The Promise of PROTAC® Protein Degraders: What's Next for Arvinas' Pipeline & Platform

John G. Houston, PhD
President and Chief Executive Officer,
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14 October 2020

ARVINAS
The PROTAC® Company

Safe harbor and forward-looking statements

This presentation contains forward-looking statements within the meaning of The Private Securities Litigation Reform Act of 1995 that involve substantial risks and uncertainties, including statements regarding the development and regulatory status of our product candidates, such as statements with respect to our lead product candidates, ARV-110, ARV-471 and ARV-766 and other candidates in our pipeline, and the timing of clinical trials and data from those trials and plans for registration for our product candidates, and our discovery programs that may lead to our development of additional product candidates, the potential utility of our technology and therapeutic potential of our product candidates, and the potential commercialization of any of our product candidates. All statements, other than statements of historical facts, contained in this presentation, including statements regarding our strategy, future operations, future financial position, future revenues, projected costs, prospects, plans and objectives of management, are forward-looking statements. The words “anticipate,” “believe,” “estimate,” “expect,” “intend,” “may,” “might,” “plan,” “predict,” “project,” “target,” “potential,” “will,” “would,” “could,” “should,” “continue,” and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words.

We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements we make as a result of various risks and uncertainties, including but not limited to: whether we will be able to successfully conduct Phase 1/2 clinical trials for ARV-110 and ARV-471, complete other clinical trials for our product candidates, and receive results from our clinical trials on our expected timelines, or at all, whether our cash resources will be sufficient to fund our foreseeable and unforeseeable operating expenses and capital expenditure requirements, and other important factors, any of which could cause our actual results to differ from those contained in the forward-looking statements, discussed in the “Risk Factors” section of our quarterly and annual reports on file with the Securities and Exchange Commission. The forward-looking statements contained in this presentation reflect our current views as of the date of this presentation with respect to future events, and we assume no obligation to update any forward-looking statements except as required by applicable law.

Congratulations to all as we approach the 20th anniversary of first PROTAC® publication. We have come a long way!

Protacs: Chimeric molecules that target proteins to the Skp1–Cullin–F box complex for ubiquitination and degradation

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Communicated by Alexander Varshavsky, California Institute of Technology, Pasadena, CA, May 10, 2001 (received for review March 29, 2001)

The intracellular levels of many proteins are regulated by ubiquitin-dependent proteolysis. One of the best-characterized enzymes that catalyzes the attachment of ubiquitin to proteins is a ubiquitin ligase complex, Skp1-Cullin-F box complex containing Hrt1 (SCF). We sought to artificially target a protein to the SCF complex for ubiquitination and degradation. To this end, we tested methionine aminopeptidase-2 (MetAP-2), which covalently binds the angiogenesis inhibitor ovalicin. A chimeric compound, protein-targeting chimeric molecule 1 (Protac-1), was synthesized to recruit MetAP-2 to SCF. One domain of Protac-1 contains the IκBα phosphopeptide that is recognized by the F-box protein β-TRCP, whereas the other domain is composed of ovalicin. We show that MetAP-2 can be tethered to $SCF^{\beta\text{-}TRCP}$, ubiquitinated, and degraded in a Protac-1-dependent manner. In the future, this approach may be useful for conditional inactivation of proteins, and for targeting disease-causing proteins for destruction.

Degradation of cellular proteins is required for normal maintenance of cellular function, including proliferation, differentiation, and cell death. One of the major pathways to regulate proteins posttranslationally is ubiquitin-dependent proteolysis. Ubiquitination occurs through the activity of ubiquitin-activating enzymes (E1), ubiquitin-conjugating enzymes (E2), and ubiquitin–protein ligases (E3), which act sequentially to catalyze the attachment of ubiquitin to lysine residues of substrate proteins (1). The E3s confer specificity to ubiquitination reactions by binding directly to substrate. Although the exact number of E3s cannot be determined with certainty from sequence data, there are probably >100 distinct F-box-containing E3s encoded within the human genome (2). One particular class of E3s, the heterotetrameric Skp1-Cullin-F box (SCF) complexes, consists of Skp1, a Cullin family member, the RING-H2 protein Hrt1 (also known as Roc1 or Rbx1), and an F box protein (3). These components are conserved from yeast to mammals. The mammalian F box protein, β-TRCP/E3RS, has been shown to bind IκBα, a negative regulator of NFκB (4). The $SCF^{\beta\text{-}TRCP}$ complex promotes the ubiquitination and subsequent degradation of IκBα, which results in activation of NFκB during the inflammatory response (3).

The recruitment of IκBα to $SCF^{\beta\text{-}TRCP}$ is mediated by a 10-aa peptide within IκBα, DRHDSGLDSM (4, 5). In response to diverse inflammatory signals, IκBα kinase (IKK) phosphorylates this motif on both serines, which triggers the binding of IκBα to β-TRCP. Because it is a well-defined ligand for a specific ubiquitin ligase, we sought to take advantage of this phosphopeptide to target an unrelated protein to $SCF^{\beta\text{-}TRCP}$ for ubiquitination and degradation.

As proof of concept, we tested the ability of the IκBα phosphopeptide (IPP) to target methionine aminopeptidase-2 (MetAP-2) to $SCF^{\beta\text{-}TRCP}$. MetAP-2 catalyzes the cleavage of N-terminal methionine from nascent polypeptides (6) and seems to be the primary target of the potent angiogenesis inhibitors fumagillin and ovalicin (OVA; refs. 7 and 8). Both of these compounds inhibit MetAP-2 by covalently binding His-231 in the active site. The consequent reduction in MetAP-2 activity is thought to block endothelial cell proliferation by causing p53-dependent arrest in the G_1 phase of the cell cycle (9). Importantly, MetAP-2 is not known to be ubiquitinated or a substrate for any SCF complex.

To determine whether MetAP-2 could artificially be targeted to $SCF^{\beta\text{-}TRCP}$, we synthesized proteolysis-targeting chimeric molecule 1 (Protac-1) that contained both the IPP and OVA. We hypothesized that the phosphopeptide moiety would bind β-TRCP, and the OVA moiety would bind MetAP-2, thereby recruiting MetAP-2 to $SCF^{\beta\text{-}TRCP}$ for ubiquitination (Fig. 1*A*). We reasoned that this strategy might work because synthetic ligands that link distinct proteins have been shown to be capable of regulating signaling pathways *in vivo* (10). In this article, we report that Protac-1 indeed binds MetAP-2 to $SCF^{\beta\text{-}TRCP}$ and thereby promotes MetAP-2 ubiquitination and degradation. Demonstrating that Protac-1 mediates the ubiquitination and degradation of a foreign substrate by SCF provides a basis to begin testing Protacs *in vivo* in addition to other targets known to promote disease.

Materials and Methods

Synthesis of IκBα-OVA Protac. OVA (1.4 mmol) was dissolved in 10 ml of methanol at 0°C, and $NaBH_4$ (3.0 mmol) was added slowly. After 30 min of stirring, methanol was removed under reduced pressure, and the resulting crude product was purified by flash column chromatography to yield ovalicinol (1.15 mmol, 82%). Fmoc-Gly was coupled to the ovalicinol to give Fmoc-Gly-ovalicinol. Specifically, dimethylformamide (DMF, 28 μl) was added to dichloromethane solution (30 ml) containing Fmoc-Gly-OH (3.56 mmol) and oxalyl chloride (7.12 mmol) at 0°C. After 3 hr of stirring at room temperature, dichloromethane was removed under nitrogen atmosphere. The resulting solid residue was redissolved in dichloromethane (10 ml) and was combined with ovalicinol (0.6 mmol) and dimethylaminopyridine (4.7 mmol) in dichloromethane (30 ml) at 0°C. The reaction mixture was stirred for 2 hr at room temperature. After dichloromethane was removed under reduced pressure, the resulting residue was

Abbreviations: E1, ubiquitin-activating enzymes; E2, ubiquitin-conjugating enzymes; E3, ubiquitin–protein ligases; SCF, Skp1–Cullin–F box; IKK, IκBα kinase; IPP, IκBα phosphopeptide; MetAP-2, methionine aminopeptidase-2; OVA, ovalicin; Protac, proteolysis targeting chimeric; IKK-EE, constitutively active IKK; OA, okadaic acid.

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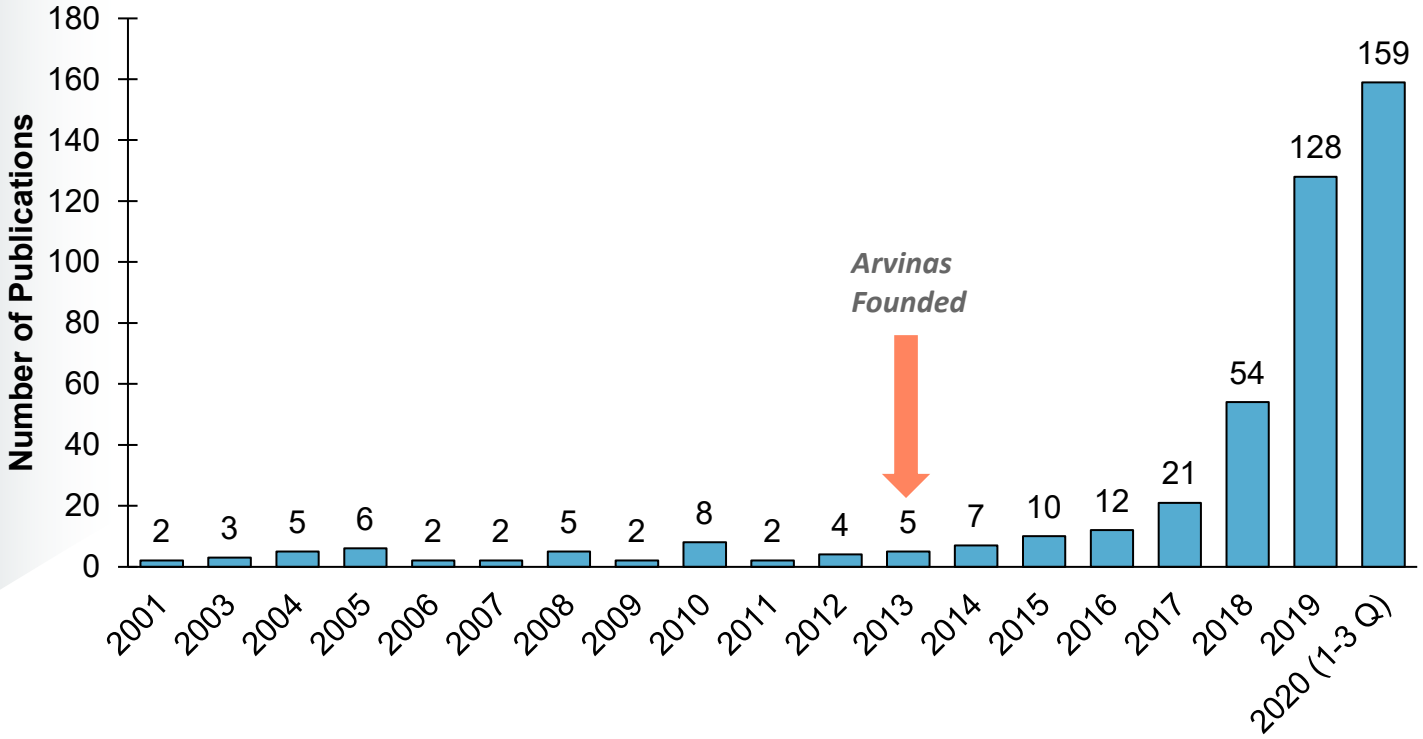
www.pnas.org/cgi/doi/10.1073/pnas.141230798

Scientific Publications for PROTAC® Degradation



Source: PubMed; Keyword words used: "Proteolysis-targeting chimera" OR "PROTAC® " OR "PROTAC® protein degraders" OR "protein degraders" OR "Targeted Protein Degradation" OR "Protein Degradation"

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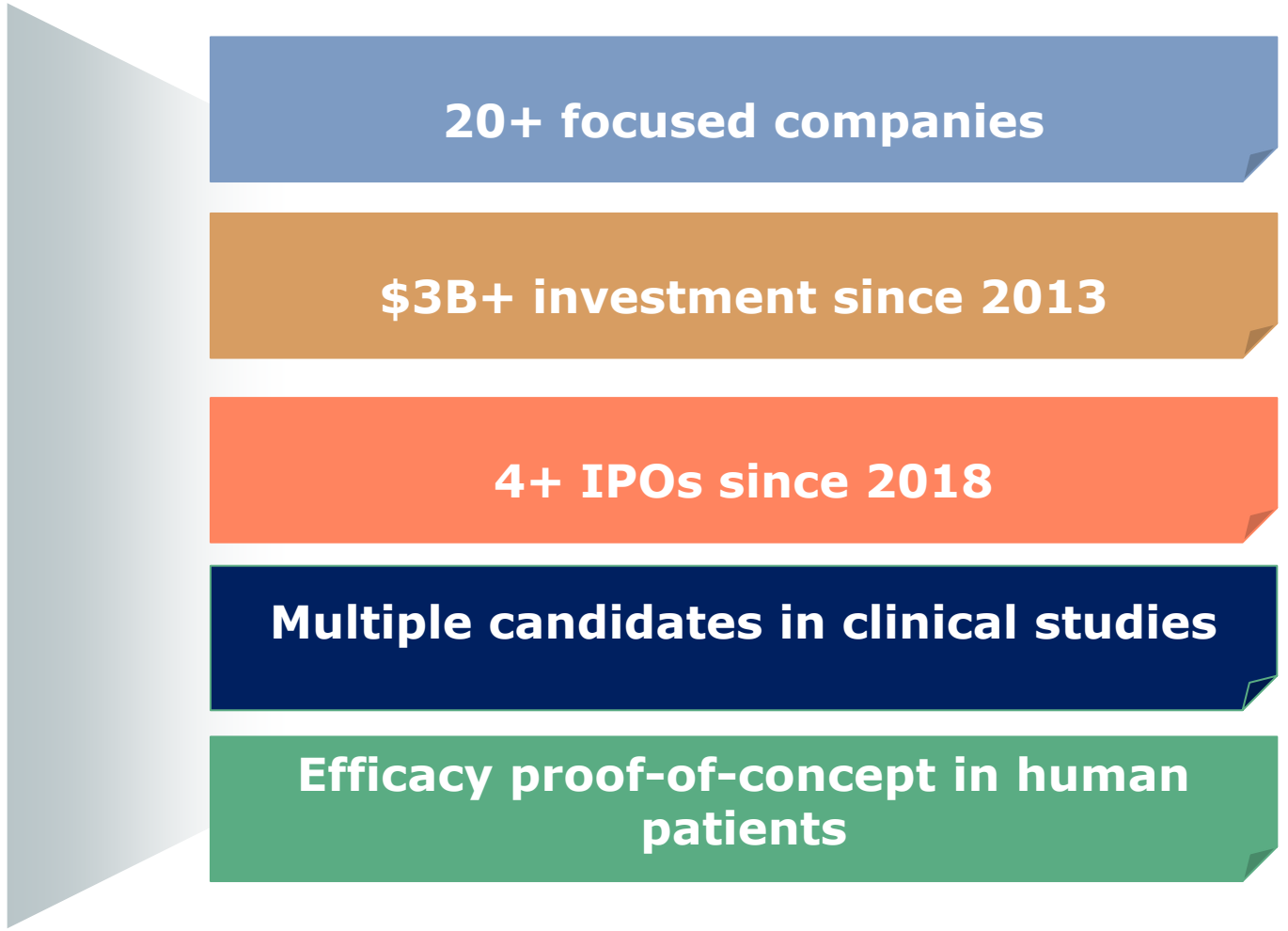
Protein degradation field has driven interest and investment, culminating in substantial patient and business impact

The expanding modalities of protein degradation

- **Heterobifunctional Small Molecules**
- **Molecular Glues**
- **Lysosome Targeting Chimeras**
- **Autophagy Targeting Chimeras**
- **Autophagosome Tethering Compounds**



Source: Company websites, S-1 filings, and industry research reports

Arvinas is 160+ colleagues strong and growing, benefitting from the experience and resources of the Connecticut biotech sector

Mission

We invent PROTAC® protein degraders designed to destroy disease-causing proteins and improve the lives of patients suffering from cancer, neurological disorders, and other serious diseases

Core Values

Pioneering, Excellence, Community, & Commitment

People

- 160+ highly experienced drug development professionals in New Haven, Connecticut
- 200+ FTEs at contract research organizations

Bioscience in Connecticut

- 39,000 employees across 2,500 companies[1]
- Strong academic base for R&D partnerships

[1]BioCT 2019 Report link

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Arvinas has led the targeted protein degradation field since its inception...

2019-2020

Proved the Concept of Our PROTAC® Discovery Engine

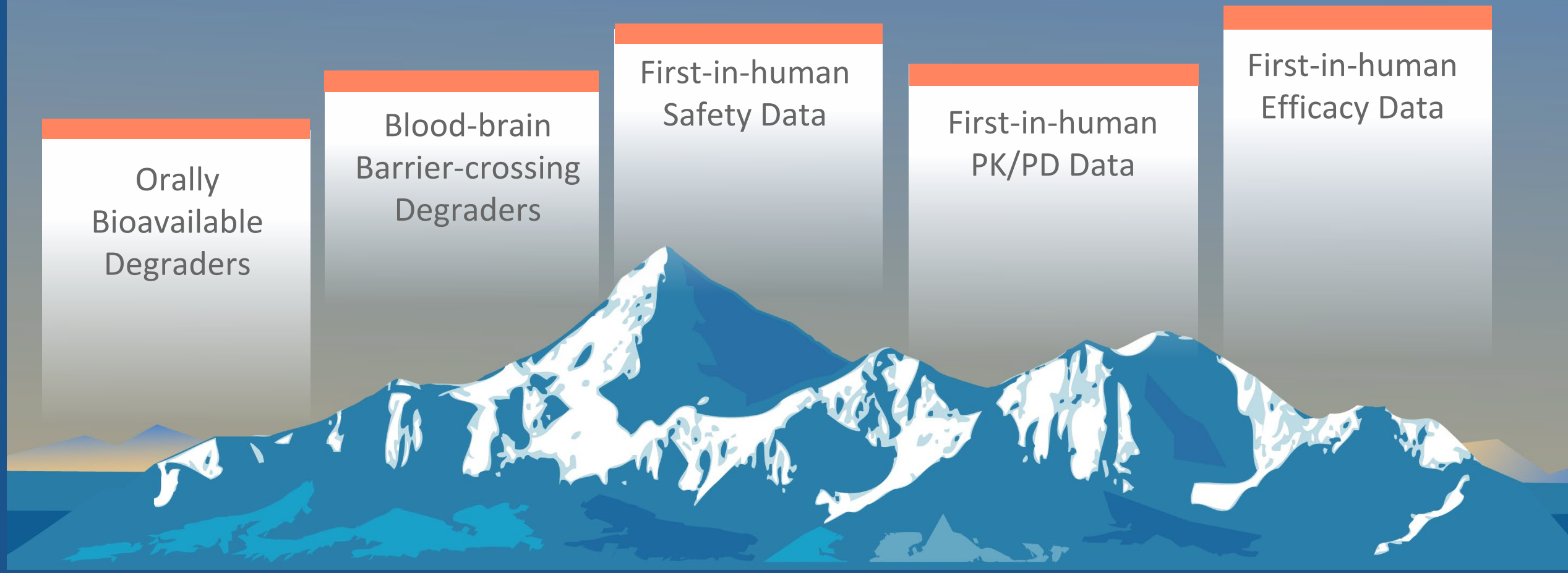
- Moved two programs into the clinic, each addressing an area of substantial unmet need for patients
- Initial evidence for efficacy, safety, and proof of degradation mechanism of PROTAC® degraders in human trials
- Expanded our wholly-owned PROTAC® pipeline to 20+ programs
- Embraced the challenge of improving agriculture with our JV, OerthBio

2013-2018

Built Arvinas' Foundation as a Pioneer in Protein Degradation

- Pioneered targeted protein degradation with our PROTAC® platform, making pivotal breakthroughs
- Capitalized Arvinas to drive growth and investment in our platform and capabilities
- Built a deep, broad pipeline of PROTAC® protein degraders
- Forged foundational partnerships

…and made significant breakthroughs along the way!



Arvinas' breakthroughs are driven by our integrated PROTAC® Discovery Engine

PROTAC® Discovery Engine

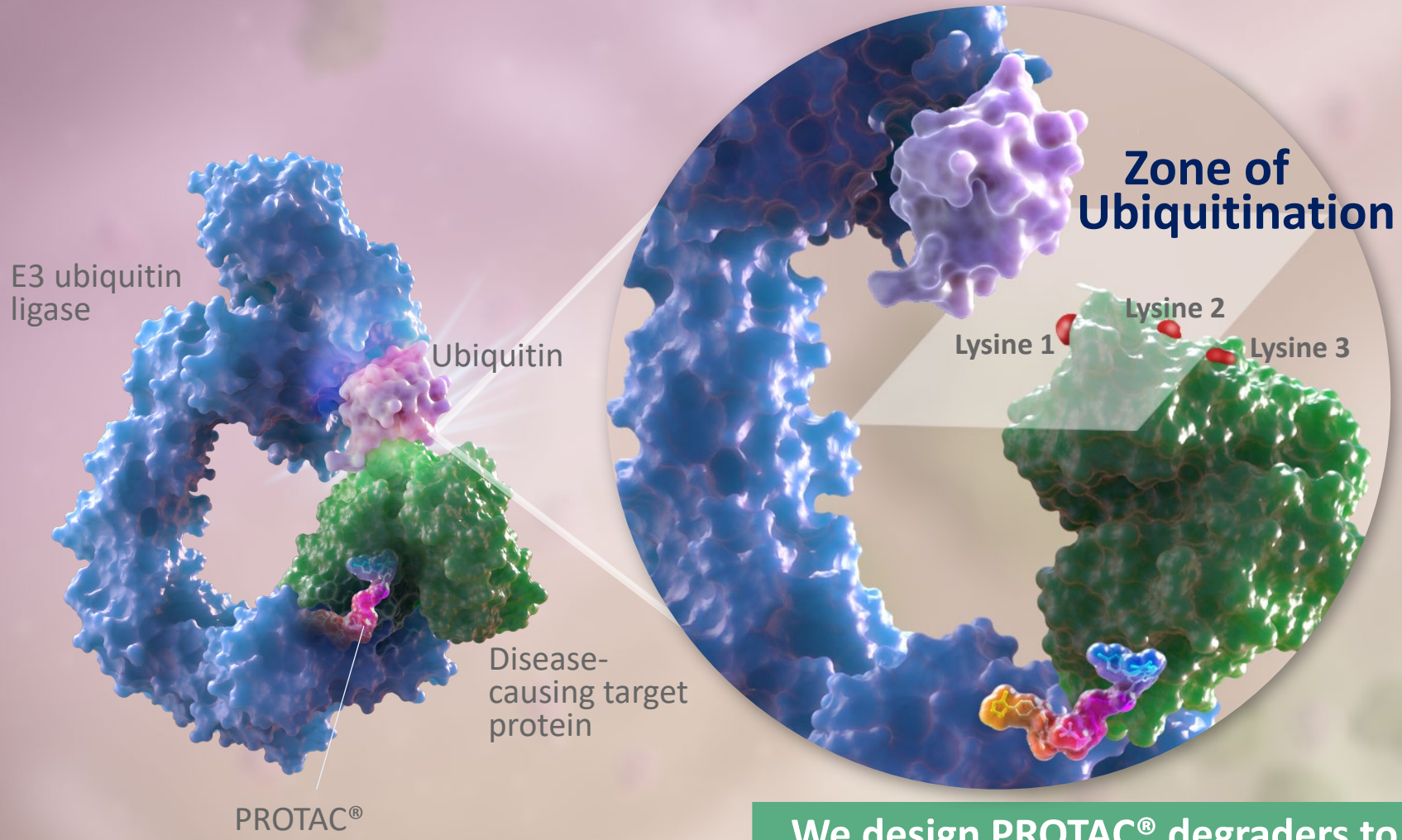
- E3 KnowledgeBASE of novel E3 ligases
- Novel warheads for undruggable targets and new ligands for E3 ligases
- Advanced screening capabilities, including proprietary DNA-encoded libraries tailored for PROTAC® development

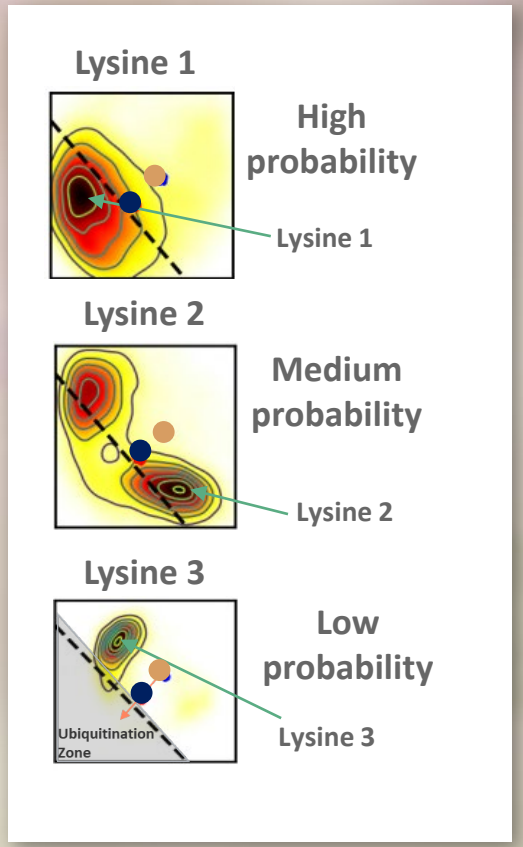
- Optimizing the Zone of Ubiquitination
- Arvinas Next Generation Linker Evolution (ANGLE)
- Predictive computational modeling
- State-of-the-art proteomics capabilities

- "Arvinas Rules" for drug-like properties, including blood-brain barrier penetration and oral bioavailability in humans
- Deep knowledge of *in vivo* PK/PD and efficacy relationships

Arvinas' platform is built from nearly 20 years of experience, know-how, and IP

Our deep understanding of the Zone of Ubiquitination informs the structure-based design of PROTAC® degraders





We design PROTAC® degraders to optimize the position of lysine residues within the Zone of Ubiquitination

Strategic partnerships expand the impact of our PROTAC® Discovery Engine

These partnerships expand PROTAC® degraders beyond oncology and beyond human therapeutics, while maintaining full ownership of our pipeline

Our fully-owned two clinical-stage PROTAC® protein degraders have the potential to address significant unmet need in advanced disease

ARV-110 (AR PROTAC®)

- **Targets the androgen receptor (AR), a highly validated driver of prostate cancer**
- **Early clinical proof-of-concept (safety, AR degradation, efficacy) demonstrated May 2020**
- **Fully-owned; US peak sales potential of $2-3B**

ARV-471 (ER PROTAC®)

- **Targets the estrogen receptor (ER), a highly validated driver of ER+/HER2- breast cancer**
- **Early clinical safety and pharmacokinetic data presented October 2019**
- **Fully-owned; US peak sales potential of $4-5B**

We are developing ARV-110 to be a potentially first- and best-in-class AR-targeted therapy for prostate cancer

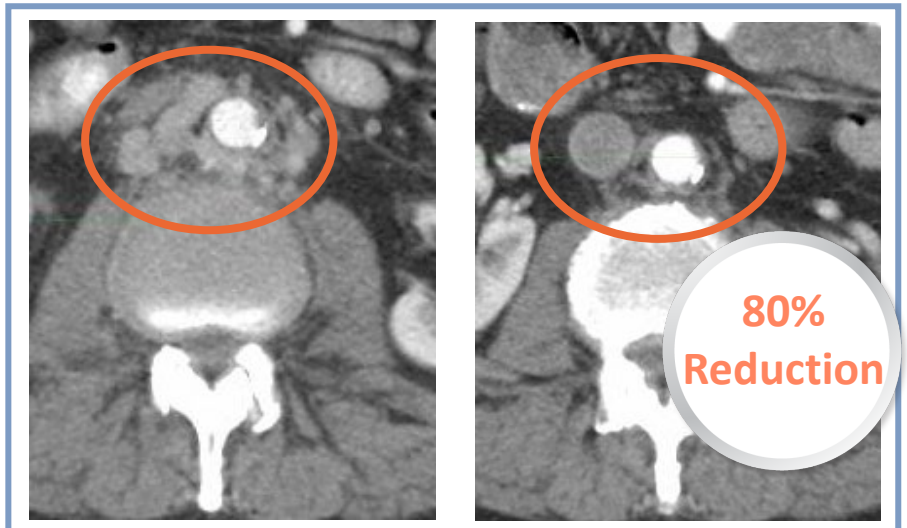
Clear initial efficacy signal in dose escalation, in the most advanced patient population tested with an AR-directed therapy

Safety profile acceptable for potential use in frontline settings

Exploring a fast-to-market, biomarker-driven strategy for accelerated approval in 2L+ mCRPC

Potential to address unmet patient need in 1L mCRPC and mCSPC (~45k patients)

RECIST Response Measurement



BASELINE
Extensive retroperitoneal adenopathy

AFTER 4 CYCLES
Near complete regression of adenopathy

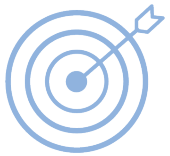
Next ARV-110 update anticipated Q4 2020

Note: Data presented at ASCO 2020 and as of 4/20/20. RECIST, response evaluation criteria in solid tumors; mCRPC, metastatic castration-resistant prostate cancer; mCSPC, metastatic castration-sensitive prostate cancer

ARV-471 is a potential first- and best-in-class ER degrader for ER+ locally advanced or metastatic breast cancer

Strong clinical profile[1]:

- Early evidence of ER degradation in the Phase 1 dose escalation
- No DLTs; dose escalation continues
- Dose-proportional pharmacokinetics



Superior ER degradation and tumor inhibition in preclinical studies

Fast-to-market strategy with potential indication in 2L+ ER+/HER2- mBC

Potential expansion to 1L ER+ breast cancer (~50k patients) in combination with CDK4/6i

Next ARV-471 update anticipated Q4 2020

[1]As of 5/29/2020.
DLT, dose-limiting toxicity

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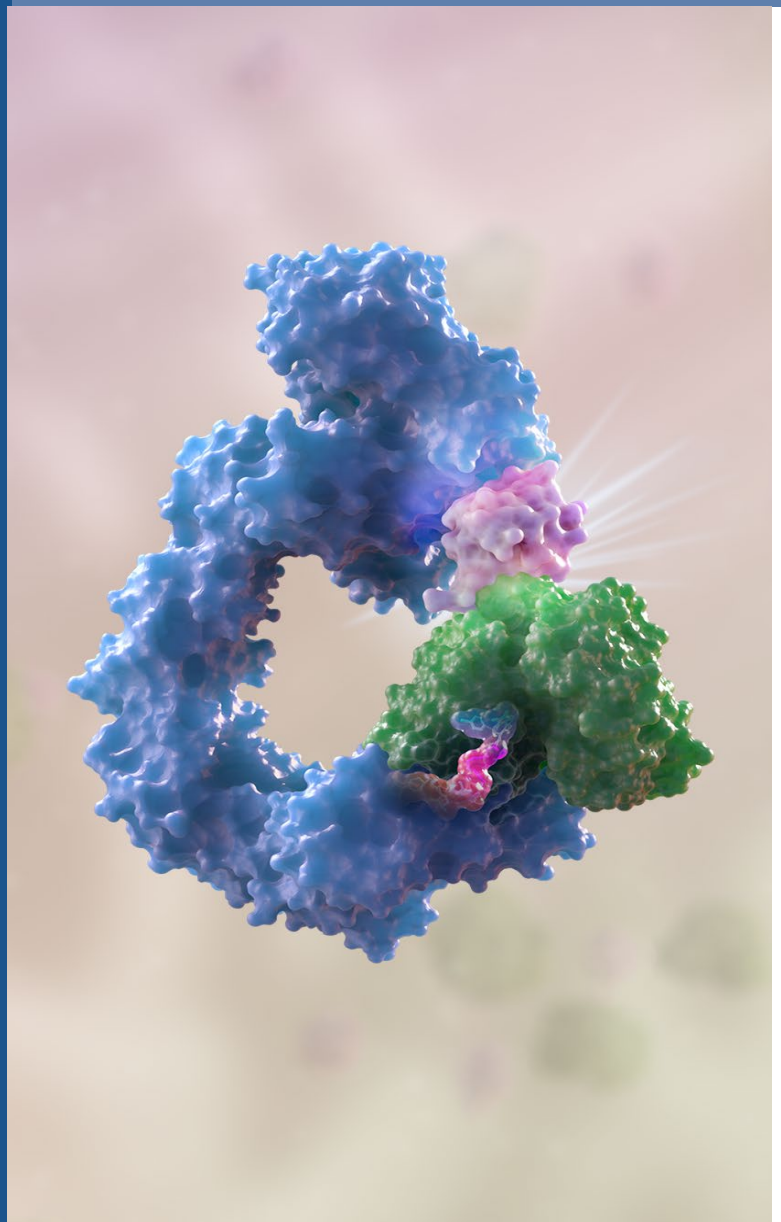
ARV-110 and ARV-471 have provided clinical proof-of-concept for PROTAC® degraders

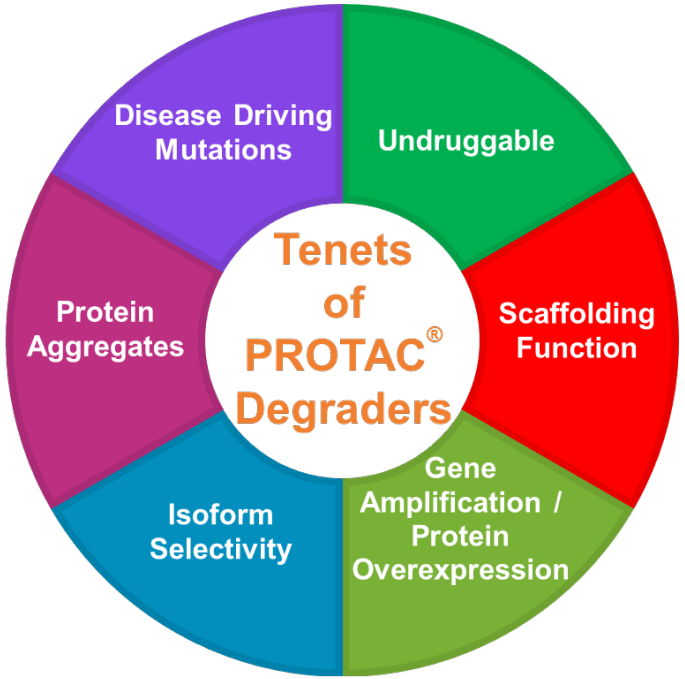


- ✓ Degradation of AR and ER demonstrates proof-of-mechanism in human patients
- ✓ Safety initially observed in two different programs in two different patient populations
- ✓ ARV-110 overcame prior resistance to AR therapy, showing the translation of ARV-110's preclinical profile into patient benefit
- ✓ Reinforces our confidence in Arvinas' extensive and promising preclinical pipeline

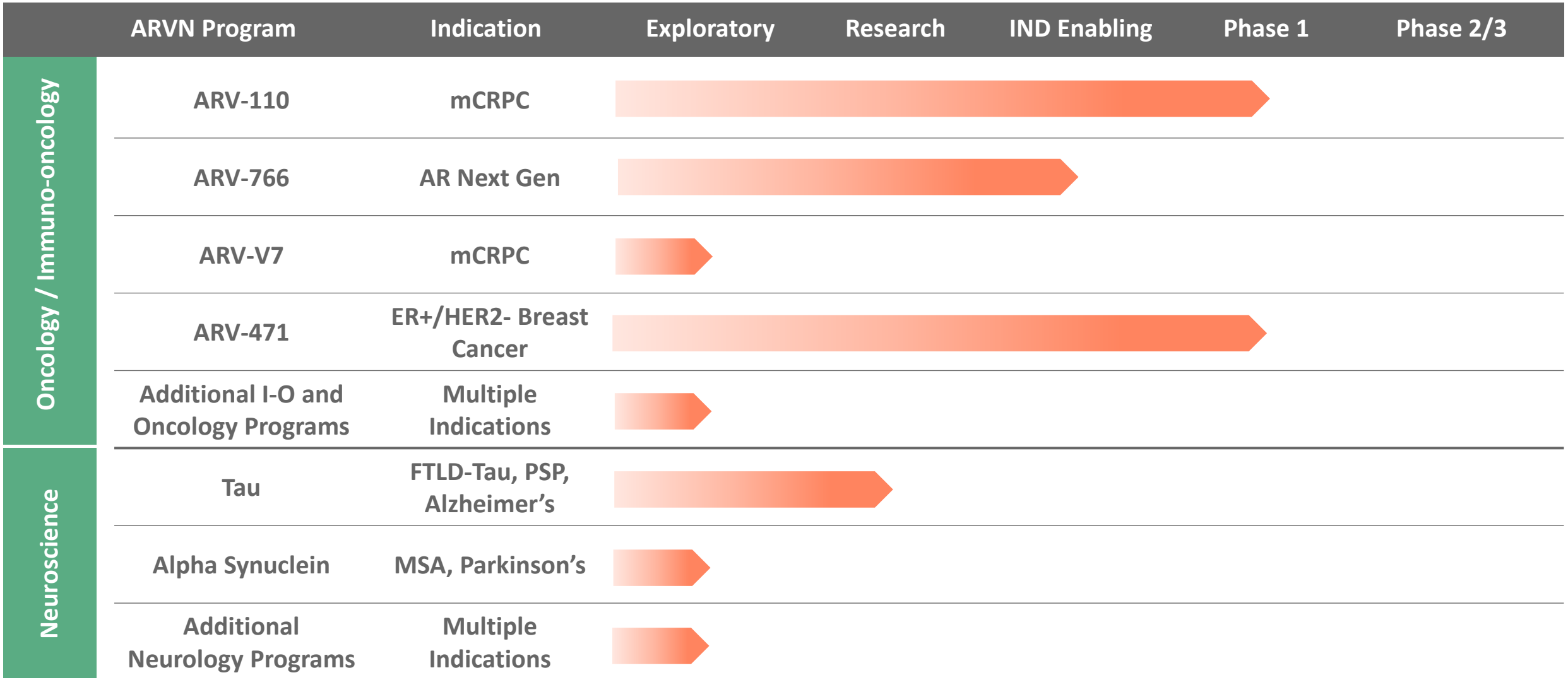
Our target selection strategy is designed to build the optimal portfolio of PROTAC® protein degraders

Guiding principles for our portfolio strategy

- **Focus on targets where degradation of the disease-causing protein will result in differential biology and patient outcomes versus other modalities**
- **Build on our established expertise and capabilities in oncology, immuno-oncology, and neuroscience**
- **Create a diversified, risk-balanced portfolio of validated and undruggable targets**



Our previously disclosed pipeline includes innovative therapies for oncology and neuroscience



Note: Pipeline is non-exhaustive. mCRPC, metastatic castration-resistant prostate cancer; ER+/HER2-, estrogen receptor+/human epidermal growth factor receptor 2-; FTLD-tau, frontotemporal lobar degeneration-tau; PSP, progressive supranuclear palsy; MSA, multiple systems atrophy

Today: Introducing five targets for which PROTAC® protein degraders have high potential to differentiate from other drug modalities

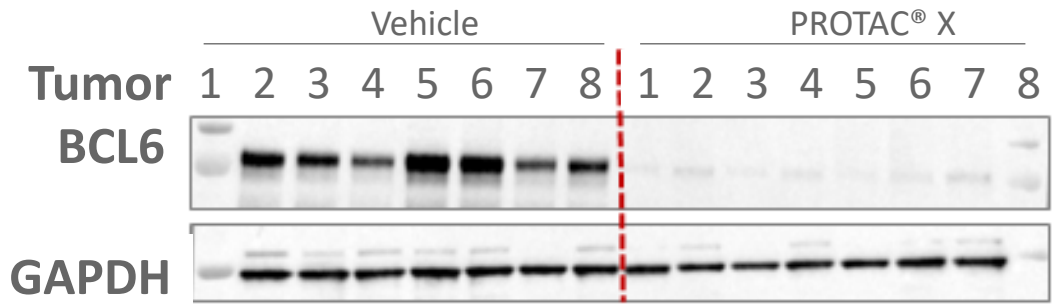
Target	Differential Biology Based on the Tenets of PROTAC® Degraders
BCL6 *Transcription factor implicated in B cell lymphomas*	Target scaffolding function of BCL6
KRAS *Oncogenic cell growth regulator*	Target "undruggable" KRAS mutants (e.g., G12V, G12D)
Myc *Oncogenic transcription factor driving tumor cell proliferation*	Directly degrade "undruggable" Myc vs. other indirect approaches
HPK1 *Suppressor of T cell activation; immuno-oncology target*	Address potential scaffolding function
mHTT *Key target for Huntington's disease*	Selectively degrade mutant huntingtin (mHTT) protein

Arvinas' BCL6 program is aiming for an oral, best-in-class targeted therapy for B-cell malignancies

BCL6

- Most B cell lymphomas are dependent on constitutive or deregulated expression of BCL6, a transcriptional repressor of:
  - Cell cycle checkpoints
  - Terminal differentiation
  - Apoptosis
  - DNA damage response
- **PROTAC® degradation would address the scaffolding function of BCL6**

After oral dosing, PROTAC® X achieved ≥95% degradation of BCL6 *in vivo*



Farage DLBCL xenograft model

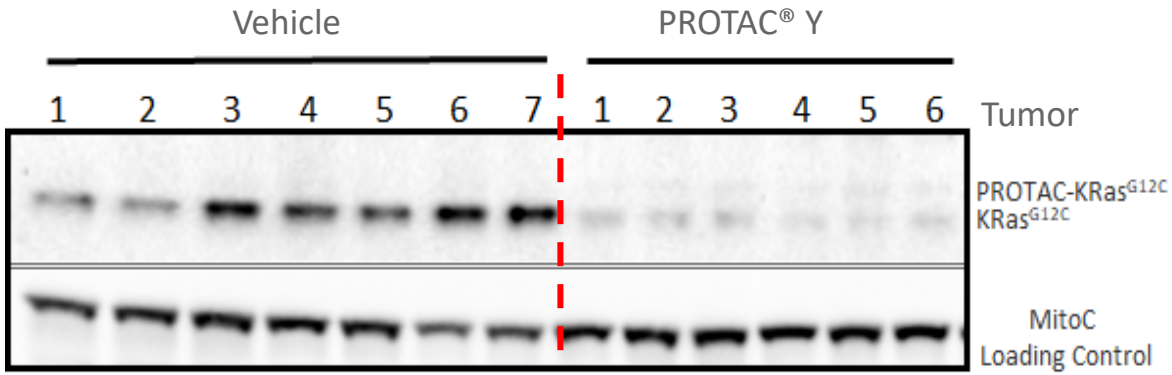
Optimizing* in vivo *tumor growth inhibition activity and selecting a candidate to take forward with anticipated IND in 2022

We are taking a comprehensive approach to degrading KRAS

KRAS

- KRAS is the most frequently mutated gene in human cancer and is a classic "undruggable" target due to its lack of deep "pockets"
- We are creating pan-KRAS mutant, in addition to mutant-specific (e.g., G12D and G12V), degraders
- **As a proof of concept, we have successfully developed *in vivo* active KRAS G12C-specific PROTAC® degraders**

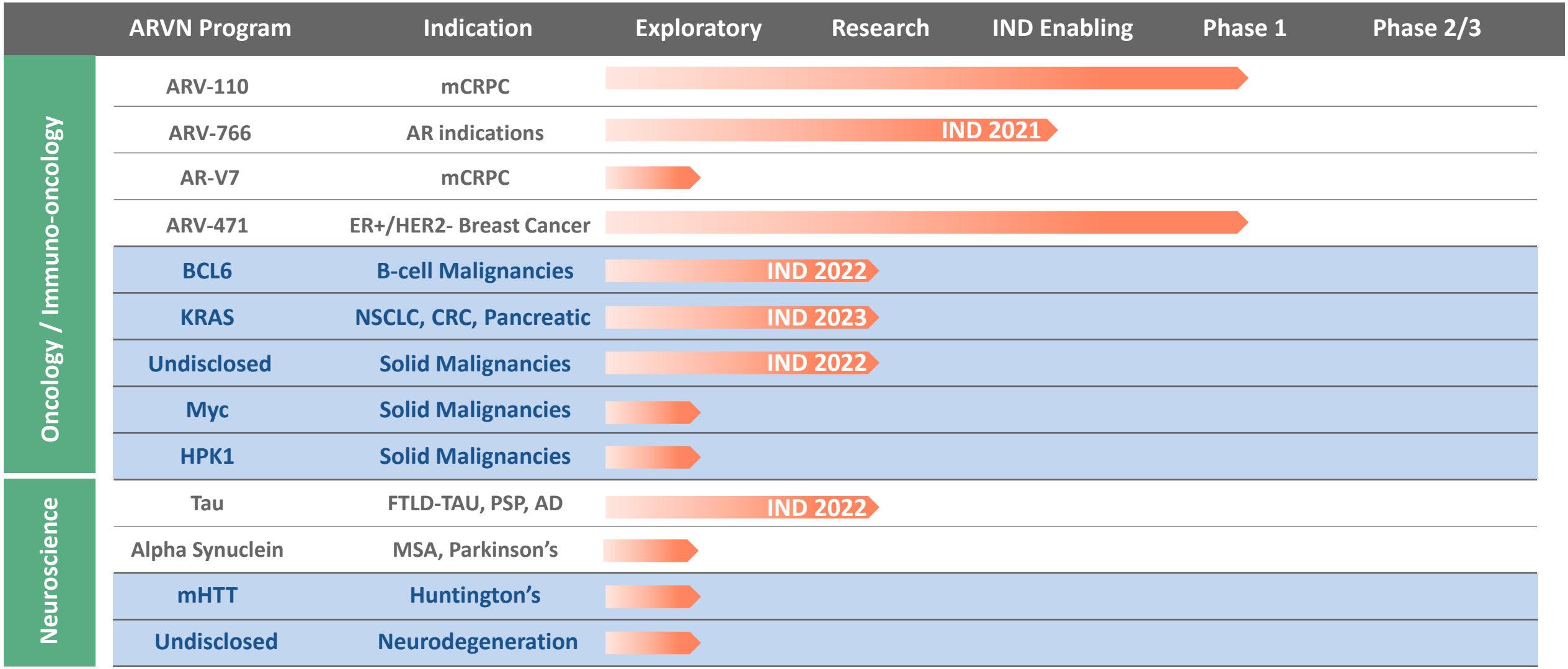
Six hours after a single dose, PROTAC® Y degraded >80% of KRAS G12C *in vivo*



MiaPaCa-2 xenograft model

Leveraging learnings from KRAS G12C development to accelerate other KRAS degraders' development with anticipated IND in 2023

Arvinas' current pipeline encompasses a range of validated and undruggable targets in oncology, I-O, and neuroscience



Note: Pipeline is non-exhaustive and IND dates are anticipated. mCRPC, metastatic castration-resistant prostate cancer; ER+/HER2-, estrogen receptor+/human epidermal growth factor receptor 2-; NSCLC, non-small-cell lung carcinoma; CRC, colorectal cancer; FTLD-tau, frontotemporal lobar degeneration-tau; PSP, progressive supranuclear palsy; MSA, multiple systems atrophy

Programs introduced today

ARVINAS

Over the next two years, we anticipate a rapid pace of milestones

	2020 Q4	2021	2022
ARV-110 (mCRPC)	• Program update • Initiation of Phase 2	• Completed Phase 1 data • Phase 2 interim data • Initiation of combination study	• Full Phase 2 data • Combination study data
ARV-471 (ER+/HER2- breast cancer)	• Interim Phase 1 data • Initiation of combination study with CDK4/6i	• Completed Phase 1 data • Initiation of Phase 2 • CDK4/6i combination study data	• Interim Phase 2 data
ARV-766 (AR PROTAC®)		• Initiate Phase 1	• Phase 1 data • Initiate Phase 2
INDs		• ARV-766	• BCL6 • Undisclosed (oncology) • Tau

Note: mCRPC, metastatic castration-resistant prostate cancer; ER+/HER2-, estrogen receptor+/human epidermal growth factor receptor 2-

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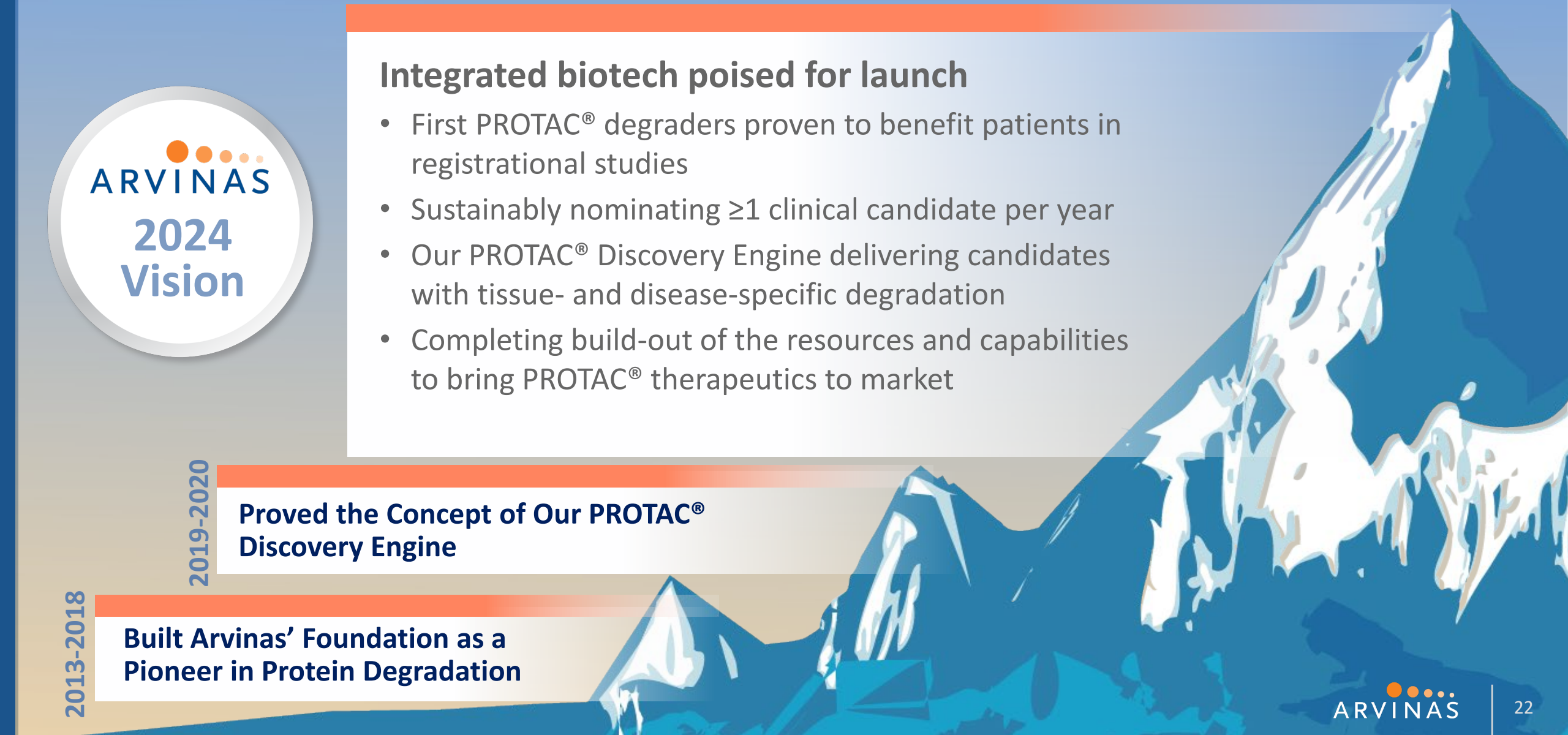
Arvinas' 2024 Vision: Ascending to new heights in bringing the benefits of PROTAC® degraders to patients

ARVINAS
2024 Vision

Integrated biotech poised for launch

- First PROTAC® degraders proven to benefit patients in registrational studies
- Sustainably nominating ≥1 clinical candidate per year
- Our PROTAC® Discovery Engine delivering candidates with tissue- and disease-specific degradation
- Completing build-out of the resources and capabilities to bring PROTAC® therapeutics to market



2019-2020

Proved the Concept of Our PROTAC® Discovery Engine

2013-2018

Built Arvinas' Foundation as a Pioneer in Protein Degradation

Thank You!