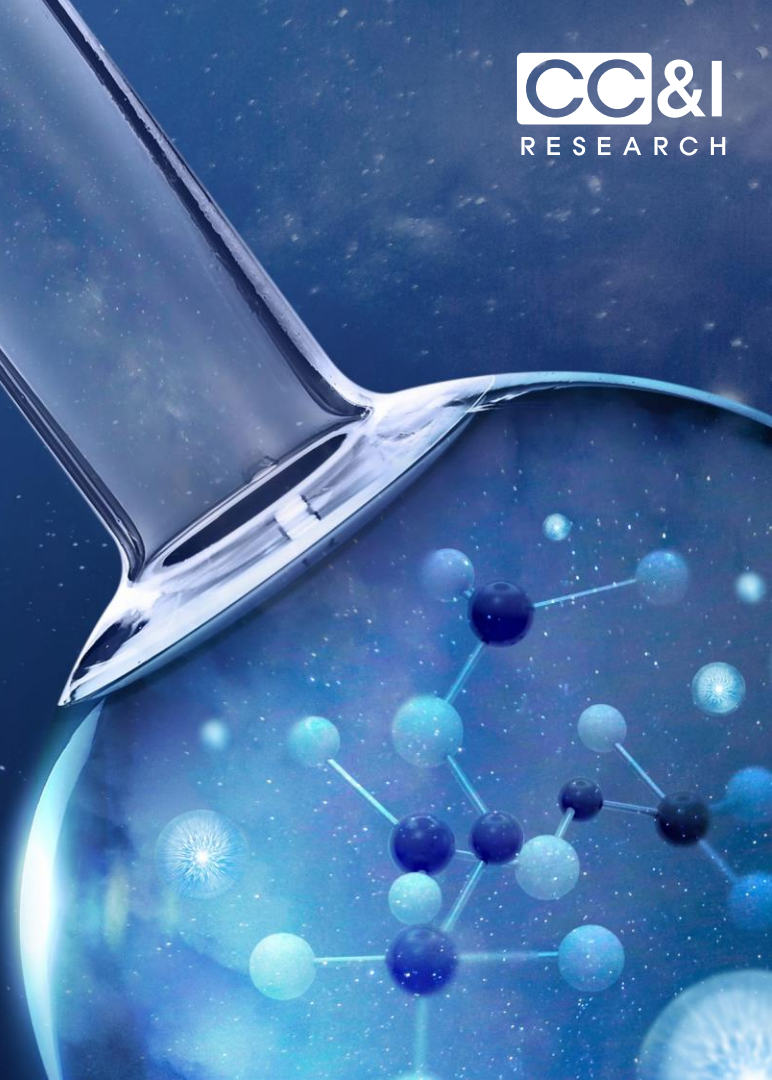
2022.08.27 하계 분자폐암 연구회 임상연구 워크숍
Session Ⅰ. Korea EGFR Registry

CC&I RESEARCH

Research in Progress from a CRO Perspective



CC&I Research 박재은(BD/CRS팀)

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Korean EGFR Registry

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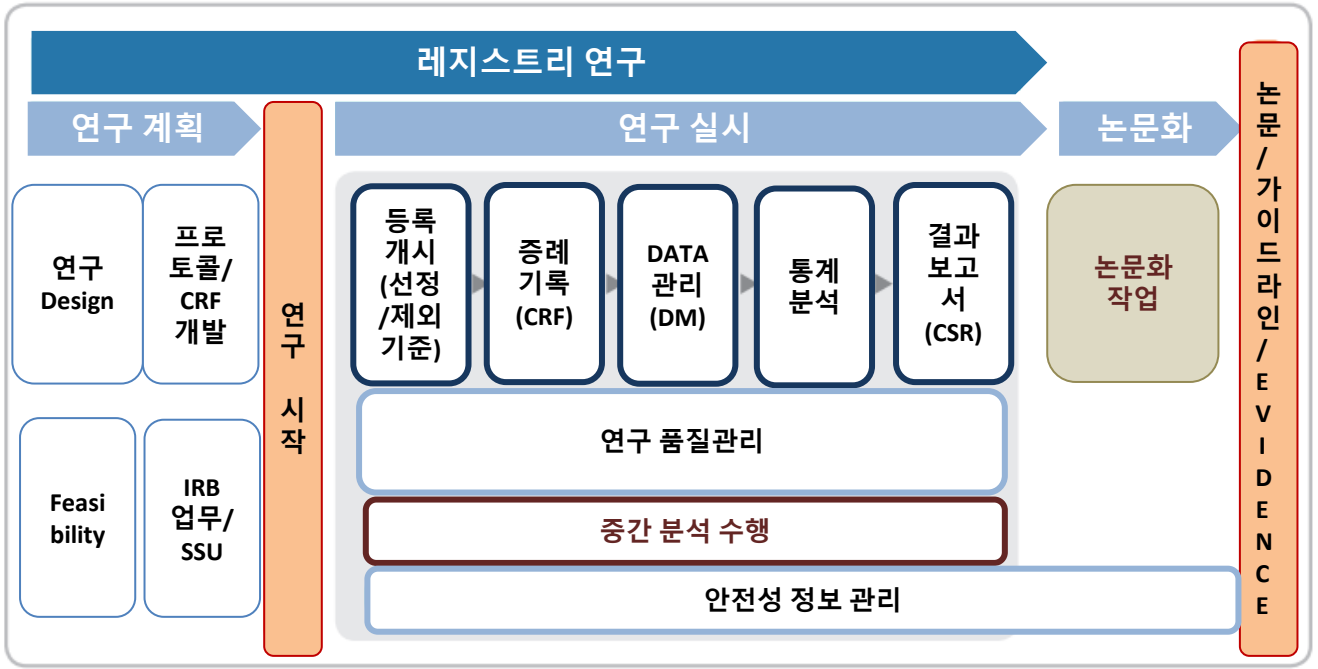
분자폐암 연구회 유한양행 CC&I RESEARCH

The progression order of clinical research

1. 레지스트리 임상 연구의 진행 상황

- 일반적으로 레지스트리 연구는 다음과 같이 진행되고 있습니다.

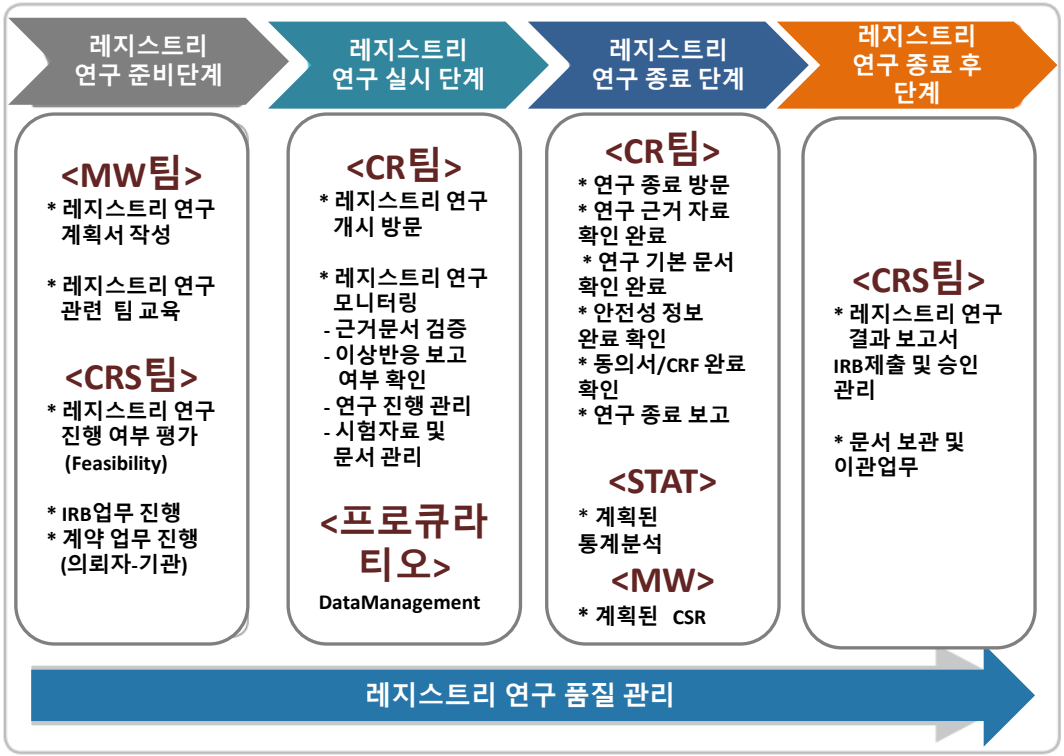


The progression order of clinical research

2. 본 레지스트리 연구의 현재 단계 및 관련 업무

The progression order of clinical research

2. 본 레지스트리 연구의 현재 단계 및 관련 업무



Korean
EGFR Registry

II

IRB Regulatory Affairs

1. IRB 진행 사항 보고
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분자폐암 연구회 유한양행 CC&I RESEARCH

1. IRB 진행 사항 보고

- 초기 심의 진행 현황(34개 기관 IRB 완료, 3개 기관 미완료)

✓ 승인 (14개 기관)	• 강남세브란스 병원, 계명동산대병원, 부산백병원, 삼성창원병원, 세브란스병원, 영남대학교병원, 용인 세브란스병원, 창원경상국립대병원, 충남대병원, 칠곡경북대병원, 한림대춘천성심병원, 화순전남대병원, 건국대병원
✓ 시정 후 승인 (21개 기관)	• 시정 **1회** 보완 후 **승인 완료**(17개 기관): 건양대병원, 경희대병원, 고려대구로병원, 고신대병원,부산대병원, 순천향대부천병원, 양산부산대병원,원광대병원,인하대병원, 한림대성심병원, 해운대백병원, 서울성모병원, 서울아산병원 여의도성모병원, 은평성모병원,의정부성모병원,인천성모병원 • 시정 **2회** 보완 후 **승인 완료**(3개 기관) : 고대안암병원,부천성모병원,한양대병원 • 시정 **2회** 보완 후 **심의 중**(1개 기관) : **중앙대병원**
✓ 기타 (2개 기관)	• **삼의 준비 중: 대구가톨릭대병원 (서류 구비 중)** • **참여 보류: 순천향대천안병원**

1. IRB 진행 사항 보고

- 계약 및 개시 현황 (IRB 완료된 33개 기관 중)

✓ 개시 완료 (19개 기관)	• **5-6월:** 해운대백병원(5/19) 계명대학교 동산병원(6/8) 세브란스병원(6/13) 삼성창원병원(6/14) 용인세브란스병원(6/16) 영남대학교병원(6/22) 고대구로병원(6/23) 부산백병원(6/28) 건양대병원(6/30) • **7-8월:** 강남세브란스 병원(7/1) 충남대병원(7/1) 경희대병원(7/13) 화순전남대병원(7/15)원광대병원(7/19) 고대안암병원(7/25) 칠곡경북대병원(7/26) 고신대학교병원(8/2) 한양대병원(8/8) 순천향부천병원(8/11) 양산부산대병원(8/19)
✓ 계약 검토 완료 후 직인 중 (12개 기관)	• 부산대병원 부천성모병원 서울성모병원 여의도성모병원 의정부성모병원 은평성모병원 인천성모병원 인하대병원 창원경상국립대병원 한림대성심병원 한림대춘천성심병원(8/31 예정)
✓ 계약서 검토 중 (2개 기관)	• 서울아산병원 (기관 2차 검토 중) • 순천향서울병원 (PI 검토 중)

2. 주요 지적 사항 및 대응 방향 공유

지적 사항

1) 연구 정보 영구 보존 – 보관 기한 & 폐기에 대해 명시

2) 취약한 대상자들을 꼭 포함해야하는지?

답변 및 수정 사항

1) 수집된 연구 정보의 보관 기간을 영구 보존에서 **최대 15년으로** 수정함(PRT 1.1 변경 사항)

2-1) 본 연구는 레지스트리 연구로서 고령의 말기암 환자가 다수 포함될 수 있고 스스로 동의 어려운 경우 대리인의 동의를 받을 수 있음. **설문을 제외하고는 비중재이므로 자발적으로 본연구에 참여하기를 희망하는 경우 역차별을 막고자 참여 제한하지 않음.** 이때 준수할 안전 보호대책을 함께 제출함

2-2) 그럼에도 집단시설(감옥) 등에 수용 중인 자는 환경적으로 연구에 들어올 가능성이 거의 없다고 판단하여 참여 제한하는 것으로 진행함.

2. 주요 지적 사항 및 대응 방향 공유

✓ **등록 가능한 취약한 대상자**	• 참여를 거부하는 경우 조직 위계상 상급자로부터 받게 될 불이익에 대한 우려가 자발적인 참여 결정에 영향을 줄 가능성이 있는 대상자(의과대학·한의과대학·약학대학·치과대학 ·간호대학의 학생, 연구기관의 근무자, 제약회사의 직원, 군인 등을 말함.), • 불치병에 걸린 사람, 실업자, 빈곤자, 응급상황에 처한 환자, 말기암에 걸린 환자 • 65세 이상 고령자, 정신질환자
✓ **등록 불가능한 취약한 대상자**	• 집단시설에 수용되어 있는 사람(감옥 등)

2. 주요 지적 사항 및 대응 방향 공유

지적 사항

3) PRT 내 '대상 집단' 설명 - 후향적 수집하는 선정기준에 대해 2021년 1월 1일 이후 TKI를 사용하고 있는 환자인지, TKI를 시작한 사람인지?

4) 렉라자정에 한해서 이상사례를 수집하는 것으로 되어 있음. 이것이 렉라자정에 유리하게 편향된 처방을 야기하지는 않을지?

답변 및 수정 사항

3) PRT의 '대상집단'에 대한 기술을 수정 하기로 함
=> **2021년 이후 TKI를 '시작'한 환자(V1.2 수정 필요)**

4) 이상사례를 렉라자정만 수집하는 것은 렉라자정 위주로 처방되는 편향이 발생할 우려가 있는 상황이 아니고 데이터 수집의 번거로움으로 **오히려 반대로 렉라자정의 처방을 연구자들이 꺼리는 편향이 발생할 수 있는 문제**임.
위와 같은 우려에도 불구하고 본 레지스트리 연구에서 이상사례를 수집하기로 결정한 이유는 **의약품 허가권자의 시판 후 감시 의무를 성실히 수행하기 위한 공익적 목적임**.

2. 주요 지적 사항 및 대응 방향 공유

혹

은

시작한

대상 집단[TARGET POPULATION]

IRB 승인일 이후 새로 진단된 EGFR 돌연변이가 있는 모든 병기의 비소세포폐암 환자 또는 전이성 및 재발성 EGFR 돌연변이 비소세포폐암으로 2021 년 1 월 1 일 이후 EGFR 표적치료제를 투약 중인 환자

선정/제외기준 [INCLUSION/EXCLUSION CRITERIA]:

주요 선정기준 [Key Inclusion Criteria]

1) 만 20 세 이상 성인으로, 대한민국 국적을 가진 자
2) 본 연구의 동의서에 자발적으로 서명한 자
3) IRB 승인일 이후 새로 진단된 EGFR 돌연변이가 있는 모든 병기의 비소세포폐암 환자 또는 전이성 및 재발성 EGFR 돌연변이 비소세포폐암으로 2021 년 1 월 1 일 이후 EGFR 표적치료제를 투약을 시작한 환자$

PRT 1.2 변경 예정

2. 주요 지적 사항 및 대응 방향 공유

지적 사항

5) 국내 다기관 연구로, 전향적 레지스트리 연구로 연구 참여자에게 연구비 내에서 실제로 제공되는 이득은 없고, 해외 여비, 회의비, 인건비 등으로 주로 구성되어 있음.

유한양행에서 이 연구를 지원하는 이유가 무엇인지?

답변 및 수정 사항

5) 유한양행에서는 2021년에 EGFR 돌연변이 비소세포폐암 환자를 대상으로 한 3세대 EGFR TKI 약제를 한국에서 최초로 허가 받았고, 해당 약물은 글로벌 제약사에 기술 수출되어 다국가 대규모 임상3상 시험을 진행하고 있음.
이에 다음과 같은 이후로 본 연구를 진행함.

① 한국에서 EGFR 양성 비소세포폐암 대상의 대규모 레지스트리 연구를 통해 **여러 병기 단계에서의 치료성적 자료를 확인**하는 **의학적 목적**이 있음.

② **진료 현장의 여러 치료 방법 속에서** 유한양행이 개발한 **신약의 치료적 지위를 확인**할 수 있다는 **추가적인 학술적 의미**가 있음.

Korean EGFR Registry

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Enrollment Status

1. 기관별 등록 현황
2. 등록대상자 코호트 현황

분자폐암 연구회 유한양행 CC&I RESEARCH

Enrollment Status

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1. 기관별 등록 현황

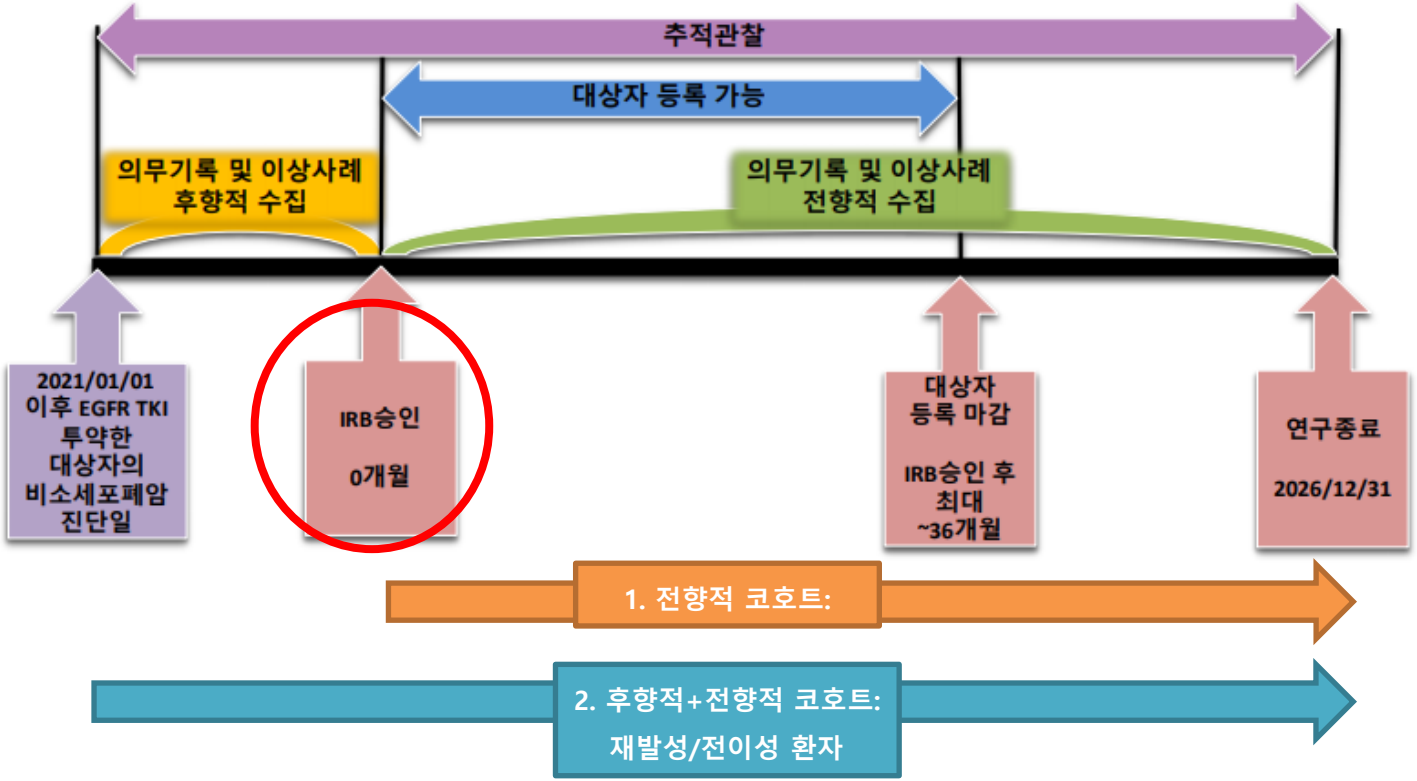
Last updated 2022.08.27

기관명	스크리닝	중복 대상자	스크리닝 탈락	등록	PD 건수	AE 건수	SAE 건수	Final Follow up					
								생존	사망	동의철회	추적관찰실	타 병원 전	기타
[03]건양대학교병원	1	0	0	1	0	0	0	0	0	0	0	0	0
[04]경희대학교병원	1	0	0	1	0	0	0	0	0	0	0	0	0
[07]고려대학교 구로병원	21	0	0	21	0	0	0	0	0	0	0	0	0
[08]고신대학교 복음병원	9	0	0	9	0	0	0	0	0	0	0	0	0
[11]부산백병원	5	0	1	4	0	0	0	0	0	0	0	0	0
[13]삼성창원병원	10	0	0	10	0	0	0	0	0	0	0	0	0
[16]세브란스병원	12	0	0	12	0	0	0	0	0	0	0	0	0
[17]순천향대학교부천병원	1	0	0	1	0	0	0	0	0	0	0	0	0
[20]양산부산대학교병원	1	0	0	1	0	0	0	0	0	0	0	0	0
[22]영남대학교병원	19	0	0	19	0	0	0	13	0	0	0	0	0
[23]용인세브란스병원	13	0	0	13	0	0	0	0	0	0	0	0	0
[24]원광대학교병원	2	0	0	2	0	0	0	0	0	0	0	0	0
[36]해운대 백병원	2	0	0	2	0	0	0	0	0	0	0	0	0
[37]화순전남대학교병원	5	0	0	5	0	0	0	0	0	0	0	0	0
합계	102	0	1	101	0	0	0	13	0	0	0	0	0

PD: Progression Disease, AE: Adverse Event, SAE: Serious Adverse Event

Enrollment Status

2. 등록 대상자 코호트 현황



Enrollment Status

2. 등록 대상자 코호트 현황

Last updated 2022.08.27

최초진단일	비소세포폐암 최초 진단일 Baseline	IRB 승인일	코호트 구분 1= 신환 2= 2021년 이후 TKI 시작	기준 Stage (최종 확인된 TNM-M) Diagnosis	cStage Diagnosis
2021-03	2021-03	2022-05-10	2		
2018-11-28	2018-11-28	2022-06-27	2	M0	IB
2022-06-16	2022-06-16	2022-05-04	1	M1b	IVA
2020-03-19	2020-03-19	2022-05-04	2	M0	IIA
2021-11-15	2021-11-26	2022-05-04	2	M1a	IVA
2021-01-07	2021-01-06	2022-05-04	2	M1c	IVB
2009-06-09	2022-05-24	2022-05-04	2	M0	IIB
2022-03-23	2022-03-23	2022-05-04	2	M1b	IVA
2022-05-12	2022-05-12	2022-05-04	1	M1c	IVB
2019-07-09	2019-07-09	2022-05-04	2	M1a	IVA
2021-05-04	2021-05-04	2022-05-04	2	M1a	IVA
2021-12-27	2022-01-04	2022-05-04	2	M1b	IVA
2020-01-21	2020-01-21	2022-05-04	2	M1a	IVA
2021-06-15	2021-06-15	2022-05-04	2	M1c	IVB
2019-04-25	2019-04-25	2022-05-04	2	M1a	IVA

Enrollment Status

2. 등록 대상자 코호트 현황

Last updated 2022.08.27

최초진단일	비소세포폐암 최초 진단일 Baseline	IRB 승인일	코호트 구분 1= 신환 2= 2021년 이후 TKI 시작	기준 Stage (최종 확인된 TNM-M) Diagnosis	cStage Diagnosis
2022-07-06	2022-07-06	2022-05-04	1	M1c	IVB
2019-03-26	2019-03-26	2022-05-04	2	M1a	IVA
2022-07-12	2022-07-12	2022-05-04	1	M1a	IVA
2013-03-21	2013-03-21	2022-05-04	2	M0	IB
2022-05-30	2022-05-30	2022-05-04	1	M0	IA2
2022-07-14	2022-07-19	2022-05-04	1	M1c	IVB
2021-08-18	2021-08-18	2022-05-04	2	M1c	IVB
2021-04-22	2021-05-04	2022-05-04	2	M1c	IVB
2022-02-22	2022-02-23	2022-06-14	2	M1a	IVA
2022-06-23	2022-06-23	2022-06-14	1	M1c	IVB
2021-12-06	2021-12-07	2022-06-14	2	M1b	IVA
2021-10-13	2021-10-14	2022-06-14	2	M1c	IVB
2022-05-04	2022-05-06	2022-06-14	2	M1c	IVB
2021-03-10	2021-03-10	2022-06-14	2	M1b	IVA
2022-04-05	2022-04-05	2022-06-14	2	M1a	IVB

Enrollment Status

2. 등록 대상자 코호트 현황

Last updated 2022.08.27

최초진단일	비소세포폐암 최초 진단일 Baseline	IRB 승인일	코호트 구분 1= 신환 2= 2021년 이후 TKI 시작	기준 Stage (최종 확인된 TNM-M) Diagnosis	cStage Diagnosis
2021-01-27	2021-01-27	2022-06-14	2	M1c	IVB
2022-05-16	2022-05-16	2022-06-14	2	M1a	IVA
2022-04-08	2022-04-08	2022-04-26	2		
2022-02-07	2022-02-07	2022-04-26	2	M1b	IVA
2022-05-16	2022-05-16	2022-04-26	1	M1c	IVB
2021-02-04	2021-02-04	2022-04-26	2	M0	IB
2022-04-19	2022-04-19	2022-04-26	2	M1b	IVA
2021-04-06	2021-04-06	2022-05-02	2	M0	IB
2021-10-13	2021-10-10	2022-05-02	2	M1b	IVA
2022-06-14	2022-06-16	2022-05-02	1	M1c	IVB
2022-02-28	2022-03-18	2022-05-02	2	M1c	IVB
2021-06-04	2021-06-07	2022-05-02	2	M1a	IVA
2021-12-24	2022-01-22	2022-05-02	2		
2022-07-22	2022-07-28	2022-05-02	1		
2022-07-22	2022-07-22	2022-05-02	1		

Enrollment Status

2. 등록 대상자 코호트 현황

Last updated 2022.08.27

최초진단일	비소세포폐암 최초 진단일 Baseline	IRB 승인일	코호트 구분 1= 신환 2= 2021년 이후 TKI 시작	기준 Stage (최종 확인된 TNM-M) Diagnosis	cStage Diagnosis
2022-07-26	2022-08-03	2022-05-02	1		
2022-07-22	2022-07-21	2022-05-02	1		
2022-06-16	2022-06-16	2022-04-12	1	M0	IB
2021-01-13	2021-01-13	2022-04-12	2	M1a	IVA
2022-05-19	2022-05-19	2022-04-12	1	M1c	IVB
2022-01-17	2022-01-17	2022-04-12	2	M0	IIIB
2022-06-03	2022-06-03	2022-04-12	1	M0	IIIA
2021-10-08	2021-10-08	2022-04-12	2	M1a	IVA
2021-10-18	2021-10-18	2022-04-12	2	M1a	IVA
2021-09-06	2021-09-06	2022-04-12	2	M1a	IVA
2022-03-30	2022-03-30	2022-04-12	2	M1b	IVA
2022-07-27	2022-07-27	2022-04-12	1	M1c	IVB
2022-07-25	2022-07-25	2022-04-12	1	M1a	IVA
2021-11-18	2021-11-18	2022-04-12	2	M1c	IVB
2021-10-05	2021-10-06	2022-05-26	2	M1c	IVB

Enrollment Status

2. 등록 대상자 코호트 현황

Last updated 2022.08.27

최초진단일	비소세포폐암 최초 진단일 Baseline	IRB 승인일	코호트 구분 1= 신환 2= 2021년 이후 TKI 시작	기준 Stage (최종 확인된 TNM-M) Diagnosis	cStage Diagnosis
2022-05-30	2022-05-30	2022-05-18	1		
2021-10-05	2021-10-05	2022-04-28	2	M1c	IVB
2022-06-30	2022-06-30	2022-04-28	1	M1c	IVB
2022-02-18	2022-02-18	2022-04-28	2	M0	IIB
2020-12-09	2020-12-09	2022-04-28	2	M0	IB
2021-11-24	2021-11-24	2022-04-28	2	M0	IB
2018-05-28	2018-05-28	2022-04-28	2	M0	IB
2021-09-08	2021-09-08	2022-04-28	2	M1a	IVA
2019-08-01	2019-08-01	2022-04-28	2	M0	IB
2019-11-05	2019-11-05	2022-04-28	2	M0	IIB
2022-05-03	2022-05-03	2022-04-28	1	M1a	IVA
2021-02-19	2021-02-19	2022-04-28	2	M1c	IVB
2021-02-17	2021-02-17	2022-04-28	2	M0	IA3
2021-09-29	2021-09-29	2022-04-28	2	M0	IIIB
2021-07-16	2021-07-16	2022-04-28	2		

Enrollment Status

2. 등록 대상자 코호트 현황

Last updated 2022.08.27

최초진단일	비소세포폐암 최초 진단일	IRB 승인일	코호트 구분 1= 신환 2= 2021년 이후 TKI 시작	기준 Stage (최종 확인된 TNM-M)	cStage
	Baseline			Diagnosis	Diagnosis
2021-08-13	2021-08-13	2022-04-28	2		
2021-12-07	2021-12-07	2022-04-28	2		
2021-12-30	2021-12-30	2022-04-28	2		
2022-05-11	2022-05-11	2022-04-28	1		
2021-03-18	2021-03-18	2022-04-28	2		
2021-12-03	2021-12-03	2022-04-20	2	M1b	IVA
2021-10-06	2021-10-06	2022-04-20	2	M1a	IVA
2022-05-19	2022-05-19	2022-04-20	1	M1a	IVA
2022-06-03	2022-06-03	2022-04-20	1	M1c	IVB
2022-02-16	2022-02-16	2022-04-20	2	M1a	IVA
2021-08-04	2021-08-04	2022-04-20	2	M1a	IVA
2022-06-20	2022-06-20	2022-04-20	1	M0	IIB
2022-06-23	2022-06-23	2022-04-20	1	M0	IA3
2022-07-13	2022-07-13	2022-04-20	1	M1c	IVB
2022-07-22	2022-07-22	2022-04-20	1	M1c	IVB

Enrollment Status

2. 등록 대상자 코호트 현황

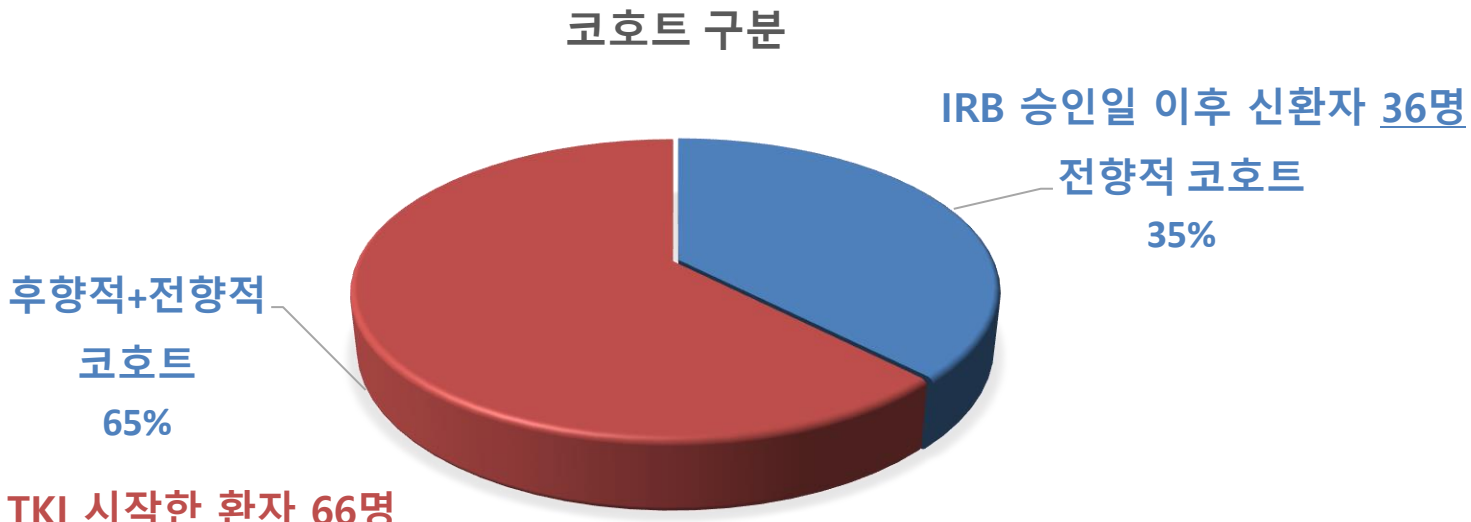
Last updated 2022.08.27

최초진단일	비소세포폐암 최초 진단일 Baseline	IRB 승인일	코호트 구분 1= 신환 2= 2021년 이후 TKI 시작	기준 Stage (최종 확인된 TNM-M) Diagnosis	cStage Diagnosis
2021-10-21	2021-10-21	2022-04-20	2	M0	IIIA
2022-05-04	2022-05-04	2022-04-20	1	M1c	IVB
2021-10-04	2021-10-04	2022-04-20	2	M1c	IVB
2022-07-06	2022-07-06	2022-05-18	1	M1c	IVB
2020-12-21	2020-12-21	2022-05-18	2	M1b	IVA
2022-06-20	2022-06-20	2022-04-19	1	M1b	IVA
2021-05-11	2021-05-11	2022-04-19	2	M1a	IVA
2022-06-23	2022-06-23	2022-05-04	1	M1a	IVA
2022-07-13	2022-07-13	2022-05-04	1		
2022-07-31	2022-07-31	2022-05-04	1		
2022-08-09	2022-08-09	2022-05-04	1		
2022-08-01	2022-08-01	2022-05-04	1		

Enrollment Status

2. 등록 대상자 코호트 현황

Last updated 2022.08.27



2021년 이후 TKI 시작한 환자 66명

Korean
EGFR Registry

IV

Study Timeline & Plan

Timeline 점검 및 향후 계획

분자폐암 연구회 유한양행 CC&I RESEARCH

Study Timeline

1. Timeline 점검

Item	Expected Timeline	Actual Timeline	Comments
PRT/CRF	2022.02.28	**2022.02.28**	
ICF	2022.02.28	**2022.03.07**	
IRB 초기 심의 접수	2022.03.11	**2022.03.31**	세브란스 병원
첫기관 SIV	2022.04.29	**2022.05.19**	해운대백병원, **2022.9월까지 전기관 개시 목표 (현재 약 65% 개시 완료)**
FPFV	**2022.05.02**	**2022.06.24**	**첫 대상자 등록 후 활발히 등록 진행 중**
LPFV	2025.07.30	-	**마지막 기관 개시**에 따라 1~2달 가량 지연될 가능성 있음.
LPLV	2026.12.31	-	
Last SDV	2027.03.31	-	

PRT: Protocol, CRF: Case report form, IRB: Institutional Review Board, SIV: Site Initiation Visit, FPFV: First Patient First Visit, LPFV: Last Patient First Visit, LPLV: Last Patient Last Visit, SDV: Source Data(Document) Verification

Study Timeline

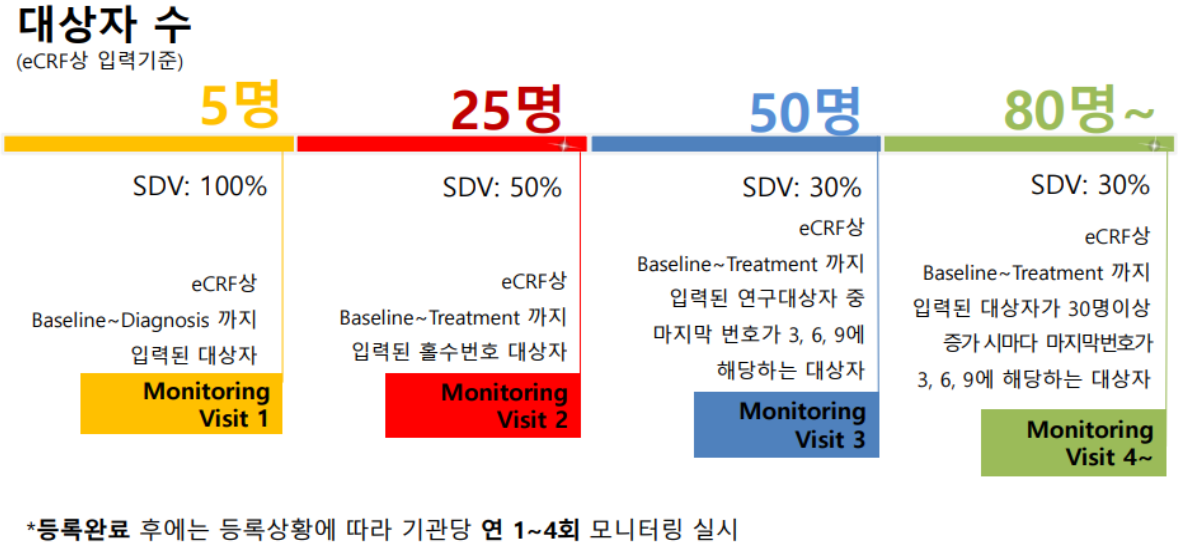
2. 향후 계획

1) 기관 계약 / 연구비 지급 / IRB 관리

2) 개시 모임 및 등록 속도에 따른 주기적 모니터링 시행

3) Newsletter 발행 (8월 말~)

4) PRT에 따른 정기적 통계 분석 진행



*등록완료 후에는 등록상황에 따라 기관당 **연 1~4회** 모니터링 실시

Korean EGFR Registry

V

Others

관련 연구 소개

분자폐암 연구회 유한양행 CC&I RESEARCH

2. 관련 연구 소개

1

AstraZeneca

STUDY REPORT SYNOPSIS

Survey on the treatment reality of patients with *EGFR* gene mutation-positive non-small cell lung cancer

ID: NCT02475720

2. 관련 연구 소개

1

Survey on the Treatment Reality of Patients With EGFR Mutation-positive NSCLC (ref)
Trial duration: **19 Jun 2015 ~ 27 March 2017**

# of subjects: **1660** participants
Retrospective study on **Japanese** subjects with EGFR mutation positive advanced/recurrent NSCLC, who commenced on **1st-line treatment between January 2008 and December 2012.**

Endpoints
Primary: Overall survival of the patients
Secondary:

- Overall survival by **patient background**
- Overall survival by **treatment sequence**
- **Treatment time by treatment**
- **Time to Treatment Failure (TTF) of Gefitinib treatment**

2. 관련 연구 소개

1

Results:

1. Patient Characteristics:

64.8% (1,073/1,656) of patients were **females** with the median age of 67.0 Years.
95.2% had adenocarcinoma
66.7% had stage IV cancer
50.1% had exon 19 deletion
41.5% had L858R mutation

2. Overall survival (OS): Median OS was **29.70** months (95% CI; 28.13-31.40).

3. Exposure rate: Exposure rate = person-years for the treatment group × 100 / total person-years

61.47% for EGFR-TKI±*α*, 8.15% for platinum doublet ± bevacizumab (BEV)
8.07% for other chemotherapy ± BE, and 22.24% for the untreated period

2. 관련 연구 소개

2

STUDY REPORT SYNOPSIS

Study report - Synopsis	
Study code	D5160R00005
Version	1.0
Date	09 May 2021

PANORAMA

Real World Molecular Testing, Treatment Patterns, and Clinical Outcomes in Patients with EGFR Mutation-Positive Locally Advanced or Advanced NSCLC

Milestones:	Start of data collection (FPI): May 26, 2016 End of data collection (LPO): May 31, 2020
Phase of development:	Not applicable – Observational [Patient Registry]
Sponsor:	AstraZeneca

ID: NCT02777658

2. 관련 연구 소개

2

Real world molecular testing, treatment patterns and clinical outcomes in patients with EGFR mutation-positive locally advanced or advanced NSCLC

Trial duration: May 2016 ~ May 2020

Investigational site: 80 sites in **Germany**
Enrollment period: 36 months
# of subjects: 159 participants (152 in primary cohort + 7 in secondary cohort)

Objectives

Primary : Molecular testing and treatment patterns in patients with **locally advanced** or **metastatic EGFR-positive NSCLC** who had **progressed on or after TKI** treatment **(Primary cohort)** Or in patients with **de-novo EGFR T790M mutation-positive locally advanced or metastatic NSCLC (secondary cohort).**

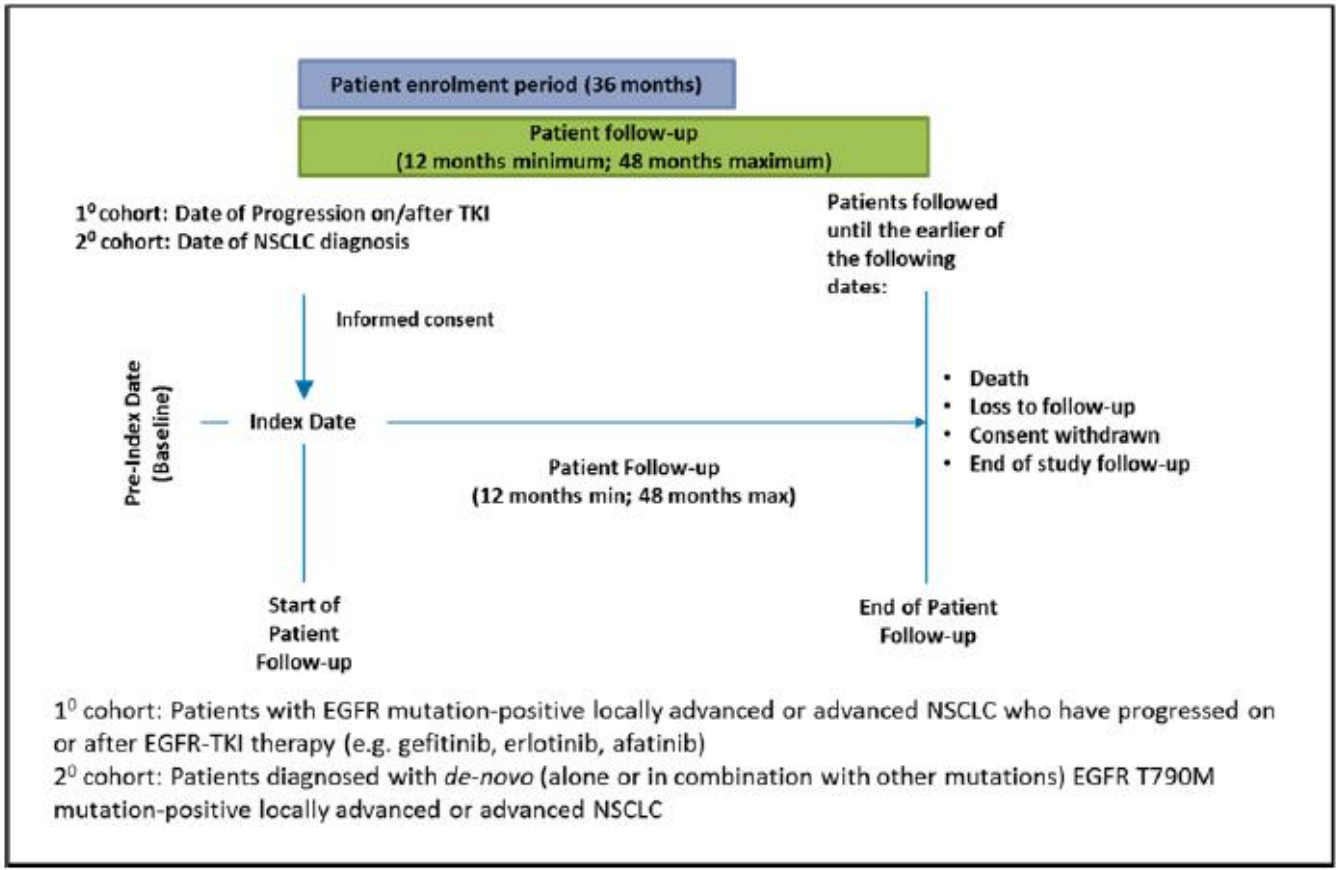
Secondary:

- **health care utilization patterns, treatment and biopsy related complications, rate of CNS metastases and associated treatments, and patient-reported health-related quality of life** (HRQoL)

2. 관련 연구 소개

2

Study design



1⁰ cohort: Patients with EGFR mutation-positive locally advanced or advanced NSCLC who have progressed on or after EGFR-TKI therapy (e.g. gefitinib, erlotinib, afatinib)

2⁰ cohort: Patients diagnosed with *de-novo* (alone or in combination with other mutations) EGFR T790M mutation-positive locally advanced or advanced NSCLC

2. 관련 연구 소개

2

Inclusion Criteria

1. Primary Study Cohort

- Provision of written informed consent (patient consent should* be within 6 weeks of disease progression, defined as Index Date) (*not mandatory)
- Adult male or female subjects
- Patients with prior confirmed EGFR mutation-positive (all mutations) locally advanced or metastatic NSCLC (Patients who developed resistance to a TKI due to any other phenotypic/histologic transformations or other mutations at the index-date will be eligible for participation in this study as long as they have prior confirmed diagnosis of EGFR mutation-positive locally advanced or metastatic NSCLC)
- Patients who have progressed on/after TKI therapy (e.g., gefitinib, erlotinib or afatinib) within the patient selection period

2. Secondary Study Cohort

- Provision of written informed consent (patient consent should* be within 6 weeks of NSCLC diagnosis, defined as Index Date)
- Adult male or female subjects
- Patients diagnosed with de-novo EGFR T790M mutation-positive locally advanced or metastatic NSCLC during the patient selection period. The de-novo T790M mutation can be alone or in combination with other mutations (e.g., L858R and T790M).

2. 관련 연구 소개

2

Statistical methods:

- All variables were analyzed in a descriptive manner. For continuous variables, the following descriptive statistics were computed: number of observations, mean, standard deviation, median, 25% and 75% quartile, minimum and maximum.
- Categorical variables were presented with absolute and relative frequencies within the single categories. If there were any missing data for categorical variables these were not excluded from analysis but displayed as a separate category with absolute and relative frequencies, too.
- Time to event analyses including overall survival (OS) were estimated using the Kaplan-Meier method to present 25th, 50th (median), and 75th percentiles of the time-to-event data together with the corresponding 95% confidence interval (CI), as well as the number and percentage of events and censored observations.
- Statistical analysis of final study results was performed using SAS™ Version 9.4. of the SAS System for Windows.

2. 관련 연구 소개

2

Results

Patient characteristics:
The full analysis set of the *primary study cohort* comprised 152 patients, 102 (67.1%) women and 50 (32.9%) men aged between 42 and 88 years at date of progression on/after TKI therapy.

Disease specification:
95.4% adenocarcinoma

Smoking status:
48.0% (n=73) non-smoker,
39.5% (n=60) previous smokers
2.6% (n=4) current smokers
15% unknown smoking status

ECOG PS:
96 patients (63.2% of patients) with ECOG 0-1
19 patients (12.5%) with ECOG 2-3
37 patients (24.3%) ECOG performance status was not evaluated.

Treatment details:

First line of treatment:
Osimertinib (71 patients, 46.7%)
Afatinib 16 (10.5%)
Gefitinib 8 (5.3%)

Second line of treatment:
88 patients (57.9%) in which osimertinib was the commonly used drug (18 patients, 11.8%).

Overall Osimertinib treated patients: 106 (69.7%). 88 (57.9%) of these patients had T790M.
7 (4.6%) with T790M but were not treated with Osimertinib.

2. 관련 연구 소개

2

Results

Time to initiation of new therapy:

7.9 months in 1st subsequent treatment, **4.8 months in 2nd subsequent treatment**, **4.7 months in 3rd subsequent treatment** and **7.0 months in 4th subsequent treatment** after progression on/after TKI therapy, respectively, independently of used drug.

CNS metastases at diagnosis und at date of progression on/after TKI therapy:
At initial diagnosis of NSCLC,
CNS metastases: 33 patients (overall CNS metastases rate: 21.7%).
No CNS metastases: 113 patients (74.3%).
Unknown CNS metastases : 6 patients (3.9%)
Rate of brain metastases was 17.8% (n=27).
Leptomeningeal metastases were found in 1 patient (0.7%),
5 patients (3.3%) the location of CNS metastasis was unknown.

At date of progression on/after TKI therapy, **overall CNS metastases was 23.0% (35 patients)**, the rate of brain metastases was 20.4% (31 patients). Existence of CNS metastases was unknown in 4 patients.

Health related quality of life (EORTC QLQ-C30 and LC13): meaningful data couldn't be found due to lack of follow up.

2. 관련 연구 소개

2

Conclusion

Most of patients with EGFR-mutation were female, non-smokers and had adenocarcinoma. Next generation sequencing (NGS) was used more often than Sanger sequencing or other platforms, and while the majority of tests was performed on formalin-fixed paraffin-embedded tissue, about a third of the patients had tests based on blood samples.

As expected, EGFR mutation status most often showed deletions in **exon 19 and L858R mutation on exon 21**. T790M mutations were detected at rather unexpectedly high frequencies (58.6% of all patients tested for T790M at/after progression). **Osimertinib was the substance most frequently administered in the first line of treatment after progression on/after TKI therapy.**

2. 관련 연구 소개

3

Article

Real-World Pattern of Treatment and Clinical Outcomes of EGFR-Mutant Non-Small Cell Lung Cancer in a Single Academic Centre in Quebec

Jason S. Agulnik [1], Goulnar Kasymjanova [1,*], Carmela Pepe [1], Manjusha Hurry [2], Ryan N. Walton [2], Lama Sakr [1], Victor Cohen [1] and David Small [1]

[1] Peter Brojde Lung Cancer Centre, Jewish General Hospital, McGill University, Montreal, QC H3T 1E2, Canada; jagulnik@jgh.mcgill.ca (J.S.A.); cpepe@jgh.mcgill.ca (C.P.); lsakr@jgh.mcgill.ca (L.S.); vcohen@jgh.mcgill.ca (V.C.); dsmall@jgh.mcgill.ca (D.S.)
[2] AstraZeneca Canada, Mississauga, ON L4Y 1M4, Canada; manjusha.hurry@astrazeneca.com (M.H.); ryan.walton@astrazeneca.com (R.N.W.)
* Correspondence: gkasymja@jgh.mcgill.ca

Abstract: The discovery of EGFR tyrosine kinase inhibitors (TKI) for the treatment of EGFR mutant (EGFRm) metastatic NSCLC is regarded as a landmark in lung cancer. EGFR-TKIs have now become a standard first-line treatment for EGFRm NSCLC. The aim of this retrospective cohort study is to describe real-world patterns of treatment and treatment outcomes in patients with EGFRm metastatic NSCLC who received EGFR-TKI therapy outside of clinical trials. One hundred and seventy EGFRm metastatic NSCLC patients were diagnosed and initiated on first-line TKI therapy between 2004 and 2018 at the Peter Brojde Lung Cancer Centre in Montreal. Following progression of the disease, 137 (80%) patients discontinued first-line treatment. Moreover, 80/137 (58%) patients received second-line treatment, which included: EGFR-TKIs, platinum-based, or single-agent chemotherapy. At the time of progression on first-line treatment, 73 patients were tested for the T790M mutation. Moreover, 30/73 (41%) patients were found to be positive for the T790M mutation; 62/80 patients progressed to second-line treatment and 20/62 were started on third-line treatment. The median duration of treatment was 11.5 (95% CI; 9.62–13.44) months for first-line treatment, and 4.4 (95% CI: 1.47–7.39) months for second-line treatment. Median OS from the time of diagnosis of metastatic disease was 23.5 months (95% CI: 16.9–30.1) and median OS from the initiation of EGFR-TKI was 20.6 months (95% CI: 13.5–27.6). We identified that ECOG PS $\leq$ 2, presence of exon 19 deletion mutation, and absence of brain metastases were associated with better OS. A significant OS benefit was observed in patients treated with osimertinib in second-line treatment compared to those who

check for updates

Citation: Agulnik, J.S.; Kasymjanova, G.; Pepe, C.; Hurry, M.; Walton, R.N.; Sakr, L.; Cohen, V.; Small, D. Real-World Pattern of Treatment and Clinical Outcomes of EGFR-Mutant Non-Small Cell Lung Cancer in a Single Academic Centre in Quebec. *Curr. Oncol.* **2021**, *28*, 5179–5191. https://doi.org/10.3390/curroncol28060434

2. 관련 연구 소개

3

Objectives:

Primary:

To describe the **treatment patterns and outcomes including real-world progression-free survival (rwPFS), response rate (RR) and overall survival (OS)** for EGFRm NSCLC patients treated at an academic centre in Montreal, **Canada**

Secondary:

To describe demographic and clinical characteristics at diagnosis of EGFRm NSCLC patients and their prognostic value

Outcome measures:

a. Patient characteristics including date of metastatic NSCLC diagnosis, stage at the time of initial diagnosis, sex, age at the time of diagnosis, ethnicity, Eastern Cooperative Oncology Group performance status (ECOG PS), smoking history.
b. Tumor characteristics include the stage of the disease, presence or absence of brain metastases, and type of EGFR mutations.
c. Type of molecular tests: the evolution of the EGFR test for our center is recorded as: Denaturing high-pressure liquid chromatography (DHPLC) from 2004 to 2007; single gene sequencing from 2008 to 2010; real-time polymerase chain reaction (PCR) from 2011 to 2014 and next-generation sequencing (NGS) from 2014 to current.
d. Real-world treatment patterns identified in our clinical practice include comprehensive treatment history from diagnosis to current treatment, treatment duration, and modality sequencing (targeted therapy, chemotherapy, radiotherapy, and best supportive care).

3

Statistical Analysis

Demographics, clinical characteristics, and treatment patterns are described using frequencies and proportions for categorical data and using means with standard deviation or medians with the associated 95% confidence interval (CI) for numeric data. Time variables (OS, rwPFS) are reported as medians with 95% CI using Kaplan–Meier statistics.

To avoid immortal time bias, the landmark survival method was used for Osimertinib survival analysis.
Landmark time was set as a start date of second-line therapy. Only events that occurred during that period were counted for this analysis.

Cox regression analysis was performed to identify prognostic factors for survival. The following factors were included in the model: sex, race, smoking, ECOG PS, type of EGFR mutation, type of EGFR-TKI testing. Statistical analyses were conducted using IBM SPSS statistics 20 software for Windows.

2. 관련 연구 소개 **Baseline demographic and clinical characteristics of patients.**

3

Characteristics N	N = 170 N (%)
Age at diagnosis (y), interquartile range (IQR)	65 (IQR: 18.25)
Sex	
Female	121 (71)
Male	49 (29)
Race	
Caucasian	117 (69)
Asian	45 (27)
Black	8 (4)
Smoking	
Never-smoker	106 (62)
Ever-smoker	64 (38)
ECOG PS	
0–1	151 (89)
2	19 (11)
>2	0
Stage at Diagnosis	
Early stage	23 (14)
Locally advanced	19 (11)
Metastatic	128 (75)
EGFR mutation	
Exon 19 (E19 del)	98 (58)
Exon 21 (L858R)	64 (37)
Exon 18 (E181)	7 (4)
Exon 20 insertion (E20)	1 (1)
Type of molecular test:	
DhPLC (2004–2007)	32 (19)
Single gene sequencing (2008–2010)	17 (10)
Real-time PCR (2011–2014)	48 (28)
NGS (2015-current)	73 (43)
Brain metastases at diagnosis	
Present	51 (30)
Not present	119 (70)
Prior therapies for advanced/metastatic NSCLC before TKI	
Yes	26 (15)
No	144 (85)

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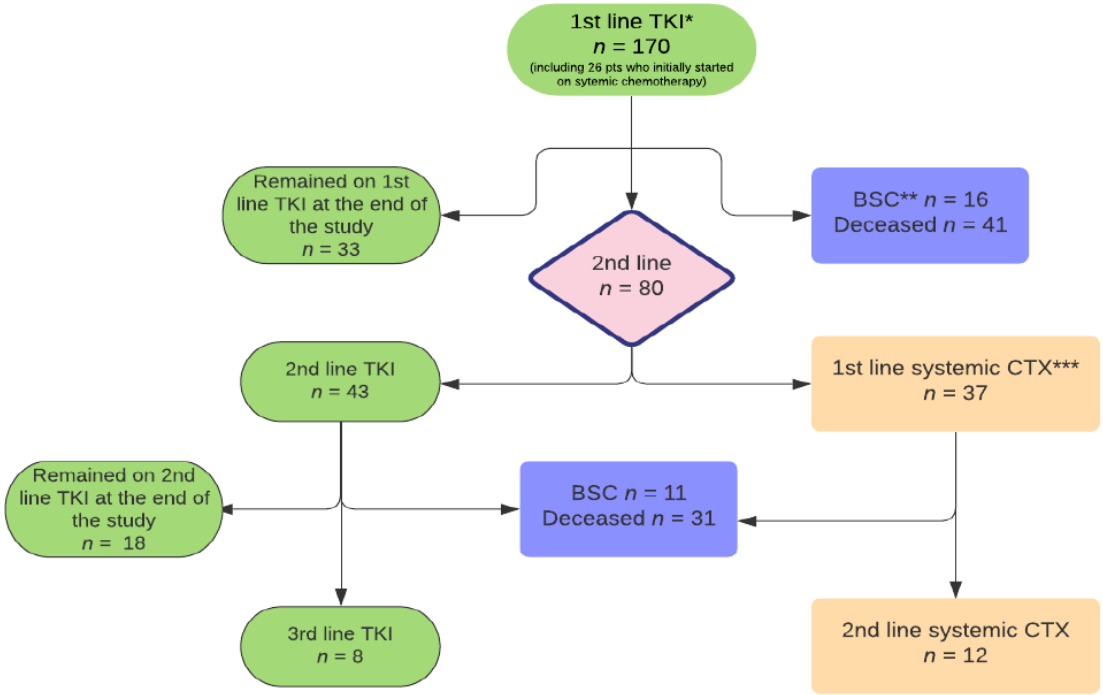
Figure 1. Flow chart of treatment



*** TKI—tyrosine kinase inhibitors; ** BSC—best supportive care; best supportive care;*** CTX—chemotherapy.**

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Table 2. Lines EGFR-TKI treatment.

EGFR-TKI	Frequency N (%)	Duration of Treatment Median (95% CI) in Mo	*p*-Value
First Line			
Gefitinib	110 (64.7)	11.7 (8.03–15.36)	0.535
Erlotinib	56 (32.9)	11.4 (7.4–15.29)	
Afatinib	4 (2.4)	not reached	
Total	170 (100)	11.5 (9.62–13.44)	
Second Line			
Osimertinib	30 (37.5)	14.8 (2.05–27.47)	0.001
Erlotinib/Gefitinib	5(6.3)	2.1 (0.45–3.89)	
Afatinib	8 (10.0)	1.9 (036–3.64	
Systemic chemo	37 (46.2)	2.5 (1.83–3.24)	
Total	80 (100)	4.4 (1.47–7.39)	
Third Line			
Osimertinib	2 (10.0)	All censored	n/a
Gefitinib/Erlotinib	4 (20.0)	All censored	
Afatinib	2 (10.0)	All censored	
Systemic chemo	12 (60.0)	2.8 (1.29–5.91)	
Total	20 (100)	3.9 (0.74–6.46)	

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Table 3. Outcomes of first-line treatment.

First-Line Outcomes	*n* (%)	Reason for Discontinuation *n* (%)	
Continued on First line	33 (19)		
Discontinued	137 (81)	Started second line	80 (58)
		BSC *	16 (12)
		Died	41 (30)
Total *n* (%)	170 (100)		137 (100)

* BSC—best supportive care.

Table 4. Response rate to first-line EGFR-TKI.

Response Rate (RR)	Afatinib	Gefitinib	Erlotinib	Total
CR +PR *n* (%)	4 (100%)	61 (55.4%)	18 (32.1%)	83 (48.8%)
SD *n* (%)	0	28 (25.4%)	16 (28.6%)	44 (25.8%)
PD *n* (%)	0	21 (19.0%)	22 (39.3%)	43 (25.4%)
Total *n* (%)	4 (100%)	110 (100%)	56 (100%)	170 (100%)

CR—complete response; PR—partial response; SD—stable disease; PD—progressive disease. $p = 0.005$.

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Table 5. Cox regression analysis for OS from the time of initiation of EGFR-TKI.

Variable	Comparator	Cox Regression Analysis					
		Univariate Analysis		*p*-Value	Multivariate Analysis		*p*-Value
		HR	95%CI		HR	95% CI	
Female	Male	0.91	0.62–1.3	0.65	0.91	0.6–1.4	0.66
Never-smoker	Ever-smoker	0.83	0.58–1.2	0.33	1.29	0.8–1.9	0.21
ECOG PS > 2	≤2	0.44	0.3–0.8	0.005	0.45	0.3–0.8	0.004
Exon 21/20/18	Exon 19 *	1.39	1.0–1.9	0.03	1.27	1.1–2.4	0.05
Gefitinib **	Erlotinib	0.83	0.5–1.2	0.31	1.10	0.7–1.7	0.67
Brain metastasis present	Absent	1.50	1.0–2.2	0.05	1.50	1.1–2.3	0.04
Non-Asian	Asian	1.26	0.8–1.9	0.28	1.21	0.8–1.9	0.43
NGS	Alternate test type ***	2.07	1.4–3.0	<0.001	2.25	1.4–3.5	<0.001

* For the purpose of this analysis, Exon 19 mutation compared to all the other. ** Four patients treated with Afatinib excluded from these analyses. *** NGS compared to combined previous testing technic.

Conclusion:

ECOG PS >2, presence of Exon 19 deletion mutation, and absence of brain metastases were associated with better OS.

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Outcomes of Patients with *EGFR*-Mutant Advanced NSCLC in a Developing Country in Southeast Asia

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Background: Although first- and second-generation EGFR TKIs are considered first-line treatment in EGFRm+ NSCLC, most patients develop resistance and progress, commonly, EGFR *T790M* mutation. The third-generation EGFR-TKI has demonstrated efficacy in patients with progressive disease harboring the *T790M* mutation and in the first-line setting, bypassing this mode of resistance. The primary objectives of this study are to describe the proportion of *EGFR*m+ NSCLC patients treated with first-, second- and third-generation EGFR TKIs, and cytotoxic chemotherapy in the first-line setting, and the time on treatment for each category. Secondary objectives are to determine the dropout rate, the rates for *T790M* mutation testing at disease progression and the type of subsequent treatment.

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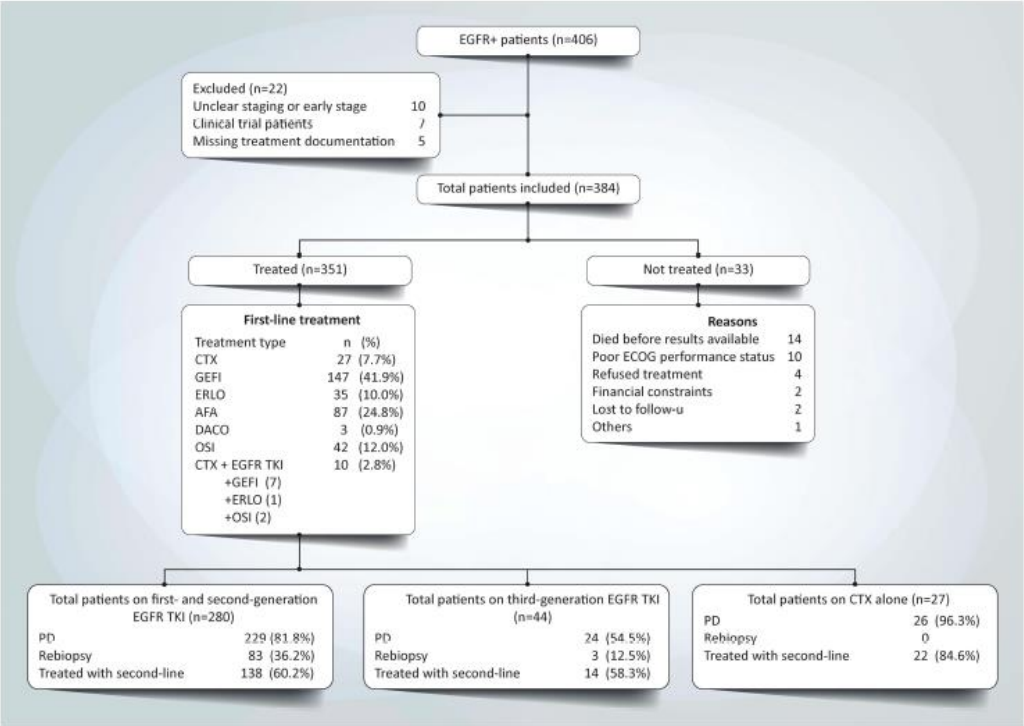

Patient flow.

Abbreviations: AFA, afatinib; CTX, chemotherapy; DACO, dacomitinib; ECOG, Eastern Cooperative Oncology Group; *EGFR+*, epidermal growth factor receptor positive;
EGFR TKI, epidermal growth factor receptor tyrosine kinase inhibitor; ERLO, erlotinib; GEFI, gefitinib; OSI, osimertinib; PD, disease progression

Table 1 Baseline Characteristics of Patients in the Analysis Set (N = 351)

Characteristic	n (%)
Age (Mean, SD)	63.2 (11.0)
Gender	
Male	135 (38.5)
Female	216 (61.5)
Ethnicity	
Malay	137 (39.0)
Chinese	180 (51.3)
India	12 (3.4)
Non-Malaysian	22 (6.3)
Smoking status	
Never smoker	283 (80.6)
Ex-smoker	59 (16.8)
Current smoker	7 (2.0)
ECOG performance status	
0	70 (19.9)
1	173 (49.3)
2	51 (14.5)
3	33 (9.4)
4	22 (6.3)
TNM stage	
IIIB and C	12 (3.4)
IVA	208 (59.3)
IVB	131 (37.3)
Histological subtype of NSCLC	
Adenocarcinoma	340 (96.9)
Non-adenocarcinoma	11 (3.1)
EGFR mutation	
Ex19Del	195 (55.6)
Ex21 L858R	113 (32.2)
Others	43 (12.3)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; TNM, tumour nodes and metastasis.

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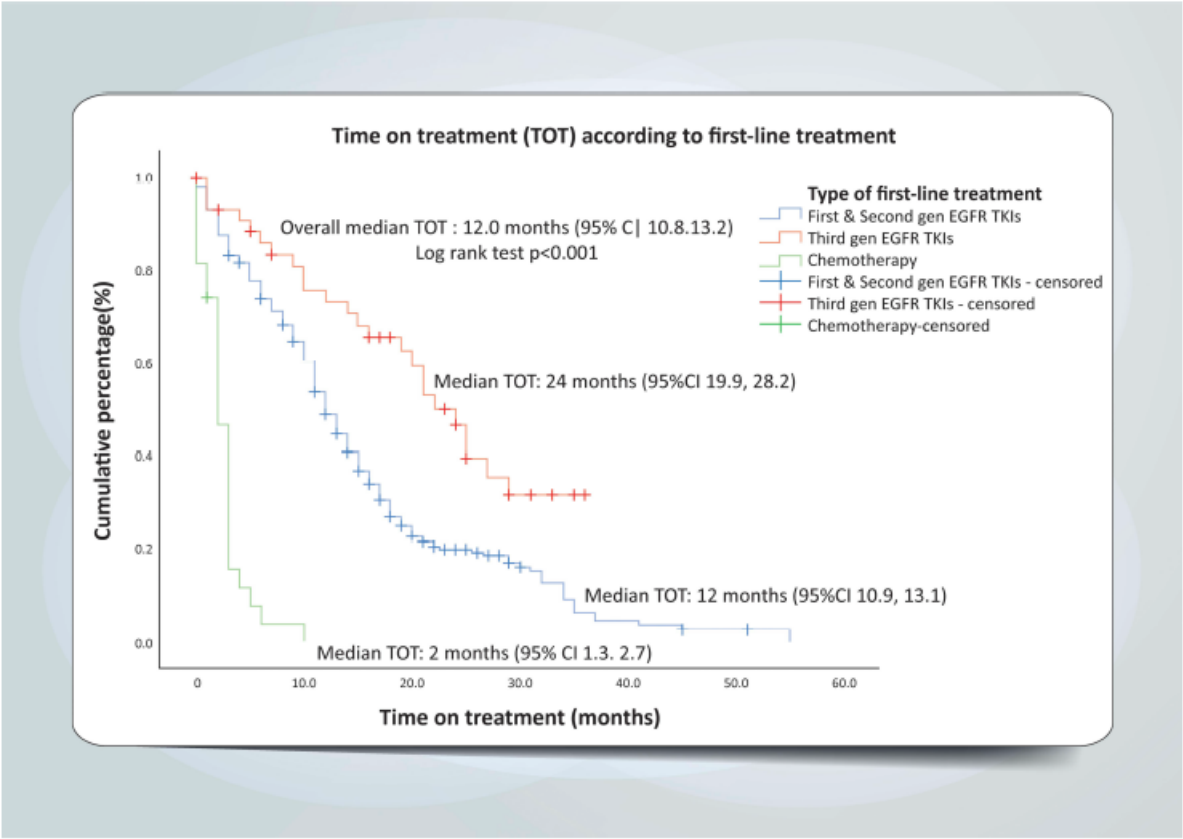

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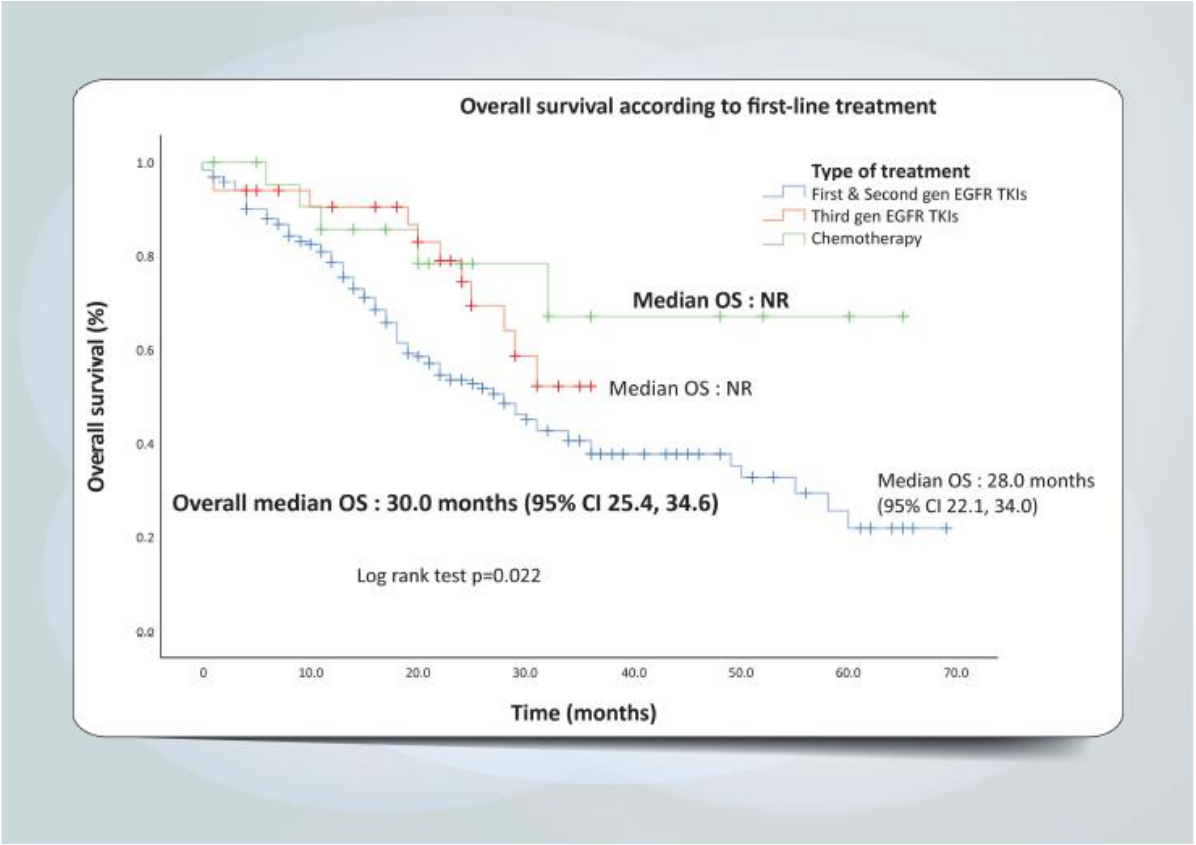

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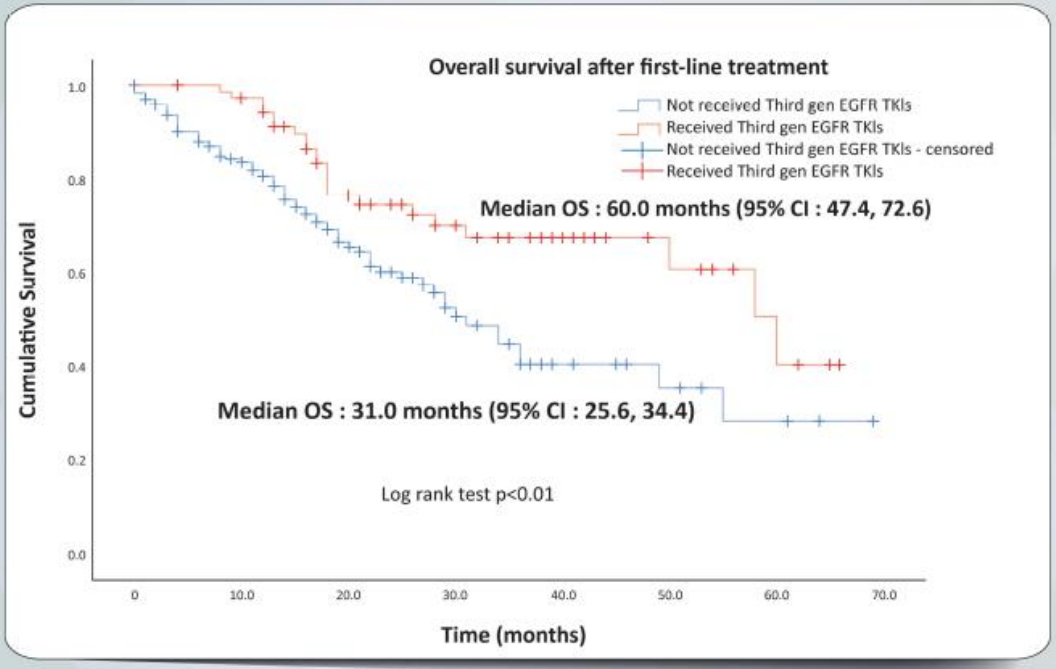

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Table 2 Second-Line Treatment in Patients Who Progressed After First-Line Treatment

First-Line Treatment	N	PD	Genetic Testing**	Second-Line Treatment				
				Yes	CTX	EGFR TKI		Others
						1st or 2nd Generation ±CTX	3rd Generation ±CTX	
CTX*	27	26	0	22	2	19	1	0
1st or 2nd generation EGFR TKI ±CTX	280	229	83	138	45	34	57	2
3rd generation EGFR TKI±CTX	44	24	3	14	6	4	1	3
Total	351	279	86	174	53	57	59	5

Note: *CTX alone; **Number of patients with no genetic testing in each category of first-line treatment regime= number of patients with PD minus number of patients with genetic testing.

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Conclusion

- Overall accessibility to first-line EGFR TKI is high but limited to first- or second-generation TKI.
- Patients who received chemotherapy as first-line therapy may have a good OS if they receive targeted therapy subsequently.
- The percentage of patients undergoing genetic testing following progression on first-line EGFR TKI remains modest.
- Liquid biopsy is a preferred option among treating physicians.
- The lack of accessibility to effective but costly newer treatments in the first- and second-line settings can adversely affect survival.
- Our study suggests that in the real-world, the management of *EGFR*m+ advanced NSCLC patients in an Asian cost restrictive setting can adversely affect the choice of first-line therapy, time on each line of treatment and subsequently overall survival of the patient.

감사합니다

Thank you

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