Should docetaxel be standard of care for patients with metastatic hormone-sensitive prostate cancer?

Pro and contra

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Following the results of the TAX-327 study, questions have been raised as to whether administering chemotherapy to men with prostate cancer before symptomatic disease progression when receiving standard hormonal treatment can improve the duration and quality of patient survival. The GETUG-AFU-15 and CHAARTED studies both assessed the efficacy and tolerability of androgen deprivation therapy (ADT) with or without docetaxel in men with metastatic hormone-naïve prostate cancer. Both studies included a mix of patients with de novo metastatic disease (~75%) and patients who developed metastases following treatment of localized disease. A short course of ADT was allowed in both trials prior to accrual. Key differences between the two studies include the number of patients with high-volume metastases (GETUG-AFU-15: 52%; CHAARTED: 65%) and number of docetaxel cycles (GETUG-AFU-15: up to nine cycles; CHAARTED six cycles). Both studies reported an improvement in progression-free survival with docetaxel plus ADT versus ADT alone. The GETUG-AFU-15 did not find a significant difference in the primary end point of overall survival (OS) [hazard ratio (HR) 0.9 [95% confidence interval (CI) 0.7–1.2]; P = 0.44] for ADT plus docetaxel versus ADT alone. The CHAARTED study met the primary end point of OS [HR 0.61 (95% CI 0.47–0.80); P = 0.0003], and in a subset analysis reported the greatest improvement in OS for patients with high-volume disease [HR 0.60 (95% CI 0.45–0.81); P = 0.006]. The following article...

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debates the results from the GETUG-AFU-15 and CHAARTED studies and asks whether medical practice should be changed for patients with metastatic hormone-naive prostate cancer based on the results of one positive study.

**Key words:** de novo metastatic, hormone-naive, prostate, ADT, docetaxel

### introduction

In the Western world, the majority of men, who are diagnosed with localized prostate cancer, have only localized disease at presentation, but ~20% of men with clinically detected disease have *de novo* metastases at diagnosis [1]. In countries, such as India and China, with less access to care the incidence of *de novo* metastatic disease increases dramatically [2, 3]. A registry study carried out between 1998 and 2009 reported limited improvement in overall survival (OS) and disease-specific survival among men with *de novo* metastatic hormone-sensitive prostate cancer [1]. Although *de novo* metastatic prostate cancer is much less common than localized disease at diagnosis, it remains a cause of prostate cancer-related death. In a retrospective pooled analysis of data from two French hospitals following 190 men with prostate cancer for a median 6.8 years, 116 men died as a result of disease progression. Of these 116 men who died from prostate cancer, 44% had localized disease and 56% had *de novo* metastatic disease at diagnosis [4].

Since growth of prostate cancer cells is driven by androgens, androgen deprivation therapy (ADT) is the standard treatment of hormone-naive disease. Despite response to ADT in ~90% of patients, the majority of men progress to castration-resistant prostate cancer (CRPC) within 1–3 years [5, 6]. Hormone-sensitive cells may become castration-resistant through adaptation from androgen-dependent to androgen-independent mechanisms as a consequence of genetic/epigenetic alterations. It is also likely that, at disease onset, a small number of cells are hormone resistant and consequently thrive despite a low androgen environment, such as that created by treatment with ADT. Both adaptation of initially hormone-sensitive cells and clonal proliferation of hormone-resistant cells can drive disease progression and resistance to hormone therapy [7] (Figure 1).

In 2004, following results from the TAX 327 study, docetaxel was approved as first-line chemotherapy for treatment of patients with metastatic CRPC and was the first drug to demonstrate improved survival in this setting. OS with mitoxantrone plus prednisone, docetaxel plus prednisone every 3 weeks and docetaxel every week was 16.3, 19.2 and 17.8 months, respectively [hazard ratio (HR) for death in the 3-weekly docetaxel group versus mitoxantrone group: 0.79; 95% confidence interval (CI) 0.67–0.93; \( P = 0.004 \)] [8, 9]. The SWOG-9916 study also demonstrated improved OS for docetaxel plus estramustine compared with mitoxantrone plus prednisone in such patients [10]. Following approval of docetaxel for first-line treatment of metastatic CRPC (mCRPC), a relevant question is whether administering chemotherapy to patients who are sensitive to hormone therapy can improve the efficacy and tolerability of docetaxel and improve patient outcomes. This review provides an overview of the two clinical trials evaluating ADT plus docetaxel administered to men with metastatic hormone-sensitive prostate cancer. The data are debated to provide provocative arguments as to whether or not the standard of care for these patients should be changed based on the available results.

### GETUG-AFU-15 study

The GETUG-AFU-15 study was the first to assess use of docetaxel in men with metastatic hormone-sensitive prostate cancer [6, 11]. Between October 2004 and December 2008, the study enrolled 385 men with a life expectancy of at least 3 months, metastatic disease and a Karnofsky performance status ≥70%. Use of ADT was permitted for up to 2 months before study entry. Neoadjuvant and adjuvant ADT, chemotherapy or both were permitted providing these treatments were discontinued ≥12 months before study entry. Patients were randomized to receive ADT (orchietomy or luteinizing hormone-releasing hormone agonists) alone (\( n = 193 \)) or ADT plus 75 mg/m² docetaxel every 3 weeks for nine cycles (\( n = 192 \)).

The majority of patients who enrolled in the study were metastatic at diagnosis [71% (272/385)] and the remaining patients developed metastases following treatment of localized disease. A short course of prior ADT was allowed: half of the patients had received 15–60 days of ADT, while others started ADT at or within 2 weeks prior to inclusion (Table 1). After a median 82.9 months follow-up, there was no statistically significant difference in the primary end point of OS between the two treatment groups: median OS was 60.9 (95% CI 46.1–71.4) months in the ADT plus docetaxel versus 46.5 (95% CI 39.1–60.6) months in the ADT-alone treatment arm (HR = 0.9; \( P = 0.44 \)). At the time of final analysis, the data were reassessed in the cohort of patients with high- and low-volume disease (high-volume disease defined as visceral metastases and/or four or more bone metastases with at least one outside of the vertebral column and pelvis), but there was no significant difference in OS for either subgroup (Table 1); however, this post hoc analysis was not sufficiently powered to assess a difference in OS between the subgroups. Although the study did not show any benefit in its

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**Figure 1.** Representation of two models for development of CRPC. In the upper figure all cells are assumed to be initially androgen-sensitive but some of them adapt to become androgen-independent during ADT. In the lower figure androgen-independent cells are assumed to exist in the untreated tumour and ADT leads to selection of androgen-independent clones.
primary end point, there was an improvement in the predefined secondary end points of both biochemical [22.9 months (95% CI 19.6–28.4) versus 12.9 (95% CI 11.9–17.7); HR = 0.72 (95% CI 0.57–0.91); P = 0.005 for ADT plus docetaxel versus ADT alone, respectively] and clinical progression-free survival (PFS) [23.5 (20.5–31.9) months versus 15.4 (12.9–19.8) months; HR = 0.75 (95% CI 0.59–0.94; P = 0.015) for ADT plus docetaxel versus ADT alone, respectively].

The median time to subsequent treatment was 20.0 months in men treated with ADT plus docetaxel compared with 15.4 months in men treated with ADT alone. Subsequent chemotherapy was mostly docetaxel (45% in the ADT plus docetaxel versus 80% in the ADT-alone treatment arms), but a few patients also received cabazitaxel (2% versus 1%). At the time of the primary analysis (2011), a total of 16 patients in the ADT plus docetaxel arm had received a novel endocrine therapy (abiraterone acetate, enzalutamide or orteronel) in a clinical study compared with 29 patients in the ADT-alone arm. Many more patients have now received these active agents, though their number is unknown.

Four potentially treatment-related deaths occurred in the ADT plus docetaxel treatment arm, two of which were neutropenia-related, and the data monitoring committee recommended use of granulocyte colony-stimulating factor (G-CSF). Subsequently, there were no further treatment-related deaths reported. A total of 72 serious adverse events were reported in the group receiving docetaxel with the most frequent being neutropenia (40 (21%)), febrile neutropenia (6 (3%)), abnormal liver function tests (3 (2%)) and neutropenia with infection (2 (1%)). Men treated with ADT alone did not report any serious adverse events.

In summary, the GETUG-AFU-15 study showed improvement in PFS, but not in OS, the primary end point, following treatment with ADT plus docetaxel versus ADT alone.

### CHAARTED study

The more recent CHAARTED study also investigated the addition of docetaxel to ADT in metastatic hormone-sensitive
Annals of Oncology reviews

should results from the CHAARTED study change clinical practice for hormone-sensitive prostate cancer?

pro: the results from the CHAARTED study are practice changing. Results from the CHAARTED study of docetaxel plus ADT for treatment of hormone-sensitive metastatic prostate cancer show the greatest improvement in OS for prostate, or any other metastatic epithelial cancer reported to date. Treatment with docetaxel leads to disease shrinkage and PSA response in at least 50% of men with CRPC, indicating that it is a potent treatment [8, 10]. The mechanisms by which docetaxel may kill prostate cancer cells might include androgen-mediated effects that would target androgen-dependent cells before they can adapt to become androgen independent [13, 14]. Several retrospective analyses have suggested that the efficacy of docetaxel may be compromised when given after novel hormone therapies, although evidence of anticancer activity remained [15–17]. Therefore, by combining docetaxel with ADT—rather than prescribing it sequentially—it may be possible to slow adaptation of prostate cancer cells to development of CRPC, and maximize the efficacy of docetaxel by giving it with rather than after ADT.

Before the CHAARTED study results were presented at international meetings [5, 12], the maximum improvement in median OS reported for currently approved drugs to treat prostate cancer was ∼4 months with HR ≥0.70 in mCRPC compared with almost 14 months with a hazard ratio of 0.61 for metastatic hormone-sensitive disease in the CHAARTED study. The CHAARTED study prespecified a specific patient cohort, had a higher number of high-risk patients (66% versus 22% in GETUG-AFU-15), prescribed fewer cycles of docetaxel (6 versus 9 cycles, CHAARTED and GETUG-AFU-15, respectively) and therefore the results of the two studies should not be compared directly.

The time to both clinical and radiological progression was improved in both the GETUG-AFU-15 and CHAARTED studies. In the absence of an improvement in OS, delaying the onset of symptoms related to CRPC can be regarded as a clinically relevant end point, but this has to be balanced against the toxicity of chemotherapy [5, 6, 12]. At disease progression, 178/319 (55%) patients in the CHAARTED study and 191/385 (50%) patients in the GETUG-AFU-15 study received docetaxel. In the ADT-alone arms of GETUG-AFU-15 and CHAARTED studies, 127/158 (80%) versus 102/136 (75%) of patients received docetaxel at disease progression, respectively. Since >75% of patients in the ADT-alone arms in both studies received docetaxel at disease progression, the efficacy of concurrent versus sequential ADT and chemotherapy was assessed.

Although the incidence of toxicities was initially high in the GETUG-AFU-15 study, the addition of G-CSF improved tolerability of the regimen. Since prostate cancer affects older men, patients with disease progression may be too frail or may have co-morbidities making them ineligible to receive chemotherapy [18, 19]. Therefore, more men are likely to be treated with chemotherapy if it is administered for hormone-sensitive disease than for mCRPC. When prostate cancer patients begin treatment with ADT, they start to experience an improvement in quality of life...
with a reduction in pain and a gain in weight, providing an ideal window of opportunity for the initiation of docetaxel in order to maximize dose intensity and clinical benefit [20, 21]. Giving chemotherapy to patients with hormone-sensitive disease makes it more likely that the patient can receive the planned dose intensity of chemotherapy; conversely in castration-resistant disease, the patient may not tolerate chemotherapy or may require a dose reduction [22, 23].

if the results from the CHAARTED study are valid, which patients with metastatic hormone-sensitive prostate cancer should be treated with ADT plus docetaxel? The results from the CHAARTED study suggest that all patients with metastatic hormone-sensitive prostate cancer judged fit enough to receive chemotherapy might benefit from treatment with docetaxel plus ADT (the overall analysis of survival is positive, not only the subgroup analysis); however, patients with metastatic high-volume, hormone-sensitive disease may experience the greatest OS benefit from treatment with ADT plus docetaxel: in the CHAARTED study, there was a 17-month improvement (49.2 versus 32.2 months; HR = 0.60, P = 0.0006) in OS in the cohort of men with high-volume disease treated with concurrent versus sequential ADT plus docetaxel [5]. In patients with low-volume metastatic disease, the HR is similar (0.63), although the difference is not statistically significant, perhaps due to lack of power or insufficient number of events related to the limited duration of follow-up. Further follow-up is needed to better understand the efficacy of ADT plus docetaxel compared with ADT alone in low-volume prostate cancer in both the GETUG-AFU-15 and CHAARTED studies. Data from STAMPEDE study, a multiarm, randomized phase III controlled clinical study evaluating the combination of ADT with novel treatment strategies, are anticipated and should provide insights as to which patients might benefit from concurrent treatment with the current standard of sequential ADT plus docetaxel.

Other studies are ongoing to address the role of docetaxel in earlier stages of disease, including high-risk localized prostate cancer and biochemical failure postlocal treatment. GETUG-12, a phase III trial evaluating docetaxel in hormone-sensitive high-risk localized prostate cancer has reported relapse-free survival benefit, although follow-up is insufficient to evaluate OS. Several studies are also addressing the role of nonchemotherapy drugs like abiraterone acetate and that of local treatment of the primary prostate cancer in patients with de novo metastatic prostate cancer [24].

Although the definition of high-volume disease in the CHAARTED study has received some criticism, several studies have been completed in patients with high-volume disease (Table 2) with definitions comparable with that used in the CHAARTED study, which has been adopted in the latest analysis of the GETUG-AFU-15 study. Furthermore, a recent study stratified 561 men with mCRPC into groups of ≤4 metastases and ≥5 metastases. Men with four or fewer metastases had a longer PFS and OS compared with men who had ≥5 metastases (HR = 2.0, 95% CI 1.7–2.4; P < 0.001), and data from the most recent analysis of GETUG-AFU-15 support these results [11, 29]. Therefore, the definition of high-volume disease used in the CHAARTED study is appropriate.

A recent subanalysis of the GETUG-AFU-15 study data found that alkaline phosphatase—an indicator of bone disease—was a better prognostic factor than the Glass risk groups used in the study design. Alkaline phosphatase might be used to assess which patients have a high burden of bone metastases and might benefit from aggressive treatment with concurrent ADT plus docetaxel [11, 30].

Selection of patients to be treated with ADT plus docetaxel requires careful consideration. Comorbidity and performance status can affect treatment tolerability, and may lead to severe toxicity or in some cases, death. In the GETUG-AFU-15 study, four deaths occurred during treatment with ADT plus docetaxel, two of which were definitely related to chemotherapy (neutropenic fever); the cause of the other two deaths was more uncertain (pulmonary embolism in one and multiorgan failure in the other). Following these deaths, the addition of G-CSF improved the tolerability of ADT plus docetaxel [6]; however, G-CSF is not reimbursed for treatment of incurable cancer in all countries.

In summary for the pro case: on the basis of the improvements in OS shown in the results from the CHAARTED study, these data should be considered practice changing and ADT plus docetaxel should be standard of care for patients with high-volume metastatic hormone-sensitive prostate cancer, who are judged to be fit enough to receive chemotherapy.

Table 2. Previous definitions of high-volume disease in hormone-sensitive disease

<table>
<thead>
<tr>
<th>Study</th>
<th>Regimen</th>
<th>Patients</th>
<th>Definition of disease spread</th>
<th>OS low- versus high-volume disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>SWOG: S8894 [25]</td>
<td>Orchidectomy ± flutamide</td>
<td>N = 1387</td>
<td>Appendicular skeletal, visceral metastases or both</td>
<td>51 versus 27 months</td>
</tr>
<tr>
<td>SWOG: S8494 [26]</td>
<td>Leuprolide ± flutamide</td>
<td>N = 603</td>
<td>Ribs, long bones, skull, soft tissues except lymph nodes</td>
<td>39 versus 26 months</td>
</tr>
<tr>
<td>SWOG/INTERGROUP [27]</td>
<td>Intermittent versus continuous ADT</td>
<td>N = 3040</td>
<td>Ribs, long bones or visceral metastases</td>
<td>Continuous treatment 6.9 versus 4.4 years</td>
</tr>
<tr>
<td>MD Anderson [28]</td>
<td>ADT ± KA/VE</td>
<td>N = 306</td>
<td>Three or more bone metastases or visceral metastases</td>
<td>7.8 versus 3.75 years</td>
</tr>
</tbody>
</table>

ADT, androgen deprivation therapy; KA/VE, ketoconazole and doxorubicin alternating with vinblastine and estramustine.
contrasts: the results from the CHAARTED study are not practice changing. ADT is effective in hormone-sensitive disease with a relative response rate of 90% and a median 1–2 years duration of response in patients with established metastases [25, 26]. The STAMPEDE study recently reported failure-free and OS of 917 men with de novo metastatic hormone-sensitive disease treated with ADT of 11.2 and 42.1 months, respectively [31]. The GETUG-AFU-15 study was the first study to assess the use of ADT in combination with docetaxel in hormone-naive prostate cancer but did not show a significant difference in the primary end point of OS [6, 11].

Not surprisingly, since two active treatments rather than one are used concurrently, PFS was significantly improved in both the CHAARTED and GETUG-AFU-15 trials with ADT plus docetaxel compared with ADT alone; however, PFS is not a well-defined end point in metastatic hormone-sensitive disease and is not a proven surrogate for OS. OS and quality of life are the most important outcomes for patients.

The population of patients included in the CHAARTED and GETUG-AFU-15 studies has some key differences including total patient number and numbers of patients with high- versus low-risk disease. In addition, both studies included a mix of de novo metastatic patients and patients who had developed metastases following treatment of localized disease and were evolving towards CRPC (localized disease: 25% versus 28%; metastases following treatment of localized disease and were evolving towards CRPC (localized disease: 25% versus 28%; de novo metastatic: 75% versus 71%) [6, 12]. Both studies had a high proportion of men with de novo metastatic disease, which is not typical for the prostate cancer population in Western countries.

The results of GETUG-AFU-15 are more mature than those of CHAARTED, which was reported when median follow-up (29 months) was much shorter than reported median OS (44 and 58 months in the two arms); results were based on Kaplan–Meier projections, and difference in OS between arms of the CHAARTED study will probably decrease, and the HR increase, with further follow-up. Also, if docetaxel is truly effective for men with hormone-sensitive prostate cancer, it is surprising that the more intense schedule of docetaxel used in GETUG-AFU-15 (nine cycles) was not more effective than that used in CHAARTED (six cycles).

The mix of patients might affect the study results, making it difficult to draw robust conclusions regarding which cohort of patients might most benefit from treatment with concurrent ADT plus docetaxel compared with sequential docetaxel. When considering the biological rationale for concurrent treatment, it seems counter-intuitive that combining cytostatic ADT with ‘cell-cycle-dependent’ docetaxel would yield improved outcomes for patients with prostate cancer compared with sequential treatment [32–34], although there is some evidence that the toxicity of docetaxel is mediated, in part, by hormonal mechanisms [13, 14].

Whenever the result of a clinical study is reported, for statistical reasons it is important to evaluate the probability of the result being a false positive or false negative. Experimental scientists have the luxury of being able to repeat important experiments several times, and are well aware that statistically significant and positive results found in one experiment may not be repeatable. The same applies to the ‘clinical experiment’ of a phase III study, but it is much more difficult to repeat large clinical studies, although registration agencies usually require consistent supporting information from a second (often smaller) study before approving a new treatment. The relationship between prior expectations of a positive study (prior probability), and the probability that a subsequent positive result is true (posterior probability) can be addressed by Bayes’ Theorem. Although there are mathematical formulae, Bayes theorem implies that, if the prior probability of a positive result is low, the probability that one positive result is true is not very high, regardless of the apparent P value. Applying this concept to the CHAARTED study, the prior probability of a positive result seems low, based on the biological rationale provided above and the negative result of the similar, but admittedly not identical GETUG-AFU-15 study reporting no improvement in OS with the addition of docetaxel to hormonal therapy. Medical practice should not be changed on the basis of one positive study and the CHAARTED study should not be considered to be practice-changing until and unless further positive studies demonstrating a treatment effect have been reported, although the large effect size means that it is less likely to be a random effect [35].

One of the primary concerns with concurrent treatment is toxicity. At least two and one treatment-related deaths occurred among patients receiving ADT plus docetaxel in the GETUG-AFU-15 and CHAARTED studies, respectively [6, 12]. The tolerability profile and efficacy of a drug in daily clinical practice rarely reflect that reported in a clinical study. Patients enrolled in clinical studies are typically fitter, younger, satisfy restrictive inclusion criteria, receive regular monitoring, have less comorbidity and often have a good prognosis compared with those in daily clinical practice. A study of 438 men with mCRPC treated with 3-weekly full-dose docetaxel at Princess Margaret Cancer Centre had higher rates of febrile neutropenia (9.6% in routine practice versus 0% in patients who received docetaxel in clinical trials and 3% in patients receiving docetaxel in the TAX-327 study) and significantly shorter survival rates in daily clinical practice than those taking part in clinical studies or in the TAX-327 study: 13.6 months (95% CI 12.1–15.1 months) in routine practice and 20.4 months (95% CI 17.4–23.4 months, P = 0.007) within clinical trials, compared with 19.3 months (95% CI 17.6–21.3 months, P < 0.001) in the TAX 327 study [36]. Another study investigated differences between physician and patient reporting of adverse events. Patients from the GETUG-AFU-15 study were asked to complete a 26-symptom questionnaire 3 and 6 months after initiating treatment. Physicians often failed to report treatment-related symptoms that patients reported as disturbing or very disturbing such as hot flashes (50.8% and 48.2% not reported by physicians), joint and muscle pain (89.5% and 88.4%) following 3 and 6 months of treatment [37]. While such effects apply to both arms of the trials, docetaxel adds toxicity and it is likely that if docetaxel was added to ADT in daily clinical practice the improvements in OS would decrease and treatment-related toxicity would increase.

In summary for the contra case: CHAARTED is an important and well-performed study that demonstrates a substantial improvement in OS, but: (i) the trial is immature with limited follow-up, (ii) the full dataset has not yet been subject to peer-review before publication; (iii) its results differ from the similar (admittedly nonidentical) GETUG-AFU-15 study; (iv) the treatment adds substantial (sometimes life-threatening) toxicity in men who could be treated with alternative minimally toxic options; (v) unusual results can occur by chance alone, and it
might be a statistical outlier. The results require confirmation, even for patients with high-volume disease, before concurrent ADT plus docetaxel are adopted as standard treatment of hormone-sensitive metastatic prostate cancer.

conclusions

There is a need to improve treatment outcomes for men with metastatic hormone-naive prostate cancer, and although the data from the CHAARTED study in men with high-volume disease suggest substantial improvement in survival, careful consideration of these and other results are required before medical practice is changed. The pro and contra arguments provided above provide an opportunity to share with patients the decision-making process that is required to optimize treatment of a man presenting with metastatic prostate cancer.

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references

A comprehensive review of lenalidomide therapy for B-cell non-Hodgkin lymphoma

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Lenalidomide is an oral non-chemotherapy immunomodulator with direct and indirect effects on non-Hodgkin lymphoma (NHL) cells and with single-agent activity in relapsed/refractory aggressive and indolent B-cell NHL, including mantle cell lymphoma (MCL), diffuse large B-cell lymphoma, and follicular lymphoma. Based on the pivotal phase II MCL-001 trial of lenalidomide in heavily pretreated patients with relapsed/refractory MCL, lenalidomide was approved by the US Food and Drug Administration for the treatment of relapsed/refractory MCL after failure of two prior therapies, one of which includes bortezomib, at a recommended starting dose of 25 mg on days 1–21 of each 28-day cycle. Lenalidomide enhanced the survival benefit in combination with rituximab in preclinical models, prompting clinical evaluation of the lenalidomide–rituximab (R2) combination. In phase II trials, lenalidomide 20 mg on days 1–21 in combination with different standard-dose rituximab schedules exhibited promising activity in both first-line and relapsed/refractory disease across multiple B-cell NHL subtypes. The feasibility of combining lenalidomide with immunochemotherapy, including R-CHOP and rituximab–bendamustine, has been demonstrated in phase I/II trials. These latter regimens are currently being evaluated in ongoing phase II and III trials. The role of lenalidomide monotherapy and R2 in maintenance therapy is also being examined. Based on available evidence, a comprehensive review of lenalidomide in all treatment phases of B-cell NHL—relapsed/refractory disease, first-line, and maintenance—is presented here.

**Key words:** diffuse large B-cell lymphoma, follicular lymphoma, lenalidomide, mantle cell lymphoma, non-Hodgkin lymphoma, rituximab

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