Duvelisib: Harnessing the Power of Dual PI3K Inhibition

Omni Berkshire Place, New York City
May 2, 2018
Forward Looking Statements

This presentation includes forward-looking statements about Verastem’s strategy, future plans and prospects, including statements regarding the development and activity of Verastem’s investigational product candidates, including duvelisib and defactinib, and Verastem's PI3K and FAK programs generally, the structure of our planned and pending clinical trials, Verastem’s potential collaboration opportunities and the timeline and indications for clinical development and regulatory submissions. The words "anticipate," "believe," "estimate," "expect," "intend," "may," "plan," "predict," "project," "target," "potential," "will," "would," "could," "should," "continue," and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. Each forward-looking statement is subject to risks and uncertainties that could cause actual results to differ materially from those expressed or implied in such statement. Applicable risks and uncertainties include the risks that approval of the NDA will not occur on the expected timeframes or at all, including by the FDA's target action date; that a filing of a European Marketing Application may not be achieved before the end of the year, if at all; that even if data from clinical trials is positive, regulatory authorities may require additional studies for approval and the product may not prove to be safe and effective; that the preclinical testing of Verastem’s product candidates and preliminary or interim data from clinical trials may not be predictive of the results or success of ongoing or later clinical trials; that the full data from the DUO study will not be consistent with the previously presented results of the study; that data may not be available when expected, including for the Phase 3 DUO™ study; that the degree of market acceptance of product candidates, if approved, may be lower than expected; that the timing, scope and rate of reimbursement for our product candidates is uncertain; that there may be competitive developments affecting our product candidates; that data may not be available when expected; that enrollment of clinical trials may take longer than expected; that our product candidates will cause unexpected safety events or result in an unmanageable safety profile as compared to their level of efficacy; that duvelisib will be ineffective at treating patients with lymphoid malignancies; that Verastem will be unable to successfully initiate or complete the clinical development of its product candidates; that the development of Verastem's product candidates will take longer or cost more than planned; that Verastem may not have sufficient cash to fund its contemplated operations; that Verastem or Infinity Pharmaceuticals, Inc. (Infinity) will fail to fully perform under the duvelisib license agreement; that Verastem may be unable to make additional draws under its debt facility or obtain adequate financing in the future through product licensing, co-promotional arrangements, public or private equity, debt financing or otherwise; that Verastem will not pursue or submit regulatory filings for its product candidates, including for duvelisib in patients with CLL/SLL or iNHL; and that Verastem’s product candidates will not receive regulatory approval, become commercially successful products, or result in new treatment options being offered to patients. Other risks and uncertainties include those identified under the heading "Risk Factors" in Verastem's Annual Report on Form 10-K for the year ended December 31, 2017 and in any subsequent filings with the U.S. Securities and Exchange Commission. The forward-looking statements contained in this press release reflect Verastem’s views as of the date of this release, and Verastem does not undertake and specifically disclaims any obligation to update any forward-looking statements.
AGENDA

CEO Welcome
Robert Forrester, President & Chief Executive Officer, Verastem Oncology

The CLL Patient Journey
Brian Koffman, MDCM, DCFP, FCFP, DABFP, MSEd, Physician, Medical Director of the Chronic Lymphocytic Leukemia (CLL) Society and CLL Patient

The Evolution of Blood Cancer Treatments
Lori Kunkel, MD, Former Chief Medical Officer, Pharmacyclics

Unmet Needs and the Role of PI3K Inhibitors
Jennifer Brown, MD, PhD, Associate Professor of Medicine, Harvard Medical School; Director, CLL Center of the Division of Hematologic Malignancies, Dana-Farber Cancer Institute

Duvelisib for the Treatment of CLL/SLL and FL
Ian Flinn, MD, PhD, Director, Blood Cancer Research Program at Sarah Cannon Research Institute, and Lead Investigator of the DUO and DYNAMO Studies

Duvelisib for the treatment of T-cell lymphomas
Steven Horwitz, MD, Medical Oncologist, Memorial Sloan Kettering Cancer Center and NYC Health + Hospitals/Bellevue

Unlocking the potential of duvelisib: Path to commercial launch
Joseph Lobacki, Chief Commercial Officer, Verastem Oncology

Question & Answer Session with Full Panel
The CLL Patient Journey
Brian Koffman, MDCM, DCFP, FCFP, DABFP, MSEd
Brian Koffman
MDCM, FCFP, DABFP, MS Ed

THANK YOU!
Disclosure

• I am alive and here today because I started on a Phase 1 clinical trial of new oral drug, PCI-32765 now known as ibrutinib or IMBRUVICA

• I am planning to be around much longer due to my very recent CAR-T trial

• I have a bias towards expert care, novel therapies, and keeping options open
Disclosure

• I am a physician, patient, advocate, retired professor, teacher, writer, blogger [http://bkoffman.blogspot.com](http://bkoffman.blogspot.com),

• Founder and Medical director of nonprofit CLL Society Inc. [http://cllsociety.org](http://cllsociety.org)

• Cancer survivor
Learning Objectives

• Use one case history (mine) and a recent online survey to illustrate how we patients make decisions and get our information.

• Recognize what patients want and don’t want out of their therapy as options change.

• Weigh patient’s view of the risks and benefits of novel therapies inside and out of clinical trials.
How I have Survived

• What I Have Done to Beat those Odds despite very High Risk Disease
  – Refusing some treatments and choosing others
  – Hiring and firing HCPs
  – Getting expert on my team
  – Becoming an “expert” patient
  – Enrolling in clinical trials
  – Insuring “next” options
  – Getting Insurance to pay
  – Joining a Support group
Diagnosed when 54 years old in 2005

The Day You NEVER Forget

(D-Day: Diagnosis Day)
I’m afraid you’ve had a paradigm shift.
**Prognosis**

11q deletion (later 17p deletion), complex karyotype, CD38+, unmutated, ZAP70 +, (now loss of Notch 1, CDKN2A, Dnmt3a, XOP1)
Kaplan Meir Curve
(or my 1 in 20 chance of living >5 years)

![Kaplan Meir Curve graph]

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<tr>
<th></th>
<th>n</th>
<th>Events</th>
<th>Obs./Exp.</th>
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<tbody>
<tr>
<td>No TP53 mutation</td>
<td>489</td>
<td>428</td>
<td>0.9</td>
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<tr>
<td>TP53 mutation</td>
<td>40</td>
<td>39</td>
<td>2.9</td>
</tr>
</tbody>
</table>

2P < .001

April 11, 2011 as 10.1200/JCO.2010.32.0838
Big Bearded Mountain Man Look
To Hide my Lymph Nodes
Complication (ITP) and Its Treatment

• Single digit platelets with spontaneous petechiae and bruising

• Failed
  – Steroids
  – IVIG
  – Rituximab
  – Cyclosporin
  – Emergency Laparoscopic Splenectomy
    • HCT dropped from 14 to 7 post-op
Bleeding after Splenectomy
Surprise Remission →
Aggressive Therapy Decision

• Combination of Rituximab and cyclosporin (with no chemotherapy) not only controlled ITP but remitted the CLL
  – 90% bone marrow involvement → 6%
  – Normal CBC and no palpable nodes but enlarged nodes on CT scan

• NO TWO PATIENTS ARE ALIKE
First Remission Allogeneic Stem Cell Transplant

- 12 out of 12 matched unrelated young male donor
- FRC conditioning, no ATG
How to Tell my Story?

http://bkoffman.blogspot.com > 1.3 million page views since established
Quick Relapse

Rejected graft, relapsed CLL and ITP
ASH 2011: The Early Buzz about PCI-32765 (ibrutinib) & CAL-101 (idelalisib)

– Cracked the biology of CLL
– Optimism about a new oral BTK and PI3K inhibitors in trials
– Broad agreement this was something very different
Paradigm Shift
Efficacy and Safety Study of PCI-32765 Combine With Ofatumumab in CLL (PCYC-1109-CA)

Purpose

The purpose of this study is to determine the efficacy and safety of a fixed-dose, daily regimen of orally administered PCI-32765 combined with ofatumumab in subjects with relapsed/refractory CLL/SLL and related diseases.
Ask your doctor if taking a pill to solve all your problems is right for you.

“Ask your doctor if taking a pill to solve all your problems is right for you.”
Deep and Durable Partial Remission

- Now 71 months on ibrutinib (IMBRUVICA)
- Markedly improved QOL
  - Improved energy with traveling around the world
- Bruising and brittle nails most persists AE
- Slow relapse at a genetic level x 18 months, then clinically picking up pace in last few months
- Left trial at OSU Feb. 19, 2018
- Started CAR-T trial at SCCA/Hutch Feb. 28, 2018
The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Know the risks and potential benefits of clinical studies and talk to your health care provider before participating. Read our disclaimer for details.

**Laboratory Treated T Cells in Treating Patients With Relapsed or Refractory Chronic Lymphocytic Leukemia, Non-Hodgkin Lymphoma, or Acute Lymphoblastic Leukemia**

**ClinicalTrials.gov Identifier:**
NCT01865617

**Recruitment Status:**
Recruiting

**First Posted:**
May 31, 2013

**Last Update Posted:**
October 26, 2017

See **Contacts and Locations**

**Sponsor:**
Fred Hutchinson Cancer Research Center

**Collaborator:**
National Cancer Institute (NCI)

**Information provided by (Responsible Party):**
Fred Hutchinson Cancer Research Center
CAR-T Trial

• Chosen due my aggressive and mutagenic disease
• Kept my options open for a novel agent if CAR-T fails
• DOWNSIDE:
  – CAR-T science and art is still in the early learning phase
  – CAR-T is usually quite toxic

• 2 months in Seattle
  – 2 admissions including one with severe inflammation where I was unable to move for days
  – Developed blood clot from immobility
  – Anemia and persistent inflammation

• Day 28+: No CLL detectable in blood, marrow and nodes
Giving Forward

• Speaking from the patients perspective to 1000s of hematologists at iwCLL, EHA and ESH

• Non-profit: THE CLL SOCIETY http://cllsociety.org
  – 65,000 page views a month
  – Established 24 Peer to Peer Support Groups
  – Free Access to Expert Opinions
  – Dozens of Patient and Caregiver Educational Forums at major universities (Dana-Farber, NIH, U. Penn, etc)
  – Research presented at ASH, ASCO and EHA
I think you'll find I'm one of the most empathetic doctors around.
http://cllsociety.org
Factors That Influence Patient Treatment Decision Making in the Era of Novel Agents: An Internet-Based Survey of 281 Patients with Chronic Lymphocytic Leukemia (CLL)

Bryan Koffman, MDCM, DCFFP, DBFMM, MS Ed1, Betsy Desimone, RN, MS2, Kaslin H Kennard, BSN3, Chad Noblan, MD, MBA, FACP4, John C. Byrd, MD5 and Anthony R. Mato, MD, MSCE6


Division of Hematology, Department of Internal Medicine, The Ohio State University, Columbus, OH

RESULTS (continued)

Only 27% of respondents would be willing to take a treatment that included chemotherapy despite its higher risks, but a potential for cure.

Similarly, 40% would be willing to receive CAR-T in a "less extreme scenario" if there offered a chance of cure. Furthermore, respondents that were +/-5 were relatively more important in treatment decisions, which were more likely to be the patients that were less comfortable with CAR-T therapy. Figure 6.

Figure 4. Willingness to Take Life-long Therapy for Long-term Control Without Potential for Cure

Main Sources of Information About CLL

- Patients were also asked for their main sources of information about CLL (Figure 7). This was found to be diverse and included relatives and friends, as well as the internet, articles, textbooks, patients who had been treated, and healthcare providers. Only 20% of respondents had received all of these sources of information. The difference between responses to this question and the main sources of information question may be due to the different ways in which the questions were asked and the variability in how much information patients had. Figure 7.

REFERENCES


In the era of modern therapies, these data provide insight into how clinicians can influence patients when making treatment decisions, which influences patients in their CLL treatment decision-making process and what resources patients use to gain information about CLL.

Conclusions

- 87% of patients reported that they are actively involved in treatment decision making. Physicians and patients are more likely to be involved as the patient’s role increases.

- Patients rely on multiple sources of information beyond their physician, with online sources mentioned more frequently, perhaps related to the convenient accessibility of the internet compared to infrequent doctor visits.

- There is broad patient acceptance of long-term non-curative treatment.

- There is significant patient hesitancy for chemotherapy, CAR-T therapy, and stem cell transplantation despite the paucity of data.

Recommendations

- All medical decisions should be shared between the patient and the doctor.

- Educated patients are more likely to participate in shared decision-making.

- Encourage and assist patient involvement in their care.

- Be prepared for second opinions, and they may not be free of charge.

- Do not assume patients are unwilling to consider long-term non-curative but low-risk therapies.

Limitations

- Our patient respondents were younger, median age 64 years old compared to the median age of 71 to 82 years old data. There were also more females (54%) than generally reported (45%). This likely reflects a selection bias of those completing the survey. Information provided was based on patient answers and could not be independently verified.

- The survey was only available online, hence the results may be influenced by the self-selection of those who use the internet and access the sources mentioned above and may reflect a group of patients who may be more sophisticated and involved in their care.

Response to Limitations

While we recognize the limits imposed by a survey that was only available online, we believe these data are a true reflection of a growing number of CLL patients who are very savvy and knowledgeable about their disease. We hope to offer a paper version of a similar survey in 2017 in order to address these concerns.

About the CLL Society Inc.

The CLL Society Inc. is a 501(c)(3) nonprofit that focuses on patient education and patient support to address the unmet needs of the CLL community.

- The CLL Society website (www.cllsociety.org) which contains the most up-to-date, accurate and patient-friendly information on CLL.

- The CLL Tribune, a quarterly online newsletter with both patient and physician authors.

- CLL specific patient support groups and educational forums.

- CLL patient peer counseling services.

The CLL Society wishes to thank the patients who participated in this important research.


diagram.png

diagram.png

diagram.png

diagram.png

RESULTS

Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean</th>
<th>SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (range)</td>
<td>64-86</td>
<td>7.21</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>56</td>
<td>40</td>
</tr>
<tr>
<td>Time from diagnosis, years (range)</td>
<td>0-27</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Disease Risk Level</td>
<td>1.60</td>
<td>0.93</td>
<td></td>
</tr>
<tr>
<td>Blyth classification groups</td>
<td>65%</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>CLL-18 mutation</td>
<td>14%</td>
<td>9%</td>
<td></td>
</tr>
<tr>
<td>Use of alfa</td>
<td>12%</td>
<td>7%</td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>31</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Original regimen</td>
<td>16%</td>
<td>6%</td>
<td></td>
</tr>
<tr>
<td>Previous regimen</td>
<td>27%</td>
<td>11%</td>
<td></td>
</tr>
<tr>
<td>Morbid (&lt;=2)</td>
<td>51%</td>
<td>47%</td>
<td></td>
</tr>
<tr>
<td>No prior treatment</td>
<td>31</td>
<td>26%</td>
<td></td>
</tr>
<tr>
<td>Prior treatment</td>
<td>32</td>
<td>28%</td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>10</td>
<td>7%</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>31</td>
<td>21%</td>
<td></td>
</tr>
<tr>
<td>Bone Marrow</td>
<td>65%</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>31</td>
<td>21%</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Survey respondents were asked to indicate whether they considered their decision to start treatment, as well as the perception of information provided, towards decision making. 86% of respondents indicated that they considered their decision towards treatment. The most important aspect of treatment was described by 31% of respondents as the site of information about CLL, expert MD and virtual reasonable. The average age of respondent was 61, 85% of respondents, and used social media. (Figure 22).

Figure 1. Factors Informed by Decision-Making in Treatment for CLL

Only 27% of respondents would be willing to take a treatment that included chemotherapy despite its higher risks, but a potential for cure.

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The CLL Society wishes to thank the patients who participated in this important research.
Patient Sources of Information about CLL

(Could choose many)

<table>
<thead>
<tr>
<th>Source</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>Websites</td>
<td>88%</td>
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<tr>
<td>HCPs</td>
<td>71%</td>
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<tr>
<td>Patient Forums</td>
<td>71%</td>
</tr>
<tr>
<td>Blogs by doctors</td>
<td>67%</td>
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<tr>
<td>Blogs by patients</td>
<td>46%</td>
</tr>
<tr>
<td>CLL Webcasts</td>
<td>44%</td>
</tr>
<tr>
<td>Books/Journals</td>
<td>41%</td>
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Source: CLL Society Reader Poll from *The CLL Tribune* Q1 2016
Figure 4. Willingness to Take Life-long Therapy for Long-term Control Without Potential for Cure

Source: CLL Society Reader Poll from The CLL Tribune Q1 2016
Willingness to Take Therapy with Higher Risks but with Potential for Cure

- **Includes Chemo**
  - All Patients: 37%
  - High-Risk Patients: 50%

- **CAR-T or BMT**
  - All Patients: 42%
  - High-Risk Patients: 51%

CLL Society Reader Poll from *The CLL Tribune* Q1 2016
What Patients Aren’t Worried About

- OUR MINOR CONCERN are short term:
  - Infusion reactions
  - Tumor lysis syndrome
  - Cytokine release syndrome
  - Acute infections
  - Acute GI, CNS Neuro, Derm

We trust our doctors to save us
What Patients Are Worried About

• OUR MAJOR CONCERN are long term:
  – Damage to our bone marrow
  – DNA mutation
  – Selection of more aggressive clones
  – Immune damage → late serious infections
  – Late complications including CVS and neurological
  – Refractory disease when we relapse
  – Secondary cancers (including MDS)

BECAUSE:

• Infections are the leading cause of death in CLL
• 50% risk of secondary cancers
So What Patients Do Want?

We want more targeted, less toxic therapies:

Because Today:
- Targeted therapies are preferred frontline for all high risk and most other patients and should be the only choice in nearly all relapsed patients.
- More targeted options needed for relapses and to match different patients’ profiles and preferences.
- CIT should be reserved for the few healthy young patients where it is potentially curative.

Because in the Future:
- Curative therapies are possible: either cellular or combinations novel agents or both used in combination.
Learning Objectives

• Use one case history (mine) and a recent online survey to illustrate how we patients make decisions and get our information.

• Recognize what patients want and don’t want out of their therapy as options change.

• Weigh patient’s view of the risks and benefits of novel therapies inside and out of clinical trials.
Brian Koffman
MDCM, FCFP, DABFP, MS Ed

Thank You
The Evolution of Blood Cancer Treatments
Lori Kunkel, MD
DNA Damaging Agents ➔ Non selective

Adapted: Rai Am J Hem 2016
The big breakthroughs and take home

Most patients respond to targeted agents

Durability can be years

Each agent has “unique” safety issues

Resistance will occur

BTKi: BLEEDING/Afib
BCL-2: TLS
Pi3K: Colitis/Pneumonitis

Alternative pathways
Mutations
The evolving unmet medical needs in CLL

Inherent resistance (Del 17p)

Acquired resistance
(BTK C418S and PLCG2 mutations, MCL-1 increase)

Appropriate sequence of targeted therapies

Tolerability
(Cumulative safety and infection risks)
Inherent resistance Del17p (p53)
BTKi, BCL2i and PI3Ki overcome inherent resistance → PFS inferior to non-Del17p

Ibrutinib-del 17p

Duvelisib-del 17p

Ventoclax-del 17p

O’Brien ASCO 2014

Stilgenbauer, Lancet 2014

Flinn, ASH 2017
Acquired resistance mechanisms

- Alternative pathways → NFKB, PIK3-ALT
- BTK C418S mutation
- PLCG2 mutations

**Ibrutinib**

**Venetoclax**

- ↑ Mcl-1
- ↑ Bcl-xL
Real world experience:

Ibrutinib resistance stems from resistance mutations, which are detectable before clinical relapse

Woyach et al., JCO 2017

- Mutations in BTK or PLCG2 are the predominant mechanism by which CLL becomes resistant to ibrutinib
- Clinical resistance is preceded by a prolonged period of asymptomatic clonal expansion
- Initial clone could be detected at an estimated median of 9.3 months before relapse
Addressing inherent and acquired resistance

• Pre-emptively target with alternative therapies before the patient becomes acutely ill with refractory disease

• Treatment earlier in disease with targeted agents
  – C418S does not appear at same rate in frontline patients
  – Less mutated or natural history of DNA damage

• Combinations of novel:novel agents

*CLL cells from duvelisib-treated patients are primed for apoptosis from sequential BCL-2 inhibition*
Side effect mitigation and therapy sequencing

• Pre-existing co-morbidities and emergent side effects are a consideration with all therapies
  – Age of patients necessitates a consideration of co-morbidities
    – atrial fibrillation, bleeding risks, use of anti-clotting factors, renal insufficiency
  – Infections are a risk and prophylaxis can play a major part in reducing the threat
  – Immune-related side effects are becoming better characterized and managed

• Sequence of therapy is an important determinant while data from combination treatments is being gathered
  – Each patient is different
    ▪ Pre-existing conditions or other medical considerations
    ▪ Adherence to therapeutic regimen
    ▪ Convenience of in-patient treatments
  – Recognition of patient goals – disease maintenance or curative intent?
The revolution from R-Chemo to targeted therapies in FL is behind what we’ve seen in CLL

**Evaluation & Diagnosis**

**1st line treatment**

**Additional treatment**

Physical exam, blood tests, etc.

- Watch and Wait
- Drug Treatment

- Fit
  - Chemo + R
  - Chemo only
  - Bendamustine +/- R

- Unfit
  - Rituxan Mono

**Maintenance**

- Fast Progressor (<24 months)
- Slow Progressor (≥24 months)

**Treatment Choice**

**Novel Agents**

- Aliqopa
- Zydelig
- Rituxan Mono
- Gazyva Mono

**Chemotherapy**

- Rituxan + Chemo
- Gazyva + Chemo
- Chemo Only
Ibrutinib has limited effect in CIT-resistant patients with follicular lymphoma (DAWN study)

- Only 20% of patients with chemoimmunotherapy-resistant follicular lymphoma respond to ibrutinib monotherapy
- Median PFS in the ITT of 4.6 months
Advent of targeted agents in the treatment of FL

- The average age of patients in the US is 67 years old
- Primary treatment options still consist of R-based chemotherapy
- BTK and BCL-2 inhibition appears to be inferior to PI3K
- Establishment of treatment modalities for chemo-refractory patients is evolving
- Combination therapies with PI3K may hold particular promise for future treatment
Summary: CLL and follicular NHL chronic disease

• Little evidence that they will be curable

• Infections and cumulative side effects remain an issue
  – Rapid evolution of the field and new management techniques are evolving

• Most patients will not achieve a CR

• Patient goals are paramount
  – Identifying the proper sequence of medications for disease maintenance based on patient-specific characteristics
  – Progression of combination therapies with potential of curative intent

• Goal → Maintain disease control as we evolve to a safe and tolerable combination regimen earlier in the disease course
Investor conference Galapagos 2014
Unmet Needs and the Role of PI3K Inhibitors

Jennifer Brown, MD, PhD
Where Does PI3K Inhibition Fit?

Jennifer R Brown, MD PhD
Director, CLL Center
Dana-Farber Cancer Institute
Associate Professor of Medicine
Harvard Medical School
May 2, 2018
Moving Toward a Chemo-Free Future in CLL

Venetoclax

Duvelisib

Idelalisib

Ibrutinib

BCL-2

BCR

PI3K

mTOR

AKT

NF-κB

NFAT

SRF

G1

S

M

Nucleus

ZAP-70

CCL3

CCL4

CD40

CD40L

BGLMA

BAFF-R

CD38

CD31

APRIL

BAFF

NLC

VCAM-1, FN

BMSC

Stromal Microenvironment

Figure was produced using Servier Medical Art, http://www.servier.com/ServierImageBank.aspx?id=1729
PI3K Signaling Pathway as a Target in B Cells

- BCR
- Integrin
- BAFFR
- CXCR4, CXCR5
- CD40
- LYN
- SYK
- p85
- p110
- PI(3,4,5)P3
- PI(4,5)P2
- PTEN
- PIP2
- AKT
- T308
- S473
- p27kip1
- GSK3β
- CyclinD
- Bad
- FoxO
- mTOR
- IKK
- NF-κB pathway
- ASK
- SAPK/JNK pathway
- Protein synthesis
- Cell survival
- Nucleus
PI3K Delta: Target for B Cell Diseases

Class I PI3K Isoforms

<table>
<thead>
<tr>
<th>Isoform</th>
<th>Expression</th>
<th>Gene KO effect on development</th>
<th>Primary physiological role</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha</td>
<td>Broad</td>
<td>Lethal</td>
<td>Insulin signaling, Angiogenesis</td>
</tr>
<tr>
<td>Beta</td>
<td>Broad</td>
<td>Lethal</td>
<td>unknown</td>
</tr>
<tr>
<td>Delta</td>
<td>Leukocytes</td>
<td>Benign</td>
<td>B-cell signaling, development &amp; survival</td>
</tr>
<tr>
<td>Gamma</td>
<td>Leukocytes</td>
<td>Benign</td>
<td>Neutrophil &amp; T-cell function</td>
</tr>
</tbody>
</table>

Tyrosine Phosphorylation

- CD19
- CD28
- RTK
- GPCR
Role of PI3Kδ in B Lymphocytes from Knockout or Kinase Dead Mice

- Signaling downstream of BCR, cytokine/chemokine receptors and RTKs in B cells is deficient
- Reduced mature B cells: follicular (B2), marginal zone, peritoneal (B1)
  - Lack of germinal centers in spleen, lymph nodes or Peyer’s patches
  - Reduced immunoglobulins and humoral response to antigen
- Deletion of p110α, β, and γ has no overt effect on B cell number or function
Duvelisib Inhibits PI3K Signaling and Induces Selective Killing of CLL Cells

Shuai Dong et al. Blood 2014;124:3583-3586
Study IPI-145-02 (Phase I): Duvelisib PK

Mean Duvelisib Plasma Concentration (ng/mL)

- 75 mg BID (n=23)
- 25 mg BID (n=28)
- IC₅₀ PI3K-γ
- IC₉₀ PI3K-δ

Time (hours post dose)

Mean Duvelisib Plasma Concentration (μM)

Patel et al. ASCO 2013
Study 145-02  R/R CLL
PFS, All Doses and 25 mg BID

- Median PFS at 25 mg BID not reached
  - 66% progression-free at 12 months
  - 59% progression-free at 24 months
Duvelisib Inhibits PI3K Signaling and Reduces Serum Factors Made By CLL Cells in Patients

N = 29 patients with at least pre-dose and 1h postdose evaluable samples, 25 mg BID dose level
Source: IPI-145-02 CSR
Different Patient Populations for Different Inhibitors?

• Problems for BTK inhibitors:
  • Cardiac comorbidity, older age
  • Bleeding risk / anticoagulation

• Problems for BCL-2 Inhibitors:
  – Renal failure a contra-indication
  – Frequent clinic or even hospital monitoring for more than a month
## OSU Experience: Long-Term Ibrutinib

<table>
<thead>
<tr>
<th>Event</th>
<th>At 2 Years</th>
<th>At 3 Years</th>
<th>At 4 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLL progression</td>
<td>5.0%</td>
<td>10.8%</td>
<td>19.1%</td>
</tr>
<tr>
<td>Transformation</td>
<td>7.3%</td>
<td>9.1%</td>
<td>9.6%</td>
</tr>
<tr>
<td>Other event</td>
<td>18.7%</td>
<td>23.9%</td>
<td>25.0%</td>
</tr>
</tbody>
</table>
OSU: Ibrutinib Discontinuation for Non-PD by Age

Maddocks et al. JAMA Oncology (2015)
OSU Experience: Survival After Ibrutinib Discontinuation

![Graph showing survival probabilities over time from Ibrutinib discontinuation](image)

- Other event: infection (n = 31)
- Other event: not infection (n = 44)
- CLL progression (n = 55)
- Transformation (n = 28)
Retrospective Analysis of Toxicities and Outcomes for Ibrutinib-Treated Patients: Discontinuations

- With a median follow-up of 17 months, estimated discontinuation rate was 42%
- Median time to discontinuation of 6 months

<table>
<thead>
<tr>
<th>Reasons for Discontinuation, %</th>
<th>Ibrutinib in Front Line</th>
<th>Ibrutinib in Relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Commercial use (n=10)</td>
<td>Clinical Trial (n=9)</td>
</tr>
<tr>
<td>Toxicity</td>
<td>50</td>
<td>78</td>
</tr>
<tr>
<td>CLL progression</td>
<td>10</td>
<td>22</td>
</tr>
<tr>
<td>Other/unrelated death</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Physician or patient preference</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>RT DLBCL</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>SCT/CAR-T cells</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Financial concerns</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Secondary malignancy</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>RT Hodgkin lymphoma</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

With a median follow-up of 17 months, estimated discontinuation rate was 42%
Median time to discontinuation of 6 months

Pooled Multi-Trial Analysis of Venetoclax Efficacy in R/R CLL

- **ORR 76%** for all patients and in patients receiving the 400 mg RP2D of venetoclax
- **Estimated PFS** in all 387 patients was **76.8% at 12 mos (95% CI 72.1-80.8)** and **57.8 at 24 mos (95% CI 51.8-63.4)**

**Patient Disposition**

<table>
<thead>
<tr>
<th>Disposition</th>
<th>N=387</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venetoclax 400 mg/day*, n</td>
<td>305</td>
</tr>
<tr>
<td>Median duration of venetoclax, months (range)</td>
<td>16.3 (0.03-54)</td>
</tr>
<tr>
<td>Discontinuation, %</td>
<td></td>
</tr>
<tr>
<td>Due to PD</td>
<td>50</td>
</tr>
<tr>
<td>Due to AEs</td>
<td>34</td>
</tr>
<tr>
<td>Due to stem cell transplant</td>
<td>10</td>
</tr>
<tr>
<td>Withdrew consent</td>
<td>3</td>
</tr>
</tbody>
</table>

**DOR and PFS in All Patients**

- DOR (n=206)
- PFS (n=387)
Role for Duvelisib in CLL

• Unmet need patient populations:
  – (Large and growing) population intolerant of BTK inhibitors, particularly older patients
    • PI3K immune related toxicity is significantly more common in younger patients
  – Steadily increasing population progressing on BTK inhibitors
  – Venetoclax very challenging to give in a community setting and not widely adopted
  – Duvelisib: effective, novel mechanism, easily given, no infusions required
Duvelisib for the Treatment of CLL/SLL and FL

Ian Flinn, MD, PhD
DUVELISIB REGISTRATION STUDIES

Ian Flinn, MD, PhD
Director, Blood Cancer Research Program at Sarah Cannon Research Institute
May 2, 2018
Duvelisib is a dual inhibitor of PI3K-δ & PI3K-γ at clinical exposures

Inhibition of LPS-stimulated monocytes and fMLP-stimulated monocytes were used to measure whole blood potencies of PI3K inhibitors against PI3K-δ & PI3K-γ, respectively. The graphs show dose responses with monocytes from human donors. Whole blood assay IC₅₀ values, which encompass enzyme inhibition, cell penetration and protein binding of inhibitors, are related to reported clinical plasma exposures of each agent at RP2D.

- Duvelisib human PK. $C_{\text{max}}$ @ 25 mg BID (RP2D) = 1062 ng/ml; MW = 417 g/mol
- Idelalisib human PK from Webb, ASH 2010. $C_{\text{max}}$ @ 150 mg BID (RP2D) = 2000 ng/ml; MW = 415 g/mol
- IPI-549 human PK from Hong, SITC 2017. $C_{\text{max,ss}}$ @ 60 mg QD (RP2D) = 4800 ng/ml, MW = 529 g/mol
Duvelisib’s dual PI3K inhibition targets both malignant B cells (-δ) and the supportive tumor microenvironment (-γ)

DYNAMO: A PHASE 2 STUDY DEMONSTRATING THE CLINICAL ACTIVITY OF DUVELISIB IN PATIENTS WITH DOUBLE-REFRACTORY INDOLENT NON-HODGKIN LYMPHOMA

Presented at 14-ICML, 14 June 2017, Lugano Switzerland by Pier Luigi Zinzani, MD, PhD. University of Bologna, IT
STUDY OVERVIEW

Duvelisib 25 mg BID Continuously

- Single arm
- n=129

Treatment until progression or unacceptable toxicity

Response Assessments
- Baseline, Cycles 3, 5, 7, 10, every 4 cycles thereafter
- Cycle = 28 days

Criteria
IWG (Cheson 2007), as assessed by independent review committee (IRC)

Primary Endpoint
ORR = best response of CR or PR per IRC

Key Secondary Endpoints
- Duration of response (DOR)
- Progression-free survival (PFS)
- Overall survival (OS)
- Safety

Accrual complete
Final Analysis: April 2016
Mature Follow-up: March 2017
### OVERALL RESPONSE RATE

<table>
<thead>
<tr>
<th></th>
<th>OVERALL N = 129</th>
<th>FL N = 83</th>
<th>SLL N = 28</th>
<th>MZL N = 18</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORR per IRC</strong></td>
<td>47%</td>
<td>43%</td>
<td>68%</td>
<td>33%</td>
</tr>
<tr>
<td><strong>P-value</strong></td>
<td>$p = 0.0001$</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td><strong>95% CI</strong></td>
<td>(38-56)</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td><strong>Complete Response</strong></td>
<td>1%</td>
<td>1%</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Partial Response</strong></td>
<td>47%</td>
<td>42%</td>
<td>68%</td>
<td>33%</td>
</tr>
<tr>
<td><strong>ORR per Investigator</strong></td>
<td>60%</td>
<td>53%</td>
<td>86%</td>
<td>50%</td>
</tr>
<tr>
<td><strong>Complete Response</strong></td>
<td>3%</td>
<td>2%</td>
<td>4%</td>
<td>6%</td>
</tr>
<tr>
<td><strong>Partial Response</strong></td>
<td>57%</td>
<td>51%</td>
<td>82%</td>
<td>44%</td>
</tr>
</tbody>
</table>

- Rapid time to response: median 2 months (range: 1.4 – 12)
- Primary endpoint met at final analysis
- Median time on duvelisib: 7 months (range: 0.4-35)
88% of patients had reduction in target lymph nodes (IRC data)
ADVERSE EVENTS OF INTEREST

- Few discontinuations due to severe AEs of interest
- Serious opportunistic infections < 4%: PCP (unconfirmed) (n=1); CMV (n=2); fungal pneumonia (n=2)
- Deaths attributed to treatment (n=6)*

*colitis (n=1); toxic epidermal necrolysis/sepsis syndrome (n=1); drug reaction/eosinophilia/systemic symptoms (n=1); pneumonitis/pneumonia (n=1); viral infection (n=1); septic shock (n=1)
DYNAMO STUDY CONCLUSIONS

• Duvelisib monotherapy is clinically active in double-refractory iNHL
  – ORR of 47% per IRC; ORR of 60% per Investigator
  – 88% of patients had tumor reduction
  – Responses were durable (median 10 months)

• Duvelisib has a manageable safety profile

• In long-term follow-up (median 18 months), duvelisib remains well tolerated

• Duvelisib showed favorable risk-benefit in double-refractory iNHL, and may represent an important treatment option for these patients
There is a significant unmet need in the treatment of Follicular Lymphoma (FL)

- The initial treatment of FL is primarily anti-CD20 based chemotherapy regimens (CIT)
  - R-CHOP / BR / R-CVP
- Following failure to CIT, there are limited treatment options. CIT rechallenge (or switch), anti-CD20 monotherapy and PI3Ki-based treatments
- BTK and BCL-2 inhibitors have demonstrated only limited efficacy for the treatment of R/R FL to date
- Additional agents and clinical studies are necessary to improve the available treatment options
- The transition to oral, targeted therapies, as seen in CLL has been slower in FL due to a lack of efficacious agents
Results from the Phase 3 DUO™ Study of Duvelisib vs Ofatumumab in Relapsed/Refractory CLL/SLL

Ian Flinn¹, Peter Hillmen², Marco Montillo³, Zsolt Nagy⁴, Árpád Illés⁵, Gabriel Etienne⁶, Julio Delgado⁷, Bryone Jean Kuss⁸, Constantine Tam⁹, Zoltán Gasztonyi¹⁰, Fritz Offner¹¹, Scott Lunin¹², Francesco Bosch¹³, Matthew Davids¹⁴, Nicole Lamanna¹⁵, Ulrich Jaeger¹⁶, Paolo Ghia¹⁷, Florence Cymbalista¹⁸, Craig Portell¹⁹, Alan Skarbnik²⁰, Amanda Cashen²¹, Virginia Kelly²², Barry Turnbull²², Stephan Stilgenbauer²³

¹Sarah Cannon Research Institute, Nashville, USA; ²St. James’s Institute of Oncology, The Leeds Teaching Hospitals, Leeds, UK; ³Niguarda Cancer Center, ASST Grande Ospedale Metropolitano Niguarda, Milan, ITA; ⁴1st Department of Internal Medicine, Semmelweis University, Budapest, HUN; ⁵Department of Hematology, Institute for Medicine, U. of Debrecen, Debrecen, HUN; ⁶Hematology Department, Institut Bergonie, Bordeaux, FRA; ⁷Hospital Clinic, Barcelona, SPA; ⁸Flinders Medical Centre (FMC), Bedford Park, AUS; ⁹Peter MacCallum Cancer Centre, Melbourne, AUS; ¹⁰Dep. of Internal Medicine and Hematology, Petz Aladár County Hospital, Győr, HUN; ¹¹Hematology, University Hospital Ghent, Gent, BEL; ¹²Florida Cancer Specialists, Venice, USA; ¹³Department of Hematology, University Hospital Vall d’Hebron, Barcelona, SPA; ¹⁴Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, USA; ¹⁵New York Presbyterian, Columbia University Medical Center, New York, USA; ¹⁶Medical University of Vienna, Vienna, AUT; ¹⁷Università Vita-Salute San Raffaele and IRCCS Istituto Scientifico San Raffaele, Milan, ITA; ¹⁸Laboratoire d’hémotologie, Hôpital Avicenne, Paris, FRA; ¹⁹Division of Hematology and Oncology, University of Virginia, Charlottesville, USA; ²⁰John Theurer Cancer Center, Hackensack Meridian Health, Closter, USA; ²¹Siteman Comprehensive Cancer Center, Washington University, St. Louis, USA; ²²Verastem Inc., Needham, USA; ²³Department III of Internal Medicine, University Hospital Ulm, Ulm, GER
### DUO: A Phase 3 Randomized Study in Relapsed/Refractory CLL/SLL

<table>
<thead>
<tr>
<th>Relapsed or Refractory CLL/SLL patients</th>
<th>319 patients Randomized 1:1</th>
</tr>
</thead>
</table>

**Response per modified iwCLL/IWG Criteria **
- Assessed by independent review committee (IRC)
- Cycle 3 (C3), C5, C7, C11, C15, C19, every 6 months thereafter
- CT scan, CBC, disease related symptoms, BM biopsy ***
- Survival assessment every 6 months

**Endpoints**
- PFS (primary)
- ORR, DOR, OS (secondary)
- Safety (AEs and lab abnormalities)

<table>
<thead>
<tr>
<th>Ofatumumab IV</th>
<th>Administration same as DUO</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=159</td>
<td>N=8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Duvelisib</th>
<th>25 mg BID continuously *</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=160</td>
<td>N=89</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Duvelisib</th>
<th>25 mg BID continuously</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=88</td>
<td></td>
</tr>
</tbody>
</table>

**Source:** Flinn et al., ASH 2017
DUO Met Primary Endpoint of PFS
Significantly Longer Median PFS with Duvelisib per IRC

DUV | OFA
---|---
Median PFS (Months) | 13.3 | 9.9
95% CI | 12.1, 16.8 | 9.2, 11.3
Hazard ratio | 0.52
p-value | < 0.0001

Source: Flinn et al., ASH 2017
Significantly Longer PFS with Duvelisib per Investigator Assessment

- 89 patients on OFA arm received duvelisib in crossover study, achieving an ORR of 73% and a median PFS of 15 months per Investigator assessment

<table>
<thead>
<tr>
<th></th>
<th>DUV</th>
<th>OFA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS (Months)</td>
<td>17.6</td>
<td>9.7</td>
</tr>
<tr>
<td>95% CI</td>
<td>15, 22</td>
<td>9, 11</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>0.40</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>&lt; 0.0001</td>
<td></td>
</tr>
</tbody>
</table>
Duvelisib Maintained PFS Advantage in All Subgroups Analyzed

<table>
<thead>
<tr>
<th></th>
<th>DUV n</th>
<th>OFA n</th>
<th>Favors Duvelisib</th>
<th>Favors Ofatumab</th>
<th>HR</th>
<th>LCL</th>
<th>UCL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>160</td>
<td>159</td>
<td></td>
<td></td>
<td>0.52</td>
<td>0.39</td>
<td>0.70</td>
</tr>
<tr>
<td>17p deletion</td>
<td>33</td>
<td>44</td>
<td>●</td>
<td>●</td>
<td>0.41</td>
<td>0.23</td>
<td>0.74</td>
</tr>
<tr>
<td>No 17p deletion</td>
<td>111</td>
<td>102</td>
<td>●</td>
<td>●</td>
<td>0.55</td>
<td>0.39</td>
<td>0.79</td>
</tr>
<tr>
<td>17p del and/or TP53 mutation</td>
<td>48</td>
<td>52</td>
<td>●</td>
<td>●</td>
<td>0.40</td>
<td>0.24</td>
<td>0.67</td>
</tr>
<tr>
<td>No 17p del and/or TP53 mutation</td>
<td>83</td>
<td>84</td>
<td>●</td>
<td>●</td>
<td>0.63</td>
<td>0.42</td>
<td>0.93</td>
</tr>
<tr>
<td>Refractory/Early Relapse</td>
<td>25</td>
<td>36</td>
<td>●</td>
<td>●</td>
<td>0.51</td>
<td>0.27</td>
<td>0.96</td>
</tr>
<tr>
<td>No Refractory/Early Relapse</td>
<td>135</td>
<td>123</td>
<td>●</td>
<td>●</td>
<td>0.53</td>
<td>0.38</td>
<td>0.73</td>
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<tr>
<td>Gr. 4 Cytopenia at Baseline</td>
<td>8</td>
<td>10</td>
<td>●</td>
<td>●</td>
<td>0.14</td>
<td>0.03</td>
<td>0.71</td>
</tr>
<tr>
<td>No Gr. 4 Cytopenia at Baseline</td>
<td>152</td>
<td>149</td>
<td>●</td>
<td>●</td>
<td>0.54</td>
<td>0.41</td>
<td>0.73</td>
</tr>
<tr>
<td>Male</td>
<td>96</td>
<td>95</td>
<td>●</td>
<td>●</td>
<td>0.61</td>
<td>0.42</td>
<td>0.87</td>
</tr>
<tr>
<td>Female</td>
<td>64</td>
<td>64</td>
<td>●</td>
<td>●</td>
<td>0.44</td>
<td>0.28</td>
<td>0.70</td>
</tr>
<tr>
<td>Age &lt; 65 years</td>
<td>48</td>
<td>58</td>
<td>●</td>
<td>●</td>
<td>0.47</td>
<td>0.29</td>
<td>0.77</td>
</tr>
<tr>
<td>Age ≥ 65 years</td>
<td>112</td>
<td>105</td>
<td>●</td>
<td>●</td>
<td>0.56</td>
<td>0.40</td>
<td>0.80</td>
</tr>
<tr>
<td>Prior Anticancer Therapy &lt; 12 Months</td>
<td>52</td>
<td>63</td>
<td>●</td>
<td>●</td>
<td>0.40</td>
<td>0.24</td>
<td>0.66</td>
</tr>
<tr>
<td>Prior Anticancer ≥ 12 Months</td>
<td>107</td>
<td>96</td>
<td>●</td>
<td>●</td>
<td>0.59</td>
<td>0.42</td>
<td>0.84</td>
</tr>
</tbody>
</table>

Hazard Ratio (95% CI)

Source: Flinn et al., ASH 2017
Significantly Higher ORR with Duvelisib per IRC

- **Overall Response Rate**
  - **DUV**: 73.8%
  - **OFA**: 45.3%
  - **p-value**: < 0.0001

- **Lymph Node Response Rate**
  - **DUV**: 85.0%
  - **OFA**: 15.7%
  - **Lymph node response**: ≥ 50% decrease in the SPD of target lymph nodes from baseline

- **ORR in patients with 17p deletion**: duvelisib 70% vs OFA 43% (p=0.0182)

Source: Flinn et al., ASH 2017
• **Severe opportunistic infections (6%)**: bronchopulmonary aspergillosis (n=4), fungal infection (n=2), PJP (n=2)*, and cytomegalovirus colitis (n=1)

• **Treatment-related AEs leading to death (n=4)**: general health deterioration (n=1); pneumonia staphylococcal (n=2); sepsis (n=1)

* Neither patient on prophylaxis at the time of the event

Source: Flinn et al., ASH 2017
**DUO Study Conclusions**

- DUO met the primary endpoint for PFS: duvelisib monotherapy achieved significant improvement in PFS vs OFA (13.3 m vs 9.9 m; HR = 0.52; p < 0.0001) per IRC
  - PFS per investigator response assessment significantly favored duvelisib vs OFA (17.6 m vs 9.7 m; p < 0.0001)
  - Similar benefit in CLL/SLL patients with 17p deletion
  - Duvelisib achieved significant improvement in ORR vs OFA (74% vs 45%; p < 0.0001) per iwCLL/IWG
  - Duvelisib significantly reduced lymph node burden > 50% in most patients vs OFA (85% vs 16%)

- With a median exposure of 50 weeks, the AE profile of duvelisib was manageable and consistent to what has been previously observed
  - AEs of interest (neutropenia, diarrhea, pneumonia, colitis, transaminase elevations, pneumonitis, rash) infrequently led to discontinuation

- DUO results support duvelisib oral monotherapy as a potential new and convenient treatment option for previously treated CLL/SLL patients
Summary of duvelisib registration-enabling studies

• Duvelisib monotherapy demonstrates significant clinical activity
  • Positive Phase 2 in double refractory iNHL and randomized Phase 3 in CLL/SLL
  • Broad and robust activity across stratification factors and sensitivity analyses

• Well-characterized, consistent and manageable safety profile
  • AEs of Special Interest infrequently led to duvelisib discontinuation in either the DYNAMO or DUO studies

• The DYNAMO and DUO results support duvelisib oral monotherapy as a potential new and convenient treatment option for previously treated CLL/SLL or FL patients
The treatment of CLL and iNHL is evolving with the introduction of new therapies

- Chemotherapy and anti-CD20 immunotherapy have a decreasing role as patients transition to oral therapies
  - Patient age and risk factors play a large part in the determination of treatment selection
- In CLL: BTK and BCL-2 inhibition have demonstrable efficacy however patient-specific considerations need to be taken into account
  - BTK: Co-morbidities, vascular risks, concomitant medications and eventual mutational progression
  - BCL-2: Diabetes, renal function, cognitive ability to adhere to protocols and proximity/access to transportation to hospital during the complexity of dosing ramp up
- In FL: PI3K inhibition has shown promising clinical activity
  - Rituximab-based chemotherapy is currently the backbone of treatment
  - BTK/BCL-2 inhibitors have demonstrated only limited efficacy for the treatment of R/R FL to date
- Additional options are needed for a physicians armamentarium in the treatment of chronic indolent lymphomas and leukemias
  - The sequential use of clinically active and manageable treatments may extend the period of disease control
  - Continued development of oral, targeted therapies, is necessary to address the unmet need
Duvelisib for the Treatment of T-Cell Lymphomas

Steve Horwitz, MD
Unmet need for new strategies in T-cell lymphoma

FDA approved agents for R/R TCL

<table>
<thead>
<tr>
<th>Drug</th>
<th>ORR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pralatrexate</td>
<td>29%</td>
</tr>
<tr>
<td>Romidepsin</td>
<td>25%-38%</td>
</tr>
<tr>
<td>Belinostat</td>
<td>26%</td>
</tr>
<tr>
<td>Brentuximab vedotin</td>
<td>85% (ALCL)</td>
</tr>
</tbody>
</table>

Progression Free Survival: Relapsed/Refractory PTCL

**BCCA**
- Pralatrexate N=109
  - 3.5 months

**Romidepsin N=130**
- 4 months

**Brentuximab ALCL N=56**
- PFS 13.3 months

**Pralatrexate N=109**
- 3.7 months

**Belinostat N=129**
- 1.6 months

**Brentuximab PTCL N=21**
- AITL N=13
  - 6.7 months

Duvelisib monotherapy was studied across a wide range of B- and T-Cell malignancies.

**PHASE 1 STUDY (IPI-145-02)**

**Dose Escalation Cohort (N = 31)**
Advanced hematologic malignancies

- 8 mg BID N = 1
- 15 mg BID N = 6
- 25 mg BID N = 7
- 35 mg BID N = 3
- 50 mg BID N = 3
- 60 mg BID N = 3
- 75 mg BID N = 6
- 100 mg BID N = 2

**MTD**

**Expansion Cohorts: 25 mg BID (N = 59)**
- CLL, iNHL, mantle cell lymphoma
- Treatment-naïve CLL

**Expansion Cohorts: 75 mg BID (N = 118)**
- CLL, iNHL, mantle cell lymphoma
- T-cell lymphomas

**Exploratory cohorts**
- Aggressive B-cell lymphomas
- Myeloid neoplasms
- T- or B-cell leukemia/lymphoma
### Duvelisib Clinical Activity in TCL in Phase 1

#### Best Response, n (%) | Median Time to Response, months (Range)
---|---
| n | CR | PR | SD | PD | ORR |  

#### All TCL
- 35 | 2 (6) | 12 (34) | 7 (20) | 12 (34) | **14 (40)** | 1.9 (1.5, 3.8)

#### CTCL
- 19 | 0 | 6 (31.6) | 6 (31.6) | 6 (33) | **6 (31.6)** | 2.4 (1.6, 3.8)

#### PTCL
- 16 | 2 (18.8) | 6 (31.3) | 1 (6.3) | 6 (37.5) | **8 (50)** | 1.9 (1.5, 3.5)

Includes evaluable patients = at least 1 on-treatment response assessment or PD without assessment
CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease
ORR = CR + PR

- Clinical activity observed across CTCL and PTCL subtypes
  - CTCL: PRs in 4 MF, 1 Sézary syndrome, and 1 MF-LCT
  - PTCL: CRs in 1 EATCL and 1 PTCL NOS
    - PRs in 2 AITCL, 2 SPTCL, 1 PTCL NOS, 1 ALCL (ALK-negative)

Horwitz et al, Blood 2018
Phosphoproteomic profile indicates on-target effects of duvelisib and suggests mechanism of resistance

Horwitz, et al. Blood, 2018
Phase I combination study of Duvelisib plus Romidepsin

3+3 design with dose expansion at MTD

Relapsed and Refractory TCL

Duvelisib monotherapy
(Lead in cycle)

Duvelisib + Romidepsin
(Dose escalation)

PTCL
(Dose expansion at MTD)

CTCL
(Dose expansion at MTD)
### Dose escalation and expansion

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Romidepsin (days 1, 8, 15)</th>
<th>DUV PO (days 1-28)</th>
<th>#pts enrolled</th>
<th>#pts evaluable for DLT</th>
<th>#pts with DLT</th>
<th>Expansion arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10 mg/m²</td>
<td>25mg BID</td>
<td>4</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>10 mg/m²</td>
<td>50mg BID</td>
<td>4</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>10 mg/m²</td>
<td>75mg BID</td>
<td>4</td>
<td>3</td>
<td>0</td>
<td>4</td>
</tr>
</tbody>
</table>

MTD: Dose Level 3; Romidepsin (10mg/m² IV) + Duvelisib (75mg PO, BID)
## Duvelisib + Romidepsin - Response

<table>
<thead>
<tr>
<th>Dose Level</th>
<th># pts Evaluable for Response/Total</th>
<th>Overall response</th>
<th>Complete Response</th>
<th>Partial Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4/4</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>3/4</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>8/8</td>
<td>5</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>TOTAL</td>
<td>15/16</td>
<td>9 (60%)</td>
<td>4 (27%)</td>
<td>5 (33%)</td>
</tr>
</tbody>
</table>

### CTCL vs. PTCL

<table>
<thead>
<tr>
<th></th>
<th>#pts Evaluable for Response</th>
<th>Overall Response Rate</th>
<th>Complete Response</th>
<th>Partial Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTCL</td>
<td>4</td>
<td>2 (50%)</td>
<td>0</td>
<td>2 (50%)</td>
</tr>
<tr>
<td>PTCL</td>
<td>11</td>
<td>7 (64%)</td>
<td>4 (36%)</td>
<td>3 (27%)</td>
</tr>
<tr>
<td>(AITL/Tfh)</td>
<td>5</td>
<td>3 (60%)</td>
<td>2 (40%)</td>
<td>1 (20%)</td>
</tr>
<tr>
<td>(PTCL-NOS)</td>
<td>4</td>
<td>3 (75%)</td>
<td>2 (50%)</td>
<td>1 (25%)</td>
</tr>
</tbody>
</table>
Duvelisib + Romidepsin adverse events

Showing events affecting ≥ 20% of patients and all grade 3 or 4 events

- Fatigue
- Nausea
- Altered Taste
- Diarrhea
- Dysphagia
- Anorexia
- Neutropenia
- Thrombocytopenia
- Rash
- Lung infection
- Pleural effusion
- Hyponatremia

2 deaths unrelated to treatment:
- Diffuse alveolar hemorrhage following allogeneic stem cell transplant
- Sepsis in setting of disease progression
Conclusions

• Preclinical studies elucidated potential mechanisms of response and resistance to Duvelisib which are being further evaluated in this present phase I study

• Safety, tolerability, and responses of least 50% were observed in systemic TCL

• There were no DLTs with the combination of Duvelisib plus Romidepsin

• Expansion cohorts of patients with PTCL and CTCL are almost complete and further expansion of the Duvelisib plus Romidepsin cohort is planned to more precisely define the activity of this combination
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This is an investigator-sponsored trial (NCT02783625) with research support from the Leukemia & Lymphoma Society, Infinity Pharmaceuticals (Cambridge, MA) and Verastem, Inc. (Needham, MA)
PRIMO: Confirm and extend activity of duvelisib monotherapy in relapsed/refractory PTCL

**Relapsed PTCL patients**
- Includes all common PTCL sub-types
- No limit of prior therapies
- No transformation to aggressive lymphoma
- ECOG Performance Status ≤2

**DOSE OPTIMIZATION**
- COHORT 1: Duvelisib* 25 mg BID start (N = 10)
- COHORT 2: Duvelisib 75 mg BID start (N = 10)

**DOSE EXPANSION**
- Duvelisib Optimal dose (N = 100)

**Study end points**
- Primary (Expansion Phase):
  - ORR on optimal dose
- Secondary:
  - Safety, DoR, DCR, PFS, OS
  - % able to reach optimal dose
  - Safety
- Exploratory:
  - PK/PD markers

* Cohort 1: At Cycle 1, if CR/PR: maintain dose; If SD and tolerable: increase dose; if PD: discontinue if intolerable

**Goal:** Establish optimal dose and confirm monotherapy activity

**Trial design details:**
- At least one prior therapy for PTCL; for CD30+ ALCL, patients must have failed or are ineligible or intolerant to brentuximab vedotin
- Intra-patient dose escalation in Cohort 1 is allowed
The Treatment of Patients with T-Cell Lymphoma Needs Additional Therapeutic Development

• There remains a significant unmet need in the treatment options for patients with T-Cell lymphoma
  • Current NCCN guidelines recommend clinical trials over chemotherapy or agents under accelerated approval (eg. HDACi or anti-folates)

• Duvelisib represents a potential new therapy for the treatment of T-Cell lymphomas
  • Encouraging activity as a single agent in Phase 1
  • Early data from Phase 1/2 combination therapy with romidepsin indicates a synergy with a potential for increased efficacy, reduced toxicity and a longer duration of response

• Additional clinical study is warranted and ongoing
  • Single agent PRIMO study could support approval
  • Identify predictors of response and resistance
    • Better match therapy to patients
    • Identify other combination partners, move into earlier lines of therapy
Unlocking the Potential of Duvelisib
Joe Lobacki, Chief Commercial Officer, Verastem
Unlocking the potential of duvelisib begins with the patient.
Adapting to Chronic Disease: The Indolent Lymphoma Patient Journey

At Risk Population

65-75 **MEDIAN AGE AT DIAGNOSIS**

Diagnosis

"I walked in a healthy person..."

Watch & Wait

**MEDIAN** 3+ **YEARS**

Long-term Treatment for Chronic Disease Control

**MEDIAN OS 10+ YEARS**

"I walked out"
Trends in the Chronic Indolent Lymphoma Patient Journey

Increased Elderly Patient Population

Prevalence, 2018

<table>
<thead>
<tr>
<th>Condition</th>
<th>US</th>
<th>Other Major Markets</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLL/SLL</td>
<td>197,000</td>
<td></td>
</tr>
<tr>
<td>FL</td>
<td>141,000</td>
<td></td>
</tr>
</tbody>
</table>

Source: Decision Resources

Increased Treatment Options
For the CLL/SLL and FL Patient, Current Targeted Treatment Options Remain Constrained

**TODAY’S OPTIONS**

- **choose your own sequence -**

**CLL/SLL**

- **BTK inhibitor**
  - **ibrutinib** *(1st line)*
  - Daily oral monotherapy

- **PI3K inhibitor**
  - **idelalisib** *(δ)* *(R/R)*
  - Daily oral therapy
  + Given with Rituxan: Travel to infusion center required

- **BCL-2 inhibitor**
  - **venetoclax** *(del(17p))*
  - Daily oral monotherapy
  * Allow up to 5 weeks for dose ramp up: hospitalization may be required

**FL**

- **PI3K inhibitors**
  - **idelalisib** *(δ)* *(R/R)*
  - Daily oral monotherapy

  - **copanlisib** *(α/δ)* *(R/R)*
  - Weekly IV infusion: Travel required

**Please notify your doctor of your personal medical history, including any prior experience with cardiac events, bleeding, diabetes, renal insufficiency, or congestive heart failure**

* Conditionally approved

---

Verastem Oncology
Duvelisib Represents a Convenient Additional Oral Treatment Option for Both CLL/SLL and FL

First in class, dual kinase inhibitor with demonstrated clinical efficacy and a well characterized and manageable safety profile

Simple, at home, oral monotherapy dosing without need for infusions

Accessible treatment in the community setting for both CLL/SLL and FL patients regardless of tumor burden or cytogenetics
Patients may consider...

**NEED**

*What’s my next step?*

*I’m not responding anymore...*

20% of FL patients are insensitive to first line chemo and have a poor ongoing prognosis¹

*I can’t continue due to AEs...*

24% of CLL/SLL patients discontinue ibrutinib due to intolerance after a median of 6 months²

Duvelisib is a first-in-class, dual PI3K inhibitor with demonstrated clinical efficacy in relapsed lymphomas

---

**ACCESSIBILITY**

*How would I get this drug?*

70% of the CLL/SLL and FL patient population are treated in community settings, away from major academic centers³

Duvelisib requires no planned hospitalization and can be delivered to the patient’s door

---

**LIFESTYLE**

*Does it change my day to day?*

55% of oncology patients give equal importance to QoL and survival⁴

Duvelisib is a daily oral monotherapy with no need to travel for infusions

---

Physicians may consider...

**CLINICAL PROFILE**

*Who is this appropriate for?*

Community oncologists treat a wide variety of lymphomas.

74% of elderly iNHL patients experience at least one major comorbidity that may limit existing treatment options.

Duvelisib may offer a single CLL/SLL and FL therapy option, with a safety profile that is well characterized and manageable.

---

**UTILITY**

*What about subpopulations?*

20% of FL patients are “fast progressors” on chemotherapy.

> 2/3 of CLL/SLL patients have medium to high tumor burden, and >1/3 have high risk genetic alterations.

Duvelisib is a chemo-free option, and has demonstrated clinical efficacy regardless of tumor burden or genetic alterations.

---

**ADMINISTRATION**

*Will my patients be willing to take this drug?*

>58% of patients feel burdened by IV hospital visits.

Duvelisib is a daily oral monotherapy, taken at home with no infusions and no planned hospitalizations.

---

CASE STUDY

Prostate Cancer

Chronic cancer market trends:

- Increased Elderly Patient Population
  ✓ Aging Baby Boomer Population
  ✓ Increased Diagnoses

- Increased Use of New Treatments
  ✓ Increase in Drug Approvals
  ✓ Increased Lines of Therapy

Resulting market expansion:

Source: BioMedTracker, accessed April 2018
Projected Expansion of CLL/SLL and FL Markets

**CLL/SLL and FL**

*Expectation for market growth:*

Broadening care through multiple lines of therapy leads to market expansion

**Total Value, Global Major Markets ($B)**

- **2016**
  - CLL/SLL: $6B
  - FL: $6B

- **2026**
  - CLL/SLL: $24B
  - FL: $18B

**Source:** Decision Resources, Projected Annual Sales in Major Markets (US, France, Germany, Italy, UK, Spain, Japan)

**CAGR >14%**
Unlocking the Potential of Duvelisib for CLL/SLL and FL patients

We are focused on providing an efficacious, safe, and convenient treatment option enhanced by a supportive experience to help patients confidently take their next step towards managing life with their chronic disease.

...because for us, and for our patients, it’s personal
Preparing for Commercial Launch

- Prepare the TEAM
- Prepare the PRODUCT
- Prepare the MARKET
**Product:** Foundation Laid to Optimize the Value of Duvelisib

- **In License (Nov 2016)**

- **2017**
  - Pursuit of an Initial Registration Path
    - Positive Phase 2 DYNAMO study in Relapsed FL
    - Positive Phase 3 DUO study in R/R CLL/SLL
    - NDA Filed: Full approval in R/R CLL and Accelerated approval in relapsed FL
    - Priority Review granted for a PDUFA date of 10/5/2018

- **2018**
  - Translation of Market Insights to a Brand Plan
    - Market assessment
    - Account segmentation & KOL mapping
    - Branding
    - Message & material development and testing
    - Pricing strategy
    - Distribution plan
  - Establishment of a Clinical Expansion Program
    - 2 sponsored trials developed and initiated
    - Active IST program
    - Formation of a Verastem Steering Committee

- **Today**
  - NDA Filed (Feb 2018)
  - PDUFA (Oct 2018)

- **2019 +**

**Verastem Oncology**
**Market:** Verastem Oncology Introduced to Key Stakeholders

- **KOL ENGAGEMENT**
  - Medical Affairs outreach
  - Verastem Steering Committee

- **EDUCATION**
  - Medical Info
  - Disease Education

- **PATIENT ADVOCACY**
  - CLL Society
  - LEUKEMIA & LYMPHOMA SOCIETY
    - fighting blood cancers

- **CONGRESSES**
  - ICML
  - ASCO

- **AD BOARDS**
  - Community Oncologists
  - Nurses & Office Managers
  - KOLs
  - Patient Steering Committee
**Market: Stakeholders Insights**

**Community Oncologists**

I rarely refer my patients to academic centers – if we can, we like to keep their treatment in the community.

This is a helpful addition. It’s easy, oral, chemotherapy-free, and doesn’t require a lot of bells and whistles, not a lot of complexity in terms or monitoring, admissions, infusion.

It has a different profile – it’s a dual kinase and looks like there is more sustained response.

Both the flexibility of being able to take this with or without food and the small capsule size are a benefit, especially for older patients.

Thank you for rescuing this drug – now let’s get to work in further developing this highly clinically active class.

**Nurses & Office Managers**

It’s hard to start over on IV from an oral program. Once our patients go on Imbruvica, they don’t want to go back to IV.

It’s a helpful addition. It’s easy, oral, chemotherapy-free, and doesn’t require a lot of bells and whistles, not a lot of complexity in terms or monitoring, admissions, infusion.

We can manage side effects – we just want to know what we need to know and what we should be watching out for.

We’re used to checkpoints and managing immune mediated events – this safety profile is completely manageable.

**KOLs**

We need additional drugs in our treatment armamentarium.

Ad Board Apr 2017

Ad Board 2017

US TDI Mar 2017

US TDI Sep 2017

Ad Board Apr 2017
Market: Campaign Underway to Advance Understanding of PI3K

For your patients with relapsed/refractory CLL/SLL and FL

Unlock the potential of PI3K inhibition

PI3Kinhibition.com
Team: Experienced Senior Leadership Assembled
Go to Market Plan

1. NDA submitted
2. NDA accepted
3. Today
4. Best of ASH
5. NCCN
6. Disease State Education Materials Creation
7. Materials Launch
8. Unbranded Message Concept Testing (Quant & Qual)
9. Branded Message Concept Testing (Quant & Qual)
10. HCP Material Testing
11. HCP/Patient Materials Creation
12. Pricing Strategy & Market Research
13. Launch and Competitive Readiness Workshops
14. US Prescriber Behavioral Segmentation
15. Go to Market Insights
16. ATU Wave 6

Marketing & Promotion

- Best of ASH
- NCCN
- Disease State Education Materials Creation
- Materials Launch
- Unbranded Message Concept Testing (Quant & Qual)
- Branded Message Concept Testing (Quant & Qual)
- HCP Material Testing
- HCP/Patient Materials Creation
- Pricing Strategy & Market Research
- Launch and Competitive Readiness Workshops
- US Prescriber Behavioral Segmentation
- Go to Market Insights
- ATU Wave 6

Team Build Out & Training

- MSL hiring
- Sales rep hiring
- Head of commercial ops
- Head of market access
- Area Vice President of Sales
- Full MSL team
- Head of business analytics
- Regional Business Directors
- Regional Business Directors
- Field based Reimbursement Managers
- Full sales force onboarded
- National Launch Meeting
- Rep Promo Launch

Jan  Feb  Mar  Apr  May  Jun  Jul  Aug  Sep  Oct

NDA submitted
NDA accepted
Today
Best of ASH
NCCN
Disease State Education Materials Creation
Materials Launch
Unbranded Message Concept Testing (Quant & Qual)
Branded Message Concept Testing (Quant & Qual)
HCP Material Testing
HCP/Patient Materials Creation
Pricing Strategy & Market Research
Launch and Competitive Readiness Workshops
US Prescriber Behavioral Segmentation
Go to Market Insights
ATU Wave 6
MSL hiring
Sales rep hiring
Head of commercial ops
Head of market access
Area Vice President of Sales
Full MSL team
Head of business analytics
Regional Business Directors
Regional Business Directors
Field based Reimbursement Managers
Full sales force onboarded
National Launch Meeting
Rep Promo Launch

Verastem Oncology
Go to Market Plan

Targeted Field Force

- Provide One Voice to the customer
- ~50 Oncology Account Specialists

Broad Coverage

- >95% commercial payer & Medicare Part D patient lives reached
- Enable Access & Support, regardless of geography

Patient-Centric Operations

- Prioritize a seamless patient experience
- Data Aggregator & Warehouse
- 3PL
- SD
- Clinic
- SPP
- HUB

Verastem Oncology
Focused Growth of Duvelisib

**Today:**
**Anchor**
Monotherapy for R/R CLL/SLL and FL
CLL: 23,000 incidence, 197,000 prevalence\(^1\)
FL: 13,000 incidence, 141,000 prevalence\(^1\)

**Broaden Reach**
Expand in CLL/SLL and FL
Expand into PTCL

**Bold Steps**
Combinations with I-O and SOC in aggressive NHL subtypes
DLBCL, MCL, Richter’s, Transformed FL

**Maximize Potential**
CAR-T combinations
NHL, Myeloma, Solid Tumors

---

1. Decision Resources, US 2018
Focused Growth of Verastem Oncology

Build a team & organization dedicated to reaching patients
Anchor with launch of our first drug & first indications
Reach duvelisib’s full potential in additional tumors
Repeat: Unlock the full potential of defactinib
Evolve to continue meeting patient needs
Question & Answer Session
Forward Looking Statements

This presentation includes forward-looking statements about Verastem's strategy, future plans and prospects, including statements regarding the development and activity of Verastem's investigational product candidates, including duvelisib and defactinib, and Verastem's PI3K and FAK programs generally, the structure of our planned and pending clinical trials, Verastem's potential collaboration opportunities and the timeline and indications for clinical development and regulatory submissions. The words "anticipate," "believe," "expect," "intend," "may," "plan," "predict," "project," "target," "potential," "will," "would," "could," "should," "continue," and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. Each forward-looking statement is subject to risks and uncertainties that could cause actual results to differ materially from those expressed or implied in such statement. Applicable risks and uncertainties include the risks that approval of the NDA will not occur on the expected timeframes or at all, including by the FDA's target action date; that a filing of a European Marketing Application may not be achieved before the end of the year, if at all; that even if data from clinical trials is positive, regulatory authorities may require additional studies for approval and the product may not prove to be safe and effective; that the preclinical testing of Verastem's product candidates and preliminary or interim data from clinical trials may not be predictive of the results or success of ongoing or later clinical trials; that the full data from the DUO study will not be consistent with the previously presented results of the study; that data may not be available when expected, including for the Phase 3 DUO™ study; that the degree of market acceptance of product candidates, if approved, may be lower than expected; that the timing, scope and rate of reimbursement for our product candidates is uncertain; that there may be competitive developments affecting our product candidates; that data may not be available when expected; that enrollment of clinical trials may take longer than expected; that our product candidates will cause unexpected safety events or result in an unmanageable safety profile as compared to their level of efficacy; that duvelisib will be ineffective at treating patients with lymphoid malignancies; that Verastem will be unable to successfully initiate or complete the clinical development of its product candidates; that the development of Verastem's product candidates will take longer or cost more than planned; that Verastem may not have sufficient cash to fund its contemplated operations; that Verastem or Infinity Pharmaceuticals, Inc. (Infinity) will fail to fully perform under the duvelisib license agreement; that Verastem may be unable to make additional draws under its debt facility or obtain adequate financing in the future through product licensing, co-promotional arrangements, public or private equity, debt financing or otherwise; that Verastem will not pursue or submit regulatory filings for its product candidates, including for duvelisib in patients with CLL/SLL or iNHL; and that Verastem's product candidates will not receive regulatory approval, become commercially successful products, or result in new treatment options being offered to patients. Other risks and uncertainties include those identified under the heading "Risk Factors" in Verastem's Annual Report on Form 10-K for the year ended December 31, 2017 and in any subsequent filings with the U.S. Securities and Exchange Commission. The forward-looking statements contained in this press release reflect Verastem's views as of the date of this release, and Verastem does not undertake and specifically disclaims any obligation to update any forward-looking statements.