# Degraders on Target: Evaluating the potential of this novel drug class

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## ABSTRACT

Targeted protein degradation (TPD) is a rapidly emerging technology, enabling the selective elimination of previously inaccessible proteins. A growing array of modalities—including heterobifunctional degraders, molecular glues, antibody-based degraders, and lysosome-targeting agents—are being developed to exploit this mechanism. This systematic review of literature, patents, clinical trials, and specialist databases will evaluate the selectivity, safety, and efficacy of TPDs and their targets.

## RESULTS

**Landscape of TPDs and their degradation Targets (FIGURE 1 and FIGURE 2)**

- 2,320 patents and 2,611 literature articles detailed development of degraders
- 623 TPDs were identified from preclinical to pre-registration with 71 degraders currently in clinical development
- Proteolysis targeting chimeras (PROTACs) are the most common (476) technology being developed for removal of proteins, but other degraders are being investigated such as DACs (11), AUTACs (9), RIBOTACs (7), SNIPERs (4), and TRAFTACs (1)
- The top 5 targets of clinical stage degraders are: androgen receptor (11 drugs), IKAROS (10 drugs), BTK(9 drugs), GSPT1 (6 drugs), and estrogen receptor (5 drugs)

**BTK degrader Efficacy and Safety (FIGURE 3 and FIGURE 4)**

- Reported values for BTK degradation induction have had similar orders of magnitude between wildtype and mutant forms, but more data is needed.
- BTK and cereblon Inhibitors share many similar yet distinct safety concerns
- Reported adverse events for BTK degraders are similar to those for BTK inhibitors, but certain events, like hepatobiliary disorders, have not been associated degraders yet.

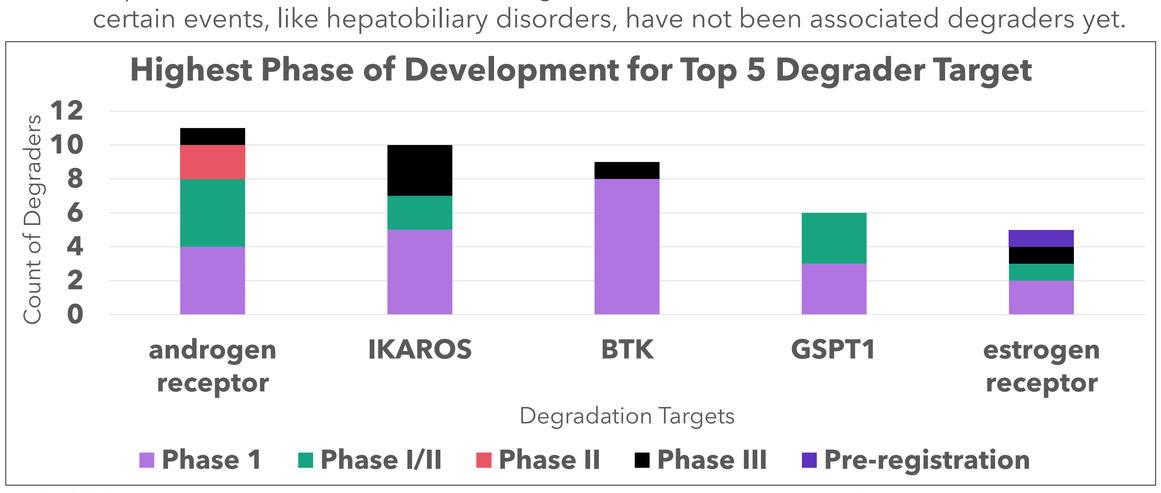


FIGURE 2: Highest phase of development for clinical stage degraders. Only the 5 degrader targets with the most development are represented in the graph. Source: Cortellis Drug Discovery Intelligence

## METHODS

Meta-analysis of TPDs in development from pre-clinical to pre-registration using Cortellis Drug Discovery Intelligence (CDDI) and OFF-X Safety Intelligence. CDDI incorporates information from journals, conferences, patents, press releases, regulatory agencies and company websites on the scientific development of drugs and targets from biological testing to launch. OFF-X monitors all adverse events (AEs) from pre-clinical, clinical and post-marketing studies from regulatory agencies, biomedical literature, congresses and scientific conferences, major clinical trial registries, company communications and Pharmacovigilance databases (i.e. FAERS, JADER). To investigate the potential of degraders as an alternative technology for target modulation, these databases were used to compare the safety and efficacy of BTK inhibitors and degraders.

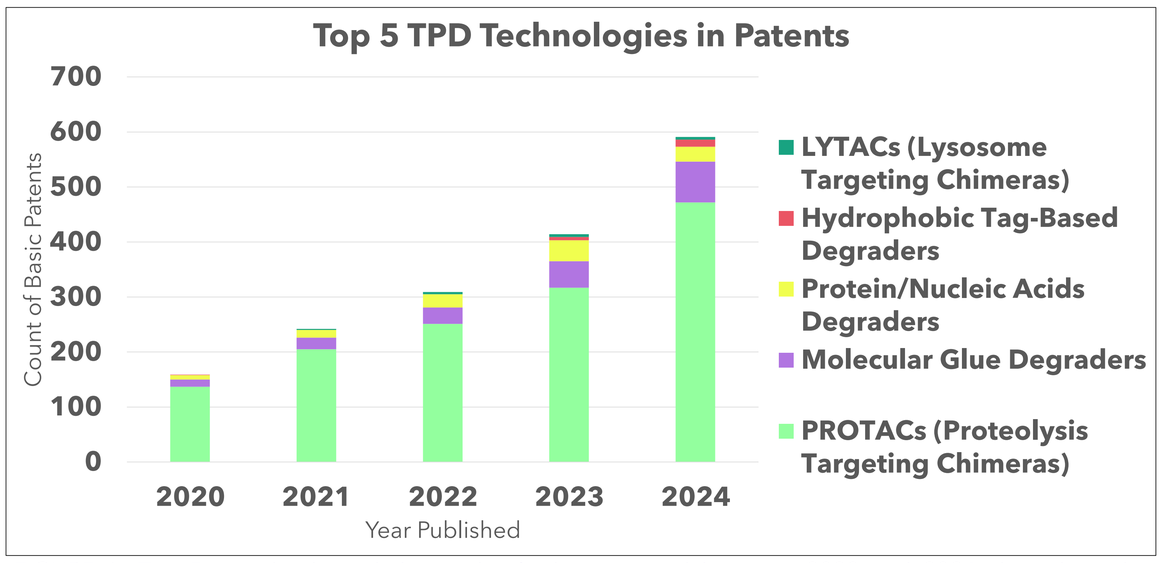


FIGURE 1: Top 5 protein degradation technologies patented between 2020 and 2024 based on the number of basic patents published. Source: Cortellis Drug Discovery Intelligence

| | BTK degradation | BTK (C481S-mutated) degradation |
|---|---|---|
| **zelebrudomide** | 0.019 μM (n=9) | 0.028 μM (n=6) |
| **TQB-3019** | 0.0001 μM (n=1) | None Reported |
| **HZ-Q-1070** | 0.101 μM (n=4) | < 0.001 μM (n=1) |
| **BGB-16673** | 0.0007 μM (n=1) | 0.001 μM (n=1) |
| **bexobrutideg** | 0.000176 μM (n=8) | $605x10^{-6}$ μM (n=2) |

FIGURE 3: EC50 values of BTK degradation induction for the BTK degraders in clinical development. Values in paratheses (n=#) are the count values reported. When more than one value was reported, the mean was shown. Source: Cortellis Drug Discovery Intelligence

| Adverse Events | Target Safety | | | BTK Inhibitors | | | | | BTK Degraders | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | BTK Inhibitors | Cereblon Inhibitors | BTK Degraders | ibrutinib Launched 2013 | acalabrutinib Launched 2017 | pirtobrutinib Launched 2023 | tirabrutinib Launched 2020 | zanubrutinib Launched 2019 | BGB-16673 Phase III | zelebrudomide Phase I | bexobrutideg Phase I |
| **Vascular disorders** | 1180 | 229 | 14 | 568 | 266 | 108 | 24 | 242 | 9 | 3 | 2 |
| **Infections and infestations** | 3089 | 477 | 42 | 1198 | 650 | 106 | 128 | 650 | 26 | 3 | 13 |
| **Cardiac disorders** | 2001 | 199 | 8 | 1140 | 523 | 70 | 7 | 376 | 2 | 5 | |
| **Gastrointestinal disorders** | 1836 | 487 | 16 | 637 | 344 | 103 | 109 | 309 | 7 | 5 | 4 |
| **Blood and lymphatic system disorders** | 1676 | 612 | 41 | 634 | 330 | 103 | 113 | 382 | 13 | 11 | 16 |
| **Skin and subcutaneous tissue disorders** | 1147 | 384 | 29 | 412 | 144 | 88 | 125 | 258 | 6 | 5 | 18 |
| **Nervous system disorders** | 877 | 536 | 13 | 291 | 236 | 26 | 48 | 113 | 5 | 4 | 4 |
| **Musculoskeletal and connective tissue disorders** | 834 | 171 | 5 | 360 | 173 | 51 | 30 | 177 | 3 | 2 | |
| **Injury, poisoning and procedural complications** | 741 | 121 | 26 | 238 | 166 | 57 | 24 | 224 | 13 | 3 | 9 |
| **Hepatobiliary disorders** | 162 | 65 | 1 | 63 | 31 | 6 | 17 | 17 | | | |
| **Investigations** | 1297 | 379 | 24 | 264 | 165 | 70 | 137 | 260 | 12 | 4 | 6 |
| **General disorders and administration site conditions** | 1176 | 368 | 17 | 508 | 232 | 80 | 45 | 213 | 11 | 3 | 3 |
| **Respiratory, thoracic and mediastinal disorders** | 759 | 269 | 7 | 273 | 168 | 58 | 39 | 162 | 1 | 2 | 3 |
| **Neoplasms benign, malignant and unspecified** | 644 | 254 | 2 | 194 | 216 | 15 | 3 | 228 | 2 | | |
| **Metabolism and nutrition disorders** | 437 | 225 | 2 | 158 | 67 | 23 | 33 | 74 | | | 2 |
| **Renal and urinary disorders** | 241 | 73 | 1 | 80 | 52 | 8 | 9 | 71 | 1 | | |
| **Congenital, familial and genetic disorders** | 63 | 194 | 1 | 14 | 4 | 8 | 4 | 6 | | | |
| **Immune system disorders** | 60 | 65 | | 29 | 11 | 1 | 5 | 3 | | | |

FIGURE 4: Publications reporting safety findings for 3 target/classes, 5 launched BTK inhibitors, and 3 BTK degraders. Adverse events shown had a medium to very high target/class score for BTK inhibitors. OFF-X target/class and drug scores are the result of a rules based algorithm that classifies the estimated strength of evidence supporting a class of drugs (same mechanism of action) to adverse event or a drug to adverse event association. Safety alerts are reported adverse events in preclinical, clinical, and real-world evidence studies. Source: OFF-X Translational Safety Intelligence

**Heat map based on OFF-X Target/Class or Drug Score:**
Very high
High
Medium
Low
Very low
Not associated

## DISCUSSION

This analysis highlights the accelerating momentum behind targeted protein degradation as a therapeutic strategy and the novel new approaches being explored. Patent activity and scientific publications have more than doubled since 2016, reflecting growing interest and investment in this modality. PROTACs are the most prevalent technology being developed, but new approaches are exploring novel targets like transcription factors and RNA or degradation pathways like autophagy and lysosomal pathways. Most of the novel degrader technologies are still being explored in the pre-clinical setting, but some, like degrader-antibody conjugates and LYTACs, are entering clinical testing.

Several high-value targets—such as Androgen receptor, IKAROS, and BTK—are currently in clinical development, underscoring the relevance of degraders in addressing diseases with significant unmet medical needs. BTK inhibitors are well known for the treatment of many B-cell related cancers and being tested in autoimmune diseases. While successful in treating these diseases, they are also known for specificity issues and related safety concerns. Targeted BTK degradation seeks to avoid issues with (1) off target inhibition and (2) the development of common resistance mutations in BTK that make many inhibitors ineffective. Pre-clinical efficacy testing points towards BTK degraders being nearly as effective on wildtype BTK as with common resistance mutants. Comparing safety profiles, BTK inhibitors and degraders share similar events such as neutropenia, hemorrhaging, and risk of infection, but so far BTK degraders have not displayed the same risks of hepatobiliary disorders. BGB-16673 is the furthest BTK degrader in development, having published positive efficacy and safety data from its phase 1 trial, but further late-stage clinical studies will be needed to have a clear picture of the clinical efficacy and safety.

Overall, the findings support the potential of degraders to offer a fundamentally distinct mechanism of action by eliminating pathogenic proteins, positioning them as a transformative drug class and highlighting its potential to reshape future treatment paradigms.


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