World Journal of Clinical Oncology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5306/wjco.v7.i2.253

World J Clin Oncol 2016 April 10; 7(2): 253-257
ISSN 2218-4333 (online)

Off-label use of targeted therapies in oncology

Dominique Levêque

Dominique Levêque, Division of Pharmacy, hôpital Hautepierre, 67000 Strasbourg, France

Author contributions: Levêque D wrote the paper.

Conflict-of-interest statement: There is no conflict of interest related to this work

Correspondence to: Dominique Levêque, PhD, Division of Pharmacy, hôpital Hautepierre, avenue Molière, 67000 Strasbourg, France. dominique.leveque@chru-strasbourg.fr
Telephone: +33-3-88128213
Fax: +33-3-88127804

Received: September 2, 2015
Peer-review started: September 8, 2015
First decision: October 16, 2015
Revised: October 23, 2015
Accepted: December 29, 2015
Article in press: January 4, 2016
Published online: April 10, 2016

Abstract

Off-label use is defined by the prescription of a marketed drug outside the conditions described in the summary of product characteristics. In oncology, off-label prescribing of targeted therapies may occur in patients with other tumor types expressing the same target. Agents associated to phenotypic approaches such as therapies against the tumoral vasculature (anti-angiogenic drugs) and new immunotherapies (checkpoint inhibitors) also carry the potential of alternative indications or combinations. Off-label use of targeted therapies is little documented and appears to be in the same range than that regarding older drugs with wide variations among agents. When compared with older agents, off-label use of targeted therapies is probably more rational through tumoral genotyping but is faced with a limited clinical support, reimbursement challenges related to the very high pricing and the cost of genotyping or molecular profiling, when applicable.

Key words: Targeted therapy; Monoclonal antibody; Off-label anticancer drug use; Reimbursement; Enzyme inhibitor

Core tip: Off-label use is defined by the prescription of a marketed drug outside the conditions described in the summary of product characteristics. This review is the first one focussing on the off-label use of targeted therapies in oncology. When compared with older agents, off-label use of targeted therapies is probably more rational through tumoral genotyping but is faced with a limited clinical support, reimbursement challenges related to the very high pricing and the cost of genotyping or molecular profiling, when applicable.

Levêque D. Off-label use of targeted therapies in oncology. *World J Clin Oncol* 2016; 7(2): 253-257 Available from: URL: http://www.wjgnet.com/2218-4333/full/v7/i2/253.htm DOI: http://dx.doi.org/10.5306/wjco.v7.i2.253

INTRODUCTION

Off-label use is defined by the prescription of a marketed drug outside the conditions described in the summary of product characteristics (also referred as the official labeling or the package insert). Off-label drug use covers many aspects such as the targeted population, the indication, the dosing regimen, the duration of treatment.

The goal of off-label prescribing is to offer a patient an alternative treatment in the absence of a licensed therapy or a lack of clinical trial access[1]. In rare cases, off-label therapy may be given instead of the approved treatment for efficacy reason (oxaliplatin and irinotecan combined with fluorouracile in metastatic pancreas cancer) or can constitute a less toxic alternative (carboplatin in stage I seminoma)[2,3].

Generally, off-label prescribing does not beneficiate from the expertise of a drug regulatory agency and its rationale is based and supported on an analysis of published data of good clinical evidence or compendia. Regarding manufacturers, they profit from off-label use because it permits the increase of sales without undergoing costly clinical trials. Ultimately, off-label prescribing has to bring an acceptable clinical response and safety profile to the patient.

Off-label use raises numerous questions of legality, responsibility, frequency, clinical evidence and reimbursement. It may be analyzed globally or more specifically from the point of view of a type of cancer, a drug or a country. Indeed, differences in labeling exist between Europe and the United States. Trotta *et al*[4] reported that for the 42 anticancer agents approved in Europe (European Medicines Agency) between 1995 and 2008, a difference of labeling with the United States (Food and Drug Administration) was identified for 47 of the 100 indications. So, rates of off-label use varies with the country of labeling, the type of tumor, the evolution of the disease, the availability of effective marketed treatments and the anticancer agent. For instance, malignancies with limited active treatments or orphan cancers are subject to off-label prescribing. In addition, drugs with few indications and possessing a non specific mechanism of action ("wide spectrum") are prone to off-label use (*i.e.*, oxaliplatine)[1].

TARGETED THERAPIES

In oncology, "targeted therapies" may be arbitrarily defined as drugs which development is based on a predetermined tumoral or endogenous target. They are generally opposed to cytotoxics even if methotrexate (amethopterine, a methyl derivative of aminopterine) could also be considered as a targeted antifolate agent[5]. These drugs (around 50 approved agents since the marketing of rituximab in 1997) are either monoclonal antibodies/fusion proteins that interact with cell membrane receptors or circulating ligands or protein/enzyme inhibitors that interfere with various tumoral signaling pathways. They mainly have narrow indications in relation with the expression of the target in a particular type of cancer (often a rare or an orphan indication) and regarding enzyme inhibitors they are mostly used orally as a single agent-therapy. Targeted therapies are very expensive (around 120000$/year in the United States)[6] when compared with previous agents or medications of others therapeutic classes and according to the country, their access to patients may be hindered by funding difficulties or partial covering.

OFF-LABEL USE OF TARGETED THERAPIES

Prevalence and clinical evidence

Off-label prescribing of targeted therapies may occur in patients with other tumor types expressing the same target (referred as precision medicine)[7]. For instance, vemurafenib, a kinase inhibitor indicated in the treatment of metastatic melanoma with activating *BRAF V600E* mutation has been used off-label in refractory *BRAF V600E* mutation positive-hairy cell leukemia[8]. Furthermore, most of kinase inhibitors are not selective meaning that they display activity against other kinases not associated with approved indications[9]. For example, sorafenib is used off-label as a FMS-like receptor tyrosine kinase-3 inhibitor in relapsed acute myeloid leukemia[10]. Agents associated to phenotypic approaches, that is to say therapies against the tumoral vasculature (anti-angiogenic drugs such as bevacizumab) and new immunotherapies (checkpoint inhibitors such as ipilimumab) also carry the potential of alternative indications or combinations.

The prevalence of off-label use focusing on targeted therapies has not been investigated in detail. These studies are not easy to perform because these agents are numerous and the class is rapidly growing (more than 30 enzyme inhibitors approved worldwide since imatinib in 2001). In addition, they are both used in the in- and outpatient settings.

A swiss study has reported a low frequence of unsupported off-label use (7.8%) for 8 recent agents in a cohort of 985 consecutive patients under systemic anticancer treatment in 2012[11]. Variations were observed among these agents with almost no off-label use for pazopanib and a high level of unsupported use for bevacizumab (29.6%)[11]. The global prevalence (supported by the European Society of Medical Oncology and unsupported) was not reported for these 8 agents.

A similar study has been conducted in the United States in 2010 using patient database and focusing on the off-label use of some expensive intravenous agents (including the monoclonal antibodies cetuximab, rituximab, trastuzumab, bevacizumab)[12]. The frequence of off-label use was 30% of that half was clinically supported by the National Comprehensive Care Network (NCCN). Among agents, the rate of off-label utilization also varied considerably between trastuzumab (1%) and rituximab (67%)[12].

Another American study based on insurance administrative database found a rate of off-label use of rituximab of 25.3% during the period 2001-2007[13]. Around 50% of off-label use was evidence-based. Among targeted therapies, rituximab is the agent that probably carries the greatest potential for off-label indications mostly beyond oncology. Indeed, a Spanish prospective investigation reported that rituximab was the most frequently used agent off-label (21.1%) among 232

drugs (considering all therapeutic classes) in 5 tertiary hospitals during one year (2011-2012)[14]. In addition, a prospective Australian national study found that off-label use of rituximab covers 63 different diagnosis with 89% of off-label use outside oncology in the year 2012[15]. This is not surprising because rituximab is a non specific lymphocytical agent having potential numerous applications in the treatment of corticosteroid-refractory autoimmune diseases.

An Italian investigation described the off-label utilization of bevacizumab during the period 2006-2007 using patient database in the region of Lombardy[16]. The anti-angiogenic monoclonal antibody was mostly used (81.7%) in patients with metastatic colorectal cancer. On-label prescribing (according to the Italian Medicines Agency) represented only 241 (30%) of the 780 patients (*i.e.*, first line treatment of metastatic colorectal cancer with fluorouracil-based chemotherapy). Off-label use concerned the timing of treatment in metastatic colorectal cancer (40%) and the use outside oncology in age-related macular degeneration (10%)[16].

More specifically, off-label use of anticancer agents has been investigated over a 10-years period (2000-2009) in a population of 2663 patients with breast cancer in the United States using an administrative data base[17]. A proportion of 13% of the patients were treated off-label mainly with cytotoxic agents. Regarding targeted therapies, off-label use of kinase inhibitors was anecdotal (0.4% of the patients). Off-label prescription of monoclonal antibodies was more prevalent (8% of the patients), particularly the agent anti-angiogenic bevacizumab (before the FDA cancelled the approval in breast cancer in 2011)[17].

Unsupported off-label use of the monoclonal antibodies panitumumab and bevacizumab has been retrospectively studied in a population of privatized insurance patients with metastatic colorectal cancer on progression, in the United States[18]. Between 2007 and 2010, off-label prescribing non-supported by the NCCN concerned 10% of the patients under bevacizumab and 16% of those under panitumumab.

Some studies have reported off-label use in populations of selected cancer patients with late-stage disease following tumor genomic testing. Preliminary experiences have described the opportunity of using tumor genomic information to guide a specific treatment in certain patients through so-called molecular tumor boards[19]. In a prospective study including 250 adult patients mostly with colorectal, breast, lung and pancreas cancers, only 10% of the patients tested could be treated mainly through a clinical trial[20]. Overall, following tumor profiling, off-label use only represented 2.8% of the patients[20]. Le Tourneau *et al*[21] investigated molecular tumor profiling representing 3 pathways (hormone receptor, PI3K/AKT/mTOR and RAF/MEK) in 741 patients with refractory metastatic disease. Around 40% of the patients were eligible to a panel of 11 off-label targeted therapies including imatinib, dasatinib, vemurafenib, sorafenib, erlotinib, lapatinib, trastuzumab and everolimus. Currently, these new strategies of treatment are not expected to bring extended off-label use because a minority of genomic alterations (10%-40%) are targetable or "druggable". Furthermore, the delay of treatment may impede access for patients whose disease progresses and in some countries like the United States, patients could be denied from treatment for covering reasons.

Overall and based on these preliminary data, off-label use of targeted therapies appears to be in the same range as that regarding older drugs (6.7%-33%) with wide variations among agents[1].

Clinical impact

As seen above, Le Tourneau *et al*[21] evaluated in a randomized phase 2 trial the clinical impact of selected molecular tumor profiling. Unfortunately, among the treated and randomized patients with "druggable tumors" (n = 195), the off-label use of targeted therapies did not improve the progression free survival (primary endpoint) when compared with those treated by chemotherapy according to the oncologist choice (around 2 mo in both arms).

A French registry has collected the off-label use of kinase inhibitors in 249 patients with sarcomas mainly pretreated (89%)[22]. Sarcoma is a very heterogeneous disease with little therapeutic options. Decision of off-label treatment was made following discussion with experts, based on a scientific rationale (96%). Sorafenib (45%), sunitinib (25%), sirolimus (9%) and imatinib (8%) were mostly used. Toxicities above or equal to grade 3 were observed in 32% of the patients. The median progression-free survival was 4.1 mo (Interval of confidence or 95%CI: 3.2-4.8) and overall, the results were judged similar to those of published trials[22].

In 2010, off-label use of the multi-kinase inhibitors sunitinib and sorafenib has been reported in 15 patients with follicular/papillary radioactive iodine refractory cancer[23]. The progression free survival was 19 mo. Since then, sorafenib gained its approval in 2013 based on a phase 3 randomized study which showed a significant improvement in the progression free survival (10.8 mo *vs* 5.8 mo with placebo)[24].

Limits

Clinically, the limits of off-label use are a lack of activity and/or the appearance of serious side effects. Tumor types carrying the same mutation and potentially eligible to off-label treatment do not respond uniformly to the targeted therapy as it has been shown in cancers with *BRAF* V600 mutations[25]. Furthermore, some off-label combinations may be detrimental. Ipilimumab and vemurafenib are both targeted therapies used as a single agent-treatment in patients with metastatic melanoma. The trial evaluating the association has been closed for safety reasons (hepatotoxicity) underscoring the risk of co-administering off-label recent agents with new mechanisms of action[26].

Regarding the re-birth of immunotherapy, this phenotypic approach that induces a T-cell response against

tumour is susceptible to be used in any kind of cancer. However, the reality is more complex and the responses vary among patients and cancers. So, the exploration of new indications should be devoted to clinical trials. Otherwise, even if in case of positive and promising results (associations of immunotherapies in metastatic melanoma), enthusiasm should be tempered[27]. Indeed, ipilimumab with nivolumab has been shown to be superior in terms of median progression free survival than the immunotherapies given alone (11.5 mo *vs* 6.9 mo for nivolumab and 2.9 mo for ipilimumab). The association was also more toxic[27]. Ipilimumab and nivolumab are currently approved as a single agent-therapy in metastatic melanoma. The off-label use of combinations of these checkpoint inhibitors is premature and is not sustainable for financial reasons.

Covering

Due to their astronomical pricing, covering recent anticancer agents in their labeled indication is a major concern in most health systems. So, off-label prescribing adds reimbursement difficulties. Covering of off-label use depends on the country, the level of clinical evidence and can constitute a barrier for certain patients. Loss of patent of monoclonal antibodies and kinase inhibitors and the forthcoming arrival of less costly biosimilars (rituximab) as well as generics may improve access in well supported clinical situations.

CONCLUSION

The prevalence of off-label use of targeted therapies in oncology is little documented but appears to be in the same range as that of cytotoxics. When compared with old agents, off-label use of targeted therapies is probably more rational through tumoral genotyping but is faced with a limited clinical support, reimbursement challenges related to the very high pricing and the cost of genotyping or molecular profiling, when applicable. Beyond positive results published through anecdotal case reports, proposals have been made to gather clinical data relative to off-label use in the United States to get better evidence[28]. Furthermore, regarding enzyme inhibitors, their activity is generally characterized by a short duration of response due to the rapid development of resistance. Sometimes, as seen with old agents, off-label use preceded a labeling (sorafenib in differentiated thyroid cancer). Some of these agents also carry a significant potential of off-label use outside oncology such as bevacizumab in ophthalmology (for economic reasons)[16,29] and rituximab in refractory autoimmune diseases.

REFERENCES

1 **Levêque D**. Off-label use of anticancer drugs. *Lancet Oncol* 2008; **9**: 1102-1107 [PMID: 19012859 DOI: 10.1016/S1470-2045(08)70280-8]

2 **Conroy T**, Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécouarn Y, Adenis A, Raoul JL, Gourgou-Bourgade S, de la Fouchardière C, Bennouna J, Bachet JB, Khemissa-Akouz F, Péré-Vergé D, Delbaldo C, Assenat E, Chauffert B, Michel P, Montoto-Grillot C, Ducreux M. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med* 2011; **364**: 1817-1825 [PMID: 21561347 DOI: 10.1056/NEJMoa1011923]

3 **Oliver RT**, Mead GM, Rustin GJ, Joffe JK, Aass N, Coleman R, Gabe R, Pollock P, Stenning SP. Randomized trial of carboplatin versus radiotherapy for stage I seminoma: mature results on relapse and contralateral testis cancer rates in MRC TE19/EORTC 30982 study (ISRCTN27163214). *J Clin Oncol* 2011; **29**: 957-962 [PMID: 21282539 DOI: 10.1200/JCO.2009.26.4655]

4 **Trotta F**, Leufkens HG, Schellens JH, Laing R, Tafuri G. Evaluation of oncology drugs at the European Medicines Agency and US Food and Drug Administration: when differences have an impact on clinical practice. *J Clin Oncol* 2011; **29**: 2266-2272 [PMID: 21537038 DOI: 10.1200/JCO.2010.34.1248]

5 **Farber S**, Diamond LK. Temporary remissions in acute leukemia in children produced by folic acid antagonist, 4-aminopteroyl-glutamic acid. *N Engl J Med* 1948; **238**: 787-793 [PMID: 18860765 DOI: 10.1056/NEJM194806032382301]

6 **Mailankody S**, Prasad V. Five years of cancer drug approvals: innovation, efficacy, and costs. *JAMA Oncol* 2015; **1**: 539-540 [PMID: 26181265 DOI: 10.1001/jamaoncol.2015.0373]

7 **Jameson JL**, Longo DL. Precision medicine--personalized, problematic, and promising. *N Engl J Med* 2015; **372**: 2229-2234 [PMID: 26014593 DOI: 10.1056/NEJMsb1503104]

8 **Dietrich S**, Glimm H, Andrulis M, von Kalle C, Ho AD, Zenz T. BRAF inhibition in refractory hairy-cell leukemia. *N Engl J Med* 2012; **366**: 2038-2040 [PMID: 22621641 DOI: 10.1056/NEJMc1202124]

9 **Davis MI**, Hunt JP, Herrgard S, Ciceri P, Wodicka LM, Pallares G, Hocker M, Treiber DK, Zarrinkar PP. Comprehensive analysis of kinase inhibitor selectivity. *Nat Biotechnol* 2011; **29**: 1046-1051 [PMID: 22037378 DOI: 10.1038/nbt.1990]

10 **Giri S**, Hamdeh S, Bhatt VR, Schwarz JK. Sorafenib in Relapsed AML With FMS-Like Receptor Tyrosine Kinase-3 Internal Tandem Duplication Mutation. *J Natl Compr Canc Netw* 2015; **13**: 508-514 [PMID: 25964636]

11 **Joerger M**, Schaer-Thuer C, Koeberle D, Matter-Walstra K, Gibbons-Marsico J, Diem S, Thuerlimann B, Cerny T. Off-label use of anticancer drugs in eastern Switzerland: a population-based prospective cohort study. *Eur J Clin Pharmacol* 2014; **70**: 719-725 [PMID: 24609468 DOI: 10.1007/s00228-014-1662-5]

12 **Conti RM**, Bernstein AC, Villaflor VM, Schilsky RL, Rosenthal MB, Bach PB. Prevalence of off-label use and spending in 2010 among patent-protected chemotherapies in a population-based cohort of medical oncologists. *J Clin Oncol* 2013; **31**: 1134-1139 [PMID: 23423747 DOI: 10.1200/JCO.2012.42.7252]

13 **Van Allen EM**, Miyake T, Gunn N, Behler CM, Kohlwes J. Off-label use of rituximab in a multipayer insurance system. *J Oncol Pract* 2011; **7**: 76-79 [PMID: 21731512 DOI: 10.1200/JOP.2010.000042]

14 **Danés I**, Agustí A, Vallano A, Alerany C, Martínez J, Bosch JA, Ferrer A, Gratacós L, Pérez A, Olmo M, Marron SM, Valderrama A, Bonafont X. Outcomes of off-label drug uses in hospitals: a multicentric prospective study. *Eur J Clin Pharmacol* 2014; **70**: 1385-1393 [PMID: 25196202 DOI: 10.1007/s00228-014-1746-2]

15 **O'Connor K**, Liddle C. Prospective data collection of off-label use of rituximab in Australian public hospitals. *Intern Med J* 2013; **43**: 863-870 [PMID: 23735074 DOI: 10.1111/imj.12206]

16 **Bonifazi M**, Rossi M, Moja L, Scigliano VD, Franchi M, La Vecchia C, Zocchetti C, Negri E. Bevacizumab in clinical practice: prescribing appropriateness relative to national indications and safety. *Oncologist* 2012; **17**: 117-124 [PMID: 22210090 DOI: 10.1634/theoncologist.2011-0184]

17 **Hamel S**, McNair DS, Birkett NJ, Mattison DR, Krantis A, Krewski D. Off-label use of cancer therapies in women diagnosed with breast cancer in the United States. *Springerplus* 2015; **4**: 209 [PMID: 25977897 DOI: 10.1186/s40064-015-0981-z]

18 **de Souza JA**, Polite B, Perkins M, Meropol NJ, Ratain MJ, Newcomer LN, Alexander GC. Unsupported off-label chemotherapy in metastatic colon cancer. *BMC Health Serv Res* 2012; **12**: 481

[PMID: 23272659 DOI: 10.1186/1472-6963-12-481]
19 **Erdmann J**. All aboard: Will molecular tumor boards help cancer patients? *Nat Med* 2015; **21**: 655-656 [PMID: 26151320 DOI: 10.1038/nm0715-655]
20 **Sohal DP**, Rini BI, Khorana AA, Dreicer R, Abraham J, Procop GW, Saunthararajah Y, Pennell NA, Stevenson JP, Pelley R, Estfan B, Shepard D, Funchain P, Elson P, Adelstein DJ, Bolwell BJ. Prospective Clinical Study of Precision Oncology in Solid Tumors. *J Natl Cancer Inst* 2015; **108**: djv332 [PMID: 26553780 DOI: 10.1093/jnci/djv332]
21 **Le Tourneau C**, Delord JP, Gonçalves A, Gavoille C, Dubot C, Isambert N, Campone M, Trédan O, Massiani MA, Mauborgne C, Armanet S, Servant N, Bièche I, Bernard V, Gentien D, Jezequel P, Attignon V, Boyault S, Vincent-Salomon A, Servois V, Sablin MP, Kamal M, Paoletti X. Molecularly targeted therapy based on tumour molecular profiling versus conventional therapy for advanced cancer (SHIVA): a multicentre, open-label, proof-of-concept, randomised, controlled phase 2 trial. *Lancet Oncol* 2015; **16**: 1324-1334 [PMID: 26342236 DOI: 10.1016/S1470-2045(15)00188-6]
22 **Eberst L**, Cropet C, Le Cesne A, Pautier P, Penel N, Adenis A, Chevreau C, Bay JO, Collard O, Cupissol D, Duffaud F, Gentet JC, Piperno-Neumann S, Marec-Berard P, Bompas E, Thyss A, Chaigneau L, Cassier P, Bertucci F, Blay JY, Ray-Coquard I. The off-label use of targeted therapies in sarcomas: the OUTC'S program. *BMC Cancer* 2014; **14**: 870 [PMID: 25420707 DOI: 10.1186/1471-2407-14-870]
23 **Dadu R**, Shah K, Busaidy NL, Waguespack SG, Habra MA, Ying AK, Hu MI, Bassett R, Jimenez C, Sherman SI, Cabanillas ME. Efficacy and tolerability of vemurafenib in patients with BRAF(V600E) -positive papillary thyroid cancer: M.D. Anderson Cancer Center off label experience. *J Clin Endocrinol Metab* 2015; **100**: E77-E81 [PMID: 25353071 DOI: 10.1210/jc.2014-2246]
24 **Brose MS**, Nutting CM, Jarzab B, Elisei R, Siena S, Bastholt L, de la Fouchardiere C, Pacini F, Paschke R, Shong YK, Sherman SI, Smit JW, Chung J, Kappeler C, Peña C, Molnár I, Schlumberger MJ. Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 3 trial. *Lancet* 2014; **384**: 319-328 [PMID: 24768112 DOI: 10.1016/S0140-6736(14)60421-9]
25 **Hyman DM**, Puzanov I, Subbiah V, Faris JE, Chau I, Blay JY, Wolf J, Raje NS, Diamond EL, Hollebecque A, Gervais R, Elez-Fernandez ME, Italiano A, Hofheinz RD, Hidalgo M, Chan E, Schuler M, Lasserre SF, Makrutzki M, Sirzen F, Veronese ML, Tabernero J, Baselga J. Vemurafenib in Multiple Nonmelanoma Cancers with BRAF V600 Mutations. *N Engl J Med* 2015; **373**: 726-736 [PMID: 26287849 DOI: 10.1056/NEJMoa1502309]
26 **Ribas A**, Hodi FS, Callahan M, Konto C, Wolchok J. Hepatotoxicity with combination of vemurafenib and ipilimumab. *N Engl J Med* 2013; **368**: 1365-1366 [PMID: 23550685 DOI: 10.1056/NEJMc1302338]
27 **Larkin J**, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD, Schadendorf D, Dummer R, Smylie M, Rutkowski P, Ferrucci PF, Hill A, Wagstaff J, Carlino MS, Haanen JB, Maio M, Marquez-Rodas I, McArthur GA, Ascierto PA, Long GV, Callahan MK, Postow MA, Grossmann K, Sznol M, Dreno B, Bastholt L, Yang A, Rollin LM, Horak C, Hodi FS, Wolchok JD. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. *N Engl J Med* 2015; **373**: 23-34 [PMID: 26027431 DOI: 10.1056/NEJMoa1504030]
28 **McClellan MB**, Daniel GW, Dickson D, Perlmutter J, Berger DP, Miller V, Nussbaum S, Malin J, Romine MH, Schilsky RL. Improving evidence developed from population-level experience with targeted agents. *Clin Pharmacol Ther* 2015; **97**: 478-487 [PMID: 25676878 DOI: 10.1002/cpt.90]
29 **Martin DF**, Maguire MG. Treatment choice for diabetic macular edema. *N Engl J Med* 2015; **372**: 1260-1261 [PMID: 25692914 DOI: 10.1056/NEJMe1500351]

P- Reviewer: Kleeff J, Ogino S **S- Editor**: Qiu S
L- Editor: A **E- Editor**: Li D

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com