Enzalutamide in systemic treatment of prostate cancer

ABSTRACT

Prostate cancer is one of the most common tumours in the human population and the most frequently diagnosed among genitourinary tumours. Despite relatively high efficacy of systemic treatment in prostate cancer, it is still one of the most important causes of premature cancer mortality in men. There are several causes of this phenomenon. One of the most important reasons for such are complications of disease spread and localisation of metastatic lesions. Others include complications related to implemented treatment, especially if chemotherapy is being administered. However, it is still the specific biological transformation and tumour evolution into state of resistance to castration (CRPC), which develops with time and under hormonal therapy, that is the major clinical challenge. Progress in the field of molecular biology enabled identification of the crucial role of signal transduction pathway dependent on the androgen receptor (AR) in CRPC. Enzalutamide is the first anti-androgen that interferes with the mechanism of progression related to AR gene amplification and/or AR over-expression. The results of the PREVAIL phase 3 trial in a population of men with metastatic CRPC not previously exposed to docetaxel were presented at ASCO GU 2014. These data prove a significant advantage of enzalutamide use over placebo in regard to all study end-points. Enzalutamide is a drug that prolongs progression-free survival and overall survival in different populations of men with CRPC.

Key words: castration-resistant prostate cancer, androgen receptor, enzalutamide

Introduction

Prostate cancer is one of the most common diagnosed cancers. In Poland it is the second most frequent cancer in men, which accounts for more than 13% of newly diagnosed cases. Its risk increases rapidly after age of 60 years and reaches its maximum at 75 years of age or more (five-fold), and in 2013 it resulted in the diagnosis of 12,000 cases. At the same time, prostate cancer is one of the most important reasons for premature men’s deaths. The incidence rates of prostate cancer increase along with the ageing population and contemporary life-style. Due to available effective treatment modalities, its mortality is not increasing. The serious clinical issue related to prostate cancer is its evolution to castration-resistant status castration-resistant prostate cancer (CRPC). Resistance to castration is a biological stage of the disease that is a consequence related to specific molecular alterations that occur in tumour cells, and the cancer progresses despite effective inhibition of androgen synthesis (serum concentration of testosterone < 50 ng/dL or 1.7 nmol/L). These alteration are, among others, androgen receptor coding gene amplification and/or its over-expression on cancer cells, and structural alterations of receptor protein that lead to its increased activity (after stimuli caused also by physiological and non-specific ligands). One of the most important factors here is the increased ability to convert adrenal androgens or production of de novo of testosterone and
its derivates in tumour tissue with secondary autocrine stimulation [1].

**Mechanism of action of enzalutamide in the context of CRPC molecular biology**

Due to enormous progress in the field of molecular biology of prostate cancer the signal transduction pathway related to androgen receptor (AR) has been identified to be of crucial importance in the development and progression of prostate cancer in sensitivity as well as resistance to castration.

Androgen receptor belongs to family of steroid receptors with transcription factor activity. While inactive it is located in cytosol bound to heat shock proteins (HSPs). Binding to the ligand initiates its dissociation from complex of AR-HSPs, and then AR dimerisation and translocation from cytosol to the cell nucleus. There the activation of androgen-dependent genes occurs, which results in cells proliferation. It has been proven that castration resistance, as a very complex phenomenon by itself, is mainly the effect of testosterone production in tumour tissue and para- and autocrine stimulation of prostate cancer cells and/or molecular changes in AR. These changes may be quantitative and/or qualitative, such as: AR over-expression, prolongation of physiological AR/transcriptional complex with AR half-life time, mutations increasing AR affinity to physiological ligands, mutations increasing AR affinity to ligands which normally do not activate the receptor, and finally — constitutive activating mutations of AR (which are independent from ligand stimuli).

Enzalutamide is the first and the most clinically advanced novel drug of anti-androgen activity used in daily clinical practice. Its affinity to AR is 5–8-fold higher when compared to bicalutamide [2] and, unlike former generations of antiandrogens, it lacks agonistic activity against its the molecular target molecule. It has been designed to effectively inhibit AR activity and to allow the bypassing of the mechanism of tumour progression resulting from the aforementioned molecular alterations of androgen receptor in the phase of castration resistance. The mechanism of action enzalutamide is based on inhibition of the full-length molecule of androgen receptor, inhibition of its translocation from cytosol to cellular nuclei, and inhibition of its transcription activity by modulation of interaction between AR and co-regulatory molecules in promoter regions of AR-dependent genes [3].

**Clinical data**

Enzalutamide in the treatment of patients with castration-resistant prostate cancer

**AFFIRM trial**

Chronologically the first conducted phase III clinical trial with enzalutamide was a study evaluating the efficacy of the drug in a population of patients with metastatic CRPC (mCRPC) after failure of previous treatment with docetaxel (AFFIRM) [4]. The primary end-point of this placebo-controlled trial was the overall survival (OS). Median OS for enzalutamide was 18.4 months (95% confidence interval [95% CI] 17.3–not reached), which was significantly better when compared with the median in the control arm — 13.6 months (95% CI 11.3–15.8 months, hazard ratio [HR] 0.63; 95% CI 0.53–0.75). The superiority of enzalutamide over placebo has been proven for secondary end-points such as: the proportion of patients with reduction in the prostate-specific antigen (PSA) level by 50% or more (54% vs. 2% in control arm); the soft-tissue response rate (29% vs. 4%); time to biochemical (PSA) progression (8.3 vs. 3.0 months); radiographic progression-free survival (rPFS) (8.3 vs. 2.9 months); and time to the first skeletal-related event (16.7 vs. 13.3 months).

**The PREVAIL study**

During the American Society of Clinical Oncology — Genitourinary Annual Meeting 2014 (ASCO-GU) results of the international, randomised, multicentre, phase III, prospective PREVAIL trial were presented [5, 6]. The study evaluated the treatment effect of enzalutamide on OS and rPFS (co-primary end-points) in a population of 1717 chemo-naive men with mCRPC.

Asymptomatic or mildly symptomatic patients were randomised (1:1 ratio) to receive a daily dose of 160 mg of enzalutamide orally or matching placebo. Concomitant steroid use was allowed but not obligatory (finally about 4% patients received steroids in both arms). Patients were enrolled into the study during a two-year period — from September 2010 to September 2012. The study population consisted mainly of white Caucasians (> 76% of patients in both arms), in very good performance status (Eastern Cooperative Oncology Group [ECOG] 0 in 67–69% of study population), with median age 71–72 years, and with diagnosis of high-grade adenocarcinoma of the prostate — ≥ 8 according to Gleason score in 50.6% and 52.4% — for the enzalutamide and the placebo arm, respectively. The mean baseline PSA concentration was 54 ng/mL in the experimental arm and 44 ng/mL in the comparator arm. Bone metastatic lesions were diagnosed at baseline in 85% of patients,
soft-tissue metastatic lesions in 59.3%, and visceral involvement (liver and/or lungs) in 11.2% of patients treated with enzalutamide. Sites of metastatic lesions were well balanced between the study arms.

The study was prematurely halted after the first interim analysis, due to a significant difference between study arms in overall survival in favour of enzalutamide (reduction of risk of death by 30% [HR 0.70; 95% CI 0.59–0.83, \( p = 0.0001 \)] and reduction of the risk of radiographic progression by 81% [HR 0.19; 95% CI 0.15–0.23, \( p = 0.0001 \)]. At that time, after a mean follow-up time of about 22 months, the estimated median OS was 32.4 months (95% CI, 31.5–not reached) in the enzalutamide arm vs. 30.2 months (95% CI, 28–not reached) in patients receiving placebo. The subgroup analysis revealed significant benefit of enzalutamide with respect to median OS in each analysed subpopulation, except patients from North America and patients with visceral metastatic lesions (liver and/or lungs).

At the same time, the median of rPFS for enzalutamide was not reached, but it was 3.9 months (95% CI 3.7–5.4) in the placebo arm. In the subgroup analysis highly significant benefits with respect to rPFS were achieved in every subpopulation (HR < 0.5). The mean time of treatment duration (administered until disease achieved in every subpopulation (HR < 0.5). The mean time of treatment duration (administered until disease progression, death, intolerable toxicity, or consent withdrawal) was three-fold longer in the enzalutamide arm than in the control arm (16.6 vs. 4.6 months).

The results of analysis based on the data collected after a longer time of follow-up were published in 2016: after an additional 20 months for rPFS, nine months for OS and an additional four months for monitoring of adverse events related to the conducted treatment [7]. It was based on a modified population of patients in which 325 men received enzalutamide [158 patients from the arm receiving enzalutamide from the beginning of the study and 68 men who were moved to the enzalutamide therapeutic group after un-blinding of the study (26% of experimental arm) and 167 patients who changed treatment group during cross-over].

Finally, 68% risk reduction for death or radiographic progression during enzalutamide treatment was documented (HR 0.32, 95% CI 0.28–0.37, \( p < 0.0001 \)) as well as risk reduction for death by 23% (HR 0.77, 95% CI 0.67–0.88, \( p = 0.0002 \)). The investigator assessed median rPFS to be 20.0 months (95% CI 18.9–22.1) for enzalutamide and 5.4 months (95% CI 4.1–5.6) for placebo. Median OS for enzalutamide was 35.3 months (95% CI 32.2–not reached) and 31.3 months (95% CI 28.8–34.2) for placebo. The most frequently reported adverse events related to enzalutamide treatment were: fatigue, back pain, constipation, and arthralgia, but these were assessed after exclusion of the population of patients who received enzalutamide after study unblinding and cross-over.

The aforementioned additional analysis confirmed the benefit of treatment with enzalutamide with respect to rPFS and, what is most important, to OS. It should be underlined that this effect has been documented despite the differences between study arms with respect to the type of subsequent anti-tumour treatment with their proven beneficial effect on OS. The subsequent treatment was administered to 81% patients from the control arm and 52% patients from the enzalutamide arm. The treatment with enzalutamide or abiraterone acetate was given to two-fold more men from the comparator arm (64% vs. 30%, respectively).

The secondary end-points in this study were: objective response rate (ORR), including complete response rate (CR) and partial response rate (PR), median time to PSA progression (TTP PSA), time to deterioration of quality of life (based on evaluation performed with FACT-P questionnaire — Functional Assessment of Cancer Therapy — Prostate), and confirmed PSA response rate with reduction of PSA concentration by ≥ 50% and ≥ 90% compared to baseline results.

Objective response rate (according to definitions of RECIST [Response Evaluation Criteria for Solid Tumours]) was 58.8% and 5.0% in the enzalutamide arm and the placebo arm, respectively (\( p < 0.0001 \)). There were 19.7% vs. 1% and 39.1% vs. 3.9% rates of complete and partial remission, respectively. Time to PSA progression was 11.2 months for the experimental arm as compared to 2.8 months for the placebo arm (HR 0.17, \( p < 0.0001 \)), while the confirmed PSA response rate (decline of PSA ≥ 50% and ≥ 90% compared to baseline) was 78.0% and 46.8% in the enzalutamide arm and 3.5% and 1.2% in the placebo arm (\( p < 0.0001 \)). These parameters prove the possibility to delay the decision regarding systemic treatment with chemotherapy by 17 months.

Based on these data enzalutamide was recognised as an effective agent with respect to activity and safety measures. Due to recognition of such large difference between enzalutamide and placebo, the decision to unblind the study was undertaken. As a result of this decision, 167 patients from the control arm crossed-over to the group receiving active treatment.

The TERRAIN trial

In 2016 the results of the TERRAIN study were published [8], and its protocol was prepared more-less simultaneously with the protocols of the PREVAIL and PROSPER trials. In this trial, designed as a prospective, blinded, randomised (assignment in 1:1 ratio), phase II trial, the efficacy and safety of enzalutamide and bicalutamide treatment in a population of men with castration-resistant prostate cancer were compared. The progression of the disease was defined as PSA progression (according to the commonly accepted definition
for biochemical progression in CRPC), progression according to RECIST criteria, or progression of bone metastatic lesions according to PCWG2 (Prostate Cancer Working Group) criteria.

It included men with asymptomatic or mildly symptomatic metastatic disease despite progression on effective pharmacological castration (ADT, androgen-deprivation therapy) enrolled into the study. This status was defined as: BPI-SF (Brief Pain Inventory — Short Form) score as the answer to question no. 3 < 4, no need for use of opioids, performance status according to ECOG (Eastern Cooperative Oncology Group) score system 0–1, and expected time of life at least 12 months. Men with prostate cancer progressing on previously given anti-androgen treatment and chemotherapy and with metastatic lesions in the central nervous system were excluded. The experimental treatment along with ADT was conducted in standard dose for both study drugs (160 mg daily for enzalutamide and 50 mg daily for bicalutamide) until disease progression. Progression was defined as radiographic progression, skeletal-related events (SRE) occurrence, or initiation of subsequent anti-cancer treatment. Stratification took into consideration the method of castration (bilateral orchietomy or use of agonist/antagonist of luteinising hormone-releasing hormone [LHRH]) before or after the diagnosis of metastatic prostate cancer. The primary end-point of the study was progression-free survival (PFS) in the intention-to-treat population. Safety data was analysed in the entire population of patients who received at least one dose of anti-androgen.

Recruitment was performed between March 2011 and July 2013 and a total of 375 men were enrolled (184 and 191 men to receive enzalutamide and bicalutamide, respectively). Median PFS was significantly better in the enzalutamide arm as compared to the bicalutamide arm (15.7 months; 95% CI 11.5–19.4 vs. 5.8 months; 95% CI 4.8–8.1 [HR 0.44; 95% CI 0.34–0.57, p < 0.0001]).

The TERRAIN trial proved the significant advantage of enzalutamide over bicalutamide in respect to radiographic progression-free survival, objective response rate, time to biochemical progression (PSA progression), and biochemical response, regardless of: patients age, performance status at baseline, PSA concentration at baseline, time of initiation of hormonotherapy, or previous treatment with anti-androgen. The authors highlighted the unsupported use of bicalutamide in patients diagnosed with CRPC in clinical practice. This practice is in conflict with the summary of product characteristics for bicalutamide, data indicating only a short-lasting effect of such hormonal manipulation and mechanism of action of this anti-androgen – namely the component of agonistic activity that creates the risk for disease acceleration, especially in the case of AR over-expression as the primary triggering factor of CRPC transformation.

The PROSPER trial

There was a hypothesis, based on previously collected data regarding the efficacy of enzalutamide in the treatment of patients with castration-resistant prostate cancer, that the drug may also offer benefit to CRPC patients without clinically relevant metastatic lesions and rapidly rising serum PSA as the only manifestation of disease progression (PSA DT [PSA doubling time] ≤ 10 months). This is the group of patients with the highest risk of metastatic spread. To verify the aforementioned hypothesis, a prospective phase III trial has been conducted in this population, in which patients were randomly assigned (in a 2:1 ratio) to receive treatment with enzalutamide in a typically administered dose (160 mg daily) or placebo [9]. The primary end-point was metastasis-free survival (MFS), which was defined as the time from the beginning of the treatment until radiographic evidence for cancer progression or patient’s death (even if it occurred before radiographic signs of metastatic spread).

There were 1401 men with median PSA DT of 3.7 months enrolled and randomised to both therapeutic groups. At the time of data cut-off (June 2017), in 219 out of 933 patients treated with enzalutamide (23%) and in 228 out of 468 men receiving placebo (49%) metastatic disease was diagnosed or death occurred. Median metastatic-free survival for enzalutamide and placebo was 36.6 and 14.7 months, respectively (HR for metastatic spread or death 0.29; 95% CI 0.24–0.35, p < 0.001). There was significantly improved time to initiation of subsequent anti-cancer therapy after treatment with enzalutamide as compared to placebo — 39.6 vs. 17.7 months, respectively (HR 0.21, p < 0.001). Such treatment was initiated in 15% of patients from the active drug arm. In the control arm the rate was 48%. Median time to biochemical progression (progression from serum PSA) for enzalutamide was several times longer than for placebo and reached 37.2 months vs. 3.9 months, respectively (HR 0.07, p < 0.001). The disease progression was diagnosed in 22% of men from the experimental arm and 69% of patients in the control arm receiving placebo. At the time of the first interim analysis, with evaluation of overall survival, death was ascertained in 11% and 13% of patients from the enzalutamide and placebo arms, respectively, and these were rates of death in patients in whom no radiographic signs of progression had been detected. It has been proven that these were sudden deaths not related to the conducted anti-cancer treatment, except two cases of men treated with enzalutamide. Analogically, clinically significant adverse events (of grade ≥ 3) were reported in 31% and 23% of patients. It should
be stressed that observations had been performed in a period of time four-times longer than typically set in protocols of clinical trials for follow-up.

In this way, it was proven that the treatment with enzalutamide was safe and resulted in a 71% reduction of relative risk for radiographic progression or death in CRPC patients with no measurable metastatic lesions but dynamic PSA progression.

Safety issues. Toxicity profile and treatment effect on quality of life

After analysis of safety data from the clinical trials cited above, it should be stated that enzalutamide is well tolerated and safe. In the PREVAIL study (enzalutamide in chemo-naive CRPC patients) adverse events occurred frequently (in 96.9% of patients receiving active drug and in 93.2% of patients in the control arm); however, in 42.9% and 37.1%, then in 32% and 26.8%, respectively, these were categorised as severe (G ≥ 3) or serious. At the same time, the mean time to occurrence of G ≥ 3 adverse events in the enzalutamide arm was almost two-times longer as compared to placebo (22.3 vs. 13.3 months). This indicates that most of the observed adverse events were caused by cancer rather than the toxic effect of the drug. It should be highlighted that only in 5.6% and 6.0%, respectively, were adverse events the reason for treatment discontinuation and in 4.2% and 3.8% — the cause of death.

The most common adverse events related to the drug were: fatigue (35.6%), back pain (27%), constipation (22.2%), arthralgia (20.3%), hypertension (13.4%), and elevated serum alanine amino transferase activity (0.9%). Side effects categorised as cardiologic were reported in 10.1% of patients (7.8% in the placebo arm). It should be stressed that in the PREVAIL study there were no previously reported (AFFIRM study) events of seizures that had been raised as being a specific danger related to the drug. The time to deterioration of quality of life (based on FACT-P questionnaire) was twice as long in the experimental arm (11.3 vs. 5.6 months in the control arm).

In 2015 the results of analysis of the aforementioned PREVAIL study regarding enzalutamide health-related quality of life (HRQoL), pain, and SRE were published [10].

HRQoL was assessed at baseline and during the course of treatment with FACT-P (Functional Assessment of Cancer Therapy-Prostate) questionnaires and EQ-5D questionnaires, while pain assessment was based on BPI-SF (Brief Pain Inventory Short Form) questionnaire. The performed evaluation regarded changes of the parameter values as compared to baseline, the relative percentage improvement, and time to deterioration of HRQoL, pain intensity, percentage of patients with SRE, as well as time to SRE in an intention-to-treat population.

The median time on treatment with enzalutamide was 16.6 months (interquartile range [IQR] 10.1–21.1) and 4.6 months (range 2.8–9.7). The performed analysis revealed significant differences in changes in assessments of quality of life (assessment performed at week 61 compared to baseline) in favour of enzalutamide with respect to all end-points of the FACT-P questionnaire and analogue visual scale of EQ-5D. The median time to deterioration of quality of life as assessed with FACT-P questionnaire score was 11.3 months (95% CI 11.1–13.9) in the enzalutamide arm as compared to 5.6 months (5.5–5.6) observed in the placebo group (HR 0.62 [95% CI 0.54–0.72], p < 0.0001). There was a significantly higher rate of patients in the enzalutamide arm as compared to the placebo group reporting significant improvement of quality of life based on FACT-P score (327 [40%] out of 826 vs. 181 [23%] out of 790), EQ-5D index (224 [28%] out of 812 vs. 99 [16%] out of 623), visual analogue scale (218 [27%] out of 803 vs. 106 out of [18%] 603, p < 0.0001 for all assessments). The median time to deterioration of pain (the time of highest pain intensity based on BPI-SF questionnaire) was 5.7 months (95% CI 5.6–5.7) in the experimental arm and 5.6 months (5.4–5.6) in the control arm (HR 0.62 [95% CI 0.53–0.74], p < 0.0001). The events of deterioration of pain in week 13 were less common in the enzalutamide arm compared to the placebo arm (220 [29%] out of 769 vs. 257 [42%] out of 610, p < 0.0001); however, it was not observed for assessment performed in week 25 (225 [32%] out of 705 vs. 135 [38%] out of 360, p = 0.068). At the time of data cut-off events of SRE were reported in 278 (32%) out of 872 patients receiving active drug and 309 (37%) out of 845 patients in the comparator group. The median time to the first SRE was 31.1 months (95% CI 29.5–not reached) and 31.3 months (95% CI 23.9–not reached) in the enzalutamide arm and placebo group (HR 0.72 [95% CI 0.61–0.84], p < 0.0001), respectively.

Based on the data discussed above, it was concluded that the drug offers significant clinical benefit with respect to all anti-cancer activity parameters as well as quality of life parameters in patients treated with enzalutamide.

In the TERRAIN trial, giving the possibility to compare enzalutamide and bicalutamide, there was an observation regarding higher incidence in the enzalutamide arm of such side effects as: fatigue (28% vs. 20%), back pain (19% vs. 18%), and flushes (15% vs. 11%). However, such adverse events as nausea (17% vs. 14% in the enzalutamide arm) and arthralgia (in 16% vs. 10%, respectively) were more frequently related to administration of bicalutamide. Clinically significant (grade ≥ 3) adverse events related to enzalutamide or
bicalutamide were quite rare. One out of 10 deaths observed in the trial was probably related to treatment with enzalutamide (syndrome of generalised systemic inflammatory reaction) as compared to one out of three deaths observed in the bicalutamide arm.

In general, the toxicity profile of enzalutamide favours its use over.

**Summary**

Although castration-resistant prostate cancer remains a lethal disease, recent years have brought spectacular progress in its treatment.

Randomised clinical trials conducted so far indicate several agents that, in a clinically and statistically significant manner, improve overall survival, progression-free survival (biochemical and/or radiographic and/or clinical), as well as quality-of-life in treated patients.

Cytotoxic drugs from the taxanes group were approved at first: docetaxel (based on results from the TAX 327 trial) [11] and cabazitaxel (TROPIC trial) [12]. For years it was docetaxel that dominated in clinical practice, remaining the most effective treatment option in CRPC. However, the important issue regarding chemotherapy, especially in the case of cabazitaxel, is its toxicity.

Recent decades have been a time of intensive experimental efforts with use of anticancer vaccines and other strategies to improve immune reactivity against cancer. To date, the results of only one prospective phase III clinical trial — the IMPACT trial with sipuleucel T in 512 patients with asymptomatic or mildly symptomatic progressive mCRPC [13] — have been published. The drug significantly improves OS with a lack of effect with respect to PFS. However, the use of Sipuleucel T was restricted due to the complicated drug preparation procedure. Moreover, the agent lost its approval in CRPC. Despite this fact, it seems that use of immunotherapy should be restricted to the treatment of patients with (clinically) asymptomatic biochemical progression of prostate cancer and in cases where there is adequate time to generate clonal response against the tumour.

From a practical point of view, the most important targeted drugs approved in CRPC are abiraterone acetate and enzalutamide. These drugs have different toxicity profiles. Enzalutamide, as mentioned above, blocks androgen receptor and inhibits binding to its ligands, while abiraterone acetate inhibits androgen synthesis in gonads, suprarenal glands, and within tumour tissue. In the COU-AA-301 trial (given after chemotherapy with docetaxel) and in the COU-AA-302 trial (chemotherapy-naive patients) abiraterone was characterised by significantly improved median progression-free survival (biochemical, radiographic, and clinical) as well as overall survival.

Enzalutamide plays a similar role in common clinical practice because according to published results of prospective clinical trials evaluating its efficacy and safety in CRPC treatment after chemotherapy (AFFIRM trial) or before chemotherapy (PREVAIL, TERRAIN, PROSPER trials), the drug proved its advantage with respect to all classic and clinically important (from the perspective of clinicians and, what is more important, patients) endpoints. The indirect comparisons and analyses [14] indicate the equipotency of novel agents in terms of their therapeutic effect on overall survival [HR 0.95 (95% CI 0.71–1.26)]. On the other hand, comparative analyses based on meta-analysis of 19 clinical trials [15] suggest superiority of enzalutamide over abiraterone acetate. According to the results presented in the aforementioned publication, enzalutamide offers the possibility to increase the median overall survival by 5.6 months over abiraterone acetate (p < 0.001, HR 0.81) and median PFS by 8.3 months (p < 0.001, HR 0.47) if both drugs are administered before chemotherapy with docetaxel. The differences are even more pronounced if the results are adjusted by tumour histology grade according to Gleason score (to 19.5 months and 14.6 months, respectively). However, the differences in median PPFS are rather small in the case of use of these drugs after docetaxel chemotherapy [1.2 months in favour of enzalutamide (p = 0.02)] with no benefit achieved in terms of median OS.

**References**


