AZD5153: Sierra’s Newest Development Asset
SAFE HARBOR STATEMENT

Except for statements of historical fact, any information contained in this presentation may be a forward-looking statement that reflects the Company’s current views about future events and are subject to risks, uncertainties, assumptions and changes in circumstances that may cause events or the Company’s actual activities or results to differ significantly from those expressed in any forward-looking statement. In some cases, you can identify forward-looking statements by terminology such as “may”, “will”, “should”, “plan”, “predict”, “expect,” “estimate,” “anticipate,” “intend,” “goal,” “strategy,” “believe,” and similar expressions and variations thereof. Forward-looking statements may include statements regarding the Company’s business strategy, cash flows and funding status, potential growth opportunities, preclinical and clinical development activities, the timing and results of preclinical research, clinical trials and potential regulatory approval and commercialization of product candidates. Although the Company believes that the expectations reflected in such forward-looking statements are reasonable, the Company cannot guarantee future events, results, actions, levels of activity, performance or achievements. These forward-looking statements are subject to a number of risks, uncertainties and assumptions, including those described under the heading “Risk Factors” in documents the Company has filed with the SEC. These forward-looking statements speak only as of the date of this presentation and the Company undertakes no obligation to revise or update any forward-looking statements to reflect events or circumstances after the date hereof.

Certain information contained in this presentation may be derived from information provided by industry sources. The Company believes such information is accurate and that the sources from which it has been obtained are reliable. However, the Company cannot guarantee the accuracy of, and has not independently verified, such information.

TRADEMARKS:

The trademarks included herein are the property of the owners thereof and are used for reference purposes only. Such use should not be construed as an endorsement of such products.
Delivering on our Mission to Develop Targeted Therapies for Rare Cancers

Successfully executing on MOMENTUM pivotal clinical trial
- Over-enrolled (ahead of anticipated timing)
- Data expected 1Q 2022
- NDA filing expected mid-2022

Data analyses from SIMPLIFY-1 and -2 have reinforced our conviction that MMB could become the cornerstone therapy for patients with myelofibrosis

In-licensing AZD5153 supports our mission
- Potential to improve outcomes in MF patients with MMB / 5153 combo
- Potential to expand development into other cancer types
- Low capital investment until post MMB pivotal data
- Solid IP runway
Strategic Rationale for Adding a BET Inhibitor to Sierra’s Portfolio

MF landscape is evolving with multiple combination studies ongoing

BET inhibition has shown initial proof-of-concept with disease-modifying potential

MMB could be the JAKi backbone of choice for BETi and other emerging MOAs with its favorable hematologic profile and potential benefits for myelosuppressed patients

Clinical validation of a MMB + BETi combination expands Sierra’s opportunity

1. Potential for deeper and more durable responses and disease modification in MF
2. Protects and lengthens MMB’s peak adoption if combination therapies become the mainstay of MF treatment; and
3. Pipeline expansion opportunities in other hematologic or solid tumor indications, through potential combos with SRA737, I/O, PARP and other MOAs
AZD5153: a Potent, Highly Selective & Differentiated BET Inhibitor

Selective inhibitor of the two BRD4 BET protein bromodomains (BD1, BD2)
- Differentiated bivalent inhibitory activity results in more potent and complete target inhibition relative to monovalent binders

Potent antiproliferative activity in heme cell-lines, typically with GI$_{50}$ values of $\leq$100nM

Significant single agent anti-tumor activity in hematological xenograft models and in primary PDX models harboring BRD4 amplification

Potent modulation of clinically-relevant on-target biomarkers (e.g., MYC, HEXIM) corresponding to substantive TGI

Synergistic preclinical efficacy in combination with diverse agents
- Interestingly, profound synergy was observed between AZD5153 and the AZ ATRi, suggesting potential utility in combination with SRA737

Sources: Rhyasen et al, Molecular Cancer Ther; 15 (11); 2563-74 and Rhyasen et al; Plos ONE; July 2018.
AZD5153 Clinical Observations

Active, well-tolerated, manageable safety as monotherapy and in combination with olaparib

- Has been dosed as monotherapy for >80 weeks and in combo with olaparib for >39 weeks
- Dose dependent exposure observed in the clinic
- Exposure-dependent modulation of PD biomarkers observed in peripheral blood samples from patients treated with AZD5153
- Expected correlation between exposure and platelet count decrease was observed
- Thrombocytopenia was manageable and reversible at doses above MEC
- Monotherapy overall appeared safe and tolerable with most common AEs being GI events, fatigue, thrombocytopenia, dysgeusia, dyspnea and anemia
  - Far majority were Grade 1-2

Momelotinib + AZD5153 May Be a Powerful JAKi + BETi Combo

Potential Benefits Include:

- Improvements in splenomegaly, symptoms and anemia
- Lack of dose-limiting myelosuppression
- Durable dose intensity

- Disease modifying anti-fibrotic, anti-inflammatory & anti-clonal activity
- Synergistic NF-kB inhibition

- Bivalent binding mode leads to modification of pathological cellular processes
- Improved potency and more complete target inhibition
Phase 2 MMB / AZD5153 Combo Study in MF – Initiation Planned for 1H 2022

Planned Phase 2 study will be designed to optimize dosing and provide proof-of-concept for Phase 3 trial design.

Pharmacodynamic biomarker assessments will confirm target engagement and combination activity.

Data from this trial will inform future development plans, including a potential registration-enabling Phase 3 study.

This study will also support our hypothesis that momelotinib is an optimal combination agent in myelofibrosis.