FDA Introductory Comments

Oncologic Drugs Advisory Committee Meeting
April 21, 2022

Nicole Gormley, MD
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Office of Oncologic Diseases
PI3K Inhibitor Overview

**PI3K Class IA**
- Receptor Tyrosine Kinases
- PI3K
- PTEN
- PIP2 → PIP3

**PI3K Class IB**
- G-protein Coupled Receptors
- PI3K
- PTEN
- PIP2 → PIP3

**mTORC2**
- AKT
- FOXO → Apoptosis
- BAD → Apoptosis
- GSK-3 → Glucose metabolism

**mTORC1**
- AKT
- FOXO → Apoptosis
- BAD → Apoptosis
- GSK-3 → Glucose metabolism

**Cell growth translation**
- **Cell cycle regulation**
- **DNA repair**
- **Apoptosis**
- **Glucose metabolism**

**Abbreviations:** PI3K: Phosphatidylinositol 3-kinase
PI3K Inhibitor Overview

ISOFORM IC50 (nM)

<table>
<thead>
<tr>
<th></th>
<th>PI3Kα</th>
<th>PI3Kβ</th>
<th>PI3Kγ</th>
<th>PI3Kδ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idelalisib</td>
<td>820</td>
<td>565</td>
<td>89</td>
<td>2.5</td>
</tr>
<tr>
<td>Copanlisib</td>
<td>0.5</td>
<td>3.7</td>
<td>6.4</td>
<td>0.7</td>
</tr>
<tr>
<td>Duvelisib</td>
<td>1602</td>
<td>85</td>
<td>27</td>
<td>2.5</td>
</tr>
<tr>
<td>Umbralisib*</td>
<td>&gt;10000</td>
<td>1116</td>
<td>1065</td>
<td>22</td>
</tr>
</tbody>
</table>

* Also inhibits casein kinase CK1ε
PI3K Inhibitor Toxicities

• PI3K
  – Delta (δ) and Gamma (γ) isoforms are preferentially expressed on leukocytes
    • Infections
      – Pneumonia, opportunistic infections, CMV reactivation
    • Immune-mediated toxicities
      – δ isoform is important for $T_{regulatory}$ lymphocyte function
      – Hepatitis, pneumonitis, colitis, and rash
        » Younger patients or those less heavily pretreated may be at greater risk
    – Alpha (α) isoform is ubiquitously expressed and essential to cellular growth and metabolism, glucose homeostasis
      • Results in hyperglycemia and hypertension

Abbreviations: CMV-Cytomegalovirus
# PI3K Inhibitor Toxicities

<table>
<thead>
<tr>
<th></th>
<th>Idelalisib N=146</th>
<th>Copanlisib N=244</th>
<th>Duvelisib N=442</th>
<th>Umbralisib N=371</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade ≥ 3 AE</td>
<td>71%</td>
<td>85%</td>
<td>84%</td>
<td>51%</td>
</tr>
<tr>
<td>SAEs</td>
<td>50%</td>
<td>51%</td>
<td>65%</td>
<td>26%</td>
</tr>
<tr>
<td>Discontinuations due to AE</td>
<td>23%</td>
<td>24%</td>
<td>35%</td>
<td>15%</td>
</tr>
<tr>
<td>Dose Reduction due to AE</td>
<td>41%</td>
<td>24%</td>
<td>23%</td>
<td>10%</td>
</tr>
<tr>
<td>Grade ≥ 3 Infection</td>
<td>23%</td>
<td>23%</td>
<td>27%</td>
<td>20%</td>
</tr>
<tr>
<td>Grade ≥ 3 Neutropenia</td>
<td>28%</td>
<td>29%</td>
<td>43%</td>
<td>17%</td>
</tr>
<tr>
<td>Grade ≥ 3 Diarrhea/Colitis</td>
<td>14%</td>
<td>5%</td>
<td>23%</td>
<td>7%</td>
</tr>
<tr>
<td>Grade ≥ 3 AST/ALT increase</td>
<td>18%</td>
<td>2%</td>
<td>8%</td>
<td>7%</td>
</tr>
<tr>
<td>Grade ≥ 3 Rash</td>
<td>4%</td>
<td>2%</td>
<td>9%</td>
<td>3%</td>
</tr>
<tr>
<td>Grade ≥ 3 Pneumonitis</td>
<td>5%</td>
<td>7%</td>
<td>7%</td>
<td>1%</td>
</tr>
<tr>
<td>Grade ≥ 3 Hyperglycemia</td>
<td>-</td>
<td>34%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Grade ≥ 3 Hypertension</td>
<td>-</td>
<td>29%</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Abbreviations: AE- Adverse Event; SAE- Serious Adverse Event
PI3K Inhibitor Toxicities

Boxed Warning

Idelalisib
- Hepatotoxicity
- Diarrhea/colitis
- Pneumonitis
- Infections
- Intestinal perforation

Duvelisib
- Infections
- Diarrhea/colitis
- Cutaneous reactions
- Pneumonitis

Warnings and Precautions

Hepatotoxicity
- I, D, U
Diarrhea/colitis
- I, D, U
Pneumonitis
- I, C, D
Infections
- I, C, D, U
Cutaneous reactions
- I, C, D, U
Neutropenia
- I, C, D, U

Hyperglycemia
- C
Hypertension
- C
Intestinal perforation
- I

Communication REMS

Idelalisib
Duvelisib

Abbreviations: I- Idelalisib; D- Duvelisib; U- Umbralisib; C- Copanlisib
PI3K Inhibitor Regulatory History

2014

Idelalisib
  • Relapsed follicular lymphoma (FL) and relapsed small lymphocytic lymphoma (SLL) in patients who have received two prior systemic therapies (AA)
  • Relapsed chronic lymphocytic leukemia (CLL) in combination with rituximab in patients for whom rituximab alone would be considered appropriate therapy due to other co-morbidities

2017

Copanlisib
  • Relapsed FL who have received at least two prior systemic therapies (AA)

2018

Duvelisib
  • Relapsed or refractory FL after at least two prior systemic therapies (AA)
  • Relapsed or refractory CLL or SLL after at least two prior therapies

2021

Umbralisib
  • Patients with relapsed or refractory marginal zone lymphoma (MZL) who have received at least one prior anti-CD20 based regimen (AA)
  • Patients with relapsed or refractory FL who have received at least three prior lines of systemic therapy (AA)

Duvelisib relapsed FL indication voluntarily withdrawn (12/2021)

2022

Idelalisib relapsed FL and SLL indications voluntarily withdrawn (2/2022)
Umbralisib FL and MZL indications voluntarily withdrawn (4/2022)

Abbreviations: AA- Accelerated Approval, FL- Follicular lymphoma, CLL- Chronic lymphocytic leukemia, SLL- Small lymphocytic lymphoma, MZL- Marginal zone lymphoma
Regulatory Approval Pathways

• Regular Approval

• Accelerated Approval
  – Treatment of serious or life-threatening illness
  – Provides a meaningful benefit over available therapy
  – Approval is based on an endpoint reasonably likely to predict clinical benefit or an intermediate endpoint
  – Post-approval trials to verify anticipated clinical benefit

21 CFR 314.510
Evidentiary Criteria for Approval

- Drugs granted accelerated approval or regular approval must meet the same statutory standards for safety and effectiveness
- Safety
  - Sufficient information to determine that the drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling
- Effectiveness
  - Substantial evidence of effectiveness
    - Based on adequate and well-controlled investigations
    - The drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling

Guidance for Industry: Expedited Programs for Serious Conditions- Drugs and Biologics. FD&C Act Section 505(d) (21 U.S.C. § 355(d))
<table>
<thead>
<tr>
<th>Drug/Combination</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorambucil (1957)</td>
<td>CLL and lymphomas</td>
</tr>
<tr>
<td>Cyclophosphamide (1959)</td>
<td>Malignant lymphomas</td>
</tr>
<tr>
<td>Vincristine (1963)</td>
<td>NHL</td>
</tr>
<tr>
<td>Doxorubicin (1974)</td>
<td>NHL</td>
</tr>
<tr>
<td>Fludarabine (1991)</td>
<td>R/R CLL</td>
</tr>
<tr>
<td>Rituximab (1997) and</td>
<td>R/R FL; Untreated FL in combination and as</td>
</tr>
<tr>
<td>Rituximab Hyckela (2017)</td>
<td>maintenance; CLL with flu/cy</td>
</tr>
<tr>
<td>Zevalin (2002)</td>
<td>R/R FL</td>
</tr>
<tr>
<td>Bendamustine (2008)</td>
<td>CLL</td>
</tr>
<tr>
<td>Ofatumumab (2009)</td>
<td>Untreated CLL with chlorambucil; With flu/cy for</td>
</tr>
<tr>
<td></td>
<td>relapsed CLL; Extended treatment after 2 lines;</td>
</tr>
<tr>
<td></td>
<td>Refractory CLL</td>
</tr>
<tr>
<td>Obinutuzumab (2013)</td>
<td>With chlorambucil for untreated CLL; With</td>
</tr>
<tr>
<td></td>
<td>bendamustine for R/R FL; With chemo for</td>
</tr>
<tr>
<td></td>
<td>untreated FL</td>
</tr>
<tr>
<td>Lenalidomide (2013)</td>
<td>In combination with rituximab for relapsed FL</td>
</tr>
<tr>
<td></td>
<td>or relapsed MZL</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug/Combination</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibrutinib (2013)</td>
<td>CLL/SLL; CLL/SLL with 17p del; WM; MZL after 1</td>
</tr>
<tr>
<td></td>
<td>prior CD20-based therapy*</td>
</tr>
<tr>
<td>Idelalisib (2014)</td>
<td>Relapsed CLL</td>
</tr>
<tr>
<td>Venetoclax (2016)</td>
<td>CLL/SLL</td>
</tr>
<tr>
<td>Acalabrutinib (2017)</td>
<td>CLL/SLL</td>
</tr>
<tr>
<td>Copanlisib (2017)</td>
<td>Relapsed FL after 2 prior therapies *</td>
</tr>
<tr>
<td>Duvelisib (2018)</td>
<td>R/R CLL/SLL at least 2 prior therapies</td>
</tr>
<tr>
<td>Zanubrutinib (2019)</td>
<td>WM; R/R MZL after 1 prior CD20-based regimen*</td>
</tr>
<tr>
<td>Tazemetostat (2020)</td>
<td>R/R FL positive for EZH2 mutation after 2 prior</td>
</tr>
<tr>
<td></td>
<td>therapies*; R/R FL with no alternative options*</td>
</tr>
<tr>
<td>Umbralisib (2021)</td>
<td>R/R MZL after 1 prior CD20 based regimen*; R/R</td>
</tr>
<tr>
<td></td>
<td>FL after 3 prior therapies*</td>
</tr>
<tr>
<td>Axicabtagene</td>
<td>R/R FL after two lines*</td>
</tr>
<tr>
<td>Ciloleucel (2021)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CLL: Chronic lymphocytic leukemia; iNHL: Indolent non-Hodgkin lymphomas; R/R: relapsed, refractory; MCL: Mantle cell lymphoma; Flu/cy: Fludarabine, cyclophosphamide; FL: follicular lymphoma; MZL: Marginal zone lymphoma; NHL- Non-Hodgkin lymphoma; WM: Waldenstrom’s macroglobulinemia

* Indicates accelerated approval
Issues for Discussion

• Potential Detriment in Overall Survival
• Toxicity and Tolerability
• Dosing
• Limitations of Single-arm Trials
# Multiple Randomized Trials with Concerning Overall Survival

<table>
<thead>
<tr>
<th>Study</th>
<th>Population &amp; Treatment</th>
<th>Deaths PI3Ki arm</th>
<th>Deaths Control arm</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>312-0123</td>
<td>Untreated CLL&lt;br&gt;• Bendamustine and rituximab ± idelalisib</td>
<td>8% (12/157)</td>
<td>3% (4/154)</td>
<td>3.34 (1.08, 10.39)</td>
</tr>
<tr>
<td>313-0124</td>
<td>Previously treated indolent NHL&lt;br&gt;• Rituximab ± idelalisib</td>
<td>5% (10/191)</td>
<td>1% (1/95)</td>
<td>4.74 (0.6, 37.12)</td>
</tr>
<tr>
<td>313-0125</td>
<td>Previously treated indolent NHL&lt;br&gt;• Bendamustine and rituximab ± idelalisib</td>
<td>8% (27/320)</td>
<td>6% (9/155)</td>
<td>1.51 (0.71, 3.23)</td>
</tr>
<tr>
<td>DUO</td>
<td>Previously treated CLL&lt;br&gt;• Duvelisib vs ofatumumab</td>
<td>50% (80/160)</td>
<td>44% (70/159)</td>
<td>1.09 (0.79, 1.51)</td>
</tr>
<tr>
<td>CHRONOS-3</td>
<td>Previously treated indolent NHL&lt;br&gt;• Rituximab ± copanlisib</td>
<td>18% (56/307)</td>
<td>21% (32/151)</td>
<td>0.87 (0.57, 1.35)</td>
</tr>
<tr>
<td>UNITY-CLL</td>
<td>Untreated and previously treated CLL&lt;br&gt;• Umbralisib + ublituximab vs GC</td>
<td>-</td>
<td>-</td>
<td>1.23</td>
</tr>
</tbody>
</table>

**Abbreviations:** CI, confidence interval; CLL, chronic lymphocytic leukemia; GC, Obinutuzumab + Chlorambucil; NHL, non-Hodgkin lymphoma; PI3Ki, phosphatidylinositol 3-kinase inhibitor.
PI3K Inhibitor Dosing Concerns

- Limited dose exploration
- Exposure-response relationships for safety
- Lack of an exposure-response relationship for efficacy
- High rates of discontinuation, interruption and modification

<table>
<thead>
<tr>
<th>Treatment Modification</th>
<th>Idelalisib N = 146</th>
<th>Copanlisib N = 244</th>
<th>Duvelisib N = 442</th>
<th>Umbralisib N = 371</th>
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<tr>
<td>Discontinuation due to AE</td>
<td>23%</td>
<td>24%</td>
<td>35%</td>
<td>15%</td>
</tr>
<tr>
<td>Dose reduction due to AE</td>
<td>41%</td>
<td>24%</td>
<td>23%</td>
<td>10%</td>
</tr>
<tr>
<td>Dose interruption due to AE</td>
<td>41%</td>
<td>64%</td>
<td>64%</td>
<td>45%</td>
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</table>
PI3K Inhibitor Withdrawals

• Idelalisib
  – Initial accelerated approval for R/R FL or SLL after 2 prior therapies in 2014
  – 3 Subpart H PMRs were issued:
    – PMR 1: Dose optimization in R/R FL and SLL among responders
    – PMR 2: Safety and efficacy from GS-US-313-0124, a phase 3 trial of idelalisib + rituximab in previously treated iNHL
    – PMR 3: Safety and efficacy from GS-US-313-0125, a phase 3 trial of idelalisib + bendamustine + rituximab in previously treated iNHL
  – March 2016, 3 trials terminated for increased deaths, including - 0124 and 0125 confirmatory trials

Abbreviations: FL- follicular lymphoma; SLL- Small lymphocytic lymphoma; iNHL- Indolent Non-Hodgkin Lymphoma; R/R- relapsed refractory; PMR- postmarketing requirement
PI3K Inhibitor Withdrawals

• Idelalisib (cont.)
  – FDA regulatory actions based on increased deaths
    • Limitation of use added to the label that idelalisib is not indicated for first-line treatment, is not indicated in combination with bendamustine and rituximab in FL, and updates to the boxed warning and warnings and precautions
    • New PMR issued 2180-10 to conduct a trial to establish the safe and effective dose of idelalisib in patients with R/R FL who have no other therapeutic options
      – Study GS-US-313-1580
  – February 2022
    • Citing challenges in enrollment to the confirmatory trial, the sponsor decided to voluntarily withdraw the indication from the U.S. market

Abbreviations: FL- follicular lymphoma; R/R- relapsed refractory; PMR- postmarketing requirement
PI3K Inhibitor Withdrawals

• Duvelisib
  – Initial accelerated approval for R/R FL after 2 prior therapies in 2018
    • 1 Subpart H PMR was issued
      – PMR 3494-1: Conduct a randomized phase 3 trial in patients with R/R FL that verifies the clinical benefit.
    – December 2021
      • Citing changes in the treatment landscape, the sponsor decided to voluntarily withdraw the indication from the U.S. market

Abbreviations: FL- follicular lymphoma; R/R- relapsed refractory
PI3K Inhibitor Withdrawals

• Umbralisib Update - April 15, 2022
  – Voluntary withdrawal of umbralisib and ublituximab applications for the U2 regimen based on the UNITY-CLL trial
    o Overall survival concerns
  – Voluntary withdrawal of the FL and MZL indications for umbralisib under accelerated approval

Abbreviations: FL- follicular lymphoma; MZL- Marginal zone lymphoma
Single Arm Trial Limitations

• Safety findings are challenging to interpret
  – E.g., attribution to the drug or underlying disease
• Efficacy findings are challenging to interpret
  – Response rates may not predict clinical benefit
  – Reliance on cross-trial comparisons to determine if the product provides a benefit over available therapy is difficult
• Time-to-event endpoints (e.g., PFS and OS) are not interpretable

Abbreviations: PFS- progression-free survival; OS- overall survival
Overall Survival Endpoint

• Safety and an efficacy endpoint
  – E.g., attribution to the drug or underlying disease
• Incorporates the effect of toxicity
Discussion Topic

• Please discuss the observed toxicity of the PI3K inhibitor class and whether randomized data are warranted with an assessment of OS to support the evaluation of benefit-risk in patients with hematologic malignancies.
Voting Question

Given the observed toxicities with this class, previous randomized trials with a potential detriment in OS, and a narrow range between effective and toxic doses, should future approvals of PI3K inhibitors be supported by randomized data?
Phosphatidylinositol 3-kinase (PI3K) Inhibitors in Hematologic Malignancies

Oncologic Drugs Advisory Committee Meeting
April 21, 2022

Nicholas Richardson, DO, MPH
Division of Hematologic Malignancies II
Office of Oncologic Diseases
Outline

Purpose
  o Approach for future PI3K inhibitors developed for patients with hematologic malignancies

Approved PI3K inhibitors
  o Idelalisib
  o Copanlisib
  o Duvelisib
  o Umbralisib

Issues
  o Potential detriment in overall survival
  o Toxicity and tolerability
  o Dosing
  o Limitations of single-arm trials

Abbreviation: PI3K, phosphatidylinositol 3-kinase
FDA Review Team

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Runyan Jin, PhD
George Shen, PhD
Yajun Liu, PhD
Hongfei Zhang, PhD
Approved PI3K Inhibitors

**Idelalisib**
- Initial approval
  - CLL
  - FL* & SLL*
  - July 2014
- Label Update
  - 3 randomized trials show worse OS
  - March 2016
- FDA Safety Alert
  - March 2016
- Label Update
  - LOU - frontline treatment
  - Safety Data
  - March 2016
- Withdrawal of FL and SLL indications
  - Feb 2022

**Idelalisib**
- Initial approval
  - • CLL
  - • FL* & SLL*
  - July 2014
- Label Update
  - 3 randomized trials show worse OS
  - March 2016
- FDA Safety Alert
  - March 2016
- Label Update
  - LOU - FL
  - Safety Data
  - March 2016
- Withdrawal of FL and SLL indications
  - Feb 2022

**Copanlisib**
- Initial approval
  - • FL*
  - Sept 2017
- FDA Safety Alert
  - Sept 2017
- NDA based on CHRONOS-3 submitted
  - Sept 2017
- NDA based on CHRONOS-3 withdrawn
  - Sept 2017
- Withdrawal of FL indication
  - Dec 2021

**Duvelisib**
- Initial approval
  - • CLL/SLL
  - • FL*
  - Sept 2017
- FDA Safety Alert
  - Sept 2017
- NDA based on CHRONOS-3 submitted
  - Sept 2017
- NDA based on CHRONOS-3 withdrawn
  - Sept 2017
- Withdrawal of FL indication
  - Dec 2021

**Umbralisib**
- Initial approval
  - FL* & MZL
  - Feb 2021
- FDA Safety Alert
  - Feb 2021
- NDA based on UNITY submitted
  - Feb 2021
- Withdrawal of FL and SLL indications
  - Feb 2022

**Abbreviations:**
- CLL, chronic lymphocytic leukemia
- FL, follicular lymphoma
- LOU, limitation of use
- MZL, marginal zone lymphoma
- NDA, new drug application
- OS, overall survival
- SLL, small lymphocytic lymphoma

www.fda.gov
Idelalisib (Zydelig)

Abbreviation: PI3K, phosphatidylinositol 3-kinase
Idelalisib Approvals

• Granted regular approval in relapsed CLL in July 2014
  o Relapsed CLL, in combination with rituximab, in patients for whom rituximab alone would be considered appropriate therapy due to other co-morbidities

### Study 312-0116

<table>
<thead>
<tr>
<th>Design</th>
<th>Population</th>
<th>Treatment</th>
<th>Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized (1:1)</td>
<td>Relapsed CLL</td>
<td>Idelalisib + Rituximab (I + R) Placebo + Rituximab (Pbo + R)</td>
<td>Primary: Progression-free survival (PFS)</td>
</tr>
<tr>
<td>Placebo-controlled</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

|                        | I + R        | Pbo + R                                                    |
|---                     | N = 110      | N = 110                                                    |
| PFS Events, n (%)      | 25 (23)      | 70 (64)                                                    |
| Median PFS, months (95% CI) | 19.4 (12.3, NR) | 6.5 (4.0, 7.3)   |
| Adjusted HR (95% CI)   | 0.15 (0.09, 0.24) |                                                             |

Abbreviations: CI, confidence interval, CLL, chronic lymphocytic leukemia, HR, hazard ratio, NR, not reached
Idelalisib Approvals

- Granted accelerated approval in relapsed FL and SLL in July 2014
  - Relapsed FL and SLL in patients who have received at least two prior systemic therapies

### Study 101-09

<table>
<thead>
<tr>
<th>Design</th>
<th>Population</th>
<th>Treatment</th>
<th>Endpoint</th>
<th>ORR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single-arm trial</td>
<td>Relapsed FL (N = 72) Relapsed SLL (N = 26)</td>
<td>Idelalisib 150 mg orally twice daily</td>
<td>Primary: Overall response rate (ORR)</td>
<td>FL = 54% (42, 66) SLL = 58% (37, 77)</td>
</tr>
</tbody>
</table>

Abbreviations: FL, follicular lymphoma, SLL, small lymphocytic lymphoma
## Idelalisib Approval Components

### Boxed Warning
- Hepatotoxicity
- Diarrhea or Colitis
- Pneumonitis
- Intestinal Perforation

### Warnings & Precautions
- Rash
- Neutropenia
- Anaphylaxis

### Accelerated Approval Postmarketing Requirements
- Dose optimization
- Two randomized trials in indolent NHL
  - Idelalisib ± Rituximab
  - Idelalisib ± BR

### Safety Postmarketing Requirements
- Pneumonitis
- Long-term safety

### Communication REMS
- Inform providers of serious risks

Abbreviations: BR, bendamustine and rituximab, NHL, non-Hodgkin lymphoma, REMS, risk evaluation and mitigation strategy
March 2016
Three Randomized Trials Terminated Due to Increased Deaths

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Treatment Arms</th>
</tr>
</thead>
<tbody>
<tr>
<td>312-0123</td>
<td>Untreated CLL</td>
<td>• Idelalisib + BR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Placebo + BR</td>
</tr>
<tr>
<td>313-0124</td>
<td>Previously treated indolent NHL (excluded rituximab refractory)</td>
<td>• Idelalisib + rituximab</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Placebo + rituximab</td>
</tr>
<tr>
<td>313-0125</td>
<td>Previously treated indolent NHL (excluded bendamustine refractory)</td>
<td>• Idelalisib + BR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Placebo + BR</td>
</tr>
</tbody>
</table>

Idelalisib Dose: 150 mg twice daily (BID) for all studies
Bendamustine Dose: 90 mg/m², up to 6 cycles
Rituximab dose: 375 mg/m², dose schedule varied across studies

Abbreviations: BR, bendamustine and rituximab, CLL, chronic lymphocytic leukemia, NHL, non-Hodgkin lymphoma
**March 2016**

**Three Randomized Trials Terminated Due to Increased Deaths**

<table>
<thead>
<tr>
<th>Study</th>
<th>Population &amp; Treatment</th>
<th>Deaths Idelalisib</th>
<th>Deaths Control</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
</table>
| 312-0123    | • Untreated CLL  
              • Bendamustine and rituximab ± idelalisib               | 8% (12/157)       | 3% (4/154)     | 3.34 (1.08, 10.39)  |
| 313-0124    | • Previously treated indolent NHL  
              • Rituximab ± idelalisib                                  | 5% (10/191)       | 1% (1/95)      | 4.74 (0.6, 37.12)   |
| 313-0125    | • Previously treated indolent NHL  
              • Bendamustine and rituximab ± idelalisib                 | 8% (27/320)       | 6% (9/155)     | 1.51 (0.71, 3.23)   |

Abbreviations: CI, confidence interval, CLL, chronic lymphocytic leukemia, NHL, non-Hodgkin lymphoma
## Increased Deaths Due to Toxicity

<table>
<thead>
<tr>
<th>Study 312-0123 Untreated CLL</th>
<th>Study 313-0124 R/R indolent NHL</th>
<th>Study 313-125 R/R indolent NHL</th>
</tr>
</thead>
<tbody>
<tr>
<td>I + BR N = 157</td>
<td>I + R N = 191</td>
<td>I + BR N = 320</td>
</tr>
<tr>
<td>Pbo + BR N = 154</td>
<td>Pbo + R N = 95</td>
<td>Pbo + BR N = 155</td>
</tr>
<tr>
<td><strong>Total Deaths</strong></td>
<td><strong>Death due to AE</strong></td>
<td><strong>Infection</strong></td>
</tr>
<tr>
<td>12 (8%)</td>
<td>12 (8%)</td>
<td>8 (5%)</td>
</tr>
<tr>
<td>4 (3%)</td>
<td>3 (2%)</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>10 (5%)</td>
<td><strong>8 (4%)</strong></td>
<td>2 (1%)</td>
</tr>
<tr>
<td>1 (1%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>27 (8%)</td>
<td>20 (6%)</td>
<td>8 (2%)</td>
</tr>
<tr>
<td>9 (6%)</td>
<td>5 (3%)</td>
<td>2 (1%)</td>
</tr>
</tbody>
</table>

**Death due to AE**

- 12 (8%)
- 3 (2%)
- 8 (4%)
- 0
- 20 (6%)
- 5 (3%)

**Infection**

- 8 (5%)
- 1 (<1%)
- 2 (1%)
- 0
- 8 (2%)
- 2 (1%)

**Respiratory**

- 0
- 0
- 2 (1%)
- 0
- 6 (2%)
- 0

**Cardiac**

- 2 (1%)
- 0
- 1 (<1%)
- 0
- 2 (<1%)
- 1 (<1%)

**Abbreviations:** AE, adverse event; BR, bendamustine and rituximab; CLL, chronic lymphocytic leukemia; I, idelalisib; NHL, non-Hodgkin lymphoma; Pbo, placebo; R, rituximab; R/R, relapsed or refractory
March 2016
Three Randomized Trials Demonstrated Increased Toxicity

- **Idelalisib arm** - blue
- **Control arm** - green

<table>
<thead>
<tr>
<th>Study</th>
<th>Grade ≥3 AE</th>
<th>Serious AE</th>
<th>Discontinuation due to AE</th>
<th>Reduction due to AE</th>
<th>Interruption due to AE</th>
</tr>
</thead>
<tbody>
<tr>
<td>312-0123</td>
<td>96%</td>
<td>80%</td>
<td>86%</td>
<td>72%</td>
<td>62%</td>
</tr>
<tr>
<td>Untreated CLL</td>
<td>72%</td>
<td>37%</td>
<td>44%</td>
<td>14%</td>
<td>25%</td>
</tr>
<tr>
<td>313-0124</td>
<td>92%</td>
<td>62%</td>
<td>44%</td>
<td>10%</td>
<td>20%</td>
</tr>
<tr>
<td>R/R indolent NHL</td>
<td>38%</td>
<td>8%</td>
<td>7%</td>
<td>3%</td>
<td>12%</td>
</tr>
<tr>
<td>313-0125</td>
<td>96%</td>
<td>86%</td>
<td>46%</td>
<td>39%</td>
<td>29%</td>
</tr>
<tr>
<td>R/R indolent NHL</td>
<td>92%</td>
<td>72%</td>
<td>64%</td>
<td>65%</td>
<td>65%</td>
</tr>
</tbody>
</table>

Abbreviations: AE, adverse event, BR, bendamustine + rituximab, CLL, chronic lymphocytic leukemia, I, idelalisib, NHL, non-Hodgkin lymphoma, R, rituximab, R/R, relapsed or refractory
## Difference in Toxicity Driven by PI3K-Associated Toxicities

<table>
<thead>
<tr>
<th>Study 312-0123 Untreated CLL</th>
<th>Study 313-0124 R/R indolent NHL</th>
<th>Study 313-125 R/R indolent NHL</th>
</tr>
</thead>
<tbody>
<tr>
<td>I + BR N = 157</td>
<td>I + R N = 191</td>
<td>I + BR N = 320</td>
</tr>
<tr>
<td>Pbo + BR N = 154</td>
<td>Pbo + R N = 95</td>
<td>Pbo + BR N = 155</td>
</tr>
<tr>
<td>Grade ≥3 Infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>45%</td>
<td>22%</td>
<td>40%</td>
</tr>
<tr>
<td>20%</td>
<td>4%</td>
<td>19%</td>
</tr>
<tr>
<td>Grade ≥3 Neutropenia*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>65%</td>
<td>64%</td>
<td>41%</td>
</tr>
<tr>
<td>12%</td>
<td>10%</td>
<td>37%</td>
</tr>
<tr>
<td>9%</td>
<td>3%</td>
<td>13%</td>
</tr>
<tr>
<td>Grade ≥3 Diarrhea-Colitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9%</td>
<td>3%</td>
<td>0</td>
</tr>
<tr>
<td>19%</td>
<td>2%</td>
<td>13%</td>
</tr>
<tr>
<td>Grade ≥3 ALT/AST increase*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>26%</td>
<td>1%</td>
<td>27%</td>
</tr>
<tr>
<td>1%</td>
<td>0</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Grade ≥3 Rash</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17%</td>
<td>8%</td>
<td>19%</td>
</tr>
<tr>
<td>10%</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Any Grade Pneumonitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6%</td>
<td>6%</td>
<td>8%</td>
</tr>
<tr>
<td>3%</td>
<td>1%</td>
<td>1%</td>
</tr>
</tbody>
</table>

*Based on laboratory data

**Abbreviations:** BR, bendamustine and rituximab; CLL, chronic lymphocytic leukemia; I, idelalisib; NHL, non-Hodgkin lymphoma; Pbo, placebo; R, rituximab; R/R, relapsed or refractory

[www.fda.gov](http://www.fda.gov)
Randomized Data Led to Additional Safety Mitigation

• FDA Safety Alert
• Dear Healthcare Provider Letter
• Updated Boxed Warning and REMS
• Updated Safety Information in Label
• Limitations of Use
  – Idelalisib is not indicated and is not recommended for first-line treatment of any patient
  – Idelalisib is not indicated and is not recommended in combination with bendamustine and/or rituximab for the treatment of follicular lymphoma

Abbreviations: REMS, risk evaluation and mitigation strategy
Idelalisib Accelerated Approval Postmarketing Requirement (PMR) Updated

• The terminated -0124 and -0125 trials in indolent NHL were the confirmatory trials for the FL and SLL indications

• New PMR issued
  – Conduct a trial establishing a safe and effective dosing regimen of idelalisib in patients with relapsed or refractory FL who have no other therapeutic options and require treatment.
  – Ongoing Study 313-1580: *Dose Optimization Study of Zydelig in Follicular Lymphoma*

Abbreviations: FL, follicular lymphoma, NHL, non-Hodgkin lymphoma, SLL, small lymphocytic lymphoma
Withdrawal of Idelalisib FL and SLL Indications

• Study 313-1580: *Dose Optimization Study of Zydelig in Follicular Lymphoma*
  – Enrollment Challenges

• Inability to conduct a clinical trial to verify benefit
  – February 2022 – FL and SLL indications voluntarily withdrawn from U.S. market

Abbreviations: FL, follicular lymphoma, SLL, small lymphocytic lymphoma
Idelalisib Dosing Considerations

Idelalisib – approved dose 150 mg BID

• Monotherapy
  – Maximum tolerated dose (MTD) not reached
  – Exposure-response for efficacy plateaued at 150 mg BID
  – Higher exposure associated with increased risk of toxicity
  – High rates of treatment modifications due to toxicity
  – Lower doses (e.g., 100 mg BID) may be efficacious and tolerable

• Idelalisib Combination – 150 mg BID selected
  – Limited dose exploration
  – No E-R for efficacy
  – E-R relationship for safety
  – High rates of treatment modifications due to toxicity
  – Lower doses (e.g., 100 mg BID) may be efficacious and tolerable in combination

Abbreviations: E-R, exposure-response, PK, pharmacokinetic
Copanlisib (Aliqopa)

Abbreviation: PI3K, phosphatidylinositol 3-kinase
Copanlisib Approval

• Granted accelerated approval in relapsed follicular lymphoma (FL) in September 2017
  - Relapsed FL who have received at least two prior systemic therapies

<table>
<thead>
<tr>
<th>CHRONOS-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td>Single-arm trial</td>
</tr>
</tbody>
</table>

Abbreviations: ORR, overall response rate
## Copanlisib Toxicity in NHL

<table>
<thead>
<tr>
<th>Event</th>
<th>Copanlisib N = 244</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Exposure, months (range)</td>
<td>4.3 (0.2, 47.4)</td>
</tr>
<tr>
<td>Death due to Adverse Event</td>
<td>4%</td>
</tr>
<tr>
<td>Grade ≥3 Adverse Event</td>
<td>85%</td>
</tr>
<tr>
<td>Serious Adverse Event</td>
<td>51%</td>
</tr>
<tr>
<td>Discontinuation due to Adverse Event</td>
<td>24%</td>
</tr>
<tr>
<td>Reduction due to Adverse Event</td>
<td>24%</td>
</tr>
<tr>
<td>Interruption due to Adverse Event</td>
<td>64%</td>
</tr>
</tbody>
</table>

| Grade ≥3 Hyperglycemia*                    | 34%                 |
| Grade ≥3 Hypertension                      | 29%                 |
| Grade ≥3 Infection                         | 23%                 |
| Grade ≥3 Neutropenia*                      | 29%                 |
| Grade ≥3 Diarrhea-Colitis                  | 5%                  |
| Grade ≥3 ALT/AST increase*                | 2%                  |
| Grade ≥3 Rash                              | 2%                  |
| Any Grade Pneumonitis                      | 7%                  |

*Based on laboratory data

Abbreviations: ALT, alanine aminotransferase, AST, aspartate aminotransferase, NHL, non-Hodgkin lymphoma
Warnings & Precautions

- Infection
- Hyperglycemia
- Hypertension
- Pneumonitis
- Neutropenia
- Rash

Accelerated Approval Postmarketing Requirements

- Randomized trial in indolent NHL
  - Copanlisib ± immunochemotherapy

Safety Postmarketing Requirements

- Long-term safety
- Safety from randomized trial in indolent NHL
- QT study
- Hepatic and renal impairment
- Drug-drug interaction

Abbreviations: NHL, non-Hodgkin lymphoma
# CHRONOS-3 Study in Indolent NHL

## CHRONOS-3

<table>
<thead>
<tr>
<th>Design</th>
<th>Population</th>
<th>Treatment</th>
<th>Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized (2:1)</td>
<td>Relapsed indolent NHL* (FL, MZL, SLL, WM)</td>
<td>Copanlisib + Rituximab (N = 307)</td>
<td>Primary: PFS</td>
</tr>
<tr>
<td>Placebo-controlled</td>
<td></td>
<td>Placebo + Rituximab (N = 151)</td>
<td></td>
</tr>
</tbody>
</table>

*Eligibility*
- Progression-free or treatment-free $\geq 12$ months after last CD20 therapy or
- Considered unfit for chemotherapy and progression-free or treatment-free $\geq 6$ months after last CD20 therapy

Abbreviations: FL, follicular lymphoma, MZL, NHL, non-Hodgkin lymphoma, PFS, progression-free survival, SLL, small lymphocytic lymphoma, WM, Waldenström's macroglobulinemia
# CHRONOS-3 PFS Results in Indolent NHL

<table>
<thead>
<tr>
<th>Design</th>
<th>Population</th>
<th>Treatment</th>
<th>Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized (2:1)</td>
<td>Relapsed indolent NHL</td>
<td>Copanlisib + Rituximab (C + R)</td>
<td>Primary: PFS</td>
</tr>
<tr>
<td>Placebo-controlled</td>
<td>(FL, MZL, SLL, WM)</td>
<td>Placebo + Rituximab (Pbo + R)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>C + R</th>
<th>Pbo + R</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 307</td>
<td>N = 151</td>
</tr>
<tr>
<td>PFS Events, n (%)</td>
<td>118 (38)</td>
<td>87 (58)</td>
</tr>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>21.5 (17.8, 33.0)</td>
<td>13.8 (10.2, 17.5)</td>
</tr>
<tr>
<td>Adjusted HR (95% CI)</td>
<td>0.52 (0.39, 0.69)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; FL, follicular lymphoma; HR, hazard ratio; MZL, marginal zone lymphoma; NHL, non-Hodgkin lymphoma; PFS, progression-free survival; SLL, small lymphocytic lymphoma; WM, Waldenström's macroglobulinemia
**CHRONOS-3 Overall Survival Results**

### Indolent NHL – Intent-to-treat

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Deaths</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Copanlisib/Rituximab</td>
<td>307</td>
<td>56 (18%)</td>
<td>0.87 (0.57, 1.35)</td>
</tr>
<tr>
<td>Placebo/Rituximab</td>
<td>151</td>
<td>32 (21%)</td>
<td></td>
</tr>
</tbody>
</table>

### Follicular lymphoma

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Deaths</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Copanlisib/Rituximab</td>
<td>184</td>
<td>30 (16%)</td>
<td>0.95 (0.52, 1.74)</td>
</tr>
<tr>
<td>Placebo/Rituximab</td>
<td>91</td>
<td>16 (18%)</td>
<td></td>
</tr>
</tbody>
</table>
### CHRONOS-3 Deaths in Safety Population

<table>
<thead>
<tr>
<th></th>
<th>Copanlisib/Rituximab N = 307 n (%)</th>
<th>Placebo/Rituximab N = 146 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Deaths</td>
<td>56 (18%)</td>
<td>32 (22%)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>23 (7%)</td>
<td>8 (5%)</td>
</tr>
<tr>
<td>Adverse event</td>
<td>15 (5%)</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Other</td>
<td>12 (4%)</td>
<td>15 (10%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>6 (2%)</td>
<td>8 (5%)</td>
</tr>
</tbody>
</table>

Deaths due to adverse events were higher in the copanlisib arm.
CHRONOS-3 Safety in Indolent NHL

Proportion (%)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Copanlisib arm (C + R, N = 307)</th>
<th>Rituximab arm (R, N = 146)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade ≥3 AE</td>
<td>91</td>
<td>57</td>
</tr>
<tr>
<td>Serious AE</td>
<td>47</td>
<td>18</td>
</tr>
<tr>
<td>Discontinuation due to AE</td>
<td>31</td>
<td>8</td>
</tr>
<tr>
<td>Reduction due to AE</td>
<td>27</td>
<td>7</td>
</tr>
<tr>
<td>Interruption due to AE</td>
<td>67</td>
<td>36</td>
</tr>
</tbody>
</table>

Abbreviations: AE, adverse event; C, copanlisib; NHL, non-Hodgkin lymphoma; R, rituximab
## Difference in Toxicity Driven by PI3K-Associated Toxicities

<table>
<thead>
<tr>
<th></th>
<th>CHRONOS-3 (Indolent NHL)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Copanlisib + Rituximab</td>
<td>Placebo + Rituximab</td>
</tr>
<tr>
<td></td>
<td>N = 307</td>
<td>N = 146</td>
</tr>
<tr>
<td>Grade ≥3 Hyperglycemia*</td>
<td>67%</td>
<td>12%</td>
</tr>
<tr>
<td>Grade ≥3 Hypertension</td>
<td>41%</td>
<td>10%</td>
</tr>
<tr>
<td>Grade ≥3 Infection</td>
<td>22%</td>
<td>8%</td>
</tr>
<tr>
<td>Grade ≥3 Neutropenia*</td>
<td>40%</td>
<td>24%</td>
</tr>
<tr>
<td>Grade ≥3 Diarrhea-Colitis</td>
<td>6%</td>
<td>0</td>
</tr>
<tr>
<td>Grade ≥3 ALT/AST increase*</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Grade ≥3 Rash</td>
<td>3%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Any Grade Pneumonitis</td>
<td>8%</td>
<td>1%</td>
</tr>
</tbody>
</table>

*Based on laboratory data

**Abbreviations:** ALT, alanine aminotransferase; AST, aspartate aminotransferase; NHL, non-Hodgkin lymphoma; PI3K, phosphotidylinositol-3 kinase
CHRONOS-3 Application Withdrawal

- The supplemental new drug application based on CHRONOS-3 to support treatment of adult patients with indolent NHL was withdrawn from the FDA in December 2021

Abbreviations: NHL, non-Hodgkin lymphoma
Copanlisib Dosing Considerations

Copanlisib – approved dose 60 mg IV weekly (3 weeks on/1 week off)

• Monotherapy
  – Limited dose finding in hematologic malignancies
  – 0.8 mg/kg or 60 mg selected as maximum tolerated dose (MTD)
  – PK/PD data suggested comparable efficacy for 45 mg and 60 mg
  – No significant E-R relationships observed for efficacy or safety at 60 mg dose
  – High rates of treatment modifications due to toxicity at 60 mg

• Combination
  – No dose finding conducted for use in combination – 60 mg dose selected

Abbreviations: E-R, exposure-response, PD, pharmacodynamic, PK, pharmacokinetic
Duvelisib (Copiktra)

Abbreviation: PI3K, phosphatidylinositol 3-kinase
Duvelisib Approvals

• Granted regular approval in relapsed or refractory CLL or SLL in September 2018
  ○ Relapsed or refractory CLL or SLL after at least two prior therapies

### Study IPI-145-07 (DUO)

<table>
<thead>
<tr>
<th>Design</th>
<th>Population</th>
<th>Treatment</th>
<th>Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized (1:1)</td>
<td>Relapsed or refractory CLL or SLL</td>
<td>Duvelisib (N = 160) Ofatumumab (N = 159)</td>
<td>Primary: Progression-free survival (PFS)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Duvelisib N = 160</th>
<th>Ofatumumab N = 159</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS Events, n (%)</td>
<td>93 (58)</td>
<td>110 (69)</td>
</tr>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>13.3 (12.1, 16.8)</td>
<td>9.9 (9.2, 11.3)</td>
</tr>
<tr>
<td>Adjusted HR (95% CI)</td>
<td>0.52 (0.39, 0.69)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CLL, chronic lymphocytic leukemia, SLL, small lymphocytic lymphoma
Duvelisib Approvals

- Granted accelerated approval in relapsed or refractory FL in September 2018
  - Relapsed or refractory FL after at least two prior systemic therapies

<table>
<thead>
<tr>
<th>Study IPI-145-06 (DYNAMO)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Design</strong></td>
</tr>
<tr>
<td>Single-arm trial</td>
</tr>
</tbody>
</table>

Abbreviations: FL, follicular lymphoma
# Duvelisib Toxicity in NHL

<table>
<thead>
<tr>
<th></th>
<th>Duvelisib N = 442</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Exposure, months (range)</td>
<td>9.0 (0.1, 53.0)</td>
</tr>
<tr>
<td>Death due to Adverse Event</td>
<td>4%</td>
</tr>
<tr>
<td>Grade ≥3 Adverse Event</td>
<td>84%</td>
</tr>
<tr>
<td>Serious Adverse Event</td>
<td>65%</td>
</tr>
<tr>
<td>Discontinuation due to Adverse Event</td>
<td>35%</td>
</tr>
<tr>
<td>Reduction due to Adverse Event</td>
<td>23%</td>
</tr>
<tr>
<td>Interruption due to Adverse Event</td>
<td>64%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>PI3K-Associated Toxicities</th>
<th>Duvelisib N = 442</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade ≥3 Infection</td>
<td></td>
<td>27%</td>
</tr>
<tr>
<td>Grade ≥3 Neutropenia*</td>
<td></td>
<td>43%</td>
</tr>
<tr>
<td>Grade ≥3 Diarrhea-Colitis</td>
<td></td>
<td>23%</td>
</tr>
<tr>
<td>Grade ≥3 ALT/AST increase*</td>
<td></td>
<td>8%</td>
</tr>
<tr>
<td>Grade ≥3 Rash</td>
<td></td>
<td>9%</td>
</tr>
<tr>
<td>Any Grade Pneumonitis</td>
<td></td>
<td>7%</td>
</tr>
</tbody>
</table>

*Based on laboratory data

Abbreviations: AE, adverse event, ALT, alanine aminotransferase, AST, aspartate aminotransferase, NHL, non-Hodgkin lymphoma, PI3K, phosphatidylinositol 3-kinase
DUO Study Safety
Relapsed or Refractory CLL or SLL

• Duvelisib arm - blue
• Ofatumumab arm - green

<table>
<thead>
<tr>
<th>Event</th>
<th>Duvelisib (N = 158)</th>
<th>Ofatumumab (N = 155)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death due to AE</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>Grade ≥3 AE</td>
<td>87</td>
<td>48</td>
</tr>
<tr>
<td>Serious AE</td>
<td>73</td>
<td>32</td>
</tr>
<tr>
<td>Discontinuation due to AE</td>
<td>36</td>
<td>29</td>
</tr>
<tr>
<td>Reduction due to AE</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Interruption due to AE</td>
<td>78</td>
<td>10</td>
</tr>
</tbody>
</table>

Abbreviations: AE, adverse event, CLL, chronic lymphocytic leukemia, SLL, small lymphocytic lymphoma
## Difference in Toxicity Driven by PI3K-Associated Toxicities

<table>
<thead>
<tr>
<th></th>
<th>DUO (CLL or SLL)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Duvelisib</td>
<td>Ofatumumab</td>
</tr>
<tr>
<td></td>
<td>N = 158</td>
<td>N = 155</td>
</tr>
<tr>
<td>Grade ≥3 Infection</td>
<td>33%</td>
<td>11%</td>
</tr>
<tr>
<td>Grade ≥3 Neutropenia*</td>
<td>48%</td>
<td>35%</td>
</tr>
<tr>
<td>Grade ≥3 Diarrhea-Colitis</td>
<td>26%</td>
<td>2%</td>
</tr>
<tr>
<td>Grade ≥3 ALT/AST increase*</td>
<td>7%</td>
<td>1%</td>
</tr>
<tr>
<td>Grade ≥3 Rash</td>
<td>11%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Any Grade Pneumonitis</td>
<td>8%</td>
<td>0</td>
</tr>
</tbody>
</table>

*Based on laboratory data

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CLL, chronic lymphocytic leukemia; PI3K, phosphatidylinositol 3-kinase; SLL, small lymphocytic lymphoma
Duvelisib Approval Components

**Boxed Warning**
- Infection
- Diarrhea or Colitis
- Rash
- Pneumonitis

**Warnings & Precautions**
- Hepatotoxicity
- Neutropenia

**Communication REMS**
- Inform providers of serious risks

**Accelerated Approval Postmarketing Requirements**
- Randomized trial in relapsed or refractory FL that verifies the clinical benefit of duvelisib

**Safety Postmarketing Requirements**
- Long-term safety
- Final OS analysis of DUO trial

Abbreviations: FL, follicular lymphoma, OS, overall survival, REMS, risk evaluation and mitigation strategy
Final OS Analysis of DUO Trial

<table>
<thead>
<tr>
<th></th>
<th>Duvelisib (N = 160)</th>
<th>Ofatumumab (N = 159)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths</td>
<td>80 (50%)</td>
<td>70 (44%)</td>
</tr>
<tr>
<td>Median OS</td>
<td>52.3 months</td>
<td>63.3 months</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.09 (0.69, 1.51)</td>
<td></td>
</tr>
</tbody>
</table>
Withdrawal of Duvelisib FL Indication

**DUETTO**

<table>
<thead>
<tr>
<th>Design</th>
<th>Population</th>
<th>Treatment</th>
<th>Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized (1:1)</td>
<td>Relapsed or refractory FL</td>
<td>Duvelisib + Rituximab</td>
<td>Primary: Progression-free survival</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rituximab or R-CVP</td>
<td></td>
</tr>
</tbody>
</table>

- **DUETTO: Never initiated**

- **Inability to conduct a clinical trial to verify benefit**
  - December 2021 – FL indication voluntarily withdrawn from U.S. market

Abbreviations: FL, follicular lymphoma, R-CVP, rituximab, cyclophosphamide, vincristine, prednisone
Duvelisib Dosing Considerations

Duvelisib – approved dose 25 mg BID

• Monotherapy
  – Limited dose finding
  – 75 mg BID identified as maximum tolerated dose (MTD)
  – No E-R relationship for efficacy observed at 25 mg BID
    • 25 mg BID and 75 mg BID had comparable efficacy; 15 mg BID also demonstrated activity
  – PD marker p-AKT showed near maximal suppression at 25 mg BID
  – E-R relationship for safety between 8 – 75 mg BID
  – High rates of treatment modifications due to toxicity at 25 mg BID

Abbreviations: E-R, exposure-response, PD, pharmacodynamic
Umbralisib (Ukoniq)

**PI3K Class IA**
- PI3Kα
- PI3Kβ

**PI3K Class IB**
- PI3Kδ
- PI3Kγ

**Copanlisib**
- Copanlisib
- Duvelisib

**Umbralisib**
- Umbralisib
- Duvelisib

*Also inhibits C1kε*

Abbreviations: PI3K, phosphatidylinositol 3-kinase
Umbralisib Approval

- Granted accelerated approval in relapsed or refractory FL and MZL in February 2021
  - Relapsed or refractory FL who have received at least three prior lines of systemic therapy
  - Relapsed or refractory MZL who have received at least one prior anti-CD20-based regimen

<table>
<thead>
<tr>
<th>Study UTX-TGR-205</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Design</strong></td>
</tr>
<tr>
<td>Single-arm trial</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: FL, follicular lymphoma, MZL, marginal zone lymphoma
Umbralisib FDA Safety Alert – UNITY-CLL Trial

UNITY-CLL

<table>
<thead>
<tr>
<th>Design</th>
<th>Population</th>
<th>Treatment</th>
<th>Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized (1:1)</td>
<td>Untreated and previously treated CLL</td>
<td>Umbralisib + Ublituximab (U2) Obinutuzumab + Chlorambucil</td>
<td>Primary: Progression-free survival</td>
</tr>
</tbody>
</table>

- FDA issued a safety alert on February 3, 2022
  - Possible increased risk of death
    - Overall survival hazard ratio 1.23

Abbreviation: CLL, chronic lymphocytic leukemia
Umbralisib Withdrawal Update – April 15, 2022

• Voluntary withdrawal of umbralisib and ublituximab applications for the U2 regimen based on the UNITY-CLL trial
  – Overall survival concerns

• Voluntary withdrawal of the FL and MZL indications for umbralisib under accelerated approval
PI3K Inhibitor Class Issues

- Potential detriment in overall survival
- Toxicity and tolerability
- Dosing
- Limitations of single-arm trials
Multiple Randomized Trials with Concerning Overall Survival

<table>
<thead>
<tr>
<th>Study</th>
<th>Population &amp; Treatment</th>
<th>Deaths PI3Ki arm</th>
<th>Deaths Control arm</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>312-0123</td>
<td>• Untreated CLL</td>
<td>8% (12/157)</td>
<td>3% (4/154)</td>
<td>3.34 (1.08, 10.39)</td>
</tr>
<tr>
<td></td>
<td>• Bendamustine and rituximab ± idelalisib</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>313-0124</td>
<td>• Previously treated indolent NHL</td>
<td>5% (10/191)</td>
<td>1% (1/95)</td>
<td>4.74 (0.6, 37.12)</td>
</tr>
<tr>
<td></td>
<td>• Rituximab ± idelalisib</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>313-0125</td>
<td>• Previously treated indolent NHL</td>
<td>8% (27/320)</td>
<td>6% (9/155)</td>
<td>1.51 (0.71, 3.23)</td>
</tr>
<tr>
<td></td>
<td>• Bendamustine and rituximab ± idelalisib</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DUO</td>
<td>• Previously treated CLL/SLL</td>
<td>50% (80/160)</td>
<td>44% (70/159)</td>
<td>1.09 (0.79, 1.51)</td>
</tr>
<tr>
<td></td>
<td>• Duvelisib vs ofatumumab</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHRONOS-3</td>
<td>• Previously treated indolent NHL</td>
<td>18% (56/307)</td>
<td>21% (32/151)</td>
<td>0.87 (0.57, 1.35)</td>
</tr>
<tr>
<td></td>
<td>• Rituximab ± copanlisib</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UNITY-CLL</td>
<td>• Untreated and previously treated CLL</td>
<td>-</td>
<td>-</td>
<td>1.23</td>
</tr>
<tr>
<td></td>
<td>• Umbralisib + ublituximab vs GC</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; CLL, chronic lymphocytic leukemia; GC, Obinutuzumab + Chlorambucil; NHL, non-Hodgkin lymphoma; PI3Ki, phosphatidylinositol 3-kinase inhibitor; SLL, small lymphocytic lymphoma
## PI3K Inhibitors Impart Substantial Risk

<table>
<thead>
<tr>
<th>Event</th>
<th>Idelalisib N = 146</th>
<th>Copanlisib N = 244</th>
<th>Duvelisib N = 442</th>
<th>Umbralisib N = 371</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade ≥3 adverse event</td>
<td>71%</td>
<td>85%</td>
<td>84%</td>
<td>51%</td>
</tr>
<tr>
<td>Serious adverse event</td>
<td>50%</td>
<td>51%</td>
<td>65%</td>
<td>26%</td>
</tr>
<tr>
<td>Grade ≥3 Infection</td>
<td>23%</td>
<td>23%</td>
<td>27%</td>
<td>20%</td>
</tr>
<tr>
<td>Grade ≥3 Neutropenia*</td>
<td>28%</td>
<td>29%</td>
<td>43%</td>
<td>17%</td>
</tr>
<tr>
<td>Grade ≥3 Diarrhea-Colitis</td>
<td>14%</td>
<td>5%</td>
<td>23%</td>
<td>7%</td>
</tr>
<tr>
<td>Grade ≥3 ALT/AST increase</td>
<td>18%</td>
<td>2%</td>
<td>8%</td>
<td>7%</td>
</tr>
<tr>
<td>Grade ≥3 Rash</td>
<td>4%</td>
<td>2%</td>
<td>9%</td>
<td>3%</td>
</tr>
<tr>
<td>Any Grade Pneumonitis</td>
<td>5%</td>
<td>7%</td>
<td>7%</td>
<td>1%</td>
</tr>
<tr>
<td>Grade ≥3 Hyperglycemia*</td>
<td>-</td>
<td>34%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Grade ≥3 Hypertension</td>
<td>-</td>
<td>29%</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*Based on laboratory data

**Abbreviations:** ALT, alanine aminotransferase; AST, aspartate aminotransferase; PI3K, phosphatidylinositol-3 kinase
In randomized trials, PI3K inhibitors have demonstrated:

- Higher fatal adverse events
- Higher Grade ≥3 adverse events
- Higher serious adverse events
- Higher rates of treatment modifications due to adverse events
PI3K Inhibitor Dosing

- Limited dose exploration
- Exposure-response relationships for safety
- Lack of an exposure-response relationship for efficacy
- Identifying an optimal dose remains uncertain

Abbreviations: PI3K, Phosphatidylinositol-3 kinase
PI3K Inhibitors Have Exposure-Response for Safety

- PI3K Inhibitors have exposure-response relationships for safety
- PI3K inhibitors have not necessarily demonstrated exposure relationship for efficacy

- **Duvelisib, Grade ≥3 Infection**
- **Umbralisib, Grade ≥3 ALT/AST**
- **Idelalisib, Grade ≥3 Diarrhea**
- **Umbralisib, Any Grade Diarrhea**
- **Duvelisib, Grade ≥3 Pneumonia**
- **Umbralisib, Grade ≥3 ALT/AST**
PI3K Inhibitor Tolerability

- PI3K inhibitor dosing impacts tolerability

<table>
<thead>
<tr>
<th>Treatment Modification</th>
<th>Idelalisib N = 146</th>
<th>Copanlisib N = 244</th>
<th>Duvelisib N = 442</th>
<th>Umbralisib N = 371</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinuation due to AE</td>
<td>23%</td>
<td>24%</td>
<td>35%</td>
<td>15%</td>
</tr>
<tr>
<td>Dose reduction due to AE</td>
<td>41%</td>
<td>24%</td>
<td>23%</td>
<td>10%</td>
</tr>
<tr>
<td>Dose interruption due to AE</td>
<td>41%</td>
<td>64%</td>
<td>64%</td>
<td>45%</td>
</tr>
</tbody>
</table>

Abbreviations: AE, adverse event, PI3K, phosphatidylinositol-3 kinase
PI3K Inhibitor Tolerability

- PI3K inhibitor doses may be poorly tolerated
- Patient-reported side effects in early phase trials can inform tolerability

Abbreviations: BID, twice daily; QD, once daily
Single-Arm Data to Support Approvals with PI3K Inhibitors

• Limitations of single-arm trials
  o Challenging to interpret safety and efficacy
  o Cross-trial comparisons
  o Response rate may not predict clinical benefit
  o Time-to-event endpoints are not interpretable

• Requirement for confirmatory trials
  o Indication withdrawals for idelalisib and duvelisib
Randomized Trials

• Preferred approach to demonstrating causal effects of a treatment
• Comparable groups with respect to known and unknown factors
  – Unbiased estimators of difference across randomized groups
• Reduces or balances selection bias
• Able to assess time-to-event endpoints
Overall Survival

• FDA requires overall survival information in any trial that uses PFS as a primary endpoint

• Overall survival is an objective measure of clinical benefit

• Overall survival is an efficacy and safety endpoint
  o Encompasses toxicity
  o Does not require same statistical considerations when used as a primary safety endpoint

• Overall survival can only be assessed in a randomized trial

• Supports benefit-risk determination
Evidentiary Criteria for Approval

• Safety
  – Sufficient information to determine that the drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling.

• Effectiveness
  – Substantial evidence of effectiveness
    • Based on adequate and well-controlled investigations
    • The drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling
Conclusions

- PI3K inhibitors demonstrate substantial toxicity
- Toxicity translated to potential detriment in overall survival
- Limited tolerability
- Insufficient dose exploration and optimization
- Single-arm trials in indolent NHL have limitations

- Sponsors are required to provide evidence that the drug is safe and effective
Discussion Topic

• Please discuss the observed toxicity of the PI3K inhibitor class and whether randomized data are warranted with an assessment of overall survival to support the evaluation of benefit-risk in patients with hematologic malignancies.
Voting Question

• Given the observed toxicities with this class, previous randomized trials with a potential detriment in OS, and a narrow range between effective and toxic doses, should future approvals of PI3K inhibitors be supported by randomized data?
Backup Slides Shown
Patient-Generated Data in Oncology Drug Development

• “A complete understanding of tolerability should include direct measurement from the patient on how they are feeling and functioning while on treatment” ¹

• FDA encourages sponsors to collect patient-reported symptoms, overall side effect bother, and physical/role functioning in oncology trials.²

• It is practical and feasible to collect patient-reported symptoms and function, including early phase trials, using existing methods/tools.

• PROs can inform dose selection, tolerability, and complement clinician-reported safety information.

¹FOCR White Paper “Broadening the definition of tolerability in cancer clinical trials to better measure the patient experience” (2018)
²Draft Guidance “Core Patient-Reported Outcomes in Cancer Clinical Trials” (2021)
Overall Survival

- Overall survival (OS) is typically defined as the time from randomization to death from any cause
  - Randomization tends to balance all factors, known or unknown (e.g. survival interval initiation points)
- OS is a preferred efficacy and a safety endpoint in oncology clinical trials
  - An objective measure of clinical benefit
  - Incorporates impact of toxicity
- The non-parametric log rank test has typically been used as statistical test for significant differences in survival between treatments (when a hypothesis test is pre-specified)
- OS is typically summarized via the hazard ratio (HR) and comparisons of median survival time
  - According to convention, in oncology settings, HRs are calculated such that values exceeding one indicate higher risk of death for the investigative treatment group
  - Confidence intervals for the HR are evaluated in the absence of or in addition to a statistical test
  - Other descriptions, such as the probability of surviving to set timepoints can also be useful
  - A pre-specified ITT analysis is preferred; sensitivity analyses evaluate robustness of estimates
- OS supports the overall benefit-risk determination for regulatory decisions
Early OS Data

• Long natural history of certain diseases has motivated use of primary endpoints other than OS for efficacy claims

• Statistical analysis plans for trials using PFS or ORR as primary endpoints have not always included event-driven pre-specified OS analyses
  – HR interpretation may be challenging due to patients crossing-over treatments
  – Potential confounding due to subsequent therapies
  – Low ratio of events to sample size
  – OS usually considered exploratory in such settings

• **OS is a safety consideration, with particular class concerns:**
  – Pattern of observed OS HRs >1 (in more than one study)
  – Prior information on risk for products (AEs or risk of death - see label warnings)
  – The totality of evidence informs safety even in the absence of statistical testing
  – Observed OS results, prior information, and observed toxicity profiles should adequately rule out harm and help support a conclusion that the products are safe
Exploratory Analyses of OS for PI3K Class

• **Consider available survival information**
  – None of the studies for PI3K included prespecified number of OS events
  – Low number of observed events (as low as 3% of the planned sample size) leading to uncertainty in estimates

• **Estimated HR and confidence interval provide descriptive information**
  – Point estimates for HR >1 across multiple studies
  – Wide confidence intervals do not adequately rule out potential harm

• **Death rates by treatment arm provide important summaries**
  – Death rates were higher in investigative treatment arms
Summary of OS Evaluation

• The confidence intervals for the HR are wide, with large upper bounds. The large upper bounds indicate **death hazards may be up to multiple times that in the control arm.**

• There are **higher death rates in the investigative treatment groups** and OS HR estimates in several studies across the PI3K class.

• While there are a low number of events and uncertainty in the estimates, when potentially harmful OS HRs are observed in multiple studies in the PI3K class, **a chance finding is questionable.**
Summary of OS for PI3K Inhibitors

• Sponsors have an obligation to demonstrate their products are safe and effective.

• The observed OS estimates, especially considering prior information, observed toxicity profiles, and questionable dose selection do not adequately rule out harm or support a conclusion that these products are safe.
Looking Forward
(Early OS in Randomized Studies)

• While FDA has demonstrated its commitment to timely approval of safe and effective cancer treatments through use of earlier endpoints, survival is the paramount objective for interventions
  – **A plan for evaluating OS should be pre-specified** when designing studies even if not conducting hypothesis testing for efficacy
  – A pre-specified plan will be useful for a safety evaluation of OS, in which potential harm to patients may be adequately ruled out based on a pre-specified data cut

• **Sponsors have an obligation to demonstrate their products are safe and effective**
  – Approaches to early assessment and interpretation of OS may be useful, such as adapting trial monitoring approaches that may include:
    • Futility analyses
    • Bayesian prediction
Idelalisib Combination: E-R for Safety

Grade ≥ 3 Infection
(Study GS-US-312-0115)

Any grade ALT/AST elevation
(Study GS-US-312-0115)

References: NDA 205858 S-6 Clinical Pharmacology Review
Duvelisib: PK/PD

pAKT (S473) Percent Positive in CLL Cells

RR-CLL/SLL
(baseline to 1 hr and 24 hrs postdose C1D1)

TN-CLL
(baseline to 1 hr and 24 hrs postdose C1D1)

25 mg
75 mg

Dose Selection for Oncology
Dose Optimization Rather Than MTD

Cytotoxic Chemotherapy

- Effect/Response vs. Dose/Drug Exposure
- Toxicity vs. Efficacy

Targeted Therapies

- Effect/Response vs. Dose/Drug Exposure
- Toxicity vs. Efficacy
What are the Dosing Implications for a Positive E-R for Safety, but Flat E-R Efficacy?

“More” is not always better

**Efficacy** may be on the plateau—increasing dose is unlikely to improve efficacy

E-R for **safety** indicates AEs are related to drug exposure

It may be possible to reduce dose without impacting efficacy while reducing AEs
Oncology Center of Excellence
Project Optimus

Mission: To ensure that doses of cancer drugs are optimized to maximize efficacy as well as safety and tolerability

Specific Goals
• Communicate expectations for dose-finding and dose optimization, through Guidance, workshops, other public meetings

• Provide opportunities for and encourage drug developers to meet with FDA Oncology Review Divisions early in their development programs, well before conducting trials intended for registration, to discuss dose-finding and dose optimization.

• Develop strategies for dose finding and dose optimization that leverages nonclinical and clinical data in dose selection, including randomized evaluations of a range of doses in trials. An emphasis of such strategies will be placed on performing these studies as early as possible in the development program and as efficiently as possible to bring promising new therapies to patients.
Traditional Dose Selection Strategy

**Dose Escalation**

- Dose Levels: 1, 2, 3, 4
- MTD*: Maximum tolerated dose
- Patients: Patient with No DLT*, Patient with DLT*

**Hallmarks:**
- Few patients at each dose
- Short observation period for DLTs
- Emphasis on DLTs, but not other safety

**Registration**

- MTD
- Patients with Cancer
- Control

*DLT= Dose-limiting toxicity, *MTD= Maximum tolerated dose

www.fda.gov
Updated: Optimized Dose Selection Strategy

Dose Escalation

Select Dose Range

Dose Optimization

Randomized Evaluation of Several Dosages

Comparison to Standard-of-Care

Randomized Comparison to Standard-of-Care

Dose Level 2

Dose Level 4

Optimized Dose

Control

Patients with Cancer

Patients with Cancer

Select Dose Range

Dose Level

Time

Dose Level

Dose Level
Dose Optimization Strategies

• Give consideration to nonclinical data including in vitro/in vivo receptor occupancy/target engagement data

• Enroll sufficient patients to characterize the PK (e.g., linearity, absorption, elimination) of the drug after multiple doses

• Consider PK/PD relationships with biomarkers and study outcomes

• Utilize modeling and simulation to predict outcomes by dose level

• At the dose levels being considered, expansion of several dose cohorts may be necessary to assess activity and tolerability at other dose levels

• Randomized, parallel dose response trials may be an appropriate strategy to assess doses when feasible

• Multiple doses may be compared prior to or as a part of registration trial(s) by adding an additional dosage arm
Dose Optimization Strategies for Combinations

• Don’t simply use the approved monotherapy dose in the combination.

• Evaluate safety, efficacy, PK and E-R for efficacy/safety for each product alone first.

• For two new drugs, study multiple doses of both drugs, especially the more active drug/toxic drug
  – For add-on therapy, exploration of the approved drug may be warranted as well

• Utilize small dose escalation increments in the combination setting.

• Evaluate E-R for efficacy and safety for the combination regimen.

• Assess potential DDI which may increase systemic exposures higher than the monotherapy, especially at steady-state.