PharmaSUG China 2024 - Paper DS

Implementation and tips on How to handle the ILD case in ADC trials

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ABSTRACT

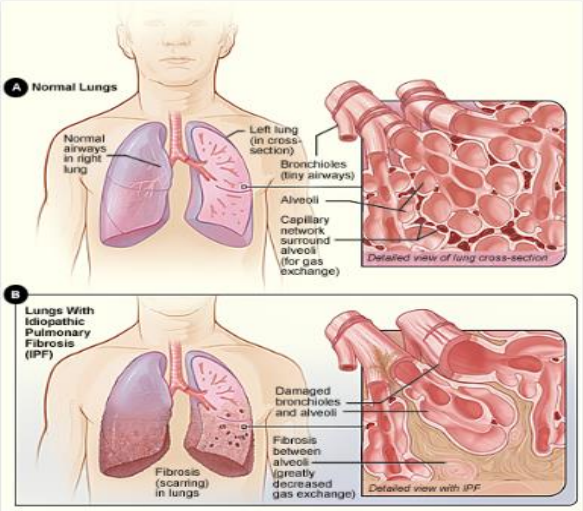
Interstitial lung disease (ILD) is a general term for a heterogeneous group of parenchymal lung diseases. It is an important identified risk in oncology clinical trials especially for Antibody-Drug Conjugates (ADCs). The mechanisms of ILD induced by these anti-cancer drugs are not clearly elucidated. However, collecting, adjudicating, reporting the ILD data is essential for safety evaluation and management in oncology clinical trials.

This paper aims to share the experience of ILD data characterizing process and dealing approaches from the perspective of biometrics, go through the practices and some implementation rules that we have adopted in dealing with this kind of data and will also provide some current guidance for your reference.

INTRODUCTION

Antibody–drug conjugates (ADCs) is a substance made up of a monoclonal antibody and cancer-killing drug via a linker, unlike conventional chemotherapy treatments, which can damage healthy cells, antibody drug conjugates (ADCs) are targeted medicines that deliver chemotherapy agents to cancer cells. Although ADC drugs have been used with great success in clinical practice, a number of toxic side effects have also emerged, Interstitial lung disease (ILD) is one of those adverse effects, despite the the majority of drug-induced pneumonia/ILD events are low-grade events, it's still considered as a critical identified risk and usually defined as an adverse event of special interest (AESI) in clinical trials of oncology.

Interstitial lung diseases (ILDs) are a group of several disorders that can cause scarring in lungs. The scar tissue in lungs affects lungs' ability to carry oxygen and can make it harder to breathe normally. Given ILD/Pneumonia includes more than 100 lung diseases, and various of clinical manifestations, in addition, clear official guidelines on drug induced ILD in clinical trials is still lacking. There are challenges associated with identifying and analyzing ILD in clinical trials which may impact patient's safety, it's crucial to appropriate identify and manage this toxic effect in clinical trials.



Normal lungs and lungs with a type of ILD (idiopathic pulmonary fibrosis). *Figure A shows the location of the lungs and airways in the body and a detailed view of the lung's airways and air sacs. Figure B shows fibrosis, or scarring, in the lungs.*

ADJUDICATION OF ILD

High-level description of potential ILD identification and adjudication process

A Pre-specified MedDRA Preferred Term List should be maintained by sponsor. PTs eligible for adjudication would consist of all narrow terms in the ILD Standardized MedDRA Queries (SMQs) using the latest MedDRA version in effect for each clinical study, selected broad PTs, and PTs of Acute respiratory failure and Respiratory failure. In addition, if a new PT is added to the narrow ILD SMQ of the most current version of MedDRA, and that PT exists outside the narrow ILD SMQ in an earlier version of MedDRA in use in an active study, cases matching that term will also be sent for adjudication. A third party or a committee sometimes will be established to conduct the adjudication process, to ensure the independence and accurate of this judgment process.

Below is the list of selected broad PTs (PT code is used to link it up instead of preferred terms):

- Acute respiratory distress syndrome
- Allergic eosinophilia
- Granulomatous pneumonitis
- Organizing pneumonia
- Pulmonary sarcoidosis
- Restrictive pulmonary disease
- Rheumatoid lung, and Sarcoidosis

Please note that this is actually so-called Customized MedDRA Queries (CMQs) process, sponsor defined tools/process developed to address their investigational drugs safety analysis needs. Here we're using CMQs for ILD data identification, but CMQs are typically defined per TA, compound, or study-by study basis as study-specific rules applicable to the sponsor only, and throughout the entire process , statistics/programming team need to work closely with medical/clinical team, it is important to document why and what changed (i.e., removal or addition of the existing/pre-defined AE groupings) and it is best to set up standard programming and clinical reviewing/confirming process and timeline if a CMQ method is utilized.

Reconciliation between RAVE and third-party committee transfer

After the process of collecting and characterizing ILD/ Pneumonia -related data, reconciliation work will be conducted to see if any discrepancies between EDC data and third party committee result, two categories ILD and potential ILD (the definition of potential ILD means PT in the search list AND (it is TEAE or happened in the post-treatment period but related as per investigator) will be summarized according to the reconciliation results, and both categories will be presented in the CSR analysis.

Below are some common scenarios of discrepancies:

	Rave AE #	RAVE AE PT	AC AE #	AC AE PT	Comment and decision
Case 1	8	aaa	8	aaa	This is the expected case where RAVE and AC transfer agree on AE.
Case 2	9	xyz	9	aaa	This is discrepancy A (**site changed PT** to something not in the ILD search list, but AC already adjudicated the case). **Analysis Decision: include this as potential ILD.**
Case 3	AE #23 deleted from RAVE		23	bbb	This is discrepancy B (site removed AE completely, but AC already adjudicated the case). **Analysis Decision: this will not be summarized. If such cases occur, add a footnote to table.**
Case 4			888	ccc	This is discrepancy C (site never had this AE, but AC thinks this is an ILD). **Analysis Decision: same as Case 3.**
Case 5	11	ccc	11	ccc	If this AE is not a TEAE (not post-treatment period but related). **Analysis Decision:include this as potential ILD.**

AC: ILD Adjudication committee.
PTs included in ILD search per charter: aaa, bbb, ccc.
PTs NOT included in ILD search: xyz.

It's worth noting that the MedDRA version used by third party or adjudication committee and the MedDRA version of the RAVE database for a study is not necessarily the same, a RAVE study may have MedDRA v21.0 while adjudication committee may have v23.1; or conversely a RAVE study may be up-versioned to a later version in the future, but adjudication committee may not have received the updated PT search list for it. This MedDRA version difference may not result in discrepancy depending on the specific situation, but this is a fact we need to be aware of.

Although there are no relevant requirements from the FDA or other agencies currently, it's highly recommended to present the ILD decisions made by the investigator and sponsor and provide a detailed evaluation process in submission materials. For grade 4 or 5 or related ILD or scenarios that adjudication approaches inconsistent within same compound, a reasonable explanation should be provided if there are inconsistencies in the decisions made by the investigator and sponsor.

MAPPING AND REPORTING OF ILD

ILD Data Mapping into SDTM

Basically, the data of ILD will be mapped into SUPPAE and SUPPDD if related to death, if custom SDTM domain related to the ILD information are planned to be submitted, then all the ILD records should be included in custom domain as well.

Mapping examples: SUPPAE

- ILD AC data transfer:

SUBJECT	AENUM	EVENTID	PTTERM	ADDPTTERM	EVENTTYPE	ILDYN	ILDRELYN	ILDDTHYN	ADJONSETDATE1	ADJEVENTGRADE	EVIDENCE1
10001	2	8813	Pneumonitis		ILD Event	Yes	Yes		03-SEP-2021	1	Yes

- EDC AE:

SUBJECT	RECORDPOSITN	AETERM	AETERM_DECOD	AESTDAT	AEENDAT	AEONGO	AEACN	AECONTRT	AEACNOTH	AEOUT	AESI
10001	1	Thrombocytopenia	Thrombocytopenia	05AUG2021:00...	19AUG2021:00...	No	Dose reduced	0	0	Recovered/Resloved	
10001	2	Drug Induced Pneumonitis	Pneumonitis	19SEP2021:00...	06OCT2021:00...	No	Dose withdra	1	0	Recovered/Resloved	Interstitial Lung Disease/pneumonitis

SUBJECT	AETERM_DECOD	AESTDAT	AEENDAT	AEOUT	AESI	AENUM	PTTERM	ILDYN
10001	Pneumonitis	19SEP2021:00...	06OCT2021:00...	Recovered/Res...	Interstitial Lung...	2	Pneumonitis	Yes

- After mapping:

USUBJID	AESEQ	AENKID	AETERM	AEDECOD	AESTDTC	AEENDTC	QNAM	QVAL
DSXXX-10001	1	AE002	Drug Induced P...	Pneumonitis	2021-09-19	2021-10-06	ILDYN	Y

- Move to SUPPAE:

STUDYID	RDOMAIN	USUBJID	IDVAR	IDVARVAL	QNAM	QLABEL	QVAL	QORIG	QEVAL
DSXXX	AE	DSXXX-10001	AESEQ	1	ILDYN	Case of ILD	Y	eDT	ADJUDICATOR

*All the above are dummy data.

Reporting of ILD data in TLFs

There's no doubt that presenting ILD data in a clear and concise manner in TLFs for submission is crucial. This part will not discuss the common detailed derive logic, instead, we try to list some of the points that need to be kept in mind during the hand-on working process.

Consider Treatment-Emergent Adverse Event criteria when presenting ILD results.

The practice that most companies adopted is treating ILD as an AESI, thus the data presented in corresponding AE tables should fulfill the criteria of Treatment-Emergent Adverse Event. However, there are some approaches which include all the ILD data regardless of TEAE Flag especially in ADC trials. The approach we have adopted is the latter, there will be two sources of ILD data, one is ILDs reported by the investigator as recorded on the AE CRF page, and the other one is ILD cases transferred from ILDAC. Both types of data will be summarized in the CRS TLF output, even if it's not TEAE. Whichever method is chosen, there should be pre-specified definition in Study protocol and statistical analysis plan (SAP).

	ARM A (N=xxx)	ARM B (N=xxx)
Subjects with at least one ILD/pneumonitis	xx (xx.x)	xx (xx.x)
Worst CTCAE Grade		
5	xx (xx.x)	xx (xx.x)
3 or 4	xx (xx.x)	xx (xx.x)
4	xx (xx.x)	xx (xx.x)
3	xx (xx.x)	xx (xx.x)
2	xx (xx.x)	xx (xx.x)
1	xx (xx.x)	xx (xx.x)
Missing	xx (xx.x)	xx (xx.x)
	xx (xx.x)	xx (xx.x)
Subjects with Treatment-Related ILD/pneumonitis	xx (xx.x)	xx (xx.x)
Worst CTCAE Grade		
5	xx (xx.x)	xx (xx.x)
3 or 4	xx (xx.x)	xx (xx.x)
4	xx (xx.x)	xx (xx.x)
3	xx (xx.x)	xx (xx.x)
2	xx (xx.x)	xx (xx.x)
1	xx (xx.x)	xx (xx.x)
Missing	xx (xx.x)	xx (xx.x)
	xx (xx.x)	xx (xx.x)
Subjects with ILD/pneumonitis Leading to Dose Reduction	xx (xx.x)	xx (xx.x)
Subjects with ILD/pneumonitis Leading to Study Drug Interruption	xx (xx.x)	xx (xx.x)
Subjects with ILD/pneumonitis Leading to Study Drug Discontinuation	xx (xx.x)	xx (xx.x)
Subjects with Treatment-Related ILD/pneumonitis Leading to Study Drug Discontinuation	xx (xx.x)	xx (xx.x)
Subjects with ILD/pneumonitis Leading to Death	xx (xx.x)	xx (xx.x)

Common AESI Overall Summary table.

For "Outcome of the worst NCI CTCAE AESI event"

1. Although the common practice does not necessarily render the AESI outcome in the TLFs, we do present the outcome in TLFs, and for the outcome calculation, there are some rules need to be noticed.

   NOT directly take the outcome of the AE record with the worst grade, but concatenate AE records first to form a unique episode, then use the outcome of the last AE record of the episode to report in the table. The grade for the episode is the highest grade. Add a footnote to the table to explain "Outcome data is reported by investigator and is the eventual outcome of an AE episode in case of grade/seriousness change."

Example 1

ILD AC data:

PROTOCOL	FORM\	SUBJECT	AENUM	EVENTI	PTTERM	ADDPTT	EVENTTYPE	ILDYN	ILDRELY	ILDDTH\	ILDDT	ADJONSET	ADJEVE	EVIDENCE1
DSXXX-10002	2	10002	35	7013	Pneumonitis		ILD Event	Yes	Yes			27-Oct-20	3	Yes

EDC AE data:

Subject	First dose	AE PT	AE number	AE start date	AE end date	Grade	SAE?	Causality	Action taken	AE outcome
10002	C1D1/14JAN2020	Pneumonitis	35	25-Oct-2020	11-Nov-2020	2	No	Related	Dose Reduced	Recovering/Resolving
10002	C1D1/14JAN2020	Pneumonitis	36	12-Nov-2020		1	No	Related	Dose Not Changed	Not Recovered/Not Resolved

2. In case of multiple episodes of the same AESI, pick the episode with the worse grade to report outcome in this table. In case of tie again (same worst grade), pick the worst outcome. (Worst outcome in descending order: Fatal→ Not recovered/Not resolved → Recovering/Resolving → Recovered/Resolved with sequelae → Recovered/Resolved→ UNK).

Example 2

ILD AC data:

PROTOCOL	FORM\	SUBJECT	AENUM	EVENTI	PTTERM	ADDPTT	EVENTTYPE	ILDYN	ILDRELY	ILDDTH\	ILDDT	ADJONSET	ADJEV
DSXXX-10003	2	10003	7	1799	Pneumonitis		ILD Event	Yes	Yes			12-Jul-20	3
DSXXX-10003	2	10003	35	7013	Pneumonitis		ILD Event	Yes	Yes			22-Sep-20	3

EDC AE data:

	Subject	First dose	AE PT	AE number	AE start date	AE end date	Grade	SAE?	Causality	Action taken	AE outcome	
Episode 1	10003	C1D1/14JAN2020	Pneumonitis	7	12-Jul-2020	02-Aug-2020	3	No	Related	Dose Reduced	Recovering/Resolving	
	10003	C1D1/14JAN2020	Pneumonitis	8	03-Aug-2020		2	No	Related	Dose Not Changed	Not Recovered/Not Resolved	Outcome of EP1
Episode 2	10003	C1D1/14JAN2020	Pneumonitis	35	20-Sep-2020	28-Sep-2020	2	Yes	Not related	Dose Reduced	Recovered/Resolved	Outcome of EP2

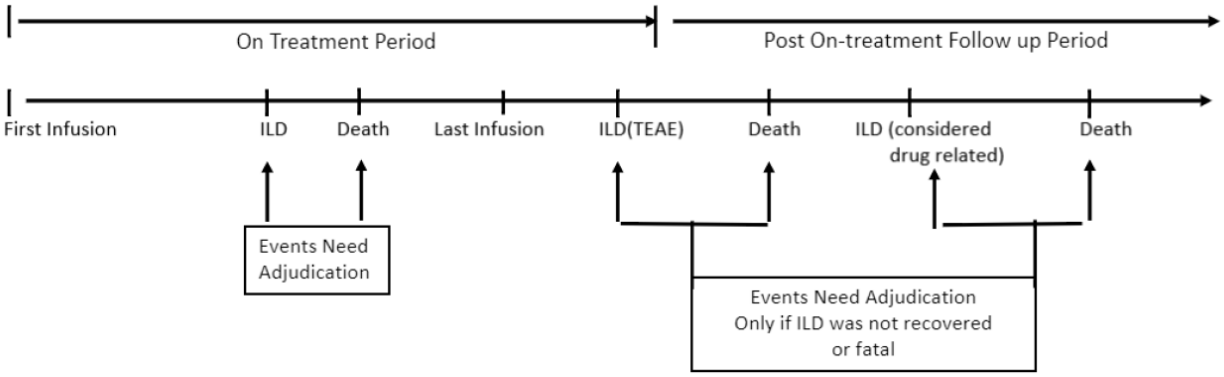
For "ILD associated with death"

Basically, the adjudication process is more complex when death related ILDs are involved. only when death event meet criteria will be assessed to determine if the cause of death is due to ILD. Below are the three scenarios:

1. For Subjects who had an ILD event which has been adjudicated as study drug related ILD by the ILD AC, all deaths occurring within the protocol defined on-treatment period will be adjudicated.
2. If a Subject has an ILD which has been adjudicated as study drug related ILD by the ILD AC occurring within on treatment period and continued (outcome of not recovered/not resolved) beyond on-treatment period and subject died, then that death should be adjudicated. If the death occurred during survival follow up, and there is no relevant data available (imaging studies or clinical notes) to determine that the ILD was or was not recovered before the event of death, and no clinical

information indicating the cause of death, the death will not be sent for adjudication but will be cancelled within the platform and the reason documented.

3. If an ILD occurred outside of the on-treatment period that the investigator assessed as related to study drug, the ILD event should be adjudicated, and if the event has been adjudicated as study drug related ILD by the ILD AC and it continued (outcome not recovered/not resolved) and the subject died, then the death should be adjudicated. If the death occurred during survival follow up, and there is no relevant data available (imaging studies or clinical notes) to determine that the ILD had or had not recovered before the event of death, the death will not be sent for adjudication but will be cancelled within the platform and the reason documented.



Tables related to deaths associated with ILD typically involve two main areas:

1. Table: AESI associated with death

   For this table, use adjudicated results about death from ILDAC to filter the ILD AESI associated with death (adjudicated grade=5).

2. Table: TEAE associated with death

   Death should be selected based on AE outcome= 'fatal' per CRF, this must be 1:1 matched with AE grade=5. Otherwise, DM should query this and resolve before DBL.

CURRENT GUIDEANCE ON ILD

In general, there is a lack of clear guidance for the management and implementation of drug-induced ILD in clinical trials, especially for statistical aspects. However, related documentation of FDA Medical Queries (FMQs) for Adverse Events of Special Interest and Standard Safety Tables and Figures (ST&F) Integrated Guide published on September/2022, which may give some reference when dealing with specific ILD scenarios.

What's FMQs?

FDA Medical Queries (FMQ): Standard groupings of adverse event terms designed by FDA to help identify potential safety issues during review of clinical trial adverse event data. FMQs contain 104 standardized groupings of PTs ,each FMQ represents a distinct medical concept, for example: 'Initial insomnia', 'middle insomnia', 'early morning awakening' combined to 'insomnia'.

Difference between FMQs and SMQs

The biggest difference between FMQs and SMQ is the Group strategy and focus point, MedDRA's hierarchy tend to combine PTs using multiple strategies, such as pathology, physiology, etiology, manifestation site, etc. while FMQs more focused premarket safety assessment, mainly goal is to create clinically meaningful grouping, and only groups AE PTs.

Key message

The rationale for FDA's efforts in developing FMQs mainly because of inconsistent standards of AE, ILDs definition and classification in FMQs are slightly different with SMQs, FMQs will include a broader range of PTs compared with SMQs, it's highly recommended that when developing the company all ILD process, using the FMQs as reference, when doing some safety analysis, if certain combinations overlap with the FMQs, it can also be completely considered to use the criteria of the FMQs to count and present the AE results.

PT	Final Classification
Alveolitis Allergic	Narrow
Bronchopneumopathy	Narrow
Bronchopulmonary Aspergillosis	Narrow
Bronchopulmonary Aspergillosis Allergic	Narrow
Goodpasture's Syndrome	Narrow
Graft Versus Host Disease In Lung	Narrow
Granulomatous Pneumonitis	Narrow
Haemorrhagic Pneumonia	Narrow
Immune-Mediated Pneumonitis	Narrow
Lung Transplant Rejection	Narrow
Lupus Pneumonitis	Narrow
Mendelson's Syndrome	Narrow
Organic Dust Toxic Syndrome	Narrow
Pneumonia Lipoid	Narrow
Pneumonitis Chemical	Narrow
Pulmonary Sarcoidosis	Narrow
Rheumatoid Lung	Narrow

CONCLUSION

As no specific guidelines are available for the diagnosis and management of drug related ILD in oncology clinical trials, the process of each company may do something different when identifying, evaluating, and analyzing the ILD data. Therefore, how to make this process standardized is critical. In this paper, we are mainly focus on the ILD adjudication process and reporting in TLFs, also bring the concept of CMQs and some recommendation related to the FMQs. In addition to these elements, the protocol and CRF (Case report form) as well as SAP should include the instructions for ILD as well, relationship with TEAE, detailed definition, etc.

Overall, this is a multi-departmental collaborative process, statisticians, programmers, DM should be in close communication with medical or pharmacovigilance members during the conduct of the clinical trial. More importantly, the establishment and maintenance of standardized process is crucial to ensure timely detection of ILDs and proper analysis of these data.

ACKNOWLEDGE

I would like to express my gratitude to Ju Chen and Yuan Geng for the comments, and my team members Serena Wu, Xiangyu Song for their support.

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