Exp Oncol 2021
43, 1, 1–5

POINT OF VIEW

Experimental ONCOLOGY

EXPERIENCE AND PROSPECTS FOR THE USE OF OFF-LABEL DRUGS IN ONCOLOGY

S.M. Drogovoz[1], V.I. Starikov[2], L.B. Ivantsyk[1], K.G. Shchokina[1,]*
[1]*National University of Pharmacy, Kharkiv 61002, Ukraine*
[2]*Kharkiv National Medical University, Kharkiv 61022, Ukraine*

According to the World Health Organization, half of all drugs available on the global pharmaceutical market are sometimes used for indications that are not included in the instruction for use. This method of therapy has the term "off-label use" which means the use "out of instruction". Today, off-label drugs are also prescribed for cancer treatment. For example, a drug developed to treat one type of tumor can sometimes be used to treat other types of cancer. The treatment of certain types of pain with tricyclic antidepressants is also an example of the off-label drugs used in oncology. An example of an off-label prescription is anxiolytic medicine lorazepam, which can be used off-label as an antiemetic in cancer patients. Low doses of naltrexone are applied to treat cancer and autoimmune diseases. A retrospective analysis of modern oncotherapy indicates that oncologists often use off-label drugs in combination therapy, especially in the treatment of patients with concomitant diseases, in case of progressive development of the tumor, or to reduce the toxicity and cost of treatment components. American oncologists are of the opinion that if all the drugs prescribed by the International Recommendations failed in the treatment of cancer, doctors can prescribe off-label medications, but only if their effectiveness and safety are clearly established. The problem of the off-label use of drugs in oncology has not yet been studied in detail, however, this direction has certain promising prospects.
Key Words: **antitumor drugs, off-label use.**

DOI: 10.32471/exp-oncology.2312-8852.vol-43-no-1.15583

In modern medical practice, drugs are prescribed in accordance with the instructions, and their use is controlled by regulatory authorities (for example, the Food and Drug Administration (FDA) in the USA, the Ministry of Health in Ukraine, etc.).

According to the WHO, half of all drugs available on the global pharmaceutical market are sometimes used for indications that are not included into instructions [1]. In 1997, the FDA defined this method of therapy with the term "off-label use" — use "out of instructions", namely, according to indications, at a dose or regimen, in a population of patients not approved by drug instructions. Therefore, such use of drugs is not officially confirmed by the results of clinical trials [2]. However, in any case, the term "off-label use" does not mean abuse of drugs or neglect of recommendations for their safety. Off-label prescribing is common in all areas of medicine, and for some medications it is becoming common clinical practice. For more than 35 years, pharmacotherapy regulators (FDA, Ministry of Health, etc.) have been trying to find the optimal solution to the problem of using off-label drugs, especially in terms of legislation [3–5].

Today, off-label drugs are also prescribed in the treatment of cancer [6–8]. A feature of pharmacotherapy in oncology is that anti-cancer drugs have a wide range of targets. Therefore, in the treatment of many types of tumors, combined chemotherapy is usually prescribed. Examples of the combined chemotherapy in oncology include the simultaneous administration of cytostatic, immunobiological and targeted drugs in the following regimens:

- R-CHOP — for the treatment of non-Hodgkin lymphoma;
- BEACOPP — for the treatment of Hodgkin lymphoma;
- CMF, FAC, CAF, TAC — for the treatment of breast cancer;
- E-FOLFOX, B-FOLFIRI — for the treatment of colorectal cancer.

These combinations may include one or more drugs that are traditionally used to treat a particular type of tumor or are used off-label. Therefore, a drug designed to treat one type of tumor can sometimes be used to treat other types of cancer. In addition, such combinations of drugs change over time, as oncologists study their differences, effectiveness and safety, and find out which ones are the most optimal [9].

However, some combinations of off-label anticancer drugs can be highly toxic. For example, a clinical trial of a combination of ipilimumab and vemurafenib in patients with metastatic skin melanoma was conducted. These drugs have the same mechanism of action and potentiate side effects of each other, in particular, they increase hepatotoxicity [10]. Therefore, a clinical trial of this combination was interrupted for safety reasons. Another example of failed off-label therapy is the combination of ipilimumab with nivolumab. This combination was more effective in treating metastatic melanoma (it increased the median survival and slowed the progression of the disease) unlike their separate administration (11.5 months *vs* 6.9 months for nivolumab and 2.9 months for ipilimumab). However, this combination was more toxic than its individual components. In addition, the use of a combination of these drugs was economically disadvantageous. Therefore, at present, this combination is not approved as a therapy for metastatic melanoma. It should

Submitted: February 26, 2020.
*Correspondence: E-mail: acya@ukr.net
Abbreviation used: FDA – Food and Drug Administration.

be noted that antitumor therapy is costly (sometimes about $ 120,000 per year) compared with other groups of drugs, so it is not available to all patients [9, 11].

A retrospective analysis of modern oncotherapy indicates that oncologists often use off-label drugs in combined therapy, especially in the treatment of patients with concomitant diseases, with the progressive development of the tumor, or to reduce the toxicity and cost of treatment components. These experts believe that the main reasons for the administration of off-label anticancer drugs are as follows:

- The existing standards for evaluating clinical trials of drugs in cancer pharmacotherapy in terms of duration and impact on the quality of patients' life are too stringent.
- There are difficulties with the approval of new indications of anticancer drugs.
- There is a lack of incentive for pharmaceutical companies to seek approval of new evidence if the anticancer drug which is no longer under patent protection.
- It's quite difficult, and sometimes completely impossible to conduct clinical trials of drugs, especially in case of rare types of cancer.
- In oncology, some generic drugs are used off-label more often than the original drugs with approved indications [12–14].

At the same time, American oncologists are of the opinion that if all the drugs prescribed by the International Recommendations failed in the treatment of cancer, doctors can prescribe off-label drugs, but only if their effectiveness and safety are accurately established [15]. Consequently, in tumors with the same mutation that do not respond to the target standard therapy, oncologists are potentially eligible to administer the off-label pharmacotherapy. So, there is currently clinical evidence that trastuzumab (herceptine) in combination with paclitaxel can be used to treat patients with metastatic breast cancer. A number of studies conducted in Europe and the USA on various regimens of paclitaxel and its combinations with other cytostatic agents led to the conclusion that it is necessary to include this drug in adjuvant treatment programs for early breast cancer, especially for patients from group of risk. The efficacy of combining paclitaxel with antiangiogenic drugs (bevacizumab) and its combination with various cytostatics (carboplatin, doxorubicin + cyclophosphamide) in patients with early and advanced basal breast cancer is being studied [16]. For the treatment of patients with advanced forms of breast cancer, trastuzumab fully complies with international requirements for criteria of effectiveness/safety. Treatment with trastuzumab in combination with chemotherapy courses is pathogenetically substantiated and helps to increase survival rate and improve the quality of life of these patients [16–18]. The efficacy of bevacizumab (avastine) has been proven in metastatic colon and rectal carcinoma in combination with intravenous chemotherapy with fluorouracil (5-fluorouracil) [18]. Similar data are also available for the combination of paclitaxel with carboplatin in patients with inoperable, locally progressive, recurring or metastatic non-small cell lung cancer and in patients with metastatic colorectal cancer. Data from a Phase 2 study of InterAACT, the first randomized study of patients with inoperable progressive squamous cell carcinoma of the anal canal, suggest that carboplatin in combination with paclitaxel halves the risk of death. There is also information about the effectiveness of nivolumab in the treatment of this disease [18].

Consequently, the use of trastuzumab for the treatment of breast and stomach cancer, bevacizumab for the treatment of colorectal cancer, non-small cell lung cancer and breast cancer can be a good example of the use of off-label drugs in oncology [17, 18].

In 1991, in the United States, it was found that one third of all patients with malignant neoplasms received at least one off-label drug, and in a similar study conducted in 1997, it was found that already 60% of cancer patients received off-label drugs. In Germany, oncology is the most active field of medicine for the use of off-label drugs. Often also outside the approved protocols, German oncologists prescribe drugs used in neurology, psychiatry, rheumatology, for infectious and viral diseases (for example, HIV/AIDS), dermatology and gynecology [18–20].

In addition, oncologists today periodically face a problem when there are several approved treatment protocols for one type of tumor at the same time. This is especially true for rare types of tumors. At the same time, there is another problem of off-label pharmacotherapy in oncology, namely, such patients often receive new drugs as part of clinical trials of drugs for indications that are not mentioned in the instructions [21]. Sometimes this is the only way out for the patient with ineffective traditional therapy. The results of these studies are published in medical journals and are under discussion by the cancer community. Practicing oncologists use off-label therapy data for subsequent use of drugs outside the instructions. Therefore, in the future, the drug can be widely used to treat another type of tumor, even if the FDA and/or other regulatory body have not confirmed its indications.

The appointment of off-label drugs for targeted therapy in oncology is possible in patients with various types of tumors that affect the same target. Pharmacotherapy using genotypic approaches (anti-angiogenic and new immunological drugs) also has the potential for alternative off-label indications in oncology. The use of off-label therapy is not always documented (approved) and may be in the same range as traditional antitumor drugs with a wide spectrum of action [22]. For example, it was proved that paclitaxel also has anti-angiogenic activity, which is not associated with its cytotoxic effect, but is mediated by a change in the response of endothelial cells to factors of angiogenesis [16].

The use of off-label therapy based on tumor genotyping is often more rational than traditional antitumor drugs. However, this therapy faces a limited clinical evidence base, insurance problems, and a very high cost of genotyping. Therefore, many oncologists believe that at present these new tumor treatment strategies will not lead to widespread use of off-label drugs, since genomic changes are present in 10–40% of patients, i.e. minority.

Off-label administration is especially common and can reach 50% in patients receiving chemotherapy. A study including 200 oncologists showed that 3 out of 5 doctors prescribed off-label drugs during chemotherapy. This is due to the fact that the instructions for such an anti-blastoma drug usually indicate one type of tumor, but it can be used in chemotherapy for different types of cancer [23].

One of the journals in clinical oncology conducted a study of the frequency of use of off-label drugs in 4 oncology clinics [8]. The results of this study indicate that almost 50% of the drugs were prescribed off-label. An example of an off-label prescription is lorazepam (anxiolytic), which can be used off-label as an antiemetic in cancer patients. In addition, in oncology, lorazepam is most often used sublingually, which is also missing in the instruction for this drug.

When analyzing the pharmacotherapy database of the National Institute of Epidemiology and Cancer Treatment, it was found that in the treatment of breast cancer in 2082 women over the age of 65, out of 36 chemotherapeutic drugs, only 22% were approved by the FDA for use in breast cancer [6].

Recently, in oncology there are often prescribed monoclonal antibodies, in particular rituximab (75% of off-label appointments). Rituximab, originally developed for the treatment of non-Hodgkin's lymphoma, has recently been finding more and more off-label indications. A similar study was conducted in the United States in 2010 using monoclonal antibodies cetuximab, rituximab, trastuzumab, bevacizumab [20]. The off-label use rate of these drugs was 30% and was clinically supported by the US National Cancer Network. Among these drugs, the frequency of off-label cancer therapy varied significantly between trastuzumab (1%) and rituximab (67%). In the American study of the insurance administrative database, it was found that in the period 2001–2007, 25.3% of rituximab prescriptions were off-label, and already about 50% of off-label use of this drug was confirmed by clinical evidence [23].

Therefore, today rituximab turned out to be the drug that has the greatest potential for off-label indications in oncology. Thus, it was found that rituximab was the most frequently used off-label drug (21.1%) among 232 drugs (including all therapeutic classes) in 5 hospitals for one year (2011–2012). In addition, a retrospective Australian study found that rituximab has the potential for numerous off-label indications in the treatment of hormone-resistant autoimmune diseases [24].

Antiangiogenic drugs (monoclonal antibodies) were mainly used off-label in patients with metastatic colorectal cancer (81.7%). Thus, according to the Italian Medicines Agency, these drugs are the first-line therapy for metastatic colorectal cancer (30% in 780 patients) [25]. Therefore, the administration of off-label oncological preparations depends on the duration of treatment and the stage of colorectal cancer (40%), and it is also possible to use them outside oncology, for example, with age-related macular degeneration of the retina (10%).

Thus, the frequency of use of off-label drugs in oncology varies depending on their availability on the country pharmaceutical market, effectiveness and safety, type of tumor, stage of development of the disease, etc. In addition, off-label drugs are often prescribed for malignant tumors with limited sensitivity to conventional antitumor drugs. Drugs with a non-specific mechanism of action, a wide range of pharmacological effects and several indications for use (for example, oxaliplatin) also have prospects for using off-label [26].

In the USA, a study of the use of off-label antitumor drugs in 2663 patients with breast cancer was conducted for 10 years (2000–2009). It was found that 13% of patients were treated with off-label drugs, mainly with the help of cytotoxic drugs. Regarding targeted therapy, for example the off-label use of multikinase inhibitors, was very low (0.4% of patients). Monoclonal antibodies were the more widely used off-label drugs (8%), in particular, bevacizumab, which the FDA approved for the treatment of breast cancer in 2011. The unapproved use of monoclonal antibodies panitumumab and bevacizumab in the United States has been retrospectively studied in private clinics in patients with advanced metastatic colorectal cancer [11, 27].

In France, the results of using multicase off-label inhibitors in 249 patients diagnosed with sarcoma are systematized [28]. Sarcoma is a heterogeneous disease with low therapeutic potential. The decision to off-label use of multikinase inhibitors in sarcoma was made after discussing with clinical oncologists the clinical results of using sorafenib (45%), sunitinib (25%), sirolimus (9%) and imatinib (8%). Their toxicity corresponded to the 3rd degree and was observed in 32% of patients. The median survival of patients without disease progression with the use of these off-label drugs averaged 4.1 months. In 2010, the use of off-label multikinase inhibitors of sunitinib and sorafenib was analyzed in 15 patients with refractory cancer: the median survival was 19 months. In 2013, sorafenib received FDA approval based on a phase III randomized clinical trial that showed significant improvement in progression-free patients (10.8 months *vs* 5.8 months compared with placebo).

Today, the effect of anti-blastoma drugs when using off-label ones is aimed mainly at specific tumor targets and they are considered as targeted antitumor drugs. These off-label drugs (more than 50 approved

drugs since rituximab was introduced into clinical practice in 1997) are mainly monoclonal antibodies that interact with cell membrane receptors, circulating ligands, or protein enzyme inhibitors that inhibit tumor development in various ways. Many off-label drugs have a narrow spectrum of action — a specific type of cancer (often rare or orphan symptoms) [29–31].

Consequently, the administration of targeted off-label anti-tumor therapy is possible for different types of tumors, but in fact it is aimed at the same target. For example, vemurafenib, approved in the treatment of metastatic melanoma of the skin with an activating mutation BRAF V600E, was used as an off-label drug for refractory positive mutation of hairy cell leukemia. In addition, the action of most multikinase inhibitors is not selective, which means that they are active against other kinases that are not associated with the approved indications. For example, an inhibitor of FMS-like tyrosine kinase-3, sorafenib, is used as an off-label drug for relapsing acute myeloid leukemia. In addition, some of these drugs have significant potential for using off-label for non-oncological diseases, for example, bevacizumab in ophthalmology (age-related macular degeneration, macular degradation) and rituximab in refractory autoimmune diseases (age-related macular degeneration of the retina) [31].

The problem of using off-label drugs in oncology has not yet been studied in detail. It's difficult to run these studies, since these drugs are numerous and their number is growing rapidly (more than 30 enzyme inhibitors approved for worldwide use since 2001).

The treatment of certain types of pain with tricyclic antidepressants is also an example of off-label use of drugs in oncology. These drugs belong to the first-generation antidepressants, they are currently rarely used to treat depressive conditions, as there are safer and more effective modern antidepressants. However, the clinic found that tricyclic antidepressants effectively eliminate cancer pain, although there is no such indication in their instructions. Earlier developed drugs in this group are usually used off-label more often than newer ones. Low doses of naltrexone (an opioid receptor antagonist) are used to treat cancer and autoimmune diseases, as well as focal segmental glomerulosclerosis [30].

Despite the fact that the use of off-label drugs in oncology is quite common today, some private medical insurance companies do not recognize the use of off- label drugs. However, state medical insurance companies in many countries officially accept the use of off-label drugs in the treatment of tumors, in case of scientific evidence of their effectiveness and safety, even if the FDA has not approved the drug for such use.

Thus, compared with some traditional drugs, off-label oncotherapy is sometimes targeted and probably rational due to tumor genotyping, but faces limited clinical support and financial problems due to the high cost of genotyping or molecular profiling. Today, in addition to the already published reliable positive results of off-label drugs in cancer therapy, practicing oncologists are proposing to collect information and create a database of clinical data capturing the experience of using off-label drugs in oncology [27]. Pharmacotherapy in pediatric oncology remains a problem. Differences in the development of tumors in children and adults usually make it difficult for children to prescribe drugs based on clinical data obtained from adults [32, 33]. In addition, new anticancer drugs usually become available to children only after long-term use in adult patients. The doctor has the right to decide in favor of the non-standard use of the medicine, however, he must take responsibility for the results of treatment. In case of severe, difficult to cure or incurable oncological diseases, this is the responsibility of the oncologist, and it is in oncology that off-label prescriptions are the most often encountered. Therefore, oncologists and their patients more readily use off-label drugs unlike the representatives of other medical specialties.

REFERENCES

1. **Dal Pan GJ.** WHO Drug Information: Monitoring the safety of off label medicine use. WHO Drug Information 2009; **23**: 21–2.

2. **Stafford RS.** Regulating off label drug use: rethinking the role of the FDA. N Engl J Med 2008; **358**: 1427–9.

3. **Khamar B**. Off label use of medicines: Medical research and medical practice. Indian J Ophthalmol 2007; **55**: 411–2.

4. **Martsevich SYu, Navsardian AR, Komkova NA.** Off-label prescription of medicinal products. Possible causes and consequences. The legal regulation in Russian Federation. Rational Pharmacother Cardiol 2017; **13:** 667–73 (in Russian).

5. **Rakeev P, Drogovoz SM.** Off-label use of drugs in psychiatry. In Topical issues of new drugs development: Abstracts of XXIV international scientific and practical conference of young scientists and student, April 20, 2017. Kh, 2017; **2**: 164.

6. **Levêque D.** Off label use of anticancer drugs. Lancet Oncol 2008; **9**: 1102–7.

7. **Lukianchuk JO, Drogovoz SM.** Side effects of off label drugs. Topical issues of new drugs development: Abstracts of XXV International Scientific and Practical Conference of Young Scientists and Student, Kharkiv, April 18–20, Kh, 2018; 267.

8. **Pfister DG.** Off label use of oncology drugs: the need for more data and then some. J Clin Oncol 2012; **30**: 1–3.

9. **Sox HC.** Evaluating off-label uses of anticancer drugs: time for a change. Ann Intern Med 2009; **150**: 353–4.

10. **Drogovoz SM, Matveeva EV, Lukianchuk YuA**. Factors contributing to side effects of drugs. Pharmacol Toxical 2018; **2**: 92–6 (in Russian).

11. **Stephens K, Gurenlian J.** Ethical and legal considerations of off label drug use [Electronic resource]. 2018. Access mode: http://decisionsindentistry. com/article/ethical–and–legal–considerations–of–off–label–drug–use/.

12. **Jennifer K.** Pharmaceutical Regulation and Offlabel Uses [Electronic resource]. National Institute on Aging research 2016; 1–14. Access mode: http://www.nber.org/aging/valmed/WhitePaper-Kao9.2016.pdf.

13. **Tabarrok AT.** Assessing the FDA via the anomaly of off label drug. Independent Review 2000; **5, 1**: 25–53.

14. **Fairbairn D, Izzard C and Holtorf M.** Promotion and use of off label pharmaceuticals in Europe, the US and China [Electronic resource]. Financier Worldwide Magazine 2011. Access mode: http://www.cliffordchance.com.

15. American Society of Clinical Oncology (2006) Reimbursement for cancer treatment: coverage of off label drug indications. J Clin Oncol 2006; **24, 19**: 3206–8.

16. **Zaporozhan VN, Bugaitsov SG, Stepula VV, Storozhenko SA.** Experience of using herceptin in treatment of advanced forms of HER2-positive breast cancer. Onkologiya 2010; **12**: 147–9 (in Russian).

17. ESMO 2018: Carboplatin and paclitaxel may become new standard of treatment of cancer of anal canal. InterAACT Study. Access mode: htts://rosoncoweb.ru/news/oncology/2018/11/06-4.

18. **Ponomariova OV.** International experience of paclitaxel use in the treatment of patients with early breast cancer. Onkologiya 2011; **13**: 234–8.

19. **FDA News Release.** FDA Commissioner announces Avastin decision: Drug not shown to be safe and effective in breast cancer patients. 2011. [Electronic resource]. Access mode: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm280536.htm.

20. **Rückeshäuser P.** Off label use: the legal problems of drug application beyond the licensed use. Hamburg 2011; 1–386.

21. **Schelling P.** Die rechtlichen Aspektebeim "Off–Label–Use" [Electronic resource]. Snternist 2008; **3**: 322–7. Access mode : http://www.bdi.de.

22. **Poole SG, Dooley MJ.** Off label prescribing in oncology. Support Care Cancer 2004; **12**: 302–5.

23. **Casali PG, Executive Committee of ESMO.** The off-label use of drugs in oncology: a position paper by the European Society for Medical Oncology (ESMO). Ann Oncol 2007; **18**: 1923–5.

24. **Ballard CDJ, Peterson GM, Thompson AJ, Beggs SA.** Off-1abe1 use of medicines in pediatric inpatients at an Australian teaching hospital. J Paediatr Child Health 2012; **49**: 544–8.

25. **Guide B, Nocco L.** The debate concerning the off 1abe1 prescriptions of drugs: a comparison between Italian US law. Opinio Juris Compar 2011; **1**: 45.

26. **Delpeuch A, Leveque D, Rob L, Bergerat JP.** Off-label use of oxaliplatin in patients with metastatic breast cancer. Anticancer Res 2011; **31**: 1765–7.

27. **Gillick MR.** Controlling off label medication use. Ann Intern Med 2009; **150**: 344–7.

28. **Emmerich J, Dumarcet N, Lorence A.** France's new framework for regulating off label drug use. N Engl J Med 2012; **367**: 1279–81.

29. **Drogou F, Netboute A, Giai J, *et al.*** Off-label drug prescriptions in French general practice: A crosse-sectional study. BMj 2019; **9**: 4. Access mode: https://bmjopen.bmj.com/content/9/4/e026076.long.

30. **Skanland SS, Cieślar-Pobuda A.** Off-label uses of drugs for depression. Eur J Pharmacol 2019; **865**: 1–11.

31. **Lukianchuk JO, Drogovoz SM.** Off label use of drugs in oncology. Topical issues of new drugs development: Abstracts of XXIV International Scientific and Practical Conference of Young Scientists and Student, Kharkiv, April 20, Kh, 2017; 158.

32. **Kimland E, Odlind V**. Off label drug use in pediatric patients. Clin Pharmacol Therap 2012; **91**: 796–801.

33. **Frattarelli DA, Galinkin JL, Green TP, *et al.*** Off-label use of drugs in chidren. Pediatrics 2014; **133**: 563–7.

ДОСВІД ТА ПЕРСПЕКТИВИ ВИКОРИСТАННЯ "OFF-LABEL" ПРЕПАРАТІВ В ОНКОЛОГІЇ

С.М. Дроговоз[1], В.І. Старіков[2], Л.Б. Іванцик[1], К.Г. Щокіна[1]

[1]Національний фармацевтичний університет, Харків 61002, Україна

[2]Харківський національний медичний університет, Харків 61022, Україна

За даними Всесвітньої організації охорони здоров'я, половина всіх лікарських засобів, доступних на світовому фармацевтичному ринку, іноді використовується за показаннями, які не включені в інструкцію із застосування. Цей метод терапії відомий під терміном **"використання не за призначенням (off-label)", що означає використання "поза інструкцією"**. Сьогодні для лікування раку також призначаються off-label препарати. Наприклад, препарат, розроблений для лікування одного типу пухлин, іноді може застосовуватися для лікування інших видів раку. Лікування певних видів болю трициклічними антидепресантами також є прикладом застосування off-label препаратів в онкології. Прикладом призначення off-label є анксіолітичний препарат лоразепам, який можна використовувати як протиблювотний засіб у хворих на рак. Низькі дози налтрексону застосовуються для лікування раку та аутоімунних захворювань. Ретроспективний аналіз сучасної онкотерапії вказує на те, що онкологи часто використовують комбіновану терапію off-label препаратами, особливо при лікуванні пацієнтів із супутніми захворюваннями, у разі прогресуючого розвитку пухлини або для зниження токсичності та вартості компонентів лікування. Американські онкологи дотримуються думки, що якщо всі препарати, передбачені міжнародними рекомендаціями, не дають результатів під час лікування раку, лікарі можуть призначати off-label лікарські засоби,