AUREA

Phase II, multicenter, non-randomized, single-arm, open-label trial of atezolizumab in combination of split-doses of gemcitabine plus cisplatin in patients with locally advanced or metastatic urothelial carcinoma

STATISTICAL ANALYSIS REPORT

JULY 2023

Done by: MFAR CLINICAL RESEARCH S.L

1. Table of Contents

The database was locked down on XXX.

2. STUDY DESIGN

The SOGUG-AUREA study is a multicenter, open labelled, single arm, Phase II clinical trial of atezolizumab in combination of split-dose cisplatin plus gemcitabine in patients with locally advanced or metastatic urothelial carcinoma (additional details on the eligibility criteria of the study are found in section 6 of the study protocol).

The design includes screening phase, combined treatment initial phase, monotherapy treatment phase, follow-up phase and translational research with biopsies, blood samples and faecal samples.

The dose scheme includes the initial dose of atezolizumab (1200 mg) intravenously administered every 21 days (one cycle) up to disease progression, unacceptable toxicity or absence of clinical benefit. Dose adjustment or dose reductions of atezolizumab are not expected. Additional information on the treatment, modifications, and dose delays is available in section 7 of the study protocol. SOGUG-AUREA is an Investigator Initiated Study, the Sponsor will supply Atezolizumab for up to 24 months of treatment for each patient. For those patients in which the PI considers that the best option for the patient is continuing atezolizumab for more than 24 months, available commercial Site supplies should be used, after managed local administrative regulation.

3. SCREENING FAILURE

Table 1: Frequency screening failures

Overall	Overall (N=)
Screening Failing	
No	
Yes	
Screening Failure Specify	

Table 2: List of patients with screening failure

Patient number	Screening Failing	Screening Failure Specify

Table 3: Patients without screening failure by hospital

Overall	Overall (N=)
Hospital	
COMPLEJO HOSPITALARIO DE JAÉN	
COMPLEXO HOSPITALARIO UNIVERSITARIO DE OURENSE	
CONSORCIO HOSPITALARIO PROVINCIAL DE CASTELLÓN	
HOSPITAL CLÍNICO SAN CARLOS	
HOSPITAL DE LA SANTA CREU I SANT PAU	
HOSPITAL SON LLATZER	
HOSPITAL UNIVERSITARIO 12 DE OCTUBRE	
HOSPITAL UNIVERSITARIO CENTRAL DE ASTURIAS	
HOSPITAL UNIVERSITARIO INSULAR DE GRAN CANARIA	
HOSPITAL UNIVERSITARIO LA PAZ	
HOSPITAL VIRGEN DE LA SALUD	
INSTITUT CATALÀ D´ONCOLOGIA L´HOSPITALET ICO	

4. Study populations

4.1. Intent-To-Treat

Intent-To-Treat (ITT): All patients that have been enrolled in the trial.

Table 4: ITT population

Overall	Overall (N=)
Intent-to-treat population	
No	
Yes	
ITT population exclusion reason	
NA	
Screening Failure	

Table 5: ITT exclusion reason

Patient number	Intent-to-treat population	ITT population exclusion reason

4.2. PER PROTOCOL

Evaluable population **per protocol (PP)**: All patients fulfilling all eligibility criteria without any protocol deviation that makes the patient invalid for the primary endpoint evaluation.

Table 6: PP population

Overall	Overall (N=)
Per protocol population	
No	
Yes	
PP population exclusion reason	
NA	
Screening Failure	

Table 7: PP exclusion reason

Patient number	Per protocol population	PP population exclusion reason

4.3. SAFETY POPULATION

Safety population (SP): All patients receiving at least one dose of the study treatments.

Table 8: Safety population

Overall	Overall (N=)
Safety population	
No	
Yes	
Safety population exclusion reason	
NA	
Screening Failure	

Table 9: Safety exclusion reason

Patient number	Safety population	Safety population exclusion reason

5. Basal information

This section is carried out in the ITT population (N = XX patients).

5.1. Non-cisplatin eligible

Table 10: Frequency non-cisplatin eligible

Overall	Overall (N=)
ECOG 2	
Yes	
No	
Age > 70 years	
Yes	
No	
Creatinine clearance >30 µmol/L and <60 µmol/L	
Yes	
No	
Other non-cisplatino elegible reason	
Yes	
No	
Specify other non-cisplatino elegible reason	

Table 11: Frequency non-cisplatin eligible combined

Overall	Overall (N=)
Non-cisplatino elegible reasons combined	

5.2. Cancer history

5.2.1. Primary cancer

Table 12: Frequency primary cancer location

Overall	Overall (N=)
Cancer Location	
Urothelial cancer	
Location Specify	
Renal pelvis	
Ureter	
Bladder	
Urethra	

Table 13: Frequency TNM status at diagnosis

Overall	Overall (N=)
Initial T Stage	
T1	
T2	
T2a	
T2b	
T3	
T3b	
T4	
T4a	
T4b	
Tis	
Ta	
Tx	
Initial N Stage	
N0	
N1	
N2	
N3	
Nx	
Initial M Stage	
M0	
M1	
M1a	
M1b	
Mx	
Cancer Stage	
0a	
0is	
I	
II	
III	

Overall	Overall (N=)
IIIA	
IIIB	
IV	
IVA	
IVB	
Unknown	
Differentiation	
Well differentiated	
Moderately differentiated	
Poorly differentiated	
Undifferentiated	
Unknown	
Cancer History Grade	
High	
Low	
Unknown	

Table 14: List of patients with Unknown Cancer Stage

Patient Number	Hospital	Cancer Stage
004-007	HOSPITAL UNIVERSITARIO LA PAZ	Unknown

Table 15: Frequency metastasis location

Overall	Overall (N=66)
Metastasis	
Yes	28 (42.4%)
No	38 (57.6%)
Metastasis Liver	
NA	61 (92.4%)
Liver	5 (7.6%)
Metastasis Peritoneum	
NA	64 (97.0%)
Peritoneum	2 (3.0%)
Metastasis Pleura	
NA	65 (98.5%)
Pleura	1 (1.5%)
Metastasis Lung	
NA	52 (78.8%)
Lung	14 (21.2%)
Metastasis Kidney	
NA	65 (98.5%)
Kidney	1 (1.5%)
Metastasis Bone	
NA	60 (90.9%)
Bone	6 (9.1%)
Metastasis Renal	
NA	65 (98.5%)
Renal	1 (1.5%)
Metastasis Soft tissues	
NA	65 (98.5%)
Soft tissues	1 (1.5%)
Metastasis Skin	
NA	65 (98.5%)
Skin	1 (1.5%)
Metastasis Lymph nodes	
NA	48 (72.7%)
Lymph nodes	18 (27.3%)
Metastasis Other	
NA	64 (97.0%)
Other	2 (3.0%)
Metastasis Other specify	
NA	64 (97.0%)
Adrenal	1 (1.5%)
Suprarrenal	1 (1.5%)

Table 16: Frequency current metastasis location

Overall	Overall (N=)
Current status	
Locally advanced	
Metastasic	
Current Metastasis Colon	
NA	
Colon	
Current Metastasis Pleural effusion	
NA	
Pleural effusion	
Current Metastasis Liver	
NA	
Liver	
Current Metastasis Large intestine	
NA	
Large intestine	
Current Metastasis Mediastinum	
NA	
Mediastinum	
Current Metastasis Pancreas	
NA	
Pancreas	
Current Metastasis Peritoneum	
NA	
Peritoneum	
Current Metastasis Lung	
NA	
Lung	
Current Metastasis Kidney	
NA	
Kidney	
Current Metastasis Bone	
NA	
Bone	
Current Metastasis Renal	
NA	
Renal	
Current Metastasis Soft tissues	
NA	
Soft tissues	
Current Metastasis Skin	
NA	
Skin	
Current Metastasis Jejunum	
NA	
Jejunum	
Current Metastasis Lymph nodes	
NA	
Lymph nodes	

Overall	Overall (N=)
Current Metastasis Other	
NA	
Other	
Current Metastasis Other specify	
NA	
Adrenal	
Paraaortic	
Vagina	

Table 17: Frequency calculated metastasis location

Overall	Overall (N=)
Lung - Metastasis	
No	
Yes	
Other - Adrenal - Metastasis	
No	
Yes	
Renal - Metastasis	
No	
Yes	
Peritoneum - Metastasis	
No	
Yes	
Lymph nodes - Metastasis	
No	
Yes	
Mediastinum - Metastasis	
No	
Yes	
Diaphragma - Metastasis	
No	
Yes	
Other - left cardiophrenic fat - Metastasis	
No	
Yes	
Liver - Metastasis	
No	
Yes	
Kidney - Metastasis	
No	
Yes	
Bone - Metastasis	
No	
Yes	
Other Metastasis	
No	
Yes	
Large intestine - Metastasis	

Overall	Overall (N=)
No	
Yes	
Jejunum - Metastasis	
No	
Yes	
Mesenterium - Metastasis	
No	
Yes	
Other - penile implant - Metastasis	
No	
Yes	
Ileus - Metastasis	
No	
Yes	
Other - supraclavicular - Metastasis	
No	
Yes	
Other-inter-aortocava - Metastasis	
No	
Yes	
Pleural effusion - Metastasis	
No	
Yes	
Pleura - Metastasis	
No	
Yes	
Pancreas - Metastasis	
No	
Yes	
Other - Gallbladder - Metastasis	
No	
Yes	
Other: omentum - Metastasis	
No	
Yes	
Soft tissues - Metastasis	
No	
Yes	
Ascites - Metastasis	
No	
Yes	
Skin - Metastasis	
No	
Yes	
Colon - Metastasis	
No	
Yes	

Table 18: Frequency treatments

Overall	Overall (N=)
Surgery	
Yes	
No	
Primary Surgery	
NA	
Yes	
Surgery Outcome	
NA	
R0	
R1	
R2	
Unknown	
Radiotherapy	
Yes	
No	
Radiotherapy cycles	
NA	
1	
2	
Unknown	
Radiotherapy cycles	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Radiotherapy Cumulative dose (Gy)	
Radiotherapy Cumulative dose (Gy)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Previous treatment	
Yes	
No	
Unknown	
Other cancer history	
Yes	
No	
Cancer History Type	
Cancer History Treatment	

Overall	Overall (N=)

5.3. DEMOGRAPHIC DATA

Table 19: Frequency demographic data

Overall	Overall (N=)
Patient Age	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Gender	
Male	
Female	
Weight (Kg)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Race	
Caucasian	
Latin	
Systolic Blood Pressure (mmHG)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Diastolic Blood Pressure (mmHG)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Temperature (ºC)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Height (cm)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Respiratory rate (breaths per minute)	
N	
Mean (95%CI)	
SD	

Overall	Overall (N=)
Median (95%CI)	
Range	
Pulse rate (bpm)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Body Mass Index (kg/m2)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
ECOG	
0	
1	
2	
Physical exam	
Normal	
Abnormal	

5.4. Comorbidities and concomitant medication

Table 20: Frequency comorbidities and concomitant medication

Overall	Overall (N=)
Comorbidities	
No	
Yes	
Concomitant Medication	
No	
Yes	

Table 21: Frequency comorbidities in patients

Comorbidities	N	%

*Some patients can have several comorbidities

Table 22: Frequency other comorbidities in patients

Comorbidities	N	%

*Some patients can have several comorbidities

Table 23: Frequency concomitant medication in patients

Concomitant medication	N	%

*Some patients can have several concomitant medications

Table 24: Frequency other concomitant medication in patients

Other concomitant medication	N	%

*Some patients can have several concomitant medications

5.5. Hematology and coagulation

Table 25: Frequency hematology and coagulation

Overall	Overall (N=)
Hemoglobin Value (g/dL)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Platelets Value (10e3/µL)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Neutrophils Value (10e3/µL)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	

5.6. Biochemistry, serology and thyroid function

Table 26: Frequency biochemistry, serology and thyroid function

Overall	Overall (N=)
Creatinine Value (mg/dL)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Creatinine Clearing Value (ml/min)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Bilirubin Value (mg/dL)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Bilirubin Value < ULN	
Yes	
ALT Value (U/L)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
ALT Value < ULN	
No	
Yes	
AST Value (U/L)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
AST Value < ULN	
No	
Yes	
GGT Value (U/L)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
GGT Value < ULN	
No	

Overall	Overall (N=)
Yes	
Unknown	

5.7. Other determinations

Table 27: Frequency other determinations

Overall	Overall (N=)
Urine Analysis ND	
Done	
Not done	
Urine Analysis	
Missing data	
Negative	
Traces	
+1	
+2	
+3	
+4	
Urine Analysis Blood	
NA	
Positive	
Negative	
Urine Analysis Glucose	
NA	
Normal	
Abnormal	
Urine Analysis Protein	
NA	
Positive	
Negative	
Pregnancy Test Value	
NA	
Negative	
Unknown	
Electrocardiogram	
Done	
Ecg Value	
Normal	
Abnormal	
FEVI	
Done	
Not done	
FEVI Value	
NA	
Normal	
Abnormal	

6. Treatment compliance

The following analyses in this section are carried out in the safety population (N = XX patients).

6.1. Initial phase: Combined treatment (C1-C6)

atezolizumab, cisplatin and gemcitabine

Table 28: Adherence to atezolizumab, cisplatin and gemcitabine

Overall	Overall (N=)
Number of cycles administered (Initial phase) - Atezolizumab	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Number of cycles administered (Initial phase) - Atezolizumab	
1	
2	
3	
4	
5	
6	
Atezolizumab treatment duration (months)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Number of cycles administered (partial/complete) - Cisplatin	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Number of cycles administered (complete) - Cisplatin	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Number of cycles administered (partial/complete) - Cisplatin	
1	
2	
3	
4	
5	
6	
Number of cycles administered (complete) - Cisplatin	
0	

Overall	Overall (N=)
1	
2	
3	
4	
5	
6	
Cisplatin treatment duration (months)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Number of cycles administered (partial/complete) - Gemcitabine	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Number of cycles administered (complete) - Gemcitabine	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Number of cycles administered (partial/complete) - Gemcitabine	
1	
2	
3	
4	
5	
6	
Number of cycles administered (complete) - Gemcitabine	
0	
1	
2	
3	
4	
5	
6	
Gemcitabine treatment duration (months)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	

Table 29: Atezolizumab, cisplatin and gemcitabine omissions

Overall	Overall (N=)
Omission (Initial phase) - Atezolizumab	
No	
Yes	
Number of patients with omission (Initial phase) - Atezolizumab	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Number of patients with omissions (Initial phase) - Atezolizumab	
0	
1	
Omission - Cisplatin	
No	
Yes	
Number of patients with an omission - Cisplatin	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Number of patients with two omissions - Cisplatin	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Number of patients with an omission - Cisplatin	
0	
1	
2	
3	
5	
Number of patients with two omissions - Cisplatin	
0	
1	
Omission - Gemcitabine	
No	
Yes	
Number of patients with an omission - Gemcitabine	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Number of patients with two omissions - Gemcitabine	
N	
Mean (95%CI)	
SD	
Median (95%CI)	

Overall	Overall (N=)
Range	
Number of patients with an omission - Gemcitabine	
0	
1	
2	
3	
5	
Number of patients with two omissions - Gemcitabine	
0	
1	

Table 30: List of omissions reasons

Atezolizumab - Omission reason	**N**	**%**
Other		
Cisplatin - Omission reason	**N**	**%**
AE		
Other		
Gemcitabine - Omission reason	**N**	**%**
AE		
Other		

Table 31: List of other omissions reasons specify

Atezolizumab - Omission reason	**N**	**%**
Cisplatin - Omission reason	**N**	**%**
Gemcitabine - Omission reason	**N**	**%**

Table 32: Atezolizumab, cisplatin and gemcitabine delays

Overall	Overall (N=)
Delay (Initial phase) - Atezolizumab	
No	
Yes	
Number of cycles with delay (Initial phase) - Atezolizumab	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Number of cycles with delay (Initial phase) - Atezolizumab	
0	
2	
1	
3	
4	
Delay	
No	
Yes	
Number of cycles with a delay - Cisplatin	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Number of cycles with two delays - Cisplatin	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Number of cycles with a delay - Cisplatin	
0	
1	
2	
3	
4	
Number of cycles with two delays - Cisplatin	
0	
1	
2	
Delay - Gemcitabine	
No	
Yes	
Number of cycles with a delay - Gemcitabine	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Number of cycles with two delays - Gemcitabine	

Overall	Overall (N=)
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Number of cycles with a delay - Gemcitabine	
0	
1	
2	
3	
4	
Number of cycles with two delays - Gemcitabine	
0	
1	
2	

Table 33: List of delay reasons

Atezolizumab - Delay reason	**N**	**%**
AE		
Other		
Cisplatin - Delay reason	**N**	**%**
AE		
Other		
Gemcitabine - Delay reason	**N**	**%**
AE		
Other		

Table 34: List of other delay reasons

Atezolizumab - Delay reason	**N**	**%**
Cisplatin - Delay reason	**N**	**%**
Gemcitabine - Delay reason	**N**	**%**

Table 35: Cisplatin and gemcitabine dose decrease

Overall	Overall (N=)
Dose reduction	
No	
Yes	
Number of cycles with a dose reduction - Cisplatin	
N	

Overall	Overall (N=)
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Number of cycles with two dose reductions - Cisplatin	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Number of cycles with a dose reduction - Cisplatin	
0	
1	
2	
Number of cycles with two dose reductions - Cisplatin	
0	
Minimum dose in dose reductions - Cisplatin	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Dose reduction - Gemcitabine	
No	
Yes	
Number of cycles with a dose reduction - Gemcitabine	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Number of cycles with two dose reductions - Gemcitabine	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Number of cycles with a dose reduction - Gemcitabine	
0	
1	
2	
Number of cycles with two dose reductions - Gemcitabine	
0	
Minimum dose in dose reductions - Gemcitabine	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	

Table 36: List of dose decrease reasons

Cisplatin - Dose reduction reason	N	%
AE		
Gemcitabine - Dose reduction reason	**N**	**%**
AE		
Other		

Table 37: List of other dose decrease reasons (AEs)

Cisplatin - Dose reduction reason	N	%
Gemcitabine - Dose reduction reason	**N**	**%**

Table 38: Cisplatin and gemcitabine re-scalation after dose reduction

Overall	Overall (N=)
Dose re-scalation after dose reduction	
No	
Yes	
Number of cycles with a re-scalation after dose reduction - Cisplatin	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Number of cycles with two re-scalation after dose reduction - Cisplatin	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Number of cycles with a re-scalation after dose reduction - Cisplatin	
0	
1	
Number of cycles with two re-scalation after dose reduction - Cisplatin	
0	
Minimum dose in dose re-scalation after dose reduction - Cisplatin	
N	
Mean	
SD	
Median	
Range	
Dose re-scalation after dose reduction - Gemcitabine	
No	
Yes	
Number of cycles with a re-scalation after dose reduction - Gemcitabine	

Overall	Overall (N=)
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Number of cycles with two re-scalation after dose reduction - Gemcitabine	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Number of cycles with a re-scalation after dose reduction - Gemcitabine	
0	
1	
Number of cycles with two re-scalation after dose reduction - Gemcitabine	
0	
Minimum dose in dose re-scalation after dose reduction - Gemcitabine	
N	
Mean	
SD	
Median	
Range	

Table 39: List of re-scalation after dose reduction reasons

Cisplatin - Re-scalation after dose reduction reason	N	%

Gemcitabine - Re-scalation after dose reduction reason	N	%

6.2. Monotherapy phase: Adherence to atezolizumab and entire treatment

Table 40: Adherence to atezolizumab, monotherapy phase and entire treatment

Overall	Overall (N=)
Number of cycles administered (Monotherapy phase) - Atezolizumab	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Number of cycles administered (Monotherapy phase) - Atezolizumab	
0	
1	
2	
3	
…	
Atezolizumab treatment duration (months)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Number of cycles administered (Entire treatment) - Atezolizumab	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Number of cycles administered (Entire treatment) - Atezolizumab	
1	
2	
3	
…	
Atezolizumab treatment duration (months)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	

Table 41: Atezolizumab omissions, monotherapy phase and entire treatment

Overall	Overall (N=)
Omission (Monotherapy phase) - Atezolizumab	
No	
Yes	
Number of cycles with omission (Monotherapy phase) - Atezolizumab	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Number of cycles with omissions (Monotherapy phase) - Atezolizumab	
0	
1	
Omission (Entire treatment) - Atezolizumab	
No	
Yes	
Number of cycles with omission (Entire treatment) - Atezolizumab	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Number of cycles with omissions (Entire treatment) - Atezolizumab	
0	
1	

Table 42: List of omissions reasons

Atezolizumab - Omission reason (Monotherapy)	N	%

Atezolizumab - Omission reason (Entire treatment)	N	%

Table 43: List of omissions reasons specify

Atezolizumab - Omission reason (Entire treatment)	N	%

Table 44: Atezolizumab delays, monotherapy phase and entire treatment

Overall	Overall (N=)
Delay (Monotherapy phase) - Atezolizumab	
No	
Yes	
Number of cycles with delay (Monotherapy phase) - Atezolizumab	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Number of cycles with delay (Monotherapy phase) - Atezolizumab	
0	
1	
2	
Delay (Entire treatment) - Atezolizumab	
No	
Yes	
Number of cycles with delay (Entire treatment) - Atezolizumab	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Number of cycles with delay (Entire treatment) - Atezolizumab	
0	
1	
2	

Table 45: List of delay reasons

Atezolizumab - Delay reason (Monotherapy)	N	%
Atezolizumab - Delay reason (Entire treatment)	**N**	**%**

Table 46: List of other delay reasons

Atezolizumab - Delay reason (Monotherapy)	N	%

Atezolizumab - Delay reason (Entire Treatment)	N	%

7. End of treatment

The following analyses in this section are carried out in the safety population (N = XX patients).

Table 47: End of treatment

Overall	Overall (N=)
End of Atezolizumab Treatment Reason	
Progression according RECIST 1.1	
Death	
Study treatment completion	
AE not related to the treatment study	
Unnacceptable toxicity	
Investigator decision	
Withdraw consent	
Other	
End of Atezolizumab Treatment Reason Specify	
End of Cisplatin Treatment Reason	
Study treatment completion	
Unnacceptable toxicity	
Progression according RECIST 1.1	
Death	
AE not related to the treatment study	
Investigator decision	
Withdraw consent	
Other	
End of Gemcitabine Treatment Reason	
Study treatment completion	
Unnacceptable toxicity	
Progression according RECIST 1.1	
Death	
AE not related to the treatment study	
Investigator decision	
Withdraw consent	
Other	

Note: the following reasons have been recoded to minimize categories - Kidney function impairment/Urinary tract infection/: AE not related to the treatment study

Table 48: End of treatment (Grouped to minimize categories)

Treatment	Atezolizumab (N=)	Cisplatin (N=)	Gemcitabine (N=)	Total (N=)
End of treatment reason				
Study treatment completion				
Progression disease				
Unnacceptable toxicity				

Treatment	Atezolizumab (N=)	Cisplatin (N=)	Gemcitabine (N=)	Total (N=)
Death				
AE not related to the treatment study				
Investigator decision				
Withdraw consent				
Other				

Note: the following reasons have been recoded to minimize categories - Symptomatic deterioration/Progression according RECIST 1.1/Clinical Progression: Progression disease

Figure 1: Atezolizumab treatment discontinuation

Figure 2: Cisplatin treatment discontinuation

Figure 3: Gemcitabine treatment discontinuation

8. Efficacy analysis

The following analyses in this section are carried out in the Per Protocol population (N = XX patients).

8.1. Primary objective

8.1.1. Overall response rate (ORR)

To evaluate the preliminary efficacy of atezolizumab plus split-dose gemcitabine and cisplatin (GC) for the first-line setting, in patients with histologically confirmed advanced (locally advanced and metastatic) urothelial cancer in terms of overall response rate (ORR) assessed by the investigator using the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

Overall Response Rate (ORR): Assessed by the investigator using the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. This will be considered as the percentage/proportion of patients with confirmed complete response (CR) or partial response (PR) as their overall best response throughout the study period.

Table 49: Frequency best overall response

Best OR Confirmed	N	%	95%CI
CR			
PR			
SD			
PD			
NE/UK			
UK			
Total			

Table 50: List of patients with NE/UK as best overall response

Patient number	Best OR Confirmed	Resp. 1.1	Tumor Assessment Target Sum	Status	EOS Date	End of Trial Reason	Exitus Reason	Exitus Reason Specify

Table 51: Frequency best overall response without UK/NE

Best OR Confirmed	N	%	95%CI
CR			

Best OR Confirmed	N	%	95%CI
PR			
SD			
PD			
NE			
UK			
Total			

Table 52: List of patients with CR/PR as best overall response

Patient number	Hospital	Best OR Confirmed

Table 53: Frequency overall response rate

Overall Response Rate (confirmed)	N	%	95%CI
Yes (CR/PR)			
No			
Total			

Table 54: Frequency overall response rate without UK/NE

Overall Response Rate (confirmed)	N	%	95%CI
Yes (CR/PR)			
No			
Total			

Figure 4: Waterfall plot

8.1.1.1. ORR vs Age>70

Table 1: Age>70 by Overall response rate

Age > 70 years	No (N=)	Yes (N=)	Total (N=)	p-value
Overall Response Rate (confirmed)				
N				
No				
Yes (CR/PR)				

(1) Fisher's exact test

(*) The percentages take into account missing data, the p-values do not

Table 2: Age>70 by Overall response rate without UK/NE

Age > 70 years	No (N=)	Yes (N=)	Total (N=)	p-value
Overall Response Rate (confirmed)				
N				
Yes (CR/PR)				
No				

(1) Fisher's exact test

(*) The percentages take into account missing data, the p-values do not

8.1.1.2. ORR vs Renal Impairment

Table 3: Renal Impairment by Overall response rate

Creatinine clearance >30 µmol/L and <60 µmol/L	No (N=)	Yes (N=)	Total (N=)	p-value
Overall Response Rate (confirmed)				
N				
No				
Yes (CR/PR)				

(1) Fisher's exact test

(*) The percentages take into account missing data, the p-values do not

Table 4: Renal Impairment by Overall response rate without UK/NE

Creatinine clearance >30 µmol/L and <60 µmol/L	No (N=)	Yes (N=)	Total (N=)	p-value
Overall Response Rate (confirmed)				
N				
Yes (CR/PR)				
No				

(1) Fisher's exact test

(*) The percentages take into account missing data, the p-values do not

8.1.1.3. ORR vs ECOG 2

Table 5: ECOG 2 by Overall response rate

ECOG 2	No (N=)	Yes (N=)	Total (N=)	p-value
Overall Response Rate (confirmed)				
N	51	15	66	
No	26 (51.0%)	8 (53.3%)	34 (51.5%)	
Yes (CR/PR)	25 (49.0%)	7 (46.7%)	32 (48.5%)	

(1) Fisher's exact test

(*) The percentages take into account missing data, the p-values do not

Table 6: ECOG 2 by Overall response rate without UK/NE

ECOG 2	No (N=)	Yes (N=)	Total (N=)	p-value
Overall Response Rate (confirmed)				
N				
Yes (CR/PR)				
No				

(1) Fisher's exact test

(*) The percentages take into account missing data, the p-values do not

8.1.1.4. ORR vs HEMOGLOBIN

Table 7: HEMOGLOBIN by Overall response rate

Hemoglobin (g/dL)	<10 (N=)	>=10 (N=)	Total (N=)	p-value
Overall Response Rate (confirmed)				
N				
No				
Yes (CR/PR)				

(1) Fisher's exact test

(*) The percentages take into account missing data, the p-values do not

Table 8: HEMOGLOBIN by Overall response rate without UK/NE

Hemoglobin (g/dL)	<10 (N=)	>=10 (N=)	Total (N=)	p-value
Overall Response Rate (confirmed)				
N				
Yes (CR/PR)				
No				

(1) Fisher's exact test

(*) The percentages take into account missing data, the p-values do not

8.1.1.5. ORR vs LIVER METASTASIS

Table 9: LIVER METASTASIS by Overall response rate

Liver metastasis at baseline	No (N=)	Yes (N=)	Total (N=)	p-value
Overall Response Rate (confirmed)				
N				
No				
Yes (CR/PR)				

(1) Fisher's exact test

(*) The percentages take into account missing data, the p-values do not

Table 10: LIVER METASTASIS by Overall response rate without UK/NE

Liver metastasis at baseline	No (N=)	Yes (N=)	Total (N=)	p-value
Overall Response Rate (confirmed)				
N				
Yes (CR/PR)				
No				

(1) Fisher's exact test

(*) The percentages take into account missing data, the p-values do not

8.2. Secondary objectives

8.2.1. Time to response

To evaluate the time to response (TtR) associated with the study treatment, understood as the time from the first dose of the study treatment to the confirmed response (CR or PR) based on RECIST 1.1 criteria.

Time to response (TtR): Time from first dosing date to the date of the documented ORR as determined using RECIST 1.1 criteria.

Table 55: Time to response

Overall	Overall (N=)
Time to response (months)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	

8.2.2. Duration of response

Duration of response (DoR): Time from first confirmed response (CR or PR) to the date of the documented PD as determined using RECIST 1.1 criteria or death due to any cause, whichever occurs first.

Table 56: Duration of response

Overall	Overall (N=)
Duration of response (months)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	

Table 57: Duration of response of responders (Best Overall Response CR or PR)

Best Overall Response (Recist 1.1)	CR (N=)	PR (N=)	Total (N=)
Duration of response (months)			
N			
Mean (95%CI)			
SD			
Median (95%CI)			
Range			

Table 11: Patients with duration of response greater than 24 months

Patient number	Hospital	Duration of response (months)	Best Overall Response (Recist 1.1)

Figure 5: Spider plot

8.2.3. Clinical benefit rate

To evaluate the clinical benefit rate (CBR), defined as the percentage of patients who have achieved complete response, partial response and stable disease. Stable disease should be maintained for at least 6 months to be considered as CBR event, from baseline (treatment start) to last tumor assessment with SD (or PR/CR in patients with non-confirmed response).

Table 58: Clinical benefit rate

ClinicalBenefitRate	N	%	95%CI
No			
Yes (CR/PR/Manteined SD)			
Total			

8.2.4. Follow-up time

Table 59: Follow-up time in months (since study inclusion until death or last FU)

Overall	Overall (N=)
Follow-up time (months)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	

8.2.5. PFS

Progression-free Survival (PFS): Median Progression free survival (mPFS) is defined as the time from the date of inclusion to the date of the first documented disease progression or death due to any cause, whichever occurs first. PFS will be determined based on tumour assessment (RECIST version 1.1 criteria). The local Investigator's assessments will be used for analyses. Patients who are alive and have not progressed at the last follow-up will be censored at the date of the last available image determination (CT scan or MRI). Patients with no additional image test other than that at baseline will be censored to the day after inclusion. Patients initiating new anticancer therapy (without progression to the study treatment) will be censored to the date of new anticancer therapy initiation.

Table 60: Progression information

Progression	N	%	95%CI
No			
Yes			
Total			

Table 61: Progression status

Overall	Overall (N=)
PFS status	
Alive without progression	
Death	
Progression	

Figure 6: PFS

Table 62: Median/mean PFS (estimated by Kaplan-Meier)

	Median (months)	CI 95%	RMST	CI 95%
Progression Free Survival				

Table 63: PFS estimated survival ratio

Progression Free Survival	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	CI 95%
At 3 months				
At 6 months				
At 9 months				
At 12 months				

8.2.5.1. PFS vs Age>70

Figure 7: PFS vs Age>70

Table 64: Median/mean PFS (estimated by Kaplan-Meier) vs Age>70

	Median (months)	CI 95%	RMST	CI 95%
Yes				
No				

Table 65: PFS estimated survival ratio vs Age>70

PFS	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	CI 95%
Yes				
At 3 months				
At 6 months				
At 9 months				
At 12 months				
No				
At 3 months				
At 6 months				
At 9 months				
At 12 months				

8.2.5.2. PFS vs Renal Impairment

Figure 8: PFS vs Renal Impairment

Table 66: Median/mean PFS (estimated by Kaplan-Meier) vs Renal Impairment

	Median (months)	CI 95%	RMST	CI 95%
Yes				
No				

Table 67: PFS estimated survival ratio vs Renal Impairment

PFS	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	CI 95%
Yes				
At 3 months				
At 6 months				
At 9 months				
At 12 months				
No				
At 3 months				
At 6 months				
At 9 months				
At 12 months				

8.2.5.3. PFS vs ECOG 2

Figure 9: PFS vs ECOG 2

Table 68: Median/mean PFS (estimated by Kaplan-Meier) vs ECOG 2

	Median (months)	CI 95%	RMST	CI 95%
Yes				
No				

Table 69: PFS estimated survival ratio vs ECOG 2

PFS	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	CI 95%
Yes				
At 3 months				
At 6 months				
At 9 months				
At 12 months				
No				
At 3 months				
At 6 months				
At 9 months				
At 12 months				

8.2.5.4. PFS vs HEMOGLOBIN

Figure 10: PFS vs HEMOGLOBIN

Table 70: Median/mean PFS (estimated by Kaplan-Meier) vs HEMOGLOBIN

	Median (months)	CI 95%	RMST	CI 95%
<10				
>=10				

Table 71: PFS estimated survival ratio vs HEMOGLOBIN

PFS	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	CI 95%
<10				
At 3 months				
At 6 months				
At 9 months				
At 12 months				
>=10				
At 3 months				
At 6 months				
At 9 months				
At 12 months				

8.2.5.5. PFS vs LIVER METASTASIS

Figure 11: PFS vs LIVER METASTASIS

Table 72: Median/mean PFS (estimated by Kaplan-Meier) vs LIVER METASTASIS

	Median (months)	CI 95%	RMST	CI 95%
No				
Yes				

Table 73: PFS estimated survival ratio vs LIVER METASTASIS

PFS	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	CI 95%
No				
At 3 months				
At 6 months				
At 9 months				
At 12 months				
Yes				
At 3 months				
At 6 months				
At 9 months				
At 12 months				

8.2.6. OS

To determine the overall survival (OS) of patients with locally-advanced or mUC treated with the intended treatment regimen, understood as the time from first dosing date to the date of death. A subject who has not died will be censored at the last known date alive.

Table 74: Current situation information

Status	N	%	95%CI
Alive			
Death			
Total			

Table 75: Death reason

Overall	Overall (N=)
Exitus Reason	
NA	
Progression disease	
Toxicity due to study treatment	
Other	
Exitus Reason Specify	

Figure 12: OS

Table 76: Median/mean OS (estimated by Kaplan-Meier)

	Median (months)	CI 95%	RMST	CI 95%
Overall Survival				

Table 77: OS estimated survival ratio

Overall Survival	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	CI 95%
At 3 months				
At 6 months				
At 9 months				
At 12 months				
At 24 months				

8.2.6.1. OS vs Age>70

Figure 13: OS vs Age>70

Table 78: Median/mean OS (estimated by Kaplan-Meier) vs Age>70

	Median (months)	CI 95%	RMST	CI 95%
Yes				
No				

Table 79: OS estimated survival ratio vs Age>70

OS	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	CI 95%
Yes				
At 3 months				
At 6 months				
At 9 months				
At 12 months				
No				
At 3 months				
At 6 months				
At 9 months				
At 12 months				

8.2.6.2. OS vs Renal Impairment

Figure 14: OS vs Renal Impairment

Table 80: Median/mean OS (estimated by Kaplan-Meier) vs Renal Impairment

	Median (months)	CI 95%	RMST	CI 95%
Yes				
No				

Table 81: OS estimated survival ratio vs Renal Impairment

OS	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	CI 95%
Yes				
At 3 months				
At 6 months				
At 9 months				
At 12 months				

OS	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	CI 95%
No				
At 3 months				
At 6 months				
At 9 months				
At 12 months				

8.2.6.3. OS vs ECOG 2

Figure 15: OS vs ECOG 2

Table 82: Median/mean OS (estimated by Kaplan-Meier) vs ECOG 2

	Median (months)	CI 95%	RMST	CI 95%
Yes				
No				

Table 83: OS estimated survival ratio vs ECOG 2

OS	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	CI 95%
Yes				
At 3 months				
At 6 months				
At 9 months				
At 12 months				
No				
At 3 months				
At 6 months				
At 9 months				
At 12 months				

8.2.6.4. OS vs HEMOGLOBIN

Figure 16: OS vs HEMOGLOBIN

Table 84: Median/mean OS (estimated by Kaplan-Meier) vs HEMOGLOBIN

	Median (months)	CI 95%	RMST	CI 95%
<10				
>=10				

Table 85: OS estimated survival ratio vs HEMOGLOBIN

OS	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	CI 95%
<10				
At 3 months				
At 6 months				
At 9 months				
At 12 months				
>=10				
At 3 months				
At 6 months				
At 9 months				
At 12 months				

8.2.6.5. OS vs LIVER METASTASIS

Figure 17: OS vs LIVER METASTASIS

Table 86: Median/mean OS (estimated by Kaplan-Meier) vs LIVER METASTASIS

	Median (months)	CI 95%	RMST	CI 95%
No				
Yes				

Table 87: OS estimated survival ratio vs LIVER METASTASIS

OS	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	CI 95%
No				
At 3 months				
At 6 months				
At 9 months				
At 12 months				
Yes				
At 3 months				
At 6 months				
At 9 months				
At 12 months				

9. SAFETY ANALYSIS

The following analyses in this section are carried out in the safety population (N = XX patients).

In the following tables, the adverse event which are not completely ruled out as toxicities or serious are considered toxicities and SAEs respectively.

Table 12: Overall safety

Overall	Overall (N=)
Adverse Events	
No	
Yes	
AE Grade >=3	
No	
Yes	
Toxicity: AE related to Atezolizumab	
No	
Yes	
Toxicity: AE related to Cisplatin	
No	
Yes	
Toxicity: AE related to Gemcitabine	
No	
Yes	
Toxicity: AE related to all treatments	
No	
Yes	
Toxicity: AE related to any treatment	
No	
Yes	
Toxicity grade >=3	
No	
Yes	
Toxicity related to Atezolizumab grade >=3	
No	
Yes	
Toxicity related to Cisplatin grade >=3	
No	
Yes	
Toxicity related to Gemcitabine grade >=3	
No	
Yes	
Toxicity related to all treatments grade >=3	
No	
Yes	
SAE	
No	

Overall	Overall (N=)
Yes	

Table 13: Toxicities with 5% threshold

Toxicity	Frequency	Percentage (%)

Table 14: Grade of toxicities with 5% threshold overall

Toxicity	No	G-UK	G-1	G-2	G-3	G-4	G-5

Table 15: List of toxicities grade ≥ 3 in all patients

Patient Number	AE CTCAE	AE Grade	AE Related	AE Related to

Table 16: AEs with 5% threshold

AE	Frequency	Percentage (%)

Table 17: Grade of AEs with 5% threshold overall

AE	No	G-UK	G-1	G-2	G-3	G-4	G-5

Table 18: List of all SAEs

Patient Number	AE CTCAE	AE CTCAE Other	AE Grade	AE Start Date	AE Stop Date	AE Related	AE Related to	AE SAE	AE Intensity

9.1. Annex 1

Table 19: List of all toxicities

Patient Number	AE CTCAE	AE CTCAE Other	AE Grade	AE Start Date	AE Stop Date	AE Related	AE Related to	AE SAE	AE Intensity

Figure 18: Global Toxicities with a frequency greater than 5%

Figure 19: Global irAEs with a frequency as toxicity greater than 5%

Figure 20: Summary of adverse events.

All AEs have been grouped into blocks when the start date is consecutive to the end of the same previous AE (no more than 1 day has passed) for the same patient. The highest severity within the block is the one that remains. Additionally, if one of the events was related to the medication, that relationship is maintained for the entire block.

Events	SAE (N pts)				No SAE (= Total AEs - SAEs)	
	N pts SAE	N eventos SAE	N eventos muerte	N SAE Rlt	N pts	N eventos

A threshold of 5% was set for No SAEs.