



Hospital Universitario
Ramón y Cajal
Servicio de Farmacia



HERCEPTIN 150 MG VIAL C/1

ROCHE FARMA

ESPECIFICACIONES TECNICAS PROCEDIMIENTO NEGOCIADO: TRASTUZUMAB

Evaluable y seleccionado por la Comisión de Farmacia y Terapéutica, e incluido en la Guía Farmacoterapéutica del Área 4.

GRUPO TERAPÉUTICO: L01XC – Otros citostáticos: anticuerpos monoclonales

Presentación en viales de 15 mL de vidrio transparente de tipo I, con tapón de goma butílica laminada con una película de fluoro-resina, que contiene 150 mg de trastuzumab, perfectamente identificados con:

- Nombre comercial
 - Nombre del principio activo
 - Dosis en miligramos
 - Lista de excipientes
 - Forma farmacéutica
 - Vía de administración
 - Lote
 - Caducidad
 - Condiciones de conservación
 - Código Nacional
 - Laboratorio fabricante
-
- Información técnica complementaria relativa a:
 - Posología y forma de administración
 - Nivel de información sobre utilización del medicamento en situaciones especiales: geriatría, pediatría, embarazo, lactancia, insuficiencia renal y hepática, diálisis, patologías concomitantes e interacciones.

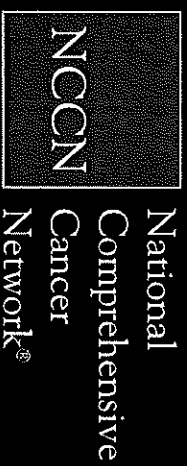


- Nivel de información sobre vigilancia farmacológica y toxicológica: medidas preventivas de efectos adversos potencialmente graves y medidas a tomar en caso de intoxicación con el medicamento.
 - Compatibilidad con fármacos de uso concomitante habitual.
-
- Envase acondicionado a las características técnicas de la especialidad: cartonaje y eliminación (impacto ambiental); embalaje exterior identificado lote y caducidad.

La Guía de tratamiento del cáncer de mama de The National Comprehensive Cancer Network (NCCN) (2.2017) recomienda el uso de trastuzumab asociado a los regímenes de quimioterapia convencionales en el tratamiento neoadyuvante, adyuvante o metastásico del cáncer de mama en pacientes que presentan sobreexpresado el receptor HER2. Además, la Guía de tratamiento del cáncer gástrico de The National Comprehensive Cancer Network (NCCN) (1.2017) recomienda el uso de trastuzumab en combinación con quimioterapia estándar, para el tratamiento de pacientes adultos con adenocarcinoma gástrico o de la unión gastroesofágica metastásico, HER2 positivo.

Se adjunta bibliografía.

Fdo Teresa Bermejo Vicedo
Jefe Servicio de Farmacia



NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Breast Cancer

Version 2.2017 — April 6, 2017

NCCN.org

NCCN Guidelines for Patients® available at www.nccn.org/patients

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PREOPERATIVE/ADJUVANT THERAPY REGIMENS^{1,2,3,4}

Regimens for HER2-negative disease^{5,6}

Preferred regimens:

- Dose-dense AC (doxorubicin/cyclophosphamide) followed by paclitaxel every 2 weeks
- Dose-dense AC (doxorubicin/cyclophosphamide) followed by weekly paclitaxel
- TC (docetaxel and cyclophosphamide)

Other regimens:

- Dose-dense AC (doxorubicin/cyclophosphamide)
- AC (doxorubicin/cyclophosphamide) every 3 weeks (category 2B)
- CMF (cyclophosphamide/methotrexate/fluorouracil)
- AC followed by docetaxel every 3 weeks
- AC followed by weekly paclitaxel
- EC (epirubicin/cyclophosphamide)
- TAC (docetaxel/doxorubicin/cyclophosphamide)

Regimens for HER2-positive disease^{6,7,8,9}

Preferred regimens:

- AC followed by T + trastuzumab ± pertuzumab¹⁰ (doxorubicin/cyclophosphamide followed by paclitaxel plus trastuzumab ± pertuzumab, various schedules)
- TCH (docetaxel/carboplatin/trastuzumab) ± pertuzumab

Other regimens:

- AC followed by docetaxel + trastuzumab ± pertuzumab¹⁰
- Docetaxel + cyclophosphamide + trastuzumab
- FEC (fluorouracil/epirubicin/cyclophosphamide) followed by docetaxel + trastuzumab + pertuzumab¹⁰
- FEC followed by paclitaxel + trastuzumab + pertuzumab¹⁰
- Paclitaxel + trastuzumab¹¹
- Pertuzumab + trastuzumab + docetaxel followed by FEC¹⁰
- Pertuzumab + trastuzumab + paclitaxel followed by FEC¹⁰

¹Retrospective evidence suggests that anthracycline-based chemotherapy regimens may be superior to non-anthracycline-based regimens in patients with HER2-positive tumors.
²Randomized clinical trials demonstrate that the addition of a taxane to anthracycline-based chemotherapy provides an improved outcome.

³CMF and radiation therapy may be given concurrently, or the CMF may be given first. All other chemotherapy regimens should be given prior to radiotherapy.

⁴Chemotherapy and endocrine therapy used as adjuvant therapy should be given sequentially with endocrine therapy following chemotherapy.

⁵The regimens listed for HER2-negative disease are all category 1 (except where indicated) when used in the adjuvant setting.

⁶Nab-paclitaxel may be substituted for paclitaxel or docetaxel due to medical necessity (ie, hypersensitivity reaction). If substituted for weekly paclitaxel or docetaxel, then the weekly dose of nab-paclitaxel should not exceed 125 mg/m².

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

⁷In patients with HER2-positive and axillary node-positive breast cancer, trastuzumab should be incorporated into the adjuvant therapy (category 1). Trastuzumab should also be considered for patients with HER2-positive node-negative tumors ≥ 1 cm (category 1).

⁸Trastuzumab should optimally be given concurrently with paclitaxel as part of the AC followed by paclitaxel regimen, and should be given for one year total duration.

⁹A pertuzumab-containing regimen can be administered to patients with ≥ T2 or ≥ N1, HER2-positive, early-stage breast cancer preoperatively. Patients who have not received a pertuzumab-containing regimen can receive adjuvant pertuzumab.

¹⁰Trastuzumab given in combination with an anthracycline is associated with significant cardiac toxicity. Concurrent use of trastuzumab and pertuzumab with an anthracycline should be avoided.

¹¹Paclitaxel + trastuzumab may be considered for patients with low-risk stage I, HER2-positive disease, particularly those not eligible for other standard adjuvant regimens due to comorbidities.

DOSING SCHEDULE FOR COMBINATIONS FOR HER2-POSITIVE DISEASE: PREFERRED REGIMENS

AC followed by T chemotherapy with trastuzumab⁹

- Doxorubicin 60 mg/m² IV day 1
- Cyclophosphamide 600 mg/m² IV day 1
- Cycled every 21 days for 4 cycles.

Followed by:

- Paclitaxel 80 mg/m² by 1 h IV weekly for 12 wks

With:

- Trastuzumab 4 mg/kg IV with first dose of paclitaxel

Followed by:

- Trastuzumab 2 mg/kg IV weekly to complete 1 y of treatment. As an alternative, trastuzumab 6 mg/kg IV every 21 days may be used following the completion of paclitaxel, and given to complete 1 y of trastuzumab treatment.

Evaluate left ventricular ejection fraction (LVEF) prior to and during treatment.*

AC followed by T chemotherapy with trastuzumab + pertuzumab

- Doxorubicin 60 mg/m² IV day 1
- Cyclophosphamide 600 mg/m² IV day 1
- Cycled every 21 days for 4 cycles.

Followed by:

- Pertuzumab 840 mg IV day 1 followed by 420 mg IV
- Trastuzumab 8 mg/kg IV day 1 followed by 6 mg/kg IV
- Paclitaxel 80 mg/m² IV days 1, 8, and 15

Cycled every 21 days for 4 cycles

- Trastuzumab 6 mg/kg IV day 1

Cycled every 21 days to complete 1 y of trastuzumab therapy

Evaluate LVEF prior to and during treatment.*

*The optimal frequency of LVEF assessment during adjuvant trastuzumab therapy is not known. The FDA label recommends LVEF measurements prior to initiation of trastuzumab and every 3 mo during therapy.

Dose-dense AC followed by paclitaxel chemotherapy with trastuzumab¹⁰

- Doxorubicin 60 mg/m² IV day 1
- Cyclophosphamide 600 mg/m² IV day 1
- Cycled every 14 days for 4 cycles.

Followed by:

- Paclitaxel 175 mg/m² by 3 h IV infusion day 1

Cycled every 14 days for 4 cycles.

With:

- Trastuzumab 4 mg/kg IV with first dose of paclitaxel

Followed by:

- Trastuzumab 2 mg/kg IV weekly to complete 1 y of treatment. As an alternative, trastuzumab 6 mg/kg IV every 21 days may be used following the completion of paclitaxel, and given to complete 1 y of trastuzumab treatment.

Evaluate LVEF prior to and during treatment.*

(All cycles are with myeloid growth factor support, See NCCN Guidelines for MGF)

TCH chemotherapy¹¹

- Docetaxel 75 mg/m² IV day 1
- Carboplatin AUC 6 IV day 1
- Cycled every 21 days for 6 cycles

With:

- Trastuzumab 4 mg/kg IV wk 1

Followed by:

- Trastuzumab 2 mg/kg IV for 17 wks

Followed by:

- Trastuzumab 6 mg/kg IV every 21 days to complete 1 y of trastuzumab therapy

OR

- Trastuzumab 8 mg/kg IV wk 1

Followed by:

- Trastuzumab 6 mg/kg IV every 21 days to complete 1 y of trastuzumab therapy

Evaluate LVEF prior to and during treatment.*

TCH chemotherapy + pertuzumab¹²

- Trastuzumab 8 mg/kg IV day 1 followed by 6 mg/kg IV
- Pertuzumab 840 mg IV day 1 followed by 420 mg IV
- Docetaxel 75 mg/m² IV day 1
- Carboplatin AUC 6 IV day 1

Cycled every 21 days for 6 cycles

Followed by:

- Trastuzumab 6 mg/kg IV every 21 days to complete 1 y of trastuzumab therapy

Evaluate LVEF prior to and during treatment.*

The selection, dosing, and administration of anti-cancer agents and the management of associated toxicities are complex. Modifications of drug dose and schedule and initiation of supportive care interventions are often necessary because of expected toxicities and individual patient variability, prior treatment, and comorbidity. The optimal delivery of anti-cancer agents therefore requires a health care delivery team experienced in the use of anti-cancer agents and the management of associated toxicities in patients with cancer.

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

CHEMOTHERAPY REGIMENS FOR RECURRENT OR METASTATIC BREAST CANCER^{1,2}

Preferred single agents:

Anthracyclines

- Doxorubicin
- Pegylated liposomal doxorubicin

Taxanes

- Paclitaxel

Anti-metabolites

- Capecitabine
- Gemcitabine

Other microtubule inhibitors

- Vinorelbine
- Eribulin

Other single agents:

- Cyclophosphamide
- Carboplatin
- Docetaxel
- Albumin-bound paclitaxel
- Cisplatin
- Epirubicin
- Ixabepilone

Chemotherapy combinations:

- CAF/FAC (cyclophosphamide/doxorubicin/fluorouracil)
- FEC (fluorouracil/epirubicin/cyclophosphamide)
- AC (doxorubicin/cyclophosphamide)
- EC (epirubicin/cyclophosphamide)
- CMF (cyclophosphamide/methotrexate/fluorouracil)
- Docetaxel/capecitabine
- GT (gemcitabine/paclitaxel)
- Gemcitabine/carboplatin
- Paclitaxel/bevacizumab³

Preferred first-line agents for HER2-positive disease:

- Pertuzumab + trastuzumab + docetaxel (category 1)⁴
- Pertuzumab + trastuzumab + paclitaxel⁴

Other agents for HER2-positive disease:

- Ado-trastuzumab emtansine (T-DM1)
- Trastuzumab + paclitaxel ± carboplatin
- Trastuzumab + docetaxel
- Trastuzumab + vinorelbine
- Trastuzumab + capecitabine

Agents for trastuzumab-exposed HER2-positive disease:

- Lapatinib + capecitabine
- Trastuzumab + capecitabine
- Trastuzumab + lapatinib (without cytotoxic therapy)
- Trastuzumab + other agents^{4,5,6}

¹There is no compelling evidence that combination regimens are superior to sequential single agents.

²Nab-paclitaxel may be substituted for paclitaxel or docetaxel due to medical necessity (ie, hypersensitivity reaction). If substituted for weekly paclitaxel or docetaxel, then the weekly dose of nab-paclitaxel should not exceed 125 mg/m².

³Randomized clinical trials in metastatic breast cancer document that the addition of bevacizumab to some first- or second-line chemotherapy agents modestly improves time to progression and response rates but does not improve overall survival. The time-to-progression impact may vary among cytotoxic agents and appears greatest with bevacizumab in combination with weekly paclitaxel.

Note: All recommendations are category 2A unless otherwise indicated.

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⁴Patients previously treated with chemotherapy plus trastuzumab in the absence of pertuzumab in the metastatic setting may be considered for one line of therapy including both trastuzumab plus pertuzumab in combination with or without cytotoxic therapy (such as vinorelbine or taxane). Further research is needed to determine the ideal sequencing strategy for anti-HER2 therapy.

⁵Trastuzumab given in combination with an anthracycline is associated with significant cardiac toxicity. Concurrent use of trastuzumab and pertuzumab with an anthracycline should be avoided.

⁶Trastuzumab may be safely combined with all non-anthracycline containing preferred and other single agents listed above for recurrent or metastatic breast cancer.

DOSING SCHEDULES FOR CHEMOTHERAPY REGIMENS FOR HER2-POSITIVE RECURRENT OR METASTATIC BREAST CANCER

Preferred first-line agents for HER2-positive disease:

- Pertuzumab + trastuzumab + docetaxel³⁰
- Pertuzumab 840 mg IV day 1 followed by 420 mg IV
- Trastuzumab 8 mg/kg IV day 1 followed by 6 mg/kg IV
- Docetaxel 75–100 mg/m² IV day 1
- Cycled every 21 days.

Pertuzumab + trastuzumab + paclitaxel³¹

- Pertuzumab 840 mg IV day 1 followed by 420 mg IV cycled every 21 days
- Trastuzumab
 - ▶ 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly
 - or
 - ▶ 8 mg/kg IV day 1 followed by 6 mg/kg IV cycled every 21 days³²
- Paclitaxel 80 mg/m² IV day 1 weekly³¹

- Paclitaxel 175 mg/m² day 1 cycled every 21 days

Other agents for HER2-positive disease:

- Ado-trastuzumab emtansine (T-DM1)³³
- 3.6 mg/kg IV day 1
- Cycled every 21 days.

Paclitaxel/carboplatin + trastuzumab³⁴

- Carboplatin AUC 6 IV day 1
- Paclitaxel 175 mg/m² IV day 1
- Cycled every 21 days.
- Trastuzumab
 - ▶ 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly
 - or
 - ▶ 8 mg/kg IV day 1 followed by 6 mg/kg IV every 21 days³²

Weekly paclitaxel/carboplatin + trastuzumab³⁵

- Paclitaxel 80 mg/m² IV days 1, 8, & 15
- Carboplatin AUC 2 IV days 1, 8, & 15
- Cycled every 28 days.

• Trastuzumab

- ▶ 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly
- or
- 8 mg/kg IV day 1 followed by 6 mg/kg IV every 21 days³²

Trastuzumab + paclitaxel

- Paclitaxel
 - ▶ 175 mg/m² IV day 1 cycled every 21 days³⁶

or

- ▶ 80–90 mg/m² IV day 1 weekly³⁷

• Trastuzumab

- ▶ 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly
- or
- ▶ 8 mg/kg IV day 1 followed by 6 mg/kg IV every 21 days³²

Trastuzumab + docetaxel

- Docetaxel
 - ▶ 80–100 mg/m² IV day 1 cycled every 21 days³⁸
- or
- ▶ 35 mg/m² IV days 1, 8, and 15 weekly³⁹

• Trastuzumab

- ▶ 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly
- or
- ▶ 8 mg/kg IV day 1 followed by 6 mg/kg IV every 21 days³²

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DOSING SCHEDULES FOR CHEMOTHERAPY REGIMENS FOR HER-2 POSITIVE RECURRENT OR METASTATIC BREAST CANCER

Trastuzumab + vinorelbine^{40,41}

- Vinorelbine
 - ▶ 25 mg/m² IV day 1 weekly
 - or
 - ▶ 30–35 mg/m² IV days 1 and 8
- Cycled every 21 days.

Trastuzumab

- ▶ 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly
- or
- ▶ 8 mg/kg IV day 1 followed by 6 mg/kg IV every 21 days³²

Trastuzumab + capecitabine⁴²

- Capecitabine 1000–1250 mg/m² PO twice daily days 1–14 cycled every 21 days
- Trastuzumab
 - ▶ 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly^{36,43}
 - or
 - ▶ 8 mg/kg IV day 1 followed by 6 mg/kg IV every 21 days³²

Agents for trastuzumab-exposed HER2-positive disease:

Lapatinib + capecitabine⁴⁴

- Lapatinib 1250 mg PO daily days 1–21
 - Capecitabine 1000 mg/m² PO twice daily days 1–14
- Cycled every 21 days.

Trastuzumab + capecitabine⁴⁵

- Capecitabine 1000–1250 mg/m² PO twice daily days 1–14
- Cycled every 21 days.

Trastuzumab

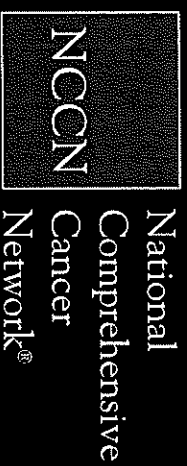
- ▶ 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly^{36,43}
- or
- ▶ 8 mg/kg IV day 1 followed by 6 mg/kg IV every 21 days³²

Trastuzumab + lapatinib⁴⁶

- Lapatinib 1000 mg PO daily
- Trastuzumab
 - ▶ 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly
 - or
 - ▶ 8 mg/kg IV day 1 followed by 6 mg/kg IV every 21 days³²

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NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Gastric Cancer

Version 1.2017 — March 21, 2017

NCCN.org

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PRINCIPLES OF SYSTEMIC THERAPY

Systemic Therapy for Unresectable Locally Advanced, Recurrent or Metastatic Disease (where local therapy is not indicated)

• **Trastuzumab should be added to first-line chemotherapy for HER2 overexpressing metastatic adenocarcinoma**

(See Principles of Pathologic Review and HER2 Testing [GAST-B])

- ▶ Combination with fluoropyrimidine and cisplatin (category 1)¹³
- ▶ Combination with other chemotherapy agents (category 2B)
- ▶ Trastuzumab is not recommended for use with anthracyclines

First-Line Therapy

Two-drug cytotoxic regimens are preferred because of lower toxicity.

Three-drug cytotoxic regimens should be reserved for medically fit patients with good PS and access to frequent toxicity evaluation.

• Preferred Regimens:

- ▶ Fluoropyrimidine (fluorouracil[†] or capecitabine) and cisplatin¹⁴⁻¹⁷ (category 1)
- ▶ Fluoropyrimidine (fluorouracil[†] or capecitabine) and oxaliplatin^{15,18,19}

• Other Regimens:

- ▶ Paclitaxel with cisplatin or carboplatin²⁰⁻²²
- ▶ Docetaxel with cisplatin^{23,24}
- ▶ Fluoropyrimidine^{16,25,26} (fluorouracil[†] or capecitabine)
- ▶ Docetaxel^{27,28}
- ▶ Paclitaxel^{29,30}
- ▶ Fluorouracil^{†,*} and irinotecan³¹
- ▶ DCF modifications
 - ◊ Docetaxel, cisplatin, and fluorouracil^{†,32}
 - ◊ Docetaxel, oxaliplatin, and fluorouracil³³
 - ◊ Docetaxel, carboplatin, and fluorouracil (category 2B)³⁴
 - ▶ ECF (epirubicin, cisplatin, and fluorouracil) (category 2B)³⁵
 - ▶ ECF modifications (category 2B)^{3,4}
 - ◊ Epirubicin, oxaliplatin, and fluorouracil
 - ◊ Epirubicin, cisplatin, and capecitabine
 - ◊ Epirubicin, oxaliplatin, and capecitabine

Second-Line Therapy

Dependent on prior therapy and PS:

• Preferred Regimens:

- ▶ Ramucirumab and paclitaxel (category 1)³⁶
- ▶ Docetaxel (category 1)^{27,28}
- ▶ Paclitaxel (category 1)^{29,30,37}
- ▶ Irinotecan (category 1)³⁷⁻⁴⁰
- ▶ Ramucirumab (category 1)⁴¹
- ▶ Fluorouracil^{†,*} and irinotecan^{38,42,43} (if not not previously used in first-line therapy)

Other Regimens:

- ▶ Irinotecan and cisplatin^{18,44}
- ▶ Docetaxel and irinotecan⁴⁵ (category 2B)

*Capecitabine may not be used interchangeably with fluorouracil in regimens containing irinotecan.

†Leucovorin is indicated with certain fluorouracil-based regimens. For important information regarding the leucovorin shortage, please see Discussion (MS-30).

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Continued

PRINCIPLES OF SYSTEMIC THERAPY

- Systemic therapy regimens recommended for advanced esophageal and esophagogastric junction (EGJ) adenocarcinoma, squamous cell carcinoma of the esophagus, and gastric adenocarcinoma may be used interchangeably (except as indicated).
- Regimens should be chosen in the context of performance status (PS), medical comorbidities, and toxicity profile.
- **Trastuzumab should be added to chemotherapy for HER2 overexpressing metastatic adenocarcinoma.**
- Two-drug cytotoxic regimens are preferred for patients with advanced disease because of lower toxicity. Three-drug cytotoxic regimens should be reserved for medically fit patients with good PS and access to frequent toxicity evaluation.
- Modifications of category 1 regimen or use of category 2A or 2B regimens may be preferred (as indicated), with evidence supporting a more favorable toxicity profile without compromising efficacy.¹
- Doses and schedules for any regimen that is not derived from category 1 evidence are a suggestion, and are subject to appropriate modifications depending on the circumstances.
- Alternate combinations and schedules of cytotoxics based on the availability of the agents, practice preferences, and contraindications are permitted.
- Perioperative chemotherapy,^{2,3} or postoperative chemotherapy plus chemoradiation⁴ is the preferred approach for localized gastric cancer.
- Postoperative chemotherapy is recommended following primary D2 lymph node dissection.^{5,6} (See Principles of Surgery [GAST-C])
- In the adjuvant setting, upon completion of chemotherapy or chemoradiation, patients should be monitored for any long-term therapy-related complications.

- ¹Van Cutsem E, Moiseyenko VM, Tjulandini S, et al. Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group. *J Clin Oncol* 2006;24:4991-4997.
- ²Ychou M, Boige V, Pignon J-P, et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. *J Clin Oncol* 2011;29:1715-1721.
- ³Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med* 2006;355:11-20.
- ⁴Smalley SR, Benedetti JK, Haller DG, et al. Updated analysis of SWOG-directed intergroup study 0116: a phase III trial of adjuvant radiochemotherapy versus observation after curative gastric cancer resection. *J Clin Oncol* 2012;30:2327-2333. (See GAST-F 6 of 11).
- ⁵Noh SH, Park SR, Yang HK, et al. Adjuvant capecitabine plus oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): 5-year follow-up of an open-label, randomised phase 3 trial. *Lancet Oncol* 2014; 15:1389-1396.
- ⁶Park SH, Sohn TS, Lee J, et al. Phase III Trial to compare adjuvant chemotherapy with capecitabine and cisplatin versus concurrent chemoradiotherapy in gastric cancer: final report of the adjuvant chemoradiotherapy in stomach tumors trial, including survival and subset analyses. *J Clin Oncol* 2015;33:3130-3136.

Continued

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PRINCIPLES OF SYSTEMIC THERAPY—REGIMENS AND DOSING SCHEDULES††

SYSTEMIC THERAPY FOR METASTATIC OR LOCALLY ADVANCED CANCER (WHERE LOCAL THERAPY IS NOT INDICATED)

FIRST-LINE THERAPY

Trastuzumab (with chemotherapy)

Trastuzumab 8 mg/kg IV loading dose

on Day 1 of cycle 1, then

Trastuzumab 6 mg/kg IV every 21 days¹³

or

Trastuzumab 6 mg/kg IV loading dose on

Day 1 of cycle 1, then 4 mg/kg IV every 14 days

PREFERRED REGIMENS

Fluoropyrimidine and cisplatin

Cisplatin 75–100 mg/m² IV on Day 1

Fluorouracil 750–1000 mg/m² IV continuous

infusion over 24 hours daily on Days 1–4

Cycled every 28 days¹⁴

Cisplatin 50 mg/m² IV daily on Day 1

Leucovorin 200 mg/m² IV on Day 1

Fluorouracil 2000 mg/m² IV continuous infusion

over 24 hours daily on Day 1

Cycled every 14 days^{15,16}

Cisplatin 80 mg/m² IV daily on Day 1

Capecitabine 1000 mg/m² PO BID on Days 1–14

Cycled every 21 days¹⁷

PREFERRED REGIMENS—continued

Fluoropyrimidine and oxaliplatin

Oxaliplatin 85 mg/m² IV on Day 1

Leucovorin 400 mg/m² IV on Day 1

Fluorouracil 400 mg/m² IV Push on Day 1

Fluorouracil 1200 mg/m² IV continuous

infusion over 24 hours daily on Days 1 and 2

Cycled every 14 days¹⁸

Oxaliplatin 85 mg/m² IV on Day 1

Leucovorin 200 mg/m² IV on Day 1

Fluorouracil 2600 mg/m² IV continuous

infusion over 24 hours on Day 1

Cycled every 14 days¹⁵

Capecitabine 1000 mg/m² PO BID on Days 1–14

Oxaliplatin 130 mg/m² IV on Day 1

Cycled every 21 days¹⁹

OTHER REGIMENS

Paclitaxel with cisplatin or carboplatin

Paclitaxel 135–200 mg/m² IV on Day 1

Cisplatin 75 mg/m² IV on Day 2

Cycled every 21 days²⁰

Paclitaxel 90 mg/m² IV on Day 1

Cisplatin 50 mg/m² IV on Day 1

Cycled every 14 days²¹

Paclitaxel 200 mg/m² IV on Day 1

Carboplatin AUC 5 IV on Day 1

Cycled every 21 days²²

Docetaxel and cisplatin

Docetaxel 70–85 mg/m² IV on Day 1

Cisplatin 70–75 mg/m² IV on Day 1

Cycled every 21 days^{23,24}

Fluoropyrimidine

Leucovorin 400 mg/m² IV on Day 1

Fluorouracil 400 mg/m² IV Push on Day 1

Fluorouracil 1200 mg/m² IV continuous

infusion over 24 hours daily on Days 1 and 2

Cycled every 14 days¹⁶

Fluorouracil 800 mg/m² IV continuous

infusion over 24 hours daily on Days 1–5

Cycled every 28 days²⁵

Capecitabine 1000–1250 mg/m²

PO BID on Days 1–14²⁶

Cycled every 21 days²⁶

††Systemic therapy regimen and dosing schedules are based on extrapolations from published literature and clinical practice.

The selection, dosing, and administration of anticancer agents and the management of associated toxicities are complex. Modifications of drug dose and schedule and initiation of supportive care interventions are often necessary because of expected toxicities and because of individual patient variability, prior treatment, nutritional status, and comorbidity. The optimal delivery of anticancer agents therefore requires a health care delivery team experienced in the use of anticancer agents and the management of associated toxicities in patients with cancer.

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HERCEPTIN SUBCUTANEO 600 MG VIAL 5 ML C/1

ROCHE FARMA

ESPECIFICACIONES TECNICAS PROCEDIMIENTO NEGOCIADO: TRASTUZUMAB

Evaluable y seleccionado por la Comisión de Farmacia y Terapéutica, e incluido en la Guía Farmacoterapéutica del Área 4.

GRUPO TERAPÉUTICO: L01XC – Otros citostáticos: anticuerpos monoclonales

Presentación en viales de 6 mL de cristal transparente de tipo I, con tapón de goma butílica laminada con una película de fluoro-resina, que contienen 5 mL de solución (600 mg de trastuzumab), perfectamente identificados con:

- Nombre comercial
 - Nombre del principio activo
 - Dosis en miligramos
 - Lista de excipientes
 - Forma farmacéutica
 - Vía de administración
 - Lote
 - Caducidad
 - Condiciones de conservación
 - Código Nacional
 - Laboratorio fabricante
- Información técnica complementaria relativa a:
- Posología y forma de administración
 - Nivel de información sobre utilización del medicamento en situaciones especiales: geriatría, pediatría, embarazo, lactancia, insuficiencia renal y hepática, diálisis, patologías concomitantes e interacciones.

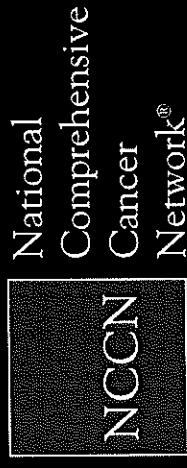
- Nivel de información sobre vigilancia farmacológica y toxicológica: medidas preventivas de efectos adversos potencialmente graves y medidas a tomar en caso de intoxicación con el medicamento.
 - Compatibilidad con fármacos de uso concomitante habitual.
-
- Envase acondicionado a las características técnicas de la especialidad: cartonaje y eliminación (impacto ambiental); embalaje exterior identificado lote y caducidad.

La Guía de tratamiento del cáncer de mama de The National Comprehensive Cancer Network (NCCN) (2.2017) recomienda el uso de trastuzumab asociado a los regímenes de quimioterapia convencionales en el tratamiento neoadyuvante, adyuvante o metastásico del cáncer de mama en pacientes que presentan sobreexpresado el receptor HER2. Además, la Guía de tratamiento del cáncer gástrico de The National Comprehensive Cancer Network (NCCN) (1.2017) recomienda el uso de trastuzumab en combinación con quimioterapia estándar, para el tratamiento de pacientes adultos con adenocarcinoma gástrico o de la unión gastroesofágica metastásico, HER2 positivo.

Se adjunta bibliografía.



Fdo Teresa Bermejo Vicedo
Jefe Servicio de Farmacia



NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Breast Cancer

Version 2.2017 — April 6, 2017

NCCN.org

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PREOPERATIVE/ADJUVANT THERAPY REGIMENS ^{1,2,3,4}

Regimens for HER2-negative disease ^{5,6}

Preferred regimens:

- Dose-dense AC (doxorubicin/cyclophosphamide) followed by paclitaxel every 2 weeks
- Dose-dense AC (doxorubicin/cyclophosphamide) followed by weekly paclitaxel
- TC (docetaxel and cyclophosphamide)

Other regimens:

- Dose-dense AC (doxorubicin/cyclophosphamide)
- AC (doxorubicin/cyclophosphamide) every 3 weeks (category 2B)
- CMF (cyclophosphamide/methotrexate/fluorouracil)
- AC followed by docetaxel every 3 weeks
- AC followed by weekly paclitaxel
- EC (epirubicin/cyclophosphamide)
- TAC (docetaxel/doxorubicin/cyclophosphamide)

Regimens for HER2-positive disease ^{6,7,8,9}

Preferred regimens:

- AC followed by T + trastuzumab ± pertuzumab ¹⁰ (doxorubicin/cyclophosphamide followed by paclitaxel plus trastuzumab ± pertuzumab, various schedules)
- TCH (docetaxel/carboplatin/trastuzumab) ± pertuzumab

Other regimens:

- AC followed by docetaxel + trastuzumab ± pertuzumab ¹⁰
- Docetaxel + cyclophosphamide + trastuzumab
- FEC (fluorouracil/epirubicin/cyclophosphamide) followed by docetaxel + trastuzumab + pertuzumab ¹⁰
- FEC followed by paclitaxel + trastuzumab + pertuzumab ¹⁰
- Paclitaxel + trastuzumab ¹¹
- Pertuzumab + trastuzumab + docetaxel followed by FEC ¹⁰
- Pertuzumab + trastuzumab + paclitaxel followed by FEC ¹⁰

⁷In patients with HER2-positive and axillary node-positive breast cancer, trastuzumab should be incorporated into the adjuvant therapy (category 1). Trastuzumab should also be considered for patients with HER2-positive node-negative tumors ≥1 cm (category 1).

⁸Trastuzumab should optimally be given concurrently with paclitaxel as part of the AC followed by paclitaxel regimen, and should be given for one year total duration.

^{9A} pertuzumab-containing regimen can be administered to patients with ≥T2 or ≥N1, HER2-positive, early-stage breast cancer preoperatively. Patients who have not received a pertuzumab-containing regimen can receive adjuvant pertuzumab.

¹⁰Trastuzumab given in combination with an anthracycline is associated with significant cardiac toxicity. Concurrent use of trastuzumab and pertuzumab with an anthracycline should be avoided.

¹¹Paclitaxel + trastuzumab may be considered for patients with low-risk stage I, HER2-positive disease, particularly those not eligible for other standard adjuvant regimens due to comorbidities.

¹Retrospective evidence suggests that anthracycline-based chemotherapy regimens may be superior to non-anthracycline-based regimens in patients with HER2-positive tumors.

²Randomized clinical trials demonstrate that the addition of a taxane to anthracycline-based chemotherapy provides an improved outcome.

³CMF and radiation therapy may be given concurrently, or the CMF may be given first. All other chemotherapy regimens should be given prior to radiotherapy.

⁴Chemotherapy and endocrine therapy used as adjuvant therapy should be given sequentially with endocrine therapy following chemotherapy.

⁵The regimens listed for HER2-negative disease are all category 1 (except where indicated) when used in the adjuvant setting.

⁶Nab-paclitaxel may be substituted for paclitaxel or docetaxel due to medical necessity (ie, hypersensitivity reaction). If substituted for weekly paclitaxel or docetaxel, then the weekly dose of nab-paclitaxel should not exceed 125 mg/m².

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

NCCN Guidelines Version 2.2017

Invasive Breast Cancer

DOSING SCHEDULE FOR COMBINATIONS FOR HER2-POSITIVE DISEASE: PREFERRED REGIMENS

AC followed by T chemotherapy with trastuzumab⁹

- Doxorubicin 60 mg/m² IV day 1
 - Cyclophosphamide 600 mg/m² IV day 1
- Cycled every 21 days for 4 cycles.

Followed by:

Paclitaxel 80 mg/m² by 1 h IV weekly for 12 wks

With:

- Trastuzumab 4 mg/kg IV with first dose of paclitaxel

Followed by:

- Trastuzumab 2 mg/kg IV weekly to complete 1 y of treatment. As an alternative, trastuzumab 6 mg/kg IV every 21 days may be used following the completion of paclitaxel, and given to complete 1 y of trastuzumab treatment.*

Evaluate left ventricular ejection fraction (LVEF) prior to and during treatment.*

AC followed by T chemotherapy with trastuzumab + pertuzumab

- Doxorubicin 60 mg/m² IV day 1
 - Cyclophosphamide 600 mg/m² IV day 1
- Cycled every 21 days for 4 cycles.

Followed by:

- Pertuzumab 840 mg IV day 1 followed by 420 mg IV
 - Trastuzumab 8 mg/kg IV day 1 followed by 6 mg/kg IV
 - Paclitaxel 80 mg/m² IV days 1, 8, and 15
- Cycled every 21 days for 4 cycles

- Trastuzumab 6 mg/kg IV day 1

Cycled every 21 days to complete 1 y of trastuzumab therapy

Evaluate LVEF prior to and during treatment.*

*The optimal frequency of LVEF assessment during adjuvant trastuzumab therapy is not known. The FDA label recommends LVEF measurements prior to initiation of trastuzumab and every 3 mo during therapy.

The selection, dosing, and administration of anti-cancer agents and the management of associated toxicities are complex. Modifications of drug dose and schedule and initiation of supportive care interventions are often necessary because of expected toxicities and individual patient variability, prior treatment, and comorbidity. The optimal delivery of anti-cancer agents therefore requires a health care delivery team experienced in the use of anti-cancer agents and the management of associated toxicities in patients with cancer.

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Dose-dense AC followed by paclitaxel chemotherapy with trastuzumab¹⁰

- Doxorubicin 60 mg/m² IV day 1
 - Cyclophosphamide 600 mg/m² IV day 1
- Cycled every 14 days for 4 cycles.

Followed by:

- Paclitaxel 175 mg/m² by 3 h IV infusion day 1
- Cycled every 14 days for 4 cycles.

With:

- Trastuzumab 4 mg/kg IV with first dose of paclitaxel

Followed by:

- Trastuzumab 2 mg/kg IV weekly to complete 1 y of treatment. As an alternative, trastuzumab 6 mg/kg IV every 21 days may be used following the completion of paclitaxel, and given to complete 1 y of trastuzumab treatment.*

Evaluate LVEF prior to and during treatment.*
(All cycles are with myeloid growth factor support, See NCCN Guidelines for MGF)

TCH chemotherapy¹¹

- Docetaxel 75 mg/m² IV day 1
 - Carboplatin AUC 6 IV day 1
- Cycled every 21 days for 6 cycles

With:

- Trastuzumab 4 mg/kg IV wk 1

Followed by:

- Trastuzumab 2 mg/kg IV for 17 wks

Followed by:

- Trastuzumab 6 mg/kg IV every 21 days to complete 1 y of trastuzumab therapy

OR

- Trastuzumab 8 mg/kg IV wk 1

Followed by:

- Trastuzumab 6 mg/kg IV every 21 days to complete 1 y of trastuzumab therapy
- Evaluate LVEF prior to and during treatment.*

TCH chemotherapy + pertuzumab¹²

- Trastuzumab 8 mg/kg IV day 1 followed by 6 mg/kg IV
 - Pertuzumab 840 mg IV day 1 followed by 420 mg IV
 - Docetaxel 75 mg/m² IV day 1
 - Carboplatin AUC 6 IV day 1
- Cycled every 21 days for 6 cycles

Followed by:

- Trastuzumab 6 mg/kg IV every 21 days to complete 1 y of trastuzumab therapy
- Evaluate LVEF prior to and during treatment.*

CHEMOTHERAPY REGIMENS FOR RECURRENT OR METASTATIC BREAST CANCER^{1,2}

Preferred single agents:

Anthracyclines

- Doxorubicin
- Pegylated liposomal doxorubicin

Taxanes

- Paclitaxel

Anti-metabolites

- Capecitabine
- Gemcitabine

Other microtubule inhibitors

- Vinorelbine
- Eribulin

Other single agents:

- Cyclophosphamide
- Carboplatin
- Docetaxel
- Albumin-bound paclitaxel
- Cisplatin
- Epirubicin
- Ixabepilone

Chemotherapy combinations:

- CAF/FAC (cyclophosphamide/doxorubicin/fluorouracil)
- FEC (fluorouracil/epirubicin/cyclophosphamide)
- AC (doxorubicin/cyclophosphamide)
- EC (epirubicin/cyclophosphamide)
- CMF (cyclophosphamide/methotrexate/fluorouracil)
- Docetaxel/capecitabine
- GT (gemcitabine/paclitaxel)
- Gemcitabine/carboplatin
- Paclitaxel/bevacizumab³

Preferred first-line agents for HER2-positive disease:

- Pertuzumab + trastuzumab + docetaxel (category 1)⁴
- Pertuzumab + trastuzumab + paclitaxel⁴

Other agents for HER2-positive disease:

- Ado-trastuzumab emtansine (T-DM1)
- Trastuzumab + paclitaxel ± carboplatin
- Trastuzumab + docetaxel
- Trastuzumab + vinorelbine
- Trastuzumab + capecitabine

Agents for trastuzumab-exposed HER2-positive disease:

- Lapatinib + capecitabine
- Trastuzumab + capecitabine
- Trastuzumab + lapatinib (without cytotoxic therapy)
- Trastuzumab + other agents^{4,5,6}

¹There is no compelling evidence that combination regimens are superior to sequential single agents.

²Nab-paclitaxel may be substituted for paclitaxel or docetaxel due to medical necessity (ie, hypersensitivity reaction). If substituted for weekly paclitaxel or docetaxel, then the weekly dose of nab-paclitaxel should not exceed 125 mg/m².

³Randomized clinical trials in metastatic breast cancer document that the addition of bevacizumab to some first- or second-line chemotherapy agents modestly improves time to progression and response rates but does not improve overall survival. The time-to-progression impact may vary among cytotoxic agents and appears greatest with bevacizumab in combination with weekly paclitaxel.

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Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

⁴Patients previously treated with chemotherapy plus trastuzumab in the absence of pertuzumab in the metastatic setting may be considered for one line of therapy including both trastuzumab plus pertuzumab in combination with or without cytotoxic therapy (such as vinorelbine or taxane). Further research is needed to determine the ideal sequencing strategy for anti-HER2 therapy.

⁵Trastuzumab given in combination with an anthracycline is associated with significant cardiac toxicity. Concurrent use of trastuzumab and pertuzumab with an anthracycline should be avoided.

⁶Trastuzumab may be safely combined with all non-anthracycline containing preferred and other single agents listed above for recurrent or metastatic breast cancer.

DOSING SCHEDULES FOR CHEMOTHERAPY REGIMENS FOR HER2-POSITIVE RECURRENT OR METASTATIC BREAST CANCER

Preferred first-line agents for HER2-positive disease:

- Pertuzumab + trastuzumab + docetaxel³⁰
 - Pertuzumab 840 mg IV day 1 followed by 420 mg IV
 - Trastuzumab 8 mg/kg IV day 1 followed by 6 mg/kg IV
 - Docetaxel 75–100 mg/m² IV day 1
- Cycled every 21 days.

Pertuzumab + trastuzumab + paclitaxel³¹

- Pertuzumab 840 mg IV day 1 followed by 420 mg IV cycled every 21 days
- Trastuzumab
- ▶ 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly

or

- ▶ 8 mg/kg IV day 1 followed by 6 mg/kg IV cycled every 21 days³²
- Paclitaxel 80 mg/m² IV day 1 weekly³¹

or

- Paclitaxel 175 mg/m² day 1 cycled every 21 days

Other agents for HER2-positive disease:

Ado-trastuzumab emtansine (T-DM1)³³

- 3.6 mg/kg IV day 1
- Cycled every 21 days.

Paclitaxel/carboplatin + trastuzumab³⁴

- Carboplatin AUC 6 IV day 1
 - Paclitaxel 175 mg/m² IV day 1
- Cycled every 21 days.

Trastuzumab

- ▶ 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly
- or
- ▶ 8 mg/kg IV day 1 followed by 6 mg/kg IV every 21 days³²

Weekly paclitaxel/carboplatin + trastuzumab³⁵

- Paclitaxel 80 mg/m² IV days 1, 8, & 15
 - Carboplatin AUC 2 IV days 1, 8, & 15
- Cycled every 28 days.

Trastuzumab

- ▶ 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly

or

- ▶ 8 mg/kg IV day 1 followed by 6 mg/kg IV every 21 days³²

Trastuzumab + paclitaxel

- Paclitaxel
- ▶ 175 mg/m² IV day 1 cycled every 21 days³⁶

or

- ▶ 80–90 mg/m² IV day 1 weekly³⁷

Trastuzumab

- ▶ 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly

or

- ▶ 8 mg/kg IV day 1 followed by 6 mg/kg IV every 21 days³²

Trastuzumab + docetaxel

- Docetaxel
- ▶ 80–100 mg/m² IV day 1 cycled every 21 days³⁸

or

- ▶ 35 mg/m² IV days 1, 8, and 15 weekly³⁹

Trastuzumab

- ▶ 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly

or

- ▶ 8 mg/kg IV day 1 followed by 6 mg/kg IV every 21 days³²

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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DOSING SCHEDULES FOR CHEMOTHERAPY REGIMENS FOR HER-2 POSITIVE RECURRENT OR METASTATIC BREAST CANCER

Trastuzumab + vinorelbine^{40,41}

- Vinorelbine
 - ▶ 25 mg/m² IV day 1 weekly
 - or
 - ▶ 30–35 mg/m² IV days 1 and 8
- Cycled every 21 days.

• Trastuzumab

- ▶ 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly
- or
- ▶ 8 mg/kg IV day 1 followed by 6 mg/kg IV every 21 days³²

Trastuzumab + capecitabine⁴²

- Capecitabine 1000–1250 mg/m² PO twice daily days 1–14
- cycled every 21 days

• Trastuzumab

- ▶ 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly^{36,43}
- or
- ▶ 8 mg/kg IV day 1 followed by 6 mg/kg IV every 21 days³²

Agents for trastuzumab-exposed HER2-positive disease:

Lapatinib + capecitabine⁴⁴

- Lapatinib 1250 mg PO daily days 1–21
 - Capecitabine 1000 mg/m² PO twice daily days 1–14
- Cycled every 21 days.

Trastuzumab + capecitabine⁴⁵

- Capecitabine 1000–1250 mg/m² PO twice daily days 1–14
- Cycled every 21 days.

• Trastuzumab

- ▶ 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly^{36,43}
- or
- ▶ 8 mg/kg IV day 1 followed by 6 mg/kg IV every 21 days³²

Trastuzumab + lapatinib⁴⁶

- Lapatinib 1000 mg PO daily
- Trastuzumab
 - ▶ 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly
 - or
 - ▶ 8 mg/kg IV day 1 followed by 6 mg/kg IV every 21 days³²

Note: All recommendations are category 2A unless otherwise indicated.
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NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Gastric Cancer

Version 1.2017 — March 21, 2017

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PRINCIPLES OF SYSTEMIC THERAPY

- Systemic therapy regimens recommended for advanced esophageal and esophagogastric junction (EGJ) adenocarcinoma, squamous cell carcinoma of the esophagus, and gastric adenocarcinoma may be used interchangeably (except as indicated).
- Regimens should be chosen in the context of performance status (PS), medical comorbidities, and toxicity profile.
- **Trastuzumab should be added to chemotherapy for HER2 overexpressing metastatic adenocarcinoma.**
- Two-drug cytotoxic regimens are preferred for patients with advanced disease because of lower toxicity. Three-drug cytotoxic regimens should be reserved for medically fit patients with good PS and access to frequent toxicity evaluation.
- Modifications of category 1 regimen or use of category 2A or 2B regimens may be preferred (as indicated), with evidence supporting a more favorable toxicity profile without compromising efficacy.¹
- Doses and schedules for any regimen that is not derived from category 1 evidence are a suggestion, and are subject to appropriate modifications depending on the circumstances.
- Alternate combinations and schedules of cytotoxics based on the availability of the agents, practice preferences, and contraindications are permitted.
- Perioperative chemotherapy,^{2,3} or postoperative chemotherapy plus chemoradiation⁴ is the preferred approach for localized gastric cancer.
- Postoperative chemotherapy is recommended following primary D2 lymph node dissection.^{5,6} (See Principles of Surgery [GAST-C])
- In the adjuvant setting, upon completion of chemotherapy or chemoradiation, patients should be monitored for any long-term therapy-related complications.

¹Van Cutsem E, Moiseyenko VM, Tjulandin S, et al. Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group. *J Clin Oncol* 2006;24:4991-4997.

²Ychou M, Boige V, Pignon J-P, et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. *J Clin Oncol* 2011;29:1715-1721.

³Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med* 2006;355:11-20.

⁴Smalley SR, Benedetti JK, Haller DG, et al. Updated analysis of SWOG-directed intergroup study 0116: a phase III trial of adjuvant radiochemotherapy versus observation after curative gastric cancer resection. *J Clin Oncol* 2012;30:2327-2333. (See GAST-F 6 of 11).

⁵Noh SH, Park SR, Yang HK, et al. Adjuvant capecitabine plus oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): 5-year follow-up of an open-label, randomised phase 3 trial. *Lancet Oncol* 2014; 15:1389-1396.

⁶Park SH, Sohn TS, Lee J, et al. Phase III Trial to compare adjuvant chemotherapy with capecitabine and cisplatin versus concurrent chemoradiotherapy in gastric cancer: final report of the adjuvant chemoradiotherapy in stomach tumors trial, including survival and subset analyses. *J Clin Oncol* 2015;33:3130-3136.

Continued

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

PRINCIPLES OF SYSTEMIC THERAPY

Systemic Therapy for Unresectable Locally Advanced, Recurrent or Metastatic Disease (where local therapy is not indicated)

- ▶ **Trastuzumab should be added to first-line chemotherapy for HER2 overexpressing metastatic adenocarcinoma**
(See Principles of Pathologic Review and HER2 Testing [GAST-B])¹³
- ▶ Combination with fluoropyrimidine and cisplatin (category 1)¹³
- ▶ Combination with other chemotherapy agents (category 2B)
- ▶ Trastuzumab is not recommended for use with anthracyclines

First-Line Therapy

Two-drug cytotoxic regimens are preferred because of lower toxicity.

Three-drug cytotoxic regimens should be reserved for medically fit patients with good PS and access to frequent toxicity evaluation.

- Preferred Regimens:
 - ▶ Fluoropyrimidine (fluorouracil[†] or capecitabine) and cisplatin¹⁴⁻¹⁷ (category 1)
 - ▶ Fluoropyrimidine (fluorouracil[†] or capecitabine) and oxaliplatin^{15,18,19}

• Other Regimens:

- ▶ Paclitaxel with cisplatin or carboplatin²⁰⁻²²
- ▶ Docetaxel with cisplatin^{23,24}
- ▶ Fluoropyrimidine^{16,25,26} (fluorouracil[†] or capecitabine)
- ▶ Docetaxel^{27,28}
- ▶ Paclitaxel^{29,30}
- ▶ Fluorouracil^{†,*} and irinotecan³¹
- ▶ DCF modifications
 - ◊ Docetaxel, cisplatin, and fluorouracil^{†,32}
 - ◊ Docetaxel, oxaliplatin, and fluorouracil³³
 - ◊ Docetaxel, carboplatin, and fluorouracil (category 2B)³⁴
- ▶ ECF (epirubicin, cisplatin, and fluorouracil) (category 2B)³⁵
- ▶ ECF modifications (category 2B)^{3,4}
 - ◊ Epirubicin, oxaliplatin, and fluorouracil
 - ◊ Epirubicin, cisplatin, and capecitabine
 - ◊ Epirubicin, oxaliplatin, and capecitabine

Second-Line Therapy

Dependent on prior therapy and PS:

- Preferred Regimens:
 - ▶ Ramucirumab and paclitaxel (category 1)³⁶
 - ▶ Docetaxel (category 1)^{27,28}
 - ▶ Paclitaxel (category 1)^{29,30,37}
 - ▶ Irinotecan (category 1)³⁷⁻⁴⁰
 - ▶ Ramucirumab (category 1)⁴¹
 - ▶ Fluorouracil^{†,*} and irinotecan^{38,42,43} (if not not previously used in first-line therapy)

Other Regimens:

- ▶ Irinotecan and cisplatin^{18,44}
- ▶ Docetaxel and irinotecan⁴⁵ (category 2B)

*Capecitabine may not be used interchangeably with fluorouracil in regimens containing irinotecan.

[†]Leucovorin is indicated with certain fluorouracil-based regimens. For important information regarding the leucovorin shortage, please see Discussion (MS-30).

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Continued

PRINCIPLES OF SYSTEMIC THERAPY—REGIMENS AND DOSING SCHEDULES^{††}

SYSTEMIC THERAPY FOR METASTATIC OR LOCALLY ADVANCED CANCER (WHERE LOCAL THERAPY IS NOT INDICATED)

FIRST-LINE THERAPY

Trastuzumab (with chemotherapy)

Trastuzumab 8 mg/kg IV loading dose on Day 1 of cycle 1, then

Trastuzumab 6 mg/kg IV every 21 days¹³

or

Trastuzumab 6 mg/kg IV loading dose on Day 1 of cycle 1, then 4 mg/kg IV every 14 days

PREFERRED REGIMENS

Fluoropyrimidine and cisplatin

Cisplatin 75–100 mg/m² IV on Day 1

Fluorouracil 750–1000 mg/m² IV continuous infusion over 24 hours daily on Days 1–4
Cycled every 28 days¹⁴

Cisplatin 50 mg/m² IV daily on Day 1

Leucovorin 200 mg/m² IV on Day 1

Fluorouracil 2000 mg/m² IV continuous infusion over 24 hours daily on Day 1
Cycled every 14 days^{15,16}

Cisplatin 80 mg/m² IV daily on Day 1

Capecitabine 1000 mg/m² PO BID on Days 1–14
Cycled every 21 days¹⁷

PREFERRED REGIMENS—continued

Fluoropyrimidine and oxaliplatin

Oxaliplatin 85 mg/m² IV on Day 1

Leucovorin 400 mg/m² IV on Day 1

Fluorouracil 400 mg/m² IV Push on Day 1

Fluorouracil 1200 mg/m² IV continuous

infusion over 24 hours daily on Days 1 and 2
Cycled every 14 days¹⁸

Oxaliplatin 85 mg/m² IV on Day 1

Leucovorin 200 mg/m² IV on Day 1

Fluorouracil 2600 mg/m² IV continuous

infusion over 24 hours on Day 1

Cycled every 14 days¹⁵

Capecitabine 1000 mg/m² PO BID on Days 1–14

Oxaliplatin 130 mg/m² IV on Day 1

Cycled every 21 days¹⁹

OTHER REGIMENS

Paclitaxel with cisplatin or carboplatin

Paclitaxel 135–200 mg/m² IV on Day 1

Cisplatin 75 mg/m² IV on Day 2

Cycled every 21 days²⁰

Paclitaxel 90 mg/m² IV on Day 1

Cisplatin 50 mg/m² IV on Day 1

Cycled every 14 days²¹

Paclitaxel 200 mg/m² IV on Day 1

Carboplatin AUC 5 IV on Day 1

Cycled every 21 days²²

Docetaxel and cisplatin

Docetaxel 70–85 mg/m² IV on Day 1

Cisplatin 70–75 mg/m² IV on Day 1

Cycled every 21 days^{23,24}

Fluoropyrimidine

Leucovorin 400 mg/m² IV on Day 1

Fluorouracil 400 mg/m² IV Push on Day 1

Fluorouracil 1200 mg/m² IV continuous

infusion over 24 hours daily on Days 1 and 2
Cycled every 14 days¹⁶

Fluorouracil 800 mg/m² IV continuous

infusion over 24 hours daily on Days 1–5

Cycled every 28 days²⁵

Capecitabine 1000–1250 mg/m²

PO BID on Days 1–14

Cycled every 21 days²⁶

^{††}Systemic therapy regimen and dosing schedules are based on extrapolations from published literature and clinical practice.

The selection, dosing, and administration of anticancer agents and the management of associated toxicities are complex. Modifications of drug dose and schedule and initiation of supportive care interventions are often necessary because of expected toxicities and because of individual patient variability, prior treatment, nutritional status, and comorbidity. The optimal delivery of anticancer agents therefore requires a health care delivery team experienced in the use of anticancer agents and the management of associated toxicities in patients with cancer.

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Continued

GAST-F
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