

Enzalutamide

REFUSÉE

Le Comité d'experts, après évaluation, refuse d'inscrire le médicament proposé dans la demande.
La Liste Modèle des Médicaments Essentiels fait état des raisons que les membres du Comité ont identifiées pour refuser l'inscription.

Section: [8. Immunomodulators and antineoplastics](#) > [8.2. Antineoplastics and supportive medicines](#) > [8.2.4. Hormones and antihormones](#)

Codes ATC: **L02BB04**

Indication	Malignant neoplasms of prostate	Code ICD11: 2D32.Z
INN	Enzalutamide	
Type de médicament	Chemical agent	
Type de liste	Liste complémentaire	
Formulations	Oral > Solid: 40 mg	
Historique des statuts LME	Demande refusée en 2017 (TRS 1006) Demande refusée en 2019 (TRS 1021) Demande refusée en 2021 (TRS 1035)	
Sexe	Mâle	
Âge	Adolescents et adultes	
Équivalence thérapeutique	La recommandation concerne ce médicament spécifique	
Renseignements sur le brevet	Main patents have expired but secondary patents might remain active in some jurisdictions. For more information on specific patents and license status for developing countries visit www.MedsPal.org Lire la suite sur les brevets.	
Wikipédia	Enzalutamide	
DrugBank	Enzalutamide	

Recommandation du comité d'experts

The Expert Committee noted that prostate cancer is the second most common cancer in men worldwide and the fourth most common cancer overall, and that treatment options for metastatic, castration-resistant prostate cancer are limited. The Committee acknowledged that enzalutamide and abiraterone, as oral treatments, offer several advantages over other treatment options as they do not require intravenous administration, leukapheresis, or the use of radiopharmaceutical compounds. The Committee recalled its previous recommendations not to include enzalutamide on the EML, recommending instead listing abiraterone based on advantages offered by dosing strategies, lower pill burden, better adherence and availability of generics which would allow potential cost savings. The Committee noted that the current cost of enzalutamide is very high for both patients and health systems. The Committee noted that enzalutamide for metastatic, castration-resistant prostate cancer largely meets the EML criteria for survival benefit (i.e. at least 4 to 6 months survival gain) and the European Society of Medical Oncology's magnitude of clinical benefit scale (ESMO-MCBS) v1.1 score, and appears to demonstrate comparable efficacy and safety to abiraterone. However, no direct trial data are available, leaving some uncertainty about which medicine is the best therapeutic option. Enzalutamide has a different mechanism of action and a different toxicity profile, making it a first-choice medicine in patients not eligible to be treated with or unable to tolerate abiraterone. Unlike abiraterone, enzalutamide does not require concomitant use of prednisolone. The Committee considered that having multiple treatment options included on the EML may provide opportunities for countries to negotiate better prices as part of their national procurement processes. In some countries, competition and price reduction will be facilitated by the fact both abiraterone and enzalutamide have generic versions available.

Therefore, the Committee recommended that enzalutamide be included on the complementary list of the EML as a therapeutic alternative to abiraterone. The listing of abiraterone should be qualified with a square box indicating enzalutamide as an alternative for national selection. The Committee considered that this could provide opportunities for cost savings at the country level and increase access to medicines associated with favourable outcomes. As currently the prices of abiraterone and enzalutamide are a major obstacle for health care systems, the Committee recommends that countries address this problem through multiple actions, including price negotiations, competitive tendering and expanded use of generics. The Committee recommended that the Medicines Patent Pool explore with manufacturers how to facilitate affordable access to enzalutamide through public health-oriented licences. The Committee also requested that WHO prioritize abiraterone and enzalutamide as potential candidates for prequalification to facilitate access to affordable and quality-assured products.

Contexte

In 2017, the Committee considered an application requesting the inclusion of enzalutamide on the EML for the treatment of metastatic castration-resistant prostate cancer, but did not recommend inclusion. Instead, the Committee recommended a comprehensive review of prostate cancer medicines, including abiraterone, be considered at its meeting in 2019 (1). In 2019, following consideration of an application proposing the addition of abiraterone and enzalutamide to the EML for treatment of metastatic castration-resistant prostate cancer, the Committee recommended the addition of abiraterone, but not enzalutamide (2). The Committee noted that abiraterone and enzalutamide had been shown to be effective treatments for metastatic castration-resistant prostate cancer, both in chemotherapy-naïve and pretreated patients. The Committee noted that abiraterone had not shown any relevant clinical advantage over enzalutamide in terms of efficacy outcomes or safety. However, the Committee recognized the potential advantages offered by abiraterone in terms of: emerging dosing strategies (lower doses may be possible when administered with food); reduced pill burden potentially improving adherence; wider availability of generics; and potential associated cost savings. Given that metastatic prostate cancer often requires treatment over longer periods (i.e. more than 1 year) and that low dosing and availability of generics would be associated with substantial cost savings, the Committee did not to recommend listing enzalutamide as an alternative to abiraterone under a square box listing. While enzalutamide is an effective therapeutic option for metastatic castration-resistant prostate cancer, its use instead of abiraterone could result in considerable additional expenditure at the country level, without additional clinical benefit. The Committee considered that the addition of abiraterone alone to the EML serves to support its use, promoting competition between brand and generic medicines, and improving access and affordability.

Pertinence pour la santé publique

Prostate cancer is the second most common cancer in men and the fourth most common cancer overall. In 2018, about 1.3 million men were diagnosed with prostate cancer worldwide (3). With early treatment, and if tumours are localized, the prognosis for prostate cancer patients is often favourable. However, some patients will relapse despite androgen deprivation therapy (so-called castration), which leads to castration-resistant prostate cancer when the disease is no longer responsive to androgen deprivation therapy, thus limiting the available treatment options. Access to second-generation therapies such as enzalutamide therefore becomes critical to extending patients' lives and allowing them to have an improved quality of life. Six treatments are currently used to treat castration-resistant prostate cancer. Enzalutamide and abiraterone acetate are the only orally administered therapies. Other treatments are invasive and require intravenous administration, leukapheresis or the use of radiopharmaceuticals.

Bénéfices

Enzalutamide in metastatic castration-resistant prostate cancer The application presented the same data from the AFFIRM and PREVAIL trials that were presented in the 2019 application. The AFFIRM trial was a phase III, randomized, double-blind, placebo-controlled, multicentre trial to study the efficacy and safety of enzalutamide in participants with metastatic castration-resistant prostate cancer who had previously taken docetaxel (4). A total of 1199 adult males, aged 41 to 92 years, were randomized in a 2:1 ratio, where 800 participants received a dose of 160 mg of enzalutamide once a day, 399 participants received a placebo, and all continued on androgen deprivation therapy. Overall survival was 18.4 months for the enzalutamide arm versus 13.6 months for the placebo arm (hazard ratio (HR) for death 0.63, 95% confidence intervals (CI) 0.53 to 0.75; $P < 0.001$). Progression-free survival was 8.3 months for enzalutamide versus 2.9 months for placebo (HR 0.40, 95% CI 0.35 to 0.47; $P < 0.001$). The PREVAIL trial was a

phase III, randomized, double-blind, placebo-controlled clinical trial that investigated enzalutamide as the first-line therapy in 1717 participants with metastatic castration-resistant prostate cancer (5). The study was halted after interim analysis results showed benefit for enzalutamide. Significantly fewer deaths were reported in the enzalutamide arm compared with the placebo arm (28% versus 35%; HR 0.71, 95% CI 0.60 to 0.84; $P < 0.001$). Comparisons of enzalutamide and abiraterone acetate in metastatic castration-resistant prostate cancer Two separate meta-analyses pooled data from eight randomized trials of novel drugs that target the androgen receptor pathway (enzalutamide, abiraterone and orteronel) in participants with metastatic castration-resistant prostate cancer (6,7). The meta-analyses included the AFFIRM and PREVAIL trials, and two trials of enzalutamide versus bicalutamide (TERRAIN and STRIVE). Only AFFIRM and PREVAIL reported overall survival. Since the heterogeneity between the clinical trials was high, a random-effects model was used to calculate HRs for overall survival and progression-free survival. Pooled HRs for overall survival were similarly significant for enzalutamide (HR 0.71, 95% credible interval (CrI) 0.54 to 0.89) and abiraterone (HR 0.78, 95% CrI 0.61 to 0.98). Pooled HRs for progression-free survival favoured enzalutamide (HR 0.36, 95% CrI 0.21 to 0.59) over abiraterone (HR 0.59, 95% CrI 0.35 to 1.00) (7). A retrospective analysis of 2591 and 807 patients with metastatic castration-resistant prostate cancer who started treatment with abiraterone and enzalutamide, respectively, concluded that patients on abiraterone acetate therapy had higher medication adherence and lower risk for dose reduction than those on enzalutamide therapy (8). The authors proposed that improved medication adherence may be associated with longer duration of treatment and better survival. A separate analysis of the same patient population compared the duration of treatment in patients started on abiraterone and enzalutamide (9). At 3 months, patients on abiraterone had fewer discontinuations of metastatic castration-resistant prostate cancer treatments (HR 0.73, 95% CI 0.59 to 0.91; $P = 0.004$) or of any prostate cancer treatment (HR 0.61, 95% CI 0.45 to 0.83; $P = 0.002$) compared with patients on enzalutamide. The median duration of metastatic castration-resistant prostate cancer treatments was 4.1 months longer for patients on abiraterone than those on enzalutamide (18.3 versus 14.2 months; $P < 0.001$). The authors suggested that patients started on abiraterone acetate, compared with those started on enzalutamide, had a longer combined duration of metastatic castration-resistant prostate cancer or prostate cancer treatments. Both of these studies were funded by Janssen Scientific Affairs, the manufacturer of abiraterone. A 2019 phase II, randomized, open-label, crossover trial investigated the optimal sequencing of enzalutamide and abiraterone plus prednisone in participants with metastatic castration-resistant prostate cancer (10). Participants were randomized to receive abiraterone acetate 1000 mg orally once daily + prednisone 5 mg orally twice daily until prostate-specific antigen (PSA) progression followed by crossover to enzalutamide 160 mg orally once daily (group A, 101 participants) or the opposite sequence (group B, 101 participants). Enzalutamide showed activity as a second-line novel androgen receptor pathway inhibitor based on time to second PSA progression. In contrast, abiraterone acetate did not. Median time to second PSA progression was longer in group A than group B (19.3 months versus 15.2 months; HR 0.66, 95% CI 0.45 to 0.97; $P = 0.036$) at a median follow-up of 22.8 months (interquartile range 10.3–33.4). PSA responses to second-line therapy were seen in 36% of participants for enzalutamide and 4% of participants for abiraterone. The application also presented a summary of evidence for enzalutamide in non-metastatic castration-resistant prostate cancer and in hormone-sensitive metastatic prostate cancer. Enzalutamide in non-metastatic castration-resistant prostate cancer The PROSPER trial was a phase III, randomized, double-blind, placebo-controlled trial of enzalutamide plus androgen deprivation therapy in 1401 participants with non-metastatic castration-resistant prostate cancer and with a rapidly rising PSA level (11). Enzalutamide treatment was associated with a 71% lower risk of metastasis or death compared with placebo. The median metastasis-free survival was 36.6 months in the enzalutamide group versus 14.7 months in the placebo group (HR 0.29, 95% CI 0.24 to 0.35; $P < 0.001$). The time to the first use of subsequent antineoplastic therapy was longer with enzalutamide treatment than with placebo (39.6 months versus 17.7 months; HR 0.21, 95% CI 0.17 to 0.26; $P < 0.001$) with subsequent antineoplastic therapy used in 15% of participants in the enzalutamide group and 48% of participants in the placebo group. The final analysis of overall survival in the PROSPER trial (October 2019) showed that treatment with enzalutamide was associated with a 27% lower risk of death than placebo (12). Median overall survival was 67 months (95% CI 64.0 months to not reached) in the enzalutamide arm and 56.3 months (95% CI 54.4 to 63.0 months) in the placebo arm (HR 0.73, 95% CI 0.61 to 0.89; $P = 0.001$).

Torts

The different studies that analysed the efficacy of enzalutamide also reported adverse effects associated with it. In the AFFIRM trial, the incidence of grade 3 or higher adverse events was lower in the enzalutamide arm compared with the placebo arm (45.3% versus 53.1%) (4). Grade 3 or higher fatigue, diarrhoea, musculoskeletal pain, headache and seizures occurred slightly more frequently in participants treated with enzalutamide. Adverse events causing death occurred in 3% and 4% of participants treated with enzalutamide and placebo, respectively. In the PREVAIL trial, grade 3 or higher adverse events were reported in 43% of

participants in the enzalutamide arm compared with 37% of participants in the placebo arm (5). The most commonly reported adverse events occurring at least 2% more frequently in the enzalutamide arm were fatigue, back pain, constipation and arthralgia. The most commonly reported adverse event of grade 3 or higher in the enzalutamide arm was hypertension, which occurred in 7% of participants. In the PROPSE trial, adverse events of grade 3 or higher occurred in 31% of participants receiving enzalutamide compared with 23% of participants receiving placebo (11). The most common grade 3–4 adverse events reported in the crossover trial (10) were hypertension (27% in group A versus 18% in group B) and fatigue (10% in group A versus 4% in group B). Serious adverse events were reported in 15% of participants in group A and 20% of participants in group B. No treatment-related deaths occurred. The meta-analysis by Kang et al. found that the risk of adverse events did not differ between enzalutamide and control arms (7). If grade 3 or higher adverse events occur, or if the patient develops toxicity, enzalutamide should be stopped for 1 week or until symptoms subside to grade 2 or less. Of note, enzalutamide strongly interacts with medicines that inhibit CYP2C8; therefore if co-administration cannot be avoided, the dose of enzalutamide should be reduced to 80 mg once daily for as long as the drug continues to be effective and tolerated.

Preuves supplémentaires

Additional evidence (not in the application) Low-dose abiraterone dosing A 2018 prospective phase II, randomized, non-inferiority trial investigated the activity of low-dose abiraterone (250 mg/day) administered with a low-fat meal compared with standard dose abiraterone (1000 mg/day) administered under fasting conditions in 72 patients with metastatic castration-resistant prostate cancer (13). The primary endpoint was log change in PSA, as a pharmacodynamic biomarker for efficacy. Secondary endpoints included progression-free survival, PSA response ($\geq 50\%$ reduction), change in androgen levels and pharmacokinetics. Low-dose abiraterone was found to be non-inferior to standard-dose abiraterone, according to the predefined non-inferiority criteria. Mean log change in PSA was -1.59 and -1.19 in the low- and standard-dose arms, respectively. PSA response and progression-free survival did not differ between the treatment arms. The decrease in androgen levels was similar in both treatment arms. On the basis of this trial, the low-dose abiraterone with food regimen has been included in the guidelines of the National Comprehensive Cancer Network for prostate cancer as an alternative to the standard-dose treatment regimen (14). A survey of 118 medical oncologists in India reported that 93.2% of practitioners believed that the use of low-dose abiraterone would improve compliance and 100% agreed that it would reduce costs of treatment (15). Just over half (55%) of respondents were prescribing low-dose abiraterone only in limited-resource settings, 6.8% said they had changed their practice after publication of the above-mentioned trial (13) and 28.8% indicated that they would change to low-dose abiraterone prescribing. Only 9.3% of respondents said they would not use low-dose abiraterone. Cost savings to the Indian health care system of changing to low-dose abiraterone were estimated to be US\$ 182 million a year (15).

Rapport coût/efficacité

Many of the cost–benefit studies for enzalutamide have used the price of the originator product. Generic enzalutamide is now also available and as the competition among generic suppliers expands, prices should decline considerably. The application recommends that WHO consider the cost–effectiveness when the drugs are expensive (from the originator) and when the drugs are less expensive (from generic suppliers), and look at reasonable scenarios for generic prices falling over time. The application describes prices for a 40 mg capsule of enzalutamide in different countries, ranging from as high as US\$ 119.18 in the United States of America to as low US\$ 2.31 from generic manufacturers in India. In 2016, Canada-based Biolyse Pharma offered to sell generic enzalutamide to the US Medicare programme for US\$ 3 for a 40 mg tablet, or US\$ 12 for a daily dose of 160 mg. But generic prices could fall much further, given active pharmaceutical ingredient (API) costs. In previous years, before generics were available, some publicly quoted prices for the API enzalutamide were in the range of US\$ 6000 to US\$ 13 000 per kilogram. The National Institute for Health and Care Excellence (NICE) of the United Kingdom of Great Britain and Northern Ireland published technology appraisal guidance for enzalutamide as a second-line treatment for metastatic castration-resistant prostate cancer after docetaxel (16). It recommends enzalutamide as an option for treating adult patients with hormone-relapsed metastatic prostate cancer only if their disease has progressed during or after docetaxel-containing chemotherapy, they have not had treatment with abiraterone and the manufacturer provides enzalutamide with the discount agreed in the patient access scheme. NICE also considered that enzalutamide should be compared with abiraterone for patients who had received one course of chemotherapy, and with best supportive care for patients who had received two or more chemotherapy courses. For patients who had received one course of chemotherapy, the NICE Appraisal Committee noted that the analysis reflecting its preferred assumptions, but not the actual patient access scheme discount for abiraterone, gave an incremental cost–effectiveness ratio (ICER) of £22 600 per quality-

adjusted life year (QALY) gained for enzalutamide compared with abiraterone. The Committee accepted that this ICER was associated with uncertainty, but it was satisfied that it would remain lower than £30 000 per QALY gained on balance. For patients who had received two or more chemotherapy courses, the Committee noted that the ICER estimated by the manufacturer for enzalutamide compared with best supportive care was £45 500 per QALY gained and that the ICER estimated by the Evidence Review Group was £48 000 per QALY gained. The Committee agreed that enzalutamide would be considered an end-of-life treatment as defined by NICE for this subgroup. The magnitude of the additional weight that would need to be assigned to the QALY benefits would justify enzalutamide being recommended as a cost-effective use of National Health Service resources. The Committee did not see sufficient evidence to make any recommendations on the clinical- and cost-effectiveness of sequential use of enzalutamide and abiraterone. As in the 2019 application, a summary of numerous studies that investigated the cost-effectiveness of enzalutamide in various settings was presented. The application anticipates that API costs for enzalutamide will decline over time to between US\$ 300 and US\$ 900 per kilogram, resulting in daily treatment costs as low as US\$ 0.048 to US\$ 0.144.

Directives de l'OMS

Not available

Disponibilité

Originator brand enzalutamide, manufactured by Astellas Pharma, has worldwide regulatory approval. One generic version is available in India.

Autres considérations

Based on the results of the AFFIRM study (4), enzalutamide received a score of 4 on the European Society of Medical Oncology's magnitude of clinical benefit scale (ESMO-MCBS) v1.1 for use as a second-line treatment of metastatic castration-resistant prostate cancer after docetaxel (17). Based on the results of the PREVAIL study (5,18), enzalutamide received a score of 3 on the ESMO-MCBS v1.1 for use as a first-line treatment of metastatic castration-resistant prostate cancer (17). The EML Cancer Medicines Working Group noted that enzalutamide met the criteria for survival benefit and ESMO-MCBS score to be considered for inclusion in the EML and appeared to demonstrate comparable efficacy and safety to abiraterone, which is currently included on the EML. However, no direct trial data are available. Consideration was given to what the added benefit of including enzalutamide on the EML might be, in the absence of any clinical advantage over abiraterone. There is currently no evidence that having both agents available would result in improved access or cost benefits in terms of market competition. However, having options available may provide opportunities for countries to negotiate better prices as part of their national procurement processes. Nevertheless, the Working Group concluded that in view of financial concerns it did not support inclusion of enzalutamide on the EML. The Working Group also noted the evidence on the use of low-dose abiraterone and considered that this was an area where WHO could advocate for this cost-saving approach to treatment.

1. The selection and use of essential medicines. Report of the WHO Expert Committee, 2017 (including the 20th WHO Model List of Essential Medicines and the 6th WHO Model List of Essential Medicines for Children). Geneva: World Health Organization; 2017 (WHO Technical Report Series, No. 1006; <https://apps.who.int/iris/handle/10665/259481>, accessed 2 June 2021).
2. The selection and use of essential medicines. Report of the WHO Expert Committee, 2019 (including the 21st WHO Model List of Essential Medicines and the 7th WHO Model List of Essential Medicines for Children). Geneva: World Health Organization; 2019 (WHO Technical Report Series, No. 1021; <https://apps.who.int/iris/handle/10665/330668>, accessed 10 April 2021).
3. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68(6):394–424.
4. Scher HI, Fizazi K, Saad F, Taplin ME, Sternberg CN, Miller K, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. *N Engl J Med*. 2012;367(13):1187–97.
5. Beer TM, Armstrong AJ, Rathkopf DE, Loriot Y, Sternberg CN, Higano CS, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. *N Engl J Med*. 2014;371(5):424–33.
6. Roviello G, Sigala S, Sandhu S, Bonetta A, Cappelletti MR, Zanotti L, et al. Role of the novel generation of androgen receptor pathway targeted agents in the management of castration-resistant prostate cancer: a literature based meta-analysis of randomized trials. *Eur J Cancer*. 2016;61:111–21.
7. Kang M, Jeong CW, Kwak C, Ku JH, Kim HH. Comparing the clinical efficacy of abiraterone acetate, enzalutamide, and orteronel in patients with metastatic castration-resistant prostate cancer by performing a network meta-analysis of eight randomized controlled trials. *Oncotarget*. 2017;8(35):59690–7.
8. Behl AS, Ellis LA, Pilon D, Xiao Y, Lefebvre P. Medication adherence, treatment patterns, and dose reduction in patients with metastatic castration-resistant prostate cancer receiving abiraterone acetate or enzalutamide. *Am Health Drug Benefits*. 2017;10(6):296–303.
9. Pilon D, Behl AS, Ellis LA, Emond B, Lefebvre P, Dawson NA. Duration of treatment in prostate cancer patients treated with abiraterone acetate or enzalutamide. *J Manag Care Spec Pharm*. 2017;23(2):225–35.

10. Khalaf DJ, Annala M, Taavitsainen S, Finch DL, Oja C, Vergidis J, et al. Optimal sequencing of enzalutamide and abiraterone acetate plus prednisone in metastatic castration-resistant prostate cancer: a multicentre, randomised, open-label, phase 2, crossover trial. *Lancet Oncol.* 2019;20(12):1730–9.
11. Hussain M, Fizazi K, Saad F, Rathenborg P, Shore N, Ferreira U, et al. Enzalutamide in men with nonmetastatic, castration-resistant prostate cancer. *N Engl J Med.* 2018;378(26):2465–74.
12. Sternberg CN, Fizazi K, Saad F, Shore ND, De Giorgi U, Penson DF, et al. Enzalutamide and survival in nonmetastatic, castration-resistant prostate cancer. *N Engl J Med.* 2020;382(23):2197–206.
13. Szmulewitz RZ, Peer CJ, Ibraheem A, Martinez E, Kozloff MF, Carthon B, et al. Prospective international randomized phase ii study of low-dose abiraterone with food versus standard dose abiraterone in castration-resistant prostate cancer. *J Clin Oncol.* 2018;36(14):1389–95.
14. NCCN Clinical Practice Guidelines in Oncology. Prostate cancer. Version 2.2021. Plymouth Meeting: National Comprehensive Cancer Network; 2021 (https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf, accessed 6 April 2021).
15. Patel A, Tannock IF, Srivastava P, Biswas B, Gupta VG, Batra A, et al. Low-dose abiraterone in metastatic prostate cancer: is it practice changing? Facts and facets. *JCO Glob Oncol.* 2020;6:382–6.
16. Enzalutamide for metastatic hormone-relapsed prostate cancer previously treated with a docetaxel-containing regimen. Technology appraisal guidance [TA316]. London: National Institute for Health and Care Excellence; 2014 (<https://www.nice.org.uk/guidance/ta316>, accessed 3 June 2021).
17. ESMO-magnitude of clinical benefit scale. The ESMO-MCBS score card [internet]. Lugarno: European Society for Medical Oncology; 2015 (<https://www.esmo.org/score/cards>, accessed 3 June 2021).
18. Lortol Y, Miller K, Sternberg CN, Fizazi K, De Bono JS, Chowdhury S, et al. Effect of enzalutamide on health-related quality of life, pain, and skeletal-related events in asymptomatic and minimally symptomatic, chemotherapy-naïve patients with metastatic castration-resistant prostate cancer (PREVAIL): results from a randomised, phase 3 trial. *Lancet Oncol.* 2015;16(5):509–21.

