ARC-8: Phase 1/1b Randomized Study of Quemliclustat + Gemcitabine/Nab-Paclitaxel ± Zimberelimab in Patients With Treatment-Naive Metastatic Pancreatic Adenocarcinoma

Poster Board #: L14

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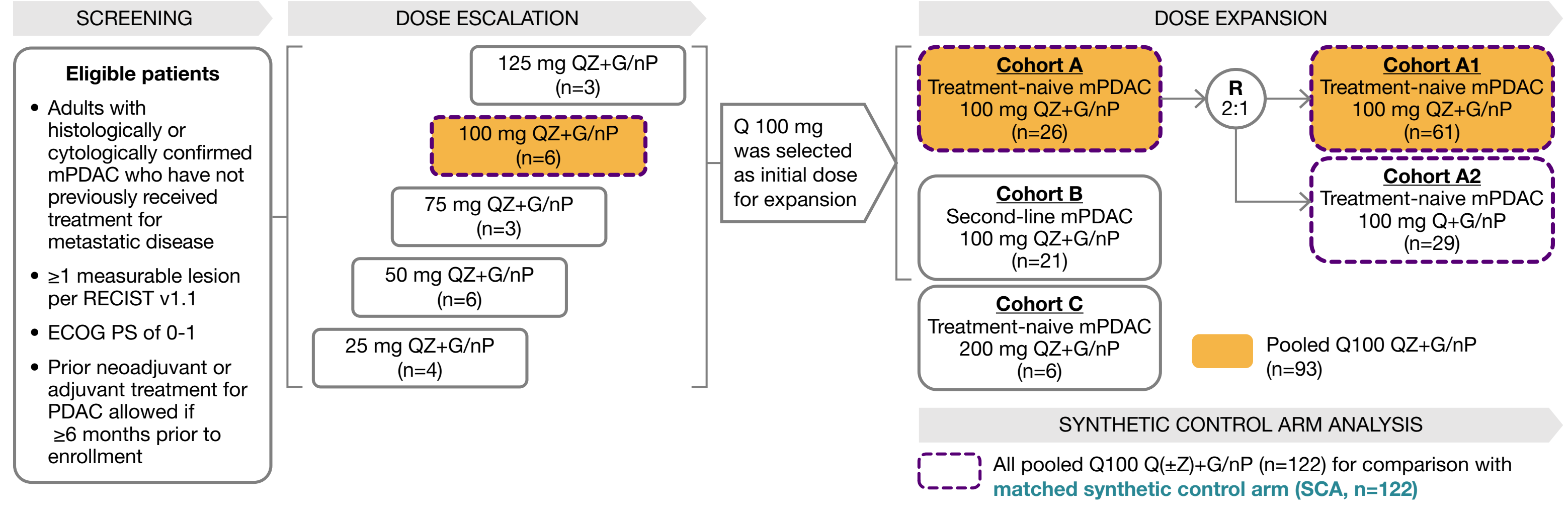
INTRODUCTION

- Metastatic pancreatic ductal adenocarcinoma (mPDAC) remains one of the most difficult-to-treat tumor types, with a median survival of <1 year after diagnosis[1]
  - Liver metastasis is a poor prognostic factor in mPDAC, with a median overall survival (OS) of 8.6 months (vs 13.8 months without liver metastasis) with the treatment of gemcitabine/nab-paclitaxel (G/nP)[2]
- In PDAC, extracellular adenosine produced from adenosine triphosphate in the tumor microenvironment suppresses antitumor immune responses[3,4]
- Quemliclustat (Q) is a potent and selective small-molecule inhibitor of soluble and cell-bound CD73, a key enzyme involved in the production of extracellular adenosine within the tumor microenvironment[5-7]
  - CD73 expression is elevated in PDAC and correlates with poor clinical outcomes[8,9]
- Zimberelimab (Z), a monoclonal antibody that binds PD-1 on T and NK cells preventing PD-L1–mediated immunosuppressive effects, and its monotherapy has demonstrated efficacy across multiple tumor types[10,11]
- ARC-8 aims to evaluate Q±Z in combination with G/nP in mPDAC

METHODS

- ARC-8 (NCT04104672) is a phase 1b dose escalation and expansion study in patients with treatment-naive mPDAC
- Q 100 mg (Q100) was previously determined as the recommended dose for expansion based on pharmacokinetic, pharmacodynamic, and tolerability data, with no maximum tolerated dose identified in the dose escalation phase[12]
- Patients were treated with Q100 IV q2w with standard doses of G/nP with Z (240 mg IV q2w) in the dose expansion (Cohort A; QZ+G/nP) and in randomized (2:1) cohorts either with Z (Cohort A1; QZ+G/nP) or without Z (Cohort A2; Q+G/nP) (**Figure 1**)
- Adverse events (AEs) were recorded and graded per NCI CTCAE v5.0
- Clinical activity was assessed every 8 weeks per RECIST v1.1; endpoints included safety, overall response rate (ORR), OS, and progression-free survival (PFS)

Figure 1. Study Design



SCREENING

Eligible patients
- Adults with histologically or cytologically confirmed mPDAC who have not previously received treatment for metastatic disease
- ≥1 measurable lesion per RECIST v1.1
- ECOG PS of 0-1
- Prior neoadjuvant or adjuvant treatment for PDAC allowed if ≥6 months prior to enrollment

DOSE ESCALATION

125 mg QZ+G/nP (n=3)
100 mg QZ+G/nP (n=6)
75 mg QZ+G/nP (n=3)
50 mg QZ+G/nP (n=6)
25 mg QZ+G/nP (n=4)

Q 100 mg was selected as initial dose for expansion

DOSE EXPANSION

Cohort A Treatment-naive mPDAC 100 mg QZ+G/nP (n=26)
R 2:1
Cohort A1 Treatment-naive mPDAC 100 mg QZ+G/nP (n=61)
Cohort A2 Treatment-naive mPDAC 100 mg Q+G/nP (n=29)
Cohort B Second-line mPDAC 100 mg QZ+G/nP (n=21)
Cohort C Treatment-naive mPDAC 200 mg QZ+G/nP (n=6)
🟧 Pooled Q100 QZ+G/nP (n=93)

SYNTHETIC CONTROL ARM ANALYSIS

▭ All pooled Q100 Q(±Z)+G/nP (n=122) for comparison with matched synthetic control arm (SCA, n=122)

Study treatment may continue until disease progression, unacceptable toxicity, consent withdrawal, or by the investigator's decision

ECOG PS, Eastern Cooperative Oncology Group performance status; G/nP, gemcitabine/nab-paclitaxel; mPDAC, metastatic pancreatic ductal adenocarcinoma; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors; Q, quemliclustat; Z, zimberelimab.

RESULTS

Patient Characteristics

- As of June 19, 2023, 122 patients with treatment-naive mPDAC received Q100, including 93 patients treated with quadruplet QZ+G/nP (Pooled Q100 QZ+G/nP; dose escalation, n=6; Cohort A, n=26; and Cohort A1, n=61) and 29 patients treated with triplet Q+G/nP (Cohort A2; **Figure 1**)
- Median ages for Cohort A2, Cohort A1, and Pooled Q100 QZ+G/nP were 65.0 years, 66.0 years, and 66.0 years, respectively; 69.0%, 68.9%, and 64.5% had Eastern Cooperative Oncology Group performance status (ECOG PS) of 1 and 58.6%, 68.9%, and 66.7% had liver metastasis at baseline, respectively (**Table 1**)
- As of the cutoff date, 13.8%, 3.3%, and 4.3% of patients in Cohort A2, Cohort A1, and Pooled Q100 QZ+G/nP, respectively, were ongoing on treatment, and 37.9%, 29.5%, and 28.0%% were ongoing study follow-up (**Table 1**)
  - The most common reason for study treatment discontinuation was progressive disease (55.2%, 63.9%, and 61.3%, respectively), followed by withdrawal from treatment by patient (6.9%, 11.5%, and 12.9%, respectively)

Table 1. Patient Characteristics and Disposition

	A2: Q+G/nP (n=29)	A1: QZ+G/nP (n=61)	Pooled Q100 QZ+G/nP (n=93)	All pooled Q100 Q(±Z)+G/nP (n=122)
Median age (IQR)	65.0 (61, 70)	66.0 (58, 72)	66.0 (58, 72)	65.5 (59, 72)
Aged ≥65, n (%)	16 (55.2)	36 (59.0)	54 (58.1)	70 (57.4)
Female, n (%)	14 (48.3)	30 (49.2)	44 (47.3)	58 (47.5)
Race, White/Asian/Black/other or NR, %	82.8 / 6.9 / 3.4 / 6.9	73.8 / 8.2 / 6.6 / 11.4	74.2 / 8.6 / 5.4 / 11.8	76.2 / 8.2 / 4.9 / 10.7
ECOG PS, 0/1, (%)	31.0 / 69.0	31.1 / 68.9	35.5 / 64.5	34.4 / 65.6
Liver metastasis present at baseline,[a] n (%)	17 (58.6)	42 (68.9)	62 (66.7)	79 (64.8)
Prior pancreatic cancer surgery,[b] n (%)	8 (27.6)	7 (11.5)	13 (14.0)	21 (17.2)
Any prior systemic anticancer therapy, n (%)	4 (13.8)	6 (9.8)	11 (11.8)	15 (12.3)
Any prior radiotherapy, n (%)	1 (3.4)	4 (6.6)	9 (9.7)	10 (8.2)
Median months since initial diagnosis[c] (min/max)	1.3 (0, 49)	0.9 (0, 55)	0.9 (0, 55)	1.1 (0, 55)
Ongoing treatment, n (%)	4 (13.8)	2 (3.3)	4 (4.3)	8 (6.6)
Discontinued all treatment, n (%)	25 (86.2)	59 (96.7)	89 (95.7)	114 (93.4)
Ongoing study follow-up, n (%)	11 (37.9)	18 (29.5)	26 (28.0)	37 (30.3)
Discontinued study, n (%)	18 (62.1)	43 (70.5)	67 (72.0)	85 (69.7)

ECOG PS, Eastern Cooperative Oncology Group performance status; G/nP, gemcitabine/nab-paclitaxel; IQR, interquartile range; NR, not reported; Q, quemliclustat; Z, zimberelimab.
[a] Derived from baseline tumor assessment data. [b] Derived from prior procedures data. [c] Stage not specified.

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RESULTS (continued)

Safety

- All patients reported at least one treatment-emergent AE (TEAE); among Cohort A2, Cohort A1, and Pooled Q100 QZ+G/nP patients, 89.7%, 85.2%, and 83.9% had grade ≥3 TEAE and 24.1%, 23.0%, and 22.6% had AEs that led to discontinuation of study treatment, respectively (**Table 2**)
- Most commonly reported grade ≥3 TEAEs were neutropenia (37.9%, 34.4%, and 38.7%, respectively) and anemia (27.6%, 26.2%, and 23.7%, respectively)
- Five deaths were reported with causes of death of respiratory failure (n=2), sepsis (n=1), gastrointestinal bleeding (n=1), and stroke (n=1); none of these were considered related to Q or Z
- No new safety signals were observed

Table 2. Summary of Adverse Events

	A2: Q+G/nP (n=29)	A1: QZ+G/nP (n=61)	Pooled Q100 QZ+G/nP (n=93)	All pooled Q100 Q(±Z)+G/nP (n=122)
Any TEAE	29 (100)	61 (100)	93 (100)	122 (100)
At least one Grade ≥3 TEAE	26 (89.7)	52 (85.2)	78 (83.9)	104 (85.2)
Serious TEAE	15 (51.7)	29 (47.5)	50 (53.8)	65 (53.3)
Grade 5 TEAE	0	4 (6.6)	5 (5.4)	5 (4.1)
AE leading to modification/interruption[a]	24 (82.8)	52 (85.2)	82 (88.2)	106 (86.9)
AE leading to discontinuation[a]	7 (24.1)	14 (23.0)	21 (22.6)	28 (23.0)
IRR (per CRF)	3 (10.3)	4 (6.6)	6 (6.5)	9 (7.4)
Immune-mediated AE (per CRF)	2 (6.9)	6 (9.8)	10 (10.8)	12 (9.8)

AE, adverse event; CRF, case report form; G/nP, gemcitabine/nab-paclitaxel; IRR, infusion-related reaction; Q, quemliclustat; TEAE, treatment-emergent AE; Z, zimberelimab.
[a] Any study drug.

Efficacy

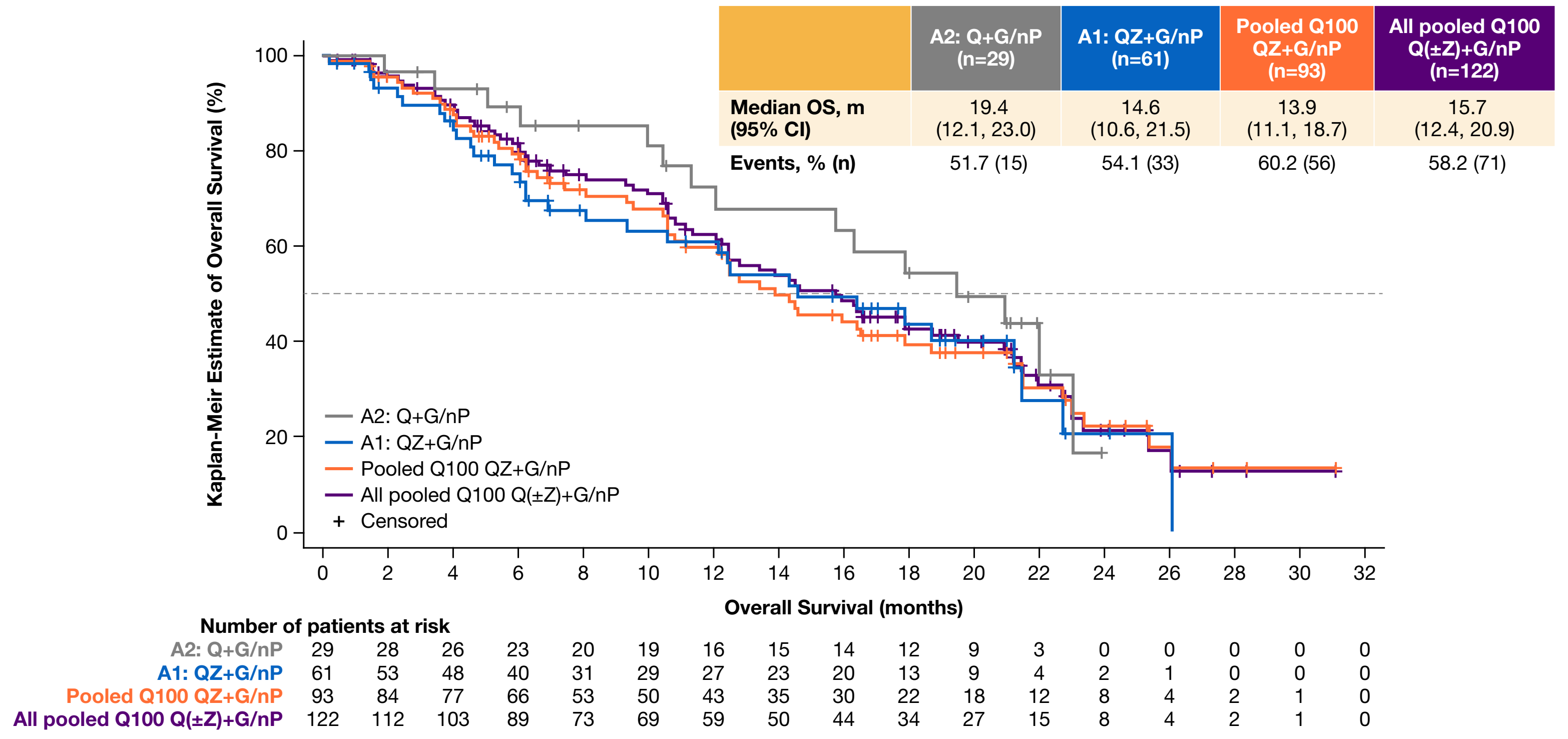
- ORR (unconfirmed) was 41% (95% CI, 24-61), 34% (95% CI, 23-48), and 38% (95% CI, 28-48) for Cohort A2, Cohort A1, and Pooled Q100 QZ+G/nP, respectively; median duration of response (DOR) was 5.5, 3.7, and 4.7 months, respectively (**Table 3**)
- The median PFS was 8.8 months (95% CI, 6.4-12.6), 4.9 months (95% CI, 3.7-6.0), and 5.4 months (95% CI, 4.9-7.3) for Cohort A2, Cohort A1, and Pooled Q100 QZ+G/nP, respectively (**Table 3**)
- ORR, DOR, median PFS, and PFS rates were consistently higher/longer in Cohort A2 compared with Cohort A1 (**Table 3**)
- The median OS was 19.4 months (95% CI, 12.1-23.0), 14.6 months (95% CI, 10.6-21.5), and 13.9 months (95% CI, 11.1-18.7) for Cohort A2, Cohort A1, and Pooled Q100 QZ+G/nP, respectively (**Table 3**, **Figure 2**)
- Median OS and OS rates were greater in Cohort A2 compared with Cohort A1 (**Table 3**, **Figure 2**)
- Cohort A2 had a smaller proportion of patients with liver metastasis at baseline (58.6%) compared with Cohort A1 (68.9%) and Pooled Q100 QZ+G/nP (66.7%) (**Table 4**)
- Median OS was 21.2 months (95% CI, 13.9-25.4) in Pooled Q100 QZ+G/nP without liver metastasis at baseline, compared with 11.1 months (95% CI, 8.1-14.5) in those with liver metastasis at baseline (**Table 4**)
- Median OS was 21.5 months (95% CI, 14.5-NE) in Pooled Q100 QZ+G/nP with a history of prior surgery, compared with 12.5 months (95% CI, 10.4-16.4) in those without prior surgery

Table 3. Summary of Efficacy

	A2: Q+G/nP (n=29)	A1: QZ+G/nP (n=61)	Pooled Q100 QZ+G/nP (n=93)	All pooled Q100 Q(±Z)+G/nP (n=122)
ORR, % (95% CI)	41 (24, 61)	34 (23, 48)	38 (28, 48)	39 (30, 48)
Confirmed ORR, % (95% CI)	38 (21, 58)	25 (15, 37)	26 (17, 36)	29 (21, 38)
Median DOR, months (95% CI)	5.5 (4.1, 11.2)	3.7 (2.6, 10.5)	4.7 (3.3, 9.3)	5.4 (3.7, 9.3)
Median PFS, mo (95% CI)	8.8 (6.4, 12.6)	4.9 (3.7, 6.0)	5.4 (4.9, 7.3)	6.3 (5.4, 7.7)
Median OS, mo (95% CI)	19.4 (12.1, 23.0)	14.6 (10.6, 21.5)	13.9 (11.1, 18.7)	15.7 (12.4, 20.9)
12-mo OS, %	72.3	60.9	59.6	62.7
18-mo OS, %	54.2	43.5	39.3	42.8
Median OS follow-up, mo (95% CI)	21.1 (19.8, 22.3)	17.6 (16.6, 20.3)	20.3 (17.1, 24.6)	21.0 (19.0, 22.8)
Subsequent systemic anticancer therapy, %	48.3	42.6	46.2	46.7

Based on RECIST v1.1.
DOR, duration of response; G/nP, gemcitabine/nab-paclitaxel; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; Q, quemliclustat; RECIST, Response Evaluation Criteria in Solid Tumors; Z, zimberelimab.

Figure 2. Overall Survival by Kaplan Meier Analysis



	A2: Q+G/nP (n=29)	A1: QZ+G/nP (n=61)	Pooled Q100 QZ+G/nP (n=93)	All pooled Q100 Q(±Z)+G/nP (n=122)
Median OS, m (95% CI)	19.4 (12.1, 23.0)	14.6 (10.6, 21.5)	13.9 (11.1, 18.7)	15.7 (12.4, 20.9)
Events, % (n)	51.7 (15)	54.1 (33)	60.2 (56)	58.2 (71)

Number of patients at risk

	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32
A2: Q+G/nP	29	28	26	23	20	19	16	15	14	12	9	3	0	0	0	0	0
A1: QZ+G/nP	61	53	48	40	31	29	27	23	20	13	9	4	2	1	0	0	0
Pooled Q100 QZ+G/nP	93	84	77	66	53	50	43	35	30	22	18	12	8	4	2	1	0
All pooled Q100 Q(±Z)+G/nP	122	112	103	89	73	69	59	50	44	34	27	15	8	4	2	1	0

G/nP, gemcitabine/nab-paclitaxel; OS, overall survival; Q, quemliclustat; Z, zimberelimab.

RESULTS (continued)

- To further understand the performance of the triplet regimen (Cohort A2), an analysis by the presence/absence of liver metastasis at baseline was conducted

Table 4. Overall Survival by Presence of Liver Metastasis at Baseline

Without Liver Metastasis at baseline	A2: Q+G/nP (n=12)	A1: QZ+G/nP (n=19)	Pooled Q100 QZ+G/nP (n=31)	All pooled Q100 Q(±Z)+G/nP (n=43)
Events (%)	4 (33.3)	7 (36.8)	16 (51.6)	20 (46.5)
Median OS, months	**22.0**	**21.2**	**21.2**	**21.5**
95% CI	17.9, NE	14.6, NE	13.9, 25.4	17.9, 25.4
With Liver Metastasis at baseline (Prev. ~65%)	**A2: Q+G/nP (n=17)**	**A1: QZ+G/nP (n=42)**	**Pooled Q100 QZ+G/nP (n=62)**	**All pooled Q100 Q(±Z)+G/nP (n=79)**
Events (%)	11 (64.7)	26 (61.9)	40 (64.5)	51 (64.6)
Median OS, months	**12.1**	**12.2**	**11.1**	**12.1**
95% CI	10.0, 20.9	6.2, 17.9	8.1, 14.5	10.0, 15.7

Based on Kaplan Meier analysis.
G/nP, gemcitabine/nab-paclitaxel; NE, not estimable; OS, overall survival; Q, quemliclustat; Z, zimberelimab.

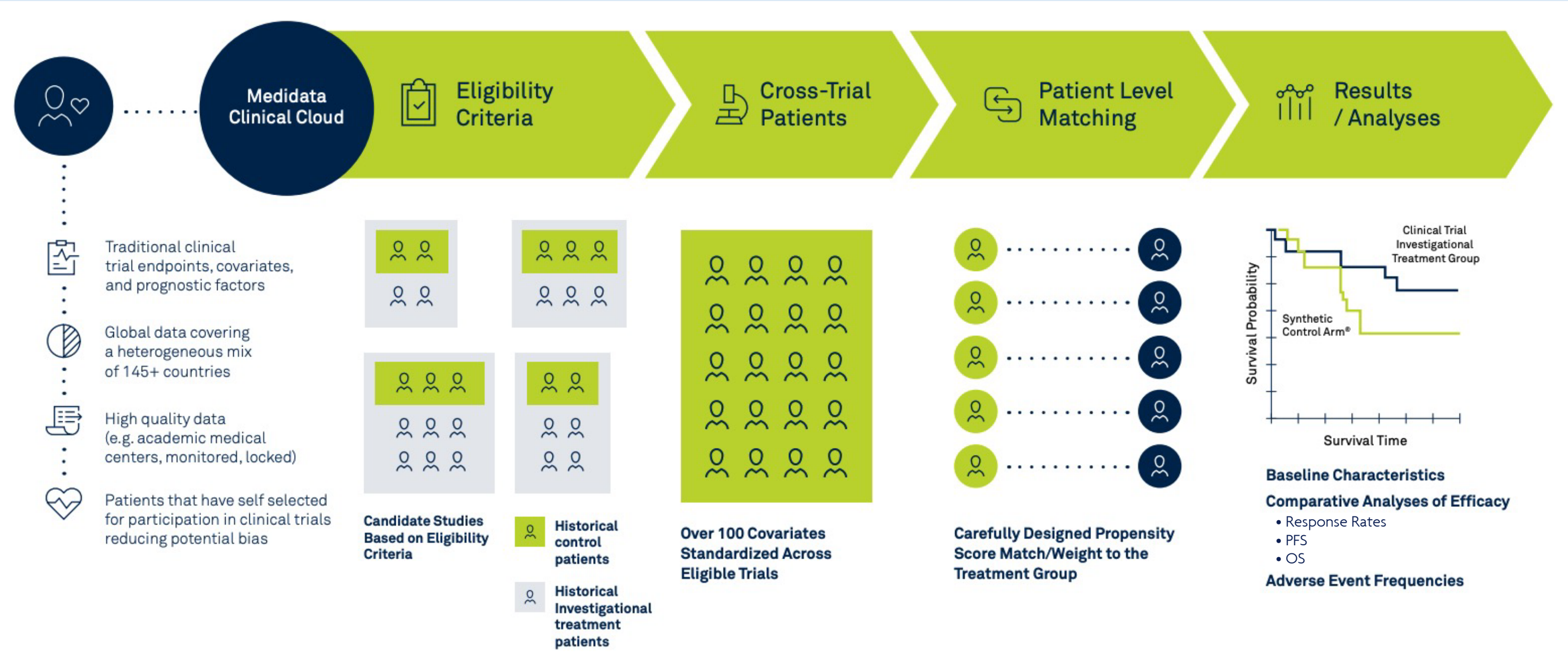
- The ~2-fold difference in median OS based on the presence of liver metastasis for Cohort A2, Cohort A1, and Pooled Q100 QZ+G/nP led to the development of an ad hoc exploratory analysis with a pooled arm from ARC-8, comprising the Pooled Q100 QZ+G/nP and Cohort A2, and a synthetic cohort arm (**Table 4**)

ARCUS & MEDIDATA AI SYNTHETIC CONTROL ARM PROJECT

OBJECTIVES

- Construct a synthetic control arm (SCA) to address the differences in patient characteristics in the ARC-8 cohorts (**Table 1**) using historical clinical trial data from patients treated with G/nP, balanced to the baseline characteristics of ARC-8 study participants (**Figure 3**)
  - SCA-eligible pool from historical clinical trials that meet ARC-8 key entry criteria included 515 patients
  - SCA included historical data from up to 4 global phase 2 and 3 trials (~50% each) with G/nP as the target intervention; the trials started in 2013-2019 and were completed in 2018-2023
  - SCA was generated and matched to the All pooled Q100 Q(±Z)+G/nP (n=122), comprising dose escalation Q100 QZ+G/nP (n=6), Cohort A (n=26), Cohort A1 (n=61), and Cohort A2 (n=29, **Figure 1**)
  - SCA was constructed using greedy nearest-neighbor matching in propensity score without replacement[13] with exact matching on baseline liver metastasis while outcome data were blinded
- Assess treatment effects on objective response rate, PFS, and OS in the SCA patients
- Compare the treatment effects and clinical activity between matched SCA and ARC-8 participants (**Figure 3**)

Figure 3. How a Synthetic Control Arm® Is Built



PFS, progression-free survival; OS, overall survival.

SCA SUMMARY: PRIMARY ANALYSIS (N=122)

Baseline demographics and characteristics

- Patients were matched from the SCA-eligible pool based on key criteria, including ECOG PS, liver metastasis status at baseline, and history of prior surgery for PDAC (**Table 5**)

Table 5. SCA Population Baseline Demographics and Disease Characteristics Before and After Matching

	Before Matching	After Matching	
% (n)	SCA Eligible (n=515)	All pooled Q100 Q(±Z)+G/nP (n=122)	SCA (n=122)
ECOG PS 0	47.6 (245)	34.4 (42)	37.7 (46)
ECOG PS 1	52.4 (270)	65.6 (80)	62.3 (76)
Liver metastases at baseline	80.6 (415)	64.8 (79)	64.8 (79)
Prior surgery for PDAC	8.9 (46)	17.2 (21)	15.6 (19)

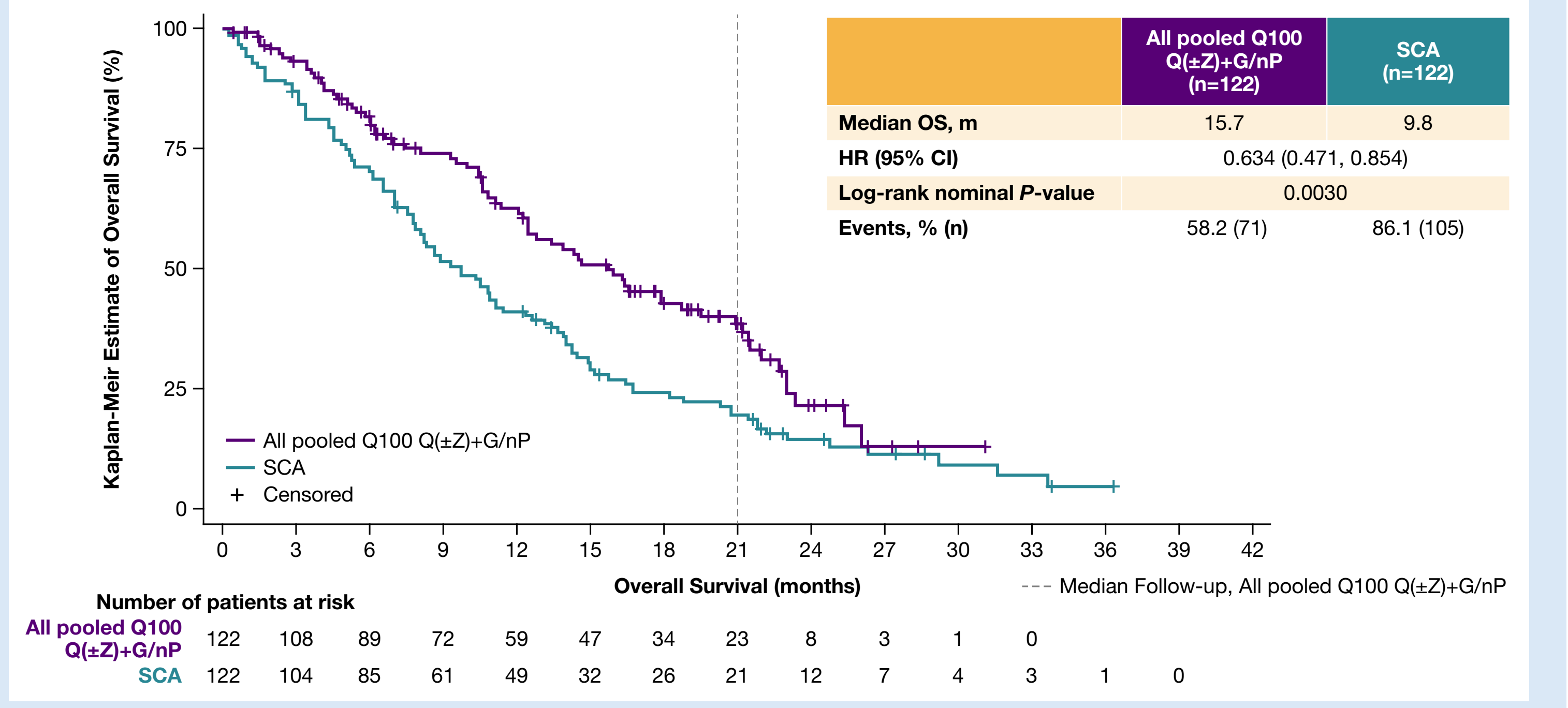
ECOG PS, Eastern Cooperative Oncology Group performance status; G/nP, gemcitabine/nab-paclitaxel; PDAC, pancreatic ductal adenocarcinoma; Q, quemliclustat; SCA, synthetic control arm; Z, zimberelimab.

SCA SUMMARY: PRIMARY ANALYSIS (N=122) (continued)

Efficacy

- Longer OS for the All pooled Q100 Q(±Z)+G/nP group was observed (**Figure 4**)
  - 37% risk reduction of death with hazard ratio (HR) 0.63 (95% CI, 0.47-0.85)
  - 5.9-month increase in median OS; 15.7 months vs 9.8 months
- Trend in longer PFS for the All pooled Q100 Q(±Z)+G/nP group was observed
  - 22% risk reduction of progression/death with HR 0.78 (95% CI, 0.58-1.05)
  - 0.8-month increase in median PFS; 6.3 months vs 5.5 months
- Objective response rate was similar between the All pooled Q100 Q(±Z)+G/nP group 38.5% (95% CI, 29.9-47.8) and SCA 41.0% (95% CI, 32.2-50.3)

Figure 4. Overall Survival: Pooled Q(±Z)+G/nP vs SCA



	All pooled Q100 Q(±Z)+G/nP (n=122)	SCA (n=122)
Median OS, m	15.7	9.8
HR (95% CI)	0.634 (0.471, 0.854)	
Log-rank nominal *P*-value	0.0030	
Events, % (n)	58.2 (71)	86.1 (105)

Number of patients at risk

	0	3	6	9	12	15	18	21	24	27	30	33	36	39
All pooled Q100 Q(±Z)+G/nP	122	108	89	72	59	47	34	23	8	3	1	0		
SCA	122	104	85	61	49	32	26	21	12	7	4	3	1	0

G/nP, gemcitabine/nab-paclitaxel; OS, overall survival; Q, quemliclustat; SCA, synthetic control arm; Z, zimberelimab.

CONCLUSIONS

- Results from ARC-8 demonstrate the addition of Q100±Z to G/nP was safe and tolerable, with no new safety signals or significant added toxicity to G/nP
- ORR, PFS, and OS were greater in Cohort A2 compared with Cohort A1; however, similar median OS values were seen across the different study arms once patients with/without liver metastasis were evaluated separately
  - The OS data, including data by liver metastasis at baseline, were numerically greater than benchmark data[2]
- The OS data for all study arms containing Q, including the prolonged OS for the All pooled Q100 Q(±Z)+G/nP compared with SCA based on an ad hoc exploratory analysis, are promising and support further development of Q in mPDAC
- Biomarker studies are ongoing and the results will be presented at an upcoming congress

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