A Phase 3 Randomized, Double-blind, Multi-center Study of Adjuvant Nivolumab versus Placebo in Subjects with High Risk Invasive Urothelial Carcinoma

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This study has been transitioned to CTIS with ID 2022-500630-29-00 check the CTIS register for the current data. We hypothesise that treatment with nivolumab will extend disease-free survival, compared with placebo, as adjuvant therapy in all...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Bladder and bladder neck disorders (excl calculi)
Study type	Interventional

Summary

ID

NL-OMON47449

Source
ToetsingOnline

Brief title
CheckMate 274

Condition

- Bladder and bladder neck disorders (excl calculi)

Synonym
Fully resected Bladder Cancer & Adjuvant therapy

Research involving
Human

Sponsors and support

Primary sponsor: Bristol-Myers Squibb
Source(s) of monetary or material Support: Bristol-Myers Squibb (Sponsor)

Intervention

Keyword: Bladder Cancer, Cisplatin, Fully resected, Nivolumab

Outcome measures

Primary outcome

To compare the disease free survival (DFS) for nivolumab versus placebo in Subjects with tumours expressing PD-L1 (>1% membranous staining in tumour cells) and All randomized subjects

Secondary outcome

• To compare non-urothelial tract recurrence free survival (NUTRFS) for nivolumab versus placebo in subjects with tumours expressing PD-L1 (>1% membranous staining in tumour cells) and all randomized subjects

• To compare the disease specific survival (DSS) for nivolumab and placebo in subjects with tumours expressing PD-L1 (>1% membranous staining in tumour cells) and all randomized subjects

• To compare the overall survival (OS) for nivolumab versus placebo in subjects with tumours expressing PD-L1 (>1% membranous staining in tumour cells) and all randomized subjects.

Study description

Background summary

CA209-274 is a phase 3 randomized, double-blind, placebo controlled study of

adjuvant nivolumab in subjects who have undergone radical resection of invasive urothelial carcinoma (IUC) originating in the bladder or upper urinary tract (renal pelvis or ureter) and are at high risk of recurrence.

Subjects may have received neo-adjuvant cisplatin based chemotherapy; subjects who underwent radical resection without neo-adjuvant cisplatin chemotherapy must be ineligible for or refusing adjuvant cisplatin based chemotherapy.

Patients with invasive disease at radical resection of IUC are at high risk of recurrence and are in need additional treatment options. Most urothelial tumours originate in the urinary bladder (90%) or upper urinary tract (~9-10% in renal pelvis/ureter). Invasive tumours in the upper urinary tract are typically managed with radical resection alone (radical nephroureterectomy [RNU] or radical ureterectomy [RU]).

Standard of care treatment for muscle invasive bladder cancer (MIBC) is cisplatin based neo-adjuvant chemotherapy followed by radical cystectomy. Patients who have invasive residual disease at radical resection and have not received neo-adjuvant cisplatin may go on to receive adjuvant cisplatin based chemotherapy which, despite not having shown definitive clinical benefit, is used in 20% of patients undergoing radical cystectomy in the US. Up to 60% of patients who undergo radical cystectomy are not candidates for adjuvant cisplatin based chemotherapy because they received neoadjuvant chemotherapy or they are cisplatin ineligible.

This population has a significant unmet need as there are no treatment options available to help reduce the risk of recurrence and improve survival. The checkpoint inhibition approach is attractive in this setting considering the lack of effective, available treatment options and the positive preliminary results with PD-1/PD-L1 blockade in advanced bladder cancer.

Study objective

This study has been transitioned to CTIS with ID 2022-500630-29-00 check the CTIS register for the current data.

We hypothesise that treatment with nivolumab will extend disease-free survival, compared with placebo, as adjuvant therapy in all randomized patients and in patients with PD-L1 expressing tumours (membranous staining in > 1%) who are at high risk of recurrence after undergoing radical resection of invasive urothelial carcinoma (IUC).

Study design

Approximately 700 subjects will be randomized in a blinded fashion 1:1 to nivolumab versus placebo within 120 days of radical resection and stratified by

nodal status (N+ vs. N0/x with < 10 nodes removed vs. N0 with < 10 nodes removed), tumour PD-L1 expression (>1%, < 1%/ indeterminate), and use of cisplatin neo-adjuvant chemotherapy.

Treatment, in the absence of prohibitive toxicities, disease recurrence/progression, or withdrawal of consent will be continued for a maximum of 1 year. The co-primary endpoint is DFS in subjects with tumours expressing PD-L1 at >1% (2.5% alpha) and in all randomized subjects (2.5% alpha).

The overall sample size is set up to allow a clinically meaningful effect to be statistically significant at alpha level of 2.5% (two-sided) in the all randomized group. Even weighting of the alpha distribution between DFS assessment in all randomized (N = 700) and PD-L1 expressers (~ 46% of the all randomized population) reflects an assumption of enrichment of nivolumab efficacy in the PD-L1 expressers.

At the time of the original the original study design, the anticipated prevalence of PD-L1+ was 46% and the PD-L1-ve population in the study was capped at 54%. During the execution of the study the PD-L1+ rate was approximately 42%, for this reason in the revised protocol 04 the cap was removed to make the study sample representative of the study population. Hence, it is anticipated that the final population will include approximately 42% of patients who are PD-L1+.

The number of randomised subjects with upper tract urothelial cancer (UTUC; renal pelvis and ureter cancers) will be capped at approximately 20% (128 subjects) of total global enrolment. Once approximately 128 subjects with UTUC are randomised, only subjects with bladder cancer will be enrolled.

Following discontinuation of study therapy, subjects will be followed for survival and those that have not had a non-urothelial tract recurrence will be followed for recurrence.

Intervention

Nivolumab monotherapy or placebo, administered IV at 240 mg, every 2 weeks until recurrence, unacceptable toxicity or discontinuation from study for a maximum of 1 year.

Study burden and risks

As part of the trial, patients will be expected to attend multiple clinic visits where they will undergo physical examinations, vital sign measurements including blood tests for safety assessment. Pregnancy testing (for females of child bearing potential) and monitoring for adverse events.

Subjects will be evaluated for presence or continued lack of tumour until non-urothelial tract recurrence as below:
• Non-cystoscopy tumour imaging assessments (CT of chest, and CT or MRI of abdomen, pelvis, upper urinary tract, and all known sites of disease) will occur;
o Every 12 weeks from the date of first dose to Week 96
o Then every 16 weeks from Week 96 to Week 160
o Then every 24 weeks until non-urothelial tract recurrence or treatment is discontinued (whichever occurs later) for a maximum of 5 years

• Cystoscopy in subjects with upper GU primaries who still have bladder intact will occur (in addition to other tumour imaging assessments;
o Every 12 weeks from the date of first dose to Week 48
o Then every 24 weeks from Week 48 to Week 96
o Then every 48 weeks until non-urothelial tract recurrence or treatment is discontinued (whichever occurs later) for a maximum of 5 years.

Blood will also be collected at certain visits for research purposes (PK, immunogenicity and biomarker studies). The frequency of visits and number of procedures carried out during this trial would typically be considered over and above standard of care. The procedures are carried out by trained medical professionals and every effort will be made to minimise any risks or discomfort to the patient. Treatment for cancer often has side effects, including some that are life threatening.

An independent Data Monitoring Committee (DMC) will be utilised in this trial to ensure that the safety data is reviewed during the study.

New Immune system targeted therapy (immunotherapies) such as Nivolumab could potentially provide clinical benefit and improvement in the outcome for patients with this disease (disease improvement and improvement in survival). However, with all experimental drugs and clinical trials, there are known and unknown risks. Study medication and procedure related risks are outlined in the patient information sheet in detail to ensure the patients are fully informed before agreeing to take part in the study.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. All subjects must be status post radical surgical resection (R0) for Invasive Urothelial Carcinoma performed within 120 days prior to randomization.Subjects with carcinoma in situ in ureteral or urethral margins are eligible for study entry , 2. All subjects must have pathologic evidence of urothelial carcinoma (originating in bladder, ureter, or renal pelvis) at high risk of recurrence based on pathological staging of radical surgery tissue(see protocol for more details), 3. Dominant component of histology needs to be urothelial carcinoma or transitional cell carcinoma. Foci of varied histologies (e.g. minor variants) are accepted, 4. All subjects must have disease-free status defined as no clinical or radiographic evidence of recurrence of disease documented by a complete physical examination and imaging studies within 4 weeks of randomization. Subjects with equivocal nodes less than 15 mm in short axis may be eligible after discussion with BMS medical monitor. All suspect lesions identified during screening radiographic procedures should be discussed with the Medical Monitor prior to randomisation.
i)Imaging studies must include CT of chest and CT or MRI of abdomen, pelvis, and all known sites of resected disease including cystoscopy in subjects with upper GU primaries who still have bladder intact. Brain imaging (MRI except where contraindicated in which CT scan is acceptable) must be completed within 4 weeks prior to randomization for subjects with clinical suspicion of CNS disease.

ii)Subjects who are found to have high risk NMIBC at the time of screening are not eligible for study entry. Patients with low-risk papillary lesions may enter the study if rendered free of disease at cystoscopy. Subjects with intermediate-risk NMIBC may enter the study if intravesical chemotherapy or BCG is not required. Screening cystoscopy may occur within 60 days of randomisation and is encouraged to be done prior to other imaging. Any suspect lesions seen of cystoscopy should be biopsied to rule-out the possibility of high-risk lesions., Low-risk NMIBC is defined as low-gread lesions or papillary urothelial neoplasms of low malignant potential (PUNLMP: WHO/ISP 2004 grading system), or TaG1 lesions (WHO 1973 grading system) that are less than 3cm in diameter.
High-risk NMIBC is defined as any T1 lesion, and lesion containing carcinoma in situ (CIS) either alone or concomitantly with papillary disease (e.g. CIS with Ta/T1 lesions0, and any Ta high-grade (TaHG; WHO/ISUP 2004 grading system) or TaG3 (WHO 1973 grading system) lesion.
Intermediate-risk NMIBC is defined as lesions not meeting the criteria of high-risk or low-risk., 5. Tumor tissue from the most recently resected site of disease (preferable) or from the transurethral resection that, yielded the initial muscle invasive diagnosis must be provided for biomarker analyses. In order to be randomized, a subject must have a PD-L1 expression level classification (>=1%, < 1%, indeterminate) as determined by the central lab. , 6. Life expectancy >= 6 months, 7. Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 or 1. Subjects who have not received cisplatin based neoadjuvant chemotherapy and are considered ineligible for cisplatin adjuvant chemotherapy, may enter the study with ECOG PS 2 (see Appendix 2), 8. Prior surgery that required general anesthesia must be completed at least 4 weeks before study drug administration. Surgery requiring local/epidural anesthesia must be completed at least 72 hours before study drug administration. TUR must be completed 14 days before randomisation

Exclusion criteria

1. Partial cystectomy in the setting of bladder cancer primary tumor or partial nephrectomy in the setting of renal pelvis primary tumor., 2. Adjuvant systemic or radiation therapy for urothelial or prostatic carcinoma following radical surgical resection of urothelial carcinoma., 3. Any serious or uncontrolled medical disorder that, in the opinion of the investigator, may increase the risk associated with study participation or study drug administration, impair the ability of the subject to receive protocol therapy, or interfere with the interpretation of study results., 4. Prior malignancy active within the previous 3 years except for locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, prostate cancer with evidence of undetectable Prostate Specific Antigen (PSA) or carcinoma in situ of the prostate, cervix or breast. Patients with known history of recent metastatic urothelial carcinoma will be excluded, 5. Subjects with active,

known or suspected autoimmune disease. Subjects with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll., 6. Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids and adrenal replacement doses > 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease., 7. Subjects with history of life-threatening toxicity related to prior immune therapy (eg. anti-CTLA-4 or anti-PD-1/PD-L1 treatment or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways) except those that are unlikely to re-occur with standard countermeasures (eg, hormone replacement after adrenal crisis)., 8. All toxicities attributed to prior anti-cancer therapy other than nephropathy, neuropathy, hearing loss, alopecia and fatigue must have resolved to Grade 1 (NCI CTCAE version 4) or baseline before administration of study drug. Subjects with toxicities attributed to prior anti-cancer therapy which are not expected to resolve and result in long lasting sequelae, such as neuropathy after platinum based therapy, are permitted to enroll. See protocol inclusion criterion 2) i) (5) for renal function eligibility. Neuropathy must have resolved to Grade 2 (NCI CTCAE version 4)., 9. Treatment with any chemotherapy, radiation therapy, biologics for cancer, intravesical therapy, or investigational therapy within 28 days of first administration of study treatment.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Health services research

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	30-12-2016
Enrollment:	16
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Opdivo
Generic name:	Nivolumab

Ethics review

Approved WMO Date:	15-02-2016
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-07-2016
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-02-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-03-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-11-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-12-2017
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-06-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-08-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-01-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-02-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-04-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-05-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-05-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-11-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-04-2020
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-05-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-08-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	30-09-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-11-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-02-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-09-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-04-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EU-CTR	CTIS2022-500630-29-00
EudraCT	EUCTR2014-003626-40-NL
CCMO	NL55662.018.16