Ludwig Boltzmann Institut
Health Technology Assessment

Horizon Scanning in Oncology
41st Prioritization – 4th quarter 2019

General Information, efficacy and safety data

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Please note:

Within this document you find general information about the drug of interest and the indication it is intended to be used for. Further we have included full text publications of phase III trials, assessing the safety and efficacy of the drugs of interest.

Introduction

As part of the project „Horizon Scanning in Oncology“ (further information can be found here: http://hta.lbg.ac.at/page/horizon-scanning-in-der-onkologie), 9 information sources are scanned frequently to identify emerging anticancer drugs.

Every 3 months, these anticancer therapies are filtered (i.e. in most cases defined as availability of phase III results; for orphan drugs also phase II) to identify drugs at/around the same time as the accompanying drug licensing decisions of the EMA.

An expert panel consisting of oncologists and pharmacists then applies 5 prioritisation criteria to elicit those anti-cancer therapies which might be associated with either a considerable impact on financial resources or a substantial health benefit.

For the 41st prioritisation (10/2019), ten drugs were filtered out of 578 identified and were sent to prioritisation. Of these, three drugs were ranked as ‘highly relevant’ by the expert panel, seven as ‘relevant’ and none as ‘not relevant’. For ‘highly relevant’ drugs, further information including, for example, abstracts of phase III studies and licensing status is contained in this document.

The summary judgements of the expert panel for all prioritised drugs are provided in the following table.

No.	Filtered Drugs – 41st prioritisation 4th quarter 2019	Overall category
1.	Atezolizumab (Tecentriq®) plus bevacizumab versus sunitinib in patients with previously untreated metastatic renal cell carcinoma (RCC)	Relevant
2.	Atezolizumab (Tecentriq®) in combination with carboplatin plus nab-paclitaxel chemotherapy compared with chemotherapy alone as first-line treatment for metastatic non-squamous NSCLC	Highly relevant
3.	Nivolumab (Opdivo®) plus ipilimumab in advanced NSCLC	Highly relevant
4.	Encorafenib, binimetinib (Mektovi®), and cetuximab in BRAF V600E–mutated colorectal cancer (CRC)	Relevant
5.	Cabazitaxel (Jevtana®) versus abiraterone or enzalutamide in metastatic prostate cancer	Relevant
6.	Androgen deprivation therapy (ADT) with enzalutamide (Xtandi®) or placebo in men with metastatic hormone-sensitive prostate cancer (HSPC)	Highly relevant
7.	Niraparib (Zejula®) in patients with newly diagnosed advanced ovarian cancer	Relevant
8.	Veliparib (ABT-888) with first-line chemotherapy and as maintenance therapy in ovarian cancer	Relevant
9.	Pexidartinib (Turalio™) versus placebo for advanced tenosynovial giant cell tumour (TGCT)	Relevant
10.	Quizartinib (AC220) versus salvage chemotherapy in relapsed or refractory FLT3-ITD acute myeloid leukaemia (AML)	Relevant

Lung cancer

Atezolizumab (Tecentriq®) in combination with carboplatin plus nab-paclitaxel chemotherapy compared with chemotherapy alone as first-line treatment for metastatic non-squamous non-small cell lung cancer (NSCLC)

Overview

Drug Description		atezolizumab is a humanised IgG1 anti- programmed death-ligand 1 (PD-L1) monoclonal antibody
Patient Indication		patients with histologically or cytologically confirmed stage IV non-squamous NSCLC who received no previous chemotherapy (for stage IV non-squamous NSCLC)
Incidence in Austria		cancer of the lung, trachea and bronchia: 4,877 newly diagnosed per year (2016), 57.3/100,000/year (European Standard Population, 2013) [1]. NSCLC is the most common type of lung cancer (85-90% of lung cancer cases).
Current standard treatment		✪ for locally advanced or metastatic NSCLC, the aim of treatment is to prolong survival, improve quality of life, and control disease-related symptoms ✪ treatment strategies should take into account the tumour histology and molecular pathology, as well as the patient's age, performance status, comorbidities, and preferences ✪ patients who smoke should be encouraged to cease, as cessation improves treatment outcomes ✪ the following are recommended for first-line treatment of patients with advanced non-squamous (stages IIIB and IV) NSCLC, and no specific modifications to the epidermal growth factor receptor (EGFR) or ALK genes: - PD-L1 under 50% (no gene mutation, fusion protein or biomarker): o atezolizumab plus bevacizumab, carboplatin and paclitaxel o pembrolizumab, with pemetrexed and platinum chemotherapy o pemetrexed in combination with cisplatin - PD-L1 50% or over (no gene mutation, fusion protein or biomarker): o pembrolizumab, with pemetrexed and platinum chemotherapy o pembrolizumab [2, 3].
Ongoing Phase III		NCT02367781 (IMpower130) until 12/2019 NCT03991403 until 12/2022 NCT02366143 until 12/2019 NCT02657434 until 11/2019 NCT02409342 until 04/2022 [4]
Approval status for this indication	**EMA**	-
	FDA	-
Approval status for other indications	**EMA**	according to product information (03/2019), atezolizumab is indicated: ✪ as monotherapy for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma (UC): - after prior platinum-containing chemotherapy, or - who are considered cisplatin ineligible, and whose tumours have a PD-L1 expression ≥ 5%

		✪ in combination with bevacizumab, paclitaxel and carboplatin for the first-line treatment of adult patients with metastatic non-squamous NSCLC. In patients with EGFR mutant or ALK-positive NSCLC, atezolizumab, in combination with bevacizumab, paclitaxel and carboplatin, is indicated only after failure of appropriate targeted therapies ✪ as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic NSCLC after prior chemotherapy. Patients with EGFR mutant or ALK-positive NSCLC should also have received targeted therapies before receiving atezolizumab [5].
	FDA	according to label information (03/2019), atezolizumab is indicated in: ✪ UC: - for the treatment of adult patients with locally advanced or metastatic UC who: o are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 (PD-L1 stained tumor-infiltrating immune cells covering ≥ 5% of the tumor area), as determined by an FDA-approved test, or o are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status, or o have disease progression during or following any platinum-containing chemotherapy, or within 12 months of neoadjuvant or adjuvant chemotherapy (accelerated approval) ✪ NSCLC: - in combination with bevacizumab, paclitaxel, and carboplatin, for the first-line treatment of adult patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations - for the treatment of adult patients with metastatic NSCLC who have disease progression during or following platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for NSCLC harboring these aberrations prior to receiving atezolizumab ✪ Triple-Negative Breast Cancer (TNBC): - in combination with paclitaxel protein-bound for the treatment of adult patients with unresectable locally advanced or metastatic TNBC whose tumors express PD-L1 (PD-L1 stained tumor-infiltrating IC of any intensity covering ≥ 1% of the tumor area), as determined by an FDA approved test (accelerated approval) ✪ Small Cell Lung Cancer (SCLC): - in combination with carboplatin and etoposide, for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC) [6].
Costs		Tecentriq® 1200 mg concentrate for solution for infusion = € 4,799.20 (ex-factory price) [7] IMpower130 trial patients received induction atezolizumab treatment (1200 mg intravenously every 3 weeks) in combination with chemotherapy comprising carboplatin plus nab-paclitaxel or chemotherapy alone according to the same schedule for four or six 21-day cycles. The number of induction treatment cycles (four or six) was at the discretion of the investigator and determined or documented before randomisation. Following induction, patients in the atezolizumab plus chemotherapy group received maintenance treatment with 1200 mg intravenous atezolizumab and patients in the chemotherapy group received best supportive care or pemetrexed switch maintenance therapy, at the investigator′s discretion. In

	the atezolizumab plus chemotherapy group, maintenance therapy was administered until investigator-assessed loss of clinical benefit or toxicity. Induction treatment: 1 cycle = € 4,799.20, 4 cycles € 19,196.8, 6 cycles € 28,795.2 -> + costs for chemotherapy Maintenance phase: 1200 mg atezolizumab/every 3 weeks = € 4,799.20/one dose. Mean treatment duration in the atezolizumab plus chemotherapy group was 8.9 months for atezolizumab -> approx. 12 doses = € 57,590.4

1.1.1 Published articles (PubMed):

Lancet Oncology; available online May 20, 2019 (West et al.): *"Atezolizumab in combination with carboplatin plus nab-paclitaxel chemotherapy compared with chemotherapy alone as first-line treatment for metastatic non-squamous non-small-cell lung cancer (IMpower130): a multicentre, randomised, open-label, phase 3 trial" [8]*

Background
Atezolizumab (a monoclonal antibody against PD-L1), which restores anticancer immunity, improved overall survival in patients with previously treated non-small-cell lung cancer and also showed clinical benefit when combined with chemotherapy as first-line treatment of non-small-cell lung cancer. IMpower130 aimed to assess the efficacy and safety of atezolizumab plus chemotherapy versus chemotherapy alone as first-line therapy for non-squamous non-small-cell lung cancer.

Methods
IMpower130 was a multicentre, randomised, open-label, phase 3 study done in 131 centres across eight countries (the USA, Canada, Belgium, France, Germany, Italy, Spain, and Israel). Eligible patients were aged 18 years or older, and had histologically or cytologically confirmed stage IV non-squamous non-small-cell lung cancer, an Eastern Cooperative Oncology Group performance status of 0 or 1, and received no previous chemotherapy for stage IV disease. Patients were randomly assigned (2:1; permuted block [block size of six] with an interactive voice or web response system) to receive atezolizumab (1200 mg intravenously every 3 weeks) plus chemotherapy (carboplatin [area under the curve 6 mg/mL per min every 3 weeks] plus nab-paclitaxel [100 mg/m² intravenously every week]) or chemotherapy alone for four or six 21-day cycles followed by maintenance therapy. Stratification factors were sex, baseline liver metastases, and PD-L1 tumour expression. Co-primary endpoints were investigator-assessed progression-free survival and overall survival in the intention-to-treat wild-type (ie, *EGFR*wt and *ALK*wt) population. The safety population included patients who received at least one dose of the study drug. This study is registered with ClinicalTrials.gov, number NCT02367781.

Findings
Between April 16, 2015, and Feb 13, 2017, 724 patients were randomly assigned and 723 were included in the intention-to-treat population (one patient died before randomisation, but was assigned to a treatment group; this patient was excluded from the intention-to-treat population) of the atezolizumab plus chemotherapy group (483 patients in the intention-to-treat population and 451 patients in the intention-to-treat wild-type population) or the chemotherapy group (240 patients in the intention-to-treat population and 228 patients in the intention-to-treat wild-type population). Median follow-up in the intention-to-treat wild-type population was similar between groups (18.5 months [IQR 15.2–23.6] in the atezolizumab plus chemotherapy group and 19·2 months [15.4–23.0] in the chemotherapy group). In the intention-to-treat wild-type population, there were significant improvements in median overall survival (18.6 months [95% CI 16.0–21.2] in the atezolizumab plus chemotherapy group and 13.9 months [12.0–18.7] in the chemotherapy group; stratified hazard ratio [HR] 0.79 [95% CI 0.64–0.98]; p=0.033) and median progression-free survival (7.0 months [95% CI 6.2–7.3] in the atezolizumab plus chemotherapy group and 5.5 months [4.4–5.9] in the chemotherapy group; stratified HR 0.64 [95% CI 0.54–0.77]; p<0.0001]). The most common grade 3 or worse treatment-related adverse events were neutropenia (152 [32%] of 473 in the atezolizumab plus chemotherapy group vs. 65 [28%] of 232 in the chemotherapy group), anaemia (138 [29%] vs. 47 [20%]), and decreased neutrophil count (57 [12%] vs. 19 [8%]). Treatment-related serious adverse events were reported in 112 (24%) of 473 patients in the atezolizumab plus chemotherapy group and 30 (13%) of 232 patients in the chemotherapy group. Treatment-related (any treatment) deaths

occurred in eight (2%) of 473 patients in the atezolizumab plus chemotherapy group and one (<1%) of 232 patients in the chemotherapy group.

Interpretation
IMpower130 showed a significant and clinically meaningful improvement in overall survival and a significant improvement in progression-free survival with atezolizumab plus chemotherapy versus chemotherapy as first-line treatment of patients with stage IV non-squamous non-small-cell lung cancer and no *ALK* or *EGFR* mutations. No new safety signals were identified. This study supports the benefit of atezolizumab, in combination with platinum-based chemotherapy, as first-line treatment of metastatic non-small-cell lung cancer.

Nivolumab (Opdivo®) plus ipilimumab in advanced NSCLC

Overview

Drug Description		nivolumab is a a fully human anti–PD-1 antibody
Patient Indication		patients with squamous or non-squamous stage IV or recurrent NSCLC
Incidence in Austria		cancer of the lung, trachea and bronchia: 4,877 newly diagnosed per year (2016), 57.3/100,000/year (European Standard Population, 2013) [1]. NSCLC is the most common type of lung cancer (85-90% of lung cancer cases).
Current standard treatment		✪ for locally advanced or metastatic NSCLC, the aim of treatment is to prolong survival, improve quality of life, and control disease-related symptoms ✪ treatment strategies should take into account the tumour histology and molecular pathology, as well as the patient's age, performance status, comorbidities, and preferences ✪ patients who smoke should be encouraged to cease, as cessation improves treatment outcomes ✪ the following are recommended for first-line treatment of patients with advanced non-squamous (stages IIIB and IV) NSCLC, and no specific modifications to the EGFR or ALK genes: - PD-L1 under 50% (no gene mutation, fusion protein or biomarker): o Atezolizumab plus bevacizumab, carboplatin and paclitaxel o pembrolizumab, with pemetrexed and platinum chemotherapy o pemetrexed in combination with cisplatin - PD-L1 50% or over (no gene mutation, fusion protein or biomarker): o pembrolizumab, with pemetrexed and platinum chemotherapy o pembrolizumab [2, 3].
Ongoing Phase III		NCT02477826 (CheckMate 227) until 08/2022 NCT03469960 until 05/2023 NCT03351361 until 06/2022 NCT03215706 until 11/2020 [4]
Approval status for this indication	**EMA**	-
	FDA	-
Approval status for other indications	**EMA**	according to product information (10/2019), nivolumab is indicated in: ✪ melanoma: o as monotherapy or in combination with ipilimumab for the treatment of advanced (unresectable or metastatic) melanoma in adults. Relative to nivolumab monotherapy, an increase in progression-free survival (PFS) and overall survival (OS) for the combination of nivolumab with ipilimumab is established only in patients with low tumour PD-L1 expression. ✪ adjuvant treatment of melanoma: o as monotherapy for the adjuvant treatment of adults with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection ✪ NSCLC: o as monotherapy for the treatment of locally advanced or metastatic NSCLC after prior chemotherapy in adults.

		✪ renal cell carcinoma (RCC): o as monotherapy is for the treatment of advanced RCC after prior therapy in adults o nivolumab in combination with ipilimumab is indicated for the first-line treatment of adult patients with intermediate/poor-risk advanced RCC ✪ classical Hodgkin Lymphoma (cHL): o as monotherapy for the treatment of adult patients with relapsed or refractory cHL after autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin ✪ squamous cell cancer of the head and neck (SCCHN): o as monotherapy is for the treatment of recurrent or metastatic SCCHN in adults progressing on or after platinum-based therapy ✪ UC: o as monotherapy is for the treatment of locally advanced unresectable or metastatic UC in adults after failure of prior platinum-containing therapy [5].
	FDA	according to label information (09/2019) nivolumab is indicated for the treatment of: ✪ patients with unresectable or metastatic melanoma, as a single agent or in combination with ipilimumab ✪ patients with melanoma with lymph node involvement or metastatic disease who have undergone complete resection, in the adjuvant setting ✪ patients with metastatic NSCLC and progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving nivolumab ✪ patients with metastatic SCLC with progression after platinum-based chemotherapy and at least one other line of therapy ✪ patients with advanced RCC who have received prior anti-angiogenic therapy ✪ patients with intermediate or poor risk, previously untreated advanced RCC, in combination with ipilimumab ✪ adult patients with cHL that has relapsed or progressed after: o autologous hematopoietic stem cell transplantation (HSCT) and brentuximab vedotin, or o 3 or more lines of systemic therapy that includes autologous HSCT ✪ patients with recurrent or metastatic SCCHN with disease progression on or after a platinum-based therapy ✪ patients with locally advanced or metastatic UC who: o have disease progression during or following platinum-containing chemotherapy o have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy ✪ adult and paediatric (12 years and older) patients with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic CRC that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, as a single agent or in combination with ipilimumab ✪ patients with hepatocellular carcinoma who have been previously treated with sorafenib [6].
Costs		4 ml Opdivo® concentrate for solution for infusion 10 mg/ml = € 572.00 (ex-factory price) 10 ml Opdivo® concentrate for solution for infusion 10 mg/ml = € 1430.00 (ex-factory price) [7]

	CheckMate 227 trial patients in Part 1a were randomly assigned in a 1:1:1 ratio to receive nivolumab (at a dose of 3 mg per kilogram of body weight every 2 weeks) plus ipilimumab, nivolumab monotherapy (240 mg every 2 weeks), or platinum-doublet chemotherapy every 3 weeks for up to four cycles. In Part 1b, patients were randomly assigned in a 1:1:1 ratio to receive nivolumab plus ipilimumab, nivolumab (360 mg every 3 weeks) plus platinum-doublet chemotherapy (every 3 weeks for up to four cycles), or platinum-doublet chemotherapy alone (every 3 weeks for up to four cycles). Assuming an average body weight of 70 kg, 210 mg of nivolumab would be needed for one dose = € 3,432.00

1.1.2 Published articles (PubMed):

NEJM; available online September 28, 2019 (Hellmann et al.): *"Nivolumab plus Ipilimumab in Advanced Non–Small-Cell Lung Cancer" [9]*

Background
In an early-phase study involving patients with advanced non–small-cell lung cancer (NSCLC), the response rate was better with nivolumab plus ipilimumab than with nivolumab monotherapy, particularly among patients with tumors that expressed programmed death ligand 1 (PD-L1). Data are needed to assess the long-term benefit of nivolumab plus ipilimumab in patients with NSCLC.

Methods
In this open-label, phase 3 trial, we randomly assigned patients with stage IV or recurrent NSCLC and a PD-L1 expression level of 1% or more in a 1:1:1 ratio to receive nivolumab plus ipilimumab, nivolumab alone, or chemotherapy. The patients who had a PD-L1 expression level of less than 1% were randomly assigned in a 1:1:1 ratio to receive nivolumab plus ipilimumab, nivolumab plus chemotherapy, or chemotherapy alone. All the patients had received no previous chemotherapy. The primary end point reported here was overall survival with nivolumab plus ipilimumab as compared with chemotherapy in patients with a PD-L1 expression level of 1% or more.

Findings
Among the patients with a PD-L1 expression level of 1% or more, the median duration of overall survival was 17.1 months (95% confidence interval [CI], 15.0 to 20.1) with nivolumab plus ipilimumab and 14.9 months (95% CI, 12.7 to 16.7) with chemotherapy (P = 0.007), with 2-year overall survival rates of 40.0% and 32.8%, respectively. The median duration of response was 23.2 months with nivolumab plus ipilimumab and 6.2 months with chemotherapy. The overall survival benefit was also observed in patients with a PD-L1 expression level of less than 1%, with a median duration of 17.2 months (95% CI, 12.8 to 22.0) with nivolumab plus ipilimumab and 12.2 months (95% CI, 9.2 to 14.3) with chemotherapy. Among all the patients in the trial, the median duration of overall survival was 17.1 months (95% CI, 15.2 to 19.9) with nivolumab plus ipilimumab and 13.9 months (95% CI, 12.2 to 15.1) with chemotherapy. The percentage of patients with grade 3 or 4 treatment-related adverse events in the overall population was 32.8% with nivolumab plus ipilimumab and 36.0% with chemotherapy.

Interpretation
First-line treatment with nivolumab plus ipilimumab resulted in a longer duration of overall survival than did chemotherapy in patients with NSCLC, independent of the PD-L1 expression level. No new safety concerns emerged with longer follow-up. (Funded by Bristol-Myers Squibb and Ono Pharmaceutical; CheckMate 227 ClinicalTrials.gov number, NCT02477826.)

Prostate cancer

Androgen deprivation therapy (ADT) with enzalutamide (Xtandi®) or placebo in men with metastatic hormone-sensitive prostate cancer (HSPC)

Overview

Drug Description		enzalutamide is an androgen-receptor inhibitor
Patient Indication		patients with patients metastatic HSPC, either de novo or after recurrence after prior local therapy.
Incidence in Austria		prostate cancer: 5,245 newly diagnosed per year (2016), 138.3/100,000 men/year (European Standard Population, 2013) [10]
Current standard treatment		❁ for men with mHSPC, NICE guidelines recommend: - bilateral orchidectomy or continuous LHRH agonist therapy - anti-androgen monotherapy with bicalutamide; or - combined androgen blockade (not first-line) ❁ NICE has also published an evidence summary for the off-label use of docetaxel (in combination with ADT) for the treatment of mHSPC. Docetaxel is licensed in the UK for the treatment of metastatic hormone-resistant prostate cancer. A draft of an update to the NICE guideline for prostate cancer recommends offering docetaxel to people who do not have significant comorbidities, starting treatment within 12 weeks of starting ADT, to be administered in six 3-weekly cycles with or without daily prednisolone. ❁ although not currently recommended by NICE, abiraterone is licensed for the treatment of newly diagnosed, high risk mHSPC in adult men in combination with ADT plus prednisone or prednisolone [11].
Ongoing Phase III		NCT02677896 (ARCHES) until 12/2023 NCT04076059 (China ARCHES) until 09/2023 [4]
Approval status for this indication	**EMA**	-
	FDA	-
Approval status for other indications	**EMA**	according to product information (01/2019), enzalutamide is indicated for: ❁ the treatment of adult men with high-risk non-metastatic castration-resistant prostate cancer (CRPC) ❁ the treatment of adult men with metastatic CRPC who are asymptomatic or mildly symptomatic after failure of ADT in whom chemotherapy is not yet clinically indicated ❁ the treatment of adult men with metastatic CRPC whose disease has progressed on or after docetaxel therapy [5].
	FDA	according to label information (07/2018), enzalutamide is indicated for: ❁ the treatment of patients with CRPC [6].
Costs		4x28 Xtandi® 40 mg soft capsules = € 2,854.95 (ex-factory price) [7] ARCHES trial patients in the enzalutamide + ADT group received enzalutamide at a dose of 160 mg/day; median treatment duration in this group was 12.8 months. According to this trial regimen, 28 days of enzalutamide treatment would cost € 2,854.95 (12.8 months -> € 36,543.36). In addition, costs for ADT incur.

1.1.3 Published articles (PubMed):

Journal of Clinical Oncology; available online June 6, 2019 (Armstrong et al.): *"ARCHES: A Randomized, Phase III Study of Androgen Deprivation Therapy With Enzalutamide or Placebo in Men With Metastatic Hormone-Sensitive Prostate Cancer" [12]*

Background
Enzalutamide, a potent androgen-receptor inhibitor, has demonstrated significant benefits in metastatic and nonmetastatic castration-resistant prostate cancer. We evaluated the efficacy and safety of enzalutamide in metastatic hormone-sensitive prostate cancer (mHSPC).

Methods
ARCHES (ClinicalTrials.gov identifier: NCT02677896) is a multinational, double-blind, phase III trial, wherein 1,150 men with mHSPC were randomly assigned 1:1 to enzalutamide (160 mg/day) or placebo, plus androgen deprivation therapy (ADT), stratified by disease volume and prior docetaxel chemotherapy. The primary end point was radiographic progression-free survival.

Findings
As of October 14, 2018, the risk of radiographic progression or death was significantly reduced with enzalutamide plus ADT versus placebo plus ADT (hazard ratio, 0.39; 95% CI, 0.30 to 0.50; P < .001; median not reached v 19.0 months). Similar significant improvements in radiographic progression-free survival were reported in prespecified subgroups on the basis of disease volume and prior docetaxel therapy. Enzalutamide plus ADT significantly reduced the risk of prostate-specific antigen progression, initiation of new antineoplastic therapy, first symptomatic skeletal event, castration resistance, and reduced risk of pain progression. More men achieved an undetectable prostate-specific antigen level and/or an objective response with enzalutamide plus ADT (P < .001). Patients in both treatment groups reported a high baseline level of quality of life, which was maintained over time. Grade 3 or greater adverse events were reported in 24.3% of patients who received enzalutamide plus ADT versus 25.6% of patients who received placebo plus ADT, with no unexpected adverse events.

Interpretation
Enzalutamide with ADT significantly reduced the risk of metastatic progression or death over time versus placebo plus ADT in men with mHSPC, including those with low-volume disease and/or prior docetaxel, with a safety analysis that seems consistent with the safety profile of enzalutamide in previous clinical trials in castration-resistant prostate cancer.

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