grade 2-4 myelitis, Grade 4 or recurrent pancreatitis of any grade, Grade 2 or higher myocarditis, Grade 3 or 4 nephritis, Grade 4 or recurrent Grade 3 myositis, Grade 2 or higher pericarditis, Grade 4 or recurrent Grade 3 immune-mediated adverse reactions, Grade 3 or 4 infusion-related reactions	Permanently discontinue treatment
Degarelix	For severe allergic reactions	Cease administration
Leuprolide	For thromboembolic events such as myocardial infarction, cerebral infarction, pulmonary embolism, etc. For allergic reactions such as dyspnea, asthma, rhinitis, angioneurotic edema, hypotension, urticaria, rash, pruritus, or interstitial pneumonia	Cease administration
Bortezomib	For hematological toxicity: Grade $\geq 3$ neutropenia with fever, Grade 4 neutropenia lasting more than 7 days, platelet count $<10 \times 10^9/L$	Suspend administration for up to 2 weeks
	For hematological toxicity: If the platelet count on the day of administration is $<25 \times 10^9/L$	Suspend administration
	For Grade $\geq 3$ non-hematological toxicity	Suspend administration
Cytarabine	For severe hematological depression: peripheral platelet count $<50,000/mm^3$ or polymorphonuclear granulocytes $<1,000/mm^3$	Adjust dose or suspend treatment
Azacitidine	Based on hematology laboratory test values, serum electrolytes, and renal toxicity	Adjust dose
Omacetaxine mepesuccinate	For hematological toxicity: Grade 4 neutropenia (absolute neutrophil count $<0.5 \times 10^9/L$ ) occurring within one cycle	Delay the next cycle of treatment and reduce the

		number of administration days by 2 in the next cycle
	For non-hematological toxicity	Interrupt and/or delay administration

Table 16 Management of skin adverse reactions

Grade	Clinical symptoms	Treatment recommendations	Assessment and examination
Maculopapular rash/rash			
Grade 1	Macules/papules covering <10% of the total BSA, with or without symptoms (e.g., pruritus, burning, or tightness)	1. Continue medication therapy 2. For those with dryness and pruritus, apply skin moisturizers and consider using first- or second-generation antihistamines as needed	1. Assess after 2 weeks, closely monitoring changes in rash severity; if no improvement, proceed to the next grade's management 2. Continue the current dose and closely monitor changes in the rash 3. Conduct blood routine tests and liver and kidney function tests if necessary
Grade 2	Macules/papules covering 10%-30% of BSA, with or without symptoms (e.g., pruritus, burning, or tightness); limited daily activities; no signs of local infection.	1. Add tacrolimus ointment, oral doxycycline or minocycline, and oral antihistamines 2. Apply acne cream to the rash surface; use furacilin facial masks for wet compresses; for pruritus relief, use antihistamines such as levocetirizine, desloratadine, diphenhydramine, etc.	1. Continue the current dose and closely monitor changes in the rash 2. Conduct blood routine tests and liver and kidney function tests if necessary; consider referring to a dermatologist and performing a skin biopsy

Grade 3	Macules/papules covering >30% of BSA, with or without symptoms (e.g., erythema, purpura, or epidermal peeling), significantly affecting daily activities, with potential for local infection.	<ol style="list-style-type: none"> <li>1. Consider suspending medication therapy</li> <li>2. Perform bacterial/fungal/viral cultures if necessary; in addition to maintaining Grade 2 treatment, add prednisone.</li> <li>3. Apply hydrocortisone ointment or aureomycin ointment, which can be combined with oral doxycycline or dimethylaminotetracycline.</li> <li>4. For facial rashes, apply desonide cream or anti-inflammatory and antipruritic cream</li> </ol>	<ol style="list-style-type: none"> <li>1. Assess after 2 weeks; if no improvement, discontinue the medication</li> <li>2. After discontinuation, continue treating the rash and consult a dermatologist if necessary. When the rash improves to <math>\leq</math> Grade 2, consider resuming medication at a reduced dose, following Grade 2 treatment</li> <li>3. Conduct blood routine tests and liver and kidney function tests if necessary</li> </ol>
Pruritus			
Grade 1	Mild or localized	<ol style="list-style-type: none"> <li>1. Continue medication therapy</li> <li>2. Administer oral antihistamines</li> <li>3. Use medium-strength topical glucocorticoids</li> </ol>	Conduct blood routine tests and liver and kidney function tests if necessary
Grade 2	Intense or widespread; intermittent; skin damage (e.g., edema, papules, desquamation, lichenification, exudation/crusting) due to scratching; limited daily activities.	<ol style="list-style-type: none"> <li>1. Continue medication therapy with enhanced antipruritic measures</li> <li>2. Administer oral antihistamines</li> <li>3. Consider discontinuing medication for some severe cases</li> </ol>	<ol style="list-style-type: none"> <li>1. Consult a dermatologist and refer if necessary</li> <li>2. Conduct blood routine tests and liver and kidney function tests if necessary</li> </ol>
Grade 3	Intense or widespread;	<ol style="list-style-type: none"> <li>1. Suspend medication therapy</li> <li>2. Administer oral</li> </ol>	1. Consider hospitalization, urgent dermatological

	persistent; significantly impaired daily self-care or sleep	antihistamines: gamma-aminobutyric acid agonists (gabapentin, pregabalin) 3. For refractory pruritus, consider aprepitant or omalizumab (if serum IgE levels are elevated)	consultation, and skin tissue biopsy 2. Conduct blood routine tests and liver and kidney function tests if necessary; consider obtaining a biopsy if necessary
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Table 17 Management of gastrointestinal adverse reactions

Grade	Clinical symptoms	Treatment recommendations	Assessment and examination
Abdominal pain/diarrhea			
Grade 1	Asymptomatic; clinical or diagnostic observation only required (Grade 1 diarrhea: $\leq 4$ times/day)	1. Continue medication therapy 2. Oral rehydration and use of antidiarrheal drugs as needed for symptomatic relief 3. Avoid a high-fiber/lactose diet	1. Differentiate between infectious diarrhea and drug-related diarrhea through stool routine tests, stool cultures, and systemic infection indicators monitoring. 2. Note: Envolimab and Atezolizumab are anti-PD-L1 monoclonal antibodies; abdominal pain/diarrhea caused by these agents should be managed according to the guidelines for managing immune checkpoint inhibitor toxicities.
Grade 2	Abdominal pain; mucous or bloody stool (Grade 2 diarrhea: 4-6 times/day)	1. Suspend medication therapy 2. Aggressively address symptoms	
Grade 3	Severe abdominal pain; changes in bowel habits; requiring medicinal intervention; peritoneal irritation signs (Grade 3 diarrhea: $\geq 7$ times/day)	1. Suspend medication therapy 2. Administer rehydration to prevent or treat dehydration, provide dietary guidance (nil by mouth, liquid diet, total parenteral nutrition), and closely monitor changes in electrolyte balance	
Vomiting			

Grade 1	No intervention required	<p>1. Focus on prevention</p> <p>2. Develop individualized prevention and treatment plans based on the emetogenic risk of the planned anticancer treatment regimen, the patient's own high-risk factors, and the severity of previous nausea and vomiting.</p>	<p>1. Cytarabine and Azacitidine pose a moderate emetogenic risk. The standard dual regimen of 5-HT<sub>3</sub>RA combined with dexamethasone can be used for prevention. For patients with anxiety or depression tendencies, olanzapine may be added. For patients with other risk factors or previous treatment failure with "corticosteroids + 5-HT<sub>3</sub>RA", a combination regimen of dexamethasone + 5-HT<sub>3</sub>RA + NK-1RA should be used.</p> <p>2. Atezolizumab poses a low emetogenic risk. A single antiemetic drug is recommended, such as 5-HT<sub>3</sub>RA, dexamethasone, dopamine receptor antagonists (e.g., metoclopramide), or chlorpromazine</p> <p>3. Other drugs pose a mild emetogenic risk. For patients with no history of nausea and vomiting, routine antiemetic drugs are not necessary before chemotherapy. If vomiting occurs, subsequent treatment should follow the prevention and management of nausea and vomiting caused by low emetogenic regimens</p>
Grade 2	Outpatient intravenous rehydration; medical intervention required		
Grade 3	Requires nasogastric feeding, total parenteral nutrition, or hospitalization		

Table 18. Management of Thrombocytopenia

Grade	Clinical symptoms	Treatment recommendations	Assessment and
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			examination
Grade 1	$75 \times 10^9/L < PLT < 100 \times 10^9/L$	Closely monitor platelet count and bleeding status	1. Assess the cause of thrombocytopenia and administer cause-specific treatment. 2. Consider the impact of the cancer patient's status on platelet levels: age, Eastern Cooperative Oncology Group (ECOG) score, nutritional status, comorbidities, cancer type, and staging, etc.
Grade 2	$PLT < 75 \times 10^9/L$	Administer recombinant human interleukin-11 (rhIL-11), recombinant human thrombopoietin (rhTPO), or thrombopoietin receptor agonist (TPO-RA). Discontinue treatment when $PLT \geq 100 \times 10^9/L$ compared to pre-treatment levels.	
Grade 3	$PLT < 10 \times 10^9/L$	Administer prophylactic platelet transfusion alone or combined with rhIL-11, rhTPO, or TPO-RA. Discontinue treatment when $PLT \geq 100 \times 10^9/L$ compared to pre-treatment levels.	

### 7.3 Focus on patients in special populations

Patients in special populations encompass elderly individuals, children, pregnant and lactating women, and those with hepatic or renal insufficiency. Compared to the general population, the physiological and pathological states of these patients may alter the pharmacokinetics-pharmacodynamics of drugs within the body. Elderly patients often suffer from multiple diseases and are prescribed multiple medications, placing them at high risk for adverse drug reactions (ADRs). Clinical trials frequently fail to establish the safety and efficacy of drugs for pediatric patients, except for certain anticancer agents. Anticancer drugs may pose potential risks to fetuses through pregnant and lactating patients; therefore, this factor should be considered when administering medication, and patient education on drug use should be provided. For patients with hepatic or renal insufficiency receiving anticancer drugs, the dosages of drugs metabolized by the liver or excreted by the kidneys should be adjusted based on the patient's hepatic and renal function. Refer to Tables 11 and 12 for the use of anticancer drug subcutaneous formulations in special populations.

### 7.4 Patient education on drug use

To ensure close collaboration between patients and healthcare professionals throughout the treatment process and maximize treatment efficacy, it is essential to educate patients and their families. Cancer patients and/or their families/caregivers should be informed about the potential types and manifestations of adverse events during medication use before starting drug therapy. A clear understanding of drug-related adverse reactions by patients and/or their families/caregivers is crucial for early identification, timely reporting, and effective management of adverse reactions. Specific educational points include:

- a) The names, dosages, and treatment cycles of therapeutic drugs;
- b) Categories and manifestations of drug-related adverse reactions, their onset times, and reversibility;
- c) Management of drug adverse reactions: Before administration, carefully assess the risk of inducing adverse reactions, provide corresponding preventive measures and initial dose calculations for high-risk and special populations, closely evaluate and monitor during use, and promptly address adverse reactions to avoid severe consequences.

Before drug administration, patients should actively inform their doctors of the following information: (1) Any allergies to drugs/foods. (2) Pregnancy status or plans for pregnancy, breastfeeding status or plans for breastfeeding. (3) All medications being taken, including prescription and non-prescription drugs, vitamins, herbal medicines, and dietary supplements. (4) Any other medical issues, such as severe adverse reactions caused by previous drug therapies, anemia, infections, heart/liver/kidney/respiratory diseases, and vaccinations.

For the first drug administration, patients should be accompanied by their families/caregivers. In the event of adverse events, patients and/or their families/caregivers should directly report symptoms to the treatment team (doctors, nurses, pharmacists, etc.). The adverse reactions and self-management measures listed in Table 19 are designed to assist patients in daily self-care to mitigate the occurrence and symptoms of adverse reactions.

Table 19 Patient self-management of ADRs

Type	Manifestation	Self-management
Injection site reaction	Skin flushing, itching, chills, fever, chest tightness, headache, dizziness, and other symptoms.	<ul style="list-style-type: none"> <li>●Ensure that there is no pressure on the injection site from belts, waistbands, or other types of clothing. The injection site should be changed each time.</li> <li>●Assess the injection site for redness, stinging sensation, or inflammation. If symptoms of extravasation occur, report them immediately.</li> <li>●Do not rub the injection site after injection.</li> </ul>
Skin adverse reactions	Rash, itching, hair loss, etc.	<p>——Skin protection</p> <ul style="list-style-type: none"> <li>●When cleaning the skin, use unscented soap or body wash with lukewarm water to avoid</li> </ul>

		<p>irritation.</p> <ul style="list-style-type: none"> <li>●Apply a non-alcoholic, non-irritating moisturizer daily in the direction of hair growth until fully absorbed.</li> <li>●Avoid sun exposure when going outside and take sun protection measures such as wearing a hat, using an umbrella, or applying sunscreen.</li> </ul> <p>——Skin care</p> <ul style="list-style-type: none"> <li>●Keep the skin clean and moist by applying moisturizer 2-3 times daily.</li> <li>●Avoid rubbing the skin back and forth with soft paper towels. Bathe with warm water to prevent damage from high temperatures.</li> <li>●Wear soft, loose-fitting cotton clothing instead of synthetic fibers or stiff materials to prevent skin irritation from rough textures or friction.</li> <li>●Trim nails regularly to prevent scratching the skin with long nails. When itchy, avoid scratching and lightly pat the area to relieve discomfort.</li> <li>●Keep the air cool during sleep.</li> <li>●In case of itching or redness, apply topical cooling agents (such as menthol) or cold compress with cloth items or gently pat the affected area.</li> </ul> <p>——Prevention of hair loss</p> <ul style="list-style-type: none"> <li>●Before chemotherapy, doctors should discuss the impact of hair loss with patients and alternative chemotherapy options. This discussion is crucial for minimizing emotional distress related to hair loss.</li> <li>●During chemotherapy, measures such as wearing a cold cap can be taken to reduce the dosage of drugs reaching the scalp, thereby reducing hair loss. Alternatively, keep hair short.</li> <li>●Avoid physical and chemical factors that may accelerate shedding. Consider wearing a wig.</li> </ul>
Mucosal system diseases	Oral ulcers, oral mucosal congestion, edema.	<ul style="list-style-type: none"> <li>●Maintain oral hygiene by brushing teeth after meals and avoid wearing dentures.</li> <li>●Drink plenty of water and avoid overly hot, acidic, or irritating foods.</li> <li>●If oral ulcers have occurred, reduce inflammatory exudation by sucking on ice cubes or rinsing with saline solution or antibiotic solutions.</li> </ul>
Cardiac adverse	Dizziness, blurred	Special attention should be given to elderly

reactions	vision, fatigue, edema, or cyanosis.	patients or those with a history of cardiac disease.
Pulmonary adverse reactions	Cough with sputum, shortness of breath, chest pain, hemoptysis, rapid breathing, or dyspnea.	Special attention should be given to elderly patients, patients with asthma, chronic obstructive pulmonary disease, or other symptoms of cardiopulmonary diseases.
Liver adverse reactions	Anorexia, abdominal distension, icterus of the sclera/skin, dark urine, etc.	<ul style="list-style-type: none"> <li>●Increase intake of foods rich in vitamins, such as fruits and vegetables.</li> <li>●Avoid high-fat diets, such as red meat (beef, pork, lamb), butter, etc.</li> </ul>
Renal adverse reactions	Back pain, foamy urine, hematuria, swelling of feet/lower legs, changes in urine volume/color, etc.	<ul style="list-style-type: none"> <li>●Maintain a low-salt, low-fat, and high-quality protein diet.</li> <li>●Drink plenty of water to ensure sufficient urine output for drug excretion.</li> </ul>
Gastrointestinal adverse reactions	Vomiting, diarrhea, abdominal pain, bloody stools, etc.	<ul style="list-style-type: none"> <li>●Follow the doctor's advice to preventively use antiemetic drugs to avoid most occurrences of nausea and vomiting.</li> <li>●Try to relax before and after chemotherapy by adjusting your mindset through deep breathing, meditation with eyes closed, reading, listening to music, etc.</li> <li>●Maintain perianal skin cleanliness by using soft toilet paper for cleaning after each bowel movement and washing the perianal area with warm water to prevent skin damage.</li> <li>●Increase fluid intake appropriately.</li> <li>●If you experience four or more bowel movements per day or if there is blood in the stool, seek medical attention at the hospital. Eat easily digestible foods and eat smaller meals more frequently; reduce consumption of high-fiber, high-fat, raw or cold foods, dairy products, alcohol, coffee, sugar, etc.</li> </ul>
Thrombotic adverse reactions	Limb pain, paresthesia, swelling, or skin discoloration, etc.	<ul style="list-style-type: none"> <li>●Engage in appropriate daily activities to promote blood circulation and avoid prolonged bed rest.</li> <li>●Pay special attention to elderly patients, those who are obese, those with a history of long-term bed rest, or those with concurrent cardiopulmonary diseases.</li> </ul>
Myelosuppression	Anemia, infections, bleeding.	<ul style="list-style-type: none"> <li>●Choose high-protein, high-calorie, vitamin-rich foods, essential trace elements (iron), folic acid, and nutritious foods such as animal liver, blood products, fish and shrimp, eggs, soy products, black fungus, black sesame, red dates, and fresh vegetables and fruits.</li> <li>●Avoid contact with relatives who have infectious diseases such as the common cold.</li> </ul>
Joint pain and	Joint pain, difficulty	<ul style="list-style-type: none"> <li>●Engage in appropriate activities or aerobic</li> </ul>

arthritis	walking, joint swelling, erythema.	exercise daily to improve physical strength and sleep, and alleviate pain.  ●Warm up before exercising and pay attention to joint protection during the activity to prevent falls, especially when changing positions (such as getting out of bed or standing up after sitting for a long time);move slowly.
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## Appendix A (Informative)

### Characteristics of clinical development of subcutaneous antitumor drug formulations

#### A.1 Pharmacokinetics of subcutaneous antitumor drug formulations

Intravenous administration involves no absorption process, allowing the drug to rapidly reach moreover, long-term multiple courses of intravenous administration can lead to reduced patient tolerance and compliance. Subcutaneous administration involves an absorption process at the injection site, where drug molecules must diffuse through the interstitial layer of the skin for absorption. The absorption process after subcutaneous administration is influenced by various factors such as molecular weight, charge, hydrophilicity, volume of administration, and injection site. Physiological factors such as age and body mass can also affect the bioavailability of the same drug, resulting in significant differences<sup>[6]</sup>. Macromolecules are usually slowly absorbed by the subcutaneous extracellular matrix layer after injection, resulting in a lower  $C_{max}$  compared to intravenous administration of the same dose. For drugs with relatively high molecular weights (>16 kDa), such as common protein polypeptide drugs and nucleic acid drugs, the lymphatic system plays a crucial role in drug uptake during subcutaneous administration. Macromolecules enter the lymphatic circulation through convective transport of interstitial fluid and are transported into the bloodstream via the unidirectional flow of lymph within the lymphatic vessels<sup>[7]</sup>. Due to the slow flow rate of lymph fluid, most macromolecules reach their peak time ( $T_{max}$ ) of 2 to 14 days after subcutaneous administration, with a bioavailability of 50% to 80%<sup>[8]</sup>. For low-molecular-weight small molecule drugs (<1 kDa), their vascular endothelial permeability is unrestricted, exhibiting a high filtration rate and being slowly absorbed by capillaries. Appendix Table A.1 summarizes the pharmacokinetic parameters of antitumor drugs administered intravenously and subcutaneously in partial clinical trials. These clinical trial data indicate that for specially designed and selected antitumor drug formulations administered subcutaneously, the drug exposure can be comparable to those administered intravenously.

Table A.1 Comparative pharmacokinetics of antitumor drugs administered intravenously and subcutaneously

Drugs	Pharmacokinetic parameters	Intravenous administration	Subcutaneous administration
Trastuzumab <sup>[9]</sup>	AUC ( $\mu\text{g}\cdot\text{d}/\text{mL}$ )	1800	2090
	$T_{1/2}$ (d)	10	10
Daratumumab <sup>[10]</sup>	Trough concentration ( $\mu\text{g}/\text{mL}$ )	522	593
Rituximab <sup>[11]</sup>	AUC ( $\mu\text{g}\cdot\text{d}/\text{mL}$ )	3630.4	4088.8
	Trough concentration ( $\mu\text{g}/\text{mL}$ )	61.5	97.5
Pertuzumab/trastuzumab <sup>[12]</sup>	Pertuzumab trough concentration ( $\mu\text{g}/\text{mL}$ )	78.5	93.7
	Pertuzumab $C_{max}$ ( $\mu\text{g}/\text{mL}$ )	238	158
	Pertuzumab $T_{max}$ (d)	0.35	4.35
	Pertuzumab AUC ( $\mu\text{g}\cdot\text{d}/\text{mL}$ )	2520	2530
	Trastuzumab trough concentration ( $\mu\text{g}/\text{mL}$ )	47.1	61.6

	Trastuzumab C <sub>max</sub> (µg/mL)	180	116
	Trastuzumab T <sub>max</sub> (d)	0.40	4.45
	Trastuzumab AUC (µg·d/mL)	1690	1700
Atezolizumab <sup>[13]</sup>	AUC (µg·d/mL)	3328	2907
	Trough concentration (µg/mL)	85	89
Leuprorelin <sup>[14]</sup>	AUC (ng·h/mL)	125.8	118.6
	CL (mL/min)	139	151
Bortezomib <sup>[15]</sup>	AUC (ng·h/mL)	241	195
	C <sub>max</sub> (ng/mL)	162	22.5
Cytarabine <sup>[16]</sup>	AUC (ng·min/mL)	17059.14	20340.61
	C <sub>max</sub> (ng/mL)	4116.20	170.79
	CL (L/min)	6.21	6.10
	Vd (L)	20.10	724.35
Azacitidine <sup>[17]</sup>	AUC (ng·h/mL)	1044.26	960.53
	C <sub>max</sub> (ng/mL)	2750.0	750.0
	CL (L/h)	146.70	167.48
Bleomycin <sup>[18]</sup>	AUC (ng·h/mL) <sup>[18]</sup>	1398	1261
	CL (mL/min/m <sup>2</sup> ) <sup>[19]</sup>	67.8	60.5
	Vd (L/m <sup>2</sup> ) <sup>[19]</sup>	13.2	19.2
Omacetaxine mepesuccinate <sup>[20]</sup>	CL/F (L/h)	12.4	14.2
	T <sub>1/2</sub> (h)	9.3	8.9

## A.2 Fixed-dose regimen of subcutaneous preparations of antitumor drugs

The dosage of antitumor monoclonal antibody drugs administered intravenously is often adjusted based on body weight or body surface area, aiming to correct potential individual variances among patients as well as drug distribution and elimination. When developing subcutaneous preparations of monoclonal antibody drugs previously marketed for intravenous administration, it may be considered to change the dose regimen adjusted by body mass or body surface area to a fixed dose<sup>[21]</sup>. The fixed-dose regimen eliminates the need to account for dose differences between individuals, which can reduce the overall healthcare cost of medical treatment, reduce environmental hazards and occupational exposure caused by drug overflow, and greatly reduce the likelihood of medication errors.

There is evidence that a fixed dosage of monoclonal antibody medicines can be used without compromising therapy safety or effectiveness<sup>[22]</sup>. In general, the viability of a fixed-dose regimen is determined by the range of drug exposure and if the treatment index is large enough to account for exposure disparity generated by fixed-dose dosing across body mass ranges. Monoclonal antibody-based antitumor medicines were mostly dispersed in plasma and extracellular fluid, with no association with body mass parameters. Its elimination mechanisms include protein catabolism, the non-specific immunoglobulin G elimination pathway, and intracellular destruction following binding to the target. The latter is the main pathway of elimination, which is related to the expression level of the target protein, rather than body mass<sup>[22]</sup>. In conclusion, body weight has little effect on the distribution and elimination of monoclonal antibody antitumor drugs, and the therapeutic window for monoclonal antibody therapeutics is often broad, making them suited for

fixed dosage administration.

Trastuzumab and rituximab intravenous doses should be adjusted based on body weight and surface area, whereas subcutaneous formulations are given at a set dose. The clinical trial findings for the two methods of administration revealed that the blood trough concentration and effectiveness of subcutaneous injection were comparable to those of intravenous administration, and target receptor saturation was equal<sup>[23, 24]</sup>. The  $C_{max}$  of trastuzumab or rituximab was not associated with clinical effectiveness<sup>[25, 26]</sup>. As a result, although the  $C_{max}$  following subcutaneous injection is often lower than that after intravenous administration, the risk of inadequate drug exposure in patients is reduced<sup>[21]</sup>.

### **A.3 Related excipients for subcutaneous preparations of antitumor drugs**

Antitumor medications in subcutaneous form are classified into two types: macromolecular monoclonal antibodies and small molecule therapies. Monoclonal antibody preparations often require optimization of storage and usage settings for protein stability to assure product safety and efficacy. Monoclonal antibody subcutaneous formulations must have a restricted amount of active components. To achieve bioavailability comparable to intravenous administration, subcutaneous preparations may require a higher dosage<sup>[21]</sup>, which will eventually lead to higher liquid concentrations of subcutaneous preparations in traditional processes, posing significant challenges to product stability, including long-term storage, efficacy maintenance, and protein aggregation prevention. High-concentration preparations may cause increased viscosity and decreased solubility, increasing the possibility of protein aggregation and affecting drug stability. As a result, protein solubility, colloidal stability, structural stability, and solution homogeneity are critical aspects influencing the creation of high-concentration protein formulations. Pharmaceutical preparations need the use of an appropriate buffer system, pH range, stabilizer, and surfactant. The buffer system can maintain the solution's pH range and protein stability. Sugars (such as sucrose and trehalose) are utilized to stabilize protein structure. Salt solutions, such as sodium chloride, can change the osmotic pressure and raise the surface tension of the formula. Surfactants can increase protein solubility and decrease protein aggregation. In summary, excipients control liquid stability through a variety of molecular interactions and processes.

Hyaluronidase can be used as an adjuvant to accelerate the hydrolysis of hyaluronic acid in the extracellular matrix of the subcutaneous injection site, lowering its viscosity, increasing tissue permeability, improving drug fluidity, and promoting drug absorption. Based on this, adding hyaluronidase to the subcutaneous formulation can reduce the drug concentration, increase the drug volume, and enhance the drug absorption rate and bioavailability<sup>[27]</sup>. Trastuzumab, daratumumab, rituximab, pertuzumab/trastuzumab, and atezolizumab are currently marketed as subcutaneous anti-tumor medicines that include recombinant human hyaluronidase. During maintenance therapy, the blood trough concentration of rituximab 1400 mg subcutaneous preparation is comparable to that of intravenous infusion of rituximab 375 mg/m<sup>2</sup>, and it may be safely provided in 2~8 minutes with a maximum administration volume of 11.7 mL<sup>[28]</sup>. The exposure curve of 600 mg trastuzumab subcutaneous preparation was non-inferior to that of trastuzumab for intravenous injection based on body mass administration (8 mg/kg loading dose, 6 mg/kg maintenance dose), and the subcutaneous preparation did not require a loading dose, and the administration volume could be close to 5 mL, with good tolerance<sup>[29]</sup>.

### **A.4 Efficacy and safety of subcutaneous preparations of antitumor drugs**

Subcutaneous and intravenous anticancer medication formulations differ in terms of method of

administration, pharmacokinetics, and excipients. Medical companies have conducted non-inferiority studies comparing the effectiveness and safety of subcutaneous versus intravenous administration in the development of subcutaneous formulations. The phase III HannaH test found no significant difference in the effectiveness of trastuzumab intravenous versus subcutaneous administration in individuals with early HER-2 positive breast cancer. There was no significant difference in the overall incidence of adverse reactions between intravenous and subcutaneous injection (93.9% vs 97.3%), but there were more patients with severe adverse reactions in the subcutaneous injection group than in the intravenous group (20.9% vs 12.4%)<sup>[30]</sup>; the objective remission rates of intravenous and subcutaneous preparations were similar (88.8% vs 87.2%), and the median response time was 6 weeks. In neoadjuvant therapy, the efficacy of subcutaneous injection of trastuzumab was not inferior to intravenous administration for pCR rate (45.4% vs 40.7%)<sup>[30]</sup>. The SABRINA trial demonstrated objective remission rates of 84.9% in the rituximab intravenous group and 84.4% in the subcutaneous group; the incidence of ADRs was similar (95.0% vs. 96.0%); and the incidence of grade 3 or higher ADRs was also similar (55.0% vs. 56.0%)<sup>[31]</sup>. Objective remission rates were non-inferior with subcutaneous daratumumab to intravenous (41.0% vs 37.0%), with similar rates of adverse events<sup>[10]</sup>. Imscin 001 test showed that the progression-free survival (risk ratio was 1.08) and objective remission rate (12.0% vs 10.0%) of patients in the subcutaneous administration group and the intravenous administration group of atezolizumab were similar, and no new safety problems were found<sup>[13]</sup>. The FeDeriCa test showed that the pCR rate of pertuzumab/trastuzumab was comparable to that of intravenous pertuzumab and trastuzumab, and the safety was similar<sup>[12]</sup>. In general, the efficacy and safety of subcutaneous and intravenous preparations of anti-tumor drugs are similar.

## Appendix B (Informative)

### Other relevant information

#### B. 1 Immunogenicity of subcutaneous preparations of antitumor drugs

The immunogenicity of medications is defined as the capacity of pharmaceuticals and/or their metabolites to elicit immunological responses or immune-related activities against themselves or associated proteins. Unnecessary or unanticipated immune responses can result in the biological activity of neutralizing medications, cross-immune interactions, and unpleasant effects such as allergic reactions. Numerous variables influence immunogenicity, including patient characteristics, drug-related factors, and other unknown aspects. Patient variables included race, genetics, illness kind, and so on. Drug-related factors include variations in the amino acid sequence of monoclonal antibody therapeutics, glycosylation levels, duration of administration, dosing regimen, method of administration, mass fraction of raw materials and excipients, and contaminants. Extravascular delivery of macromolecular protein medicines frequently results in protein aggregation and precipitation. The extravascular approach is more likely to produce immunogenicity than the intravenous route, whereas subcutaneous injection is more probable than intramuscular injection. One of the most important treatment-related elements that contribute to immunogenicity is the route of administration and the development of ADA. The ADA reaction to therapeutic proteins can be classified into neutralizing and binding antibodies. Neutralizing antibodies, for example, can detect and weaken the portions of therapeutic proteins that are crucial to their biological action. The interaction between antibody and protein can alter the pharmacokinetics of the protein and indirectly impair its effectiveness by lowering total systemic exposure. The anatomical nature of the subcutaneous injection site has sparked extensive debate concerning its immunological potential. It is believed that since dendritic cells are the most powerful antigen-presenting cells in the body and the main initiator of T cell activation, and there are few dendritic cells in the subcutaneous layer, direct injection into this layer can avoid potential immunogenicity<sup>[31]</sup>. However, studies have revealed the role of skin dendritic cells in inducing immune responses, especially Langerhans cells and dermal dendritic cells distributed in the epidermis<sup>[32]</sup>. These antigen-presenting cells migrate to the subcutaneous injection layer to treat the injected macromolecular drugs and present them to T cells in the lymphatic vessels as the first immune interaction before entering the systemic blood circulation. The propensity of dendritic cells in the skin to migrate improves the immunogenicity of macromolecular medication subcutaneous injection, and the risk of ADA following subcutaneous administration may be greater than that of intravenous administration. ADA may also alter medication pharmacokinetics by stimulating reticuloendothelial system proteolysis, which increases clearance, as well as drug safety and effectiveness by lowering pharmacological activity<sup>[6]</sup>. However, the aforementioned notion has not been supported by a vast body of clinical evidence<sup>[8]</sup>. The HannaH test revealed that 3.4% (10/295) and 6.8% (20/295) of patients developed ADA following intravenous and subcutaneous trastuzumab, respectively, while 11.5% (34/295) of patients in the subcutaneous injection group produced anti-recombinant human hyaluronidase antibodies. Trastuzumab's trough concentration, pCR rate, and IRRs were unaffected by either anti-drug or anti-hyaluronidase antibodies<sup>[30]</sup>. After intravenous and subcutaneous injection of rituximab, individuals with positive ADA tests showed no influence on B cell consumption, effectiveness, pharmacokinetics, or safety<sup>[3]</sup>.

## **B.2 Infusion-related reactions of subcutaneous preparations of antitumor drugs**

IRR symptoms include flushing, rash, fever, chills, dyspnea, and hypotension. IRRs for monoclonal antibody medicines occur mostly during the initial infusion and are typically mild to moderate. In clinical practice, reducing the pace of intravenous infusion can help to lessen the severity and occurrence of IRR. In terms of pharmacokinetics, slow intravenous infusion gradually increases the blood concentration of monoclonal antibody medicines, comparable to subcutaneous delivery.

The proportion of patients with IRRs following the first and second intravenous infusion of daratumumab was 46% and 2%, respectively. However, IRRs occurred in 22% of patients following daratumumab subcutaneous injection, with the majority of them being grade 1/2 and occurring at the initial subcutaneous injection or within 6 hours of injection<sup>[21]</sup>. The incidence of IRRs after atezolizumab intravenous infusion was 3.2% (4/124), whereas no IRRs occurred after subcutaneous injection (0/247)<sup>[13]</sup>. Although subcutaneous trastuzumab therapy resulted in twice as much ADA as intravenous administration, there was no influence on the incidence of IRRs<sup>[30]</sup>. In general, existing data are sparse, and head-to-head clinical studies for diverse medications are required to investigate the incidence of IRRs following subcutaneous injection vs intravenous administration.

## **B.3 Injection site reaction of antitumor drugs subcutaneous preparation**

The safety of subcutaneous anticancer drug preparations differs from intravenous preparations, however, the occurrence is minimal, with most cases being grade 1 or 2, characterized by discomfort, erythema, edema, or itching surrounding the injection site<sup>[11, 12]</sup>. Injection site reactions can be caused by factors such as uneven operation, closeness to blood vessels during injection, physical and chemical features of biological agents, or a reaction to media components<sup>[33]</sup>, although they can be managed by monitoring and appropriate treatment. Standardized injection procedures can significantly minimize the number of injection site reactions.

Subjective discomfort at the injection site may be an indicator of compliance. Patient-related characteristics such as body weight, gender, and age may predispose people to injection site discomfort. Medical staff can assist patients decrease treatment-related anxiety by effectively managing patient expectations and actively discussing potential dangers at the injection site<sup>[34]</sup>. In addition to the direct effect of the drug, the following factors may be associated with pain after subcutaneous injection: needle characteristics, injection technology and location, injection volume, injection speed, osmotic pressure, viscosity, and pH value of the preparation, and the types of excipients, including buffers and preservatives<sup>[35]</sup>. The smaller the diameter, the shorter the needle, and the less discomfort from injection, bleeding, and bruising. However, the right needle length should be chosen according to the administration population. When injecting subcutaneously, the suggested injection angle is 45° or 90°, depending on the needle length and injection location. When the injection angle is 45°, the needle should be positioned higher on the inclined plane, and the injection thigh is more painful than the abdomen<sup>[36]</sup>. To minimize discomfort from cold injections, most biological agents should be kept at 2°C-8°C and brought to room temperature before administration. The subcutaneous injection volume is typically limited to 1.5 mL, however a larger dose might be administered if necessary. The high osmotic pressure and poor viscosity of the fluid contribute to the rise in discomfort. To reduce discomfort, irritation, and tissue damage, the solution's osmotic pressure should be less than 600 mOsm/kg and the pH should be near to the

physiological pH. In addition, a cold compress at the injection site can effectively alleviate discomfort<sup>[33]</sup>.

#### **B. 4 Patient preference**

Some patients prefer subcutaneous administration, possibly because it can save time, relieve pain and discomfort, and have fewer adverse reactions. Some patients prefer intravenous administration since the injection site is less sensitive than subcutaneous administration, the central venous catheter is used more effectively, and there is more time to adapt to the treatment environment and interact with medical staff and other patients<sup>[9]</sup>. Taking trastuzumab as an example, patients receiving chemotherapy or other intravenous administration may be more inclined to intravenous administration, probably because avoiding additional injections is more important than saving time<sup>[37]</sup>. Another retrospective analysis found that 97.4% of patients switched to trastuzumab subcutaneous injection, with the majority of these patients previously receiving intravenous treatment. The research also showed no evidence that patients preferred intravenous over subcutaneous delivery at the start of treatment<sup>[38]</sup>. In the trastuzumab preference test, 88.9% of patients chose subcutaneous injection, 9.6% preferred intravenous administration, and 1.5% expressed no preference<sup>[39]</sup>.

#### **B.5 Medical cost**

Several international studies have calculated the cost difference between intravenous and subcutaneous delivery. In comparison to intravenous injection of trastuzumab, the initial intravenous infusion time was 90 minutes, the succeeding course was 30 minutes, and the subcutaneous preparation was 2-5 minutes. In the PrefHer clinical trial conducted in the United Kingdom, the time cost and consumables cost per intravenous injection of trastuzumab were 132.05 pounds and 12.92 pounds, respectively, whereas the time cost and consumables cost per subcutaneous injection were 31.99 pounds and 1.17 pounds, respectively<sup>[40]</sup>. Trastuzumab subcutaneous delivery may save more than pound 2,000 per patient during the duration of therapy (i.e., 18 cycles) as compared to intravenous administration. Subcutaneous administration of daratumumab was associated with a 2.7 to 3.0 hours reduction in median total outpatient time spent and a 2.7 to 2.8 hours reduction in median total treatment time compared with intravenous administration<sup>[41]</sup>. The time spent at the outpatient department is determined as the difference between the patient's entrance and discharge procedures, which is longest at the initial injection and decreases as the treatment cycle progresses. The overall treatment time includes the time from entering the infusion chamber to leaving or checking out. A cost analysis of intravenous versus subcutaneous trastuzumab in the treatment of breast cancer in Hong Kong<sup>[42]</sup> found that using subcutaneous preparations might save 7.9 hours of working time for full-time nursing staff and 6.2 hours of working time for full-time pharmacists per week. According to statistics from 2017<sup>[42]</sup>, following 18 cycles of trastuzumab subcutaneous therapy, the cost of medicine procurement and medical staff time was reduced by 9451.28 dollars and 566.16 dollars, respectively, saving more than 8 million dollars per year. The current study may not reflect the real clinical situation, without considering the resource reuse of patients with central venous catheters, for example, and the cost of insertion and maintenance of catheters and treatment of potential complications (infection and thrombosis)<sup>[9]</sup>. At present, there is still a lack of cost analysis literature comparing subcutaneous and intravenous administration of antitumor drugs in mainland China.

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