A Phase 1b, Multicenter, Open Label Study Evaluating Safety, Tolerability and Preliminary Efficacy of GemRIS 225 mg in Subjects with Muscle-Invasive Transitional Cell Carcinoma of the Bladder

Published: 28-11-2017
Last updated: 04-01-2025

- Evaluate the safety and tolerability of up to 2 dosing cycles of GemRIS for up to 7 days per dosing cycle - Evaluate the pharmacokinetics of gemcitabine and 2',2'-difluorodeoxyuridine (dFdU, a gemcitabine-related metabolite) exposure in...

Ethical review	Approved WMO
Status	Completed
Health condition type	Renal and urinary tract neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON46772

Source
ToetsingOnline

Brief title
Phase 1b Safety and Tolerability Study of GemRIS in MIBC

Condition

- Renal and urinary tract neoplasms malignant and unspecified

Synonym
Muscle-Invasive Bladder Cancer

Research involving

Human

Sponsors and support

Primary sponsor: TARIS Biomedical LLC
Source(s) of monetary or material Support: TARIS Biomedical LLC

Intervention

Keyword: GemRIS, Urothelial Cell Carcinoma

Outcome measures

Primary outcome

Safety of GemRIS upon insertion, two 7-day exposures and removals.

Secondary outcome

- Tolerability of GemRIS upon insertion, two 7-day exposures and removals.

- Pharmacokinetic analysis of blood (in both Arms 1 and 2), urine (in Arm 1 only), and nodes (Arm 2 only).

- Assessment of pathologic complete response (pCR) rate at RC defined as the proportion of subjects with pathologically confirmed T0 disease in the post-treatment surgical specimen.

- Assessment of pathologic partial response (pPR) rate at RC defined as the proportion of subjects with pathologically confirmed disease post-treatment surgical specimen (includes Ta, T1, Tis).

- Assessment of tumor cell death as identified histologically by evidence of tumor cell apoptosis and cytotoxicity at the time of RC in the bladder and locoregional lymph nodes.

Study description

Background summary

Worldwide, the prevalence of bladder cancer is estimated to be 2.7 million patients. In the developing world, the majority of tumors involving the bladder are squamous cell carcinoma. However, in the developed world, 90% of cases are transitional cell carcinoma. In the US in 2015, the prevalence of bladder cancer is more than 500,000 with over 70,000 new cases diagnosed and approximately 16,000 deaths. Since 1975, the incidence of bladder cancer has increased by nearly 40%, largely due to the aging population and its concomitant disease-specific risk factors, including exposure to cigarettes and industrial carcinogens. Although the majority of patients present with non-muscle invasive disease, 20-40% present with or develop invasive disease, which may be life-threatening. Radical Cystectomy (RC) remains the standard of care in the management of this cancer, yet this surgery is associated with considerable morbidity. Systemic neoadjuvant chemotherapy has demonstrated an association with an improvement in overall survival. Specifically, pathologic partial and complete responses, as well as negative lymph node status, correlate with meaningful disease-free and overall survival benefits. Systemic chemotherapy, however, is associated with significant toxicity, and up to 80% of patients may refuse or be ineligible for neoadjuvant and/or adjuvant regimens. There is a significant unmet need for targeted intravesical delivery of neoadjuvant cytotoxic agents prior to cystectomy.

Preliminary findings from the first 10 subjects in this study (all of whom had residual, grossly visible, exophytic, papillary tumor measuring no less than 3 cm in size at the start of treatment), revealed that 5 (50%) had no tumor grossly visible post treatment, at the time of RC. Of the 5 remaining subjects with visible tumor at RC, 3 (20%) exhibited a marked reduction in exophytic tumor volume and the remaining 2 (20%) (each of whom had pT3 stage disease) had persistent macroscopic disease. Four of 10 subjects (40%) had no histologic evidence of residual muscle-invasive disease at cystectomy (one subject with a complete pathologic response (pT0). Unexpectedly, 9 of 10 subjects (90%) lacked any nodal involvement at the time of RC.

Study objective

- Evaluate the safety and tolerability of up to 2 dosing cycles of GemRIS for up to 7 days per dosing cycle
- Evaluate the pharmacokinetics of gemcitabine and 2',2'-difluorodeoxyuridine (dFdU, a gemcitabine-related metabolite) exposure in urine and plasma during both 7-day dosing cycles of GemRIS and the 14-recovery between the two GemRIS dosing cycles in Arm 1, and in Arm 2 to evaluate exposure in plasma at the beginning and the end of each dosing cycle and exposure in lymph nodes at the time of RC
- Determine the preliminary anti-tumor effects of the continuous release of gemcitabine at cystectomy in the bladder primary tumor and locoregional lymph

nodes
- Determine the immunogenic effects of the continuous release of intravesical gemcitabine at cystectomy
- Evaluate the molecular subtypes of the TURBT specimen and the correlation with other endpoints (Arm 2 only)

Study design

Prospective, multi-center, open-label, multi-arm study of gemcitabine delivered intravesically via GemRIS to subjects with Muscle-Invasive Transitional Cell Carcinoma of the Bladder (clinically referred to as MIBC). Both study arms will receive two 7-day GemRIS dosing cycles prior to undergoing radical cystectomy (RC).
For each arm, an initial GemRIS will be placed on Study Day 0 and the second will be placed on Study Day 21.
Arm 1 will include approximately 10 subjects who have a visible tumor. These subjects will proceed to RC on Study Day 28.
Arm 2 will include approximately 10 subjects who have been maximally resected (i.e., no visible tumor [or as little as possible] after a restaging transurethral resection of bladder tumor [TURBT]) and will receive an initial GemRIS within 6 weeks following TURBT. For subjects who already have pathologically confirmed MIBC, the initial GemRIS insertion can be performed as early as the same day as the repeat TURBT. For the remaining subjects, the first insertion may occur as soon as MIBC is pathologically confirmed so long as this occurs within 6 weeks so that the overall time to RC occurs within 12 weeks, consistent with the standard of care. Arm 2 subjects will proceed to RC on Study Day 42.

Intervention

Patients with newly-diagnosed histologically-confirmed muscle-invasive transitional cell carcinoma of the bladder will be screened following informed consent. Formal re-evaluation of pathologic specimens will be performed by the study site. On Study Day 0, subjects who continue to meet inclusion/exclusion criteria will receive the first GemRIS transurethrally via TARIS Inserter.
For both Arms 1 and 2, the first GemRIS will be removed via flexible cystoscopy on Study Day 7.
On Study Day 21, a second GemRIS will be placed via TARIS Inserter in both arms.
Subjects enrolled to Arm 1 will have their second GemRIS removed on Study Day 28. The GemRIS may be removed via cystoscopy or with the bladder at the time of RC. Radical cystectomy may occur within 1 week after Day 28.
Subjects enrolled to Arm 2 will also have their second GemRIS removed on Study Day 28, with RC scheduled for Study Day 42.

Study burden and risks

Gemcitabine
Gemcitabine is known to possibly cause a decrease of white blood cells in your blood. This may lead to an increased risk of infection, fever, considerable signs of fatigue, and a greater risk of black and blue marks on the skin. The risk of this side effect is less than 10%.
Allergic reactions occur very rarely, with a risk of less than 5%, and may include potential itching, shivers, facial swelling, and respiratory problems.

GemRIS
It is of great importance that the GemRIS is removed from your bladder after a maximum of 7 days. The study physician and staff will do their utmost to ensure that you are available at the latest on day 7 after insertion (for example, they will be contacting you or your family members by phone). If it is known in advance that you will not be able to comply with the visiting schedule, you will not be able to participate in this study.
There are risks that are related to exceeding the 7-day limit, including:
- exposure to gemcitabine for more than 7 days
- encapsulation of the GemRIS (bladder tissue grows around the GemRIS)
- the formation of stones in the bladder
- more frequent or more intensive bladder examinations to remove the GemRIS and/or the stones
- surgical procedure(s) to remove the GemRIS and/or the stones
- urinary tract infection
- blood poisoning
There is a risk that a GemRIS will be damaged during the insertion. If, after insertion, the bladder examination indicates that this is the case, the GemRIS will be removed immediately. There is a small risk that damage, if any, will be overlooked and in that case the GemRIS will remain in your bladder for 7 days at most. In such a case, the GemRIS might not be *fully* effective or may be passed in the urine.
There is a very small risk that the GemRIS might be passed in the urine. In that case, you must pick up the GemRIS with gloves and transfer it to a special plastic bag you will be receiving. You must report this to the study team and bring the bag to the next UMC visit.
If a GemRIS is damaged in your bladder or it comes out while you are urinating, there is a major risk that the study physician will perform additional tests or procedures, including an additional bladder examination, a CT scan, or an abdominal X-ray.

Contacts

Public
TARIS Biomedical LLC

Hartwell Avenue 113
Lexington, MA 02421
US
Scientific
TARIS Biomedical LLC

Hartwell Avenue 113
Lexington, MA 02421
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Histological proof of muscle-invasive transitional cell carcinoma of the bladder (clinical stage T2a-T3b). Subjects with evidence of metastatic nodal disease to the obturator or presacral lymph nodes only may be included (N1 M0). Subjects with any degree of fixation of the pelvic sidewall are not eligible.
2. In Arm 1, subjects must have residual visible tumor following TURBT. In Arm 2, subjects must be fully resected (i.e., no visible tumor or as little tumor as is possible) after restaging TURBT within 6 weeks prior to Study Day 0.
3. Adequate bone marrow, liver, and renal function, as assessed by the following requirements conducted within 21 days prior to dosing:
a) Hemoglobin *9.0 g/dL
b) Absolute neutrophil count (ANC) *1,500/mm3
c) Platelet count *100,000/mm3
d) Total bilirubin *1.5xULN (upper limit of normal)
e) Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) *2.5xULN
f) Glomerular Filtration Rate (GFR) *30% (*30 ml/min/1.73 m2)
4. Subjects must be willing to undergo a cystoscopy on study for investigational product insertion and removal.
5. Eligible for and willing to undergo radical cystectomy per the attending urologist.

6. Subjects must refuse neoadjuvant cisplatin-based combination chemotherapy (and understand the risks and benefits of doing so) or be deemed ineligible for cisplatin-based combination chemotherapy by the attending medical oncologist.
7. Prior radiation therapy is allowed provided that no radiation therapy was administered to the urinary bladder.
8. Written informed consent and authorization for release of personal health information obtained according to local laws.
9. Age *18 years at the time of consent.
10. Females of childbearing potential must be willing to use an effective method of contraception (hormonal or barrier method of birth control; abstinence) from the time consent is signed until 4 weeks after treatment discontinuation. Subject*s partner must also use barrier protection while subject is on study until 4 weeks after treatment discontinuation.
11. Males must be willing to use an effective method of contraception/method to avoid seminal transfer (barrier method or abstinence) from the time consent is signed until 4 weeks after treatment discontinuation. Subject*s partner must also use barrier protection while subject is on study until 4 weeks after treatment discontinuation.
12. Females of childbearing potential must have a negative pregnancy test within 21 days prior to Study Day 0.

Exclusion criteria

1. Active malignancies within 12 months with the exception of those with a negligible risk of metastasis or death treated with expected curative outcome.
2. Prior systemic chemotherapy for transitional cell carcinoma of the bladder. Any other prior systemic chemotherapy for a non-urothelial carcinoma must have been completed >5 years prior to initiation of study.
3. Previous exposure to gemcitabine instillations.
4. Currently receiving other intravesical chemotherapy.
5. Concurrent clinically significant infections as determined by the treating investigator.
6. Presence of any bladder or urethral anatomic feature that in the opinion of the investigator may prevent the safe placement, indwelling use or removal of GemRIS.
7. Documented history of vesicoureteral reflux or the presence of an indwelling ureteral stent or nephrostomy tube at the time of screening.
8. Evidence of bladder perforation during diagnostic cystoscopy.
9. Pelvic radiotherapy administered within less than 6 months prior to enrollment. Subjects who received radiotherapy *6 months prior to enrollment must demonstrate no cystoscopic evidence or symptoms of radiation cystitis.
10. Bladder Post-Void Residual Volume (PVR) of >250 mL.
11. Known hypersensitivity to gemcitabine or chemically-related drugs.
12. Known hypersensitivity to the drug constituent, device constituent or TARIS Inserter materials.
13. Active, uncontrolled urogenital bacterial, viral or fungal infections, including urinary tract infection that, in the opinion of the investigator, contraindicates participation. Skin/nail fungal infections are not exclusionary. Subjects with active shingles (varicella zoster infection) will be excluded from the study.

14. Use of an investigational product within 30 days or 5 half-lives, whichever is longer, preceding Study Day 0.
15. History or presence of any significant cardiovascular, pulmonary, hepatic, renal, gastrointestinal, gynecological, endocrine, immunological, dermatological, neurological or psychiatric disease or disorder that, in the opinion of the investigator, contraindicates participation.
16. History of diagnosis of neurogenic bladder.
17. Concomitant immunosuppressive medications, such as methotrexate or TNF inhibitors, within 2 weeks of Study Day 0, exclusive of steroid doses *5 mg daily.
18. History of any of the following within 3 months prior to Screening Visit:
- Major illness/major surgery (requiring hospitalization), including pelvic, lower back surgery or procedure unrelated to bladder cancer; most outpatient procedures are not exclusionary
- Renal or ureteral stone disease or instrumentation
- Childbirth
19. Female subject who is pregnant (as verified by urine test at time of screening) or lactating or of childbearing potential and not using acceptable methods of contraception.
20. Difficulty providing blood samples.
21. Unwilling or unable to provide informed consent or comply with the requirements of this protocol, including the presence of any condition (physical, mental or social) that is likely to affect the subject*s return for scheduled visits and follow-up.
22. Other unspecified reasons that, in the opinion of the investigator or TARIS, make the subject unsuitable for enrollment.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	29-08-2018
Enrollment:	6
Type:	Actual

Medical products/devices used

Generic name:	TARIS Inserter
Registration:	No
Product type:	Medicine
Brand name:	not available
Generic name:	not available

Ethics review

Approved WMO Date:	28-11-2017
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	22-03-2018
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	09-04-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	16-04-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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
EudraCT	EUCTR2017-004023-70-NL
ClinicalTrials.gov	NCT02722538
CCMO	NL63661.091.17

Study results

Date completed: 02-05-2019

Results posted: 06-04-2020

First publication
01-04-2020