KerrisdaleCapital

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Principia Biopharma Inc. (PRNB)

A TKO for BTK

We are short shares of Principia Biopharma, a company whose $2 billion valuation rests on a single obscure molecule known as Bruton's tyrosine kinase (BTK). Named after a pediatrician who discovered an immunodeficiency later found to be caused by a defective mutant form of the molecule, BTK plays an important role in conveying certain signals inside B cells, the part of the immune system charged with fighting off infection by producing antibodies. Drugs that inhibit the activity of BTK have enjoyed great success treating B-cell–driven cancers; Principia now hopes to use the same approach to treat autoimmune diseases caused by errant B cells that turn on their own hosts. After a large day-one pop following its IPO in September 2018, Principia's stock price didn't do much for a year, closely tracking the overall biotech sector. In the past few months, though, it has nearly doubled, driven by a murky combination of new clinical data, excitement over recent industry M&A, and anticipation of results from a Phase 2 multiple-sclerosis trial that are expected to be released within the next couple of months.

There's just one problem: Principia's drugs don't work. While the company touts the results of its Phase 2 trials in the autoimmune diseases pemphigus and immune thrombocytopenia, those small trials included no placebo groups and allowed patients to continue taking other medications that are known to be effective in treating their conditions. Examined with this massive confounding factor in mind, Principia's BTK inhibitors appear to add no value to the traditional standard of care and to pale in comparison to newer therapies. With no intrinsic value beyond the cash on its balance sheet, Principia has more than 80% downside.

This lack of efficacy fits in perfectly with the overall history of BTK inhibitors: while they work well in some B-cell malignancies, they have repeatedly fallen short in multiple different autoimmune diseases across many years – a fact that seems poorly appreciated, in part because the results of several different disappointing trials were never officially published. Based on the scientific literature, we believe the reason BTK inhibitors fail in autoimmune disease is because their main effect is to prevent the development and proliferation of new B-cell lines – while leaving *existing* B-cell populations largely unscathed. But the problem in autoimmunity lies precisely in the established subsets of misbehaving cells; new cell lines are irrelevant. Thus we believe Principia's approach is doomed to fail. Indeed, it may even be dangerous: by halting the birth of new B cells, BTK inhibitors narrow the range of novel pathogens that patients can effectively combat, leaving them open to opportunistic infections – a problem that has in some cases proven fatal for patients using drugs like Principia's.

Principia shares a name with Isaac Newton's groundbreaking work, the *Principia* (full title: *Philosophiæ Naturalis Principia Mathematica*), which set out, among other things, the law of universal gravitation. But we think a humbler statement of gravity's law is a better fit for *this* Principia: what goes up must come down.

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Executive Summary

Principia's placebo-less clinical results are weak. In pemphigus, Principia can't hold a candle to the B-cell–depleting therapy rituximab, recently approved for use in the disease and now regarded as the "gold standard." While rituximab can, over time, achieve a 90% complete-remission rate with no need for ongoing corticosteroid use, we estimate that patients on Principia's PRN1008 only managed an 11% complete-remission rate (recalculated using standard analyses rather than Principia's self-serving adjustments) *while still taking low doses of corticosteroids,* which are themselves clearly effective in pemphigus, though less so than rituximab. Meanwhile, the modest decrease in pathogenic antibodies experienced by patients on PRN1008 plus corticosteroids – at doses that Principia dubs "low" but are, by typical standards in this therapeutic area, more like "medium" – was dramatically smaller than that seen with the old corticosteroid-only standard of care. In short, PRN1008 appears to add no value in the relatively mild pemphigus cases in which it has been tried; improvements in patient health can easily be explained by their ongoing use of corticosteroids.

The situation is similar in immune thrombocytopenia ("ITP"). Many effective drugs are already available to treat the condition, with several more on the way. While Principia suggests that its drug boosts platelet counts in ITP patients, the modest and often transient increases observed are again easily explained by the fact that more than two thirds of these patients were also taking other drugs, like thrombopoietin-receptor agonists and corticosteroids, that are effective treatments in their own right. Meanwhile, PRN1008 patients appeared to experience no overall improvement in bleeding (the major problematic symptom of ITP), and 10% actually suffered from bleeding-related serious adverse events requiring hospitalization. In fact, based on the track record of other BTK inhibitors across large numbers of patients, we worry that Principia's drug could actually *cause* bleeding and thrombocytopenia, not treat them.

BTK inhibitors don't work in autoimmune disease. Companies like Celgene, AstraZeneca, and Gilead have tried over and over to use BTK inhibitors to treat autoimmune diseases like rheumatoid arthritis (an early target of Principia's), lupus, and Sjögren's syndrome – but the results have always been unimpressive. We contend that this track record of failure is a direct consequence of the biology of BTK: rather than having a broad *in vivo* effect on B-cell functioning, it primarily does something narrower: facilitate the early-stage development of new B-cell lines. This explains both the success of BTK inhibition in diseases characterized by excessive proliferation of immature B cells and the failure of BTK inhibition in diseases characterized by established populations of misbehaving mature B cells. Indeed, BTK inhibitors don't even block all of BTK's effects: while they do suppress the molecule's enzymatic activity, they leave untouched its effects as a docking site for other intracellular proteins.

Multiple-sclerosis: don't believe the hype. Recent buzz about upcoming multiple-sclerosis data for the Principia/Sanofi drug SAR442168 is a red herring. As with Principia's other trials to date, this one also lacks a clean, straightforward placebo group and fails to include true clinical endpoints (like disability progression) that measure patient health, as opposed to surrogate endpoints (like MRI-based measures). Any data are bound to be noisy and inconclusive.

Besides, the world of multiple-sclerosis treatment has recently been shaken up by the rise of ocrelizumab, a close cousin of rituximab that has achieved dramatic results in clinical trials, leaving little room for BTK inhibitors. We expect that same pattern to prevail in multiple sclerosis as in other autoimmune conditions: while true B-cell–depleting therapies have a significant positive impact by killing off the established populations of "bad" cells that cause the conditions, BTK inhibitors have no impact because they primarily affect unrelated fledgling cells.

BTK inhibitors pose troubling health risks. While it's tempting to regard Principia's drugs as equivalent to placebos in the setting of autoimmune disease, they may actually be worse than placebos because of potentially serious on-target side effects. By stopping the growth and evolution of patients' immune repertoires, BTK inhibitors foster greater susceptibility to dangerous infections – a known risk of drugs like ibrutinib and its next-generation successors. Though Principia's BTK inhibitors have thus far only been used by a small number of patients for short periods of time, there are already signs of trouble, with several instances of infection, including at least one severe case requiring hospitalization. As patient experience accumulates, we expect the risks to become more stark. Thus, not only are Principia's BTK inhibitors ineffective; they may also be unsafe.

Company Overview

Principia Biopharma: Capitalization and Finances	
Share price ($)	$57.21
Fully diluted shares (mm):	
Shares outstanding	32.8
Dilutive impact of options	2.8
Total	35.6
($mm)	
Fully diluted market cap	$ 2,035
Cash & securities*	388
Run-rate operating expenses†	90
Cash & securities per share*	$ 10.90
% downside	-81%

Source: company filings, Kerrisdale analysis
**Pro forma for Oct 2019 equity offering.*
†First three quarters of 2019 annualized.

Spun out of a UC San Francisco chemistry lab, Principia raised its initial round of funding in 2011, aiming from the start at treating autoimmune and inflammatory diseases using small-molecule drugs that interact with their targets in a particular way: by forming strong, covalent chemical bonds that are nonetheless reversible, not permanent. Most drugs don't form covalent bonds with their targets, while those that do, including the groundbreaking BTK inhibitor ibrutinib, bind irreversibly; Principia's lead drug, PRN1008 (also called rilzabrutinib), binds covalently but in such a way that the bond is readily breakable under the right conditions. (Principia's other main drug, a BTK inhibitor engineered for use in multiple sclerosis, binds irreversibly and thus is less distinguished from other BTK inhibitors.)

Hoping that this reversible covalent property would make its drugs highly potent yet safe for long-term use, Principia initiated Phase 2 clinical trials in two rare autoimmune diseases, pemphigus and immune thrombocytopenia, and went public in September 2018 at a price of $17 per share. Meanwhile, the company formed two partnerships with big pharma companies. First, in June 2017, it announced a deal with AbbVie for R&D on inhibitors of the immunoproteasome (a molecular mechanism inside immune cells that breaks down proteins) – but in March 2019 AbbVie pulled out of the deal. Then, in November 2017, Principia licensed its irreversible BTK inhibitor, intended for the treatment of multiple sclerosis, to Sanofi for an upfront payment of $40 million plus a future stream of potential milestone payments and royalties. With the suspicious collapse of the AbbVie immunoproteasome deal and the recent

suspension of the company's longstanding oncology program[1] (attributed to "market dynamics and portfolio refocus" but likely related, in our view, to weak Phase 1 results[2]), Principia has become almost entirely a bet on the use of BTK inhibitors in autoimmune diseases.

Before discussing this bet in further depth, it's worth explaining what makes Principia different from ArQule, the BTK-inhibitor company acquired by Merck for $2.7 billion in December. Many different companies have developed copycat covalent BTK inhibitors over the years, following in the footsteps of ibrutinib, but ArQule focused on solving a problem created by ibrutinib's very success: mutation. Covalent BTK inhibitors, including Principia's drugs as well as ibrutinib, bind to a particular cysteine amino acid that forms part of the larger BTK protein. But a common mode of ibrutinib resistance is for cancer cells to evolve to substitute a different amino acid, serine, for that crucial cysteine; this swap makes it impossible for covalent BTK inhibitors to attach themselves to the mutant BTK. By contrast, ArQule's BTK inhibitor binds non-covalently in a manner that is indifferent to the presence or absence of cysteine at that precise location, enabling it to successfully treat patients for whom ibrutinib stopped working.

In short, ArQule's value is all about treating B-cell malignancies that can't be addressed by conventional BTK inhibitors. Principia's approach is irrelevant in this area because, despite the wrinkle of forming "reversible" covalent bonds as opposed to typical covalent bonds, it still needs a cysteine residue to work. The features that made ArQule attractive simply don't apply to Principia. Indeed, for all the pride the company takes in its unique chemistry, the real-world benefits are hard to discern: Principia's clinical results to date have been thoroughly unimpressive.

Principia's Placebo-Less Clinical Results Are Weak

Pemphigus

Pemphigus is a rare autoimmune skin disease thought to result when a patient's own immune system produces antibodies targeting desmogleins 1 and 3 (DSG1 and DSG3), proteins that help skin cells bind together; this results in painful blistering across the body. In its investor presentation (slide 10), Principia says that the current "standard of care" for pemphigus is "high-dose [corticosteroids] (60-90 mg/day), with high toxicity; Rituxan; other immunosuppressants." The company goes on to argue that, based on data from a single-arm (placebo-less), Phase 2 clinical trial, its BTK inhibitor PRN1008/rilzabrutinib leads to good patient outcomes despite "no/low corticosteroids," drugs with known efficacy in pemphigus but many dangerous and unpleasant side effects.

[1] See Principia investor presentation, slide 3 ("PRN1371 FGFR program suspended due to market dynamics and portfolio refocus").
[2] Principia's May 2019 data presentation showed that its FGFR inhibitor seemed to have no meaningful benefit across 36 patients with various forms of cancer: most saw lesions grow, few saw them shrank, and only 30% achieved "stable disease," let alone a clinical response.

We believe Principia is burying the lede – downplaying the availability of effective therapy to make its own drug look better by contrast. While it mentions Rituxan (rituximab) in passing, here we present passages from Roche's June 2018 press release announcing the FDA's approval of Rituxan for pemphigus vulgaris (the most common form of the disease) (emphasis added):

> Rituxan is the first FDA-approved treatment for moderate to severe pemphigus vulgaris (PV) in more than 60 years…
>
> The FDA approval is based on data from the Ritux 3 trial, a Roche-supported, randomized, controlled trial conducted in France…The study compared the Ritux 3 regimen (EU-approved rituximab product plus short-term corticosteroids [CS]) to CS alone as a first-line treatment in patients with newly diagnosed moderate to severe pemphigus. The primary endpoint of the study was complete remission at month 24 without the use of steroids for two or more months. **Results of the study showed that 90 percent of PV patients treated with the Ritux 3 regimen met the endpoint,** compared to 28 percent of PV patients treated with CS alone.

This is what Principia is going up against: a recently FDA-approved therapy with a proven 90% success rate, with "success" defined in strict terms as complete remission in the absence of ongoing corticosteroid use (not the loose, permissive "no/low corticosteroids" standard applied by Principia, to which we will return).

This is not just Roche propaganda. A 2017 article in the *Journal of Clinical and Diagnostic Research,* written by independent physicians who ran their own rituximab study in India, was entitled "Rituximab: A Magic Bullet for Pemphigus" (1); another piece, co-written in 2017 by the lead principal investigator of Principia's Phase 2 pemphigus trial,[3] was entitled "Rituximab and short-course prednisone as the **new gold standard** for new-onset pemphigus vulgaris and pemphigus foliaceus" (2) (emphasis added). In a recent continuing-medical-education video aimed at dermatologists and other healthcare providers "involved in the management of patients with autoimmune diseases," Dr. Erin Wei, director of the Bullous Disease Clinic at the Harvard-affiliated Brigham and Women's Hospital in Boston, called giving rituximab early on to pemphigus patients "really a no brainer," adding that "most experts offer rituximab as a first-line treatment option" and that she and her colleagues "consider it as first line in nearly all patients…Only a very small minority of patients don't respond completely." While pemphigus patients initially treated with rituximab do sometimes relapse, both the landmark study that led to FDA approval and other recent research suggests that repeat infusions of rituximab every 6 to 12 months are effective at keeping the disease at bay in the long run, even without ongoing corticosteroids (3). (While rituximab is administered as an infrequent intravenous infusion, Principia's Phase 3 pemphigus trial design requires patients to take PRN1008 twice a day, every day.)

[3] See Nov 29, 2018, Principia press release: "Dr. Dedee Murrell…the lead principal investigator."

With the striking efficacy of rituximab in mind, let's examine the Phase 2 results that Principia has presented for PRN1008 in pemphigus.[4] With 27 patients enrolled, all taking PRN1008 plus what Principia calls "low-dose corticosteroids" (at or below 0.5 milligrams per kilogram of body weight (mg/kg) per day) for a 12-week treatment period, 54% achieved "control of disease activity" (defined primarily as the cessation of new lesion formation) by week 4, and 17% achieved "complete remission" by week 12. (Note that Principia slightly inflates its results by excluding patients who dropped out of the trial because of adverse events, even if they were found to be treatment-emergent. Including these patients in the denominator – which seems fair, since the combination of PRN1008 and "low-dose" corticosteroids clearly didn't help the patients who dropped out – reduces the CDA rate to 52% and the "complete remission" rate to 15%.[5])

Even when one takes these results at face value, it's difficult to find them impressive. Who cares about a 15-17% rate of "complete remission" among patients still on corticosteroids when rituximab can deliver a 90% rate of complete remission that *doesn't* require corticosteroids? To be fair, rituximab takes months to achieve its effects, but surely patients covered in painful blisters want to cure their condition and stop taking corticosteroids, not merely "control" the disease.

But Principia's results should not be taken at face value. We believe that the modest improvements in patient health seen in the trial stemmed from the effect of corticosteroids on patients with relatively mild disease – *not* the impact of PRN1008. Consider the patients' characteristics at baseline:

- The average Pemphigus Disease Area Index (PDAI) total activity score was 19; this is a scale that runs from 0 *to 250.* By contrast, in the landmark 2017 rituximab trial, baseline PDAI was 46.0 in the group randomized to predisone only and 33.5 in the group randomized to rituximab plus short-term prednisone – much higher scores indicating much more severe disease (4).
- While Principia elsewhere claims that the standard of care for pemphigus is 60-90 mg/day, the patients in this trial were on a "CS [corticosteroid] dose at entry" of only 14 mg/day.[6]
- In Principia's Phase 2, the mean level of anti-DSG3 antibodies in patients' serum was ~400 units per mL. In the rituximab study, it was more than double (~1,000 U/mL in the prednisone-only group and ~900 U/mL in the rituximab group) (4).

Overall, then, Principia tested its drug on relatively mild cases – and still didn't achieve impressive results.

It's important to Principia to characterize the corticosteroid doses taken by patients in the trial as "low" because it heads off the skeptic's natural question: why assume the credit for any improvement goes to PRN1008 and not the corticosteroids? If the doses were truly so "low" as

[4] Here we focus on the detailed Phase 2 Part A data. For the smaller Part B, Principia has said it will submit final data "for presentation at an upcoming medical conference," but disclosed topline figures are similar to those from Part A.
[5] See March 2019 presentation at the American Academy of Dermatology meeting, slides 8 and 9, footnotes.
[6] March 2019 AAD presentation, slide 7.

to be trivial, perhaps PRN1008 would deserve some credit, but other sources don't support Principia's "low" label. For instance, in a 2013 retrospective study that compared "patients treated with different regimens including medium- and high-dose corticosteroids," "medium" was defined as ≤ 0.5 mg/kg/d – the exact same threshold that Principia calls "low" (5). The same study (which pre-dates the approval of rituximab) also noted that "[m]any physicians still consider that the goal of pemphigus treatment is to maintain [complete remission] under the administration of low doses of [corticosteroids] (prednisone ≤ 2.5 mg/d) without trying to stop treatment." Again, the definition of "low" is far more stringent than that used by Principia: for a ~150-lb person, 2.5 mg/d equates to 0.04 mg/kg/d, less than a tenth of Principia's threshold for "low."

Interestingly, the available evidence suggests that "medium" corticosteroid doses have very similar efficacy to higher doses. In the 2013 retrospective study, for instance, "the rate of patients who achieved CRoffT [complete remission off therapy] was not significantly different among the three treatment groups [consisting of medium-dose, high-dose, and no initial corticosteroids at all], suggesting that the initial treatment regimen, which is usually adapted to initial disease severity to obtain disease control, does not greatly influence" the odds of complete remission (5). Similarly, in an earlier retrospective study of patients on two different corticosteroid dosing regimens, the cumulative doses which differed by almost a factor of 2, "both treatments resulted in high rates of clinical response" (roughly 80%), with no significant difference between them (6). It's in Principia's interest to argue that the corticosteroid doses in its trial were so low as to be ineffective – thereby casting any observed clinical benefit as the achievement of PRN1008 – but corticosteroid doses of similar size appear to have benefits little different than those of higher doses.

Arguably the most "official" definition of a "low" dose of corticosteroids comes from the 2008 "Consensus statement on definitions of disease, endpoints, and therapeutic response for pemphigus" issued by the International Pemphigus Committee – but, tellingly, Principia doesn't use it, even though its own lead principal investigator is the first named author of the statement (7). In the consensus statement, "minimal therapy" is defined as "prednisone (or the equivalent) at ≤10 mg/d and/or minimal adjuvant therapy for at least 2 mo," and "'complete remission on therapy' is defined as the absence of new or established lesions while the patient is receiving minimal therapy"; this is sometimes also referred to as "complete remission on minimal therapy," a less stringent endpoint than the more common "complete remission *off* therapy." The endpoint Principia uses, however, is its own even more permissive and self-serving creation: complete remission on ≤0.5 mg/kg/d, which, for a 150-pound person, would permit up to 34 mg/d – more than triple the consensus statement's "minimal" dose.

In effect, Principia set a low bar and then congratulated itself for occasionally clearing it. Recall that under its own calculation of complete remission on "low" (medium) therapy, the response rate was still only 17%. While Principia disclosed that the mean dose at CR was 8 mg – just below the "minimal" threshold on average – it also disclosed that the range of doses, among the

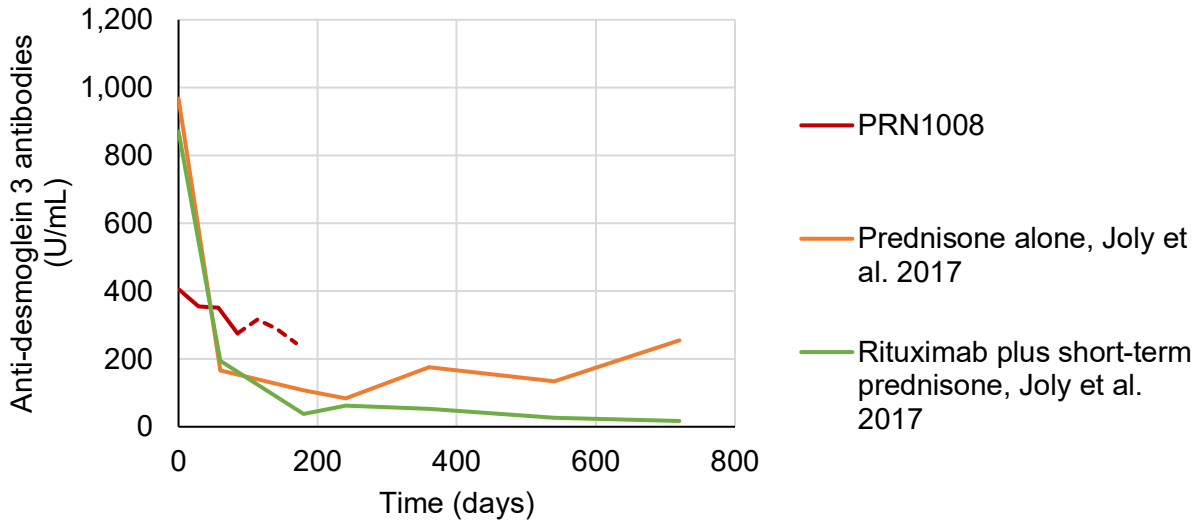
4 patients in complete remission at 12 weeks, went from 1 to 20 mg.[7] That 20mg/d patient clearly wasn't on "minimal" therapy, so the true CR rate on *minimal* therapy – based on the consensus definition of that endpoint and using the standard intent-to-treat statistical analysis – would only be 3 patients out of 27 enrolled, or just 11%.[8] And even that "consensus" endpoint, though stricter than Principia's, is controversial – for being too lax. The dramatic success of rituximab, for one thing, has shifted the emphasis to complete remission off *all* therapy. A 2019 study of rituximab's efficacy in pemphigus highlighted the issue: "Currently, a composite end point of CRMT [complete remission on minimal therapy] or better is considered an acceptable primary end point for clinical trials, but arguably the ability to discontinue all topical and oral systemic therapies with minimal or no disease activity…is also a desirable therapeutic goal that should be considered (akin to the clear or almost clear end point used for many dermatology clinical trials" (8). In less diplomatic words, so-called remission that still requires "minimal" therapy is nothing to write home about.

What about the "control of disease activity" (CDA) endpoint? Again, the results simply don't stand out relative to what could be achieved by corticosteroids alone, especially given that patients began the trial with relatively mild disease. CDA only requires that new lesions stop forming, whereas "complete remission" requires the absence of new *or* established lesions for at least two months. But corticosteroids alone achieve this level of control in the vast majority of patients; it's not a high bar. Few recent pemphigus studies seem to carefully track CDA, likely because doctors have higher ambitions for treatment efficacy. In one Thai study, though, researchers reported that "[a]lmost all PV [pemphigus vulgaris, the more common form] and PF [pemphigus foliaceus, the less common form] patients achieved disease control (93.9% and 94.7%, respectively)" on standard of care (9). In Principia's trial, looking at 26 patients, 54% achieved CDA within 4 weeks; to a close approximation, then, the median time to CDA was 4 weeks. How does this compare to the Thai study, which included 117 patients? Among the PV patients, median time to CDA was 6 weeks; among the PF patients, it was 4 weeks. In the best case (for Principia), then, patients on PRN1008 plus "low"-dose corticosteroids achieved disease control about a week earlier than they might otherwise have expected to. Hold your applause.

Finally, consider Principia's data on anti-desmoglein antibody levels, a measure of the underlying biology of pemphigus. Presumably, if the concentration of anti-desmoglein antibodies goes down, that means the treatment is actually working, and Principia shows that mean anti-DSG3 antibody levels among patients on PRN1008 plus corticosteroids do in fact decline by 32% during the treatment period.[9] But is that a lot, and should we conclude that it was caused by PRN1008 and not the corticosteroids? No and no. Compare Principia's data to what was observed in the landmark rituximab study:

[7] March 2019 AAD presentation, slide 9.
[8] Recall that Principia allows itself to exclude 3 drop-outs from the CR analysis, even though they all did receive multiple doses of PRN1008 as far out as day 44. See March 2019 AAD presentation, slide 9, footnote.
[9] [9] March 2019 AAD presentation, slide 13.

Pathogenic Antibodies in Pemphigus: Principia's Results Are Weak



Note: PRN1008 line represents mean antibodies among all patients with available data (not Principia's alternative way of reporting the figures, which includes only patients with baseline antibodies ≥100). The solid portion of the line shows results during the treatment period; the dashed portion, post-treatment follow-up.
Source: Joly et al. 2017 (4); Principia March 2019 AAD presentation, slide 13; Kerrisdale analysis

While the PRN1008-plus-corticosteroid patients did see an improvement, it's dwarfed by what patients from the rituximab study experienced – *even in the prednisone-only group.* Thus corticosteroids alone are clearly sufficient to dramatically reduce anti-DSG3 antibody levels, even from extremely high baseline values. While Principia touts its modest 32% reduction at week 12 as evidence of efficacy, the corticosteroid-only patients in the rituximab study saw their anti-DSG3 antibodies drop by more than 80% by week 9. To be fair, Principia's patients were on lower corticosteroid doses, likely accounting for the smaller and slower drop – but that still leaves no reason to believe that PRN1008 added any therapeutic value of its own.

In a way, Principia has already effectively conceded that its Phase 2 results were profoundly flawed: in the design of its follow-up Phase 3 trial (currently enrolling patients), the primary endpoint is "the ability of PRN1008 to achieve durable CR on **very low-dose CS (5 mg/day)** at 37 weeks of treatment" (emphasis added). Principia saves face by adopting the new term "*very* low-dose CS" instead of admitting that its previous "low-dose" term was misleading, but we believe the rationale for this shift is clear: the company realized that its Phase 2 trial was not credible because the endpoints were far too easy to hit even if PRN1008 added no value to the (pre-rituximab) standard of care. By making the definition of the primary endpoint stricter – allowing only 5 mg/day of corticosteroids, below even the consensus 10mg/day threshold for "minimal therapy," and focusing on complete remission rather than mere CDA – it will make the eventual results more clinically relevant; even more important, the Phase 3 will include a real

placebo group. And that's when Principia will be forced to confront the reality thus far hidden behind its single-arm, corticosteroid-confounded Phase 2 design: PRN1008 is completely ineffective in pemphigus, adding nothing to the traditional standard of care and paling in comparison to the new "magic bullet," rituximab.

Immune Thrombocytopenia (ITP)

Immune thrombocytopenia is, roughly speaking, just what doctors call it when a patient has an abnormally low number of platelets (the blood cells that help form clots) for no known reason. Though the disorder is thought to be autoimmune – caused by antibodies tagging platelets as "foreign" – such "antiplatelet antibodies are not detected in up to 50% of patients," according to one recent review of ITP clinical practice (10). Researchers often emphasize the heterogeneity of the disease and the uncertainty about its underlying cause. The main problems associated with ITP are fatigue and bleeding, which can range from mild to occasionally life-threatening.

Fortunately, those who suffer from this rare disease now have many treatment options. Typical first-line therapy includes corticosteroids (to suppress the immune system) and intravenous immunoglobulin (essentially intended to "flush" the pathogenic antibodies out of the patient's bloodstream), while second- to third-line treatments include three different FDA-approved thrombopoietin-receptor agonists (TPO-RAs, which directly stimulate production of new platelets), rituximab, splenectomy (surgical removal of the spleen), the Syk inhibitor fostamatinib, and a host of other less proven but still commonly used drugs like mycophenolate mofetil, dapsone, danazol, and azathioprine. While many of these treatments are quite effective at boosting platelet counts in most patients, relapses are fairly common over time. According to a leading ITP expert, Nichola Cooper, "50% of patients cycle through therapies" to keep their platelet counts up. However, cycling isn't the same thing as failure. Doctors who treat ITP note that patients often respond after relapse to the same drugs they were taking before or had taken at some point in the past; in the words of one doctor, "truly refractory patients are actually not that common." Cooper likewise estimated that only 5-10% of ITP patients are "refractory." That figure will likely fall further in the future, as at least three seemingly effective new drugs are now being tested in ongoing clinical trials: two FcRn inhibitors (efgartigimod from Argenx and rozanolixizumab from UCB) and an antibody designed to block a part of the immune system called the classical complement pathway (sutimlimab from Sanofi). It's a crowded space.

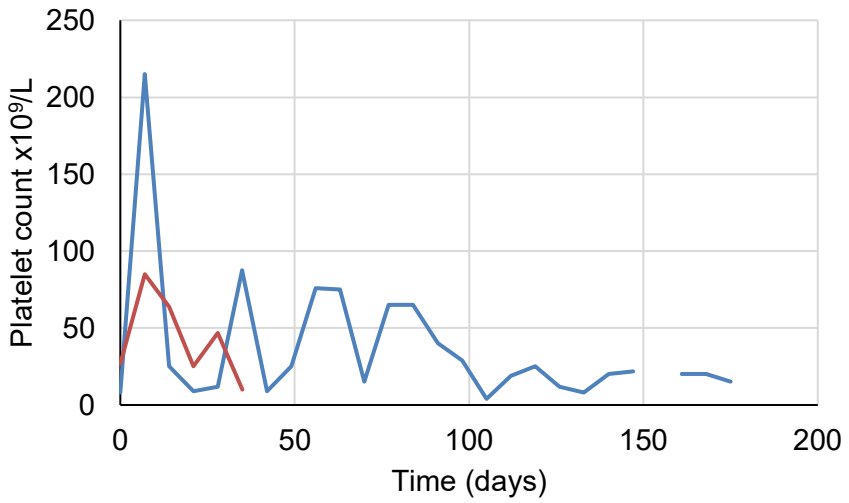
Against this backdrop of intense competition in ITP, Principia's data fall flat. In the interim results the company has presented from its Phase 2 trial, the headline "response rate" was 39% (12 patients out of 31). But there was no placebo group and thus no benchmark against which to judge this figure. ITP has long been recognized as a disease in which spontaneous remissions can and do occur; even without true remission, platelet counts can fluctuate at random.[10]

[10] For example, Cooper's review states that "[b]oth spontaneous and treatment-induced remission can occur many years after diagnosis" (10). Even back in 2006, before TPO-RAs were available, other researchers concluded in a retrospective study that patients often experienced complete remission spontaneously or on low-dose corticosteroids; the five-year probability was 61% (25). One dramatic example of platelet-count fluctuations appeared in the phase 3

There's no good reason, then, to attribute every fleeting "response" to Principia's drug. Moreover, *68% of trial participants were also on one or more concomitant ITP medications,*[11] which could include corticosteroids and TPO-RAs, making it very likely that some or all of the "responses" that Principia wants to take credit for were in fact caused by standard treatments, *not* by PRN1008/rilzabrutinib.[12]

Besides, Principia has set a low bar for itself with its definition of "response," which requires only that patients' platelet counts exceed 50 x 10^9/L for two consecutive weekly visits – at some point in time. This means that patients with a fleeting uptick in platelet counts followed by a sustained decline back to unhealthy, thrombocytopenic levels still count as "responders" even though they experienced no meaningful improvement. In fact, after a close examination of Principia's needlessly difficult-to-decipher graphs of individual platelet counts over time, we found multiple cases of exactly that pattern. For example, these two patients both count toward Principia's topline 39% response rate, even though it's hard to be impressed by the trajectory of their platelet levels, which spike up a few times but soon settle back to low levels:

Even Fleeting Improvements Count as "Responses" in Principia's ITP Data



Source: adapted from Principia investor presentation, slide 20

trials of fostamatinib. In the placebo group (pooled together from two trials), the median platelet count spiked at week 18 from ~20 to >200 x 10^9/L – a 10-fold increase driven by two patients on placebo who just happened to have high counts that week (26).

[11] Principia investor presentation (downloaded January 2020), slide 19.

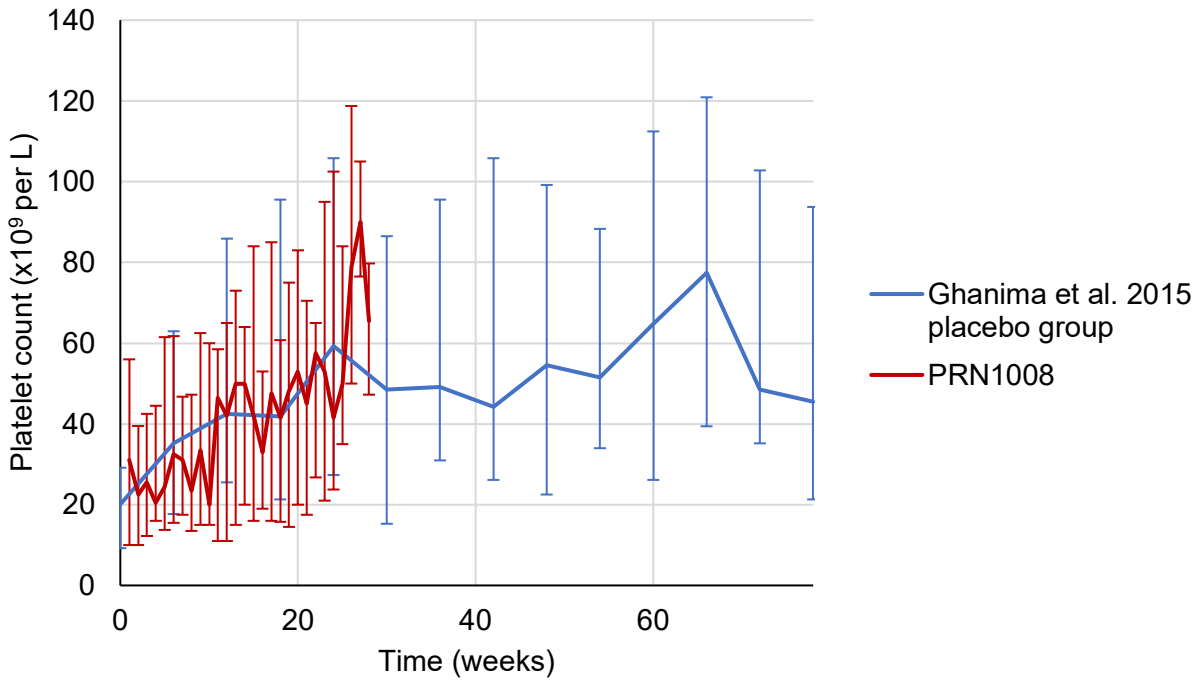
[12] Principia attempts to head off this objection by noting that the response rate among patients on concomitant therapy was similar to that among patients on rilzabrutinib alone (Principia investor presentation, slide 22). But the rilzabrutinib-only group was small, making this comparison statistically suspect. Moreover, we don't know the quality of the rilzabrutinib-only "responses" relative to those among patients on concomitant medications; it's quite possible that the more clinically meaningful and durable increases in platelet counts occurred in patients taking TPO-RAs and corticosteroids, while the unimpressive, transient increases occurred in patients taking rilzabrutinib alone.

By contrast, other clinical trials in ITP usually have less generous definitions of "response." For example, in Sanofi's recent Phase 1 trial of sutimlimab, "response" was defined as two consecutive platelet counts over 50 *by Day 14,* thus requiring both a rapid effect and disallowing the cherry-picking of any two consecutive counts that just happened to look good at some point during the trial. On this basis, sutimlimab's response rate (among 7 patients) was 57% (which itself may have been driven in part by the effects of concomitant medication). What if we applied the same standards to Principia? Based on our analysis of the platelet-count series, the stated response rate would drop to **just 16%** (5 out of 31 patients) – hardly impressive even with no placebo group to compare it to.

Of course, any binary threshold for "response" is somewhat arbitrary – just one way of summarizing the distribution of platelet counts over time among individual patients. To get at this distribution more directly, we again used Principia's difficult-to-decipher graphs to estimate median, first quartile (25th percentile), and third quartile (75th percentile) platelet counts over time. We then overlaid data from the *placebo* group in a major, >100-patient study of rituximab as a second-line agent in ITP published in 2015 (11). Comparing results across different trials is always a tricky business, but at a high level the patient populations are similar: both receiving second-line treatment for ITP after failing to respond adequately to first-line treatment; both allowed to take concomitant medications in addition to rilzabrutinib/placebo; both starting out with low platelet counts below 30 x 10^9/L. While the patients in Principia's trial tended to have a longer history of ITP than those in the rituximab-trial placebo group (possibly making them less likely to see higher platelet counts), there is also a large bias in the other direction: the placebo patients in the rituximab trial didn't have access to TPO-RAs, which have high (70-95%) initial response rates (10). Though the comparison isn't perfectly scientific, we find it informative when taken together with the other evidence that rilzabrutinib is ineffective.

As seen below, the distribution of platelet counts over time among rilzabrutinib (plus concomitant therapy) patients as compared to placebo (plus concomitant therapy) patients from the 2015 rituximab study are stunningly similar; the two series are difficult to distinguish because they're right on top of each other. Not only do the medians closely match, but the interquartile ranges also heavily overlap. (The apparent spike up at the end of the PRN1008/rilzabrutinib line is an artifact caused by the very small number of patients (four) with available data for that time point, who happen to all be "responders.")

Principia's Results in ITP Are Indistinguishable from Placebo



Note: points represent median values; error bars represent interquartile ranges.
Source: Kerrisdale analysis based on Principia investor presentation, slide 20, and Ghanima et al. 2015 (11)

What this analysis shows is that Principia's results simply aren't exceptional, even for patients initially unresponsive to corticosteroids. It's perfectly plausible that any apparent "responses" to Principia's drug are actually responses to concomitant corticosteroids and TPO-RAs coupled with spontaneous remissions and random fluctuations in platelet count. Otherwise, why would patients on Principia's drug look so similar to patients on placebo?

Although platelet counts are the usual way to measure ITP severity, they only bear an uncertain relationship to real-world health outcomes, the most important of which is the incidence of bleeding. In an indirect way, Principia actually has disclosed outcomes in bleeding, but only by presenting them as a marker of safety: "No significant change in the ITP-BAT [ITP-specific bleeding assessment tool] bleeding scale from baseline to last visit."[13] While it's nice that Principia's drug for the treatment of a disorder characterized by bleeding didn't appear to *increase* bleeding, it's hardly a sign of efficacy that there was "no significant change" despite weeks of daily or twice-daily drug use. Shouldn't there have been a *decrease*? (Indeed, in data presented by Argenx, which is developing a different type of drug for use in ITP, patients on a high dose of the drug did experience a significantly lower rate of bleeding over time (as

[13] Principia investor presentation, slide 23.

measured by a different bleeding scale), while patients on placebo experienced no significant change.[14])

Detailed safety data add further to the case against rilzabrutinib's efficacy in ITP. Out of only 31 patients in the trial, 3 (10%) experienced "serious adverse events" related to bleeding: one, a rectal hemorrhage leading to hospitalization and requiring rescue medications; the second, a severe head contusion leading to hospitalization and requiring rescue medications; and the third, a case of severe gastrointestinal bleeding leading to hospitalization and requiring platelet transfusion.[15] While Principia asserts that these bleeding events were not *caused* by its drug, which may well be true, they do call into question the drug's purported benefits: if it's a good treatment for ITP, then why do so many patients taking it still suffer from "serious" bleeding, let alone milder cases?

Indeed, it's not unreasonable to suspect that Principia's drug actually *causes* bleeding and thrombocytopenia, at least in some patients. While there's no clear evidence of this from Principia's data thus far, several other BTK inhibitors, including first-to-market ibrutinib, its more selective cousin acalabrutinib, and the next-generation noncovalent BTK inhibitor ARQ 531 all appear to cause thrombocytopenia and/or bleeding, suggesting that these side effects are characteristic of this whole class of drugs, including Principia's versions. For instance, the official ibrutinib (brand name Imbruvica) prescribing information warns (emphasis added):

> Fatal bleeding events have occurred in patients treated with IMBRUVICA®. Major hemorrhage (≥ Grade 3, serious, or any central nervous system events; e.g., intracranial hemorrhage [including subdural hematoma], gastrointestinal bleeding, hematuria, and post procedural hemorrhage) have occurred in 4% of patients, with fatalities occurring in 0.4% of 2,838 patients exposed to IMBRUVICA® in 27 clinical trials. **Bleeding events of any grade, including bruising and petechiae, occurred in 39% of patients treated with IMBRUVICA®.**
>
> …Treatment-emergent Grade 3 or 4 cytopenias including…**thrombocytopenia (8%)**…occurred in patients with B-cell malignancies treated with single agent IMBRUVICA®.

Similarly, the official acalabrutinib (Calquence) prescribing information says:

> Fatal and serious hemorrhagic events have occurred in patients with hematologic malignancies treated with CALQUENCE. Major hemorrhage (serious or Grade 3 or higher bleeding or any central nervous system bleeding) occurred in 3.0% of patients, with fatal hemorrhage occurring in 0.1% of 1029 patients exposed to CALQUENCE in clinical trials. **Bleeding events of any grade, excluding bruising and petechiae, occurred in 22% of patients.**

[14] Argenx investor presentation, August 2019, slide 21.
[15] "Phase I/II, Open-Label, Adaptive Study of Oral Bruton Tyrosine Kinase Inhibitor PRN1008 in Patients With Relapsed/Refractory Primary or Secondary Immune Thrombocytopenia," slide 12.

> …Grade 3 or 4 cytopenias, including…**thrombocytopenia (7%)**…developed in patients with hematologic malignancies treated with CALQUENCE.

While ARQ 531 hasn't been associated with bleeding events so far, the small safety data set that it has accumulated already indicates a significant risk of decreased platelet counts, with 12% of patients seeing decreases and 9% seeing "severe" (Grade 3 or higher) decreases.[16] Given this striking pattern of thrombocytopenia and bleeding associated with the use of multiple other BTK inhibitors, it's quite plausible that, compared to placebo for the treatment of ITP, Principia's rilzabrutinib will actually turn out to be *worse*.

Principia's clinical results in pemphigus and ITP form the foundation of its $2 billion valuation, yet on closer inspection they appear weak and unimpressive, difficult to distinguish from placebo. But this should come as no surprise: BTK inhibitors in general have a very poor track record in autoimmune disease; Principia's drugs just constitute one more data point.

BTK Inhibitors Don't Work in Autoimmune Disease

BTK Inhibitors Have Repeatedly Failed in Autoimmune Clinical Trials

BTK inhibitors have clearly proven their value for treating the subset of blood cancers known as B-cell malignancies, for which the BTK inhibitor Imbruvica (ibrutinib) is already a blockbuster success, with numerous competing copycat and next-generation variants on their way. But from early on in the development of this class of drugs, researchers wondered whether they might also work in autoimmune diseases, a very different therapeutic area but one also characterized by B-cell dysfunction in which the BTK protein potentially plays a role. As the years go by, however, the evidence has continued to mount that these initial hopes were incorrect: BTK inhibitors have little effect on autoimmune diseases. The table below summarizes the clinical results so far (some of which are little known because they were never officially published), which we discuss in further detail below. The pattern is clear: in autoimmune diseases the difference between BTK inhibitors and placebo has usually been statistically insignificant.

[16] ArQule November 2019 investor presentation, slide 11.

BTK inhibitors in Autoimmune Disorders: A History of Failure

Drug	Company	Disease	Trial outcome
spebrutinib	Celgene	rheumatoid arthritis	failed
acalabrutinib	AstraZeneca	rheumatoid arthritis	failed
poseltinib	Eli Lilly	rheumatoid arthritis	failed (terminated early)
fenebrutinib	Roche	lupus	failed
		rheumatoid arthritis	mixed
tirabrutinib	Gilead	Sjögren's syndrome	failed
evobrutinib	Merck KGaA	rheumatoid arthritis	failed
		RRMS	mixed
branebrutinib	Bristol-Myers Squibb	rheumatoid arthritis	failed

Note: "failed" = failed to achieve statistical significance on primary endpoint; "mixed" = failed to achieve statistical significance on key efficacy-related secondary endpoints.

Spebrutinib. Celgene obtained this drug, also called CC-292, as part of its acquisition of Avila Therapeutics back in 2012, touting the promise of BTK inhibition in "hematology, oncology, *and immune-inflammatory diseases*" (emphasis added). But, as was later reported, "Celgene lost interest in CC-292 after their BTK drug performed poorly in Phase IIa," failing to distinguish itself meaningfully from placebo in rheumatoid arthritis;[17] according to one industry source, "Celgene dropped the BTK program" altogether.

Acalabrutinib. This drug, now branded as Calquence and FDA-approved for the treatment of chronic lymphocytic leukemia, may or may not be able gain share from the well established and highly similar Imbruvica among blood-cancer patients. But this BTK inhibitor already failed in a Phase 2 trial in rheumatoid arthritis initiated in 2015. As a recent review paper put it, "the frequency of adverse events was higher" in the BTK-inhibitor group than the placebo group, while "analyses did not [show] significant

[17] Note that Principia too planned at one point to use its BTK inhibitor in rheumatoid arthritis; indeed, this use case received top billing on Principia's web site in 2015, and the company said that "BTK is an attractive therapeutic target for rheumatoid arthritis."

differences between [the BTK-inhibitor and placebo] groups in terms of primary outcome DAS28-CRP," a common measure of rheumatoid-arthritis disease severity.

Poseltinib. In 2015, Eli Lilly and the Korean pharmaceutical company Hanmi announced that they had "entered an exclusive license and collaboration agreement for the development and commercialization of Hanmi's oral Bruton's tyrosine kinase (BTK) inhibitor, HM71224," emphasizing the potential of the drug in the treatment of "many prevalent autoimmune diseases," including "rheumatoid arthritis, lupus, lupus nephritis, Sjögren's syndrome, and other related conditions." In February 2018, however, reality sunk in: Lilly terminated a clinical trial of the BTK inhibitor in rheumatoid arthritis after an interim analysis of the results "showed a lack of efficacy." In early 2019, Hanmi announced that Lilly had officially handed back the rights to the drug. In the words of a Hanmi official, "Lilly's decision came after a comprehensive review of all clinical data and the BTK inhibitor market" – a review that apparently convinced Lilly that developing such drugs was now a dead end.

Fenebrutinib. In a recent trial, Roche tested its BTK inhibitor, fenebrutinib, on patients with the autoimmune condition systemic lupus erythematosus (SLE), more commonly known just as lupus. The trial failed to achieve its primary endpoint "despite evidence of strong BTK target and pathway inhibition"; in other words, the drug was doing what it was supposed to do, but patients still didn't benefit, an outcome that, in one journalist's words, "neither the investigators nor other rheumatologists could explain."

Fenebrutinib's phase 2 results in rheumatoid arthritis were more nuanced but still weak. In a cohort of patients who had inadequately responded to the drug methotrexate, fenebrutinib appeared to be "modestly effective," in the words of one media report. But while it did outperform placebo to a statistically significant degree, it *underperformed* the blockbuster arthritis drug – a "disappointment," according to the same source. In a second cohort of patients, these ones having inadequately responded to TNF inhibitors like Humira, fenebrutinib did *not* meet its key efficacy endpoint of substantially improving arthritis symptoms; the difference between the BTK inhibitor and placebo was statistically insignificant.

Tirabrutinib. In 2014, Gilead licensed a BTK inhibitor from the Japanese pharmaceutical company Ono. In a complex four-arm trial, Gilead tested the drug in combination with two others for the treatment of Sjögren's syndrome, an autoimmune disorder in which the immune system attacks tear glands and salivary glands. On its 2019 third-quarter earnings call, Gilead revealed that this trial failed to meet its primary endpoint. While the company did allude to "evidence of activity" giving it hope for *one* of the drugs used in the trial, the BTK inhibitor wasn't it.

Evobrutinib. Merck KGaA's BTK inhibitor evobrutinib grabbed headlines in recent months because of its Phase 2 trial in multiple sclerosis, which we will discuss further below. But, while the trial met its primary endpoint, with evobrutinib outperforming

placebo on an MRI-based measure of disease progression, it failed to meet key secondary endpoints that are more closely tied to real-world health: in the words of the journal article publishing these results, "Treatment with evobrutinib at any dose had no effect on the annualized relapse rate or disability progression and was associated with elevations in liver aminotransferase levels" (a possible signal of liver damage) (12). At best, then, the results were a mixed bag.

Meanwhile, in rheumatoid arthritis, Merck conducted a trial of evobrutinib from 2016 to 2017 but, to our knowledge, never publicly discussed the outcome. According to study results posted on clinicaltrials.gov, however, the BTK inhibitor failed to clearly improve patients' symptoms. In fact, at multiple time points, the fraction of patients enjoying large (≥50% or ≥70%) improvements in symptoms was *higher* in the placebo group than in the BTK-inhibitor group; patients were better off without the drug.

Branebrutinib. Bristol-Myers Squibb tested its BTK inhibitor, originally called BMS-986142, in rheumatoid arthritis in a large, 508-patient trial conducted from 2016 to 2018, but, to our knowledge, it hasn't published the results. According to data posted on clinicaltrials.gov, the drug was a flop, failing to outperform placebo to a statistically significant degree and, across several dose levels and outcome measures, actually *underperforming* placebo. It's no wonder that, as one 2019 media report noted, "Bristol-Myers Squibb's BMS-986142 seems to have been shelved."

Beyond all these failed and equivocal results from clinical trials, there are other intriguing hints from the medical literature that BTK inhibitors don't improve autoimmune conditions – and may even *cause* them. One recently published case study involved a rare condition called paraneoplastic pemphigus (PNP) – a blistering disease very similar to pemphigus vulgaris but arising as the result of an underlying cancer (13). A patient with chronic lymphocytic leukemia (CLL) who had developed this form of pemphigus received ibrutinib to treat his underlying CLL, but initially many of the pemphigus symptoms persisted or worsened; "his PNP lesions did not improve with ibrutinib monotherapy." It was only after treatment with *rituximab* was added on that the patient "gradually improved." The authors of the case study also refer to a previously reported case of CLL-triggered paraneoplastic pemphigus that likewise "was not managed well using ibrutinib alone" but required "high-dose steroids" and other drugs. These case reports, anecdotal though they may be, add to the evidence that BTK inhibitors are ineffective against autoimmune diseases.

In fact, there is substantial evidence that BTK inhibitors can *cause* autoimmune-like problems. In one recent case report, a CLL patient developed "a severe arthritic syndrome due to ibrutinib use" (14):

> Three days into ibrutinib therapy, he experienced moderate pain and swelling in the small joints of hands and feet bilaterally. Over the next five days, this pain and swelling became progressively worse, and he developed bilateral knee pain. The pain progressed to 10/10 on the pain scale, limiting significantly his activities of daily living,

> including ambulation. … Given the severity of symptoms and at the patient's request, ibrutinib was discontinued. Within three days, the arthralgias and joint swelling subsided. These symptoms resolved completely two weeks after ibrutinib discontinuation.

This report of rheumatoid-arthritis–like side effects of BTK inhibitors was not an isolated case restricted to ibrutinib: the competing BTK inhibitor acalabrutinib has also been associated with (sometimes severe) arthralgia (joint pain) (15), as has the next-generation BTK inhibitor ARQ 531.[18] Meanwhile, another recent case report described a patient who initiated ibrutinib and quickly developed "autoimmune myelitis" (an inflammation of the spinal cord that is sometimes an early symptom of multiple sclerosis), manifesting as abnormal sensations in "the left foot…[,] the right leg, the pelvic floor, and the genital area, accompanied by bladder dysfunction." He was treated with corticosteroids. (Thus, while Principia claims that its BTK inhibitors can take the place of corticosteroids in treating autoimmune disorders, in this case autoimmune dysfunction arose concurrent with (and perhaps because of) BTK inhibition and required corticosteroids to suppress it.)

Again, these are not just one-off flukes. A recent review of real-world experience with BTK inhibitors entitled "How I treat CLL patients with ibrutinib" devoted an entire section to autoimmunity, noting a report of an "acute flare of autoimmunity right after ibrutinib initiation" and adding, "My experience largely recapitulates this report, namely, occasional flare of autoimmunity after ibrutinib initiation" (16). Such autoimmune "flares" may not dissuade patients with life-threatening cancers from using BTK inhibitors, but the fact that such drugs frequently seem to *trigger* autoimmune problems casts doubt on the notion that they will ever serve as good treatments for autoimmune disorders. In fact, even people born with a defective *Btk* gene, who otherwise suffer from very weak immune systems, seem to have an unusual rate of autoimmune symptoms like the painful joints associated with rheumatoid arthritis or the chronic diarrhea associated with Crohn's disease (17).

Taken together, BTK inhibitors' poor track record in a broad set of autoimmune clinical trials and their tendency to provoke autoimmune flare-ups belie the simplistic idea that these drugs can fix autoimmune disease just by tamping down B-cell activity. In fact, as we explain below, the underlying biology of BTK suggests that inhibiting the molecule's enzymatic activity will do nothing to address the causes of diseases like pemphigus and ITP; the approach is misguided and destined to fail.

Closing the Stable Door After the Horse Has Bolted: Inhibiting BTK Is Irrelevant to Autoimmunity

In its latest corporate presentation, Principia makes the sweeping claim that its target molecule, BTK, "has a broad role in multiple immune-mediated disease processes," referencing a handful of decade-old studies and a wide range of cell types. However, the (literal) textbook function of BTK is far narrower: to quote the glossary of *Cellular and Molecular Immunology,* BTK is "a Tec

[18] See ArQule's November 2019 investor presentation, slide 11.

family tyrosine kinase that is **essential for B cell maturation**" (18) (emphasis added). In adult humans, new B cells are constantly being generated from precursors inside the bone marrow. In an early part of this development process that serves as its first checkpoint, a preliminary version of a fledgling B cell's receptor needs to be successfully activated; otherwise, the cell will die. To quote the textbook again:

> Bruton's tyrosine kinase (Btk) is activated downstream of the pre-BCR and is required for delivery of signals from this receptor that mediate survival, proliferation, and maturation at and beyond the pre-B cell stage. In humans, mutations in the *BTK* gene result in the disease called X-linked agammaglobulinemia (XLA), which is characterized by a failure of B cell maturation.

In short, without functional BTK, fledgling B-cell precursors inside the bone marrow never "grow up." Someone born without functional BTK thus has a profoundly impaired immune system, lacking both B cells and the antibodies that those cells are supposed to produce. What does BTK do beyond this early stage in B-cell development? It's unclear: as a recent paper put it, "the role of Btk in fully developed, mature peripheral B cells is not well understood" (19).

BTK makes sense as a drug target for B-cell malignancies like CLL that are characterized by excessive proliferation of B cells in the bone marrow; by blocking BTK, drugs like ibrutinib make it impossible for new B cells to emerge, putting a stop to disease progression. But what about B-cell–mediated autoimmune diseases? In these cases, the problem isn't that patients have too many B cells coming out of their bone marrow; the problem is that they have a population of "bad" B cells that attack components of the patients' own bodies as if they were invading pathogens. Impeding the development of new B-cell lineages will do nothing to get rid of the "bad" B cells that are already in place; it's tantamount to closing the stable door after the horse has bolted.

By contrast, anti-CD20 treatments like rituximab and ocrelizumab selectively kill most B cells but allow early-stage precursors to survive and eventually repopulate patients' immune repertoires. It thus stands to reason that rituximab monotherapy has "limited clinical activity" in a disease like CLL; while it can kill the cancerous cells already in place, it won't stop the ongoing generation of new cancerous cells (20). In autoimmune diseases, on the other hand, the dramatic success of, say, rituximab in pemphigus or ocrelizumab in multiple sclerosis demonstrates the importance of simply killing off the problem cells; halting the development of new cells would not help.

There is thus a great disconnect between the primary effect of BTK inhibition (halting the maturation of new B cells in the bone marrow) and the primary needs of patients with autoimmune diseases (shutting down existing populations of autoreactive B cells) – and we are not the only ones to have noticed it. One group of immunologists researching B cells and BTK has repeatedly made the same point (21):

> [H]uman patients who are given [BTK] inhibitors already have established B cell populations, including autoimmune-prone and normal subsets. Whether blocking the

> kinase domain of BTK reduces the number of autoreactive B cells, as Btk-deficiency does in mice, or increases their relative proportion as occurs in XLA patients, is an important question that deserves study.

In other words, these researchers are raising the possibility that BTK inhibition could even *increase* autoimmune problems in humans, as suggested not just by the XLA patients they refer to but also the adverse-event case reports we discuss above.

More direct evidence that BTK doesn't play a major role in *mature* B-cell function comes from a recently published study entitled "Bruton's Tyrosine Kinase Is Not Essential for B Cell Survival beyond Early Developmental Stages" (19). In this study, researchers engineered so-called knockdown mice: though born with normal, healthy *Btk* genes that allowed them to generate functional B cells, these mice were susceptible to a chemical trigger that could "turn off" *Btk* during adulthood, at a time of the researchers' choosing. What happened to mice with existing, functional B-cell populations but no more ability to produce BTK? Essentially nothing: their B cells survived and behaved fairly normally; the mice were unscathed. Thus, in the words of the study, "mature B cells that have already passed selective checkpoints [in early development]…do not require Btk for survival…These findings raise the possibility that Btk may also be expendable for survival of mature human B cells." But if eliminating BTK entirely has no major effect on established B cells, why would inhibiting BTK with a drug do anything to help B-cell mediated autoimmune disease?

In fact, BTK inhibitors like Principia's drugs likely don't even block all of BTK's activities. That's because, as multiple researchers have documented, the complex BTK molecule has two key components: a kinase domain, which serves as an enzyme catalyzing chemical reactions, and an adaptor domain, which serves as a "docking site" for other proteins to attach to. As one study noted, "**BTK-inhibitors target only the kinase domain, leaving other BTK activities intact"** (22) (emphasis added). Thus even if BTK played an important role within the mature B cells that give rise to autoimmunity, that role might well be mediated by the molecule's adaptor domain, which BTK inhibitors like Principia's don't affect.

In sum, the biology of BTK aligns well with the performance of BTK inhibitors in the clinic: in disorders caused by excess proliferation of immature B cells, great success – but, in disorders caused by specific existing B-cell populations, repeated failure. There is no good reason to expect Principia's BTK inhibitors to break this well established pattern. The company's entire fundamental concept – that BTK inhibitors can directly address autoimmune disease – is mistaken.

Multiple Sclerosis: Don't Believe the Hype

Some analysts, seeking to justify the recent run-up in Principia's stock price, have seized on the upcoming Phase 2 readout in multiple sclerosis, suggesting that Principia will derive great value from the BTK inhibitor it licensed to Sanofi (a drug now known as SAR442168 or just '168).

Indeed, Sanofi did highlight the drug at its December 2019 Capital Markets Day, and a similar BTK inhibitor, evobrutinib, developed by the German firm Merck KGaA has already produced Phase 2 data (as discussed above) and entered Phase 3 last September.

Importantly, the MS market is currently in a state of flux, as the recently approved B-cell–depleting drug ocrelizumab (from Roche) appears to be extremely effective and has rapidly gained market share, with a very similar competitor called ofatumumab from Novartis likely to win FDA approval soon and also hit the market. Meanwhile, Sanofi's existing MS drug Aubagio will begin to face competition from generics starting in 2023; Sanofi management, hoping to defend the company's position in this therapeutic area, apparently views the BTK-inhibitor approach as a bid to stay relevant.[19]

But we believe the underlying biology doesn't add up. The stunning efficacy of ocrelizumab and ofatumumab come down to their ability to cause the death of most of the B cells in a patient's body – not the earliest-stage pro-B cells or the plasma cells that actually manufacture antibodies but, critically, the memory B cells that can persist for years after their initial activation and, in response to re-encountering their target antigen, can quickly proliferate and give rise to new antibody-generating plasma cells. By wiping out established populations of pathogenic, autoreactive memory B cells, anti-CD20 agents like ocrelizumab can give patients a clean slate. Over time, their B-cell repertoires repopulate, but because the new B-cell lineages have receptors specified by randomly reshuffled genes, they are unlikely to react in the same way against the patients' own nervous systems. BTK inhibitors, by contrast, suppress the creation of new B-cell lineages in the bone marrow – a mode of action that seems irrelevant to the etiology of MS, where the "bad" lineages have already developed and matured. Thus we see little reason to expect BTK inhibitors to work in MS (just as with other autoimmune diseases).

So will the upcoming Phase 2 data release prove this theory right? Alas, it will probably prove nothing either way. Rather than setting up a clean comparison between patients on '168 and patients on placebo, the trial seems almost designed to be confusing and inconclusive, with eight different experimental groups, each including only ~16 patients. For each of four different dose levels, there were two subgroups: one taking placebo for the first 4 weeks followed by drug for the following 12 weeks and one taking drug for the first 12 weeks followed by placebo for the following 4 weeks. There is thus no straightforward head-to-head match-up between pure drug and pure placebo. In addition, all the stated efficacy-related endpoints involve short-term MRI-based measurements; unlike in the evobrutinib Phase 2 trial, there appears to be no attempt to track more practical outcomes like relapse rates or disability progression, making results even harder to interpret. Indeed, even bullish observers have noticed these flaws, with one sell-side analyst recently remarking that "the '168 study is complex and carries some risks leading of a heterogeneous result (few patients on each cohort or different results in different cohorts at the

[19] See Cowen's note on Sanofi dated January 13, 2020: "Despite the rise of anti-CD20 B cell-depleting therapies such as Ocrevus (RHHBY) and ofatumumab (NVS), SNY thinks there will be a role for an oral therapy, and '168 may be a replacement for Aubagio post 2023 LOE [loss of exclusivity]."

same dose)" and warning that "[c]onfusion may arise in that '168's trial design could complicate the data readouts and potentially adversely impact future development."[20]

While bulls take comfort in the superficially positive evobrutinib Phase 2 results, it's important to remember that the difference between the BTK inhibitor and placebo with respect to relapse rate and disability progression was statistically insignificant. Moreover, the reported dose/response relationships were anomalous, a common sign of suspect efficacy: for instance, patients in the highest-dose group (evobrutinib 75 mg twice a day) did not actually outperform placebo with respect to MRI progression to a statistically significant degree (adjusted P value of 0.06), and while the *placebo* group included some patients whose EDSS disability score improved by 1 point over 24 weeks, the best that the highest-dose evobrutinib group achieved was just half a point (12). Even taken at face value, the results didn't stand out relative to the existing drug Tecfidera (dimethyl fumarate), tested in a reference arm of the trial; relapse rates and disability progression were comparable. In the words of one MS researcher writing informally in May 2019 (emphasis added):

> So it was positive and better than dimethyl fumarate…Yipee. However let's look at the effect on MRI lesions, it inhibits by about 70% inhibition, which is about as good, or bad, as interferon beta and **miles worse than CD20 depletion**. The relapse rate inhibition is 0.08, which isn't bad and about as good as alemtuzumab, cladribine, ocrelizumab, etc. However, one has to take this all the time, so what's the advantage?
>
> …If you put this head to head against rituximab, ocrelizumab, [ofatumumab], **would it cut the mustard? Based on MRI not really**, so you have to think where you would position this.

In other words, in an MS market increasingly crowded with highly effective treatments, the Phase 2 data for BTK inhibitors don't "cut the mustard" – and Phase 2 data are infamous for overstating drugs' true benefits.

While Principia and Sanofi contend that their BTK inhibitor is better than evobrutinib because it can more readily cross the blood–brain barrier, this notion is perplexing. Ocrelizumab and ofatumumab are large monoclonal antibodies that typically can't enter the brain, yet clinical trials have clearly shown that they're very effective in treating MS by killing B cells throughout the rest of the body. It's difficult to see how they could have such large impacts if the B cells that mattered most were inaccessible inside the brain. But if such B cells aren't important targets in MS, that '168's ability to penetrate the central nervous system is likely irrelevant, not a mark of distinction.

As one final check on the premature hype surrounding Principia and MS, it's worth considering some simple arithmetic. Just last week, one sell-side analyst began to value Principia's share of

[20] SVB Leerink's January 21, 2020, note on Principia.

'168's economics at $1 billion[21] – half of the current market cap. But Principia has already signed away the vast majority of any future sales to Sanofi, in exchange for a series of milestone payments. Even if we assume Principia receives every single remaining milestone payment, implying a 100% chance of successful development and commercialization of the drug, the total undiscounted value to Principia would only be ~$600 million after tax.[22] The remaining ~$400 million would thus represent the expected present value of Principia's ongoing royalties, stated to be "up to the mid-teens" and typically assumed to be 15%. Thus the implied *total* value of '168 (including the portion signed away to Sanofi) would be $400mm/15% or roughly $2.7 billion today – all for an asset that has yet to report a shred of clinical data, belongs to a class of drugs with a history of failure in autoimmune disease, aims to break into a therapeutic area already crowded with new and highly effective drugs, and is following in the footstep of another new drug of the same type with a two-year head start.[23] And even if all of *that* made sense, it would still account for only half of Principia's current valuation. Investors have gotten way ahead of themselves, pricing in all of the upside and none of the risk.

It's worth remembering that the risks in drug development don't only pertain to efficacy but to safety as well. Evobrutinib is a good example: market observers have expressed concern that in the Phase 2 trial the drug appeared to elevate liver-enzyme levels – often a sign of toxicity, though the underlying mechanism is unclear. What other safety risks might be lurking in the world of BTK inhibitors?

BTK Inhibitors Pose Troubling Health Risks

Every drug has side effects – some deemed "off-target" because they stem from the drug's interactions with systems it's not intended to interact with, others deemed "on-target" because they result from the drug's essential mechanism of action and thus are far more difficult to prevent. Principia claims that its BTK inhibitors are more "selective" than predecessors like ibrutinib, "with the aim of reducing off target adverse effects."[24] But what about *on-target* adverse effects?

Recall that, according to our interpretation of the scientific literature, the main effect of BTK inhibition in adult humans is to stop the development of new B-cell lineages (clones) that, under normal conditions, arise continually from the bone marrow. Each person's particular, unique, diverse B-cell repertoire evolves over the course of his or her life: those B cells armed with receptors that successfully detect and help fight off infections give rise to populations of memory B cells and long-lived plasma cells that can persist for years to guard against reinfection; meanwhile, other B-cell lineages with randomly reshuffled genes emerge from the bone marrow,

[21] BofA has set its "pipeline plug value to $1bn for ongoing partnership with Sanofi" (January 23, 2020).
[22] Total potential milestone payments of $765 million less $55 million already received to date, adjusted for taxes at a 21% rate less the benefit of deferred tax assets of $33mm as of YE 2018. See Principia 2018 10-K, p. 126, and 2019 Q3 10-Q, p. 13.
[23] Merck's evobrutinib completed its Phase 2 in January 2018; '168, January 2020.
[24] Principia investor presentation (downloaded January 2020), slide 5.

turn out to have receptors that don't match up with any infectious attack underway at the moment, and die off, to be replaced by a new set of B-cell lineages in the future.

Shutting down the production of new lineages, then, forces patients to rely solely on whatever set of B cells they had at the time of shutdown. But these cells may not have what it takes to handle future attacks. At first, this immune deficit may not matter much; perhaps the only pathogens that patients encounter are familiar ones for which they already have immunological memory, or perhaps other components of the immune system (like T cells or the complement system) can take care of the new threats. With long-term use, however – the kind that Principia envisions for people with autoimmune disorders – people taking BTK inhibitors run a high risk of severe, even fatal, infection.

This concern is far from theoretical. For example, below is the first safety warning provided by AstraZeneca regarding its BTK inhibitor, Calquence, which is more selective and thought to have fewer off-target effects than ibrutinib (emphasis added):

> *Serious and Opportunistic Infections*
> Fatal and serious infections, including opportunistic infections, have occurred in patients with hematologic malignancies treated with CALQUENCE.
>
> **Serious or Grade 3 or higher infections (bacterial, viral, or fungal) occurred in 19% of 1029 patients exposed to CALQUENCE in clinical trials,** most often due to respiratory tract infections (11% of all patients, including pneumonia in 6%). … Opportunistic infections in recipients of CALQUENCE have included, but are not limited to, hepatitis B virus reactivation, fungal pneumonia, *Pneumocystis jiroveci* pneumonia, Epstein-Barr virus reactivation, cytomegalovirus, and progressive multifocal leukoencephalopathy (PML).

The presence of Epstein–Barr virus and PML on the list of opportunistic infections seemingly triggered by BTK inhibition should spark particular concern given Principia's intent to use its BTK inhibitor to treat multiple sclerosis: PML is a multiple-sclerosis–like neurological ailment caused by the JC virus (23), while some prominent researchers believe that Epstein–Barr virus is itself the underlying cause of multiple sclerosis (24).

Thus far, Principia has only administered its BTK inhibitors to a small number of people for a short period of time; between the Phase 2 trials for pemphigus and ITP, total enrollment totaled only 58. It's too early to see many problematic infections. But we believe that, with long-term use, BTK inhibition is a ticking time bomb. Already, Principia has reported an alarming number of potentially infection-related adverse events. In the pemphigus trial, 3 out of 27 patients (11% of the total) experienced infections: two upper-respiratory-tract infections graded mild or moderate and one "serious" case of cellulitis, or localized skin inflammation, coupled with "a high fever" and leading to hospitalization.[25] In the ITP trial, adverse events included a case of

[25] Source: March 2019 presentation at the American Academy of Dermatology meeting, slide 16-17.

iridocyclitis, a form of painful eye inflammation sometimes caused by infection, that also led to hospitalization.[26] We expect additional severe infections to manifest as more patients are exposed to Principia's drugs.

For people with life-threatening forms of leukemia, the on-target dangers posed by BTK inhibitors are likely worth enduring. But for those with pemphigus or ITP – conditions that can typically be treated effectively with many other available medications – why take the risk? Even if BTK inhibitors *did* have some benefit for autoimmune disorders – which we deny – their risk/reward trade-offs would be unattractive.

Conclusion

Principia's origins lie in innovative chemistry – optimizing the strength and duration of covalent bonds between small molecules and certain classes of protein. But hitting a target very accurately is no use if it's the wrong target. For autoimmune diseases, BTK is the wrong target. That's why BTK inhibitors have repeatedly failed in such diseases, even as B-cell–depleting therapies have succeeded, and why Principia's drugs, when finally put to the test in legitimate placebo-controlled Phase 3 trials, will also fail, leaving Principia nearly worthless.

[26] Source: December 2019 presentation at the American Society of Hematology meeting, slide 13.

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