form two- or three-hinge hydrogen bonds. In contrast to crizotinib, alectinib also shows substantial inhibitory activity against the L1196M mutant of ALK, apparently because it is able to maintain an efficient (CH/π) interaction with position 1196 even after the substitution of methionine for leucine.

A Phase I/II first-in-human study (AF-001JP) performed with previously treated and crizotinib-naive patients with *ALK* rearrangement-positive advanced NSCLC was performed in Japan.[38] The participants were deemed to be *ALK* fusion gene-positive if a positive result was obtained either by reverse-transcription polymerase chain reaction (RT-PCR) analysis or by both immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH). In the Phase I portion of the study, 24 patients received alectinib with a dose escalation from 20 to 300 mg bid, with the latter being determined as the highest planned dose on the basis of the available safety information for the additive formulation in Japan. Given that DLTs were not observed, the maximum tolerated dose (MTD) was not identified in this study. The highest planned dose (300 mg bid) was thus judged to be acceptable as the recommended dose for the 46 patients enrolled in the Phase II portion of the trial. Of these 46 patients, 43 individuals (93.5%) achieved an objective response, and 44 (95.7%) achieved disease control. The median PFS had not been determined by the time of publication. This excellent clinical activity was associated with mostly mild adverse events, with those of grade 3 being detected in only 17 (37.0%) patients and those of grade 4 or death in none. The most frequently reported treatment-related adverse events were dysgeusia and liver dysfunction, both of which were of grade 1 or 2 in almost all cases. The characteristic adverse events of crizotinib treatment, including visual effects and gastrointestinal disorders (diarrhea, vomiting, and nausea), occurred at a low rate in this study of alectinib. Application for approval of alectinib in Japan was submitted on October 7, 2013.

A Phase III clinical trial (JapicCTI-132316) comparing alectinib with crizotinib in terms of PFS for the treatment of patients with *ALK* rearrangement-positive NSCLC is ongoing in Japan.[39] Major eligibility criteria include advanced or metastatic *ALK*-rearranged NSCLC (identified either by RT-PCR or by both IHC and FISH), no prior treatment with an ALK inhibitor, an Eastern Cooperative Oncology Group performance status of 0–2, and either no previous treatment or one line of prior treatment with chemotherapy (Figure 4).

A dose-finding Phase I study (AF-002JG, NCT01588028) was also performed for alectinib in the US.[40] Key eligibility

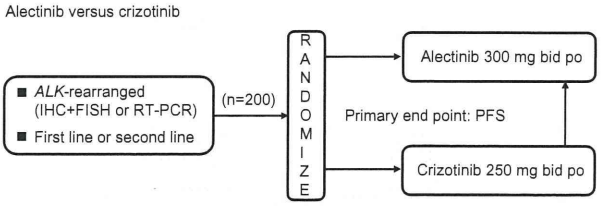

Figure 4 Ongoing Phase III study (JapicCTI-132316) of alectinib for the treatment of *ALK* rearrangement-positive non-small-cell lung cancer.[39]
Abbreviations: ALK, anaplastic lymphoma kinase; IHC, immunohistochemistry; FISH, fluorescence in situ hybridization; RT-PCR, reverse-transcription polymerase chain reaction; PFS, progression-free survival; bid, twice daily; po, oral administration.

criteria for this study included advanced NSCLC with *ALK* rearrangement confirmed by FISH, as well as failed crizotinib treatment. No treatment-related dose reductions were necessary up to a dose of 600 mg bid. Two of seven patients experienced DLTs (headache of grade 3, and neutropenia of grade 3 requiring dose-holding for 7 days) at the dose of 900 mg bid. On the basis of these results, 600 mg bid was determined as the recommended dose of alectinib for a Phase II study in the US. The ORR was 54.5% across all cohorts of the Phase I study, indicating that alectinib possesses significant clinical activity in *ALK* rearrangement-positive patients who are refractory to crizotinib. A global single-arm Phase II study of alectinib in patients with *ALK*-rearranged NSCLC resistant to crizotinib is ongoing (NCT01801111).[41] The FDA granted breakthrough-therapy designation for alectinib on the basis of the NCT01588028 data, with early approval being expected.

LDK378

LDK378 (Novartis, Basel, Switzerland) is also a potent and selective small-molecule ALK inhibitor (Figure 1).[42] In a Phase I study, 59 patients received LDK378 with dose escalation from 50 to 750 mg once daily (qd). DLTs were observed in two of the 14 patients who received the drug at 400 mg qd, in two of the nine patients at 600 mg qd, and in one of the nine patients at 750 mg qd. DLTs included diarrhea, vomiting, nausea, dehydration, and elevated serum aminotransferase levels. The MTD was thus defined as a dose of 750 mg qd. Among 88 evaluable *ALK* rearrangement-positive NSCLC patients who received LDK378 at 400–750 mg qd, the ORR was 70%. In the subset of 64 patients who had experienced crizotinib failure, the ORR was 73%.[43] These results thus suggest that LDK378 may be effective for the treatment of patients with *ALK*-rearranged NSCLC who have developed acquired resistance to crizotinib.

A Phase III clinical trial (NCT01828112) comparing LDK378 with chemotherapy (pemetrexed at 500 mg/m^2 or

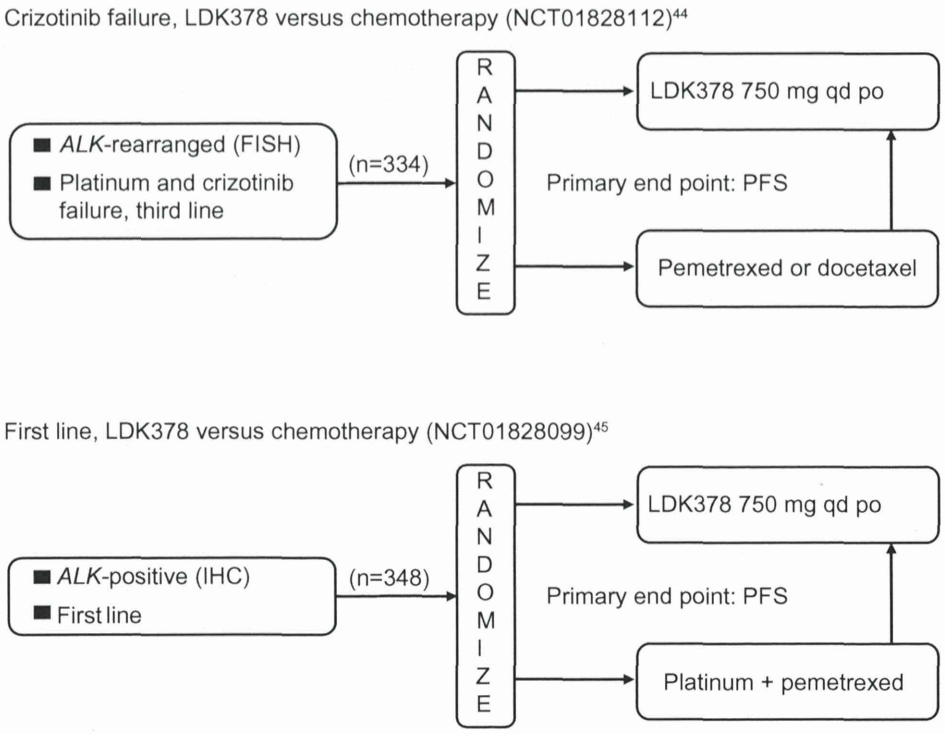

Figure 5 Ongoing Phase III studies of LDK378 for the treatment of *ALK* rearrangement-positive non-small-cell lung cancer.
Abbreviations: ALK, anaplastic lymphoma kinase; FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; qd, once daily; po, oral administration; PFS, progression-free survival.

docetaxel at 75 mg/m^2) for the treatment of *ALK*-rearranged NSCLC patients who have progressed after prior treatment with both crizotinib- and platinum-based chemotherapy is ongoing (Figure 5).[44] In addition, a Phase III clinical trial (NCT01828099) comparing LDK378 with standard first-line chemotherapy (pemetrexed plus either cisplatin or carboplatin) in previously untreated ALK positive NSCLC patients assessed by IHC is also ongoing (Figure 5).[45]

AP26113

AP26113 (Ariad Pharmaceuticals, Inc., Cambridge, MA, USA) is another highly selective small-molecule ALK inhibitor that shows activity against the L1196M mutant (Figure 1).[46] A Phase I/II study of AP26113 (NCT01449461) is ongoing.[47] In the Phase I portion of the study, 44 patients received AP26113 with dose escalation from 30 to 300 mg qd. The most common adverse events were fatigue, nausea, and diarrhea, most of which were of grade 1 or 2. One DLT (increased serum alanine aminotransferase level of grade 3) was observed in one of nine patients treated at a dose of 240 mg, and one DLT (dyspnea of grade 4) was observed in one of two patients at a dose of 300 mg. Although the MTD has not been defined, a recommended Phase II dose was identified as 180 mg qd on the basis of safety, efficacy, and pharmacokinetic data. In the Phase I portion of the study, 24 patients with *ALK*-rearranged NSCLC were evaluable for response. Fifteen of these patients achieved an ORR of 63%, including 12 of the 16 individuals who had progressed after previous crizotinib therapy (ORR 75%). In addition, four of five patients showed objective responses for metastases in the central nervous system.

Other new ALK TKIs

Other new ALK TKIs, such as ASP-3026 (Astellas Pharma, Tokyo, Japan), NMS-E628 (Nerviano Medical Sciences, Milan, Italy), X-396 (Xcovery, West Palm Beach, FL, USA), CEP-37440 (Teva Pharmaceutical Industries Ltd, Petah Tikva, Israel), TSR-011 (Tesaro, Inc., Waltham, MA, USA), and PF-06463922 (Pfizer, New York, NY, USA), are currently introduced into clinical trials.

Molecular diagnosis of *ALK* rearrangement-positive NSCLC

FISH

Break-apart FISH analysis was applied for detection of *ALK* rearrangement in clinical trials with crizotinib. In this approach, the 5′ and 3′ portions of the *ALK* gene are separately

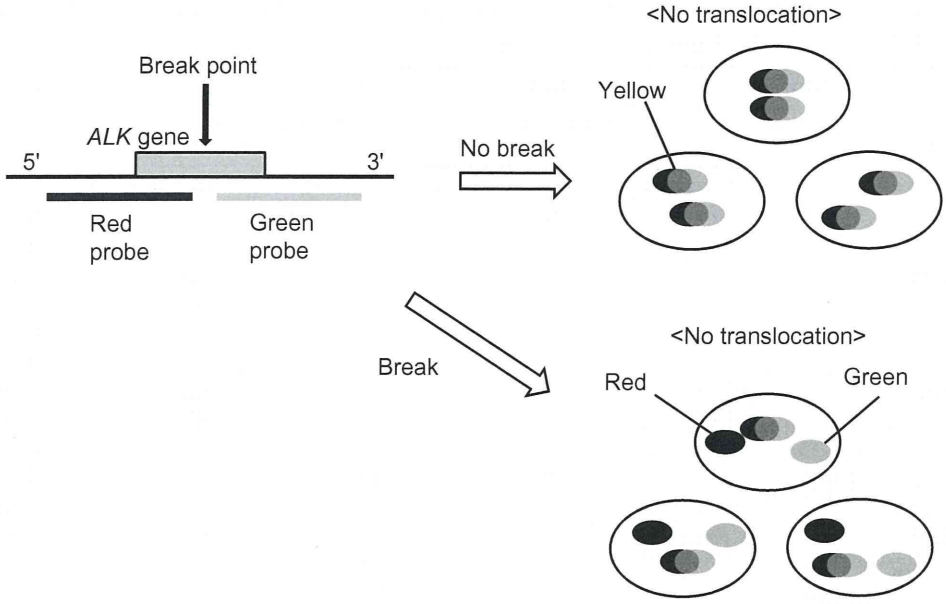

Figure 6 Schematic illustration for break-apart fluorescence in situ hybridization for detecting *ALK* rearrangements.
Abbreviation: ALK, anaplastic lymphoma kinase.

labeled with red or green fluorescent probes (Figure 6). If the signals of the two probes overlap, resulting in yellow fluorescence, then there is no translocation. If a translocation is present, the two probes are spatially separated, and each is detected as an isolated signal (red or green). Tumors are deemed positive for *ALK* rearrangement if 15% or more of the tumor cells show isolated signals. Such analysis detects *ALK* rearrangement regardless of the *ALK* fusion partner or the specific *EML4–ALK* variant. The break-apart FISH assay is a unique diagnostic approach approved for screening for *ALK* rearrangement in NSCLC by the FDA. FISH has several disadvantages, however. First, it is an expensive and low-throughput method that requires technical expertise. Second, false-negative results sometimes occur because of difficulty in interpretation of separated signals. And third, the use of FISH alone (without IHC or RT-PCR) for screening may give rise to false-positive results. Indeed, in one study, the ORR for crizotinib was only 48% among patients screened with FISH alone, but increased up to 81% among those screened with FISH in combination with IHC or RT-PCR.[48]

IHC

Given that ALK is not expressed in normal lung tissue or in lung cancer negative for *ALK* rearrangement, any level of ALK expression is considered to be abnormal and expected to be the result of *ALK* rearrangement. The abundance of ALK fusion proteins is relatively low, however, and initial attempts to detect such proteins by IHC were disappointing.[49] The subsequent development of an intercalated antibody-enhanced polymer (iAEP) method for signal enhancement (which incorporates an intercalating antibody between the primary antibody to ALK and the dextran polymer-based detection reagents) resulted in a marked increase in the sensitivity of IHC for the detection of ALK fusion proteins.[50] Several studies have since described the detection of ALK fusion proteins with high sensitivity and specificity by the application of IHC with improved detection methods (such as the iAEP method [Nichirei Biosciences] or EnVision™ FLEX+ [Dako, Glostrup, Denmark]) in combination with antibodies to ALK (ALK1, 5A4, and D5F3) (Table 2).[51–59] The sensitivity of the improved IHC procedures is especially high with the D5F3 or 5A4 antibodies. Given that IHC is a routine methodology in most pathology laboratories, it may be suitable for screening of NSCLC patients for *ALK* rearrangement after appropriate clinical optimization and validation (Figure 7).

RT-PCR

RT-PCR is a highly sensitive and specific method for the identification of *ALK* rearrangement.[60,61] In addition, unlike FISH or IHC, it can determine both the fusion partner of *ALK* (from among those previously identified) and the *EML4–ALK* variant.[62] RT-PCR requires high-quality ribonucleic acid (RNA) extracted from nonfixed or freshly frozen specimens, however. It is generally difficult to extract suitable RNA from the paraffin-embedded specimens used in daily clinical practice.

Table 2 Summary of the sensitivity and specificity of improved immunohistochemistry (IHC) procedures for the detection of anaplastic lymphoma kinase (ALK) in non-small-cell lung cancer specimens

Reference	FISH-positive cases	Antibody	Cutoff point of IHC score				Detection system
			2+ (including 2+ and 3+ cases)		1+ (including 1+, 2+, and 3+ cases) or IHC score not used		
			Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)	
51	43/132	D5F3	97.7	96.6	100	87.4	SignalStain® Boost IHC Detection
52	44/161	D5F3	NE		90.9	99.1	EnVision+
		ALK1			63.6	96.6	
53	63/196	D5F3	NE		100	98.5	OptiView/OptiView Amplification
54	7/594	ALK1	28.6	99.8	100	99.0	EnVision FLEX+
		5A4	85.7	99.8	100	98.1	UltraView/UltraView Amplification
		D5F3	71.4	99.5	100	99.0	Optiview/Optiview Amplification
55	20/351	5A4	100	99.4	100	99.4	Polymer Refine Detection Kit (Leica)
56	15/186	5A4	NE		80.0	99.4	EnVision+
57	25/262	5A4	80.0	99.2	100	98.7	Polymer Refine Detection Kit (Leica)
58	10/101	ALK1	90.0	97.8	100	75.8	ADVANCE (Dako)
59	22/153	ALK1	NE		67.0	97.0	EnVision+
		D5F3			100	99.0	

Notes: SignalStain® Boost IHC Detection (Cell Signaling Technology, Inc., Danvers, MA, USA). EnVision™+ (Dako, Glostrup, Denmark). OptiView/OptiView Amplification (Ventana Medical Systems, Inc., Tucson, AZ, USA). EnVision™ FLEX+ (Dako). UltraView/UltraView Amplification (F. Hoffmann-La Roche Ltd, Basel, Switzerland). Polymer Refine Detection Kit (Leica, Nussloch, Germany). ADVANCE (Dako).
Abbreviations: FISH, fluorescence in situ hybridization; NE, not evaluated.

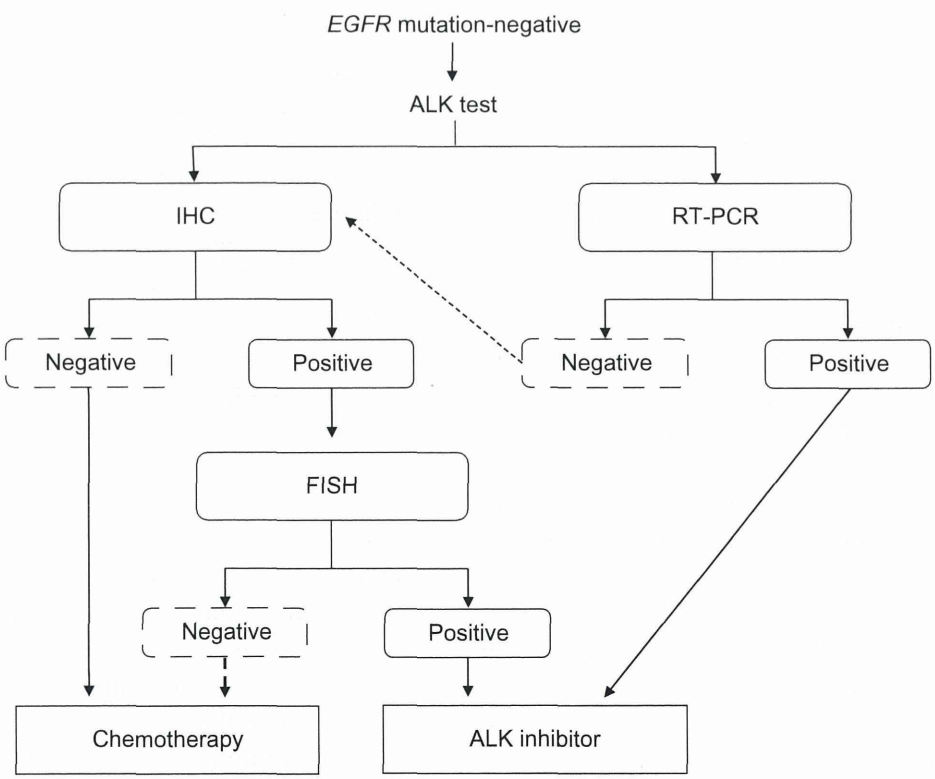

Figure 7 Proposed algorithm for testing for *ALK* rearrangement in patients with non-small-cell lung cancer.
Abbreviations: ALK, anaplastic lymphoma kinase; IHC, immunohistochemistry; RT-PCR, reverse-transcription polymerase chain reaction; FISH, fluorescence in situ hybridization.

Several new RT-PCR-based methods have recently been developed. MassARRAY is a nucleic acid-analysis platform for the detection of *EML4–ALK* that involves PCR amplification, single-base primer extension, and analysis by MALDI-TOF (matrix-assisted laser desorption ionization–time of flight) mass spectrometry.[63] The region of *EML4–ALK* complementary deoxyribonucleic acid containing the fusion point is amplified by PCR, but given that the amplicons are relatively small (70–130 bp), the quality of RNA extracted from paraffin-embedded specimens is sufficient for the analysis. RT-PCR-based assays may thus come to be more convenient and a major tool for detection of *ALK* rearrangement if the use of paraffin-embedded tissue is validated.

Future perspectives

The identification of the *EML4–ALK* fusion gene has accelerated translational research and changed clinical practice for NSCLC, with crizotinib now being in clinical use as an ALK inhibitor for the treatment of patients with *ALK* rearrangement-positive NSCLC. Although crizotinib has an excellent initial therapeutic effect, all treated patients eventually develop resistance to this drug. The development of therapeutic strategies able to overcome crizotinib resistance, including those based on the administration of new ALK inhibitors, is thus warranted. In addition, given the existence of other drivers of NSCLC, such as *EGFR* mutations as well as reactive oxygen species 1 and *RET* fusion genes, it will be important to improve and validate methods for the detection of and screening for these various genetic changes, so that the appropriate drug can be prescribed.

Disclosure

The authors report no conflicts of interest in this work.

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記 録　第3回 がん新薬開発合同シンポジウム　がん新薬開発の新しい潮流：世界をリードする医療イノベーション実現に向けて

研究者主導未承認薬開発試験の実施および規制上の諸問題*,1)
―アカデミアの立場から―

佐 藤 暁 洋**

Key Words : clinical trial, early development, GCP, investigator initiated trial, investigational drug

はじめに

国立がん研究センター早期・探索臨床研究センターは，厚生労働省の早期探索的臨床研究拠点整備事業への採択を受けて，2012年9月に設立され，2013年4月から病院・研究所と並列の独立セグメントとして正式に発足した．臨床試験支援室は，早期・探索臨床研究センターの3つのミッションである，「first in humanの医師主導治験・企業治験」「first in human終了後未承認薬での医師主導治験」「付随するトランスレーショナルリサーチ」の中で，研究者が主導する医師主導治験・臨床試験(investigator initiated trial；IIT)の支援を担っている．2013年度は，医師主導治験9試験，未承認・適応外の薬剤・医療機器を用いた臨床試験5試験(うち2試験が先進医療B)のデータセンター/モニタリング・治験調整事務局/監査/統計解析/薬事などの支援を実施し，年度内にさらに医師主導治験1試験，臨床試験2試験程度の開始が予定されており，これらを東病院のIITの臨床試験コーディネーター(clinical research coordinator；CRC)業務を含めて約35名のスタッフが支えている．

アカデミア側からみた諸問題

本稿では，アカデミア側からみた諸問題として，以下の4つをあげ，以下に述べる．

1. アカデミア開発での出口戦略：医師主導治験か先進医療Bか？
2. 医師主導治験の効率化
3. 民間企業とのコラボレーション・利益相反(conflict of interest；COI)管理
4. アクセス充実対策事業

1. アカデミア開発での出口戦略

未承認もしくは適応外の医薬品を使用して臨床試験を行う場合，最終的には承認(適応拡大を含む)を取得することを目的とする．そのための方法としては，その臨床試験の結果を申請資料の一部として使用して申請するか，試験の結果をエビデンスとして公知申請(適応拡大の場合のみ)を行うかの2つが現時点で取りうる選択肢である．また，アカデミアの臨床試験で，未承認もしくは適応外の医薬品を混合診療で使用可能な制度としては，医師主導治験と先進医療Bが存在するが，これらはいくつかの部分で異なっている(表1)．一番大きな違いとしては，医師主導治験の場合にはその結果を申請資料の一部として使用することが可能であるが，先進医療Bの場合には現時点で使用できるか不明であることである．筆者の私見にはなるが，可能であるならば申請資料に使用可能な医師主導治験の

* Challenges in investigator initiated clinical trial in Japan.

** Akihiro SATO, M.D., Ph.D.: 独立行政法人国立がん研究センター早期・探索臨床研究センター臨床試験支援室〔〒277-8577 千葉県柏市柏の葉6-5-1〕; Clinical Trial Section, Exploratory Oncology Research and Clinical Trial Center, National Cancer Center, Kashiwa, Chiba 277-8577, JAPAN

1) 2013年11月29日(金)，ステーションコンファレンス東京 5F 501ABS (サピアホール)，東京

表1　製造販売承認・保険適応への道

	医師主導治験	先進医療B
保険外併用療養費	可能(同種同効薬は×)	可能(同種同効薬もOK)
規制要件	省令GCPに従って実施	先進医療通知(non-GCP)に従って実施
製造販売承認申請	申請資料(CTD)の一部 「臨床試験の試験成績に関する資料」 (モジュール5臨床試験報告書)	参考資料？
承認区分	新規を含めて可能	薬事承認申請の効率化？ 公知申請(適応拡大)？
治験薬(機器)	First in humanを含め，未承認薬の使用が可能	First in humanを除く，未承認薬の使用が可能

表2　先進医療Bの活用方法(私見)

・治験を実施する前のエビデンス作り
- 未承認医療機器において，治験実施前にPOC取得/機器改良などを目的とした臨床試験
- 希少がんに対する未承認医薬品/医療機器開発において，オーファン指定要件「有効性または安全性が期待されること」のためのエビデンスを得る
- 未承認医薬品において，phase Iなど用量設定試験(phase IIより治験を実施)

・治験を実施せずに製造販売承認を得る
- 公知申請(適応拡大)
- 「臨床試験の試験成績に関する資料」として活用？

「希少疾病用医療機器等に関する臨床試験データの取り扱いの明確化について」(医食機発0329第1号)
医療機器であれば「先進医療により実施されるなどその実施にかかわる倫理性，科学性および信頼性が確認しうる試験成績がある場合」には「新たな治験を行う必要がない場合があると考えられる」と記載

方が現時点では優れていると考えられる．また，先進医療Bの活用方法の案を表2に示す．

2．医師主導治験の効率化

医師主導治験は，公的資金などで実施され予算を含めてリソースは企業治験の数分の1で実施せざるをえない場合が多い．一方，企業治験と比べ(オーバーではない)適切なクオリティで実施することが，アカデミアで実施されるからこそチャレンジ可能である．また，運用面に関して，規制緩和や新しい手法の開発について規制当局に対して提言していくことが重要となる．この数年で，医師主導治験の制度面での効率化はかなり進んでいるが，いまだ残っているいくつかの部分について次に述べる．

(1)同種同効薬

「療担規則」(保医発0326第5号平成24年3月26日)では，「自ら治験を実施する者による治験においては，治験に係る診療のうち，当該治験の対象とされる薬物の予定される効能または効果と同様の効能または効果を有する医薬品に係る投薬および注射に係る費用については，保険外併用療養費の支給対象とはしないものとする．」とある，“同様の”の解釈が分かれる場合もあるようだが，一般的には抗がん剤同士の併用ではもう一方の薬は同種同効薬に当たると解釈される場合が多い．最近では分子標的薬同士の併用など併用薬が高価になる場合も多く，資金の少ないアカデミア発の医薬品開発においては併用薬を研究費で購入するのが困難な場合も多い．

(2)治験薬のラベル

GCP(Good Clinical Practice；医薬品の臨床試験の実施の基準に関する省令)(平成24年12月28日 厚生省令第161号)には治験薬の管理について表3で示すような規定がされている．医師主導治験で用いられる治験薬は，国内企業から提供される場合，グローバル企業の本社から提供される場合，海外の市販薬がそのまま治験薬として提供される場合など，さまざまな場合が想定される．その場合に，提供される治験薬バイアルのラベルが英語名，バイアル本体に会社のマークが入っている・販売名がプリントされている，などの場合があり，これを治験薬GCP下でラベルを貼り替えるとなると高額な外注費用が発生

表3　治験薬のラベル

・医薬品の臨床試験の実施の基準に関する省令(平成24年12月28日厚生省令第161号)
(治験薬の管理)
- 第二十六条の二　自ら治験を実施する者は，治験薬の容器または被包に次に掲げる事項を**邦文で記載しなければならない**.
一．治験用である旨
二．自ら治験を実施する者の氏名および職名ならびに住所
三．化学名または識別記号
四．製造番号または製造記号
五．貯蔵方法，有効期間等を定める必要があるものについては，その内容
- 2　自ら治験を実施する者は，治験薬に添付する文書，その治験薬またはその容器もしくは被包(内袋を含む)には，次に掲げる事項を**記載してはならない**.
一．予定される販売名
二．予定される効能または効果
三．予定される用法または用量

することとなる．これに関しても，被験者に直接バイアルが渡らない注射薬の場合などでは，ラベルへの販売名・会社名の記載を許容する，non-GMP(Good Manufacturing Practice；医薬品等の製造品質管理基準)でのラベル貼りを許容する，国際共同治験でなくとも海外から治験薬が提供される場合には英文ラベルを許容するなどの規制緩和が望まれる．

(3)リスクベースドモニタリング

近年，リスクベースドモニタリングという概念が提唱され，3極の規制当局からもそれぞれガイダンスが出されている．わが国でも「リスクに基づくモニタリングに関する基本的考え方について」(平成25年7月1日事務連絡)が示されているところではあるが，サンプリングSDV(source data verification；原資料との照合)などのリスクベースドモニタリングを実際に行う場合に必要となる具体的な基準は，規制当局からは現在示されていない．国内では，少なくともがんの分野での治験への導入は行われておらず，実際の医師主導治験のデータや実施を通じてアカデミアからその基準などについて提案していくことが求められる．

3．民間企業とのコラボレーション・COI管理

新しい医薬品を世の中に出すためには，最終的には市販することが必要である．市販するためには製造販売承認を得ることが必要であり，そのためには製造販売業の許可を取得した企業が必要となる．これはアカデミア発のシーズであっても変わりはなく，アカデミア自らが製造販売業の許可を取得しない限りにおいては，どの段階かで必ず民間企業との共同作業が発生する．そして，アカデミアと民間企業との関係については，昨今さまざまなスキャンダルが報じられているように透明性の確保が求められる．

特に，企業が開発中の薬剤に関して，研究者が独自のアイディアで別のがん種での開発を行う場合などでは，企業から治験薬の無償提供を受けて行う医師主導治験等が行われる．また，公的資金が獲得できず，企業戦略にもある程度合致する場合には，治験薬のみではなく，試験実施の実費程度の資金提供を受ける場合もある．その場合に重要となるのは，(1)試験の独立性の確保，(2)COIの適切な管理，(3)透明性の確保，などがあげられる．次にそれらについて，国立がん研究センター早期・探索臨床研究センターでの取り組みを述べる．

(1)試験の独立性の確保

早期・探索臨床研究センターでは，プロトコール・SOPの作成，モニタリング，治験調整事務局，データセンター・登録センター，統計解析，安全性情報管理，監査，総括報告書の作成など，ほとんどすべての医師主導治験のプロセスを自前の組織もしくは自らが外注業者に直接委託する形で実施し，治験薬提供者である企業は最低限必要となる治験薬の製造・提供，国内外の他治験の情報提供等のみを担う．また，契約も企業との契約は早期・探索臨床研究センターが各施設を代表して行う形式としている．このことによって，企業は治

験薬・資金提供，最初の段階の試験計画の承認は行うが，試験の実施・結果の解釈には関与しない体制としている．

(2)COIの適切な管理

国立がん研究センターでは，公的研究費を受けるすべての研究者が年1回COI委員会に申告書を提出して審査を受けている．それに加えて，早期・探索臨床研究センターで医師主導治験を実施する治験責任医師/分担医師が試験の開始時に別途COI委員会に審査を依頼することとしている．また，企業からの資金提供については，その内容をIRB(治験審査委員会)資料に含めることによってIRBの審査も受けている．

(3)透明性の確保

企業からの薬剤・資金の提供に関しては，プロトコールおよび説明同意文書に明記するとともに，早期・探索臨床研究センターのホームページにも試験の内容とともに資金提供について明記することによって情報公開を行っている．

4．アクセス充実対策事業

2013年の7月に厚生労働省の企画競争「平成25年度医療上の必要性の高い未承認薬・適応外薬のアクセス充実対策等事業」に採択されて委託事業を開始している．

本事業は，医療上の必要性の高い未承認薬・適応外薬に対して，治験の参加基準に外れるなどの理由で治験に参加できない患者に対してアクセスを可能とするために，医師主導治験を実施し，それに必要となる文書モデルの作成や問題点の洗い出しを行うことを目的としている．まずは，医療上の必要性の高い未承認薬・適応外薬検討会議でリストアップされており，開発企業が第III相試験を実施中もしくは承認申請中の薬剤から候補薬を選定し年度内に第1号の医師主導治験を開始すべく準備を行っている段階である．本事業では医師主導治験の効率化のための問題点を洗い出すことも目的の一つとしており，上記「2．医師主導治験の効率化」で述べたような問題点も規制当局に提案して行きたいと考えている．

おわりに

本稿では，アカデミア発の開発，特に医師主導治験などによる臨床開発での諸問題についてある程度具体的な対応策とともに提起した．本稿が，われわれと同様にアカデミア発の治療開発を行う研究者，それと協働する製薬企業や規制当局の担当者の間でのディスカッションの促進や医師主導治験等の効率化へ向けての一助となることを祈念する．

<Abstract>

Challenges in investigator initiated clinical trial in Japan.

by
Akihiro SATO, M.D., Ph.D.
from
Clinical Trial Section, Exploratory Oncology Research and Clinical Trial Center, National Cancer Center, Kashiwa, Chiba, JAPAN

Corresponding author : Akihiro SATO, M.D., Ph.D., Clinical Trial Section, Exploratory Oncology Research and Clinical Trial Center, National Cancer Center, 6-5-1 Kashiwanoha, Kashiwa-shi, Chiba 277-8577, JAPAN

National Cancer Center Exploratory Oncology Research and Clinical Trial Center (EPOC) was established on April 2013 as an Academic Research Organization (ARO) for early clinical trial development. One of the missions of the EPOC is investigator initiated clinical trials (IITs) using investigational new drug.

To promote early drug development from ARO, a credible development strategy planning, promotion the efficiency of IIT operations, and appropriate conflict of interest management and collaboration with pharmaceutical companies are required.

Here we show commentaries on these topics and new expand access program in Japan. The section of development strategy shows the differences of research IND and senshiniryo B. The section of IIT operations shows unsolved regulatory problems of research IND in Japan. The section of COI management gives an example of actual COI management and col-

laboration with pharmaceutical companies in EPOC. The section of expand access program introduce a new system of early access to new investigational drug for patients in clinical trial setting.

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