TPD 연구개발 동향 및 전략 - 차별화된 약물성과 임상 디자인

(이화의생명연구원) 62차 LAB-Thursday Talk

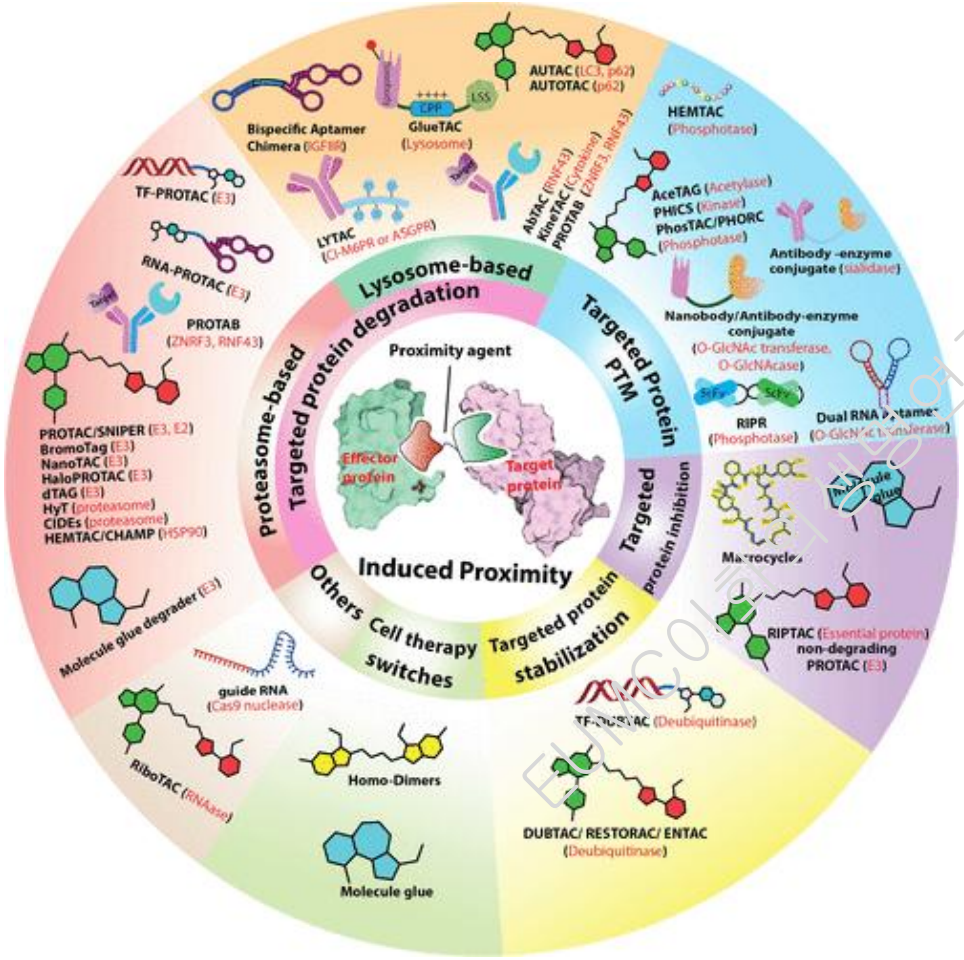
EUMC이화의생명연구원 무단배포금지

Ubix Therapeutics
㈜유빅스테라퓨틱스

서보광 대표, ㈜유빅스테라퓨틱스

Proximity-Based Modalities (Induced Proximity)

화학적 방법을 통해 **근접성을 강화하거나 새로운 근접성(neoproximity)을 생성**함으로써,
단백질을 표적화하고 생물학적 과정을 조절하는 접근법



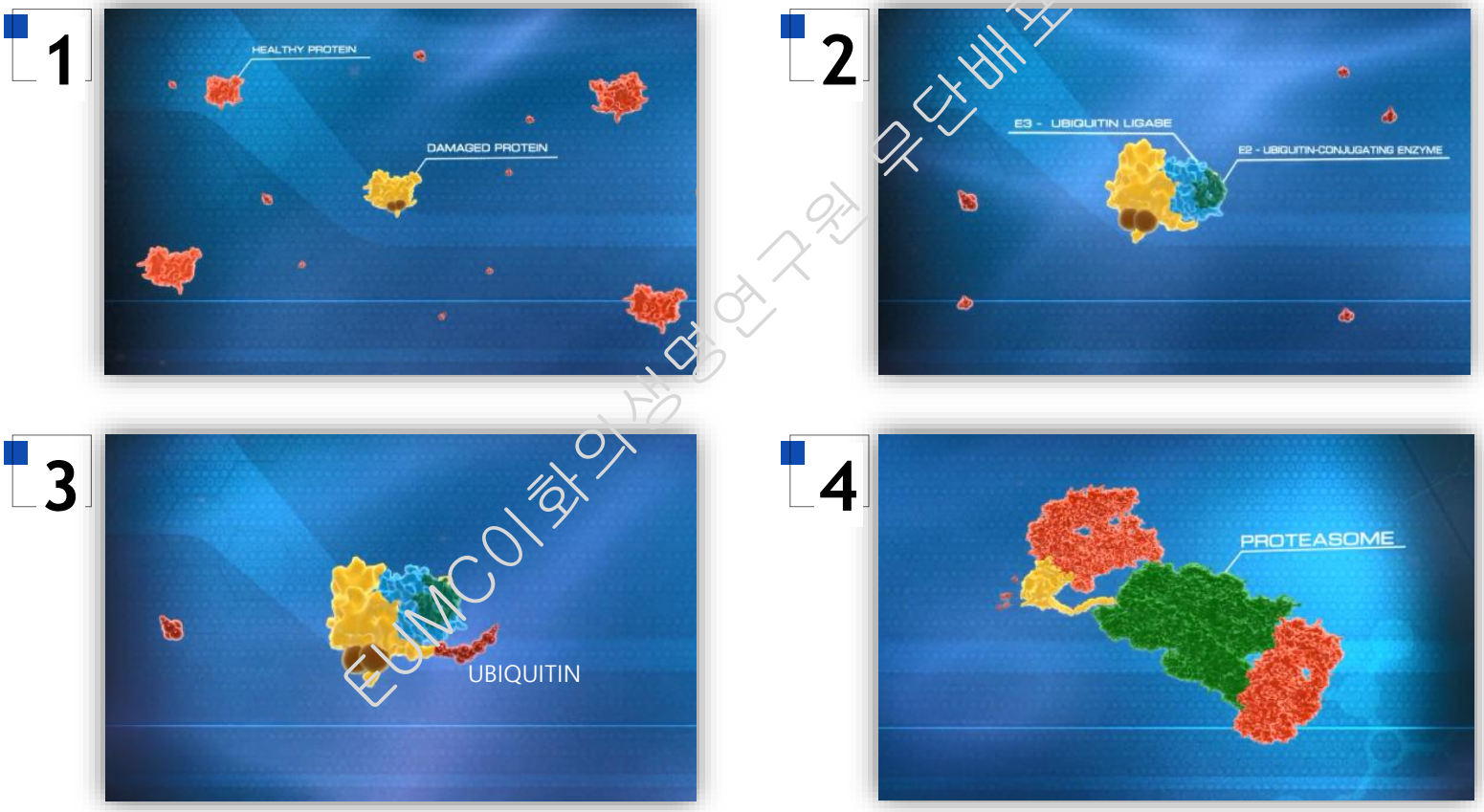
- **Targeted protein degradation**
  - Ubiquitin-Proteasome System, Autophagy-Lysosome System 등을 이용한 표적 단백질 분해
- **Targeted protein PTM**
  - 표적 단백질과 PTM(post-translational modifications) 효소 간의 proximity를 유도, 조절
- **Targeted protein inhibition**
  - 표적 단백질에 다른 결합 단백질을 모집하여, 효소 및 스캐폴딩 기능 등 표적 단백질 억제를 강화
- **Targeted protein stabilization**
  - 표적 단백질의 불안정화와 비정상적 분해가 질병을 유발하는 경우, 해당 단백질을 구조적으로 회복

타 CRO 및 연구원 무단배포금지

Ubiquitin Proteasome System (UPS)

세포 내 손상된 단백질에 **E3 Ligase**가 결합한 후,

Ubiquitin-Proteasome을 이용하여 **그 단백질을 분해하는 생체 시스템**



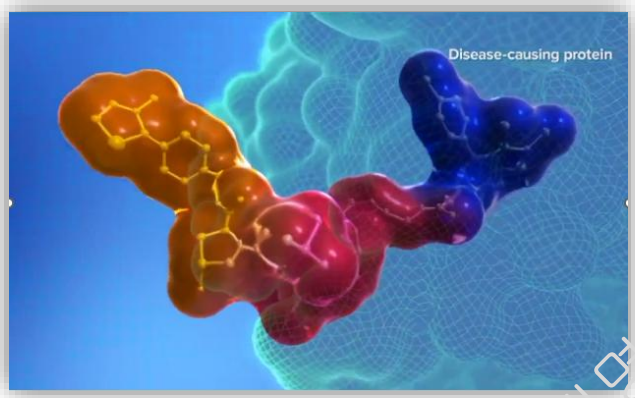
본 UMC이화의생명연구원 무단배포금지

| TPD (Targeted Protein Degradation)

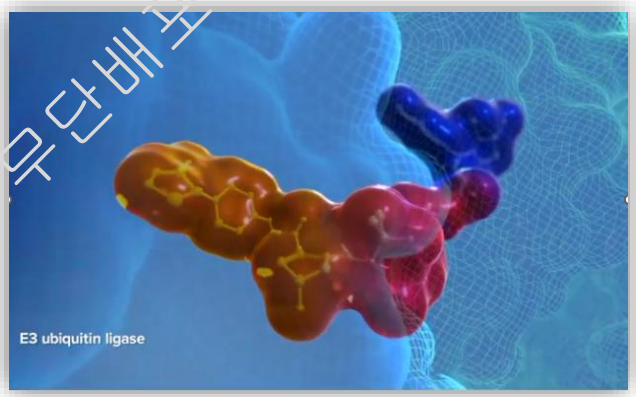
Ubiquitin-Proteasome 시스템을 활용하여,

세포 내 표적 단백질(Target)을 선택적으로 분해하는 강력한 저해제 기술

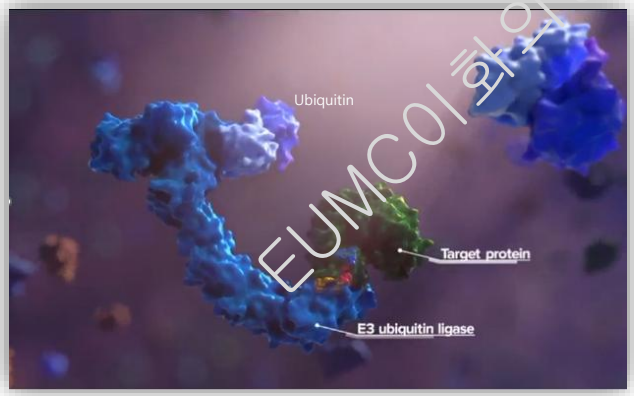
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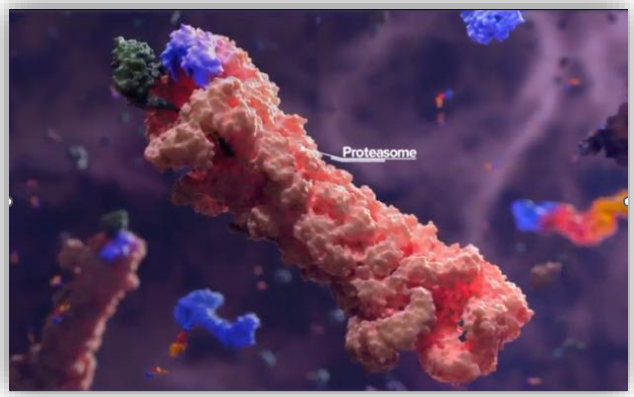
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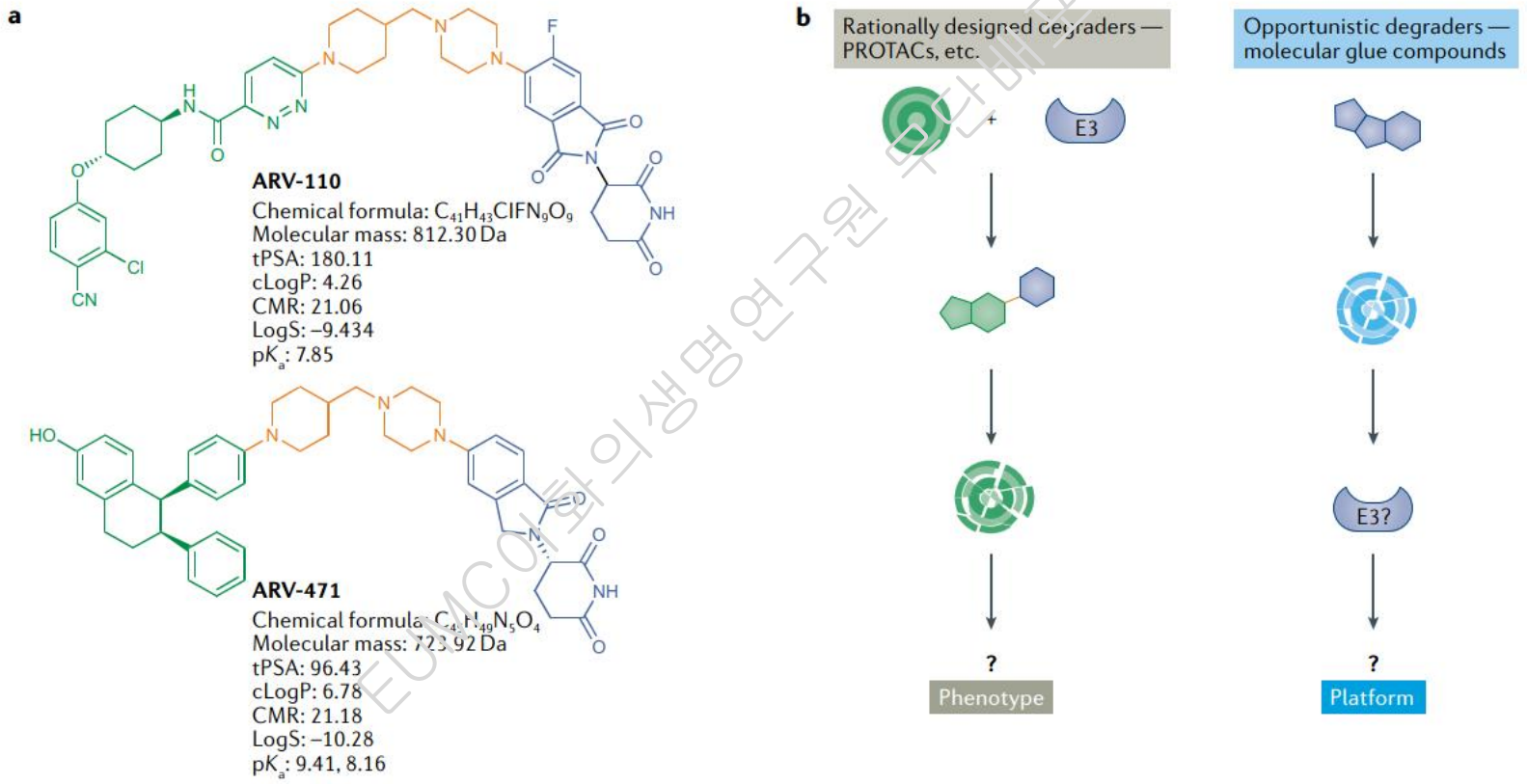


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| TPD 약물 디자인 과정

TPD[a]는 Target, E3 ligase 간의 3차원 구조를 기반으로 디자인(rational design)하는데 반해, MG(Molecular Glue)[b]는 우연히 생리적 활성을 가진 약물을 발굴, 최적화(HTS)하는 과정을 거침.

- 최근에는 MG 영역에서도 rational design 기법이 도입되는 추세.



EUMC이화의생명연구원 무단배포금지

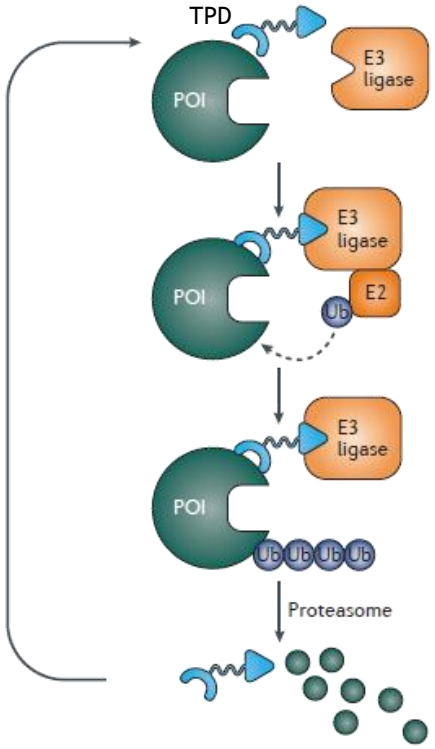
* Source : TPD targeted protein degraders. The past is prologue, Nature Reviews, 2021.

기존 저분자 저해제의 한계

TPD 치료제를 통해 **저분자 저해제의 한계 극복** 가능

- Ternary complex 형성이라는 일시적인 '사건(event)'에 의해 표적 단백질 분해 유도
- 효소 및 비효소 기능 동시 저해 가능

TPD 작용 원리



Ternary structure 형성

- 타겟-TPD 결합력 약화에도 표적 분해 유도

표적 단백질 분해 유도

- 단백질 효소 및 비효소 작용 모두 억제

Event-driven pharmacology

- 1개의 TPD 분자로 재사용 가능, 여러 표적 단백질의 분해 유도

TPD 치료제 장점

✓ 기존 치료제 내성 변이로 인한 저항성 극복

✓ Difficult-to-target 표적 단백질에 적용 가능

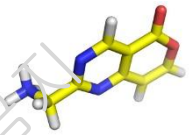
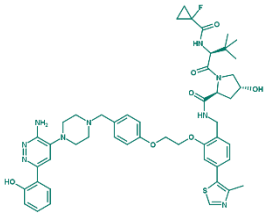
✓ Scaffold 등 비효소 작용 억제로 신호전달 차단, 강력한 효능

✓ 과발현 표적 단백질 억제

EUMO이화의생명연구원 무단배포금지

| TPD 기술의 장점 : Superior therapeutic optionality



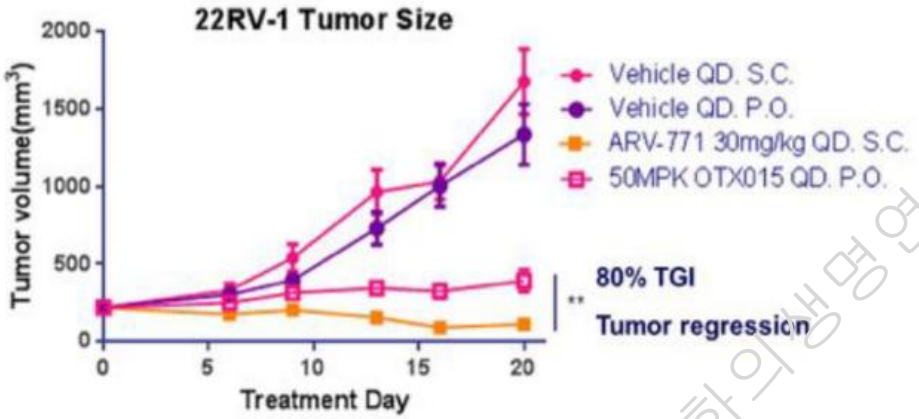



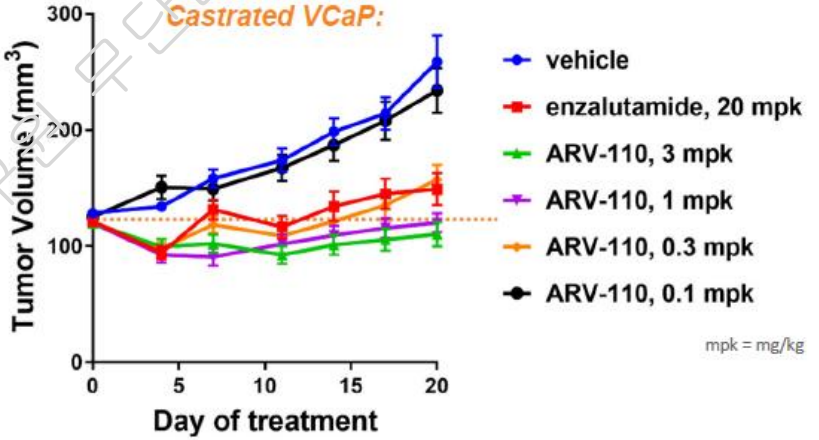
	Antibody	CRISPR/RNAi	Traditional Small Molecule	TPD
Undruggable Targets	O	O	×	O
Intracellular Targets	×	O	O	O
Catalytic MOA	×	O	×	O
Elimination of Targeted Protein	×	O	×	O
Systemic Exposure	O	×	O	O
Oral Bioavailability	×	×	O	O
Efficiency in Development	×	×	O	O

EUMC이화의생명연구원 무단배포금지

| TPD 기술의 장점 : Catalytic nature, high-efficacy

Chemical inhibitor 대비 **낮은 농도/용량에서 우월한 효능**





ARV-771 : BET PROTAC (JQ1 based)
OTX-015 : BET inhibitor (JQ1 derivative)

Enzalutamide : AR antagonist
ARV-110 : AR PROTAC

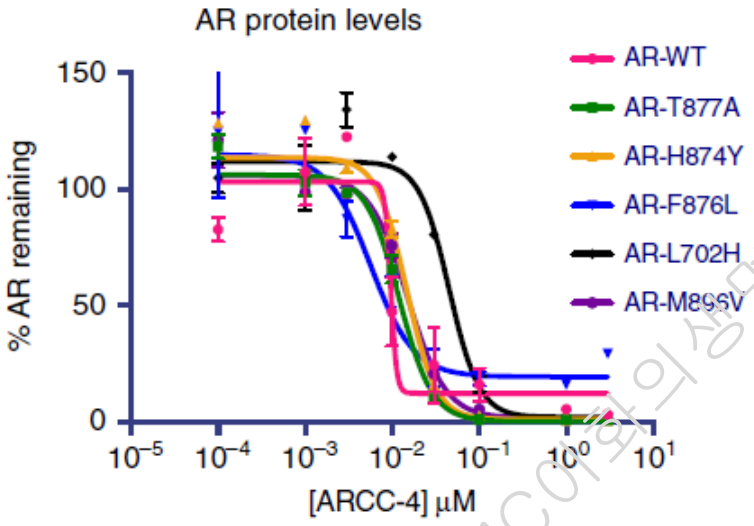
본 IMC이화의생명연구원 무단배포금지

PNAS 2016 Jun 28; 113(26): 7124-7129

Arvinas, 2nd Annual Targeted Protein Degradation Summit, October 2019

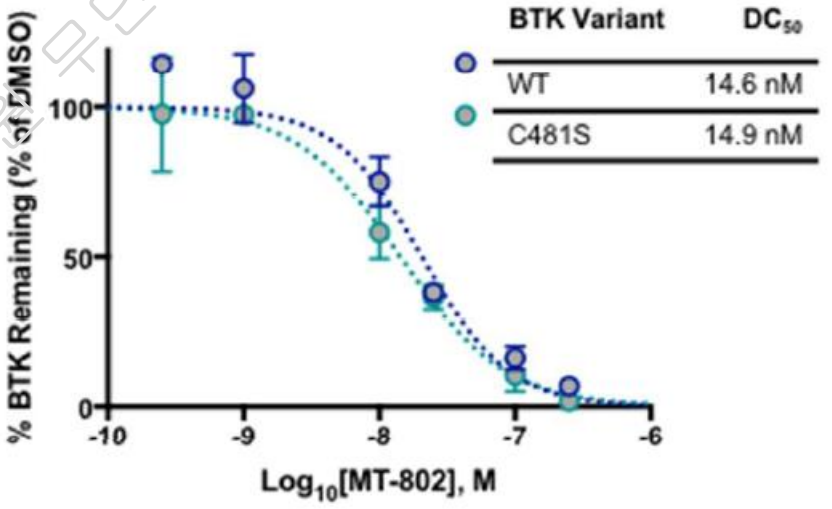
| TPD 기술의 장점 : Drug resistance 극복

전형적인 내성 기전인 target protein의 **mutation, amplification 극복 가능**



ARCC-4 : Enzalutamide based AR PROTAC

Commun Biol. (2018) 1:100



MT-802 : Ibrutinib based BTK PROTAC

Biochemistry 2018, 3;57(26):3564-3575

EUMC이화의생명연구원 무단배포금지

| TPD 글로벌 개발 동향 (1)

Arvinas, C4, Kymera, Nurix 등의 바이오텍 선도업체 주도로 임상 translational phase 진입,

2026년 Arvinas의 ARV-471(ER degrader) 신약허가

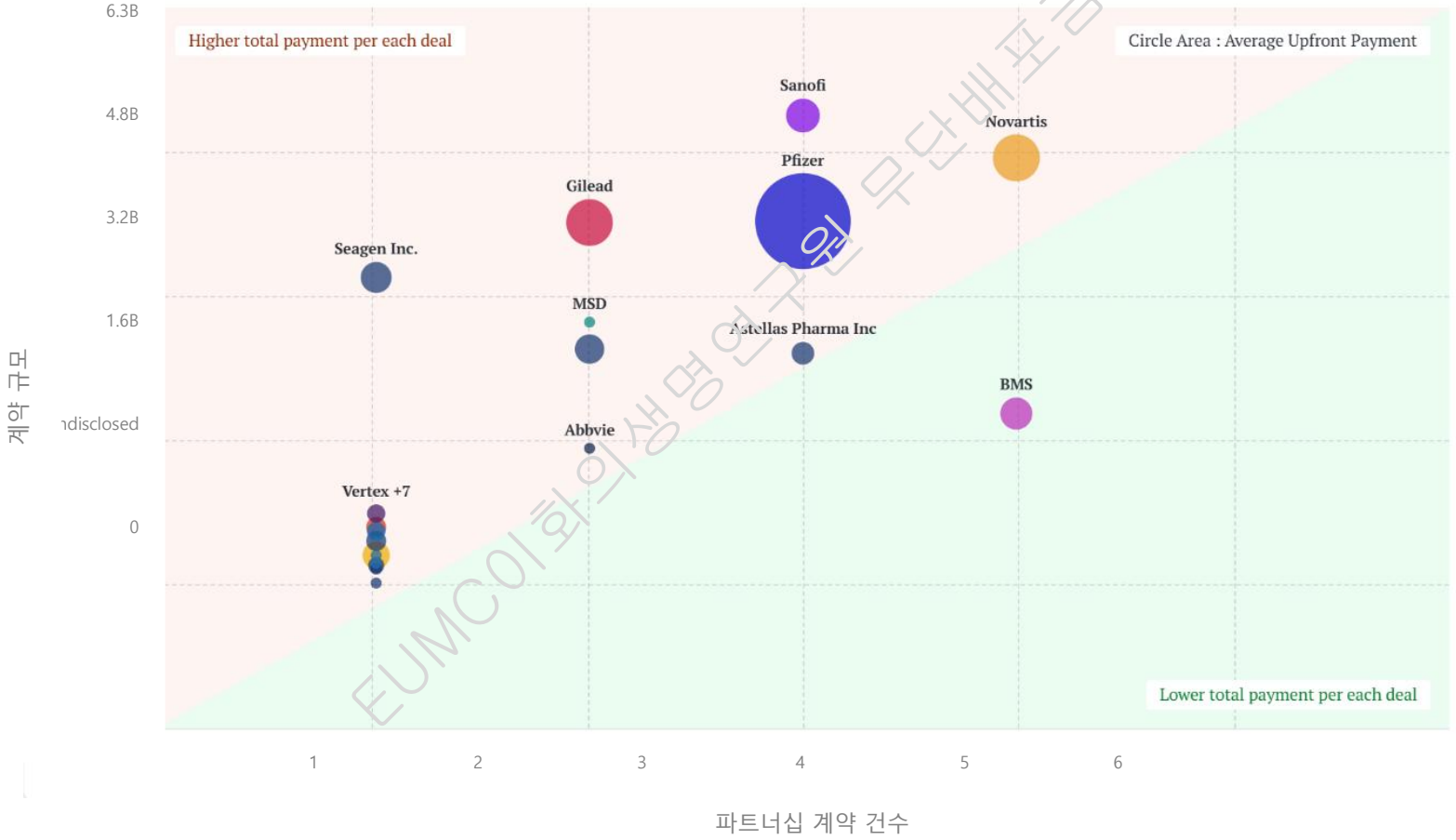
Rank	Highest stage in Phase III, II, I/II	Highest stage in Phase I	No. of clinical piplines	No. of preclinical piplines	No. of sponsored clinical trials	No. of patent families	No. of license-out transactions	No. of license-in transactions
1	ARVINAS	NURIX THERAPEUTICS	ARVINAS	UNIVERSITY OF MICHIGAN	PFIZER	ARVINAS	ARVINAS	BOEHRINGER INGELHEIM
2	BEIGENE	HAISCO PHARMACEUTICAL	BEIGENE	ICAHN SCHOOL OF MEDICINE AT MOUNT SINAI	BEIGENE	KYMERA THERAPEUTICS	C4 THERAPEUTICS	GENENTECH
3	BRISTOL-MYERS SQUIBB	ACCUTAR BIOTECHNOLOGY	KYMERA THERAPEUTICS	CHINESE ACADEMY OF SCIENCES	HENGRUI	DANA-FARBER CANCER INSTITUTE	UBIX THERAPEUTICS	PFIZER
4	PFIZER (ARVINAS)	ASTELLAS PHARMA	ACCUTAR BIOTECHNOLOGY	ASTRAZENECA	ARVINAS	BEIGENE	NURIX THERAPEUTICS	ROCHE
5	KYMERA THERAPEUTICS	LEADINGTAC	NURIX THERAPEUTICS	CYRUS THERAPEUTICS	ACCUTAR BIOTECHNOLOGY	HAISCO PHARMACEUTICAL	SHANGHAITECH UNIVERSITY	SANOFI
6	HINOVA PHARMA	HEZHENG PHARMACEUTICAL	HINOVA PHARMA	MD ANDERSON	KINTOR PHARMA	C4 THERAPEUTICS	UNIVERSITY OF DUNDEE	BAYER
7	HENGRUI	HEJING PHARMACEUTICALS	HAISCO PHARMACEUTICAL	UNIVERSITY OF ALABAMA AT BIRMINGHAM	KYMERA THERAPEUTICS	NURIX THERAPEUTICS	BEACTICA THERAPEUTICS	BETTA PHARMACEUTICALS
8	SANOFI (KYMERA)	UBIX THERAPEUTICS	HENGRUI	ANHORN MEDICINES	HAISCO PHARMACEUTICAL	YALE UNIVERSITY	BRIDGENE BIOSCIENCES	BIAOXIN BIOTECH
9	KINTOR PHARMA	CULLGEN INC	C4 THERAPEUTICS	ARVINAS	HINOVA PHARMA	ROCHE	CHENGDU PIONEER	CAPTOR THERAPEUTICS
10	NOVARTIS (ARVINAS)	FOGHORN THERAPEUTICS	BRISTOL-MYERS SQUIBB	DANA-FARBER CANCER INSTITUTE	NURIX THERAPEUTICS	CHINESE ACADEMY OF SCIENCES	DONG-A ST	GALAPAGOS
11	C4 THERAPEUTICS	BETTA PHARMACEUTICALS (C4 THERAPEUTICS)	ASTELLAS PHARMA	CHINA PHARMACEUTICAL UNIVERSITY	CELGENE	CHINA PHARMACEUTICAL UNIVERSITY	ENDOTARGET	GILEAD SCIENCES
12	RANOK THERAPEUTICS	POLYMED BIOPHARM	CULLGEN INC	ENDOTARGET	ASTELLAS PHARMA	ACCUTAR BIOTECHNOLOGY	JIMIN KEXIN	HEJING PHARMACEUTICALS
13	DIALECTIC THERAPEUTICS	HUADONG MEDICINE	DIALECTIC THERAPEUTICS	KYMERA THERAPEUTICS	BETTA PHARMACEUTICALS	BRISTOL-MYERS SQUIBB	KYMERA THERAPEUTICS	INNO.N
14			FOGHORN THERAPEUTICS	UBIX THERAPEUTICS	C4 THERAPEUTICS	CULLGEN INC	POLYMED BIOPHARM	NATIONAL CENTER FOR ADVANCING TRANSLATIONAL SCIENCES
15			UBIX THERAPEUTICS	JINGRUI PHARMACEUTICALS	CULLGEN INC	LEADINGTAC	SHAANXI UNIVERSITY OF SCIENCE AND TECHNOLOGY	NEOIMMUNETECH

US CN EP KR

* Source: Cai et al, 2025 Global landscape of PROTAC: Perspectives from patents, drug pipelines, clinical trials, and licensing transactions

| TPD 글로벌 개발 동향 (2)

Arvinas, C4 Therapeutics를 필두로 Pfizer, Amgen, Novartis 등
글로벌 제약기업들의 **집중적인 관심 하에 지속적으로 사업화 사례** 도출 중



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* Source: Bio-research.ai

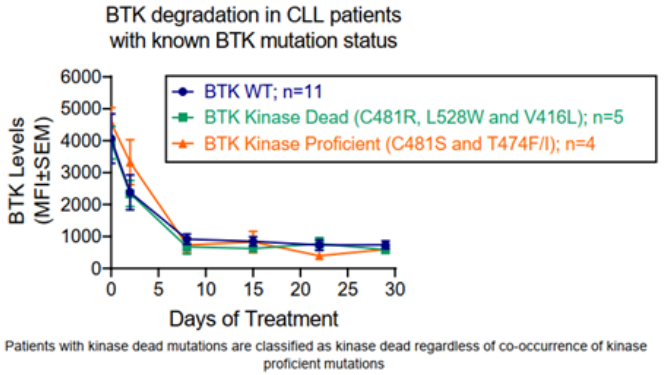
개발전략 및 고려 요소 (1) Mutant Coverage - NX-2127, ARV-110

Ubix Therapeutics

임상을 통해 다양한 종류의 **mutant coverage 프로파일** 확인 및 향후 개발전략에 반영

Treatment with NX-2127 Leads to BTK Degradation and Clinical Response in CLL Patients Irrespective of Mutation Status

NX-2127 Preliminary Efficacy in Patients with CLL

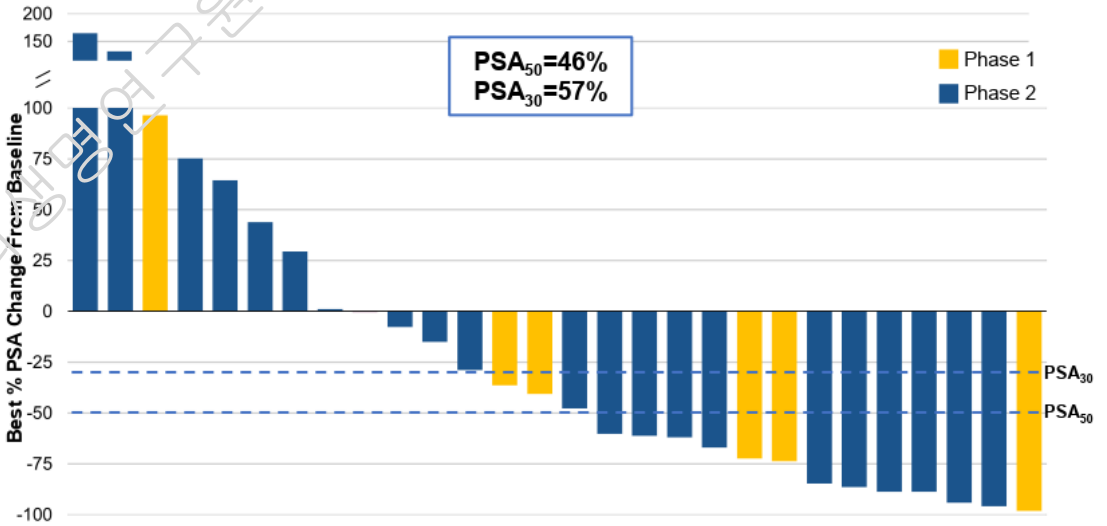


Patients with kinase dead mutations are classified as kinase dead regardless of co-occurrence of kinase proficient mutations

- BTK degradation of 80% achieved in CLL patients including those harboring BTK C481, T474, L528, and V416 resistance mutations

nurix Data Cut-off Date: September 21, 2022 *Montoya et al. ASH 2022. New Orleans, LA.* 17

Figure 2: Best percentage change in PSA from baseline in patients with tumors harboring AR T878X/H875Y mutations (n=28)*



- In 28 patients with AR T878X/H875Y-positive tumors, the PSA_{50} rate was 46% and the PSA_{30} rate was 57% (**Figure 2**)
- Across the biomarker- and PSA-evaluable phase 1/2 patient population (n=152), the PSA_{50} rate was 17% and the PSA_{30} rate was 31%

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| 개발전략 및 고려 요소 (2) Scaffolding Function - KT-474

특정 target의 경우 catalytic function 만이 아니라

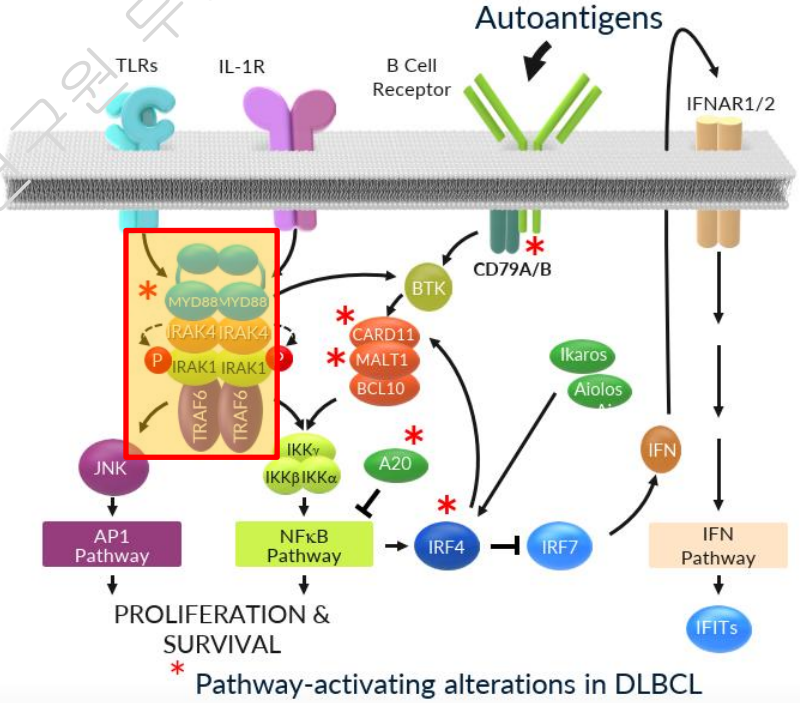
signal pathway 상의 다른 target과 상호작용하는 **scaffolding function의 차단**이 필요

IRAKIMiDs are Potent Degraders of IRAK4 and IMiD Substrates Targeting Redundant Pro-survival Pathways in MYD88^{MT} DLBCL

- Single-agent therapies targeting activated NFκB signaling in DLBCL show limited activity
- Redundant NFκB pathway activation and downregulation of Type 1 IFN common in MYD88^{MT} lymphoma
- Simultaneous degradation of IRAK4 and IMiD substrates Ikaros and Aiolos shows synergistic activity in MYD88^{MT} models

	U.S.		R.O.W.	
	Prevalence	Incidence	Prevalence	Incidence
MYD88 MT DLBCL	~8k	2.8 / 100k	~10k	1.2 / 100k
MYD88 MT Waldenström's Macroglobulinemia	~9k	0.3 / 100k	~26k	0.7 / 100k
MYD88 MT PCNS Lymphoma	~2k	0.6 / 100k	~10k	0.6 / 100k

Source: Bionest and Global Data. ROW includes E.U., U.K. and Japan.



Adapted from Yang et al. (2012) *Cancer Cell* 21, 6, pp723-737

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EDMC이화의생명연구원 무단배포금지

Inhibitor 개발 과정과 마찬가지로 TPD 개발의 경우에도 **강점 및 차별화 요소를 극대화**할 수 있는 임상 디자인 필요

San Antonio Breast Cancer Symposium®, December 6–10, 2022, Presentation GS3-03

Patient Baseline Characteristics (VERITAC)

Characteristic	Total (N=71)
Sex, n (%)	
Female	69 (97.2)
Median age, y (range)	60 (41–86)
ECOG PS, n (%)[a]	
0	47 (66.2)
1	23 (32.4)
Visceral disease, n (%)	39 (54.9)
Sites of metastasis, n (%)	
Bone	49 (69.0)
Liver	32 (45.1)
Lung	17 (23.9)
Other	5 (7.0)

Characteristic	Total (N=71)
Baseline *ESR1* status, n (%)[b]	
Mutant	41 (57.7)
Wild-type	25 (35.2)
Median no. of prior regimens (range)	
Any setting	4 (1–10)
Metastatic setting	3 (0–7)
Type of prior therapy, n (%)	
CDK4/6 inhibitor	71 (100)
Aromatase inhibitor	64 (90.1)
Fulvestrant	56 (78.9)
Chemotherapy	
Any setting	52 (73.2)
Metastatic setting	32 (45.1)

[a]Baseline ECOG PS status was unknown in 1 patient. [b]Baseline *ESR1* status was unknown or missing in 5 patients; CDK=cyclin-dependent kinase; ECOG PS=Eastern Cooperative Oncology Group performance status; *ESR1*=estrogen receptor 1 gene

ARVINAS

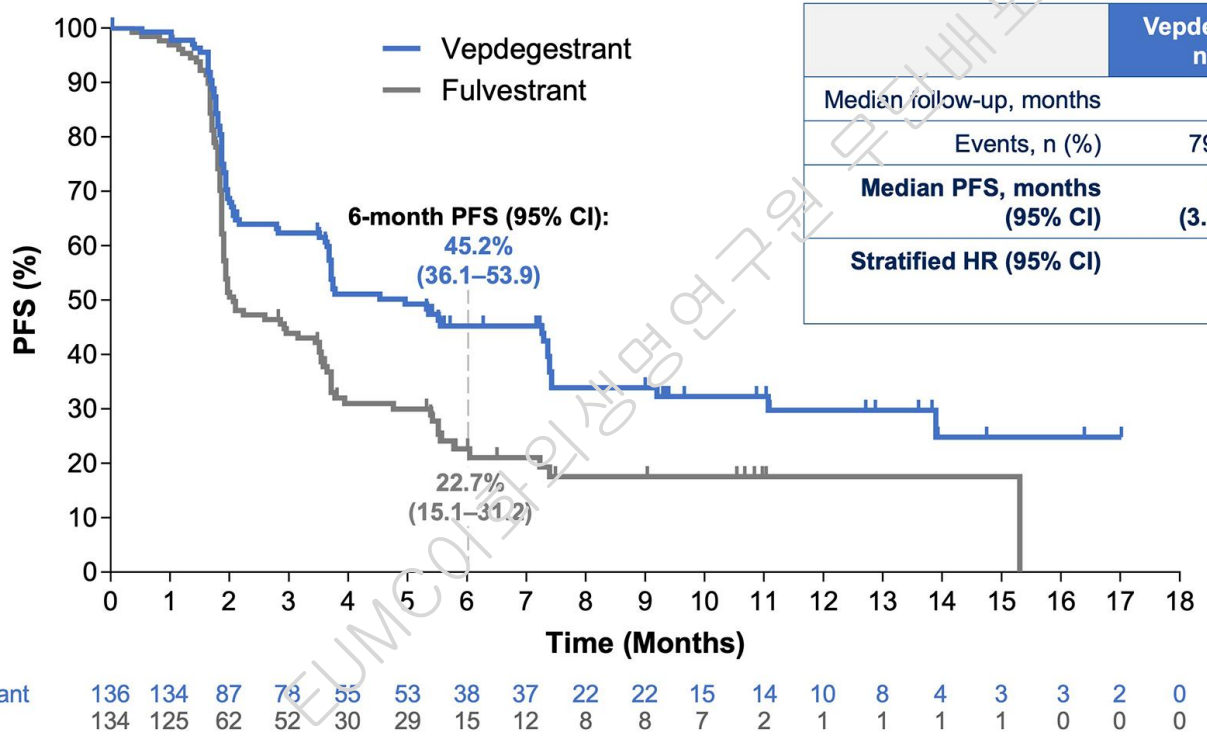
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* Source: San Antonio Breast Cancer Symposium, December 6-10, 2022, Presentation GS3-03

| 개발전략 및 고려 요소 (3) Clinical Trial Design - ARV-471

Inhibitor 개발 과정과 마찬가지로 TPD 개발의 경우에도 **강점 및 차별화 요소를 극대화**할 수 있는 임상 디자인 필요

<VERITAC-2 Primary Endpoint: PFS by BICR in Patients With *ESR1m*>



	Vepdegestrant n=136	Fulvestrant n=134
Median follow-up, months	7.4	6.0
Events, n (%)	79 (58)	95 (71)
Median PFS, months (95% CI)	**5.0 (3.7–7.4)**	**2.1 (1.9–3.5)**
Stratified HR (95% CI)	**0.57 (0.42–0.77)**	
	2-sided *P* < 0.001	

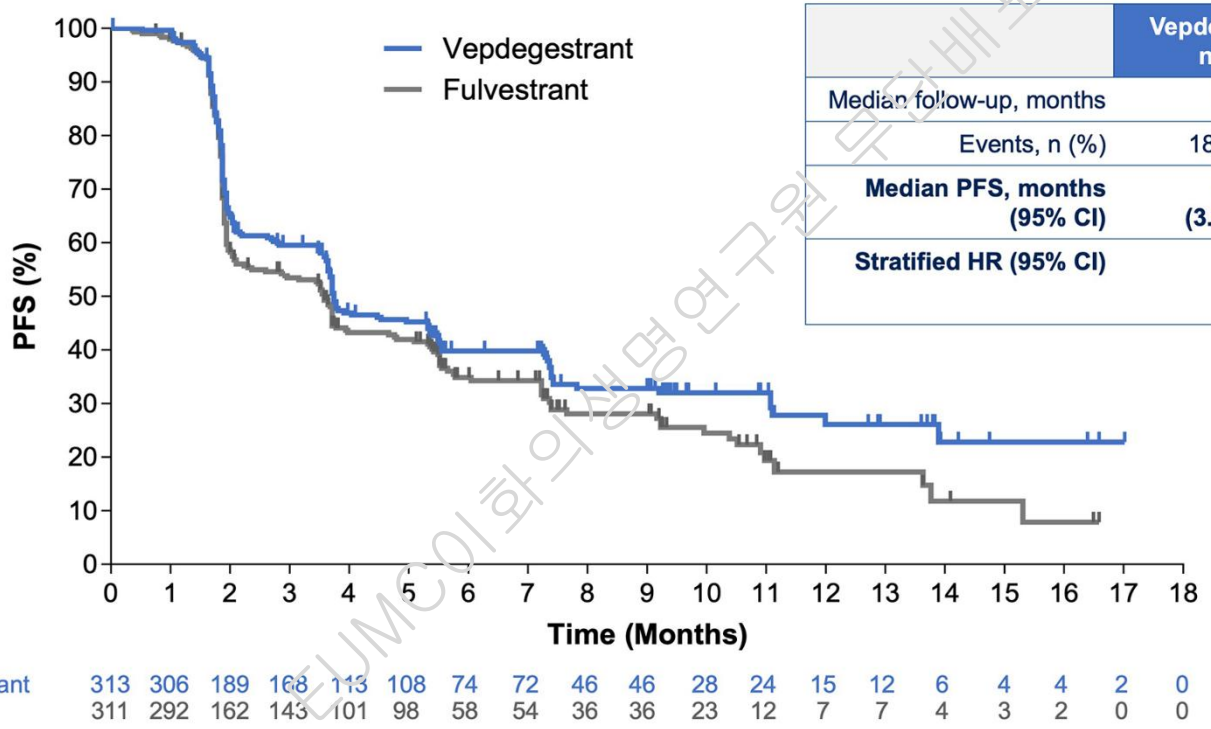
EUMC이화의생명연구원 무단배포금지

* Source: ASCO Daily News, May 31, 2025

| 개발전략 및 고려 요소 (3) Clinical Trial Design - ARV-471

Inhibitor 개발 과정과 마찬가지로 TPD 개발의 경우에도 **강점 및 차별화 요소를 극대화**할 수 있는 임상 디자인 필요

<VERITAC-2 Primary Endpoint: PFS by BICR in All Patients>



	Vepdegestrant n=313	Fulvestrant n=311
Median follow-up, months	7.4	7.2
Events, n (%)	186 (59)	198 (64)
Median PFS, months (95% CI)	**3.7 (3.6–5.3)**	**3.6 (2.2–3.8)**
Stratified HR (95% CI)	**0.83 (0.68–1.02)**	
	2-sided *P* = 0.07	

EUMC이화의생명연구원 무단배포금지

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THANK YOU

Ubix Therapeutics
㈜유빅스테라퓨틱스

(이화의생명연구원) 62차 LAB-Thursday Talk

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