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Antiepileptic Drugs in the Management of Cerebral Metastases

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INTRODUCTION

Approximately 10% to 40% of adult patients with cancer develop brain metastases.¹⁻³ Although seizures are less common among those with metastatic lesions compared with primary brain tumors, the incidence remains as high as 15% to 25%.⁴⁻⁶ Seizures can be effectively treated or prevented with any number of antiepileptic drugs (AEDs), but these agents have associated risks and side effects. The decision to treat a patient with AEDs must be made carefully, balancing the risks of seizure with potential adverse effects of therapy.

The ill effects of seizures for patients with metastatic brain tumors are numerous. Epilepsy is considered to be the most important risk factor for long-term disability in patients with brain tumors.⁷ Postoperative seizures in particular are associated with considerable morbidity, longer length of hospital stay, and higher rates of readmission.⁸⁻¹² Concerns about seizure-associated morbidity often prompt physicians to seek to aggressively treat or prevent epilepsy.

However, AEDs are associated with adverse effects that can result in substantial disability, morbidity, and mortality. The incidence and severity of adverse effects of anticonvulsants may be 20% to 40% worse in patients with brain tumors compared with the general population.¹³ More broadly, AEDs may profoundly affect a patient's quality of life, and are associated with perceived increase in cognitive deficits, social dysfunction, and adverse events such as fatigue, nausea, and weight changes.⁷ A careful analysis of the risks and benefits must therefore be heavily weighed before initiating treatment, particularly prophylactically.

Although several systematic reviews and metaanalyses on the issue have suggested no benefit to prophylactic therapy,¹⁴⁻¹⁷ a recent survey study found that greater than 63% of

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DISCLOSURE

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surgeons administer seizure prophylaxis after brain tumor resection in patients without history of antecedent seizure.¹⁸ Given the significant discrepancy between evidence and practice as well as the lack of consensus on treatment decisions, this article provides a concise summary of current evidence and clinical recommendations regarding the use of AEDs among patients with brain metastases.

INDICATIONS FOR TREATMENT

Antiepileptic therapy may be administered in the preoperative, intraoperative, and postoperative periods, with the goal of either primary or secondary prevention. Primary prevention is synonymous with traditional prophylaxis. Secondary prevention refers to AED therapy designed to mitigate the risk of additional seizures in patients who have already experienced one. This article considers the indications for treatment within each phase of care and for both types of prevention. Summaries of guidelines and studies on the issue of AED prophylaxis are provided in Tables 1 and 2, respectively.

Primary Prevention

Preoperative prophylaxis—The American Academy of Neurology (AAN) published guidelines on AED prophylaxis in patients with newly diagnosed brain tumors in 2000; these guidelines recommend against AED prophylaxis in patients who have not had a seizure.¹³ Similarly, a systematic review and clinical practice guideline published by the Congress of Neurological Surgeons (CNS) in 2010 did not recommend prophylactic anticonvulsant use for patients with CNS metastases who had not had a seizure (level 3 American Association of Neurological Surgeons/CNS recommendation, see Table 1).¹⁵

In 2019, the CNS published updated guidelines in prophylactic AED therapy for patients with brain metastases.¹⁹ These guidelines also suggested against AED prophylaxis in the absence of a seizure history, a recommendation that has subsequently been endorsed by both the American Society of Clinical Oncology (ASCO) and the Society for Neuro-Oncology (SNO).²⁰

Many of the studies included in these evidence-based reviews compared patients not receiving any prophylactic AED therapy with those who received prophylaxis preoperatively, postoperatively, or both.²¹⁻²³ No studies directly addressed the independent effect of preoperative prophylaxis on rates of postoperative seizures.

Intraoperative prophylaxis—Intraoperative AED use has not been specifically assessed in the literature, although many studies of postoperative prophylaxis included an intraoperative dose as part of the treatment regimen (see Table 2). Intraoperative treatment is of particular concern for patients undergoing awake craniotomy (primarily for resection of gliomas) but, even in this setting, practice is varied.^{24,25} One retrospective review found no association between type of AED and timing of administration for intraoperative seizure and rates of failed awake craniotomy.²⁵

Postoperative prophylaxis—Postoperative seizure prophylaxis has been extensively studied but remains a contentious issue. Postcraniotomy seizure rates for patients with no

prior history of seizure range between 7% and 18% in the literature.^{8,26} The 2000 AAN guidelines suggest that postoperative prophylaxis be left to the surgeon's discretion.¹³ Many surgeons are in favor of the use of prophylactic AEDs for patients undergoing any supratentorial craniotomy (irrespective of indication) to prevent early postoperative seizures. Although the evidence for this practice is weak and the baseline risk of seizure is low, high value is placed on avoiding early postoperative seizures because of their potentially severe neurologic consequences.⁸⁻¹⁰

In contrast, the CNS currently offers a level 3 recommendation against the use of postoperative seizure prophylaxis among patients with no prior history of seizure.¹⁹ This guideline is based on 3 studies published in 1990, 2013, and 2014.

The 1990 study published by Franceschetti and colleagues²⁷ prospectively randomized 63 patients to receive AED treatment (phenytoin or second-line phenobarbital) or routine care after undergoing operation for supratentorial tumor resection. Thirteen patients (10.2%) across groups had cerebral metastases. Seven percent of the AED cohort experienced early postoperative seizures (within 1 week of surgery) compared with 18% of the non-AED cohort ($P = .64$). Late seizures (>1 week after surgery) occurred in 12% of the AED cohort compared with 21% of the non-AED cohort ($P = .64$).

The 2013 study by Wu and colleagues²⁸ prospectively randomized 123 patients with brain tumors to either phenytoin or no AED for 7 days postoperatively. Thirty-nine patients in the AED group (62.9%) and 38 patients in the control group (62.3%) had cerebral metastases. Across disorders, 24% of the phenytoin cohort had seizures within 30 days of surgery compared with 18% of the non-AED cohort ($P = .51$).

The 2014 study by Ansari and colleagues²⁹ retrospectively reviewed AED usage and seizure frequency among 202 patients with no antecedent seizure who underwent brain tumor resection. Fifty-three patients in the AED group (39.6%) and 33 patients in the control group (48.5%) had cerebral metastases. Overall, the study found no difference in postoperative seizure risk (up to 321 days after surgery) between those who received AED prophylaxis and those who did not. The fact that brain metastases were not the sole disorder evaluated in any of the included studies is an important limitation given the heterogeneity in seizure risk and AED responsiveness among different histologies.

In the interval since the literature search was conducted for the 2019 CNS guidelines, Kamenova and colleagues³⁰ compared prophylactic postoperative AED treatment against no treatment among matched cohorts of patients undergoing brain tumor resection at 2 institutions. Fourteen patients in the AED group (12.8%) and 41 patients in the control group (19.3%) had metastases. Importantly, this study used levetiracetam, a newer agent with fewer side effects that is favored among neurosurgeons.¹⁸ The investigators found no statistically significant difference in the occurrence of postoperative seizures between the two groups, further supporting recommendations against the use of prophylactic postoperative AEDs ($n = 10$ in the levetiracetam group, $n = 21$ in the control group; $P = .69$).

Nonsurgical patients—The 2019 CNS guidelines posed the question of whether AED prophylaxis decreases the risk of seizures in nonsurgical patients with brain metastases. Based on a thorough literature review, the CNS proposed a level 3 recommendation against the use of prophylactic AEDs in this patient population.¹⁹ Two independent RCTs, by Forsyth and colleagues²³ (2003) and Glantz and colleagues²² (1996), were used to formulate this recommendation. The study by Forsyth and colleagues²³ randomized 100 patients (60 of whom had cerebral metastases) to receive either 3 months of AED (phenytoin or phenobarbital) or no AED. The incidence of seizure did not differ significantly in total or in subgroup analysis of patients with metastasis. Glantz and colleagues²² randomized 74 patients to receive valproic acid or placebo (59 of whom had cerebral metastases). The study found no statistically significant difference in seizure incidence within 12 months.

Radiosurgery patients—Stereotactic radiosurgery (SRS) is increasingly used in the management of brain metastases. Compared with whole-brain radiation therapy (WBRT), SRS carries a lower risk of seizure, ranging from 5% to 13%.³¹⁻³⁵ No clear guidelines for AED administration in this population currently exist, leading to heterogeneity in provider practice. Many clinicians take a conservative approach; a recent survey of 500 radiation oncologists found that 79% of respondents stated that they rarely or never prescribe anticonvulsants, and less than 10% usually or always recommend AED usage. Among those who prescribed AEDs during or after SRS, the recommended duration of therapy was less than 1 week, 1 to 2 weeks, and greater than 2 weeks among 35%, 25%, and 41% of respondents, respectively.³⁶ Some providers may recommend AEDs to select patients based on perceived seizure risk; for instance, there is a suspected higher seizure risk in patients with lesions in eloquent cortex.^{31,33,37} Nevertheless, there is no evidence at this time to support the use of prophylactic AEDs before SRS.

Secondary Prevention

There is professional consensus that any patient with a brain tumor who presents with a first seizure should be started on an AED given the high likelihood that seizures will recur in those with structural disorders of the brain.^{31,38} When these patients go on to receive surgical treatment, they are at a greater risk of postoperative seizure than those who have never seized.³⁹ For this reason, preoperative AED therapy should be continued into the postoperative period, as well.²⁷

CHOICE OF THERAPY

Selection of Agent

Once an indication for AED treatment is established, determining a safe and effective medication regimen for patients requires knowledge of potential adverse effects and drug-drug interactions of each agent. Drug interactions are of particular importance within the brain metastasis population given that many of these patients are receiving concurrent, potent systemic chemotherapeutic agents.

Older agents such as carbamazepine, phenytoin, phenobarbital, and valproic acid are the most well-studied AEDs among patients with brain tumors. However, current physician

practice seems to be incongruent with the agents assessed in the brain tumor literature. Among the estimated 63% of surgeons who administer seizure prophylaxis after tumor resection in patients without history of antecedent seizure, 85% use the drug levetiracetam.¹⁸ This preference has been attributed to the efficacy of levetiracetam for treating both partial and generalized epilepsy, its comparatively favorable side effect profile, and the fact that routine monitoring of serum concentration is not necessary.⁴⁰

Preference for levetiracetam is likely also driven by physician desire to avoid enzyme-inducing AEDs that may interfere with chemotherapeutic treatment.⁴¹ Table 3 lists major interactions between common AEDs and US Food and Drug Administration (FDA)–approved chemotherapeutic agents for lung, breast, colon, renal, and head and neck cancer. Strong inducers of the cytochrome P450 3A4 enzyme (eg, carbamazepine, phenobarbital, and phenytoin) have many interactions and decrease the serum concentration of several chemotherapeutic agents.^{42,43} Furthermore, phenytoin, carbamazepine, and phenobarbital significantly decrease the serum concentration of dexamethasone, which is given almost ubiquitously to patients with brain tumor in order to reduce symptomatic cerebral edema.^{44–46}

Nonhepatically cleared drugs such as lamotrigine, levetiracetam, topiramate, and gabapentin have far fewer drug-drug interactions, but not all of these agents have been assessed for prevention of seizures specifically in patients with brain tumors.¹⁶ Only recently have reviews and metaanalyses evaluated the efficacy of levetiracetam, suggesting that this agent may be superior to older agents such as phenytoin and valproic acid.^{47–49} Lacosamide is a newer agent that was shown to be effective in treating brain tumor–related epilepsy (BTRE) in 2 multicenter, observational, retrospective studies, and has few adverse effects.^{50–53}

Because of the limited and heterogeneous evidence for particular AED agents in this population, selection of an agent is primarily guided by physicians' experiences and judgment.³⁸ The benefits of newer agents (primarily levetiracetam) in terms of safety, compatibility with other treatments, and lack of need for blood level monitoring support its use for seizures caused by brain tumors.^{54,55} At the current time, there is reasonable evidence to support levetiracetam's use as a first-line agent, particularly as postcraniotomy prophylaxis among patients without prior history of seizure.

Number of Agents

Regardless of agent used, monotherapy is preferable because of improved compliance, diminished toxicity or risk of drug interactions, and decreased costs. Further, patients with BTRE who receive AED monotherapy have significantly better view of their health and perceive less adverse effects relative to those on polytherapy.⁷ Fortunately, more than 50% of adults with tumor-related epilepsy respond to monotherapy.⁵⁶ If seizures are poorly controlled on 1 agent, serum levels should be verified to be therapeutic and then the drug dose may be increased as tolerated. Failing this, a trial of an alternative monotherapy or adjuvant therapy with another agent can then be pursued.

Adverse Effects of Antiepileptic Drugs

A 2008 Cochrane Review found that, compared with placebo or observational controls, phenytoin, phenobarbital, and divalproex sodium had higher rates of adverse events (relative risk, 6.10; 95% confidence interval, 1.10–34.63) and did not decrease the rate of seizures among patients with brain tumors.¹⁷ The adverse effect profiles of specific AEDs are continuously refined, and the literature is advancing rapidly in understanding individual factors that may predispose patients to experience them.⁵⁷ Although a thorough description of each agent's potential adverse effects is outside the scope of this article, common reactions across agents include somnolence, rash, weight change, cognitive dysfunction, and teratogenicity.

As previously stated, adverse drug events and interactions with chemotherapeutic agents are less common with newer AEDs such as levetiracetam, making them preferable for the treatment of BTRE.^{54,58,59} A systematic review of 21 studies suggested that the most common adverse effect associated with levetiracetam was somnolence, and this was typically mild.⁵⁵ However, prospective studies of patients treated with levetiracetam show a 7-fold increased risk for the development of neuropsychiatric adverse events such as agitation, depression, anxiety, emotional lability, and psychotic symptoms, regardless of tumor site.⁵⁴ Patients with frontal lobe tumors who were treated with levetiracetam are more severely affected, suggesting a synergistic effect between tumor location and agent.^{54,60} Accurate monitoring of neuropsychiatric side effects is paramount, because decreased compliance because of these side effects may lead to worse seizure control.^{54,57,61}

DURATION OF THERAPY

Duration of therapy is inconsistently documented in studies of AED use in patients with brain tumors, with many describing protracted treatment courses lasting through many months of follow-up (see Table 2). Although there is no standard duration among these studies, there is no evidence to suggest that prophylactic AEDs should be continued on a long-term basis.

The few studies showing a benefit to postoperative prophylaxis have primarily reported efficacy and safety up to only 1 week after surgery, suggesting that long-term therapy offers no benefit.⁴⁰ Furthermore, increased duration of therapy, regardless of the AED used, is associated with patient perception of worsened cognition and social functioning, worse side effects, and greater distress.⁷

The AAN guidelines suggest that tapering and discontinuing anticonvulsants after the first postoperative week is appropriate, particularly in patients who are stable and are experiencing AED-related adverse effects.¹³ A 1996 AAN practice parameter on discontinuing AED therapy in the general epilepsy population suggested that adults with a seizure-free interval of 2 to 5 years, a single seizure type, normal neurologic examination/intelligence quotient, and a normal electroencephalogram have at least a 61% chance of seizure freedom with AED discontinuation.⁶² Because there are no rigorous studies on discontinuing AED treatment among patients with brain tumors, these criteria as well as the

likelihood of tumor recurrence and prognosis for long-term survival should be considered.
38,63,64

NEUROLOGY CONSULTATION

There is no practice guideline suggesting whether or when a neurologist should be consulted to manage or comanage AED therapy. In light of the growing number of novel AED agents, consideration for neurology referral is appropriate when a patient has contraindications to or side effects from AEDs traditionally prescribed by neurosurgeons. Multidrug treatment regimens may also be best monitored by neurologists, particularly when blood level monitoring, titration schedules, or nonstandard tapering of therapy are necessary.

LIMITATIONS AND FUTURE AREAS OF INVESTIGATION

Existing research on antiepileptic therapy for brain metastases is plagued by several methodological issues. Studies have included heterogeneous agents, various regimen schedules, small sample sizes, and inconsistent inclusion criteria, all predisposing to substantial bias.⁵⁵ The problem is confounded by low outcome event frequency, leading to underpowered results and early study termination.^{23,28} In addition, there is a paucity of studies evaluating newer AEDs despite their popularity among practicing neurosurgeons.

CONCLUDING REMARKS

Seizures represent a common and debilitating complication of CNS metastases. The use of prophylactic AEDs in the preoperative period remains controversial, but the preponderance of evidence suggests that it is not helpful in preventing seizure and instead poses a substantial risk of adverse events. Studies of postoperative seizure prophylaxis have not shown substantial benefit, but this practice remains widespread. Careful analysis of the risk of seizure based on patient-specific factors, such as tumor location and primary tumor histology, should guide the physician's decision on the initiation and cessation of prophylactic AED therapy.

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KEY POINTS

- Between 15% and 25% of patients with brain metastases experience a seizure at some point in the disease course.
- Patients who have not had a seizure or seizurelike episode should not be routinely placed on seizure prophylaxis preoperatively.
- Nonoperative patients do not require seizure prophylaxis in the absence of prior seizure history.
- Existing literature does not support the routine use of postoperative seizure prophylaxis, although the practice is common among neurosurgeons.
- Timing of antiepileptic drug cessation should be guided by patient-specific factors, including risk of recurrence, life expectancy, and adverse reactions to antiepileptic agents.

Table 1

Synopsis of published guidelines and practice parameters

Organization	Year	Recommendations
AAN ¹³	2000	• "In patients with newly diagnosed brain tumors, anticonvulsant medications are not effective in preventing first seizures. Because of their lack of efficacy and their potential side effects, prophylactic anticonvulsants should not be used routinely in patients with newly diagnosed brain tumors." Screening
		• "In patients with brain tumors who have not had a seizure, tapering and discontinuing anticonvulsants after the first postoperative week is appropriate, particularly in those patients who are medically stable and who are experiencing anticonvulsant-related side effects."
CNS ¹⁵	2010	• "For adults with brain metastases who have not experienced a seizure due to their metastatic brain disease, routine prophylactic use of anticonvulsants is not recommended"
CNS ¹⁹	2019	• "Prophylactic AEDs are not recommended for patients with brain metastases who did not undergo surgical resection and are otherwise seizure-free."
		• "Routine postcraniotomy AED use for seizure-free patients with brain metastases is not recommended"

Abbreviations: AAN, American Academy of Neurology; CNS: Congress of Neurological Surgeons.

Details of study design for retrospective reviews and randomized-controlled trials evaluating the use of prophylactic antiepileptic drugs among patients with central nervous system metastases

Reference	Study Design	Total (N)	Patients with Cerebral Metastases (N)	Time Frame of AED Administration	AED Used	Duration of Therapy	Adverse Effects Reported	Key Findings
North et al, ⁶⁵ 1983	RCT	140 AED; 141 control	6 AED; 7 control	Treatment started in the recovery room	Phenytoin	12 mo	12 patients in AED group withdrawn because of adverse drug reaction, unspecified	Significant reduction in frequency of epilepsy was observed in the AED group up to the 10th postoperative week
Lee et al, ⁶⁶ 1989	RCT	189 AED; 185 control	3 AED; 2 control	Intraoperative	Phenytoin	3 postoperative days	None reported	Results suggest incidence of early postoperative seizure may be lower in AED group (not statistically significant)
Franceschetti et al, ²⁷ 1990	RCT	106 AED total, 63 without antecedent seizure; 22 control	13 (no. in each cohort unclear)	Unclear	Phenobarbital or phenytoin	Duration not specified, but serum concentrations tested every 6 mo (minimum follow-up of 6 mo)	None reported/unable to access full text of article	Results suggest some effectiveness of short-term preventive AED administration to prevent early postoperative seizure among patients without seizure history (not statistically significant)
Glanz et al, ²² 1996	RCT	74	31 AED; 28 control	Randomization 15 d after diagnosis; unclear when in perioperative period AED was started	Valproic acid	Minimum follow-up of 7 mo	2 patients in AED group and 1 in control group developed rashes	AED prophylaxis with valproic acid is not effective at preventing first seizure
Forsyth et al, ²³ 2003	RCT	100	26 AED; 34 control	Randomization 1 mo after diagnosis; unclear when in perioperative period AED was started	Phenytoin; phenobarbital if patient could not tolerate phenytoin	Throughout study; mean follow-up of 5.44 mo	Nausea (9%), rash (7%), sore gums (2%), myelosuppression (2%), increased LDH level (2%)	Incidence of seizure and seizure-free survival did not differ significantly (in total and when only analyzing patients with metastatic brain tumor), although study was underpowered
Wu et al, ²⁸ 2013	RCT	62 AED; 61 control	39 AED; 38 control	Intraoperative	Phenytoin	Tapered on POD 8	12 events in 7 patients among metastasis group; 8 events in 4 patients in the glioma group. Rash (4 events), thrombocytopenia (2), decrease LOC (1), confusion (2), increased LFTs (4), nausea (1), vomiting (1), dry skin (1),	No statistically significant difference in early or late seizure frequency between AED and control groups, although study was stopped early. Extremely low seizure rate in control arm casts doubt about usefulness of perioperative AED prophylaxis

Reference	Study Design	Total (N)	Patients with Cerebral Metastases (N)	Time Frame of AED Administration	AED Used	Duration of Therapy	Adverse Effects Reported	Key Findings
Ansari et al. ²⁹ 2014	Retrospective review	134 AED; 68 control	53 AED; 33 control	Postoperative	Phenytoin, levetiracetam, carbamazepine, phenobarbital, topiramate, and valproate	Unspecified	Not reported	The odds of seizure were 1.62 times higher in the AED group than in the control group. This finding was not statistically significant
Lockney et al. ²¹ 2017	Retrospective review	162 AED; 234 control (no. of patients without antecedent seizure)	51 AED; 54 control	Treatment initiated preoperatively or postoperatively	Levetiracetam, phenytoin, carbamazepine, lacosamide, lamotrigine, clonazepam, lorazepam, topiramate, or diazepam	Variable; many continued through duration of follow-up	Reported adverse events included supratherapeutic AED levels, nystagmus, gait difficulty, somnolence, irritability, insomnia, nausea/vomiting, and visual disturbance	Prophylactic AEDs did not significantly reduce number of postoperative seizures
Kamenova et al. ³⁰ 2019	Two-center retrospective matched cohort study	109 AED; 207 control	14 AED; 41 control	Intraoperative	Levetiracetam	At discretion of treating surgeon; usually 14–30 d postoperatively	None reported	No significant difference in postoperative seizure rate between AED and control groups

Abbreviations: LDH, lactate dehydrogenase; LFTs, liver function tests; LOC, level of consciousness; POD, postoperative day.

Common antiepileptic drugs and their major interactions with Food and Drug Administration–approved chemotherapeutic drugs for lung, breast, colon, melanoma, renal cell, head and neck, and skin (melanoma) cancer

Table 3

Antiepileptic Agent	Chemotherapeutic Agents with Major Interaction		
Carbamazepine	Abemaciclib	Entrectinib	Osimertinib mesylate
	Afatinib dimaleate	Erlotinib	Paclitaxel
	Alpelisib	Etoposide	Formulation
	Axitinib	Everolimus	Palbociclib
	Brigatinib	Exemestane	Regorafenib
	Cabozantinib-S-maleate	Gefitinib	Ribociclib
	Ceritinib	Irinotecan	Sorafenib tosylate
	Cobimetinib	Ixabepilone	Tamoxifen
	Crizotinib	Lapatinib	Temsirolimus
	Dabrafenib mesylate	Lorlatinib	Toremifene
	Docetaxel	Neratinib maleate	Vemurafenib
	Doxorubicin	Olaparib	
Clonazepam	Dabrafenib mesylate	—	—
Felbamate	Dabrafenib mesylate	—	—
Gabapentin	—	—	—
Lamotrigine	—	—	—
Levetiracetam	—	—	—
Oxcarbazepine	—	—	—
Phenobarbital	Afatinib dimaleate	Osimertinib mesylate	Ribociclib
	Brigatinib	Paclitaxel	Tamoxifen
	Ceritinib	Formulation	Toremifene
	Crizotinib	Abemaciclib	Vinblastine
	Dabrafenib mesylate	Alpelisib	Axitinib
	Docetaxel	Exemestane	Cabozantinib-S-maleate
	Doxorubicin	Irinotecan	Pazopanib
	Entrectinib	Ixabepilone	Sorafenib Tosylate
	Erlotinib	Lapatinib ditosylate	Sunitinib maleate

Antiepileptic Agent	Chemotherapeutic Agents with Major Interaction			
Phenytoin	Etoposide	Neratinib maleate	Temsirolimus	
	Everolimus	Olaparib	Cobimetinib	
	Gefitinib	Palbociclib	Vemurafenib	
	Lorlatinib	Regorafenib		
Phenytoin	5-Fluorouracil	Docetaxel	Osimertinib mesylate	
	Abemaciclib	Doxorubicin	Paclitaxel	
	Afinib dimaleate	Entrectinib	Palbociclib	
	Alpelisib	Erlotinib	Pazopanib	
	Axitinib	Etoposide	Regorafenib	
	Brigatinib	Everolimus	Ribociclib	
	Cabozantinib-S-maleate	Exemestane	Sorafenib tosylate	
	Capecitabine	Gefitinib	Sunitinib maleate	
	Ceritinib	Irinotecan	Tamoxifen	
	Cobimetinib	Ixabepilone	Temsirolimus	
	Crizotinib	Lapatinib ditosylate	Topotecan	
	Dabrafenib mesylate	Lorlatinib	Toremifene	
	Dabrafenib mesylate	Neratinib maleate	Vemurafenib	
	Dexamethasone	Olaparib	Vinblastine	
Tiagabine	Dabrafenib mesylate	—	—	
Valproic acid	—	—	—	
Zonisamide	Dabrafenib mesylate	—	—	