Cancer Chemotherapy Update

Drug Monographs: Atezolizumab and Everolimus

Matthew A. Green, BS*; J. Aubrey Waddell, PharmD, FAPhA, BCOP; and
Dominic A. Solimando, Jr, MA, FAPhA, FASHP, BCOP

The complexity of cancer chemotherapy requires pharmacists be familiar with the complicated regimens and highly toxic agents used. This column reviews various issues related to preparation, dispensing, and administration of antineoplastic therapy, and the agents, both commercially available and investigational, used to treat malignant diseases. Questions or suggestions for topics should be addressed to Dominic A. Solimando, Jr., President, Oncology Pharmacy Services, Inc., 4201 Wilson Blvd #110-545, Arlington, VA 22203, email: OncRxSvc@comcast.net; or J. Aubrey Waddell, Professor, University of Tennessee College of Pharmacy; Oncology Pharmacist, Pharmacy Department, Blount Memorial Hospital, 907 E. Lamar Alexander Parkway, Maryville, TN 37804, e-mail: waddfour@charter.net. The authors are not employees of, under contract to, recipients of funding to review products from, or in any other way affiliated with either Genentech, Inc. or Novartis Pharmaceuticals Corporation. The information presented in this review is based on published data and clinical expertise and includes information not included in the product labeling. Incorporation of such published data provides a more robust assessment of the drugs and assists pharmacists in evaluation of orders for off-label use of these agents.

Drug name: Atezolizumab

Synonyms: MPDL3280A, Tecentriq

MECHANISM OF ACTION

Atezolizumab is a monoclonal immunoglobulin G antibody that binds to and inhibits the programmed death ligand 1 (PD-L1).¹ PD-L1 is expressed in a variety of tumors such as non-small cell lung cancer, melanoma, and renal cell carcinoma.² PD-L1 affects the host's immune system by down-regulating T-lymphocytes, allowing many tumor types to bypass the host immune system.²

PHARMACOKINETICS

Human pharmacokinetic data for atezolizumab are very limited. Following multiple doses of 1,200 mg intravenously, atezolizumab reaches a steady state in 6 to 9 weeks. The half-life ($T_{1/2}$) and volume of distribution (V_d) were 27 days and 6.9 L, respectively.³ Atezolizumab showed linear pharmacokinetics at doses less than or equal to 1 mg/kg.⁴ In atezolizumab doses

similar to the approved human dose, the mean serum area under the curve from time 0 to day 7 (AUC_{0-7}) and maximum serum concentration (C_{max}) were 1,940 day·µg/mL and 610 µg/mL, respectively.³ Selected therapeutic regimens of atezolizumab appear in Table 1.

PREPARATION

1. Follow institutional policies for handling hazardous medications when dispensing atezolizumab.
2. Use atezolizumab injection, 60 mg/mL.
3. The product's labeling states that the prescribed dose should be diluted in 250 mL of 0.9% sodium chloride injection.
4. The final diluted solution should be mixed by simply inverting the solution. Do not shake.

STABILITY

1. Solutions diluted for administration are stable at room temperature (20°C to 25°C [68°F to 77°F]) for 6 hours or 24 hours refrigerated (2°C to 8°C [36°F to 46°F]).
2. Do not freeze.

*Matthew A. Green is a doctor of pharmacy candidate at the University of Tennessee College of Pharmacy.

Table 1. Selected therapeutic regimens of atezolizumab

Daily dose	Route of administration	Administered on day(s)	Cycle length	Total dose/cycle	References
1,200 mg ^a	IV	1	21 days	1,200 mg	1, 2, 3, 8
Variations: Powles, et al, recommended 15 mg/kg IV every 3 weeks. ⁷					

Note: IV = intravenous.

^aConforms to dosing information listed in the manufacturer's labeling.

ADMINISTRATION

1. The first dose of atezolizumab is infused over 60 minutes. If the initial dose is tolerated, subsequent doses may be infused over 30 minutes.
2. Do not administer as an intravenous push.

TOXICITIES

Most of the toxicities listed below are presented according to their degree of severity. Higher grades represent more severe toxicities. Although there are several grading systems for cancer chemotherapy toxicities, all are similar. One of the frequently used systems is the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf). Oncologists generally do not adjust doses or change therapy for grade 1 or 2 toxicities but make, or consider, dosage reductions or therapy changes for grade 3 or 4 toxicities. Incidence values are rounded to the nearest whole percent unless incidence was less than or equal to 0.5%.

- A. Cardiovascular:** Cardiac tamponade (all grades) 1%,² (grades 3 or 4) 1%²; dehydration (all grades) 3%,⁶ (grades 3 or 4) 1%⁶; hypertension (all grades) 1% to 4%,¹ (grade 3 or 4) 1% to 2%¹; hypotension (all grades) 2% to 4%,¹ (grade 3 or 4) 1%¹; peripheral edema (all grades) 6%.⁶
- B. Constitutional:** Asthenia (all grades) 5% to 7%,^{2,6-8} (grade 3 or 4) 1% to 2%^{2,7}; chills (all grades) 4% to 11%^{2,6,7}; dry mouth (all grades) 2% to 3%^{6,7}; fatigue (all grades) 12% to 49%,^{1,2,6-8} (grade 3 or 4) 2% to 6%^{1,2,6}; hyperthermia (all grades) 3%⁷; insomnia (all grades) 3%⁶; night sweats (all grades) 3% to 4%^{2,6}; pyrexia (all grades) 9% to 22%,^{1,6,7} (grade 3 or 4) 0.32% to 0.64%¹; rhinitis (all grades) 2%.⁷
- C. Dermatologic:** Acneiform dermatitis (all grades) 4%⁶; dry skin (all grades) 4% to 9%^{2,6}; pruritus (all grades) 3% to 13%,^{1,2,6,7} (grade 3 or 4) 1%¹;

rash (all grades) 2% to 14%,^{1,2} (grade 3 or 4) 0.32%¹; urticaria (all grades) 2%.⁷

- D. Endocrine/Metabolic:** Hyperglycemia (all grades) 1%,² (grades 3 or 4) 1%²; hyperkalemia (all grades) 2%⁷; hypoalbuminemia (all grades) 2%⁷; hyponatremia (all grades) 1%,² (grades 3 or 4) 1%²; hypophosphatemia (all grades) 1% to 3%,^{2,6,7} (grades 3 or 4) 1% to 3%^{2,6,7}; hypothyroidism (all grades) 9%⁶; tumor lysis syndrome (all grades) 1%,² (grades 3 or 4) 1%.²
- E. Gastrointestinal:** Colitis (all grades) 1%,¹ (grade 3 or 4) 1%¹; constipation (all grades) 3% to 5%^{6,8}; decreased appetite (all grades) 12% to 27%,^{1,2,6-8} (grade 3 or 4) 1%¹; diarrhea (all grades) 2% to 20%,^{1,2,6-8} (grade 3 or 4) 0.32% to 1%¹; dysgeusia (all grades) 2%⁷; dyspepsia (all grades) 3%⁶; nausea (all grades) 12% to 26%,^{1,2,6-8} (grade 3 or 4) 0.4% to 2%^{1,2}; stomatitis (all grades) 4%⁶; vomiting (all grades) 3% to 18%,^{1,2,6-8} (grades 3 or 4) 0.32% to 1%.^{1,2}
- F. Hematologic:** Anemia (all grades) 3% to 15%,^{1,2,6-8} (grade 3 or 4) 1% to 9%^{1,2,6}; leukocytosis (all grades) 2%⁷; neutropenia (all grades) 1%⁸; thrombocytopenia (all grades) 3%,⁷ (grade 3 or 4) 2%.⁷
- G. Hepatic:** Increased alanine aminotransferase (all grades) 2%,² (grade 3 or 4) 1%²; increased aspartate aminotransferase (all grades) 1% to 5%,^{1,2} (grade 3 or 4) 1%.^{1,2}
- H. Infection:** Herpes zoster (all grades) 2%⁷; influenza like illness (all grades) 4% to 6%,^{2,7} (grade 3 or 4) 0.4%.²
- I. Musculoskeletal:** Arthralgia (all grades) 3% to 17%,^{1,2,6,7} (grade 3 or 4) 1%¹; ataxia (all grades) 3%⁶; bone pain (all grades) 3%⁷; muscle spasm (all grades) 2%⁷; myalgia (all grades) 2% to 5%.^{2,6,7}
- J. Neurologic:** Abdominal pain (all grades) 2%⁷; headache (all grades) 7% to 8%,^{2,6} (grade 3 or 4) 0.4% to 1%^{2,6}; pain (all grades) 3% to 5%,^{2,6,7} (grade 3 or 4) 0.4%²; pain in extremities (all grades) 2%.⁷

- K. Ocular:** Dry eye (all grades) 2%⁷; ocular hyperemia (all grades) 2%.⁷
- L. Pulmonary:** Cough (all grades) 3%⁶; dyspnea (all grades) 3% to 17%,^{1,2,6} (grades 3 or 4) 1% to 4%^{1,2}; hypoxia (all grades) 1%,² (grades 3 or 4) 1%²; pneumonitis (all grades) 2% to 3%,^{1,6,7} (grade 3 or 4) 1%.¹
- M. Treatment-Related Mortality:** Cardiac failure 1%.⁸

DOSAGE MODIFICATIONS

A. Hepatic

- For mild hepatic impairment (bilirubin $\leq$ upper limit of normal [ULN] and AST $>$ ULN or bilirubin $<$ 1 to 1.5 times ULN and any AST), no dose adjustments are necessary.³
- For moderate to severe hepatic impairment (bilirubin $>$ ULN and AST $>$ ULN or bilirubin $\geq$ 1 to 1.5 times ULN and any AST), the need for dose adjustments is unknown.³

B. Renal

- For mild to moderate renal impairment (estimated glomerular filtration rate 30 to 89 mL/min/1.73 m²), no dose adjustments are necessary.³
- For severe renal impairment (estimated glomerular filtration rate 15 to 29 mL/min/1.73 m²), the need for dose adjustments has not been studied.³

Drug name: Everolimus

Synonyms: RAD001, *Afinitor*

MECHANISM OF ACTION

Everolimus's inhibits the mammalian target of rapamycin (mTOR), a serine-threonine kinase.^{9,10} The mTor pathway plays a role in regulating cell proliferation and angiogenesis. The mTor pathway requires the cellular substrate p70 ribosomal S6 kinase 1 to be phosphorylated for proliferation.¹⁰ Angiogenesis is promoted through the hypoxia-inducible factor-1 and growth factor protein translation.¹⁰

PHARMACOKINETICS

Everolimus has a time to maximum plasma concentration (T_{max}) of 3 and 2 hours following a dose of 5 mg and 10 mg, respectively. Steady-state levels are reached after 8 days of treatment.¹⁰ Everolimus is approximately 74% bound to serum proteins. Moderate hepatic impairment does not affect the degree of protein binding. The C_{max} and minimum serum concentration (C_{min}) for a 5 mg dose are 37.9 ng/mL and 6.1 ng/mL, respectively.¹¹ For a 10 mg dose, the C_{max} was 53.8 ng/mL and the C_{min} was 14.5 ng/mL.¹⁰ The clearance of drug from the blood (CL/F) was 15.8 L/h for the 5 mg dose and 16.99 L/h for the 10 mg dose.¹⁰ Everolimus is metabolized primarily by cytochrome P450 3A4 isozyme.¹² The area under the blood concentration-time curve (AUC_{0-t}) showed a range from 316-335 h•ng/mL and 588.6 h•ng/mL for the 10 mg dose.^{10,11} The volume of distribution (V_d) for everolimus is 1,613 L and half-life ($t_{1/2}$) is 35 hours.¹² Patients that consumed a high fat diet or a light fat diet had AUC reductions of 22% and 32%, respectively, compared to the fasting state. The C_{max} was reduced by 54% and 42% with a high fat and light fat diet, respectively, compared to the fasting state.¹³ Everolimus is excreted primarily in the feces (80%), with 5% being excreted in the urine.¹³ Selected therapeutic regimens of everolimus appear in Table 2.

PREPARATION

- Follow institutional policies for preparation of hazardous medications when dispensing everolimus.
- Everolimus is available as 2.5, 5, 7.5, and 10 mg tablets and 2, 3, and 5 mg tablets for oral suspension. The manufacturer recommends against mixing the tablets and tablets for oral suspension together to achieve the desired dose.
- The product's labeling recommends¹³:
 - Not breaking or crushing tablets or oral suspension tablets.
 - Using water as the only diluent for preparing everolimus suspension.

Table 2. Selected therapeutic regimens of everolimus

Daily dose	Route of administration	Administered on day(s)	Cycle length	Total dose/cycle	References
10 mg ^a	PO	1-28	28 days	280 mg	10, 13-16

Note: PO = oral.

^aConforms to dosing information listed in the manufacturer's labeling.

4. The product's labeling describes 2 procedures for preparing the oral suspension:

a. Small glass:

- (1) Place the oral suspension tablet in a small glass (maximum size 100 mL) and add approximately 25 mL of water.
- (2) Let the tablet sit in the water for 3 minutes.
- (3) Gently stir the mixture and drink it.
- (4) Re-suspend any residue in the glass with another 25 mL of water and drink it.

b. Oral syringe:

- (1) Place the oral suspension tablet(s) in an oral syringe (at least 10 mL).
- (2) Draw 5 mL of water and 4 mL of air into the oral syringe and wait 3 minutes.
- (3) Gently invert the syringe at least 5 times to suspend the drug.
- (4) Draw an additional 5 mL of water into the syringe to re-suspend any residue, and drink it.

STABILITY

1. The tablets should be stored at room temperature (15° to 30°C [59° to 86°F]).
2. Oral suspension should be administered within 60 minutes of preparation.

ADMINISTRATION

1. Everolimus is administered orally once a day.
2. Everolimus may be taken with or without food.

TOXICITIES

Most of the toxicities listed below are presented according to their degree of severity. Higher grades represent more severe toxicities. Although there are several grading systems for cancer chemotherapy toxicities, all are similar. One of the frequently used systems is the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14/QuickReference_8.5x11.pdf). Oncologists generally do not adjust doses or change therapy for grade 1 or 2 toxicities but make, or consider, dosage reductions or therapy changes for grade 3 or 4 toxicities. Incidence values are rounded to the nearest whole percent unless incidence was less than or equal to 0.5%.

- A. Cardiovascular:** Epistaxis (all grades) 10% to 24%,^{9,14,15} (grade 3 or 4) 1%⁹; hypertension (all grades) 7% to 22%,^{11,15} (grade 3 or 4) 3%¹⁵; peripheral edema (all grades) 14% to 29%,^{9,14-16} (grade 3 or 4) 1% to 2%.^{9,14-16}
- B. Constitutional:** Decreased weight (all grades) 10% to 12%^{9,11,15}; dizziness (all grades) 7%¹⁵; dry

mouth (all grades) 6%⁹; fatigue (all grades) 25% to 55%,^{9-11,14-16} (grade 3 or 4) 3% to 8%^{9,10,14-16}; dysphonia (all grades) 4%¹⁵; insomnia (all grades) 10%⁹; pyrexia (all grades) 11% to 26%,^{9,15,16} (grade 3 or 4) 1% to 2%.^{9,15,16}

- C. Dermatologic:** Dry skin (all grades) 7% to 10%^{9,15}; palmar plantar erythrodysesthesia (all grades) 6% to 22%,^{11,15} (grade 3 or 4) 1%¹⁵; pruritus (all grades) 10% to 18%,^{9,11,14-16} (grade 3 or 4) 0.3% to 11%^{9,11,15,16}; rash (all grades) 20% to 33%,^{9,11,15,16} (grade 3 or 4) 1% to 11%.^{9,11,14-16}

- D. Endocrine/Metabolic:** Amylase increase (all grades) 11%¹¹; hyperglycemia (all grades) 6% to 42%,^{9-11,14-16} (grade 3 or 4) 3% to 8%^{9,10,14-16}; hypertriglyceridemia (all grades) 11% to 16%,^{11,14,15} (grade 3 or 4) 3% to 5%^{14,15}; hyperuricemia (all grades) 11%,¹¹ (grade 3 or 4) 11%¹¹; hypocalcemia (all grades) 22%¹¹; hypophosphatemia (all grades) 6% to 33%,^{11,15} (grade 3 or 4) 2% to 11%^{11,15}; hypokalemia (all grades) 6% to 17%,^{9,10,15} (grade 3 or 4) 2% to 5%^{9,15}; hypomagnesemia (all grades) 2% to 11%^{11,15}; hypothyroidism (all grades) 0.3%¹⁵; lipase increased (all grades) 22%,¹¹ (grade 3 or 4) 22%.¹¹

- E. Gastrointestinal:** Anorexia (all grades) 11% to 34%,^{9,11,14-16} (grade 3 or 4) 1% to 6%^{9,14-16}; constipation (all grades) 9% to 19%,^{9,15} (grade 3 or 4) 0.3% to 1%^{9,15}; diarrhea (all grades) 11% to 31%,^{9,11,14-16} (grade 3 or 4) 1% to 11%^{9,11,14-16}; dysgeusia (all grades) 9% to 15%,^{9,14-16} (grade 3 or 4) 0.3% to 1%^{9,16}; dyspepsia (all grades) 5%¹⁵; nausea (all grades) 17% to 44%,^{9,11,14-16} (grade 3 or 4) 1% to 2%^{9,14-16}; mucosal inflammation (all grades) 23%,¹⁵ (grade 3 or 4) 3%¹⁵; stomatitis (all grades) 19% to 63%,^{9,11,14-16} (grade 3 or 4) 2% to 9%^{9,11,14-16}; vomiting (all grades) 14% to 33%,^{9,15} (grade 3 or 4) 1% to 3%.^{9,15}

- F. Hematologic:** Anemia (all grades) 16% to 38%,^{9,11,14-16} (grade 3 or 4) 4% to 16%^{9,14-16}; leukopenia (all grades) 11%¹¹; neutropenia (all grades) 22%,¹¹ (grade 3 or 4) 11%¹¹; thrombocytopenia (all grades) 6% to 55%,⁹⁻¹¹ (grade 3 or 4) 3% to 11%.^{9,11}

- G. Hepatic:** Alanine aminotransferase increase (all grades) 6% to 44%,^{11,15} (grade 3 or 4) 1% to 11%^{11,15}; alkaline phosphatase increase (all grades) 11% to 25%,^{10,11} (grade 3 or 4) 8%¹⁰; ascites (all grades) 16%,⁹ (grade 3 or 4) 6%⁹; aspartate aminotransferase increase (all grades) 6% to 44%,^{9,11,15} (grade 3 or 4) 1% to 4%.^{9,15}

- H. Infection:** Hepatitis B (all grades) 7%,⁹ (grade 3 or 4) 6%⁹; pneumonia (all grades) 8% to 15%,^{9,14} (grade 3 or 4) 2% to 4%.^{9,14}

- I. Musculoskeletal:** Arthralgia (all grades) 14%,¹⁵ (grades 3 or 4) 1%¹⁵; asthenia (all grades) 16% to 18%,^{9,15,16} (grade 3 or 4) 2% to 8%^{9,15,16}; back pain (all grades) 7% to 15%,^{9,15} (grade 3 or 4) 0.3% to 2%^{9,15}; bone pain (all grades) 11%¹¹; muscle spasm (all grades) 5%¹⁵; pain in extremities (all grades) 8%,¹⁵ (grade 3 or 4) 0.3%.¹⁵
- J. Neurologic:** Abdominal (all grades) 10% to 17%,^{9,11,15} pain (grade 3 or 4) 1% to 3%^{9,15}; headache (all grades) 7% to 12%,^{9,11,15} (grade 3 or 4) 0.3% to 1%.^{9,15}
- K. Pulmonary:** Cough (all grades) 13% to 33%,^{9,14-16} (grade 3 or 4) 1% to 3%^{9,15}; dyspnea (all grades) 10% to 28%,^{9,14-16} (grade 3 or 4) 1% to 4%.^{9,14-16}
- L. Renal:** Creatinine increase (all grades) 11%^{11,15}; proteinuria (all grades) 9%,¹⁵ (grade 3 or 4) 0.3%.¹⁵
- M. Treatment-Related Mortality:** Aspergillus infection 0.3%,¹⁵ aspiration pneumonia 0.3%,¹⁵ cardiac failure 0.4%,¹⁶ respiratory failure 0.4%,¹⁶ septic shock 0.4%.¹⁶

DOSAGE MODIFICATIONS

A. Hepatic

- For Child-Pugh class A hepatic impairment, the dose should be reduced from 10 mg to 7.5 mg. If this dose is not well tolerated, reduce the dose to 5 mg.¹²
- For Child-Pugh class B hepatic impairment, the dose should be reduced from 10 mg to 5 mg. If this dose is not well tolerated, reduce the dose to 2.5 mg.¹²
- For Child-Pugh class C hepatic impairment, everolimus should not be given unless the risk benefit ratio favors the administration of everolimus. If the decision to receive everolimus is made, the dose should not exceed 2.5 mg.¹²
- The manufacturer recommends reducing the dose by 50% in patients with Child-Pugh class C hepatic impairment. If the patient has Child-Pugh class A or B hepatic impairment, adjustments may not be necessary.¹³

B. Renal

- No adjustments are required.¹³

REFERENCES

- Rosenberg J, Censits J, Powles T, et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: A single arm, multicenter, phase 2 trial. *Lancet Oncol*. 2016;387(10031):1909-1920.
- Herbst R, Soria JC, Kowanetz M, et al. Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. *Nature*. 2014;515(7528):563-567.
- Tecentriq [package insert]. San Francisco, CA: Genentech, Inc.; 2016.
- Herbst RS, Gordon MS, Fine GD, et al. A study of MPDL3280A, an engineered PD-L1 antibody in patients with locally advanced or metastatic tumors. *J Clin Oncol*. 2013;31(suppl): abstract 3000.
- Deng R, Bumbaca D, Pastuskovas C, et al. Preclinical pharmacokinetics, pharmacodynamics, tissue distribution, and tumor penetration of anti-PD-L1 monoclonal antibody, an immune checkpoint inhibitor. *MABS*. 2016;8(3):593-603.
- McDermott D, Sosman J, Sznol M, et al. Atezolizumab, an anti-programmed death-ligand 1 antibody, in metastatic renal cell carcinoma: Long-term safety, clinical activity, and immune correlates from a phase 1a study. *J Clin Oncol*. 2016;34(8):833-841.
- Powles T, Eder JP, Fine GD, et al. MPDL3280A (anti-PD-L1) treatment leads to clinical activity in metastatic bladder cancer. *Nature*. 2014;515(7528):558-562.
- Fehrenbacher L, Spira A, Ballinger M, et al. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): A multicenter open label, phase 2 randomised controlled trial. *Lancet*. 2016;387:1837-1846.
- Zhu A, Kudo M, Assenat E, et al. Effect of everolimus on survival in advanced hepatocellular carcinoma after failure of sorafenib the EVOLVE-1 randomized clinical trial. *JAMA*. 2014;312(1):57-67.
- Xu B, Wu Y, Shen L, et al. Two-dose-level confirmatory study of the pharmacokinetics and tolerability of everolimus in Chinese patients with advanced solid tumors. *J Hematol Oncol*. 2011;4(3):1-7.
- Wagle N, Grabiner B, Van Allen E, et al. Activating mTOR mutations in a patient with an extraordinary response on a phase 1 trial of everolimus and pazopanib. *Cancer Discov*. 2014;4(5):546-553.
- Peveling-Oberhag J, Zeuzem S, Yong W, et al. Effect of hepatic impairment on the pharmacokinetics of everolimus: A single-dose, open-label, parallel-group study. *Clin Ther*. 2013;35(3):215-225.
- Afinitor [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corp.; 2016.
- Motzer RJ, Escudier B, McDermott D, et al. Nivolumab versus everolimus in advanced renal-cell carcinoma. *N Engl J Med*. 2016;373(19):1803-1813.
- Choueiri TK, Escudier B, Powles T, et al. Cabozantinib versus everolimus in advanced renal-cell carcinoma. *N Engl J Med*. 2015;373(19):1814-1823.
- Yoa J, Fazio N, Singh S, et al. Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): A randomised, placebo-controlled, phase 3 study. *Lancet*. 2016;387(10022):968-977. ■