**Notable Events in Clinical Research**
- The first evidence of public health decisions guided by the findings of an open, uncontrolled study date back to biblical times (Daniel 1:5–16)
- Avicenna described ground rules for the testing of drugs in “Canon of Medicine” (1025 CE)
- Surgeon Ambroise Pare (1537) “accidentally” conducted the first study of a novel therapy on wounded soldiers
- James Lind (1747) deduced the benefit of citrus for treating scurvy by dividing afflicted sailors into experimental groups
- Hooper’s Medical Dictionary (1811) describes the concept of a “placebo,” highlighting the danger of bias in controlled studies

- U.S. physician Austin Flint (1863) uses a placebo for the first time in a study on rheumatism therapy
- In 1905, the American Medical Association established an advisory board to test potential therapies' quality and safety (and published the results in JAMA)
- The 1906 Pure Food and Drugs Act was enacted by the Bureau of Chemistry to control product quality
- In 1937, formulations of sulfanilamide in ethylene glycol killed over 100 people
- 1938 Food, Drug, and Cosmetic Act mandated companies submit New Drug Applications to the FDA

**How an Experimental Therapy Becomes a Drug**
Following pre-clinical evaluation, drug companies sponsor FDA-regulated clinical trials:

**Phase I** A potential product is tested in humans for the first time, usually in small groups of healthy individuals (20–80 people). How does the body metabolize a drug? How long does it stay in the body? Is it toxic at low doses?

**Phase II** Is this drug effective for the prescribed indication? What range of doses are acceptable? Are there short-term side effects? Typically, phase II enlists several hundred people with the given medical condition, but no other complications. While phase II can assess clinical outcomes, other biomarkers often predominate when determining the trial's outcome

**Phase III** The goal of phase III trials is to test the experimental product in larger groups of people (several hundred to thousands). The patient population is similar to those who will likely be prescribed the drug. Phase III trials are typically years long and assess long-term safety profiles. The measured outcomes are usually clinical in nature, and are designed to determine whether benefits outweigh associated risks.

**Passing the Buck**
- The cost of some prescription drugs presents a very real issue to many people
- The success of one drug will fund the research for many research campaigns
- As the scope of a clinical trial increases, so does the associated cost
- Phase III trials are therefore the highest cost to a drug development effort
- An estimated 12% of drugs that enter human trials will eventually be approved
- The promise of a positive phase II outcome has often been proven false hope after phase III
- A phase III clinical failure is akin to being stopped at the one-yard line in American football

**In This Seminar**
- Case studies will be presented highlighting the intense difficulty of phase III
- Several therapeutic areas will be explored, pointing to the difficulty of some important areas of research
- Selections were made based on the availability of chemical literature
- Biologics will not be covered
- The presented material is intended to provide a glance into the very large, complex science that is clinical trial design and is not intended to be comprehensive in any way

**Useful Resources**

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**DRUG FD A**

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**Baran Group Meeting**
25 January 2020

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**The Longest Yard**

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**Nebuchadnezzar II**
King of Babylon (605-562 BCE)

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**James Lind’s Scurvy experiment, 1747**

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**Streptomycin**

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**ClinicalTrials.gov**

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**FierceBiotech**

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**ENDPOINTS NEWS**

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**Excellent review:** [fda.gov/media/102332/download](https://fda.gov/media/102332/download)
Alzheimer's Disease (AD)

- AD is a devastating neurodegenerative brain disorder that leads to progressive loss of memory and other higher cognitive function, and ultimately leads to death.
- Age is the greatest risk factor, so longer lifespan means more AD cases.
- There are an estimated 44 million people afflicted with AD worldwide, and these numbers are projected to dramatically increase in the coming decades.
- Left unchecked, these numbers will likely bankrupt healthcare systems and overwhelm society as a whole.

AD Biomarkers

Disease Pathology

- Extraneuronal deposits consisting of 4 kDa peptides called the amyloid-β protein (Aβ)
- Caused by overproduction of Aβ, mediated by the sequential action of β- and γ-secretases.
- Intraneuronal deposits consisting of 353–441 residue protein called tau (neurofibrillary tangles).
- Mutations in Aβ precursor proteins are common for inherited early-onset AD, while allelic variants of apolipoprotein E (ApoE), which clears Aβ, are implicated in late-onset AD.
- Tau protein overproduction is triggered by Aβ, and is prone to neurotoxic aggregation.
- Tau protein is hyperphosphorylated.

Current FDA-approved therapies are symptomatic treatments that do not address underlying progressive neurodegeneration.

BACE1 as a Target for AD

- The "amyloid hypothesis" proposes that formation of Aβ plaques initiates a series of outcomes leading to dementia.
- The production of Aβ is mediated by secretase proteins, including BACE1.
- BACE1 was first cloned and identified in 1999 and has since been an attractive target towards AD therapy.
- BACE1 is a complex target whose activity is in the brain itself.

>20 BACE1 inhibitors have failed in clinical trials.

Verubecestat (Merck, 2011–2018)

- Discovered from HTS effort identifying fragments with good target binding affinity.
- NMR studies of hydrogen bonding were used to drive initial screening effort.
- Hit-to-lead optimization lead to the discovery of MK-8931 (verubecestat).

Initial Fragment Screening Hits (BACE1 Kᵋ):

- 550 nM
- 15 μM
- 2 μM

BACE1 Kᵋ = 2.4 nM

1st Gen. Med Chem Route to MK-8931

J. Med. Chem. 2016, 59, 10435

1st Generation MC route provided material early preclinical data, however...

Issues with Med. Chem. Route:

- PG required on guanidine core
- Chiral salt for increased optical purity
- Nitro reduction messy and exothermic
- DCM solvent undesired
- 13% overall yield

MCM: Memantine, donepezil, galantamine, rivastigmine

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The Longest Yard

Thomas P. Stratton

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2nd Generation Improvements (Merck Process)
- T.M.-catalyzed C–N bond formation was sought
- Protodeborination was suppressed by solvent choice and judicious stoichiometry control
- Ligand screening was crucial for reactivity and chemoselectivity problems

Verubecestat (MK-8931)

Mannich Addition Problematic:
- Kinetic competition between nucleophilic addition and α-deprotonation

Flow chemistry was leveraged to control and optimize mixer type, flow rate, residence time, stoichiometry, temperature, and conversion

3rd Generation Improvements (Merck Process)

Bonus Method: Amine Cyanation!

Problems with cyanogen bromide:
- acute toxicity
- M.P. = 52 °C; B.P. = 61.5 °C
- moisture sensitivity (releases HCN, HBr)

Org. Lett. 2019, 21, 1268
Applicable to a range of 1° and 2° amines, though not necessarily safe

Clinical Fate of Verubecestat (MK-8931)

Phase I (December 2011)
- Healthy adult volunteers were given a placebo, a single dose of 20–550 mg, or 10–250 mg once daily for 14 days
- Subjects were monitored for adverse effects and Aβ42 levels in cerebral spinal fluid
- MK-8931 was well tolerated in all cohorts and CSF Aβ42 levels were reduced 25–94%
- 32 patients with mild–moderate AD were then recruited to evaluate safety and PK
- Study established total renal clearance within 120 h (incl. patients w/ kidney problems)

Alzheimer’s Dement. 2012, 8, 704; see also clinicaltrials.gov/show/NCT01496170

Phase II (December 2011–June 2012)
- 400 mild–moderate AD patients were recruited for a long term safety study
- 12–40 mg dosage was administered for 65 weeks
- Favorable qualitative scores for clinical outcomes led to 260 week extension

see also clinicaltrials.gov/show/NCT01496170

Phase III (November 2012–April 2017)
- 1958 AD patients were enrolled in a study that spanned 238 clinics in 21 countries
- Three randomized groups: 12-mg group; 40-mg group; placebo group
- Trial terminated for futility after 50 months (5 months ahead of schedule)
- Qualitative scores for both experimental groups showed no improvement over placebo
- Recorded adverse effects absent in placebo group included rash, falls and injuries, sleep disturbance, suicidal ideation, weight loss, and hair color change
- Merck announced complete discontinuation of clinical trials on February 13, 2018


What about BACE1 and AD therapy in general?

The clinical failures of MK-8931 are just one example of many attempts to modulate BACE1, all resulting in failure. See above cited review for examples, as well as diverging strategies.

“This suggests that once dementia is present, disease progression may be independent of Aβ production or, alternatively, that the amyloid hypothesis of Alzheimer’s disease may not be correct. Because Aβ deposition takes place years before clinical symptoms become apparent, it has been proposed that treatments targeting amyloid should be implemented early in the disease process, before the onset of clinical symptoms.”

**The Longest Yard**

**Merck’s Migraine Headaches**
- Migraines are episodic headaches lasting up to 72 hours, and are typified by severe pain, often accompanied by nausea and sensitivity to light and sound.
- An estimated 13% of adults worldwide suffer from this disabling condition.
- Over-the-counter pain relievers are the most common remedy.
- FDA-approved prescription treatments were limited to the triptans until recently.
- Vasodilator properties of triptans limited their use in cardiovascular patients.

**Current FDA-approved therapies**
- **Rivatriptan** (Merck)
- **Sumatriptan** (Teva)

**CGRP as a Rational, Viable Migraine Drug Target**
- In 2005, Boehringer Ingelheim began medicinal chemistry efforts targeting calcitonin gene-related peptide (CGRP), (see J. Med. Chem. 2005, 48, 5921)
- CGRP is the major neurotransmitter of the trigeminal vascular system, which has long been implicated in the pathogenesis of migraine headaches.
- Efforts across pharmaceutical research began in earnest to validate CGRP as a legitimate target for migraine therapies and to advance a breakthrough treatment.
- Merck emerged as a leader in the field and soon disclosed their own promising findings.

**1st Generation Discovery Route**

```
MeO-\text{OMe} \quad \text{Br} \quad \text{Dmb} \quad \text{Grubbs II; then TFA} \quad \text{H}_2 \quad \text{Pd/C, Boc}_2\text{O} \\
\text{NH}_2 \cdot \text{HCl} \quad \text{NMe}_2 \quad \text{NH}\text{Cbz} \quad (15\%) \quad (51\% \text{ yield}; 2:1 \text{ dr})
```

- **Telmecapant** (MK-0974)
  J. Med. Chem. 2007, 50, 5564

- RCM very inefficient / low yielding / high catalyst loading
- Separating of diastereomers by chromatography

**2nd Generation Discovery Route**

```
\text{CO}_2\text{Bn} \quad \text{TMSCHN}_2\text{; Boc}_2\text{O; then DIBAL-H} \quad \text{MeNO}_2\text{; MsCl, Et}_3\text{N (61\%)}
\text{HO}_2\text{C} \quad \text{H}_2 \quad \text{Pd/C; EDC, HOAT; then TFA} \\
\text{NHBoc} \quad (65\%, 3 \text{ steps}) \quad (96\%, 93:7 \text{ dr})
```

- **Telmecapant**
  Org. Lett. 2008, 10, 3235

**Born out of a previous lead compound:**

```
\text{CGRP} K_i = 2\text{nM} \quad \text{cAMP IC}_{50} = 4 \text{nM} \quad \text{“serum shift” = 28-fold}
```

**BMCL 2007, 17, 4795**

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**Thomas P. Stratton**

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The Longest Yard

Clinical Fate of Telcagepant

**Phase I** (November 2004–May 2005)
- 24 healthy adults were recruited for a study to determine safety and tolerable dose
- Groups were dosed with telcagepant alone and with triptan, and placebo
- No appreciable increase in blood pressure was observed in either experimental group
  *Cephalalgia 2013, 33, 1292 see also clinicaltrials.gov/ct2/show/NCT00701389

**Phase II** (November 2005–May 2006)
- 420 healthy adults with episodic migraines were recruited in a multicenter study
- Groups were given a range of doses (25–600 mg) for acute migraine symptoms
- Experimental groups reported a significant decrease in migraine-related pain
- No significant adverse effects were reported in any experimental group relative to placebo
  *Neurology 2008, 70, 1304 see also clinicaltrials.gov/ct2/show/NCT00246337

**Phase III** (March 2007–December 2007)
- 1703 healthy adults with episodic migraines were recruited in a multicenter study
- Groups were given a range of doses (50–300 mg) for acute migraine symptoms
  - "This study confirmed previous findings that telcagepant 300 mg was effective at relieving pain and other migraine symptoms at 2 hours and providing sustained pain freedom up to 24 hours. In this study, telcagepant 150 mg was also effective. Telcagepant was generally well tolerated."
  *Neurology 2009, 73, 970 see also clinicaltrials.gov/ct2/show/NCT00432237

All seems well, so why not go after prophylaxis? Back to the clinic...

**Phase IIa** (November 2008–May 2009)
- 660 healthy adults with episodic migraines were recruited in a multicenter study
- Groups were given a range of doses (140–280 mg) twice daily for migraine prophylaxis
  - "The trial was terminated following a recommendation from the Safety Monitoring Board due to hepatotoxicity concerns. Thirteen patients [in the experimental group] had a alanine aminotransferase elevation >3x the upper limit of normal..."
  *Neurology 2014, 83, 958 see also clinicaltrials.gov/ct2/show/NCT00797667

On July 29, 2011, Merck announced it was terminating research into telcagepant, and that it would discontinue its efforts in this therapeutic area. This announcement was paired with the decision to reduce 11–13% of Merck’s total workforce.

- On July 7, 2015, Allergan purchased Merck’s migraine portfolio for $250M
- Among these assets was MK-1602, another CGRP-antagonist for migraine
- MK-1602 (Ubrogepant) was awarded FDA approval for acute migraine treatment on Dec 23, 2019
- There are currently four FDA-approved migraine treatments targeting CGRP

**Cardiovascular Disease**

- Cholesterol buildup in heart disease patients causes hardening of the arteries in a process called atherosclerosis
- Atherosclerosis restricts blood flow to the heart, which is a cause of heart attacks
- Atherosclerosis is thought to be driven by inflammation
- Lp-PLA2 is a protein produced by inflammatory cells, and high Lp-PLA2 levels are thought to predict heart attack risk

**Allergan**

**Ubrevly®** (a.k.a. MK-1602)

**Emgality**

**AJOVY**

**Amgen / Novartis**

**Teva**

**Eli Lilly**

**Med. Chem. Route** *BMCL 2003, 13, 1067*

**Phase IIa** - November 2005–August 2006

- 330 patients with cardiovascular disease were dosed with 160 mg darapladib daily or placebo
- Levels of Lp-PLA2 were significantly lower in the experimental group
- Necrotic core size, atheroma size, and blood biomarkers were all favorable for darapladib

**Phase III - December 2008–October 2011**

- 1,340 patients were enrolled across 43 sites in the USA and 31 in Europe
- 1,000 patients were treated in the treatment arm
- The 429 patients in the placebo arm were monitored up to 3 years
- The second trial followed patients who had a heart attack thirty days prior to starting treatment
- In both trials, experimental and control groups displayed statistically insignificant differences
- On May 13, 2014, GSK disclosed these failures and soon removed darapladib from their pipeline

**Allergan**

**Ubrevly®** (a.k.a. MK-1602)

**Emgality**

**AJOVY**

**Amgen / Novartis**

**Teva**

**Eli Lilly**

**Med. Chem. Route** *BMCL 2003, 13, 1067*

**Phase IIa** - November 2005–June 2006

- 959 patients were monitored for interileukin-6 levels, with significant success
- Human Genome Science CEO Tom Watkins predicted that darapladib was a "blockbuster in the making"
Congestive Heart Failure (CHF) - CHF is characterized by failure of the heart to pump enough blood to meet biological needs
- When the heart does not pump efficiently, levels of the hormone renin rise
- The accompanying fluid overload in the body can be quantified by levels of brain natriuretic peptide (BNP)
- Direct renin inhibitors emerged as an attractive target for treating heart failure and high blood pressure

Aliskiren (Novartis)

Novartis’s First-in-class renin inhibitor
- Aliskiren was awarded FDA approval for hypertension March 2007
- Given renin’s role in CHF, Novartis sponsored a study to determine the efficacy of aliskiren in conjunction with standard therapy

Discovery Route TL 2000, 41, 10085

Novartis Process Route TL 2000, 41, 10091

Clinical Fate of Aliskiren for CHF

Phase II - May 2007 Circ. Heart Fail. 2008, 1, 17
- 300 patients with stage II to stage IV heart failure were enlisted in a multicenter study
- Plasma BNP was significantly reduced in experimental group
- Minimal adverse effects were noted, and a broader study was thus undertaken

Phase III - May 2009–December 2011 JAMA 2013, 309, 1125
- Over 1,600 patients were recruited to determine aliskiren’s clinical efficacy for CHF
- BNP levels were shown to significantly decrease in the experimental group
- In spite of this, cardiovascular-related death or CHF-related rehospitalization were not significantly reduced relative to the control group
- Experimental group had significantly higher kidney failure and lower blood pressure
- Aliskiren for CHF was promptly removed from consideration for this specific indication

Further reading:
OPRD 2013, 17, 1458 OPRD 2015, 19, 611 OPRD 2016, 20, 270
**Cholesterol Drugs**

- High-Density Cholesterol (HDL) is generally described as “good” cholesterol, while Low-Density Cholesterol (LDL) is described as “bad” cholesterol.
- HDL and LDL levels have a strong correlation with low risk and high risk for heart disease, respectively.
- Cholesteryl ester transfer protein (CETP) is an enzyme that transfers cholesterol molecules from HDL to LDL.
- Torcetrapib inhibits CETP, simultaneously raising HDL while lowering LDL.

**First Generation Process Route**  **OPRD 2016, 10, 464**

- CF₃
- NH₂
- TiCl₄
- EtCHO
- EtCHO, benzotriazole
- NHCO₂Bn
- BF₃·OEt₂
- low yielding
- (racemic)
- NHCO₂Bn
- Cat. TsOH
- (78%)

**Asymmetric Process Route**  **OPRD 2006, 10, 472**

- Me
- NH₂
- H₂O
- Boc₂O, MeCl (86%)
- Me
- NHBOC
- NaCN, Bu₄NBr then TsOH (74%)
- Me
- NH₂
- CN
- CF₃
- Pd(OAc)₂ (0.75 mol%), Ph₃P-Ph (1.12 mol%), Cs₂CO₃
- H₂SO₄ (2.2 mL/g), H₂O (4 eq.) (77%, 2 steps)
- CF₃
- NH₂
- H₂O (oil; used crude)
- (94%)
- CF₃
- N
- NHCO₂Me
- NaBH₄, MgCl₂ then HCl (60%)
- CF₃
- N
- NHCO₂Me
- Torcetrapib

**Clinical Fate of Torcetrapib**


- 400 patients enrolled in a study to observe predictors of HDL and LDL levels.
- Significant increases in HDL and decreases in LDL were observed.
- Minor increases in blood pressure were observed in a small amount of cases.
- Pfizer enthusiastically pushed forward, reportedly spending over $800M to develop and test torcetrapib.
- Pfizer executive Jeff Kindler was quoted saying torcetrapib may be “one of the most important developments in our generation.”


- 15,067 patients at 260 research centers spanning 7 countries were enrolled in phase III.
- Patients were administered torcetrapib or placebo in addition to a statin.
- Significant increases in HDL and decreases in LDL were noted in the torcetrapib group.
- However, the drug was not effective in primary clinical outcomes and proved dangerous.
- Patients who received torcetrapib were 25% more likely to suffer a major adverse cardiac event, and were 58% more likely to die from any cause than the placebo group.
- Significant blood pressure increases were also observed in the torcetrapib group.
- The trial was halted three years earlier than expected due to these safety concerns.

**HIV-associated nerve pain**

- Many HIV patients experience a burning-type of pain due to nerve damage.
- Called HIV-associated distal systemic polyneuropathy (HIV-DSP).
- It is the most common nerve complication from HIV infection.

**Capsaicin**

- Capsaicin is a naturally-occurring compound found in chili peppers.
- In addition to its popularly-known uses (see above), it also has therapeutic qualities.
- Qutenza is an FDA-approved skin patch for shingles-associated nerve pain.
- NeurogesX sponsored a clinical study to determine capsaicin’s efficacy for HIV-DSP.


- 12 patients with HIV-DSP were recruited for an open-label pilot study.
- NGX-4010 (8% capsaicin patch) was applied for one hour as a one-time treatment.
- Patients were then monitored for 12 weeks, and the majority claimed a significant pain reduction.


- 800 patients with HIV-DSP were recruited to receive either NGX-4010 or placebo control.
- The larger double-blind study did not replicate the earlier findings, showing no significant pain reduction.
- In 2012, a FDA Advisory Committee analyzed all results and did not recommend approval.
Immuno Oncology

- The central tenant of cancer immunotherapy is that the immune system can be induced to recognize and eliminate malignant cells within the human body.
- In the past decade several breakthrough medications were awarded FDA approval and have validated the novel immune mediated mechanism of action for cancer therapy.
- While monoclonal antibodies (mAbs) have led the way, there is much interest in small molecule immuno oncology therapies (see BMCL 2018, 28, 319 for an excellent review).

IDO1, and Incyte’s Epacadostat

- In 1999, Indoleamine-2,3-dioxygenase 1 (IDO1) was shown to play an immunomodulatory role in fetal protection from the maternal immune system.
- Multiple tumor types (e.g. melanoma, ovarian, and colon) overexpress IDO1 and are believed to subvert this this immunomodulatory mechanism and promote local cancer tolerance.
- Studies have demonstrated a synergistic effect when IDO1 inhibitors are used in combination with approved anti-PDL1 mAbs.
- Thus, research into therapeutics targeting IDO1 has surged in the previous decade.
- Incyte’s Epacadostat entered the clinic as a first-in-class small molecule IDO1 inhibitor and garnered much attention as many others in the field were not far behind.

Clinical Studies with Epacadostat

“What was once one of the most anticipated drug classes in the industry has undergone a rapid transformation.” - FierceBiotech, May 2018

59 clinical trials for Epacadostat have been filed with the US National Library of Medicine.

Case study: Melanoma combination therapy with Merck’s Pembrolizumab (Keytruda)

Phase II - July 2014–November 2015

- 54 patients were recruited and dosed with the above drug combination
- Overall response rate was determined to be 56%
- Progression-free patient survival was 65% at six months
- Adverse effects were limited and consistent with those of Keytruda

see also clinicaltrials.gov/ct2/show/NCT02178722

Phase III - June 2016–August 2017

- 706 patients with stage III or stage IV melanoma were recruited for an international, randomized, placebo-controlled, double blind study
- “Epacadostat 100 mg twice daily plus pembrolizumab did not improve progression-free survival or overall survival compared with placebo plus pembrolizumab in patients with unresectable or metastatic melanoma. The usefulness of IDO1 inhibition as a strategy to enhance anti-PD-1 therapy activity in cancer remains uncertain.”

The Lancet Oncology 2019, 20, 1083
see also clinicaltrials.gov/ct2/show/NCT02752074

The failure of this potent, selective IDO1 inhibitor in combination with other checkpoint inhibitors has cast serious doubt on the viability of the described biology.

Future Outlook:

- Some serious setbacks have proved a formidable obstacle to advance this mode of combination therapy.
- Despite this, IDO1 inhibitors are still being investigated, and numerous clinical trials are ongoing (including for Epacadostat).

Discovery Route


- NaNO₂, 6N HCl then NH₂OH (90%)
- NaNO₂, AcOH, 6N HCl then KOH, 100 °C (81%)
- CDI (98%)
- H₂N—NH₂ Ar then TFA (98%)
- CISO₃NCO, tBuOH then NaOH (78%)
- Epacadostat

BMS-986205 ($800M acquisition from Flexus) halted in Phase III (April 2018)
clinicaltrials.gov/ct2/show/NCT03417037

PF-06840003 halted before Phase II commenced
clinicaltrials.gov/ct2/show/NCT02764151

GDC-0919 (Navoximod) halted before Phase II commenced
clinicaltrials.gov/ct2/show/NCT02048709
The Longest Yard

**Heptocellular Carcinoma (HCC)**

- HCC is the most common type of primary liver cancer (80% of cases)
- Depending on disease progression, treatment options for liver cancers include surgery to remove the tumor, embolization to block tumor blood supply, radiation, and transplantation
- The only FDA-approved drug is sorafenib, which delays tumor growth and improves survival by inhibiting certain signals used in cell growth or function

![Sorafenib (Bayer / Onyx)](image)

- Sorafenib, like many chemotherapy drugs, has a host of common and sometimes very serious side effects
- An appreciable patient population does not respond to Sorafenib
- Brivanib was developed by BMS to address these issues with Sorafenib, and targets vascular endothelial growth factor (VEGFR), which supplies blood to new tumor growth

**BMS Discovery Route**

**BMCL 2005, 15, 1429**

*J. Med. Chem. 2008, 51, 1766*

- TosMIC, NaH, DMSO; then AlCl₃, CCl₄, then NaOEt, EtOH (50%)
- EtO₂C
- CO₂Et
- Ph₂P-ONH₂
- NaH, DMF; then formamide; then POCl₃ (75% overall)
- K₂CO₃, DMF
- Brivanib - BMS VEGFR-2 Inhibitor

**BMS-504215 (API)**

(Cbz-Ala, HATU; then Pd/C, COOHNH₃⁺ (99%)

**BMS-582664 (Pro-drug)**

**Phase Ila - March 2007–May 2009**

*Clin. Cancer Res. 2011, 17, 1973*

- 55 patients with advanced HCC received a daily dose of brivanib
- CT / MRI measurements of tumor volume were used to evaluate clinical efficacy
- According to the published report, one patient demonstrated complete response, three with a partial response, and 24 patients showed stable disease state

**Phase IIb - February 2009–November 2011**

*Clin. Cancer Res. 2012, 18, 2090*

- 46 patients with advanced HCC and were unresponsive to sorafenib were recruited
- Using the same metrics as above, 2 patients showed a partial response, while 19 had stable disease following treatment
- Taken together, the phase II studies demonstrated brivanib's antitumor quality, in addition to a reported "manageable safety profile"

**Phase III - February 2009–September 2012**


*Hepatology 2014, 60, 1697; clinicaltrials.gov/ct2/show/NCT01108705*

- Several phase III trials were designed to isolate the effects of brivanib
- Statistically-significant antitumor activity was observed, but no evidence of improved overall patient survival was demonstrated
- 1,100 patients with advanced HCC were enrolled in a direct comparison study with sorafenib, with median survival rates at 9.5 and 9.9 months, respectively
- Brivanib was "less well-tolerated" relative to sorafenib according to the study, with reports of decreased appetite, fatigue, nausea, and low blood sodium
- Subsequent trials were terminated due to these findings and the brivanib program was terminated

**Conclusions and Outlook**

- The obvious: bringing a drug from the bench to the bedside is no easy task
- Findings from animal models do not always equal results in humans
- Biological results do not necessarily translate to clinical outcomes
- Researchers will continue to push on to find new cures
- Most people in this business are driven by the desire to improve the lives patients
- In 2019 alone, 48 new drugs were granted FDA approval *(see L. Barton GM)*

This area was left blank, intentionally.