



## **ROCHE FARMA SA**

### **ESPECIFICACIONES TECNICAS PROCEDIMIENTO NEGOCIADO: BEVACIZUMAB AVASTIN 400 MG 16 ML VIAL 25 mg/mL CONCENTRADO PARA PERFUSIÓN**

Incluido en la Guía Farmacoterapéutica del Área 4

**GRUPO TERAPÉUTICO:** L01XC07 – Agentes antineoplásicos e inmunomoduladores, agentes antineoplásicos, otros agentes antineoplásicos, anticuerpos monoclonales.


- Presentación en viales con tapón exento de látex perfectamente identificados con:
  - Nombre comercial
  - Nombre del principio activo
  - Lista de excipientes
  - Dosis en miligramos
  - 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: cartón y eliminación (impacto ambiental); embalaje exterior identificado lote y caducidad.



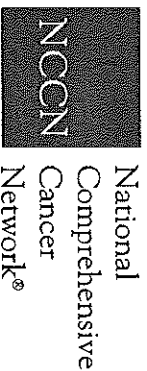


La Nacional Comprehensive Cancer Network (NCCN) recomienda el uso de bevacizumab en combinación con otros fármacos en diferentes tipos de cancer: Mama, Colon, Pulmon, Renal y Ovario.

Se adjunta bibliografía.

A blue ink signature, appearing to read 'T. Bermejo', is written over the text.  
Fdo Teresa Bermejo  
Jefe Servicio de Farmacia





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## CHEMOTHERAPY REGIMENS FOR NEOADJUVANT AND ADJUVANT THERAPY

- Cisplatin 50 mg/m<sup>2</sup> days 1 and 8; vinorelbine 25 mg/m<sup>2</sup> days 1, 8, 15, 22, every 28 days for 4 cycles<sup>a</sup>
- Cisplatin 100 mg/m<sup>2</sup> day 1; vinorelbine 30 mg/m<sup>2</sup> days 1, 8, 15, 22, every 28 days for 4 cycles<sup>b,c</sup>
- Cisplatin 75–80 mg/m<sup>2</sup> day 1; vinorelbine 25–30 mg/m<sup>2</sup> days 1 + 8, every 21 days for 4 cycles
- Cisplatin 100 mg/m<sup>2</sup> day 1; etoposide 100 mg/m<sup>2</sup> days 1–3, every 28 days for 4 cycles<sup>b</sup>
- Cisplatin 75 mg/m<sup>2</sup> day 1; gemcitabine 1250 mg/m<sup>2</sup> days 1, 8, every 21 days for 4 cycles<sup>d</sup>
- Cisplatin 75 mg/m<sup>2</sup> day 1; docetaxel 75 mg/m<sup>2</sup> day 1 every 21 days for 4 cycles<sup>e</sup>
- Cisplatin 75 mg/m<sup>2</sup> day 1, pemetrexed 500 mg/m<sup>2</sup> day 1 for nonsquamous every 21 days for 4 cycles<sup>f</sup>

### Chemotherapy Regimens for Patients with Comorbidities or Patients Not Able to Tolerate Cisplatin

Paclitaxel 200 mg/m<sup>2</sup> day 1, carboplatin AUC 6 day 1, every 21 days<sup>g</sup>

<sup>a</sup>Winton T, Livingston R, Johnson D, et al. Vinorelbine plus cisplatin vs. observation in resected non-small-lung cancer. *N Engl J Med* 2005;352:2589-2597.

<sup>b</sup>Arriagada R, Bergman B, Dunant A, et al. The International Adjuvant Lung Cancer Trial Collaborative Group. Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small cell lung cancer. *N Engl J Med* 2004;350:351-360.

<sup>c</sup>Douillard JY, Rosell R, De Lena M, et al. Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB-IIIa non-small-cell lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]): a randomised controlled trial. *Lancet Oncol* 2006;7:719-727.

<sup>d</sup>Pérol M, Chouaid C, Pérol D, et al. Randomized, phase III study of gemcitabine or erlotinib maintenance therapy versus observation, with predefined second-line treatment, after cisplatin-gemcitabine induction chemotherapy in advanced non-small-cell lung cancer. *J Clin Oncol* 2012;30:3516-3524.

<sup>e</sup>Fossella F, Pereira JR, von Pawel J, et al. Randomized, multinational, phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for advanced non-small-cell lung cancer: the TAX 326 study group. *J Clin Oncol* 2003;21:3016-3024.

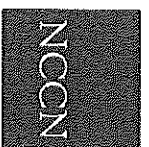
<sup>f</sup>Kreuter M, Vansteenkiste J, Fishcer JR, et al. Randomized phase 2 trial on refinement of early-stage NSCLC adjuvant chemotherapy with cisplatin and pemetrexed versus cisplatin and vinorelbine: the TREAT study. *Ann Oncol* 2013;24:986-992.

<sup>g</sup>Strauss GM, Herndon III JE, Maddaus MA, et al. Adjuvant paclitaxel plus carboplatin compared with observation in stage IB non-small cell lung cancer: CALGB 9633 with the Cancer and Leukemia Group B, Radiation Therapy Oncology Group, and North Central Cancer Treatment Group Study Groups. *J Clin Oncol* 2008;26:5043-5051.

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## CHEMOTHERAPY REGIMENS USED WITH RADIATION THERAPY

### Concurrent Chemotherapy/RT Regimens

- Cisplatin 50 mg/m<sup>2</sup> on days 1, 8, 29, and 36; etoposide 50 mg/m<sup>2</sup> days 1–5, 29–33; concurrent thoracic RT<sup>a,b,\*,\*\*</sup>
- Cisplatin 100 mg/m<sup>2</sup> days 1 and 29; vinblastine 5 mg/m<sup>2</sup>/weekly x 5; concurrent thoracic RT<sup>b,\*,\*\*</sup>
- Carboplatin AUC 5 on day 1, pemetrexed 500 mg/m<sup>2</sup> on day 1 every 21 days for 4 cycles; concurrent thoracic RT<sup>c</sup> (nonsquamous)<sup>\*,\*\*</sup>
- Cisplatin 75 mg/m<sup>2</sup> on day 1, pemetrexed 500 mg/m<sup>2</sup> on day 1 every 21 days for 3 cycles; concurrent thoracic RT<sup>d,e</sup> (nonsquamous)<sup>\*,\*\*</sup> ± additional 4 cycles of pemetrexed 500 mg/m<sup>2</sup>\*\*
- Paclitaxel 45–50 mg/m<sup>2</sup> weekly; carboplatin AUC 2, concurrent thoracic RT<sup>f,\*,\*\*</sup> ± additional 2 cycles of paclitaxel 200 mg/m<sup>2</sup> and carboplatin AUC 6\*\*

### Sequential Chemotherapy/RT Regimens (Adjuvant)

- Cisplatin 100 mg/m<sup>2</sup> on days 1 and 29; vinblastine 5 mg/m<sup>2</sup>/weekly on days 1, 8, 15, 22, and 29; followed by RT<sup>b</sup>
- Paclitaxel 200 mg/m<sup>2</sup> over 3 hours on day 1; carboplatin AUC 6 over 60 minutes on day 1 every 3 weeks for 2 cycles followed by thoracic RT<sup>g</sup>

\*Regimens can be used as neoadjuvant/preoperative/induction chemoradiotherapy.

\*\*Regimens can be used as adjuvant or definitive concurrent chemotherapy/RT.

<sup>a</sup>Albain KS, Crowley JJ, Turrisi AT III, et al. Concurrent cisplatin, etoposide, and chest radiotherapy in pathologic stage IIIB non-small-cell lung cancer: A Southwest Oncology Group Phase II Study, SWOG 9019. *J Clin Oncol* 2002;20:3454–3460.

<sup>b</sup>Curran WJ Jr, Paulus R, Langer CJ, et al. Sequential vs. concurrent chemoradiation for stage III non-small cell lung cancer: randomized phase III trial RTOG 9410. *J Natl Cancer Inst*. 2011;103:1452–1460.

<sup>c</sup>Govindan R, Bogart J, Stinchcombe T, et al. Randomized phase II study of pemetrexed, carboplatin, and thoracic radiation with or without cetuximab in patients with locally advanced unresectable non-small-cell lung cancer: Cancer and Leukemia Group B trial 30407. *J Clin Oncol* 2011;29:3120–3125.

<sup>d</sup>Choy H, Gerber DE, Bradley JD, et al. Concurrent pemetrexed and radiation therapy in the treatment of patients with inoperable stage III non-small cell lung cancer: a systematic review of completed and ongoing studies. *Lung Cancer* 2015;87:232–240

<sup>e</sup>Senan S, Brade A, Wang LH, et al. PROCLAIM: randomized phase III trial of pemetrexed-cisplatin or etoposide-cisplatin plus thoracic radiation therapy followed by consolidation chemotherapy in locally advanced nonsquamous non-small-cell lung cancer. *J Clin Oncol* 2016;34:953–962.

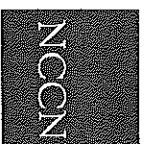
<sup>f</sup>Bradley JD, Paulus R, Komaki R, et al. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. *Lancet Oncol* 2015;16:187–199.

<sup>g</sup>Belani CP, Choy H, Bonomi P, et al. Combined chemoradiotherapy regimens of paclitaxel and carboplatin for locally advanced non-small-cell lung cancer: a randomized phase II locally advanced multi-modality protocol. *J Clin Oncol*. 2005;23:5883–5891.

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## SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE (1 OF 4)

### ADVANCED DISEASE:

- The drug regimen with the highest likelihood of benefit with toxicity deemed acceptable to both the physician and the patient should be given as initial therapy for advanced lung cancer.
- Stage, weight loss, performance status, and gender predict survival.
- Platinum-based chemotherapy prolongs survival, improves symptom control, and yields superior quality of life compared to best supportive care.
- Histology of NSCLC is important in the selection of systemic therapy.
- New agent/platinum combinations have generated a plateau in overall response rate ( $\approx 25\%$ – $35\%$ ), time to progression (4–6 mo), median survival (8–10 mo), 1-year survival rate (30%–40%), and 2-year survival rate (10%–15%) in fit patients.
- Unfit patients of any age (performance status 3–4) do not benefit from cytotoxic treatment, except erlotinib, afatinib, or gefitinib for EGFR mutation-positive and crizotinib for ALK-positive tumors of nonsquamous NSCLC or NSCLC NOS.

### First-line Therapy

- There is superior efficacy and reduced toxicity for cisplatin/pemetrexed in patients with nonsquamous histology, in comparison to cisplatin/gemcitabine.
- There is superior efficacy for cisplatin/gemcitabine in patients with squamous histology, in comparison to cisplatin/pemetrexed.
- Two drug regimens are preferred; a third cytotoxic drug increases response rate but not survival. Single-agent therapy may be appropriate in select patients.
- Response assessment after 2 cycles, then every 2–4 cycles with CT of known sites of disease with or without contrast or when clinically indicated.

### Maintenance Therapy

- Continuation maintenance refers to the use of at least one of the agents given in first line, beyond 4–6 cycles, in the absence of disease progression. Switch maintenance refers to the initiation of a different agent, not included as part of the first-line regimen, in the absence of disease progression, after 4–6 cycles of initial therapy.

### Subsequent Therapy

- Response assessment with CT of known sites of disease with or without contrast every 6–12 weeks.

See [First-line Systemic Therapy Options for](#)

[Adenocarcinoma, Large cell, NSCLC NOS on NSCL-F \(2 of 4\)](#)

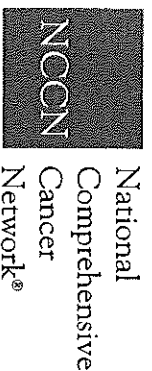
See [First-line Systemic Therapy Options for](#)

[Squamous Cell Carcinoma on NSCL-F \(3 of 4\)](#)

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## SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE (2 of 4)<sup>†</sup>

### First-Line Systemic Therapy Options

#### Adenocarcinoma, Large Cell, NSCLC NOS (PS 0-1)

- Bevacizumab/carboplatin/paclitaxel (category 1)<sup>1,\*,\*\*</sup>
- Bevacizumab/carboplatin/pemetrexed<sup>2,\*,\*\*</sup>
- Bevacizumab/cisplatin/pemetrexed<sup>3,\*,\*\*</sup>
- Carboplatin/albumin-bound paclitaxel (category 1)<sup>4</sup>
- Carboplatin/docetaxel (category 1)<sup>5</sup>
- Carboplatin/etoposide (category 1)<sup>6,7</sup>
- Carboplatin/gemcitabine (category 1)<sup>8</sup>
- Carboplatin/paclitaxel (category 1)<sup>9</sup>
- Carboplatin/pemetrexed (category 1)<sup>10</sup>
- Cisplatin/docetaxel (category 1)<sup>5</sup>
- Cisplatin/etoposide (category 1)<sup>11</sup>
- Cisplatin/gemcitabine (category 1)<sup>9,12</sup>
- Cisplatin/paclitaxel (category 1)<sup>13</sup>
- Cisplatin/pemetrexed (category 1)<sup>12</sup>
- Gemcitabine/docetaxel (category 1)<sup>14</sup>
- Gemcitabine/vinorelbine (category 1)<sup>15</sup>

#### Adenocarcinoma, Large Cell, NSCLC NOS (PS 2)

- Albumin-bound paclitaxel<sup>16</sup>
- Carboplatin/albumin-bound paclitaxel<sup>17,18</sup>
- Carboplatin/docetaxel<sup>5</sup>
- Carboplatin/etoposide<sup>6,7</sup>
- Carboplatin/gemcitabine<sup>8</sup>
- Carboplatin/paclitaxel<sup>9</sup>
- Carboplatin/pemetrexed<sup>10</sup>
- Docetaxel<sup>19,20</sup>
- Gemcitabine<sup>21-23</sup>
- Gemcitabine/docetaxel<sup>14</sup>
- Gemcitabine/vinorelbine<sup>15</sup>
- Paclitaxel<sup>24-26</sup>
- Pemetrexed<sup>27</sup>

<sup>†</sup>Albumin-bound paclitaxel may be substituted for either paclitaxel or docetaxel in patients who have experienced hypersensitivity reactions after receiving paclitaxel or docetaxel despite premedication, or for patients where the standard premedications (ie, dexamethasone, H2 blockers, H1 blockers) are contraindicated.

\*Bevacizumab should be given until progression.

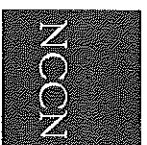
\*\*Any regimen with a high risk of thrombocytopenia and the potential risk of bleeding should be used with caution in combination with bevacizumab.

\*\*\*Criteria for treatment with bevacizumab: non-squamous NSCLC, and no recent history of hemoptysis. Bevacizumab should not be given as a single agent, unless as maintenance if initially used with chemotherapy.

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## SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE (3 of 4)<sup>†,††</sup>

### First-Line Systemic Therapy Options

#### Squamous Cell Carcinoma (PS 0-1)

- Carboplatin/albumin-bound paclitaxel (category 1)<sup>4</sup>
- Carboplatin/docetaxel (category 1)<sup>5</sup>
- Carboplatin/gemcitabine (category 1)<sup>8</sup>
- Carboplatin/paclitaxel (category 1)<sup>9</sup>
- Cisplatin/docetaxel (category 1)<sup>5</sup>
- Cisplatin/etoposide (category 1)<sup>11</sup>
- Cisplatin/gemcitabine (category 1)<sup>9,12</sup>
- Cisplatin/paclitaxel (category 1)<sup>13</sup>
- Gemcitabine/docetaxel (category 1)<sup>14</sup>
- Gemcitabine/vinorelbine (category 1)<sup>15</sup>

#### Squamous Cell Carcinoma (PS 2)

- Albumin-bound paclitaxel<sup>16</sup>
- Carboplatin/albumin-bound paclitaxel<sup>17,18</sup>
- Carboplatin/docetaxel<sup>5</sup>
- Carboplatin/etoposide<sup>6,7</sup>
- Carboplatin/gemcitabine<sup>8</sup>
- Carboplatin/paclitaxel<sup>9</sup>
- Docetaxel<sup>19,20</sup>
- Gemcitabine<sup>21-23</sup>
- Gemcitabine/docetaxel<sup>14</sup>
- Gemcitabine/vinorelbine<sup>15</sup>
- Paclitaxel<sup>24-26</sup>

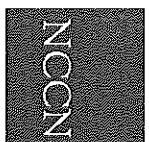
<sup>†</sup>Albumin-bound paclitaxel may be substituted for either paclitaxel or docetaxel in patients who have experienced hypersensitivity reactions after receiving paclitaxel or docetaxel despite premedication, or for patients where the standard premedications (ie, dexamethasone, H2 blockers, H1 blockers) are contraindicated.

<sup>††</sup>Cisplatin/gemcitabine/rectal ummab in the first-line setting and erlotinib or afatinib in the second-line setting are not used at NCCN institutions for these indications related to the efficacy and safety of these agents compared to the efficacy and safety of other available agents.

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## SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE (4 of 4)

- <sup>1</sup>Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small cell lung cancer. *N Engl J Med* 2006;355:2542-2550.
- <sup>2</sup>Patel JD, Socinski MA, Garon EB, et al. Pembrolizumab: a randomized phase III study of pemetrexed plus carboplatin and bevacizumab followed by maintenance pemetrexed and bevacizumab versus paclitaxel plus carboplatin and bevacizumab followed by maintenance bevacizumab in patients with stage IIIB or IV nonsquamous non-small cell lung cancer. *J Clin Oncol* 2013;31:4349-4357.
- <sup>3</sup>Bates F, Scherpereel A, Rittmeier A, et al. Randomized phase III trial of maintenance bevacizumab with or without pemetrexed after first-line induction with bevacizumab, cisplatin, and pemetrexed in advanced non-small-cell lung cancer: final results of a phase III trial. *J Clin Oncol* 2012;30:2055-2062.
- <sup>4</sup>Socinski MA, Bondarenko I, Karasava NA, et al. Weekly nab-paclitaxel in combination with carboplatin versus solvent-based paclitaxel plus carboplatin as first-line therapy in patients with advanced non-small cell lung cancer: final results of a phase III trial. *J Clin Oncol* 2012;30:2055-2062.
- <sup>5</sup>Fossella F, Perera JR, von Pawel J, et al. Randomized, multinational, phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for advanced non-small-cell lung cancer: the TAX 326 study group. *J Clin Oncol* 2003;21(16):3016-3024.
- <sup>6</sup>Klastersky J, Sculier JP, Lacroix H, et al. A randomized study comparing cisplatin or carboplatin with etoposide in patients with advanced non-small cell lung cancer. European Organization for Research and Treatment of Cancer Protocol 07861. *J Clin Oncol* 1990;8:1556-1562.
- <sup>7</sup>Frasci G, Comella P, Panza N, et al. Carboplatin-oral etoposide personalized dosing in elderly non-small cell lung cancer patients. Gruppo Oncologico Cooperativo Sud-Italia. *Eur J Cancer* 1998;34:1710-1714.
- <sup>8</sup>Danson S, Middleton WR, O Byrne KJ, et al. Phase III trial of gemcitabine and carboplatin versus mitomycin, ifosfamide, and cisplatin or mitomycin, vinblastine, and cisplatin in patients with advanced non-small cell lung carcinoma. *Cancer* 2003;98:542-553.
- <sup>9</sup>Ohe Y, Ohashi Y, Kubota K, et al. Randomized phase III study of cisplatin plus irinotecan versus carboplatin plus paclitaxel, cisplatin plus gemcitabine, and cisplatin plus vinorelbine for advanced non-small-cell lung cancer: Four-Arm Cooperative Study in Japan. *Ann Oncol* 2007;18:317-323.
- <sup>10</sup>Scagliotti GV, Kortsik C, Dark GG, et al. Pemetrexed combined with oxaliplatin or carboplatin as first-line treatment in advanced non-small cell lung cancer: a multicenter, randomized, phase II trial. *Clin Cancer Res* 2005;11:690-696.
- <sup>11</sup>Cardenal F, Lopez-Cabrezo MP, Anton A, et al. Randomized phase III study of gemcitabine-cisplatin versus etoposide-cisplatin in the treatment of locally advanced or metastatic non-small cell lung cancer. *J Clin Oncol* 1999;17:12-18.
- <sup>12</sup>Scagliotti GV, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naïve patients with advanced-stage NSCLC. *J Clin Oncol* 2008;26:3543-3551.
- <sup>13</sup>Pujol JL, Breton JL, Gervais R, et al. Gemcitabine-docetaxel versus cisplatin-vinorelbine in advanced or metastatic non-small-cell lung cancer: a phase III study addressing the case for cisplatin. *Ann Oncol* 2005;16:602-610.
- <sup>14</sup>Ian EH, Szczesna A, Krzakowski M, et al. Randomized study of vinorelbine-gemcitabine versus vinorelbine-carboplatin in patients with advanced non-small cell lung cancer. *Lung Cancer* 2005;49:233-240.
- <sup>16</sup>Green M, Manikhas G, Olov S, et al. Abraxane®, a novel Cremophor®-free, albumin-bound particle form of paclitaxel for the treatment of advanced non-small-cell lung cancer. *Ann Oncol* 2006;17:1263-1268.
- <sup>17</sup>Rizvi N, Riley G, Azzoli C, et al. Phase I/II Trial of Weekly Intravenous 130-nm Albumin-Bound Paclitaxel As Initial Chemotherapy in Patients With Stage IV Non-Small-Cell Lung Cancer. *J Clin Oncol* 2008;26:633-643.
- <sup>18</sup>Socinski MA, Bondarenko I, Karasava NA, et al. Weekly nab-paclitaxel in combination with carboplatin versus solvent-based paclitaxel plus carboplatin as first-line therapy in patients with advanced non-small cell lung cancer: final results of a phase III trial. *J Clin Oncol* 2012;30:2055-2062.
- <sup>19</sup>Fossella FV, DeVore R, Kerr RN, et al. Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small cell lung cancer previously treated with platinum-containing chemotherapy regimens. The TAX 320 Non-Small Cell Lung Cancer Study Group. *J Clin Oncol* 2000;18:2354-2362.
- <sup>20</sup>Fidias PM, Dakin SR, Lyss AP, et al. Phase III study of immediate compared with delayed docetaxel after front-line therapy with gemcitabine plus carboplatin in advanced non-small cell lung cancer. *J Clin Oncol* 2009;27:591-598.
- <sup>21</sup>Zatoukai F, Kantz E, Magyar P, et al. Gemcitabine in locally advanced and metastatic non-small cell lung cancer: the Central European phase II study. *Lung Cancer* 1998;22:243-250.
- <sup>22</sup>Sederholm C, Hillerdal G, Lamberg K, et al. Phase III trial of gemcitabine plus carboplatin versus single agent gemcitabine in the treatment of locally advanced or metastatic non-small cell lung cancer: the Swedish Lung Cancer Study group. *J Clin Oncol* 2005;23:8380-8288.
- <sup>23</sup>Perol M, Chouard C, Perol D, et al. Randomized, phase III study of gemcitabine or erlotinib maintenance therapy versus observation, with predefined second-line treatment, after cisplatin-gemcitabine induction chemotherapy in advanced non-small cell lung cancer. *J Clin Oncol* 2012;30:3516-3524.
- <sup>24</sup>Ellenbaum RC, Herndon JE, List MA, et al. Single-agent versus combination chemotherapy in advanced non-small cell lung cancer: the cancer and leukemia group B (study 9730). *J Clin Oncol* 2005;23:190-196.
- <sup>25</sup>Ceresoli GL, Gregorc V, Cordio S, et al. Phase II study of weekly paclitaxel as second-line therapy in patients with advanced non-small cell lung cancer. *Lung Cancer* 2004;44:231-239.
- <sup>26</sup>Yasuda K, Igishi T, Kawasaki Y, et al. Phase II study of weekly paclitaxel in patients with non-small cell lung cancer who have failed previous treatments. *Oncology* 2004;66:347-352.
- <sup>27</sup>Hanna NH, Shepard FA, Fossella FV, et al. Randomized phase III study of pemetrexed versus docetaxel in patients with non-small cell lung cancer previously treated with chemotherapy. *J Clin Oncol* 2004;22:1589-1597.
- <sup>13</sup>Schiller JH, Harrington D, Belani CP, et al. Comparison of four chemotherapy regimens for advanced non-small cell lung cancer. *N Engl J Med* 2002;346:92-98.

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### PRINCIPLES OF SYSTEMIC THERAPY\* (1 of 3)

#### Systemic therapy as primary or adjuvant therapy:

##### • Limited stage (maximum of 4–6 cycles):

- ▶ Cisplatin 60 mg/m<sup>2</sup> day 1 and etoposide 120 mg/m<sup>2</sup> days 1, 2, 3<sup>1</sup>
- ▶ Cisplatin 80 mg/m<sup>2</sup> day 1 and etoposide 100 mg/m<sup>2</sup> days 1, 2, 3<sup>2</sup>
- ▶ Carboplatin AUC 5–6 day 1 and etoposide 100 mg/m<sup>2</sup> days 1, 2, 3<sup>3</sup>
- ▶ During systemic therapy + RT, cisplatin/etoposide is recommended (category 1).
- ▶ The use of myeloid growth factors is not recommended during concurrent systemic therapy plus radiotherapy (category 1 for not using GM-CSF).<sup>\*\*</sup>

##### • Extensive stage (maximum of 4–6 cycles):

- ▶ Carboplatin AUC 5–6 day 1 and etoposide 100 mg/m<sup>2</sup> days 1, 2, 3<sup>4</sup>
- ▶ Cisplatin 75 mg/m<sup>2</sup> day 1 and etoposide 100 mg/m<sup>2</sup> days 1, 2, 3<sup>5</sup>
- ▶ Cisplatin 80 mg/m<sup>2</sup> day 1 and etoposide 80 mg/m<sup>2</sup> days 1, 2, 3<sup>6</sup>
- ▶ Cisplatin 25 mg/m<sup>2</sup> days 1, 2, 3 and etoposide 100 mg/m<sup>2</sup> days 1, 2, 3<sup>7</sup>
- ▶ Carboplatin AUC 5 day 1 and irinotecan 50 mg/m<sup>2</sup> days 1, 8, 15<sup>8</sup>
- ▶ Cisplatin 60 mg/m<sup>2</sup> day 1 and irinotecan 60 mg/m<sup>2</sup> days 1, 8, 15<sup>9</sup>
- ▶ Cisplatin 30 mg/m<sup>2</sup> and irinotecan 65 mg/m<sup>2</sup> days 1, 8<sup>10</sup>

#### Subsequent systemic therapy:

##### • Clinical trial preferred.

##### • Relapse ≤6 mo, PS 0–2:

- ▶ topotecan PO or IV<sup>11–13</sup>
- ▶ irinotecan<sup>14</sup>
- ▶ paclitaxel<sup>15,16</sup>
- ▶ docetaxel<sup>17</sup>
- ▶ temozolomide<sup>18,19</sup>
- ▶ nivolumab ± ipilimumab<sup>20</sup>
- ▶ vinorelbine<sup>21,22</sup>
- ▶ oral etoposide<sup>23,24</sup>
- ▶ gemcitabine<sup>25,26</sup>
- ▶ cyclophosphamide/doxorubicin/vincristine (CAV)<sup>11</sup>
- ▶ bendamustine (category 2B)<sup>27</sup>

##### • Relapse >6 mo: original regimen<sup>28,29</sup>

Consider dose reduction or growth factor support for patients with PS 2

### Response Assessment SCL-C 2 of 3

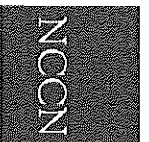
### References on SCL-C 3 of 3

\*The regimens included are representative of the more commonly used regimens for small cell lung cancer. Other regimens may be acceptable.  
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## PRINCIPLES OF SYSTEMIC THERAPY (2 of 3)

### Response assessment

- Limited-stage

- ▶ For patients receiving adjuvant therapy, response assessment should occur only after completion of initial therapy; do not repeat scans to assess response during adjuvant treatment.
- ▶ For patients receiving systemic therapy + concurrent RT, response assessment should occur only after completion of initial therapy; do not repeat scans to assess response during initial treatment.
- ▶ For patients receiving systemic therapy alone or sequential systemic therapy followed by RT, response assessment by CT chest/liver/adrenal with contrast should occur after every 2 cycles of systemic therapy and at completion of therapy.

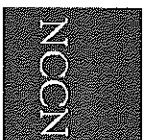
- Extensive-stage

- ▶ During systemic therapy, response assessment by CT chest/liver/adrenal with contrast should occur after every 2–3 cycles of systemic therapy and at completion of therapy.
- ▶ For patients with asymptomatic brain metastases receiving systemic therapy before whole-brain RT, brain MRI (preferred) or CT with contrast should be repeated after every 2 cycles of systemic therapy and at completion of therapy.
- Subsequent systemic therapy
  - ▶ Response assessment by CT chest/liver/adrenal with contrast should occur after every 2–3 cycles of systemic therapy.

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## PRINCIPLES OF SYSTEMIC THERAPY (3 of 3)

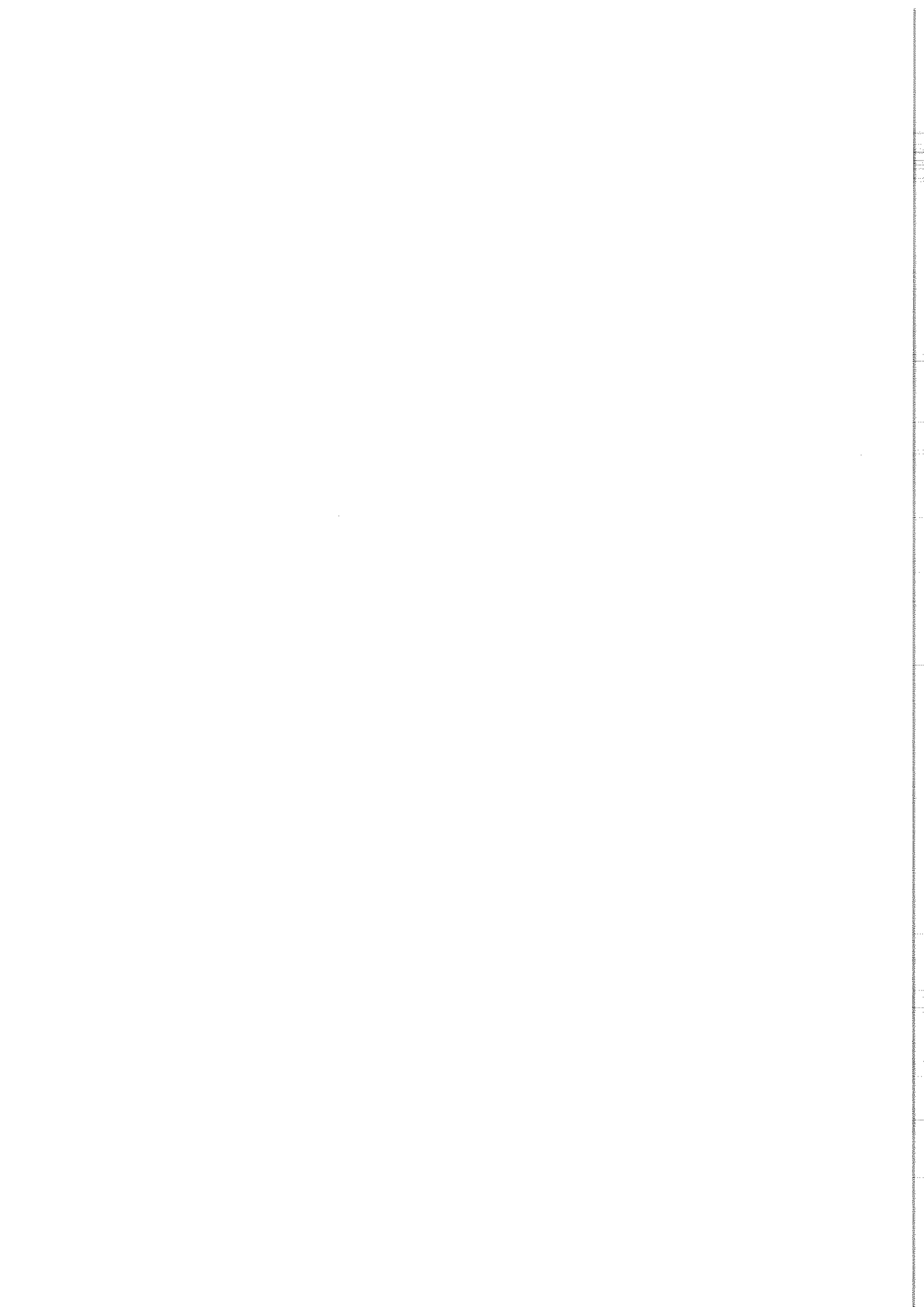
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in PFS, crossover to the sorafenib treatment arm was recommended, which likely resulted in the failure of this trial to demonstrate an OS benefit for sorafenib in the final analysis. With censoring of crossover data, treatment with sorafenib was found to be associated with an improved survival compared with placebo, 17.8 vs. 14.3 months (HR, 0.78; 95% CI, 0.62–0.97;  $P = .0287$ ).<sup>146</sup> Common grade 3 to 4 adverse effects reported more in the sorafenib group than in the placebo group were hand-foot syndrome, fatigue, and hypertension.<sup>146</sup> This study showed the effectiveness of sorafenib was primarily in patients who progressed on prior cytokine therapy. Sorafenib has also been studied as second-line therapy in patients treated with sunitinib or bevacizumab and has been found to be safe, feasible, and effective.<sup>147,148</sup> Sorafenib is listed as a category 2A subsequent therapy option.

*Sunitinib as Subsequent Therapy for Predominantly Clear Cell Carcinoma*  
Sunitinib also has demonstrated substantial anti-tumor activity in the second-line therapy of metastatic RCC after progression on cytokine therapy.<sup>114,149</sup> Studies investigating the sequential use of sunitinib and sorafenib mostly are retrospective. There are prospective data, although limited, that suggest a lack of total cross resistance between TKIs, either sorafenib followed by sunitinib failures or vice versa—an observation that is consistent with their differences in target specificities and slightly different toxicity spectra that sometimes permit tolerance of one agent over another.<sup>150–154</sup> Sunitinib is considered a category 2A subsequent therapy option.

*Pazopanib as Subsequent Therapy for Predominantly Clear Cell Carcinoma*  
The phase III trial comparing pazopanib with placebo, detailed earlier under the section titled *Pazopanib as First-line Therapy for Predominantly Clear Cell Carcinoma*, included 202 patients who received prior cytokine therapy. The average PFS in cytokine pre-treated patients was 7.4 versus 4.2 months.<sup>108</sup>

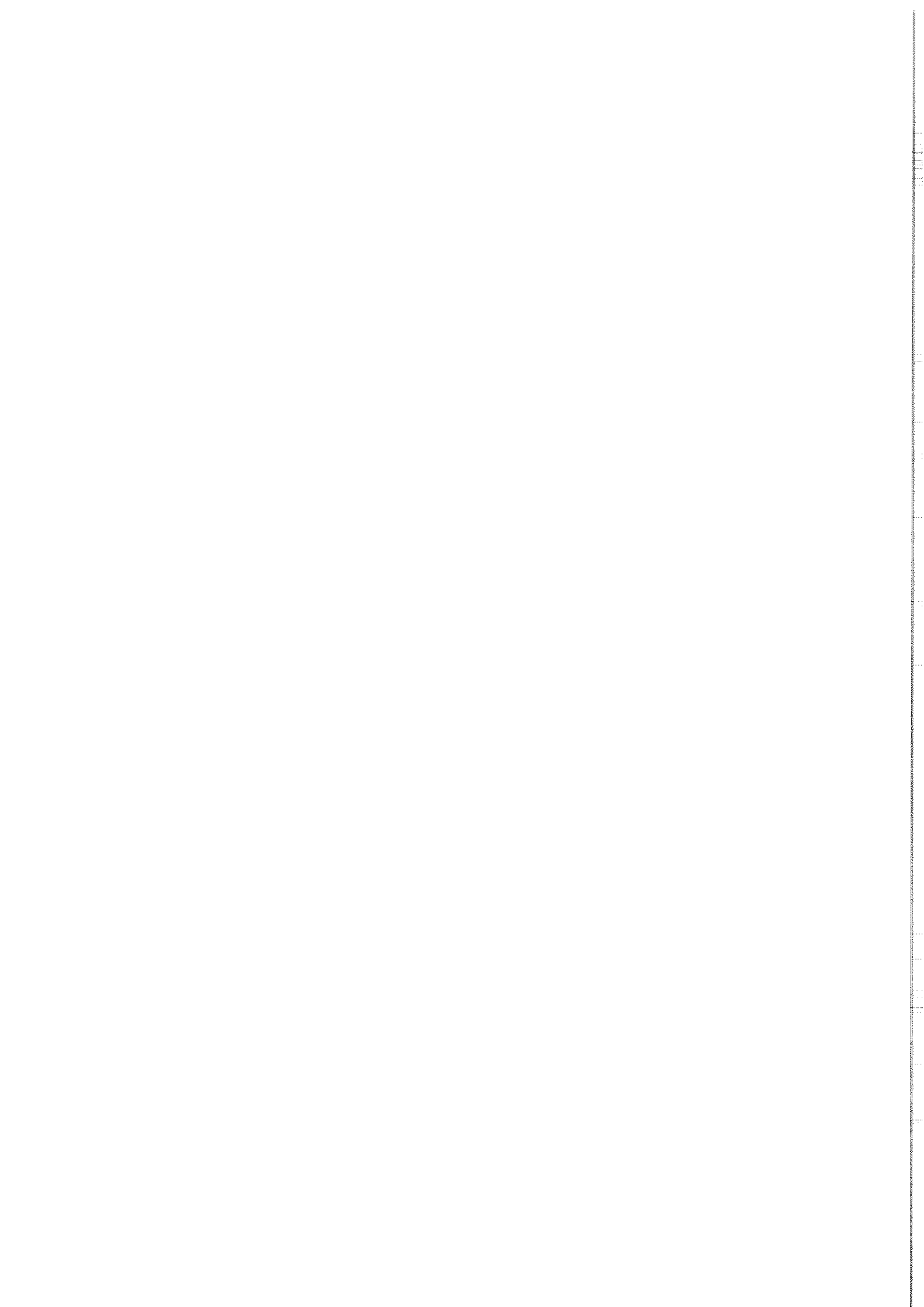
A prospective phase II trial examined the activity and toxicity of second-line treatment with pazopanib (800 mg orally daily) in 56 patients with advanced metastatic RCC previously treated with a targeted agent.<sup>155</sup> The patients enrolled in this trial had previously received first-line treatment with sunitinib ( $n = 39$ ) or bevacizumab ( $n = 16$ ). Responses were evaluated after 8 weeks of treatment using RECIST. The trial showed that 27% of patients ( $n = 15$ ) had objective response to pazopanib; 49% ( $n = 27$ ) had stable disease.<sup>155</sup> After a median follow-up of 16.7 months, the median PFS was 7.5 months (95% CI, 5.4–9.4 months).<sup>155</sup> The PFS was similar whether previous treatment was with sunitinib or bevacizumab. The estimated OS rate at 24 months was 43%.<sup>155</sup>

Another retrospective analysis reported data on 93 patients with metastatic RCC treated with multiple lines of prior targeted therapies.<sup>156</sup> Among evaluable patients ( $n = 85$ ) in this study, 15% ( $n = 13$ ) had a partial response and the median PFS observed was 6.5 months (95% CI, 4.5–9.7).

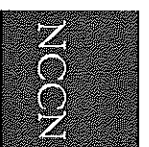
Based on the above data, the NCCN Kidney Cancer Panel considers pazopanib a category 2A subsequent therapy option.

*Other Agents as Subsequent Therapy for Predominantly Clear Cell Carcinoma*  
Phase II trials have shown benefit of bevacizumab monotherapy after prior treatment with a cytokine.<sup>157</sup> Bevacizumab is a category 2B subsequent therapy option. A phase II trial suggested benefit to temsirolimus therapy after prior treatment with a cytokine.<sup>158</sup> A phase III trial (INTORSECT) compared the efficacy of temsirolimus to sorafenib following first-line sunitinib as a treatment for patients with RCC.<sup>158</sup> The trial enrolled 512 patients with a performance status of 0 or 1 and either clear cell or non-clear cell histology. Patients were randomized to receive sorafenib at 400 mg twice daily or intravenous temsirolimus at









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## CHEMOTHERAPY REGIMENS FOR RECURRENT OR METASTATIC BREAST CANCER<sup>1,2</sup>

### 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/bevacizumab<sup>3</sup>

### Preferred first-line agents for HER2-positive disease:

- Pertuzumab + trastuzumab + docetaxel (category 1)<sup>4</sup>
- Pertuzumab + trastuzumab + paclitaxel<sup>4</sup>

### 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<sup>4,5,6</sup>

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

<sup>2</sup>Nab-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/m<sup>2</sup>.

<sup>3</sup>Randomized 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.

<sup>4</sup>Patients 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.

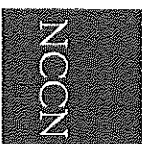
<sup>5</sup>Trastuzumab given in combination with an anthracycline is associated with significant cardiac toxicity. Concurrent use of trastuzumab and pertuzumab with an anthracycline should be avoided.

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

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## DOSING SCHEDULES FOR CHEMOTHERAPY REGIMENS FOR RECURRENT OR METASTATIC BREAST CANCER

### Preferred single agents:

#### Anthracyclines:

- Doxorubicin
  - 60–75 mg/m<sup>2</sup> IV day 1, cycled every 21 days<sup>1</sup>
  - or
  - 20 mg/m<sup>2</sup> IV day 1 weekly<sup>2</sup>
- Pegylated liposomal encapsulated doxorubicin<sup>3</sup>
  - 50 mg/m<sup>2</sup> IV day 1
  - Cycled every 28 days.

#### Taxanes:

- Paclitaxel
  - 175 mg/m<sup>2</sup> IV day 1
  - Cycled every 21 days.<sup>4</sup>
  - or
  - 80 mg/m<sup>2</sup> IV day 1 weekly<sup>5</sup>

#### Antimetabolites:

- Capecitabine<sup>6</sup>
  - 1000–1250 mg/m<sup>2</sup> PO twice daily days 1–14
  - Cycled every 21 days.
- Gemcitabine<sup>7</sup>
  - 800–1200 mg/m<sup>2</sup> IV days 1, 8, and 15
  - Cycled every 28 days.

#### Other microtubule inhibitors:

- Vinorelbine<sup>8</sup>
  - 25 mg/m<sup>2</sup> IV day 1 weekly
- Eribulin<sup>9</sup>
  - 1.4 mg/m<sup>2</sup> IV days 1 and 8
  - Cycled every 21 days.

### Other single agents:

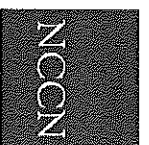
- Cyclophosphamide<sup>10</sup>
  - 50 mg PO daily on days 1–21
  - Cycled every 28 days.
- Carboplatin<sup>11</sup>
  - AUC 6 IV on day 1
  - Cycled every 21–28 days.
- Docetaxel<sup>12,13</sup>
  - 60–100 mg/m<sup>2</sup> IV day 1
  - Cycled every 21 days.
  - or
  - 35 mg/m<sup>2</sup> IV weekly for 6 wks followed by a 2-week rest, then repeat<sup>14</sup>
- Albumin-bound paclitaxel
  - 100 mg/m<sup>2</sup> or 125 mg/m<sup>2</sup> IV days 1, 8, and 15
  - Cycled every 28 days.<sup>15,16</sup>
  - or
  - 260 mg/m<sup>2</sup> IV
  - Cycled every 21 days.<sup>15</sup>
- Cisplatin<sup>17</sup>
  - 75 mg/m<sup>2</sup> IV on day 1
  - Cycled every 21 days.
- Epirubicin<sup>18</sup>
  - 60–90 mg/m<sup>2</sup> IV day 1
  - Cycled every 21 days.
- Ixabepilone<sup>19</sup>
  - 40 mg/m<sup>2</sup> IV day 1
  - Cycled every 21 days.

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.

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## DOSING SCHEDULES FOR CHEMOTHERAPY REGIMENS FOR RECURRENT OR METASTATIC BREAST CANCER

### Chemotherapy combinations:

#### CAF chemotherapy<sup>20</sup>

- Cyclophosphamide 100 mg/m<sup>2</sup> PO days 1–14
  - Doxorubicin 30 mg/m<sup>2</sup> IV days 1 & 8
  - 5-fluorouracil 500 mg/m<sup>2</sup> IV days 1 & 8
- Cycled every 28 days.

#### FAC chemotherapy<sup>21</sup>

- 5-fluorouracil 500 mg/m<sup>2</sup> IV days 1 & 8 or days 1 & 4
  - Doxorubicin 50 mg/m<sup>2</sup> IV day 1  
(or by 72-h continuous infusion)
  - Cyclophosphamide 500 mg/m<sup>2</sup> IV day 1
- Cycled every 21 days.

#### FEC chemotherapy<sup>22</sup>

- Cyclophosphamide 400 mg/m<sup>2</sup> IV days 1 & 8
  - Epirubicin 50 mg/m<sup>2</sup> IV days 1 & 8
  - 5-ouracil 500 mg/m<sup>2</sup> IV days 1 & 8
- Cycled every 28 days.

#### AC chemotherapy<sup>23</sup>

- Doxorubicin 60 mg/m<sup>2</sup> IV day 1
  - Cyclophosphamide 600 mg/m<sup>2</sup> IV day 1
- Cycled every 21 days.

#### EC chemotherapy<sup>24</sup>

- Epirubicin 75 mg/m<sup>2</sup> IV day 1
  - Cyclophosphamide 600 mg/m<sup>2</sup> IV day 1
- Cycled every 21 days.

#### CMF chemotherapy<sup>25</sup>

- Cyclophosphamide 100 mg/m<sup>2</sup> PO days 1–14
  - Methotrexate 40 mg/m<sup>2</sup> IV days 1 & 8
  - 5-fluorouracil 600 mg/m<sup>2</sup> IV days 1 & 8
- Cycled every 28 days.

#### Docetaxel/capecitabine chemotherapy<sup>26</sup>

- Docetaxel 75 mg/m<sup>2</sup> IV day 1
  - Capecitabine 950 mg/m<sup>2</sup> PO twice daily days 1–14
- Cycled every 21 days.

#### GT chemotherapy<sup>27</sup>

- Paclitaxel 175 mg/m<sup>2</sup> IV day 1
  - Gemcitabine 1250 mg/m<sup>2</sup> IV days 1 & 8 (following paclitaxel on day 1)
- Cycled every 21 days.

#### Gemcitabine/carboplatin<sup>28</sup>

- Gemcitabine 1000 mg/m<sup>2</sup> on days 1 & 8
  - Carboplatin AUC 2 IV on days 1 & 8
- Cycled every 21 days.

#### Paclitaxel plus bevacizumab<sup>29</sup>

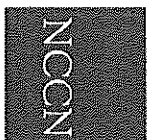
- Paclitaxel 90 mg/m<sup>2</sup> by 1 h IV days 1, 8, & 15
  - Bevacizumab 10 mg/kg IV days 1 & 15
- Cycled every 28 days.

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.

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# NCCN Guidelines Version 2.2017 Invasive Breast Cancer

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

### Preferred first-line agents for HER2-positive disease:

- Pertuzumab + trastuzumab + docetaxel<sup>30</sup>
  - 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/m<sup>2</sup> IV day 1
- Cycled every 21 days.

### Pertuzumab + trastuzumab + paclitaxel<sup>31</sup>

- 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 days<sup>32</sup>
  - Paclitaxel 80 mg/m<sup>2</sup> IV day 1 weekly<sup>31</sup>

- Paclitaxel 175 mg/m<sup>2</sup> day 1 cycled every 21 days

### Other agents for HER2-positive disease:

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

### Paclitaxel/carboplatin + trastuzumab<sup>34</sup>

- Carboplatin AUC 6 IV day 1
  - Paclitaxel 175 mg/m<sup>2</sup> 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 days<sup>32</sup>

### Weekly paclitaxel/carboplatin + trastuzumab<sup>35</sup>

- Paclitaxel 80 mg/m<sup>2</sup> 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 days<sup>32</sup>

### Trastuzumab + paclitaxel

- Paclitaxel
- ▶ 175 mg/m<sup>2</sup> IV day 1 cycled every 21 days<sup>36</sup>

or

- ▶ 80–90 mg/m<sup>2</sup> IV day 1 weekly<sup>37</sup>

### • 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 days<sup>32</sup>

### Trastuzumab + docetaxel

- Docetaxel
- ▶ 80–100 mg/m<sup>2</sup> IV day 1 cycled every 21 days<sup>38</sup>

or

- ▶ 35 mg/m<sup>2</sup> IV days 1, 8, and 15 weekly<sup>39</sup>

### • Trastuzumab

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

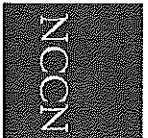
or

- ▶ 8 mg/kg IV day 1 followed by 6 mg/kg IV every 21 days<sup>32</sup>

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

Trastuzumab + vinorelbine<sup>40,41</sup>

- Vinorelbine
  - ▶ 25 mg/m<sup>2</sup> IV day 1 weekly

or

- ▶ 30–35 mg/m<sup>2</sup> 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 days<sup>32</sup>

Trastuzumab + capecitabine<sup>42</sup>

- Capecitabine 1000–1250 mg/m<sup>2</sup> PO twice daily days 1–14
- cycled every 21 days

• Trastuzumab

- ▶ 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly<sup>36,43</sup>
- or
- ▶ 8 mg/kg IV day 1 followed by 6 mg/kg IV every 21 days<sup>32</sup>

### Agents for trastuzumab-exposed HER2-positive disease:

Lapatinib + capecitabine<sup>44</sup>

- Lapatinib 1250 mg PO daily days 1–21
- Capecitabine 1000 mg/m<sup>2</sup> PO twice daily days 1–14
- Cycled every 21 days.

Trastuzumab + capecitabine<sup>45</sup>

- Capecitabine 1000–1250 mg/m<sup>2</sup> PO twice daily days 1–14
- Cycled every 21 days.

• Trastuzumab

- ▶ 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly<sup>36,43</sup>
- or
- ▶ 8 mg/kg IV day 1 followed by 6 mg/kg IV every 21 days<sup>32</sup>

Trastuzumab + lapatinib<sup>46</sup>

- Lapatinib 1000 mg PO daily

• Trastuzumab

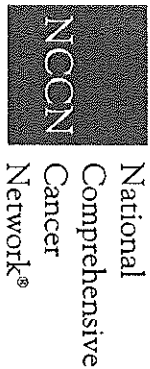
- ▶ 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly
- or
- ▶ 8 mg/kg IV day 1 followed by 6 mg/kg IV every 21 days<sup>32</sup>

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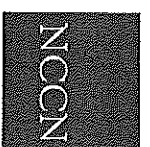
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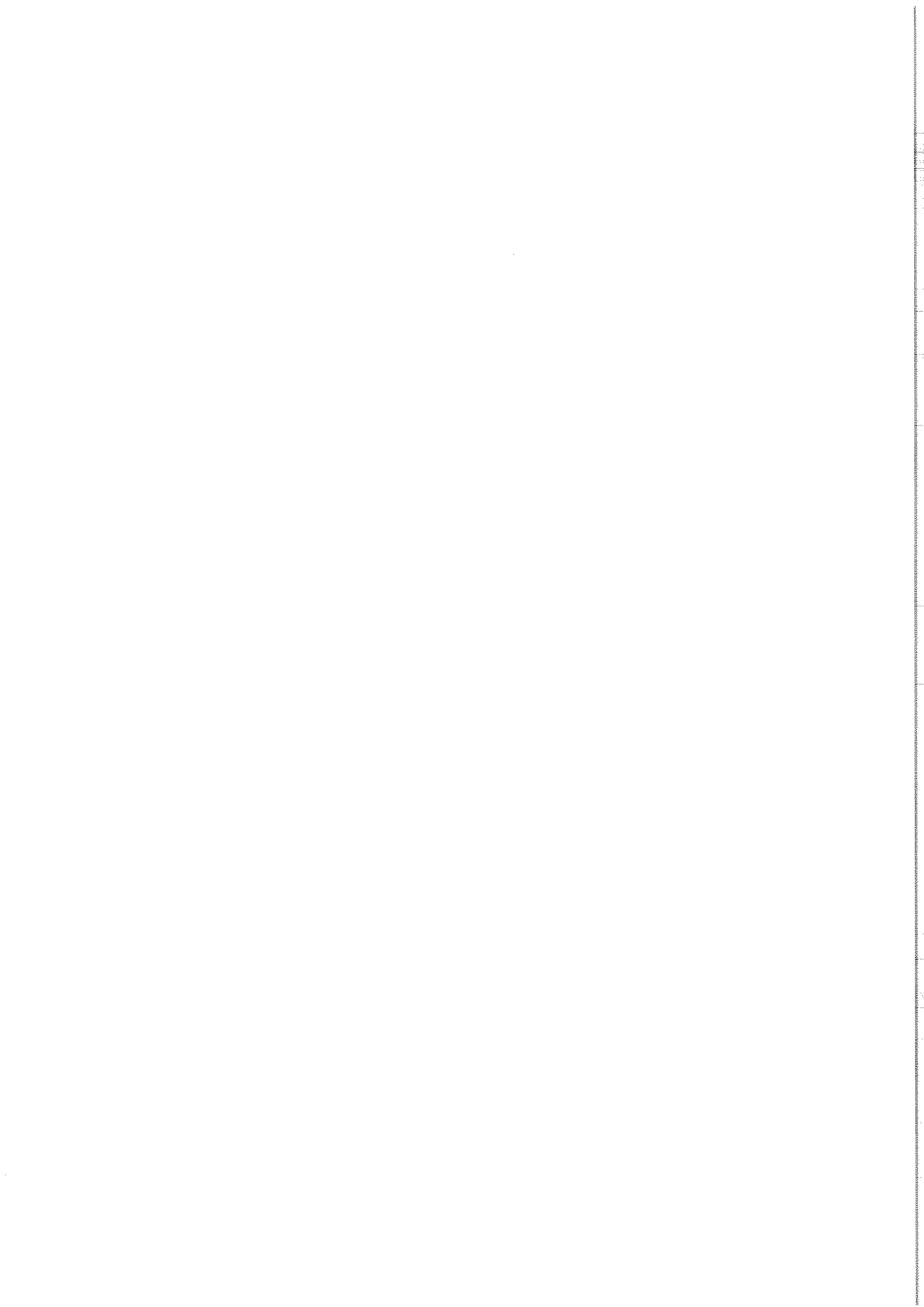
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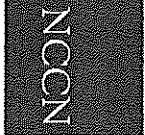
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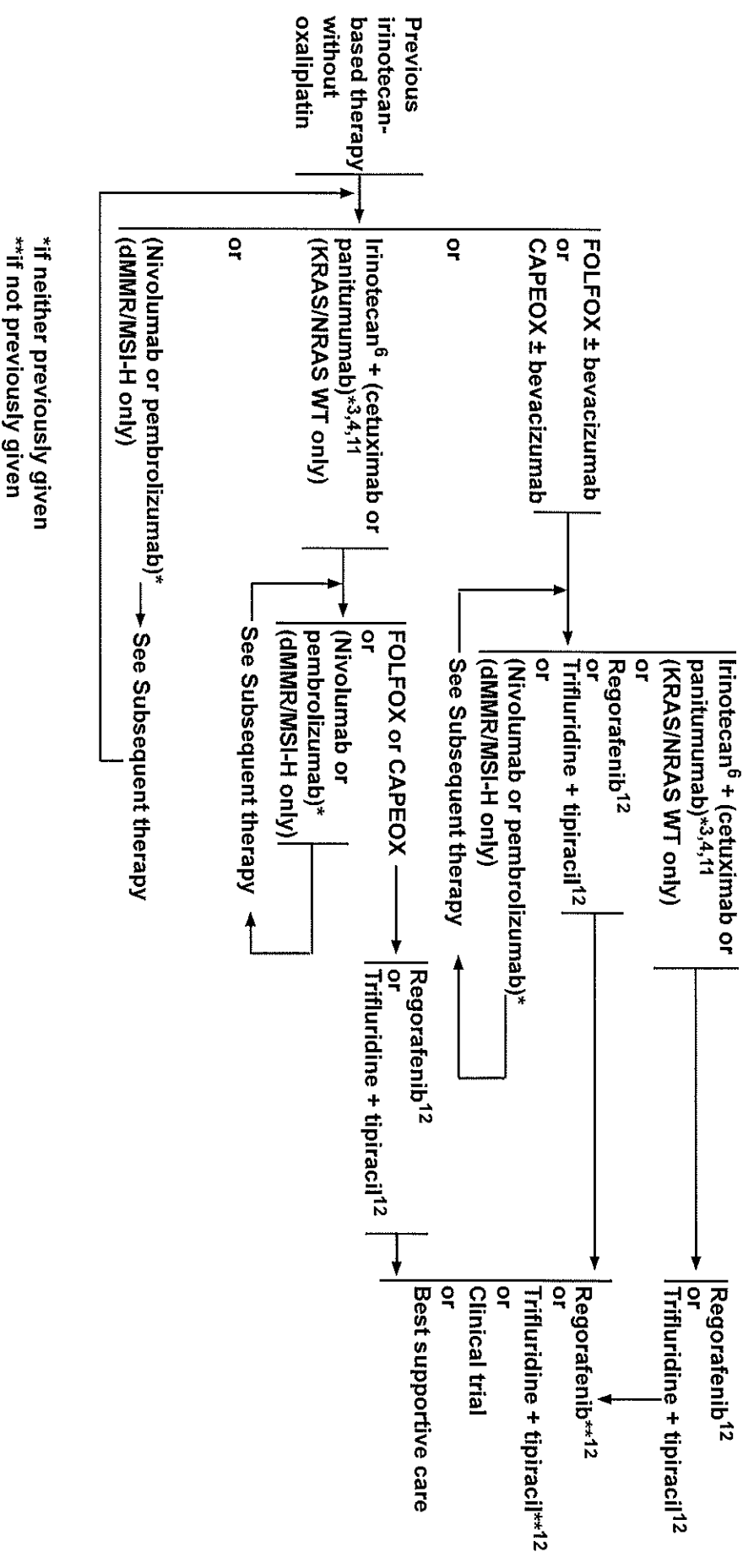




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**CONTINUUM OF CARE - SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE:<sup>1</sup> (PAGE 3 of 10)**

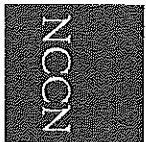
**Subsequent Therapy**



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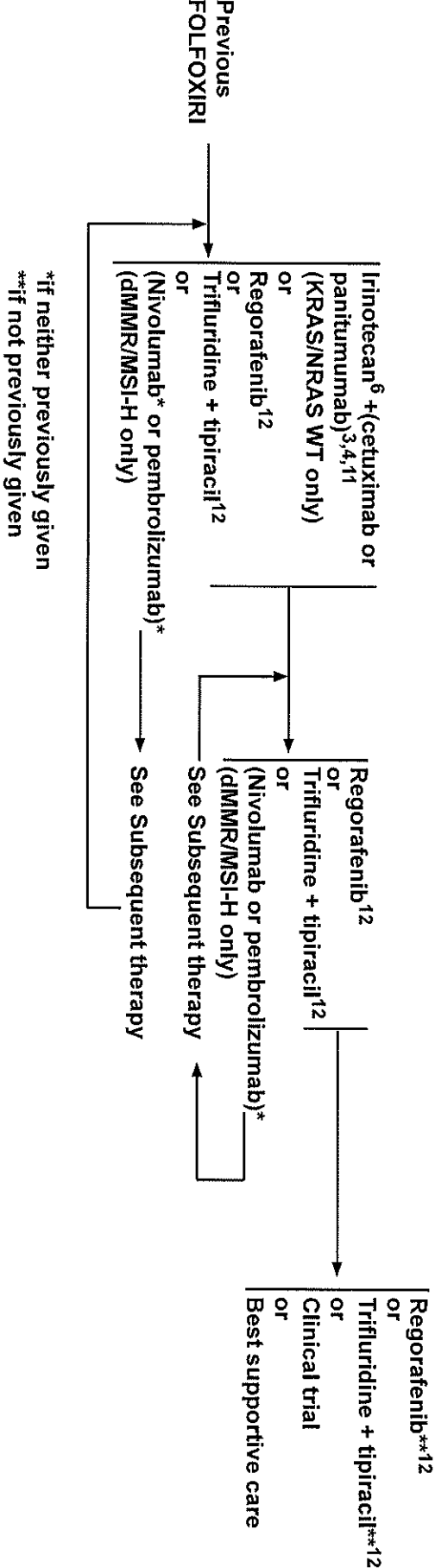


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### CONTINUUM OF CARE - SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE:<sup>1</sup> (PAGE 4 of 10)

#### Subsequent Therapy



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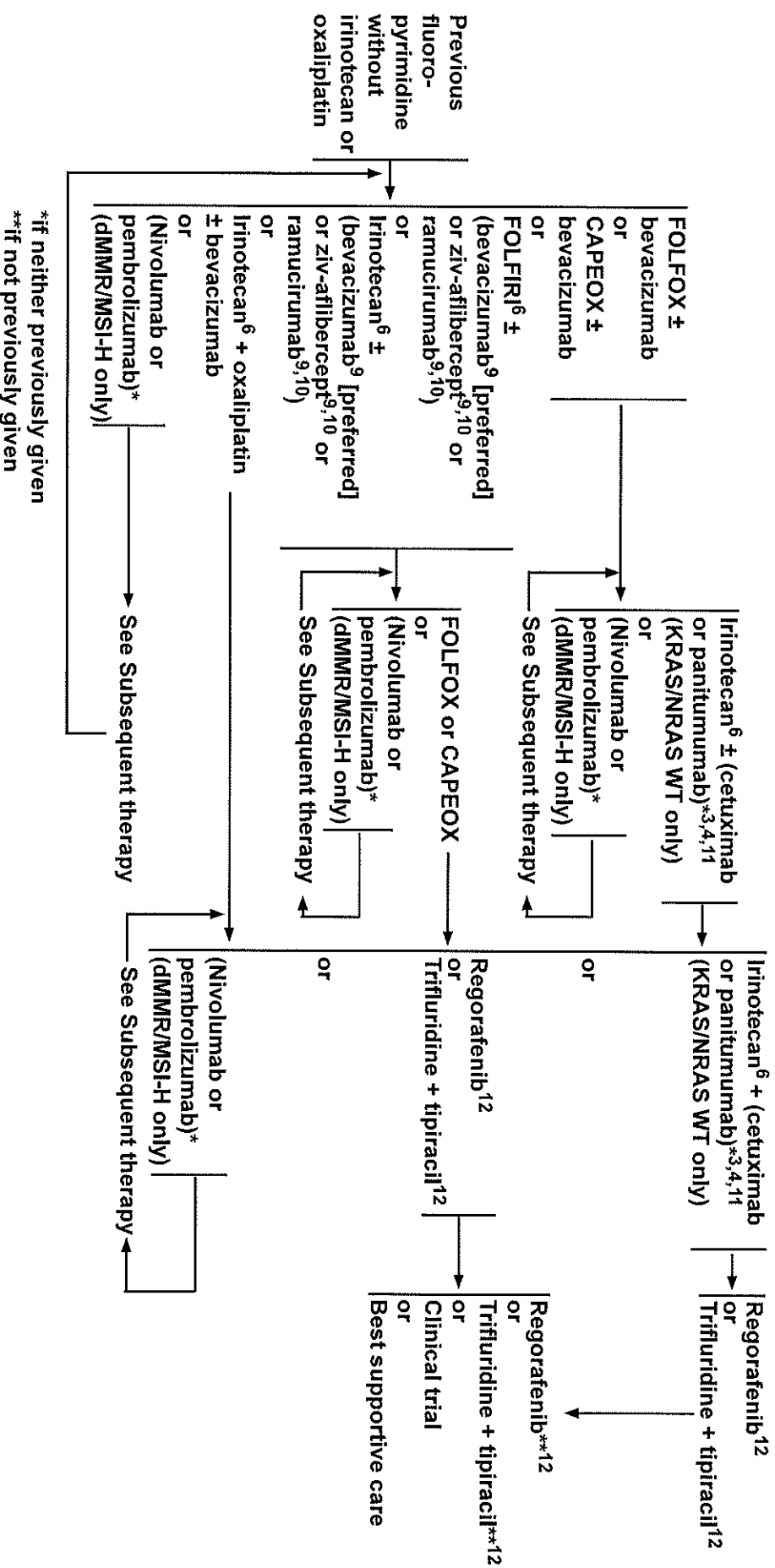




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## CONTINUUM OF CARE - SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE:<sup>1</sup> (PAGE 5 of 10)

### Subsequent Therapy

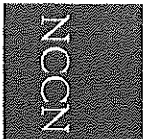


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## SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE (PAGE 6 of 10)

<sup>1</sup>For chemotherapy references, see [Chemotherapy Regimens and References \(COL-C 7-10\)](#).

<sup>2</sup>Chest/Abdominal/Pelvic CT with contrast or Chest CT and Abdominal/Pelvic MRI with contrast to monitor progress of therapy. PET/CT should not be used.

<sup>3</sup>See [Principles of Pathologic Review \(COL-A 4 of 5\)](#).

<sup>4</sup>BRAF V600E mutation makes response to panitumumab or cetuximab highly unlikely.

<sup>5</sup>The panel defines the left side of the colon as splenic flexure to rectum. Evidence suggests that patients with tumors originating on the right side of the colon (hepatic flexure through cecum) are unlikely to respond to cetuximab and panitumumab in first-line therapy for metastatic disease. Data on the response to cetuximab and panitumumab in patients with primary tumors originating in the transverse colon (hepatic flexure to splenic flexure) are lacking.

<sup>6</sup>Irinotecan should be used with caution in patients with Gilbert's disease or elevated serum bilirubin. There is a commercially available test for UGT1A1. Guidelines for use in clinical practice have not been established.

<sup>7</sup>A treatment option for patients not able to tolerate oxaliplatin or irinotecan.

<sup>8</sup>The use of single-agent capecitabine after progression on a fluoropyrimidine-containing regimen has been shown to be ineffective; therefore, this is not recommended.

<sup>9</sup>Bevacizumab is the preferred anti-angiogenic agent based on toxicity and/or cost.

<sup>10</sup>There are no data to suggest activity of FOLFIRI-ziv-aflibercept or FOLFIRI-ramucirumab in a patient who has progressed on FOLFIRI-bevacizumab, or vice versa. Ziv-aflibercept and ramucirumab have only shown activity when given in conjunction with FOLFIRI in FOLFIRI-naïve patients.

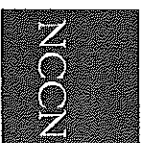
<sup>11</sup>Cetuximab or panitumumab are recommended in combination with irinotecan-based therapy or as single-agent therapy for patients who cannot tolerate irinotecan.

<sup>12</sup>Regorafenib or trifluridine + tipiracil are treatment options for patients who have progressed through all available regimens.

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## SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE - CHEMOTHERAPY REGIMENS (PAGE 7 of 10)

### mFOLFOX 6<sup>1,2,3¶</sup>

Oxaliplatin 85 mg/m<sup>2</sup> IV day 1\*

Leucovorin 400 mg/m<sup>2</sup> IV day 1\*\*

5-FU 400 mg/m<sup>2</sup> IV bolus on day 1, then 1200 mg/m<sup>2</sup>/d x 2 days  
(total 2400 mg/m<sup>2</sup> over 46–48 hours) IV continuous infusion

Repeat every 2 weeks

### CAPEOX<sup>8</sup>

Oxaliplatin 130 mg/m<sup>2</sup> IV day 1\*

Capecitabine 1000<sup>†</sup> mg/m<sup>2</sup> twice daily PO for 14 days

Repeat every 3 weeks

### mFOLFOX<sup>74</sup>

Oxaliplatin 85 mg/m<sup>2</sup> IV day 1\*

Leucovorin 400 mg/m<sup>2</sup> IV day 1\*\*

5-FU 1200 mg/m<sup>2</sup>/d x 2 days (total 2400 mg/m<sup>2</sup> over 46–48 hours)  
IV continuous infusion

Repeat every 2 weeks

### CAPEOX + bevacizumab<sup>8¶</sup>

Oxaliplatin 130 mg/m<sup>2</sup> IV day 1\*

Capecitabine 1000<sup>†</sup> mg/m<sup>2</sup> PO twice daily for 14 days

Bevacizumab 7.5 mg/kg IV day 1

Repeat every 3 weeks

### FOLFOX + bevacizumab<sup>5</sup>

Bevacizumab 5 mg/kg IV, day 1

Repeat every 2 weeks

### FOLFOX + panitumumab<sup>6</sup> (KRAS/NRAS WT only)

Panitumumab 6 mg/kg IV over 60 minutes, day 1

Repeat every 2 weeks

### FOLFOX + cetuximab<sup>7</sup> (KRAS/NRAS WT only)

Cetuximab 400 mg/m<sup>2</sup> IV over 2 hours first infusion,

then 250 mg/m<sup>2</sup> IV over 60 minutes weekly

or Cetuximab 500 mg/m<sup>2</sup> IV over 2 hours, day 1, every 2 weeks

[See References on COL-C 10 of 10](#)

\*Oxaliplatin may be given either over 2 hours, or may be infused over a shorter time at a rate of 1 mg/m<sup>2</sup>/min. Leucovorin infusion should match infusion time of oxaliplatin. Cercek A, Park V, Yaeger R, et al. *Faster FOLFOX: oxaliplatin can be safely infused at a rate of 1 mg/m<sup>2</sup>/min*. *J Oncol Pract* 2016;12:e548-553.

\*\*Leucovorin 400 mg/m<sup>2</sup> is the equivalent of levoleucovorin 200 mg/m<sup>2</sup>.

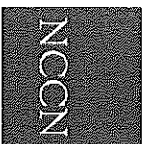
†The majority of safety and efficacy data for this regimen have been developed in Europe, where a capecitabine starting dose of 1000 mg/m<sup>2</sup> twice daily for 14 days, repeated every 21 days, is standard. Evidence suggests that North American patients may experience greater toxicity with capecitabine (as well as with other fluoropyrimidines) than European patients, and may require a lower dose of capecitabine.

¶Bevacizumab may be safely given at a rate of 0.5 mg/kg/min (5 mg/kg over 10 minutes and 7.5 mg/kg over 15 minutes).

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## SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE - CHEMOTHERAPY REGIMENS (PAGE 8 of 10)

### FOLFIRI<sup>9,10</sup>

Irinotecan 180 mg/m<sup>2</sup> IV over 30–90 minutes, day 1

Leucovorin<sup>\*\*</sup> 400 mg/m<sup>2</sup> IV infusion to match duration of irinotecan infusion, day 1

5-FU 400 mg/m<sup>2</sup> IV bolus day 1, then 1200 mg/m<sup>2</sup>/d x 2 days (total 2400 mg/m<sup>2</sup> over 46–48 hours) continuous infusion  
Repeat every 2 weeks

### FOLFIRI + bevacizumab<sup>11,11</sup>

Bevacizumab 5 mg/kg IV, day 1

Repeat every 2 weeks

### FOLFIRI + cetuximab (KRAS/NRAS WT only)

Cetuximab 400 mg/m<sup>2</sup> IV over 2 hours first infusion, then 250 mg/m<sup>2</sup> IV over 60 minutes weekly<sup>12</sup>

or Cetuximab 500 mg/m<sup>2</sup> IV over 2 hours, day 1, every 2 weeks<sup>13</sup>

### FOLFIRI + panitumumab<sup>14</sup> (KRAS/NRAS WT only)

Panitumumab 6 mg/kg IV over 60 minutes, day 1

Repeat every 2 weeks

### FOLFIRI + ziv-aflibercept<sup>15</sup>

Ziv-aflibercept 4 mg/kg IV over 60 minutes, day 1

Repeat every 2 weeks

### FOLFIRI + ramucirumab<sup>16</sup>

Ramucirumab 8 mg/kg over 60 minutes, day 1

Repeat every 2 weeks

### FOLFOXIRI<sup>17</sup>

Irinotecan 165 mg/m<sup>2</sup> IV day 1, oxaliplatin 85 mg/m<sup>2</sup> IV day 1,\*

leucovorin 400<sup>\*\*</sup> mg/m<sup>2</sup> day 1, fluorouracil 1600 mg/m<sup>2</sup>/d x 2 days (total 3200 mg/m<sup>2</sup> over 48 hours) continuous infusion starting on day 1.

Repeat every 2 weeks

The dose of 5-FU listed here was used in European studies. U.S. patients have been shown to have poorer tolerance for 5-FU. A starting dose of 5-FU consistent with the dose recommended in FOLFOX or FOLFIRI should be strongly considered for U.S. patients.

### FOLFOXIRI + bevacizumab<sup>18</sup>

Bevacizumab 5 mg/kg IV, day 1

Repeat every 2 weeks

### IROX<sup>19</sup>

Oxaliplatin 85 mg/m<sup>2</sup> IV\*

followed by irinotecan 200 mg/m<sup>2</sup> over 30–90 minutes every 3 weeks

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\*Oxaliplatin may be given either over 2 hours, or may be infused over a shorter time at a rate of 1 mg/m<sup>2</sup>/min. Leucovorin infusion should match infusion time of oxaliplatin.

Cercek A, Park V, Yaeger R, et al. Faster FOLFOX: oxaliplatin can be safely infused at a rate of 1 mg/m<sup>2</sup>/min. J Oncol Pract 2016;12:e548-553.

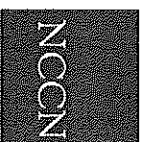
\*\*Leucovorin 400 mg/m<sup>2</sup> is the equivalent of leucovorin 200 mg/m<sup>2</sup>.

††Bevacizumab may be safely given at a rate of 0.5 mg/kg/min (5 mg/kg over 10 minutes and 7.5 mg/kg over 15 minutes).

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## SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE - CHEMOTHERAPY REGIMENS (PAGE 9 of 10)

**Bolus or infusional 5-FU/leucovorin**  
**Roswell Park regimen<sup>20</sup>**  
Leucovorin 500 mg/m<sup>2</sup> IV over 2 hours, days 1, 8, 15, 22, 29, and 36  
5-FU 500 mg/m<sup>2</sup> IV bolus 1 hour after start of leucovorin,  
days 1, 8, 15, 22, 29, and 36  
Repeat every 8 weeks

**Simplified biweekly infusional 5-FU/LV (SLV5FU2)<sup>9</sup>**  
Leucovorin<sup>\*\*</sup> 400 mg/m<sup>2</sup> IV over 2 hours on day 1,  
followed by 5-FU bolus 400 mg/m<sup>2</sup> and then 1200 mg/m<sup>2</sup>/d x 2 days  
(total 2400 mg/m<sup>2</sup> over 46–48 hours) continuous infusion  
Repeat every 2 weeks

**Weekly**  
Leucovorin 20 mg/m<sup>2</sup> IV over 2 hours on day 1, 5-FU 500 mg/m<sup>2</sup> IV  
bolus injection 1 hour after the start of leucovorin. Repeat weekly.<sup>21</sup>  
5-FU 2600 mg/m<sup>2</sup> by 24-hour infusion plus leucovorin 500 mg/m<sup>2</sup>  
Repeat every week<sup>21</sup>

**Capecitabine<sup>8</sup>**  
Capecitabine 850–1250 mg/m<sup>2</sup> PO twice daily, days 1–14  
Repeat every 3 weeks

**Capecitabine + Bevacizumab<sup>22,†</sup>**  
Bevacizumab 7.5 mg/kg IV, day 1  
Repeat every 3 weeks

**Irinotecan**  
Irinotecan 125 mg/m<sup>2</sup> IV over 30–90 minutes, days 1 and 8  
Repeat every 3 weeks<sup>23,24</sup>  
or Irinotecan 180 mg/m<sup>2</sup> IV over 30–90 minutes, day 1

Repeat every 2 weeks  
or Irinotecan 300–350 mg/m<sup>2</sup> IV over 30–90 minutes, day 1  
Repeat every 3 weeks

Irinotecan + cetuximab (KRAS/NRAS WT only)  
Cetuximab 400 mg/m<sup>2</sup> first infusion, then 250 mg/m<sup>2</sup> IV weekly<sup>25</sup>  
or Cetuximab 500 mg/m<sup>2</sup> IV over 2 hours, day 1, every 2 weeks<sup>13</sup>

Cetuximab (KRAS/NRAS WT only)  
Cetuximab 400 mg/m<sup>2</sup> first infusion, then 250 mg/m<sup>2</sup> IV weekly<sup>25</sup>  
or Cetuximab 500 mg/m<sup>2</sup> IV over 2 hours, day 1, every 2 weeks<sup>13</sup>

Panitumumab<sup>26</sup> (KRAS/NRAS WT only)  
Panitumumab 6 mg/kg IV over 60 minutes every 2 weeks

Regorafenib<sup>27</sup>  
Regorafenib 160 mg<sup>§</sup> PO daily days 1–21  
Repeat every 28 days

Trifluridine + tipiracil<sup>28</sup>  
Trifluridine + tipiracil 35 mg/m<sup>2</sup> up to a maximum dose of 80 mg per  
dose (based on the trifluridine component)  
PO twice daily days 1–5 and 8–12  
Repeat every 28 days

Pembrolizumab<sup>29</sup>  
Pembrolizumab 2 mg/kg every 3 weeks

Nivolumab<sup>30</sup>  
Nivolumab 3 mg/kg every 2 weeks  
or Nivolumab 240 mg IV every two weeks

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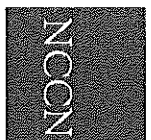
<sup>\*\*</sup>Leucovorin 400 mg/m<sup>2</sup> is the equivalent of levoleucovorin 200 mg/m<sup>2</sup>.

<sup>†</sup>Bevacizumab may be safely given at a rate of 0.5 mg/kg/min (5 mg/kg over 10 minutes and 7.5 mg/kg over 15 minutes).

<sup>§</sup>It is common practice to start at a lower dose of regorafenib (80 or 120 mg) and escalate, as tolerated.

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