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# ASCO 2017

## ASCO 2017: Abiraterone — a new, highly effective therapy for patients with castration-sensitive prostate cancer — results of STAMPEDE and LATITUDE studies

The STAMPEDE study evaluated the efficacy of abiraterone in high-risk patients with locally advanced or metastatic prostate cancer with concomitant androgen-deprivation therapy (ADT). In total 1917 patients were randomly assigned (1:1) to a control group receiving only ADT or a study group receiving ADT in combination with abiraterone + prednisone (P, 5 mg daily). Both groups were well balanced for age and disease stage (52% comprised patients with metastatic disease, 20% patients with N+/NXM0, 28% patients with N0M0), 95% of patients were newly diagnosed, and median PSA was 53 ng/ml. Standard therapy included ADT used for at least two years. Prostate irradiation was used in all patients without nodal involvement and distal metastases, and in patients with N+ feature it was recommended. The duration of treatment was dependent on disease severity and possible radical radiotherapy. Patients with M1 and patients who did not undergo radical radiotherapy continued treatment to clinical, radiological, or biochemical (PSA) progression. The remaining patients were treated for up to two years or disease progression. The primary endpoint was overall survival (OS). After median follow-up of 40 months significant reduction (by 47%) of death relative risk in the abiraterone arm was indicated [HR = 0.63 (95% CI 0.52–0.76; $p = 0.115 \times 10^{-7}$)]; three-year survival rate was 83% (ADT + AA) *vs*. 76% (ADT). A statistically highly significant reduction (by 71%) of treatment failure relative risk [HR = 0.29 (95% CI 0.25–0.34)] was also noticed in the study group as compared to the control group.

To the LATITUDE study, in total, 1199 patients were included with newly diagnosed (up to three months prior to randomisation), hormone-naive metastatic prostate cancer. This population included high-risk patients with ECOG performance status 0–2 (at least two out of three risk factors: Gleason score ≥ 8, at least three bone metastases, measurable visceral metastases). Efficacy of early addition of AA + P to ADT was assessed. Similarly to the STAMPEDE study, patients were randomly assigned to receive ADT + AA or ADT + placebo. The primary endpoints were OS and radiographic progression-free survival (rPFS). In the first interim analysis with a median follow-up of 30.4 months significant reduction of death risk by 38% (HR = 0.62, 95% CI: 0.51–0.76, $p < 0.0001$), radiological progression by 53%, and biochemical progression by 70% was shown. In view of such positive results the independent steering committee recommended unblinding the study and crossing patients to ADT+AA+P.

In the STAMPEDE study, grade 3–5 adverse events were observed in 33% and 47% of patients treated with ADT or ADT+AA, respectively.

The most common grade 3/4 adverse events reported in the LATITUDE study included: hypertension (20.3% of patients in study group *vs.* 10.0% in the control group), hypokalaemia (10.4% *vs*. 1.3%), increased ALT (5.5% *vs.* 1.3%), and AST (4.4% *vs*. 1.5%) level.

### Comment

Three years after presentation of the results of the CHAARTED study and two years after presentation of the STAMPED study results, which showed a significant reduction (by approximately 40%) in the relative death risk in patients with advanced, hormone-sensitive prostate cancer after use of docetaxel in combination with ADT versus ADT alone, two additional studies have confirmed the efficacy of ADT when combined with abiraterone. Comparable effect of combined hormone therapy (ADT + AA) with chemo-hormone-therapy confirms an importance of intensive systemic treatment in prostate cancer patients with poor prognosis (mainly with M+ or N+ feature). Comparison of the effectiveness of both treatment strategies (chemo-hormone-therapy and combined hormone therapy) can only be indirect. Both therapy patterns have a similar effect on OS, with potentially higher ADT + AA benefits in terms of delayed ra-

diological and biochemical progression (which is logical considering long-term combined hormone therapy *vs.* six cycles of chemotherapy). Indirect analysis of side effects does not indicate a better safety profile for either of the aforementioned therapeutic options. Therefore, it should be stated that abiraterone + ADT could be considered as a further option for treating hormone-naive patients with advanced prostate cancer, and possible use of such a treatment depends on the general status of the patient, the patient's preferences, and reimbursement.

## Sources


1. James ND, De Bono JS, Spears MR, et al. Adding abiraterone for men with high-risk prostate cancer (PCa) starting long-term androgen deprivation therapy (ADT): Survival results from STAMPEDE (NCT00268476). J Clin Oncol. 2017; 35 (suppl; abstr LBA5003); http://abstracts.asco.org/199/AbstView_199_186716.html.
2. Fizazi K, Tran N, Fein LE, et al. LATITUDE: A phase III, double-blind, randomized trial of androgen deprivation therapy with abiraterone acetate plus prednisone or placebos in newly diagnosed high-risk metastatic hormone-naive prostate cancer. J Clin Oncol. 2017; 35 (suppl; abstr LBA3); http://abstracts.asco.org/199/AbstView_199_181729.html.


# Capecitabine — a new standard of adjuvant treatment for patients with biliary tract cancer — results from the BILCAP study

Between 2006 and 2014, in total 447 patients with biliary cancer (CCA, cholangiocarcinoma) or gallbladder cancer (including patients after hepatic and pancreatic resection) with normal drainage of the biliary tract, and in good performance status (ECOG ≤ 2), were included into the BILCAP study. Patients were randomly assigned (1:1) to capecitabine at the dose of 1250 mg/m$^2$ (up to eight cycles) on days 1–14 of the 21-day cycle (n = 223) or observation (n = 224). The study included patients from 44 centres in the UK. The primary endpoint was overall survival time (OS) in the intention-to-treat (ITT) population. Preliminary analysis was performed after a 24-month follow-up. Median patients' age was 63 years. The performance status of the majority of patients (97%) according ECOG scale was 0–1. Localisation of primary lesion was as follows: liver — 19%, hepatic hilus — 28%, extrahepatic location — 35%, and gallbladder (with muscular layer infiltration) — 18%. R0 resections were performed in 62% of patients and R1 resection in 38%. 46% of patients were node-negative. Over 80% of living patients were observed for at least 36 months. Based on the analysis performed in the ITT population (n = 447), median OS was 51 months (95% CI 35–59) in the group receiving capecitabine in the adjuvant setting as compared to 36 months (95% CI 30–45) in the group undergoing only observation (control group) [HR=0.80 (95% CI 0.63–1.04; p = 0.097)]. Based on *per-protocol* analysis (n = 210, control group n = 220), the median OS was 53 months (95% CI 40–NR) in the study group and 36 months (95% CI 30–44) in the control group [HR 0.75 (95% CI 0.58–0.97; p = 0.028)]. Median relapse-free time (RFT) in the ITT population was 25 months (95% CI 19–37) in the study group and 18 months (95% CI 13–28) in the control group. The toxicity profile as regards grade 3 and 4 adverse events was consistent with expectations.

## Comment

The results of the BILCAP study finally reinforce the new, long-awaited standard for management of patients with biliary tract cancer after surgery with radical intention. Until now, many patients, mainly with N+ feature, received adjuvant chemotherapy based on a combination of gemcitabine and cisplatin as a standard of palliative treatment in patients with advanced biliary cancer. *Per protocol* analysis showed significant reduction of relative death risk by 25% in patients receiving capecitabine as compared to observation alone. This is very important information highlighting the importance of proper patient qualification to adjuvant treatment. It has been shown in patients with pancreatic cancer, receiving adjuvant treatment in the ESPAC-3 study, that the efficacy of adjuvant therapy is not dependent on rapid onset of treatment, but rather on administration of full-dose scheduled treatment. Thus, with regard to available data from the BILCAP study (ITT *vs. per-protocol* analysis), it should be assumed that the key to achieving the presumed adjuvant chemotherapy effect is to start treatment when the patient's performance status makes possible to complete a planned six-month chemotherapy with capecitabine.

## Sources


1. Primrose JN, Fox R, Palmer DH, et al. Adjuvant capecitabine for biliary tract cancer: The BILCAP randomized study. J Clin Oncol. 2017; 35 (suppl; abstr 4006); http://abstracts.asco.org/199/AbstView_199_186869.html.
2. Valle JW, Palmer D, Jackson R, et al. Optimal duration and timing of adjuvant chemotherapy after definitive surgery for ductal adenocarcinoma of the pancreas: Ongoing lessons from the ESPAC-3 Study. J Clin Oncol. 2014; 32: 504–512.

## ASCO 2017: Short-term, three-month adjuvant chemotherapy — a potential new standard in adjuvant treatment of some patients with stage III colorectal cancer — IDEA analysis

On 4th June at the plenary session of the ASCO 2017 Congress the results of a prospective, combined analysis of six concurrent phase III clinical trials on the duration of adjuvant treatment of patients with colorectal cancer were presented. The SCOT, TOSCA, Alliance/SWOG 80702, IDEA France (GERCOR/PRODIGE), ACHIEVE, and HORG studies evaluated whether three-month adjuvant treatment in patients with stage III colorectal cancer (13% T1–2, 66% T3, 21% T4, 72% N1, 28% N2) with oxaliplatin-based protocols (FOLFOX or XELOX) is non-inferior as compared to the same standard adjuvant treatment administered for six months. The primary endpoint was disease-free survival (DFS). The study involved 12,834 patients included in the six aforementioned studies in 12 countries between 2007 and 2015. After a median follow-up of 39 months, there were 3263 DFS events. The three-year disease-free survival rate was 74.6% for three-month adjuvant treatment and 75.5% for six-month adjuvant treatment [HR = 1.07 (95% CI 1.00–1.15)], whilst in the group of patients treated with FOLFOX regimen HR for DFS for comparison three *vs*. six months was 1.16 (95% CI 1.06–1.26) and for treatment with XELOX regimen 0.95 (95% CI 0.85–1.06). HR for DFS for comparison three *vs.* six months was 1.01 (95% CI 0.90–1.12) in patients with stage T1–3 N1 and 1.12 (95% CI 1.03–1.23) for patients with cancer T4 or N2. Neurotoxicity of at least grade 3 according to the CTCAE criteria was observed more frequently in patients treated for six months (16% *vs*. 3% for FOLFOX, 9% *vs.* 3% for XELOX, $p < 0.0001$).

### Comment

The results of the IDEA analysis are changing the standard of care for most patients with stage III colon cancer. For the first time, it has been unequivocally shown that three-month adjuvant doublet chemotherapy is not only as effective as standard six-month treatment, but also significantly less toxic. The ability to reduce (by more than 70%) the risk of neurotoxicity while maintaining high efficacy of adjuvant therapy is an enormous achievement. The perspective of good quality of life, in the context of significant reductions in the risk of relapse after oxaliplatin-based doublet chemotherapy, should translate into more effective adjuvant therapy for patients who have been treated suboptimally, mainly due to their age and therapy duration. However, it should be highlighted that three-month adjuvant chemotherapy is not a treatment dedicated to all patients in stage III colorectal cancer. It should be used only in patients with pT1–3 and pN1 feature. Taking into account all current literature data — MOSAIC, NO16968, and IDEA studies, XELOX seems to be an optimal three-month adjuvant chemotherapy regimen for patients with stage III colon cancer.

### Source

1. Shi Q, Sobrero AF, Shields AF, et al. Prospective pooled analysis of six phase III trials investigating duration of adjuvant (adjuv) oxaliplatin-based therapy (3 vs 6 months) for patients (pts) with stage III colon cancer (CC): The IDEA (International Duration Evaluation of Adjuvant chemotherapy) collaboration. J Clin Oncol 2017; 35 (suppl; abstr LBA1); http://abstracts.asco.org/199/AbstView_199_188616.html.

## ASCO 2017: Olaparib — a new therapeutic option for patients with HER2-negative metastatic breast cancer and *BRCA* mutation — OlympiAD, phase III tiral

During the plenary session of the ASCO 2017 Congress and in the New England Journal of Medicine the results of the OlympiAD (NCT02000622) study were presented, evaluating the efficacy of oral PARP inhibitor, olaparib, in patients with metastatic HER2-negative breast cancer, being *BRCA* mutation carriers. An open-label phase III clinical study enrolled 302 patients who had previously undergone no more than two palliative chemotherapy lines (median age 44 years, 71% of patients previously treated with chemotherapy, 28% with platinum-based chemotherapy, and 50% with triple-negative phenotype). Patients were randomly assigned (2:1) to receive olaparib (300 mg twice daily, orally, n = 205) or chemotherapy (depending on the investigator choice: capecitabine 2500 mg/m$^2$ orally on days 1–14 of a 21-day cycle or vinorelbine 30 mg/m$^2$ intravenously on days 1 and 8 of a 21-day cycle, or eribulin 1.4 mg/m$^2$ intravenously on days 1 and 8 of a 21-day cycle, n = 91). Treatment was continued to objective progression (RECIST 1.1) or unacceptable toxicity. The primary endpoint was progression-free survival (PFS) assessed within independent blinded central evaluation.

During the first interim analysis (median follow-up of 14 months) olaparib significantly reduced progression risk by 42% in the study group, prolonging time to progression (TTP) by approximately three months (HR

0.58, 95% CI 0.43–0.80; p = 0.0009; median PFS — 7.0 and 4.2 months, respectively). Objective response rate (ORR) in the olaparib group was 59.9% compared to 28.8% in the chemotherapy arm. Time to second progression was also prolonged (HR 0.57, 95% CI 0.40–0.83), and quality of life (assessed by the EORTC-QLQ-C30 questionnaire) of patients treated with olaparib was significantly (p = 0.0035) improved as compared to patients receiving chemotherapy. The safety profile of olaparib was similar to that observed in earlier studies with this drug. Adverse events of at least grade 3 were reported in 36.6% of patients receiving olaparib and 50.5% of patients undergoing chemotherapy.

## Comment

Approximately 3% of breast cancers occur in patients with *BRCA* mutations (in the Polish population mainly *BRCA1*). In carriers of such mutations breast cancers develop at a much younger age, are more aggressive, and most often are triple-negative. Thus, the treatment of patients with breast cancer developing on the basis of *BRCA* gene mutation is much more difficult because until now chemotherapy has been the only option of systemic therapy in clinical practice. *BRCA* mutation damages one of the two basic DNA repair mechanisms in a cell. Therefore, survival of a tumour cell with a non-functional BRCA protein and with continuous DNA damaging depends on proper functioning of PARP-dependent repair mechanisms poly (ADP-ribose) polymerase (PARP). PARP inhibitor leads to death of cancer cells by inhibiting critical DNA repair mechanism in *BRCA* mutant cell. Efficacy of olaparib has already been demonstrated in patients with ovarian cancer with *BRCA* mutation. The results of the OlympiAD study reinforce the role of olaparib as the first targeted therapy for patients with breast cancer developing on the basis of *BRCA* hereditary mutation. This is particularly important in the context of triple-negative tumours, which in the Polish population account for the vast majority of cancers developing in carriers of the *BRCA1* mutation.

## Sources


1. Robson ME, Im S, Senkus E, et al. OlympiAD: Phase III trial of olaparib monotherapy versus chemotherapy for patients (pts) with HER2-negative metastatic breast cancer (mBC) and a germline BRCA mutation (gBRCAm). J Clin Oncol. 2017; 35 (suppl; abstr LBA4); http://abstracts.asco.org/199/AbstView_199_186720.html.
2. Robson M, Im SA, Senkus E, et al. Olaparib for metastatic breast cancer in patients with a germline BRCA mutation. N Engl J Med. 2017 Jun 4; DOI: 10.1056/NEJMoa1706450.


# ASCO 2017: Single-dose radiotherapy is an effective treatment in patients with metastatic spinal canal compression (MSCC) — SCORAD study

The SCORAD study compared the efficacy of single-dose radiation with standard treatment in patients with spinal compression due to metastatic cancer (metastatic spinal canal compression, MSCC). Between 2008 and 2016 in total 688 patients at 43 centres in the UK and four in Australia were randomly assigned to irradiation with a single 8-Gy fraction (n = 345) or to irradiation with 20-Gy dose in five fractions (n = 343). Patients with prostate cancer (44%), lung cancer (18%), gastrointestinal cancers (11%), and breast cancer (11%) were involved in the study. There was comparable efficacy and safety of both radiotherapy regimens. The difference in median OS was not significant and median OS reached 12.4 weeks in the group with a single dose of RT *vs*. 13.7 weeks in the group receiving five fractions [HR = 1.02 (95% CI 0.86–1.21), p = 0.81). Tolerability of treatment was also similar — the incidence of grade 3 and 4 adverse events was 20.6% in patients after one fraction and 20.4% in patients treated with standard irradiation; grade 1 and 2 adverse events occurred less commonly in patients with one dose of RT (51.0% *vs*. 56.9%).

## Comment

The continuously increasing population of patients with chronic, generalised cancers is resulting in a growing number of patients requiring local palliative oncological treatment. Extended indications to radiotherapy, and an increasing number of procedures and patients requiring irradiation are an increasingly serious problem, particularly in the context of relatively slow growth in the number of specialists and insufficient development of infrastructure and equipment. Spinal canal compression is an emergency in oncology that requires urgent local treatment. Possible five-fold reduction in the duration of irradiation (from five days to one day) not only improves patients' comfort, but at the same time, without worsening local effects, improves the availability of radiotherapy for other patients requiring this type of cancer treatment.

## Source


1. Hoskin P, Misra V, Hopkins K, et al. SCORAD III: Randomized noninferiority phase III trial of single-dose radiotherapy (RT) compared to multifraction RT in patients (pts) with metastatic spinal canal compression (SCC). J Clin Oncol. 2017; 35 (suppl; abstr LBA10004); http://abstracts.asco.org/199/AbstView_199_186591.html.