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VORONOI

2024.08

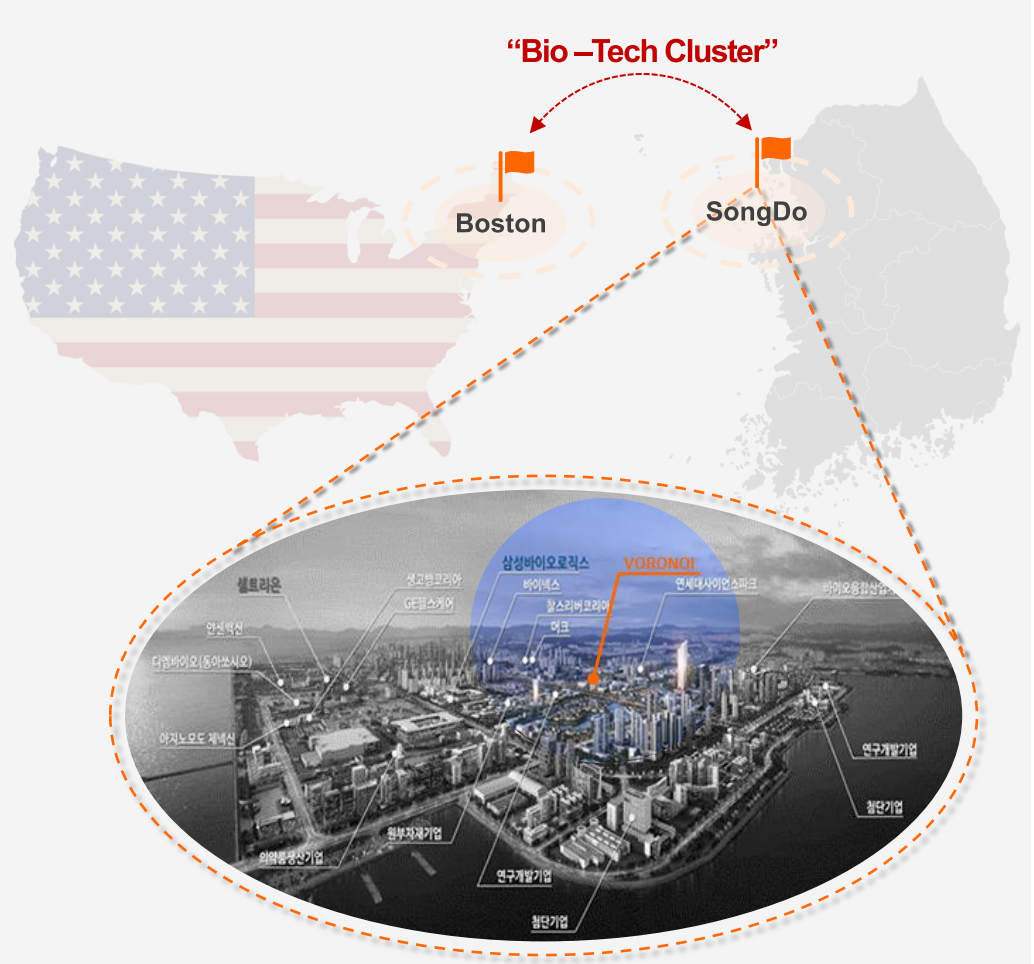
IR자료

VORONOI Overview

회사 요약

설립일	2015.02. (2022.06. KOSDAQ 상장)
대표자	김대권, 김현태
소재지	인천광역시 송도과학로 32
사업부문	신약개발
주요 연구분야	항암제 및 난치 질환 표적치료제
임직원 수 (2024.2Q)	130명
자본금 (2024.2Q)	89억원
자산 (2024.2Q)	850억원

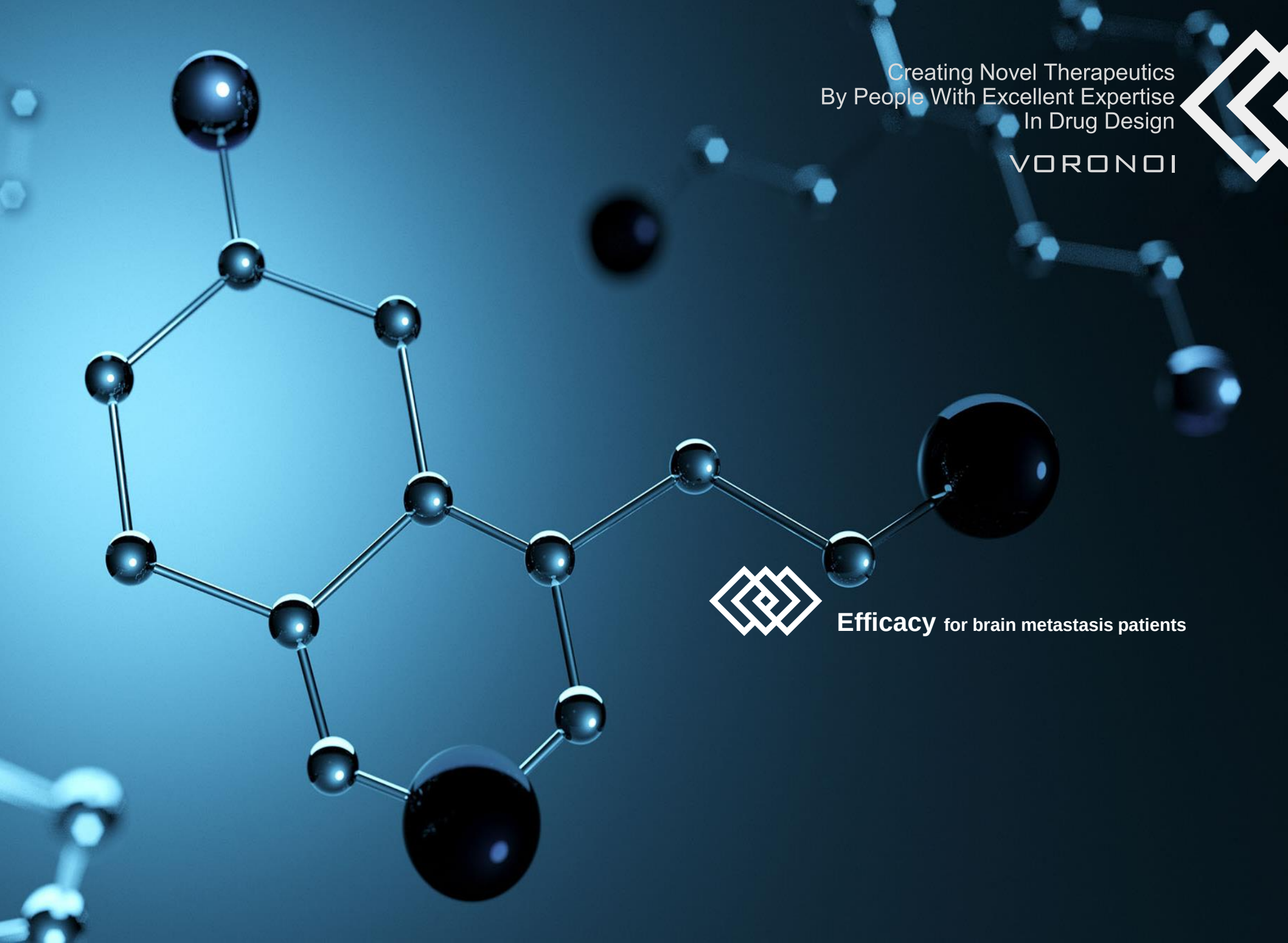
회사 구조



주요 파이프라인

NDA 신청/제출 일정(예상)

회사명	적응증	타겟	임상단계
			전임상 / 1상 / 2상 / 3상
ORIC	비소세포폐암	EGFR exon20 ins (treatment-naïve)	1상
		EGFR exon20 ins (post-amivantamab)	1상
		EGFR atypical	1상
		HER2 exon20 ins	1상
VORONOI	비소세포폐암	EGFR del19/C797S, EGFR L858R/C797S	1상
		EGFR del19, EGFR L858R (뇌 전이)	1상
		EGFR uncommon(2차)	1상
		EGFR del19, L858R, uncommon	1상
VORONOI	유방암	HER2+ positive	1상
inno.N	비소세포폐암	RET fusion	1상
VORONOI	자가면역질환	RIPK1	1상
VORONOI	폐동맥고혈압	PDGFR	1상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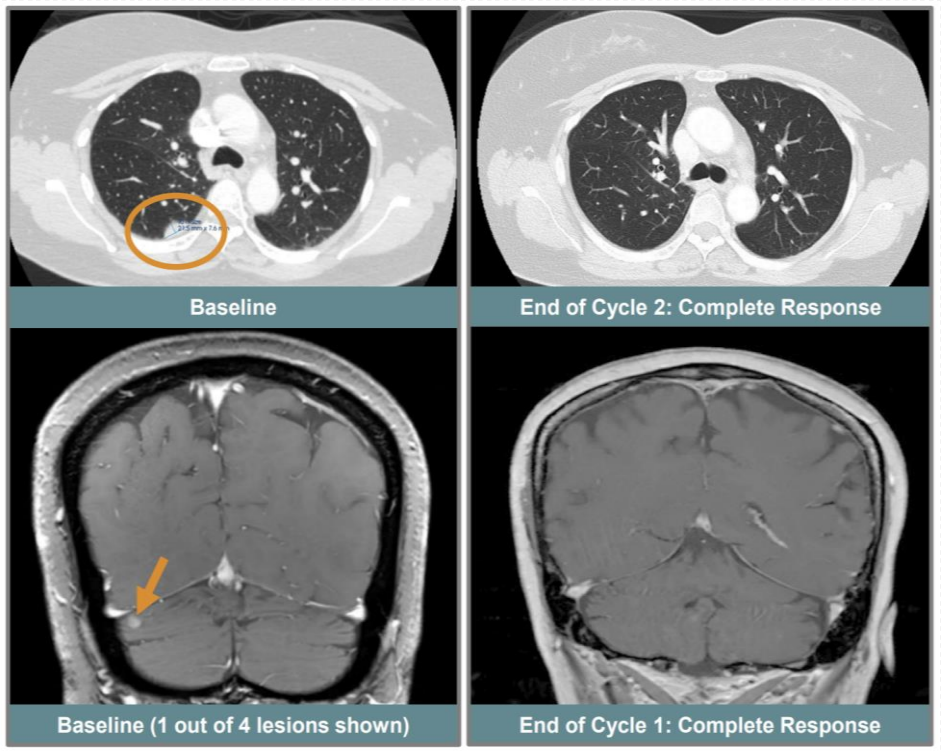
Efficacy for brain metastasis patients

VRN07. Heavily treated 환자 대상 유일한 완전 관해(CR) 임상 데이터

VRN07(ORIC-114). ESMO 2023

✓ **EGFR Exon20**



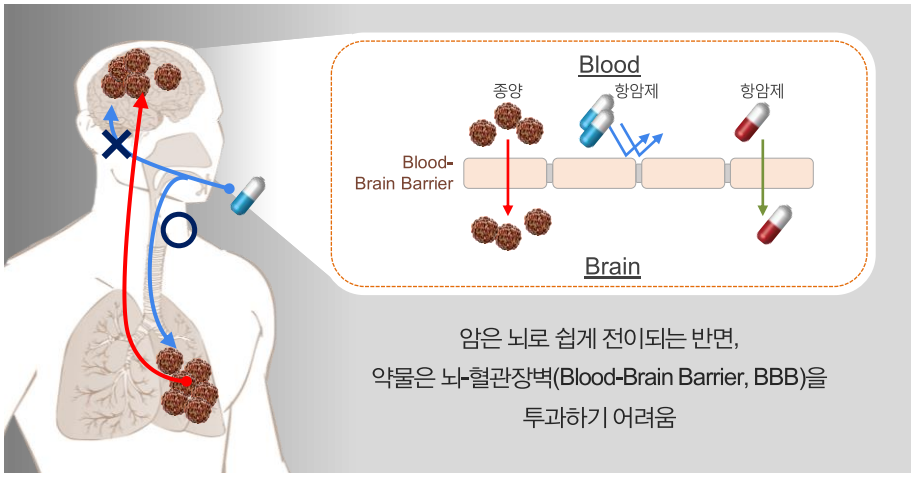
- **Patient: 55F with EGFR exon 20 mutated NSCLC**
- **Prior therapy:** Pemetrexed/cisplatin and amivantamab
- **CNS metastases at baseline:** Four active CNS non-target lesions
  - Previously untreated
  - No prior surgery
  - No prior radiation
- **ORIC-114 dose:** 75 mg QD
- **Systemic response:** Partial response after Cycle 1 (60% reduction of all target and non-target lesions) followed by complete response at the end of Cycle 2 (**100% reduction of all target and non-target lesions**), subsequently confirmed
- **CNS response:** Complete response after Cycle 1 (**100% reduction of all 4 CNS lesions**), confirmed after Cycle 2
- **Grade ≥2 treatment-related AEs:** Grade 2 mucositis and paronychia
- **Duration of treatment:** Cycle 9 (ongoing)

✓ **Chemotherapy, Amivantamab 치료 이후의 환자**
✓ **Cycle 1, CNS 완전 관해**
✓ **Cycle 2, 전신 완전 관해**

출처: ESMO2023

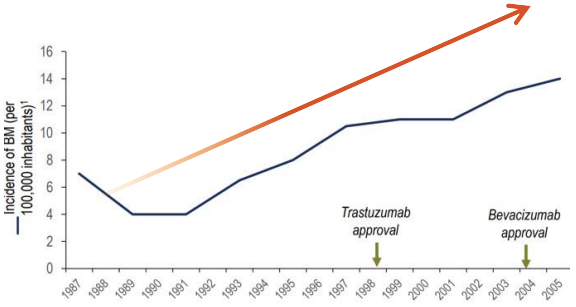
뇌전이 환자에 대한 미충족 의료 수요

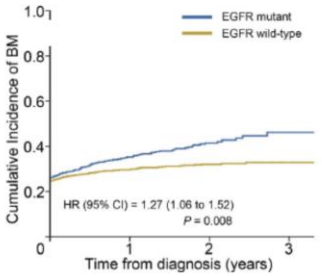
약물의 뇌혈관장벽 투과율 낮은 이유



암은 뇌로 쉽게 전이되는 반면,
약물은 뇌-혈관장벽(Blood-Brain Barrier, BBB)을
투과하기 어려움

암의 뇌전이 발생률





NSCLC 뇌전이 발생률

Indian Journal of CANCER

Management of CNS metastases in patients with EGFR mutation-positive NSCLC

Shetty, Vijith; Babu, Suresh[1]

Central nervous system (CNS) metastases are a major complication associated with non-small cell lung cancer (NSCLC) and are seen in >30% of patients.[1,2] About 25% of patients with NSCLC have CNS metastases at initial presentation, whereas 80% of patients develop it within 2 years of NSCLC diagnosis.[3] The rising incidence of CNS metastases in NSCLC is probably due to better control of extracranial disease and increase in detection rates of asymptomatic CNS metastases with improved magnetic resonance imaging techniques.[4] This review compares the efficacy and safety of various available options in the management of NSCLC with CNS metastases.

➔40% 이상의 뇌전이 환자 중 처음 진단 받으면서 이미 뇌전이있는 환자 25% 이상, 진단 2년 이내에 80% 환자 뇌전이 발생

출처: FDA website, Globaldata, Neuro-Oncology, Brain metastasis ESMO 2019
Shetty, Vijith; Babu, Suresh1. Indian Journal of Cancer 56(Suppl 1):p S31-S37, November 2019. | DOI: 10.4103/ijc.IJC_455_19

EGFR 표적치료제 뇌혈관장벽 투과율

승인된 치료제 대비 높은 뇌혈관장벽 투과율을 가진 VRN07(ORIC-114) 및 VRN11

기존 EGFR TKIs의 뇌혈관장벽 투과율

Preclinical Comparison of the Blood–brain barrier Permeability of Osimertinib with Other EGFR TKIs

Nicola Colclough, Kan Chen, Peter Johnström, Nicole Strittmatter, Yumei Yan, Gail L. Wrigley, Magnus Schou, Richard Goodwin, Katarina Varnäs, Sally J. Adua, Minghui Zhao, Don X. Nguyen, Gareth Maglennon, Peter Barton, James Atkinson, Lin Zhang, Annika Janefeldt, Joanne Wilson, Aaron Smith, Akihiro Takano, Ryosuke Arakawa, Mikhail Kondrashov, Jonas Malmquist, Evgeny Revunov, Ana Vazquez-Romero, Mohammad Mahdi Moein, Albert D. Windhorst, Natasha A. Karp, M. Raymond V. Finlay, Richard A. Ward, James W.T. Yates, Paul D. Smith, Lars Farde, Zack Cheng, and Darren A.E. Cross

DOI: 10.1158/1078-0432.CCR-19-1871 Published January 2021

Table 2.

Summary of healthy rat brain and CSF distribution constants, Kp and Kpuu, plus brain and plasma binding, fuplasma and fubrain, for 16 EGFR-TKIs.

Drug	Brain Kp	CSF Kp	fuplasma %	fubrain %	Brain Kpuu	CSF Kpuu	
Osimertinib	6.09	0.0047	1.66 (0.22)	0.057 (0.012)	21.0%	29.0%	Tagrisso
Icotinib	0.17	0.051	8.38 (0.15)	6.06 (0.77)	12.0%	61.0%	
Lazertinib	1.17	ND	1.70 (0.35)	0.126 (0.018)	8.7%	ND	Leclaza
Avitiniba	0.12	NV	0.87 (0.06)	0.623 (0.066)	8.6%	NV	
Erlotinib	0.14	0.034	8.77 (0.19)	5.18 (0.55)	8.4%	39.0%	Tarceva
Poziotinib	0.07	0.00068	1.10 (0.30)	0.912 (0.092)	6.0%	6.2%	
Naquotinib	0.24	0.014	6.98 (1.61)	0.974 (0.192)	3.4%	20.0%	
Dacomitinibb	0.76	0.0085	4.04 (0.27)	0.157 (0.023)	3.0%	21.0%	
Tesevatinib	0.99	0.0042	3.39 (0.50)	0.087 (0.008)	2.5%	12.0%	
AZ'5104	0.32	0.0056	5.64 (0.22)	0.335 (0.064)	1.9%	9.9%	
Olmutinib	0.12	NV	1.18 (0.59)	0.117 (0.016)	1.2%	NV	
Gefitinib	0.12	0.0074	4.38 (0.82)	0.341 (0.070)	0.9%	17.0%	Iressa
Rociletinib	0.008	NV	2.10 (0.61)	1.98 (0.07)	0.8%	NV	
Afatinib	0.2	0.024	9.48 (0.75)	0.297 (0.031)	0.6%	26.0%	Gilotrif
Nazartinibc	0.041	0.0071	8.94 (0.72)	1.00 (0.10)	0.5%	7.9%	

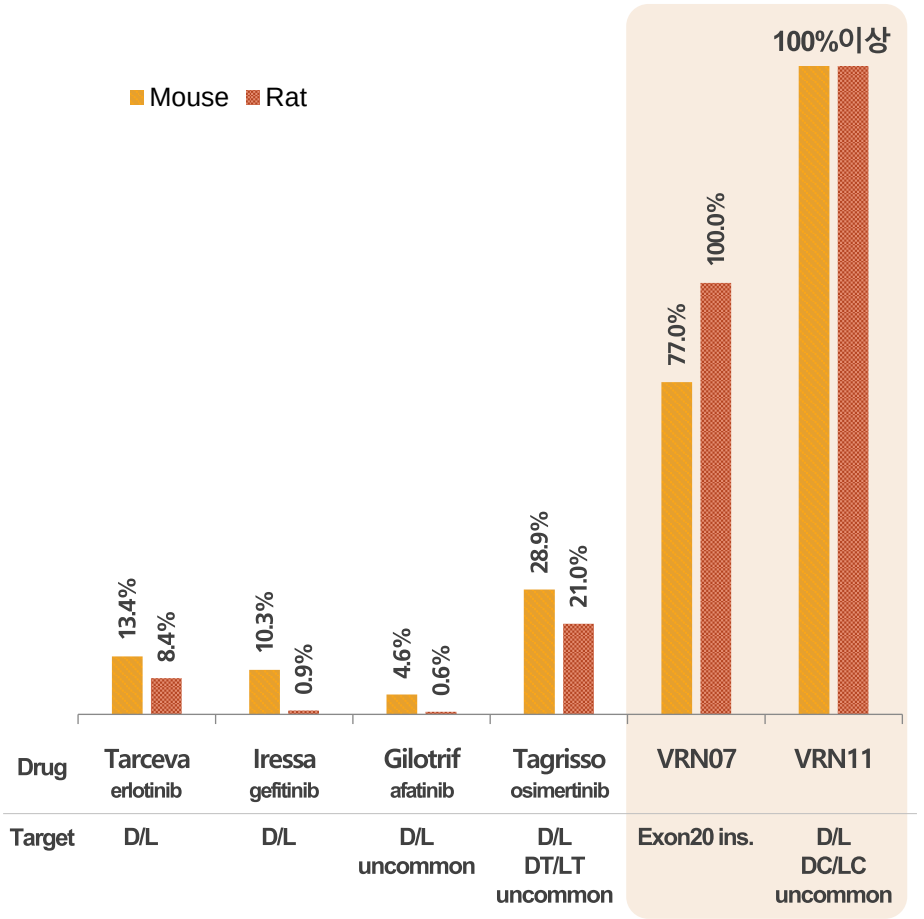
Note:

Kp determined from AUC brain/plasma and AUC CSF/plasma ratios using 6 rats per compound with one terminal sample per time point (Eq. 2) with Kpuu determined by factoring in tissue binding to Kp using Eqs. (3) and (4).

NV—no value determined—compound detected at only one or two time points.

Fraction unbound in plasma fuplasma and fraction unbound in brain fubrain average of n = 3; (SD)

EGFR 치료제의 뇌-혈관장벽 투과율 (Kp,uu, Brain/ Mouse, Rat)



출처: Nicola Colclough, et al. Clin Cancer Res 1 January 2021; 27 (1): 189–201.

VRN07. Active 뇌전이 환자에 대한 치료 효과를 확인한 최초 임상 데이터

EGFR 치료제 중 임상 최초 Active brain metastases CR 사례 확인

기존 EGFR 폐암 표적치료제 임상 한계

Patient Selection

Key inclusion criteria included presence on tissue biopsy of ≥1 of the two common *EGFR* mutations associated with TKI sensitivity (ex19del, L858R) and treatment-naïve for locally advanced or metastatic NSCLC. Key exclusion criteria included symptomatic and unstable brain metastases (patients with asymptomatic and stable brain metastases were eligible if radiation therapy or surgery was completed and no steroids were received for >2 weeks before random assignment).

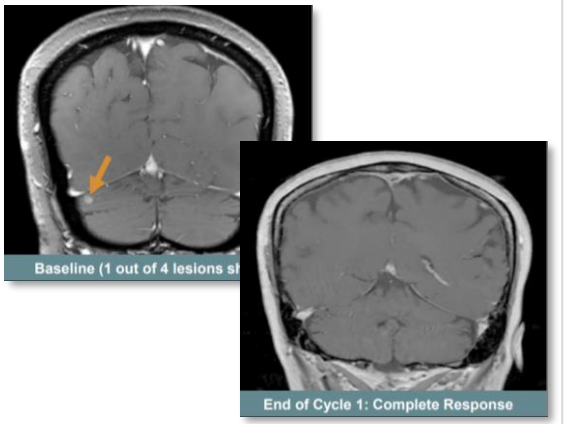
VRN07(ORIC-114), Patient Population

- Any advanced solid tumor with locally documented:
  - EGFR exon 20 insertion mutation
  - HER2 exon 20 insertion mutation
  - HER2 amplification or overexpression
  - Atypical EGFR mutation (NSCLC only)
- Prior chemotherapy
- All other prior therapies allowed, including prior exon 20 targeted therapies
- RECIST v1.1 measurable disease
- Patients with CNS metastases allowed, including asymptomatic untreated CNS metastases
- ECOG 0-1

→ **Active 뇌전이 환자 포함한 임상 환자 모집**

VRN07(ORIC-114), Active 뇌전이환자 완전관해 최초 사례

	뇌전이 환자 (%)
VRN07 ORIC-114	86 (active 포함)
Amivantamab	22
Mobocertinib	35
Furmonertinib	29
Sunvozertinib	32
BLU-451	58 (개발 중단)
Zipalertinib	38 (only stable)



- **CNS metastases at baseline:** Four active CNS non-target lesions
  - Previously untreated
  - No prior surgery
  - No prior radiation
- **CNS response:** Complete response after Cycle 1 (**100% reduction of all 4 CNS lesions**), confirmed after Cycle 2

뇌전이 환자 13명 중 총 8명 효능 확인

✓ **CR 1명**

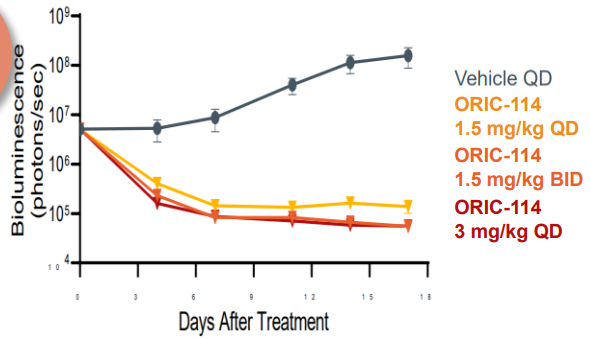
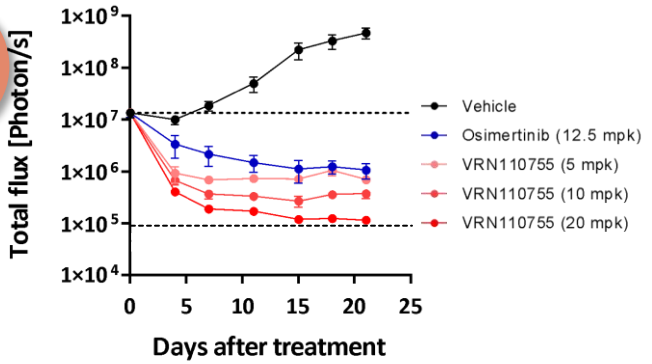
✓ **PR / SD 7명**

Active 뇌전이 환자에서 완전관해(CR) 사례 최초 확인

출처: DOI: 10.1200/JCO.23.00515 Journal of Clinical Oncology 41, no. 26 (September 10, 2023) 4208-4217, AACR2022, ESMO2023

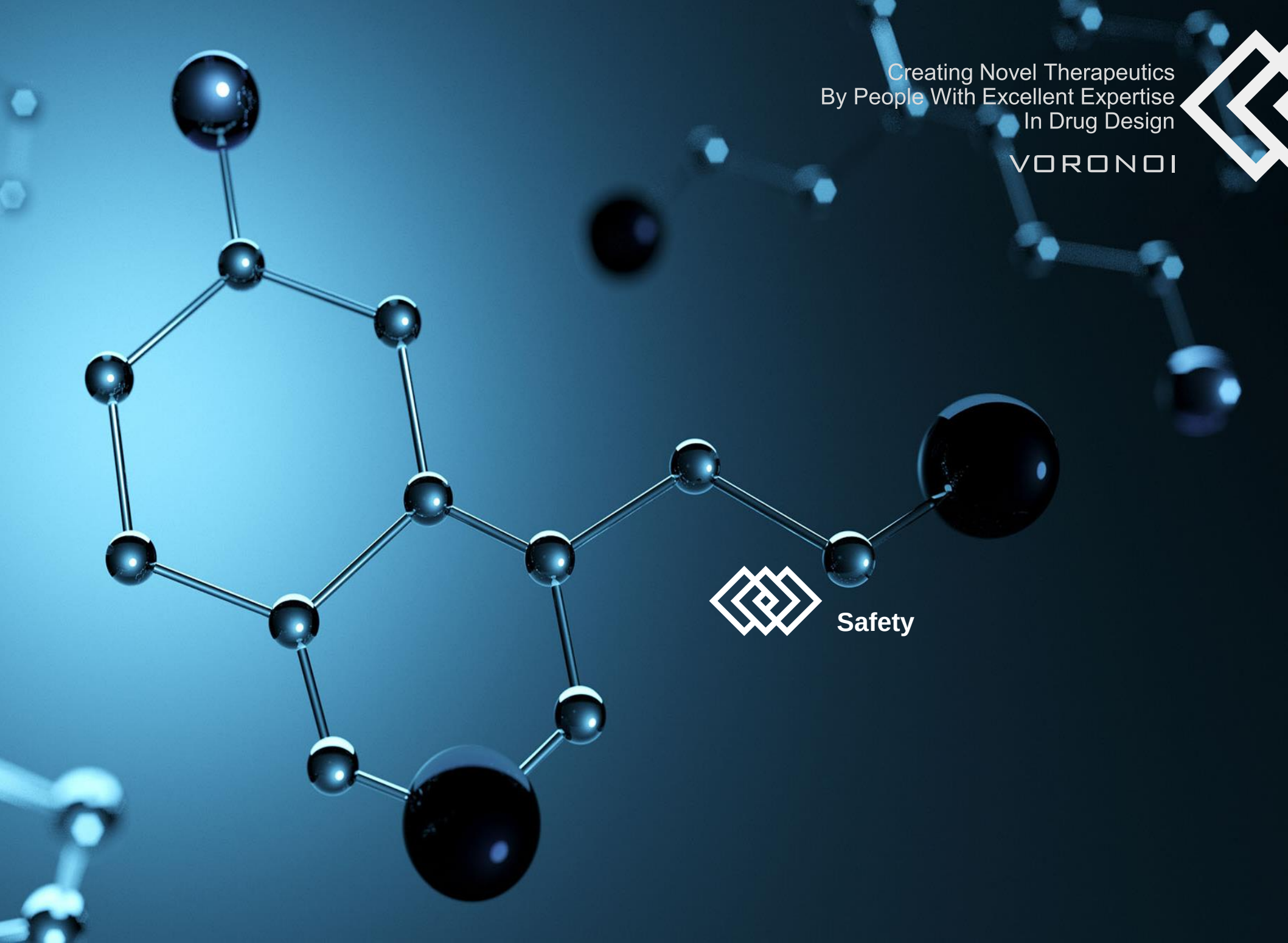
VRN07 & VRN11. Active CNS Metastases

VRN07을 통해 Active brain metastases 환자군에서의 효능 확인
VRN11에서의 치료 효과 기대

	VRN07(ORIC-114)	VRN11
In-vivo Data	77% 투과 	100% 투과 
타겟	EGFR Exon20 Ins.	EGFR del19, EGFR L858R EGFR del19/C797S, EGFR L858R/C797S EGFR uncommon mutation
BM Patients	Inclusion of patients with active brain metastases	**Include** **Brain metastasis(BM)** **and Leptomeningeal metastasis(LM) patients** - untreated and asymptomatic patients - treated and controlled* patients
Clinical trial Data	뇌전이 환자 n =13 CR 1 PR / SD 7	*2023년 10월 한국 임상 1상 IND 승인* *2024년 01월 대만 임상 1상 IND 승인*

*controlled : 뇌전이로 인한 증상을 steroid 10mg/daily로 조절 가능한 환자

출처: AACR2022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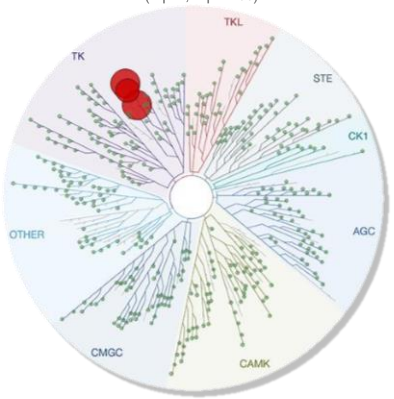
Safety

Selectivity

경쟁 약물 대비 선택성 압도적 우위, 이를 바탕으로 Off-target 부작용 없는 약물 기대

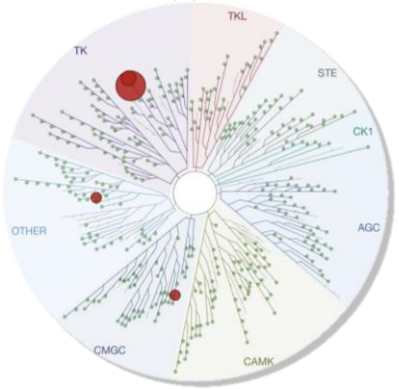
VRN07(ORIC-114)

(1 μM, top 10%)



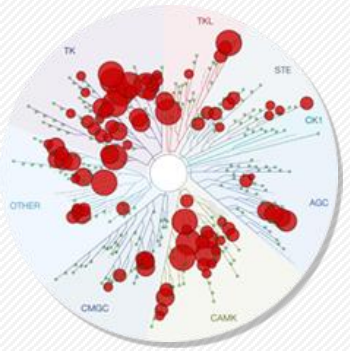
VRN11

S-core(10) = 0.01



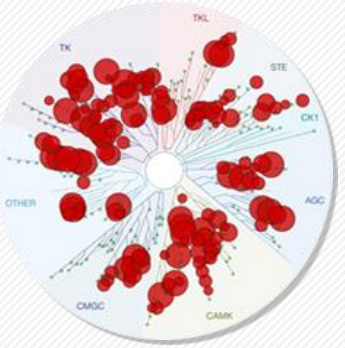
T사 B약물

S-core(10) 0.24



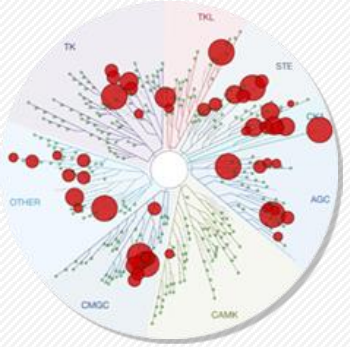
C사 T약물

S-core(10) 0.51



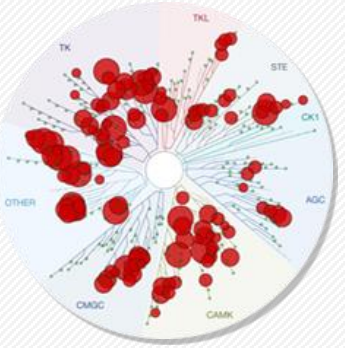
BI사 B약물

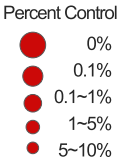
S-core(10) 0.13



B사 B약물

S-core(10) 0.32





- 빨간색 원은 Kinase 결합력을 나타냄

출처: Eurofins DiscoverX Kinomescan, 1 uM concentration

VRN07. Off-target 독성이 없는 최초의 임상 데이터

VRN07(ORIC-114). Off-target Toxicity

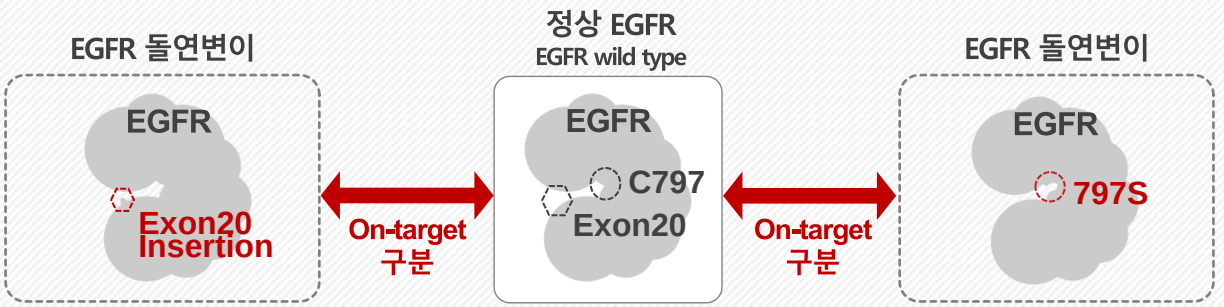
Clinical trial. Off-target Toxicity data[1,2,3,4,5,6]

약물명		Grade ≥3 부작용	
	N	Total	Off-target Toxicity
Amivantamab (Monotherapy)	114	35%	IRR 3%, decreased lymphocytes 8%, dyspnea 2%, Interstitial lung disease, ocular toxicity
Amivantamab + Chemotherapy	130	72%	IRR 5%, Neutropenia 45%, Thrombocytopenia 15%, Anemia 12%, Leukopenia 20%
Sunvozertinib	104	39%	Blood Creatine phosphokinase increased 17.3%, Lipase increased 1.9%, anemia 5.8%, Lipase increased 1.9%
Furmonertinib	28	29%	Anemia 4%, Electrocardiogram QT prolonged 7%, liver toxicity(ALT increased) 4%
Zipalertinib	73	53%	Anemia 9.6%, liver toxicity(AST increased) 4%
ORIC-114 (VRN07)	32	19%*	X

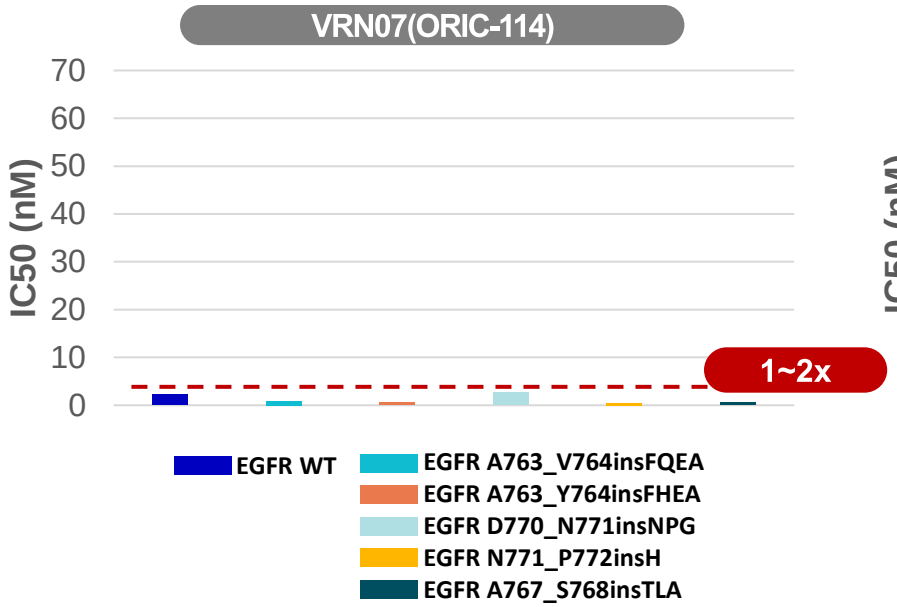
출처: [1]Keunchil Park et al., JCO 39, 3391-3402(2021), FDA RYBTRVANT Label [2]ESMO2023, [3]A. Passaro et al., Annals of Oncology, Volume 35, Issue 1,2024., [4]ASCO2023, [5]WCLC2023, [6]Zofia Piotrowska et al., JCO 41, 4218-4225(2023). *유효 용량 이상의 부작용 데이터

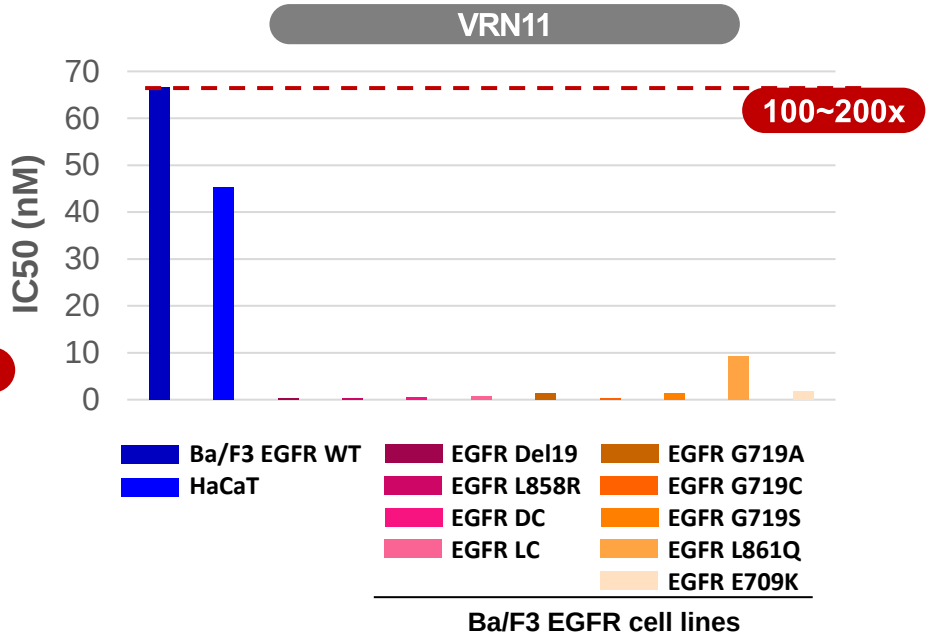
VRN07 & VRN11. On-target WT EGFR sparing

Highly potent against EGFR mutation



- 표피성장인자수용체(EGFR)를 억제하는 약물로 인해 발생하는 EGFR 관련 부작용(피부발진, 여드름양 발진, 손발톱주위염, 설사 등)





출처: AACR-NCI-EORTC, WCLC2023

VRN07 & VRN11. On-target Toxicity

VRN11, On-target/Off-target 부작용이 확인되지 않을 것으로 기대

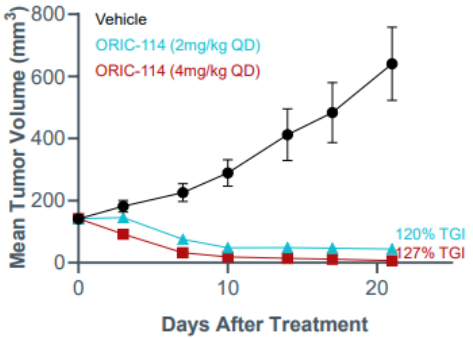
Clinical trial. On-target Toxicity data

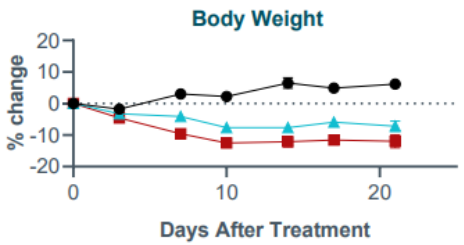
EGFR 구분	약물명	Grade ≥3 부작용	
		Total(%)	On-target Toxicity
Del19 L858R	Tagrisso	34~42% (FLAURA)	Diarrhea(설사) 3%
Del19 L858R	Leclaza	39% (Laser301)	Rash(발진) 1.1%, Diarrhea(설사) 2.3%
Del19 L858R	Leclaza +Rybrevant	75% (MARIPOSA)	<EGFR> Paronychia(손발톱주위염) 11%, Rash(발진) 15%, Diarrhea(설사) 2%, Dermatitis acneiform(여드름양 피부염) 8%, Stomatitis(구내염) 1%, Pruritus(가려움증) 0.5% <MET> Hypoalbuminemia(저알부민혈증) 5%, Peripheral edema(말초 부종) 2%
Exon20 Ins.	Sunvozertinib	39%	Diarrhea(설사) 8%, Rash(발진) 1%, Paronychia(손발톱주위염) 2%
C797S	BDTX-1535	50%*	Diarrhea(설사) <20%, Rash(발진) <20%, Stomatitis(구내염) <5%, Paronychia(손발톱주위염) <5%
Exon20 Ins.	ORIC-114 (VRN07)	19%*	Diarrhea(설사) 9% , Stomatitis(구내염), 3%, Pruritis(가려움증) 3%
Del19 L858R C797S	VRN11		

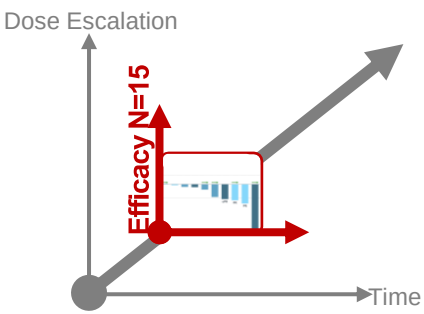
출처: ESMO2023, ASCO2023, AACR-NCI-EORTC2023, Ramalingam SS, et al.; FLAURA Investigators. N Engl J Med. 2020 Jan 2;382(1):41-50. doi: 10.1056/NEJMoa1913662. Epub 2019 Nov 21.
*유효 용량 이상의 부작용 데이터

VRN07 & VRN11. *in-vivo & Clinical trial*

VRN07(ORIC-114)



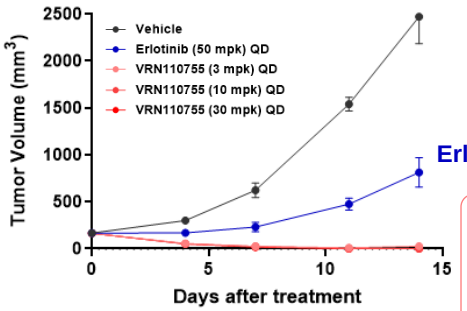




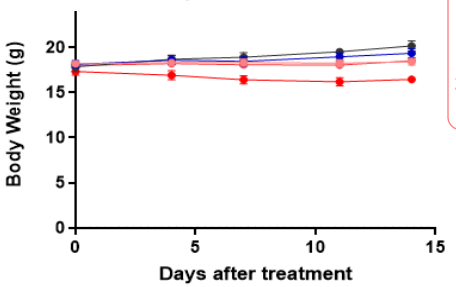
PR 3/15
CR 1/15
SD 4/15

DOR 53.3%

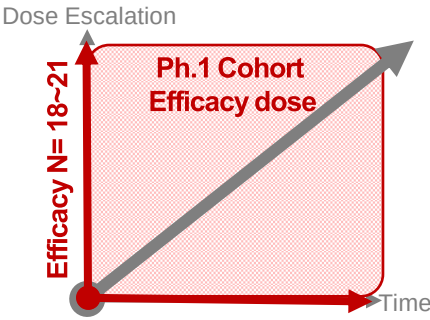
VRN11



Erlotinib 50mpk



CR	CR	CR
3mpk	10mpk	30mpk
x1	x3	x10
3mpk	10mpk	30mpk



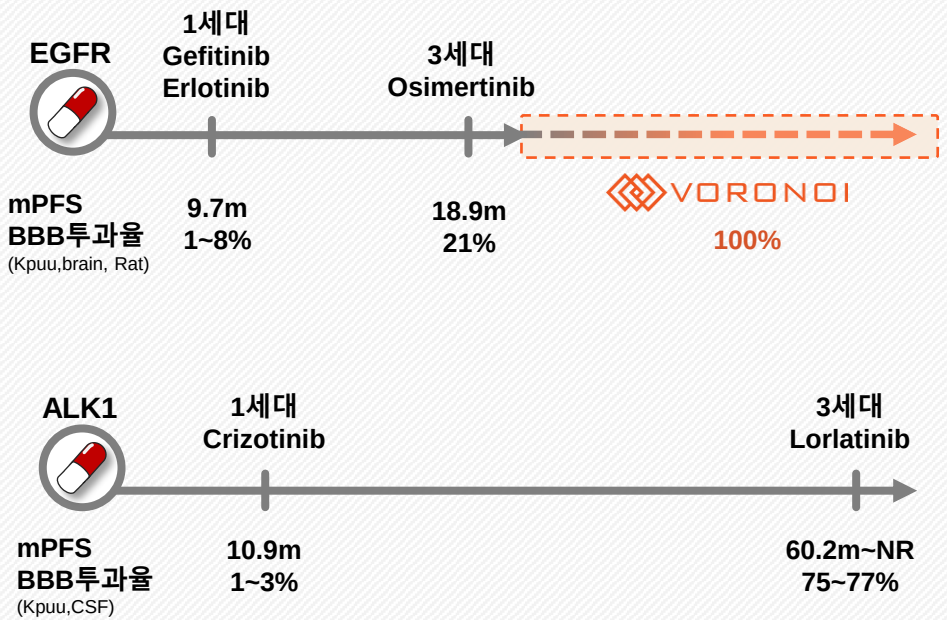
2024년 3월
환자 투약 시작

출처: AACR2021

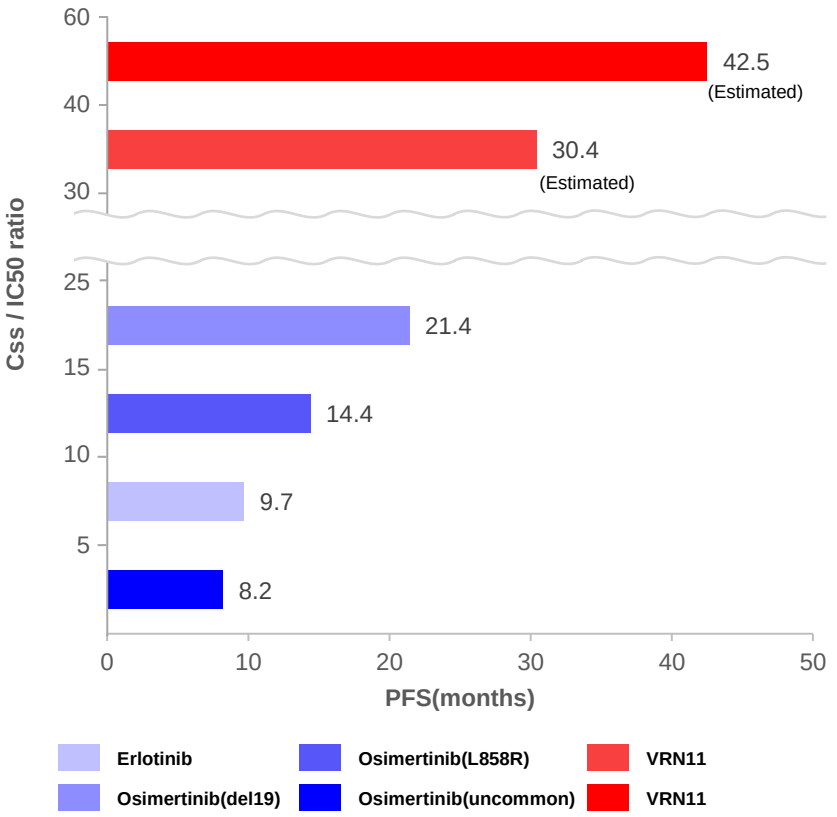
VRN11. PFS 추정치

표적치료제 세대별 무진행생존기간 비교[1,2,3]

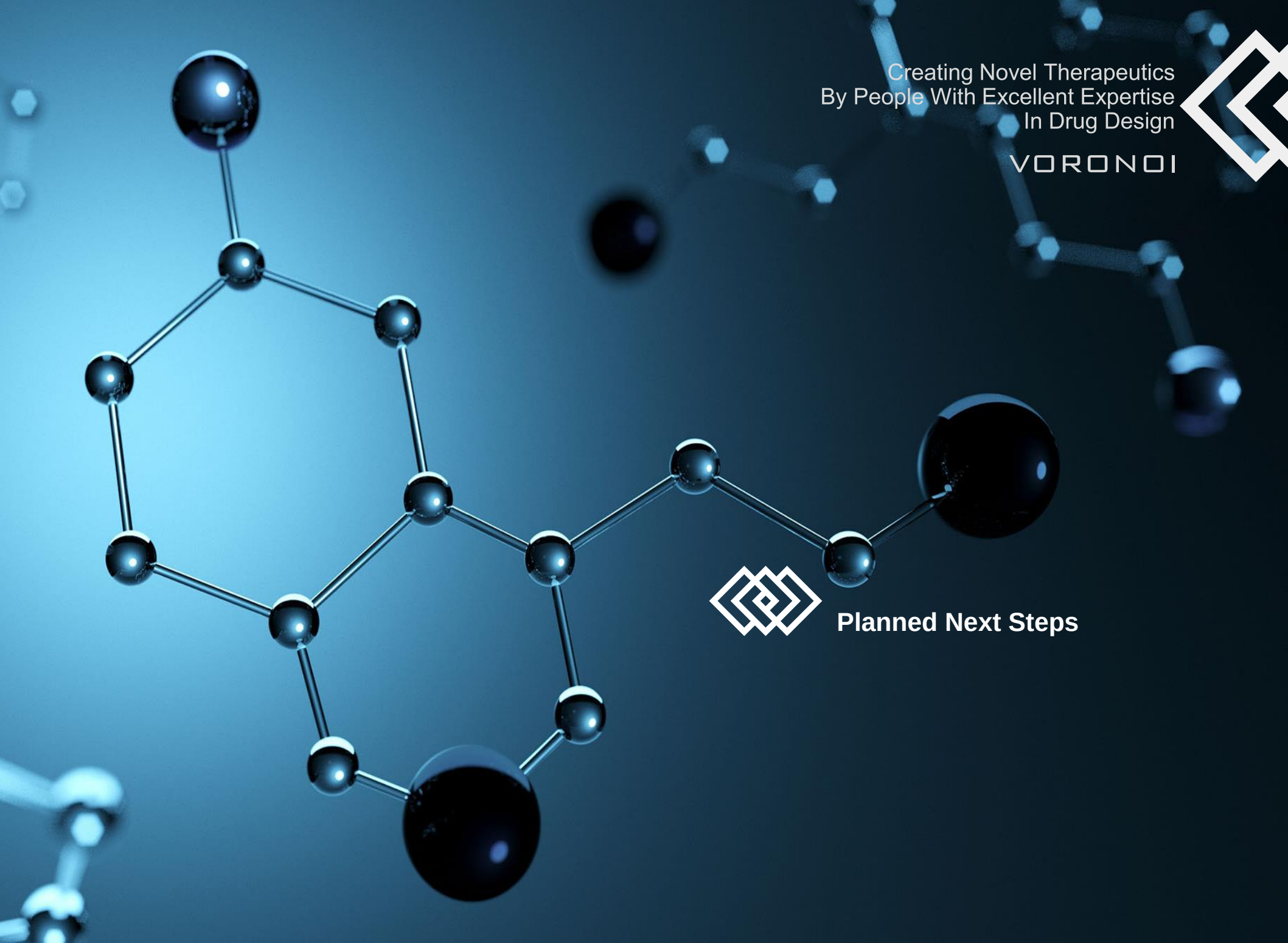
✓ EGFR, ALK; mPFS



VRN11 estimated PFS(1st line)[1,4,5]



[1]Douillard JY, et al. Br J Cancer 2014;110:55-62, Rosell R, et al. Lancet Oncol 2012;13:239-246, Soria JC, et al. N Engl J Med 2018;378:113-125
[2]Solomon BJ, et al. N Engl J Med 2014;371:2167-2177, Solomon BJ, et al. JCO 0, JCO.24.00581
[3]Toyoaki Hida, Transl Lung Cancer Res. 2023 Aug 30;12(8):1822-1825, [4]Jonathan N. Priantti, et al. JCO 42, 8642-8642(2024), [5]in-house

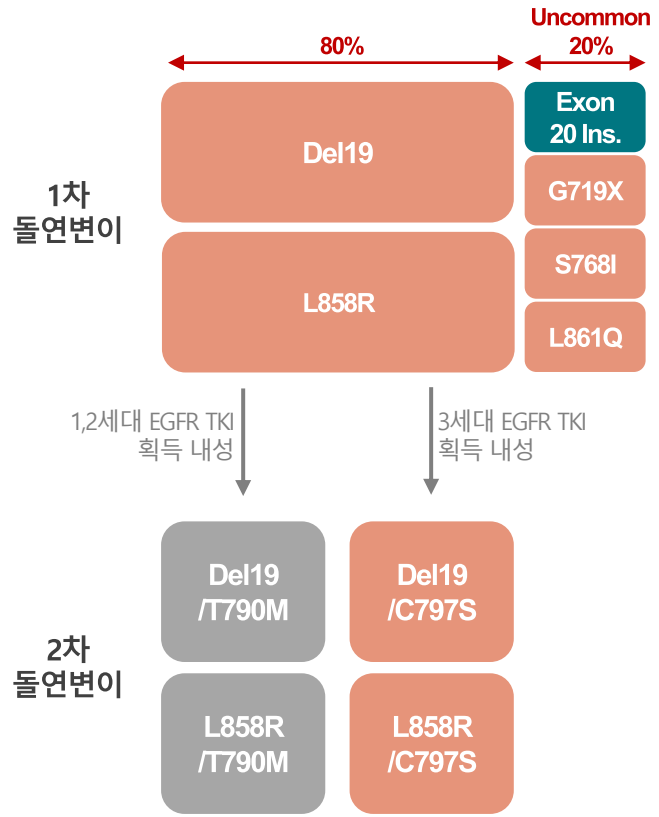

Creating Novel Therapeutics
By People With Excellent Expertise
In Drug Design
VORONOI
Planned Next Steps

EGFR 비소세포폐암(NSCLC) 시장 규모

Major Oncogenic Mutations for NSCLC

EGFR Mutations

유럽, 미국 대비 동북아 3개국(한,중,일)의 EGFR 돌연변이 발생률이 1.6~2배 이상 높음
(중국 48%, 일본 45%, 한국 43% - 미국 26%, 유럽 15%)



VRN07 타겟 돌연변이 시장 규모

First-Line Therapy	Subsequent Therapy
Amivantamab +Chemotherapy	Chemotherapy
Chemotherapy	Amivantamab

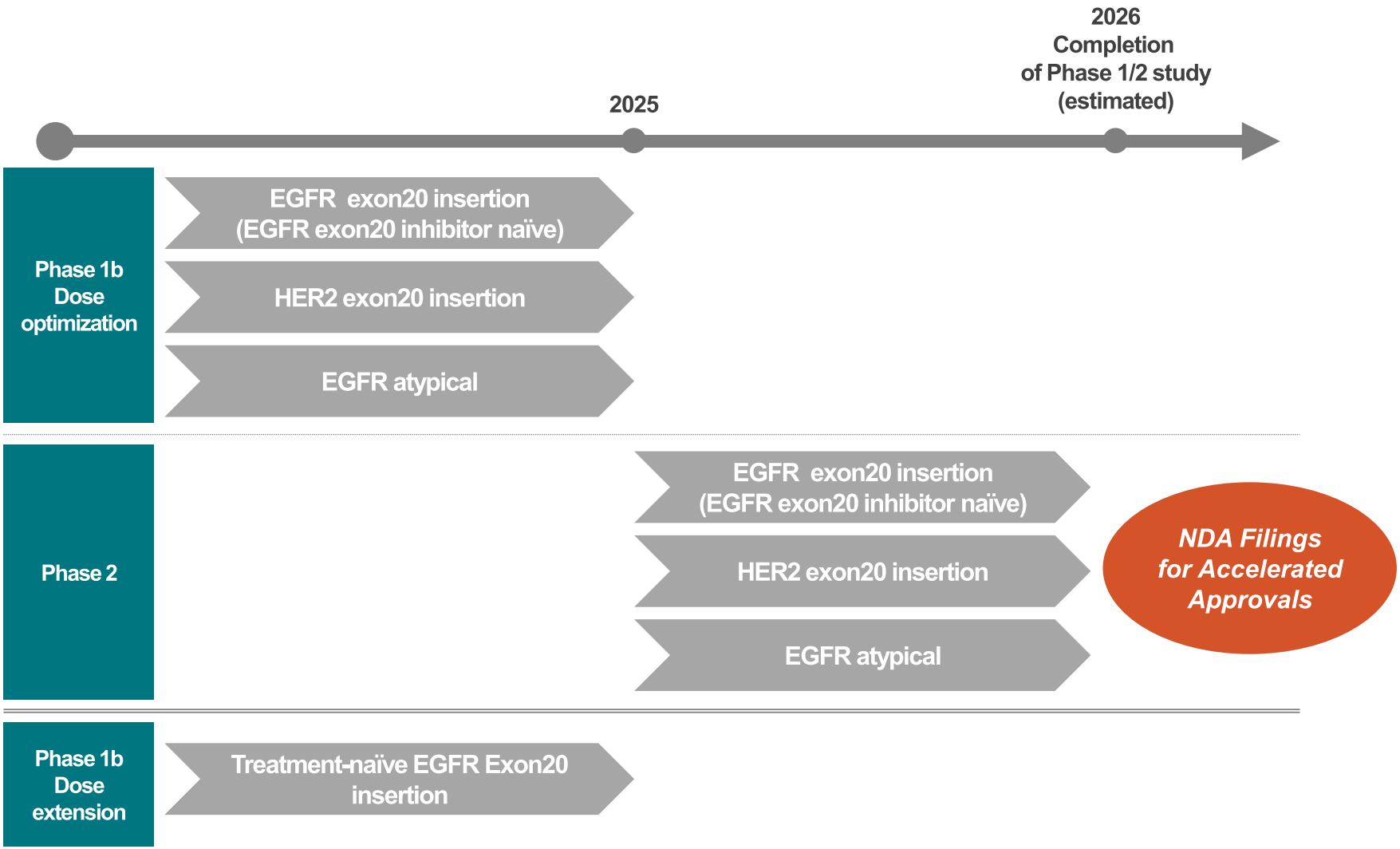
- ✓ 비소세포폐암 환자 중 EGFR Exon20 ins 돌연변이 보유 환자 3~4%
- ✓ EGFR Exon20 ins 돌연변이 전체 시장 규모 2~3조원
- ✓ 2021.05, Amivantamab 2차 치료제 가속승인
- ✓ 2024.03, Amivantamab+Chemotherapy 1차 치료제 승인

VRN11 타겟 돌연변이 시장 규모

Mutations	First-Line Therapy	Subsequent Therapy
Del19, L858R	Tagrisso	뇌 전이 환자, 미충족 의료 수요 존재
G719X, L861Q, S768I	Gilotrif, Tagrisso	뇌 전이 환자, 미충족 의료 수요 존재
Del19/C797S, L858R/C797S	승인 치료제 부재	

- ✓ EGFR Del19, L858R 돌연변이 시장 규모 10조원 이상
- ✓ EGFR uncommon 돌연변이(G719X, L861Q, S768I) 시장 규모 2~3조원
- ✓ EGFR C797S 돌연변이 시장 규모 2조원 이상
- ✓ 비소세포폐암 환자 중 뇌 전이 발생 비율 30~40% 이상

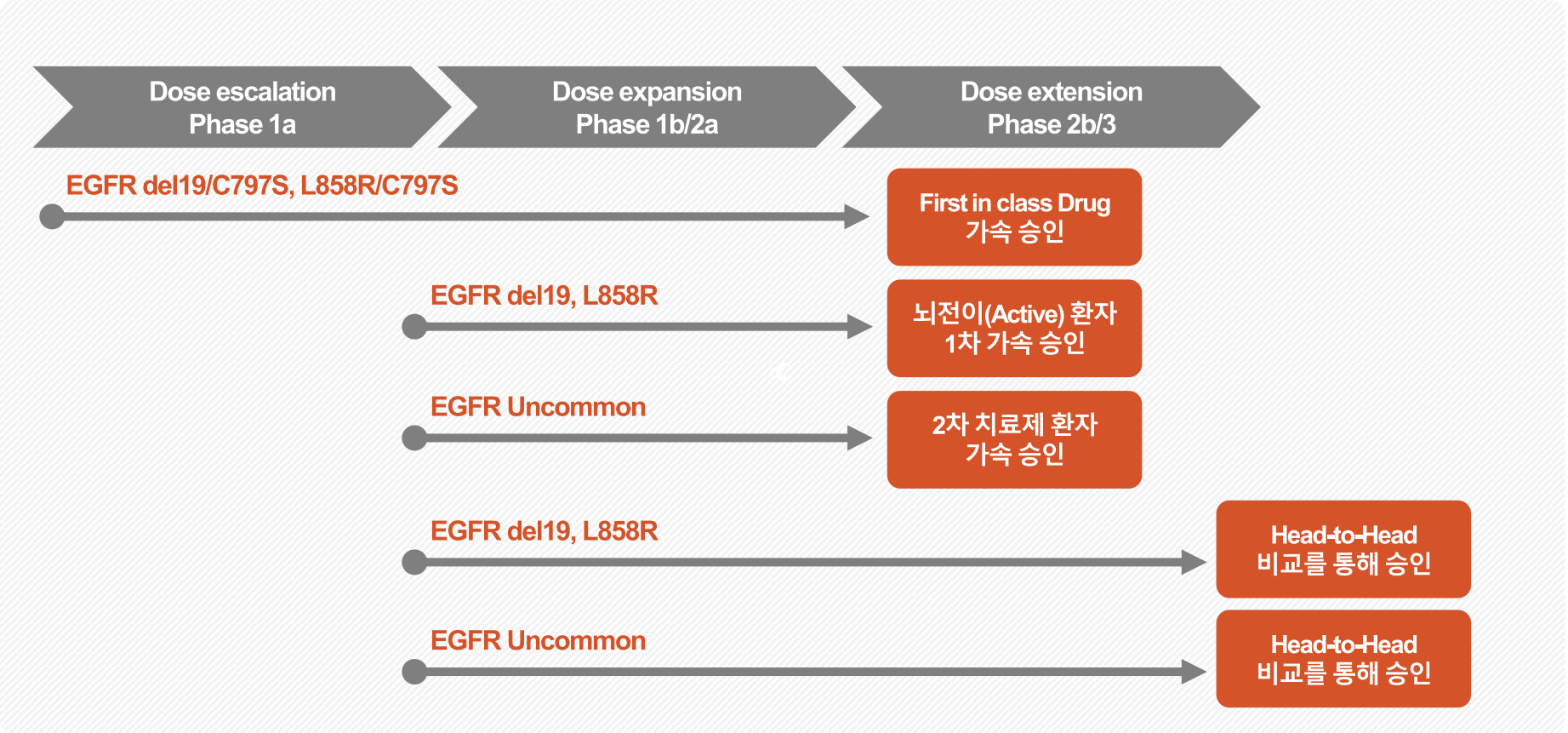
VRN07(ORIC-114). Planned Next Steps



출처: ORIC

VRN11. Planned Next Steps

EGFR 돌연변이 치료제에 존재하는 다양한 환자군에 진입 예정



한국 임상 1상 IND 승인 이후,
- 대만, 1a/1b IND 제출 및 승인 완료
- 향후 미국 임상 IND 제출 예정

EGFR 획득내성 폐암, EGFR 원발성 폐암, EGFR 뇌전이 폐암 등
다양한 EGFR 분야의 치료옵션 기대

Creating Novel Therapeutics
By People With Excellent Expertise
In Drug Design

VORONOI

Thank You