PharmaSUG 2026 - Paper AS-160

Oncology Solid Tumor Subcutaneous vs Intravenous Late-stage Study Analysis

Sumanjali Mangalarapu, Chuqing Chen, and Anilkumar Anksapur, Merck & Co., Inc., Rahway, NJ, USA.

ABSTRACT

This paper presents practical programming approaches for analyzing data of a subcutaneous versus intravenously administered study treatment, with pharmacokinetics (PK) designated as the primary endpoint. It focuses on the creation of key Clinical Data Interchange Standards Consortium (CDISC) Analysis Data Model (ADaM) datasets, their mock shells and programming logic used for key summary tables supporting the endpoints. Programming content in this paper highlights primary and secondary endpoints derivations.

Because PK as the primary endpoint is uncommon for late-stage solid tumor oncology trials, the programming required tailored analytic strategies, including model-based PK parameter estimation and specific endpoint derivations. This paper concludes that effective ADaM implementation and analyses require structured cross-functional collaboration between analysis and reporting (A&R) and Pharmacokinetics/Pharmacodynamics (PK/PD) programming teams with oversight from statisticians from the respective programming groups.

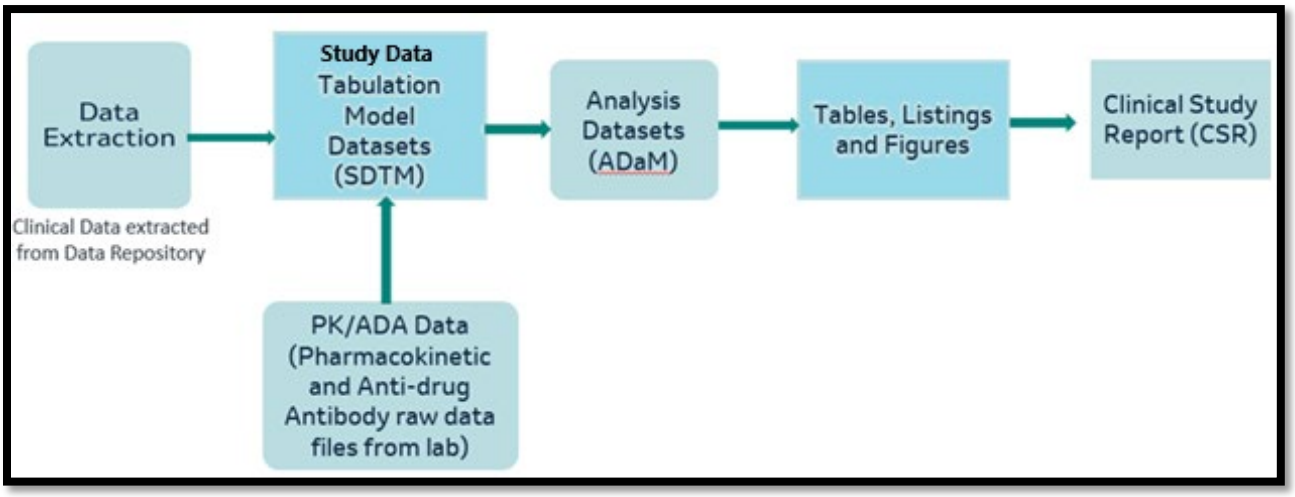
INTRODUCTION

Intravenous (IV) infusion imposes logistical burdens including prolonged chair time, reliance on infusion suites, and increased demand for healthcare staff.

Subcutaneous (SC) delivery of treatment has appeared as an attractive alternative, offering shorter administration times, enhanced patient convenience, and potential cost efficiencies.

A study was conducted to evaluate the non-inferiority of SC over IV formulation. For this purpose, model-based PK exposure comparisons between IV and SC formulations are included besides traditional oncology key analyses conducted in solid tumors.

The chart below illustrates the overall programming workflow in the late-stage analysis of the study, highlighting the collaboration between PK/PD and A&R programming teams.



Display 1: Overall process flow of deliverable components in programming team.

PK/PD ANALYSIS DATASETS

The PK/PD analysis datasets support primary endpoints by characterizing the PK relationships essential for evaluating drug efficacy and safety.

ADPC - PK CONCENTRATIONS ANALYSIS DATASET

ADPC is a CDISC ADaM dataset structured using the Basic Data Structure (BDS) format, and it has standardized, traceable, and analysis-ready PK concentration data.

The ADPC dataset has one or more records per subject, parameter, and analysis time point. The dataset has all concentration results from SDTM Pharmacokinetic Concentrations (PC) and PC Domain Supplemental Qualifiers (SUPPPC) datasets.

SDTM PC domain has lab-reported concentration measurements, sample date/times, and analyte codes. External PK raw data files are merged with SDTM PC to capture concentration results and assay details.

Following are the PK concentration samples collected over a 42-day dosing cycle for Cycle 1 (weeks 1 to 6) and Cycle 3 (weeks 13 to 18) for endpoint assessments in addition to other PK data collection times.

- SC arm: Days 1 (at time 0), 2, 3, 4, 5, 6, 7, 10, 15, 29, and 42.
- IV arm: Days 1 (at time 0 and end-of-infusion), 4, 15, 29, and 42.

USUBJID	PARAM	PARAMCD	AVISIT	ATPT	AFRLT	ROUTE
ABC-123_00000001	ABC (ng/mL)	ABC	Cycle 1 Day 1	PREDOSE	0	intravenous administration
ABC-123_00000001	ABC (ng/mL)	ABC	Cycle 1 Day 1	END OF INFUSION	0.02	intravenous administration
ABC-123_00000001	ABC (ng/mL)	ABC	Cycle 1 Day 4	POSTDOSE DAY 4	2.9	intravenous administration
ABC-123_00000001	ABC (ng/mL)	ABC	Cycle 1 Day 15	POSTDOSE DAY 15	13.94	intravenous administration
ABC-123_00000001	ABC (ng/mL)	ABC	Cycle 1 Day 29	POSTDOSE DAY 29	28	intravenous administration
ABC-123_00000001	ABC (ng/mL)	ABC	Cycle 1 Day 42	POSTDOSE DAY 42	41	intravenous administration
ABC-123_00000001	ABC (ng/mL)	ABC	Cycle 3 Day 1	PREDOSE	83.9	intravenous administration
ABC-123_00000001	ABC (ng/mL)	ABC	Cycle 3 Day 1	END OF INFUSION	84.02	intravenous administration
ABC-123_00000001	ABC (ng/mL)	ABC	Cycle 3 Day 4	POSTDOSE DAY 4	86.9	intravenous administration
ABC-123_00000001	ABC (ng/mL)	ABC	Cycle 3 Day 42	POSTDOSE DAY 42	125.02	intravenous administration
ABC-123_00000002	ABC (ng/mL)	ABC	Cycle 1 Day 1	PREDOSE	0	subcutaneous injection
ABC-123_00000002	ABC (ng/mL)	ABC	Cycle 1 Day 2	POSTDOSE DAY 2	1.03	subcutaneous injection
ABC-123_00000002	ABC (ng/mL)	ABC	Cycle 1 Day 3	POSTDOSE DAY 3	2.05	subcutaneous injection
ABC-123_00000002	ABC (ng/mL)	ABC	Cycle 1 Day 4	POSTDOSE DAY 4	3.03	subcutaneous injection
ABC-123_00000002	ABC (ng/mL)	ABC	Cycle 1 Day 5	POSTDOSE DAY 5	4.01	subcutaneous injection
ABC-123_00000002	ABC (ng/mL)	ABC	Cycle 1 Day 6	POSTDOSE DAY 6	5.1	subcutaneous injection
ABC-123_00000002	ABC (ng/mL)	ABC	Cycle 1 Day 7	POSTDOSE DAY 7	6.02	subcutaneous injection
ABC-123_00000002	ABC (ng/mL)	ABC	Cycle 1 Day 10	POSTDOSE DAY 10	9.038	subcutaneous injection
ABC-123_00000002	ABC (ng/mL)	ABC	Cycle 1 Day 15	POSTDOSE DAY 15	14	subcutaneous injection
ABC-123_00000002	ABC (ng/mL)	ABC	Cycle 1 Day 29	POSTDOSE DAY 29	28	subcutaneous injection
ABC-123_00000002	ABC (ng/mL)	ABC	Cycle 1 Day 42	POSTDOSE DAY 42	41.013	subcutaneous injection
ABC-123_00000002	ABC (ng/mL)	ABC	Cycle 3 Day 1	PREDOSE	83.8	subcutaneous injection
ABC-123_00000002	ABC (ng/mL)	ABC	Cycle 3 Day 4	POSTDOSE DAY 4	87.1	subcutaneous injection
ABC-123_00000002	ABC (ng/mL)	ABC	Cycle 3 Day 10	POSTDOSE DAY 10	93.01	subcutaneous injection
ABC-123_00000002	ABC (ng/mL)	ABC	Cycle 3 Day 42	POSTDOSE DAY 42	125.2	subcutaneous injection

Display 2: Sample ADPC data.

ADPP – PK PARAMETERS ANALYSIS DATASET

ADPP is a CDISC ADaM dataset structured using the BDS format and has derived PK parameters from Non-Linear Mixed-Effects Modeling Software (NONMEM).

ADPP dataset has data needed to analyze PK exposure between IV and SC arms for assessing primary and secondary endpoints. This dataset is created using SDTM PP and PC datasets.

SDTM PP dataset was created for this study participants based on their outputs from POPPK (Population PK) Analysis and Modeling ran on Pooled NONMEM PK analysis dataset (ADNMPK). Parameter estimates like AUC, CTROUGH, OCTROUGH and CMAX (further explained in following section) are generated based on Non-Linear Mixed-Effects Models (NLMEMs).

PK Parameter Definitions

- AUC0–6wks (AUCINT): Area under the curve for PK exposure over the dosing cycle, calculated using model-predicted concentrations.
- CTROUGH: Model-predicted concentration at Day 42 of the dosing cycle.
- CMAX: For IV administration, the concentration at end-of-infusion; for SC administration, the maximum predicted concentration during the cycle.
- OCTROUGH: Observed drug concentration at Day 42 of Cycle 3.

USUBJID	PARCAT1	PARAM	PARAMCD	AVAL	ROUTE	CYCLE	PPROTRFL
ABC-123_00000001	Predicted	AUC from 0 to 6 Weeks (ug*day/mL)	AUCINT	490	Intravenous	1	Y
ABC-123_00000001	Predicted	AUC from 0 to 6 Weeks (ug*day/mL)	AUCINT	715	Intravenous	3	Y
ABC-123_00000001	Predicted	Conc Trough (ug/mL)	CTROUGH	8	Intravenous	1	Y
ABC-123_00000001	Predicted	Conc Trough (ug/mL)	CTROUGH	15	Intravenous	3	Y
ABC-123_00000001	Predicted	Max Conc (ug/mL)	CMAX	45	Intravenous	1	Y
ABC-123_00000001	Predicted	Max Conc (ug/mL)	CMAX	52	Intravenous	3	Y
ABC-123_00000001	Observed	Observed Conc Trough (ug/mL)	OCTROUGH	9	Intravenous	3	Y
ABC-123_00000002	Predicted	AUC from 0 to 6 Weeks (ug*day/mL)	AUCINT	810	Subcutaneous	1	Y
ABC-123_00000002	Predicted	AUC from 0 to 6 Weeks (ug*day/mL)	AUCINT	1270	Subcutaneous	3	Y
ABC-123_00000002	Predicted	Conc Trough (ug/mL)	CTROUGH	9	Subcutaneous	1	Y
ABC-123_00000002	Predicted	Conc Trough (ug/mL)	CTROUGH	17	Subcutaneous	3	Y
ABC-123_00000002	Predicted	Max Conc (ug/mL)	CMAX	36	Subcutaneous	1	Y
ABC-123_00000002	Predicted	Max Conc (ug/mL)	CMAX	49	Subcutaneous	3	Y
ABC-123_00000002	Observed	Observed Conc Trough (ug/mL)	OCTROUGH	12	Subcutaneous	3	Y

Display 3: Sample ADPP data.

PER-PROTOCOL POPULATION CRITERIA

- For primary endpoints, subjects must have received the required doses and have valid PK samples allowing estimation of model-based area under curve from 0 to 6 weeks (AUC0–6wks), trough concentration CTROUGH, and observed trough concentration (OCTROUGH).
- For secondary endpoints, subjects must have received the relevant doses and have sufficient PK data to estimate model-based exposure measures for Cycle 1 and steady-state Cycle 3.

OVERVIEW OF PK ENDPOINTS

Per protocol population flag is used to create below PK endpoints.

- The primary PK endpoints include model-based exposure estimates for Cycle 1 AUC0–6wks, steady-state Cycle 3 CTROUGH, and Cycle 3 OCTROUGH.
- Secondary PK endpoints include model-based exposure estimates for Cycle 1 CTROUGH, Cycle 1 maximum concentration (CMAX), steady-state Cycle 3 AUC0–6wks, and steady-state Cycle 3 CMAX.

EFFICACY ANALYSIS DATASETS

The analysis datasets supporting efficacy evaluations include ADINTDT, ADRS and ADTTE, each serving distinct analytical purposes.

ADINTDT – INTERMEDIATE DATES DATASET FOR ADTTE

ADINTDT is an intermediate dataset used to derive time-to-event parameters in ADTTE and is not directly used in analysis. It helps identify when event dates such as randomization, discontinuation, first dose, death, disease progression etc., occurred and support censoring rules in subsequent analysis datasets such as ADTTE for derivations. Below is an example of ADINTDT dataset structure.

VIEWTABLE: Rwork.Adintdt

	STUDYI	USUBJID	TRT01P	TRT0	PARAM	PARAMCD	PARAMN	PARC	PARCAT2	ADT	ADTF	AVALC	SRCDOM	SRCVAR
1	ABC-123	ABC-123_000000001	Treatment 1	1	Data Cutoff Date	DCUTDT	3			2025-09-17		2025-09-17		
2	ABC-123	ABC-123_000000001	Treatment 1	1	Date of Death	DTHDT	6			2025-03-02		2025-03-02	DD	DDDTC
3	ABC-123	ABC-123_000000001	Treatment 1	1	Date of Treatment Discontinuation WO CR	NCRDSCD	7			2024-10-29		2024-10-29	ADSL	TR01EDT
4	ABC-123	ABC-123_000000001	Treatment 1	1	Date of Randomization	RANDDT	1			2023-10-03		2023-10-03	ADSL	RANDDT
5	ABC-123	ABC-123_000000001	Treatment 1	1	Date of First Dose	TRTSDT	2			2023-10-03		2023-10-03	ADSL	TRTSDT
6	ABC-123	ABC-123_000000001	Treatment 1	1	Uncut Death Date with Imputation	UCDTHDT	5			2025-03-02		2025-03-02	DD	DDDTC
7	ABC-123	ABC-123_000000001	Treatment 1	1	Uncut Last Known Alive Date	UCLKADT	4			2024-11-19		2024-11-19	LB	LBDTC
8	ABC-123	ABC-123_000000001	Treatment 1	1	Date of Last Non-PD Assessment Per BICR	IRCLRSDT	22	BICR	RECIST 1.1	2024-04-10		2024-04-10	RS	RSDTC
9	ABC-123	ABC-123_000000001	Treatment 1	1	Date of Progression Per BICR	IRCPDDT	21	BICR	RECIST 1.1	2024-06-20		2024-06-20	RS	RELPSDTC
10	ABC-123	ABC-123_000000001	Treatment 1	1	Date of Last Non-PD Assessment Per INV	INVLRSDT	32	INV	RECIST 1.1	2024-02-02		2024-02-02	RS	RSDTC
11	ABC-123	ABC-123_000000001	Treatment 1	1	Date of Progression Per INV	INVPDDT	31	INV	RECIST 1.1	2024-04-10		2024-04-10	RS	RSDTC

Display 4: Sample ADINTDT data.

ADRS – ANALYSIS DATASET OF RESPONSE

ADRS captures tumor response assessments in oncology clinical trials, recording both individual and overall tumor response evaluations. This ADaM dataset focused on response evaluations, particularly one of the key secondary endpoints Objective Response Rate (ORR). It includes parameters for overall and best overall response assessments (confirmed and unconfirmed) from investigator and central review sources (per RECIST v1.1 criteria). Below is an example of ADRS dataset structure.

VIEWTABLE: Rwork.Adrs

	STUDYID	USUBJID	TRT01P	TRT0	PARAM	PARAMCD	PARAM	PARCAT1	ADT	AVALC	AVAL
1	ABC-123	ABC-123_000000001	Treatment 1	1	Best Overall Response with Confirmation (INV per RECIST 1.1)	BORCFINV	13	INV	2023-11-17	SD	5
2	ABC-123	ABC-123_000000001	Treatment 1	1	Best Overall Response with Confirmation (BICR per RECIST 1.1)	BORCFIRC	3	BICR	2023-11-17	SD	5
3	ABC-123	ABC-123_000000001	Treatment 1	1	Best Overall Response Without Considering Confirmation (INV per RECIST 1.1)	BORINV	12	INV	2023-11-17	SD	5
4	ABC-123	ABC-123_000000001	Treatment 1	1	Best Overall Response Without Considering Confirmation (BICR per RECIST 1.1)	BORIRC	2	BICR	2023-11-17	SD	5
5	ABC-123	ABC-123_000000001	Treatment 1	1	Confirmed Investigator Timepoint Assessment (INV per RECIST 1.1)	ORCINV	11	INV	2023-11-17	SD	5

Display 5: Sample ADRS data.

ADTTE – TIME TO EVENT ANALYSIS DATASET

ADTTE is a standardized CDISC ADaM dataset designed to support time-to-event (TTE) analyses. Time-to-event analyses are an important class of analyses in oncology clinical trials that measure the time until a specified event occurs. ADTTE was used for secondary TTE efficacy endpoints such as Progression-Free Survival (PFS), Overall Survival (OS), Duration of Response (DOR), and Time to First Confirmed Response (T2R). Below is an example of ADTTE dataset structure.

VIEWTABLE: Rwork.Adtte

	USUBJID	PARAM	PARAMCD	PARAMN	PARCAT1	AVAL	STARTDT	ADT	CNSR	EVNTDESC	CNSDTDSC
1	ABC-123_000000001	Overall Survival	OS	1		517	2023-10-03	2025-03-02	0	Death	
2	ABC-123_000000001	Progression-Free Survival (BICR Primary Censoring Rule)	PFSIRC	11	BICR	262	2023-10-03	2024-06-20	0	Documented progression	
3	ABC-123_000000001	Progression-Free Survival (BICR Sensitivity Censoring Rule 1)	PFSIRCS1	12	BICR	262	2023-10-03	2024-06-20	0	Documented progression	
4	ABC-123_000000001	Progression-Free Survival (INV Primary Censoring Rule)	PFSINV	21	INV	191	2023-10-03	2024-04-10	0	Documented progression	
5	ABC-123_000000001	Progression-Free Survival (INV Sensitivity Censoring Rule 1)	PFSINVS1	22	INV	191	2023-10-03	2024-04-10	0	Documented progression	

Display 6: Sample ADTTE data.

INTENT-TO-TREAT (ITT) POPULATION CRITERIA

Randomized subjects are included in this ITT population.

OVERVIEW OF EFFICACY ENDPOINTS

ITT population is used to create the efficacy secondary endpoint reports.

- Overall Response Rate
- Progression-Free Survival
- Overall Survival
- Duration of Response

DISPLAYS IN SC

Although the study assessed pharmacokinetic, safety, efficacy, PRO, immunogenicity and other exploratory endpoints, this paper limits discussion on tables, listing and figures (TLFs) to the primary pharmacokinetic and secondary efficacy endpoints.

PRIMARY PHARMACOKINETIC ENDPOINTS (AUC0-6$_{WKS}$/C$_{TROUGH}$/OC$_{TROUGH}$)

The primary pharmacokinetic endpoints that show the results of Geometric Mean Ratio (GMR) and percentage confidence intervals (CI) will indicate that SC is non-inferior to IV for Cycle 1 AUC0-6wks, Cycle 3 Model-based CTROUGH and Cycle 3 OCTROUGH. These specified sensitivity analysis follows this mock shell.

Analysis of <ADPP.PARAMCD='AUCINT'/'CTROUGH'/'OCTROUGH'>
(Per Protocol Population)

Treatment	N [a]	Median (Range)	GM (95% CI)	Geometric percent CV	vs. IV	
					GMR (XX% CI)	p-value [b]
SC	XXX	XXXX.XX (XX.XX,XX.XX)	XXXX.XX (XX.XX,XX.XX)	XX.XX	X.XX (X.XX,X.XX)	<0.00001
IV	XXX	XXXX.XX (XX.XX,XX.XX)	XXXX.XX (XX.XX,XX.XX)	XX.XX	---	---

[a] Number of Subjects with evaluable PK data.
[b] The one-sided p-value non-inferiority boundary is XX.
Database Cutoff Date: 12JUL2024.

Source: [P123V01MKABC: adam-adsl; adpppm]

Display 7: Mock shell for primary Pharmacokinetic Endpoints (PE).

Analysis of AUC/C$_{trough}$/OC$_{Trough}$

The outputs are constructed based on PP population and using the logarithm of analysis values (AVAL.ADPP) for each treatment and PARAMCD.

Column name	Statistical Procedure
Median (Range)	Using logarithmic ADPP.AVAL values by PROC MEANS procedure
Geometric Means (lower CI, upper CI) at 95% CI	Using logarithmic ADPP.AVAL values by PROC MEANS procedure
Geometric percent CV*	100 x square root of (exp(stddev^2) – 1)
GMR (Comparative Geometric Mean Ratios, CIs, and p-value)	Calculated using Welch's t test statistics**

Table 1: Statistical methods for Analysis of AUC/C$_{Trough}$/OC$_{Trough}$ (Display 7). CV*- Coefficient of Variation. Welsch's t test statistics explained in Program 1.**

```
  MEAN_DIFF=MEANSC-MEANIV;

  DF=(((STDDEVSC**2)/NSC[A] + (STDDEVIV**2)/NIV[B]) **2)/((STDDEVSC**4)/((NSC**2) *(NSC-1)) +
(STDDEVIV**4)/((NIV**2) *(NIV-1)));

  MEAN_DIFF_LCI= MEAN_DIFF - (TINV (ONESIDEDALP[C], DF)) *(SQRT((STDDEVSC**2)/NSC +
(STDDEVIV**2)/NIV));

  MEAN_DIFF_UCI= MEAN_DIFF + (TINV (ONESIDEDALP, DF)) *(SQRT((STDDEVSC**2)/NSC +
(STDDEVIV**2)/NIV));

  GMR=ROUND (EXP (MEAN_DIFF),0.01);
  GMR_LCI=ROUND (EXP (MEAN_DIFF_LCI),0.01);
  GMR_UCI= ROUND (EXP (MEAN_DIFF_UCI),0.01);

  T_STAT=(MEANSC-MEANIV-LOG(GMRH0[D]))/SQRT((STDDEVSC**2)/NSC + (STDDEVIV**2)/NIV);
  P_VALUE= ROUND (1-CDF ('t', T_STAT, DF),0.0000001);

NSC[A]- Number of subjects in SC treatment in PP population.
NIV[B]- Number of subjects in IV treatment in PP population.
ONESIDEDALP[C]- One-sided alpha i.e., 0.05 provided by Statistician.
GMRH0[D]- Geometric mean ratio by Null Hypothesis i.e., 0.8 provided by Statistician.
DF- Degrees of Freedom.
CDF- Cumulative Distribution Function.
```

Program 1: Sample code for calculation of GMR, its CIs and p-value between SC vs IV treatments as in display 7.

SECONDARY EFFICACY ENDPOINTS

Objective Response Rate

The ORR is defined as the percentage of participants who achieve a confirmed complete response (CR) or partial response (PR) per RECIST 1.1 as assessed by Blinded Independent Central Review (BICR). The tables are constructed based on investigator and BICR data assessed in ADRS using ITT population from ADSL.

Analysis of Objective Response (Confirmed) Based on BICR per RECIST 1.1 (Primary Analysis With Synthesis Method)
(ITT Population)

Treatment	N	Number of Objective Responses	Objective Response Rate (%) (95% CI)	ORR ratio vs. IV	
				Estimate (95% CI)	p-Value
SC	XXX	XXX	X.X (XX.X, XX.X)	X.XX (X.XX,X.XX)	X.XXXXX
IV	XXX	XXX	X.X (XX.X, XX.X)		
Responses are based on BICR assessment per RECIST 1.1. BICR = Blinded independent central review. Database Cutoff Date: 12JUL2024					

Source: [P123V01MKABC: adam-adsl; adrs]

Display 8: Mock shell of secondary efficacy endpoints – ORR.

Analysis of ORR

The table includes the participants who have confirmed CR or PR as responses for columns 3, 4 and all participants in ITT population for columns 2, 5. Based on above mock and below programming logic, the reports are prepared.

Column Name	Statistical Procedure
N	Number of participants in population using PROC FREQ
Number of Objective responses	number of participants with CR and PR using PROC FREQ
Objective Response Rate	ORR is calculated as number of objective responses/N. The upper and lower Confidence Intervals (CI) are calculated using the beta distribution based on 2-tailed method where alpha is (0.05/2) and displayed as percentages. Refer to program 2.
ORR ratio vs IV + chemo: Estimate (95% CI)	Relative risks and its CIs for SC vs IV is calculated using PROC FREQ. Refer to program 3.
ORR ratio vs IV + chemo: P-Value	Calculated using synthesis method and cumulative distribution function by calculating the log values of relative risks, standard error of log of upper and lower CI. Refer to program 4.

Table 2: Column wise explanation for mock shell of ORR Analysis report (Display 8).

```
IF (TOTPART[A] – SUCCPART[B] + 1) > 0 THEN LCI = BETAINV[C] (ONESIDEDALP/2, SUCCPART, TOTPART* -
SUCCPART +1)
IF TOTPART > SUCCPART THEN UCI = BETAINV (1 - ONESIDEDALP/2, SUCCPART + 1, TOTPART* -
SUCCPART)

TOTPART[A]- Total participants in population. SUCCPART[B]- participants with confirmed CR/PR
responses. BETAINV[C]- Beta distribution function in SAS calculating CIs based on TOTPART
and SUCCPART.
```

Program 2: Sample code for calculation of upper and lower CI for display 8.

```
PROC FREQ DATA=<ADRS> DATA=ORDER;
   TABLES <STRATUM>*<TREATMENT>*<RESPONSES (SUCCESS AS 1 AND ALL OTHERS 0)>/RISKDIFF
RELRISK PLOTS(ONLY)=RELRISKPLOT(STATS) CMH;
   OUTPUT OUT=<RESULTS> CMH;
RUN;
```

Program 3: Sample code for calculation of column 5a - Estimate (95% CI) for display 8.

```
LOG_RELRISK=LOG(_MHRRC1_);

SE_LOGRELRISK =LOG(U_MHRRC1/L_MHRRC1)/ (2*QUANTILE ("NORMAL", 0.975));

SYNTHESIS = (LOG_RELRISK+(1-<RETENTION>) * (<HIST_LOGRELRISK>))/SQRT (SE_ LOGRELRISK**2 +
((1-<RETENTION>) * (<HIST_SE_LOGRELRISK>)) **2);

P_VALUE=1-CDF ('NORMAL', SYNTHESIS);

_MHRRC1_, U_MHRRC1, L_MHRRC1 are the relative risks, and its ci values are from results
dataset in program 3. RETENTION, HIST_LOGRELRISK, and HIST_SE_LOGRELRISK are provided by
Statistician.
```

Program 4: Sample code for calculation of p-Value for display 8.

Progression-free survival and Overall Survival

- PFS is defined as the time from randomization to the first documented disease progression per RECIST 1.1 by BICR or death due to any cause, whichever occurs first.
- OS is defined as the time from randomization to death due to any cause.

Analysis of <ADTTE.PARAMCD-'PFS'/'OS'>
(ITT Population)

	SC (N=XXX)	IV (N=XXX)
Number of Events (%)	XX (XX.X)	XX (XX.X)
Kaplan-Meier Estimates (months)		
Median (95% CI)	NR (NR, NR)	NR (NR, NR)
[Q1, Q3]	[X.X, NR]	[X.X, NR]
Person-months	XXXX.X	XXXX.X
Event Rate / 100 Person-months	XX.X	XX.X
vs IV + chemo		
Hazard Ratio (95% CI)	X.XX (X.XX, X.XX)	
OS Rate at month 3 (%) (95% CI)	XX.X (XX.X, XX.X)	XX.X (XX.X, XX.X)
OS Rate at month 6 (%) (95% CI)	XX.X (XX.X, XX.X)	XX.X (XX.X, XX.X)
OS Rate at month 9 (%) (95% CI)	XX.X (XX.X, XX.X)	XX.X (XX.X, XX.X)
OS Rate at month 12 (%) (95% CI)	XX.X (XX.X, XX.X)	XX.X (XX.X, XX.X)
NR = Not reached. Database Cutoff Date: 12JUL2024		

Source: [P123V01MKABC: adam-adsl; adtte]

Display 9: Mock shell of secondary efficacy endpoints – PFS/OS.

Analysis of PFS/OS

Row Name	Statistical Procedure
Number of Events (%)	Number of participants achieved PFS (n) excluding censored in the population (N) and its percentage (n/N) * 100
Kaplan-Meier Estimates	Median and CIs are estimated using SAS PROC LIFETEST procedure and product limit method. Refer to program 5.
Person - months	sum of duration of event days per treatment
Event rate/100 person-months	(row#1/row#3) * 100. Refer to program 6.
Hazard (HZ) ratio SC compared to IV	The HZ ratio is calculated by SAS PROC PHREG using efron ties method. Refer to program 7.
Endpoint Rates at specified duration intervals	Refer to program 8.

Table 3: Row wise explanation for mock shell of PFS/OS Analysis report (Display 9).

```
PROC LIFETEST DATA = <ADTTE> ALPHAQT=<ALPHA> PLOTS=NONE;
  TIME <ADTTE.AVAL> * <ADTTE.CNSR(1)>;
  STRATA <ADTTE.TRT01PN>;
RUN;
```

Program 5: Sample code to calculate KM estimates for display 9.

```
PERMONRATE = (EVENTS/SUM (DURATION OF EVENT)) * 100;
```

Program 6: Sample code to calculate Person-months rate for display 9.

```
PROC PHREG DATA = <ADTTE> ALPHA=<ALPHA_HR>;
      WHERE <TRT01PN> IN (1 2);
      CLASS <TRT01PN> (REF="2");
      MODEL AVAL * CNSR (1) = <TRT01PN> / RISKLIMITS TIES=EFRON;
      STRATA <STRATUM>;
      ODS OUTPUT PARAMETERESTIMATES=<OUTPUT DS>;
RUN;
```

Program 7: Sample code to calculate Hazard Ratio for display 9.

```
PROC LIFETEST DATA = <ADTTE> METHOD =KM ALPHA=<ALPHA> TIMELIST=<3 OR 6 OR 9>
OUTSURV=<OUTPUT DS> REDUCEOUT PLOTS=NONE;
      TIME AVAL * CNSR(1);
      STRATA <TRT01PN>;
RUN;
```

Program 8: Sample code to calculate the duration intervals of OS for display 9.

Duration of Response (DOR)

For participants who show confirmed CR or PR, DOR is defined as the time from the first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurs first.

Summary of Time to Response and Duration of Response
Based on BICR per RECIST 1.1 in Participants with Confirmed Response
(ITT Population)

	SC (N=XXX)	IV (N=XXX)
Number of participants with response	XX	XX
Response Duration (months)		
Median (95% CI)	X.X (X.X, NR)	X.X (X.X, NR)
Range	X.X to X.X	X.X to X.X
Number (%) of Participants with Extended Response Duration		
≥3 months	XX (XX.X)	XX (XX.X)
≥6 months	XX (XX.X)	XX (XX.X)
≥9 months	XX (XX.X)	XX (XX.X)
NR = Not Reached. Database Cutoff Date: 12JUL2024		

Source: [P123V01MKABC: adam-adsl; adtte; adrs]

Display 10: Mock shell of secondary efficacy endpoints – DOR.

Analysis of DOR

The Summary of Duration of Response table is constructed using ITT population in ADSL, ADRS (identify subjects with CR, PR), and ADTTE (Participants response duration from randomization date to the first confirmed date of CR/PR).

Row Name	Statistical Procedure
Number of participants with response)	Number of participants with CR/PR in ITT population calculated using PROC FREQ.
Response Duration	Median and CIs are calculated using program 5 as displayed in analysis of PFS/OS section. Range is calculated using PROC FREQ.
Number of participants with extended response duration	Displays the duration of survival in months. AVAL.ADTTE is divided by 30.4367 and

	categorized according to the intervals displayed in mock and availability of data.

Table 4: Row wise explanation for mock shell of DOR Analysis report.

COLLABORATION

The successful analysis for studies evaluating PK/PD and key efficacy endpoints as primary and secondary measures required close collaboration among the A&R programming team, the PK/PD programming team, Quantitative Pharmacology and Pharmacometrics (QP2) Data Scientist, and Statisticians.

- PK/PD programmers provided analysis datasets created based on modelling results that are needed for A&R programmers to generate the primary pharmacokinetic analyses.
- A&R programmers produced ADaM datasets and performed the secondary efficacy statistical analyses and other reporting as described in SAP (Statistical Analysis Plan) in addition to the primary key pharmacokinetic analyses after receipt of PK/PD data.
- Statisticians guided input selection and reviewed analytical outputs.

CONCLUSION

Preparation of PK/PD primary endpoint reports required specialized skills in advanced SAS procedures. The programming team quickly adapted and delivered solutions aligned with the study design requirements. Analyses progressed rapidly within defined timelines, with minimal adjustments to the original schedule, to meet customer commitments. Under such stringent conditions, prompt contributions, strong teamwork, and effective cross-functional collaboration combined with consistent focus proved pivotal to this high-quality, successful submission.

REFERENCES

Book Garralda. E. 2017. Developmental Therapeutics and Translational Research. Alexandria, VA: American Society of Clinical Oncology Educational Book.

Journal article Felip, E. July 2025. “Subcutaneous versus intravenous pembrolizumab, in combination with chemotherapy, for treatment of metastatic non-small-cell lung cancer: the phase III 3475A-D77 trial”. *Annals of Oncology*, Volume 36 Issue 7 Pages 775-785.

Website www.merck.com. 2024. Available at https://www.merck.com/news/merck-announces-phase-3-trial-of-subcutaneous-pembrolizumab-with-berahyaluronidase-alfa-met-primary-endpoints/

Website www.merck.com. 2025. Available at FDA Approves Merck’s KEYTRUDA QLEX™ (pembrolizumab and berahyaluronidase alfa-pmph) Injection for Subcutaneous Use in Adults Across Most Solid Tumor Indications for KEYTRUDA® (pembrolizumab) - Merck.com

Website www.clinicaltrials.gov. 2025. Available at Study Details | NCT05722015 | A Study of Subcutaneous (SC) Pembrolizumab Coformulated With Berahyaluronidase Alfa (MK-3475A) vs Intravenous Pembrolizumab in Adult Participants With Metastatic Non-small Cell Lung Cancer (NSCLC) (MK-3475A-D77) | ClinicalTrials.gov

ACKNOWLEDGMENTS

I would like to thank Merck & Co., Inc., Rahway, NJ, USA. for this opportunity to present at the PharmaSUG conference. Sincere thanks to Amy Gillespie, Mary Varughese, Jing Su, Lisa Pyle, and Sandeep Meesala for reviewing the paper and providing valuable feedback.

CONTACT INFORMATION

Your comments and questions are valued and encouraged. Contact the author at:

Author Name: Sumanjali Mangalarapu
Company: Merck & Co., Inc., Rahway, NJ, USA.
Email: sumanjali.mangalarapu@merck.com

Author Name: Chuqing Chen
Company: Merck & Co., Inc., Rahway, NJ, USA.
Email: chuqing.chen@merck.com

Author Name: Anilkumar Anksapur
Company: Merck & Co., Inc., Rahway, NJ, USA.
Email: anilkumar.anksapur@merck.com