# CORPORATE PRESENTATION

JULY 2020 | NASDAQ: BYSI




BeyondSpring

NASDAQ BYSI

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By attending this presentation, you acknowledge that you will be solely responsible for your own assessment of the market and our market position and that you will conduct your own analysis and be solely responsible for forming your own view of the potential future performance of our business

# Agenda

**Company Overview**

Plinabulin Profile

CIN (Phase 3)

Commercial Opportunities

NSCLC (Phase 3)

I/O Combos

Summary

# Experienced leadership team with 50+ product launches

**LAN** Huang, Ph.D.
CEO and Founder

万春生物科技 WANCHUN BIOTECHNOLOGY · 无锡麦涛岚华 · Memorial Sloan Kettering Cancer Center

**RICHARD** Daly
Chief Operating Officer

Takeda · Abbott

**EDWARD** Liu
Chief Financial Officer

J.P.Morgan · Jefferies · EPIPHRON

**PAUL** Friel
Vice President, Business Development

Takeda · kastle therapeutics · vyaire MEDICAL

**RAMON** Mohanlal M.D., Ph.D.
EVP R&D and CMO

gsk · VERTEX

**GORDON** Schooley, Ph.D.
EVP Of Regulatory Affairs

PACIRA · Allergan · Newport

**JAMES** Tonra, Ph.D.
Chief Scientific Officer

Lilly · REGENERON · AVA

**KENNETH** Lloyd, Ph.D.
Chief Scientific Officer, Emeritus

Wyeth · nereus · Roche

**50+** approvals and launches

**30+** initial public offerings (IPOs)

**50+** global pharma experiences

**40+** partnerships/alliances

**20+** startups

**$30+** billion financing experience

# Key takeaways

1. PROTECTIVE-2 P3 pre-specified interim: **primary endpt** (rate of prevention of Gr 4 neutropenia in Cycle 1) met at **p<0.01**
2. PROTECTIVE-2 P3: key **secondary endpt** (duration of severe neutropenia (DSN) in Cycle 1) met at **p<0.05**
3. PROTECTIVE-2 P3: key **secondary endpt** (DSN in Cycle 1, Day 1-8) met at **p<0.05** supporting Plinabulin early onset action
4. Superior efficacy of Plinabulin + Neulasta in CIN against SoC with strong clinical significance
5. Potential to disrupt the $9 billion CIN global market with first superior profile to improve G-CSF in 30 years
6. Potential to prevent infection and hospitalization, urgently needed in current COVID-19 pandemic
7. Market research shows 65%+ oncologists will use Plinabulin + G-CSF for CIN treatment if approved
8. Rolling submitted NDA for CIN in China in 1Q 2020, expected to submit in the U.S. in 2H 2020

# Near-term NDAs & robust drug development pipeline

| | Program | Indication | Trial name / collaborator | Preclinical | Phase 1 | Phase 2 | Phase 3 | Commercial rights | China NDA submission | U.S. NDA submission |
|---|---|---|---|---|---|---|---|---|---|---|
| Late stage | Plinabulin | CIN (All cancer, all chemo) | PROTECTIVE-1 (Study 105) | Phase 3 primary endpoint met at interim analysis | | | | Global[1] | Q1 2020 | H2 2020 |
| | Plinabulin + pegfilgrastim | | PROTECTIVE-2 (Study 106) | Phase 3 primary endpoint met at interim analysis | | | | | | |
| | Plinabulin + docetaxel | NSCLC ($2^{nd}$/$3^{rd}$ line) | DUBLIN-3 (Study 103) | Phase 3 second interim analysis completed | | | | Global[1] | H2 2020 | H1 2021 |
| Investigator-initiated IO | Plinabulin + nivolumab | NSCLC ($2^{nd}$/$3^{rd}$ line) | Fred Hutch/Univ. Washington/UCSD | | | | | Global[1] | | |
| | Plinabulin + nivolumab + ipilimumab | SCLC | Rutgers University | | | | | Global[1] | | |
| | Plinabulin + PD-1/PD-L1 + radiation/chemo | Multi-cancer ($2^{nd}$/$3^{rd}$ line) | MD Anderson | | | | | Global[1] | | |
| Other oncology pipeline | Protein degradation (molecular glue) | 1st target KRAS | | | | | | Global | | |
| | BPI-002 | Oral T cell co-stimulator | | | | | | Global | | |
| | BPI-003 | IKK inhibitor | | | | | | Global | | |
| | BPI-004 | Oral neo-antigen generator | | | | | | Global | | |

Note: [1] We own global rights to Plinabulin in all countries except China. In China, we own a 57.97% interest in our Chinese subsidiary, Dalian Wanchunbulin Pharmaceuticals Ltd. ("Wanchunbulin"), which owns a 100% interest in Plinabulin.

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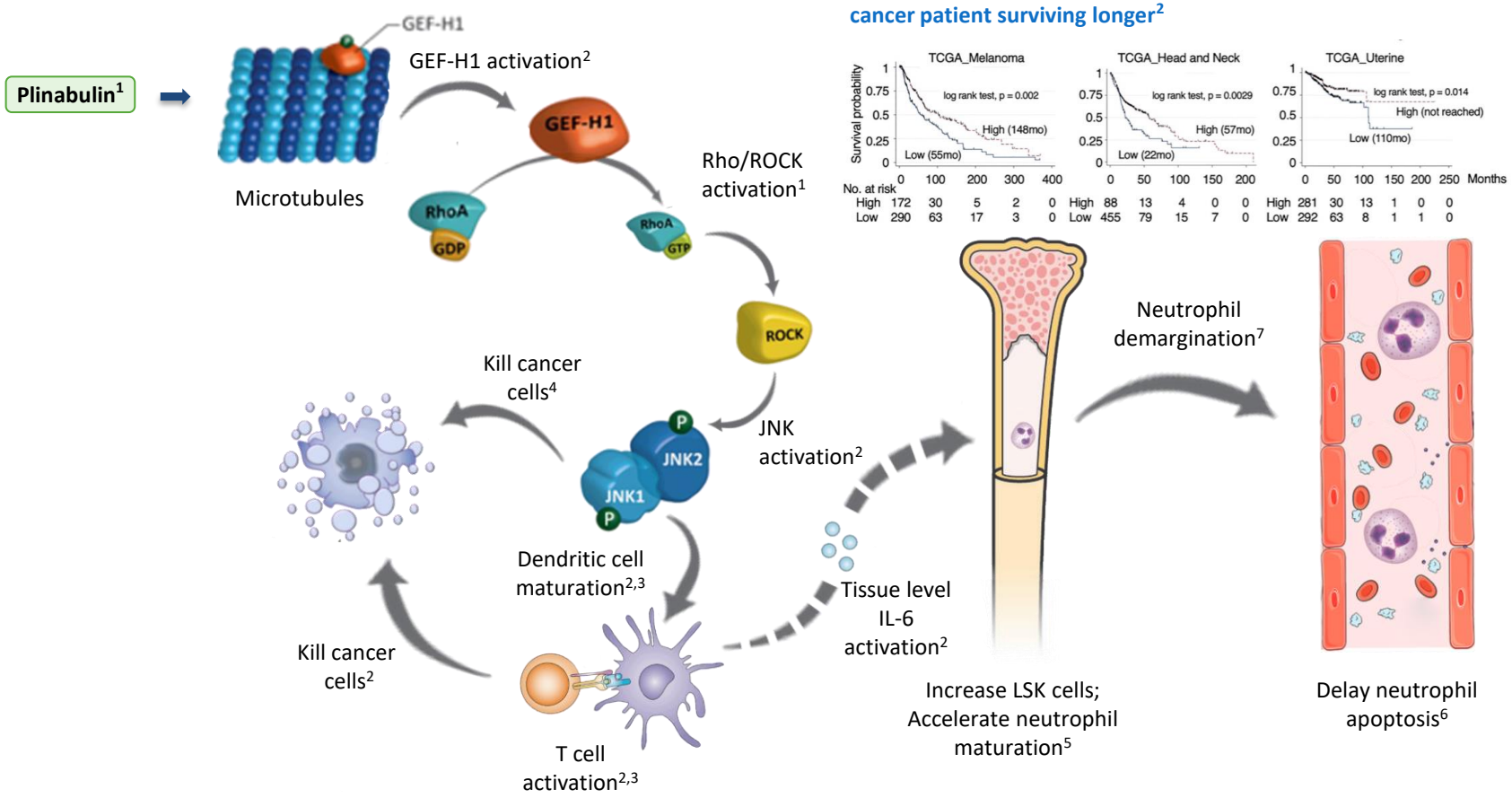
# Plinabulin: first-in-class agent, stimulating innate and adaptive immune system




## Multi-year collaboration with Mass General Hospital and University of Basel

Note: [1] La Sala et al., 2019 Chem. [2] Kashyap et al., 2019 Cell Reports. [3] Zhang et al., 2005 Mol Cell Biol. [4] Singh et al., 2011 Blood. [5] Suwa et al., 2000 Am J Physiol Heart Circ Physiol; Ghosh et al., 2018 ACR Annual Conference; Blayney et al., Society of Leukocyte Biology. [6] Asensi et al., 2004 Infection and Immunity.

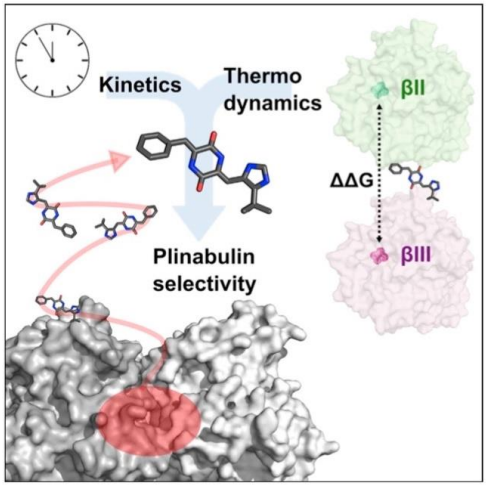
# Plinabulin differentiated tubulin binding and its effect in DC maturation and GEF-H1 release published in *Chem & Cell Reports*

Chem

CellPress

Article

## Structure, Thermodynamics, and Kinetics of Plinabulin Binding to Two Tubulin Isotypes




Plinabulin is a novel tubulin-binding agent that is currently in phase 3 clinical trials for cancer treatment and prevention of chemotherapy-induced neutropenia. Plinabulin binds within a distinct tubulin pocket, which differentiates it from other tubulin binders. Aimed at disclosing structural and energetic details of plinabulin binding to tubulin, we combine X-ray crystallography and computational modeling. We compare the plinabulin residence time with that of colchicine and combretastatin-A4. Our study helps understand potential mechanisms underlying differential effects of this family of anti-tubulin drugs.

Giuseppina La Sala, Natacha Olieric, Ashwani Sharma, ..., José Fernando Díaz, Michel O. Steinmetz, Andrea Cavalli

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HIGHLIGHTS

Plinabulin is a phase 3 anticancer and antineutropenia drug candidate

Plinabulin binding to tubulin differentiates it from other compounds

We report crystal structures of plinabulin in complex with βII- and βIII-tubulin isotypes

We performed thermodynamic and kinetic studies on plinabulin selectivity and mechanism of action

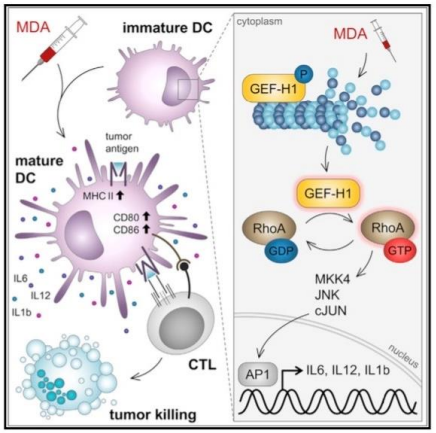
La Sala et al., Chem 5, 1–18
November 14, 2019 © 2019 Elsevier Inc.
https://doi.org/10.1016/j.chempr.2019.08.022

Cell Reports

Article

## GEF-H1 Signaling upon Microtubule Destabilization Is Required for Dendritic Cell Activation and Specific Anti-tumor Responses

Graphical Abstract

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In Brief

Certain chemotherapeutics elicit potent anti-tumor immunity. Kashyap et al. demonstrate that microtubule-destabilizing chemotherapeutics induce maturation of dendritic cells through activation of microtubule-associated protein GEF-H1. This leads to effective priming of CD8 T cells against tumor antigens. GEF-H1 is critical for anti-tumor immunity of microtubule-targeting chemotherapy.

Highlights

- Microtubule destabilization in dendritic cells drives DC maturation and T cell activation
- GEF-H1 is released from microtubules, leading to its activation
- GEF-H1 release triggers the RhoA-JNK-c-Jun signaling axis and AP-1 transcriptional response
- GEF-H1 is critical for DC maturation, antigen cross-presentation, and anti-tumor immunity

Kashyap et al., 2019, Cell Reports 28, 3367–3380
September 24, 2019 © 2019 The Author(s).
https://doi.org/10.1016/j.celrep.2019.08.057

CellPress

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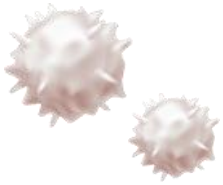
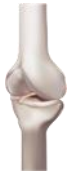
# The chemotherapy market gap

Healthcare professionals (HCPs) consider preventing CIN very important to ensure patients receive the maximum benefit of chemotherapy[1]

**MONOTHERAPY GRANULOCYTE-COLONY STIMULATING FACTOR (G-CSF) DOESN'T ALLOW FOR CHEMOTHERAPY OPTIMIZATION[3]**

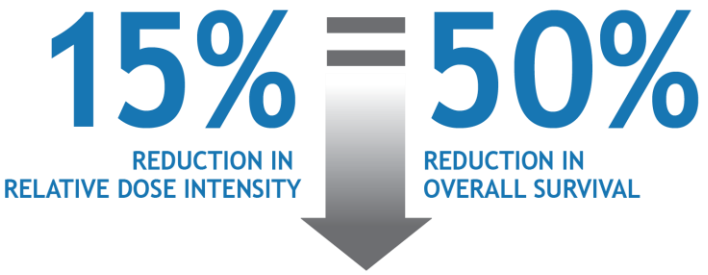


**CIN**
remains the #1 reason for chemotherapy disruption[2]



**BONE PAIN**
remains significant clinical issue[3]

**SLIGHT CHANGES IN DOSING OR DELIVERY CAN HAVE A DEVASTATING IMPACT ON SURVIVAL[4]**




**MONOTHERAPY G-CSF IS SUBOPTIOMAL AND LEAVES A SIGNIFICANT CLINICAL GAP**

**PLINABULIN + G-CSF HAS POTENTIAL TO ADDRESS THIS IMPORTANT UNMET CLINICAL NEED**

Source: [1] Proprietary market research, BYSI Summer/Fall 2019. [2] LaLami. [3] Moore. [4] Bonadonna G, Valagussa P, Moliterni A et al. Adjuvant cyclophosphamide, methotrexate, and fluorouracil in node-positive breast cancer. N Engl J Med 1995;332:901-906

# Current standard of care for CIN still presents severe unmet medical needs

**Efficacy issue**

| Neulasta after TAC for breast cancer | | |
|---|---|---|
| **Efficacy** | **Neulasta 6 mg[1] n=29** | **Neulasta 6 mg[2] n=61** |
| Neutropenia (grade 3/4) | 96.6% | 100% |
| **Neutropenia (grade 4)** | **93.1%** | **83.3%** |
| DSN | 1.4 ± 0.7 | 1.8 ± 1.2 |
| Mean ANC nadir ($10^9$/L) | 0.255 ± 0.287 | 0.266 |

- Guidelines for grade 3/4 neutropenia are to reduce or delay chemotherapy dosing by 5-7 days[5]
- In cancer patients with <85% relative dose intensity (RDI), patient survival is 50% of those with >=85% RDI[5]
- TAC is a very effective chemo treatment with ORR at 83%[6], but because of its high severe neutropenia rate, TAC needs to be changed to less effective TC (with ORR at 42%)[7] and TA (with ORR at 51%)[8]

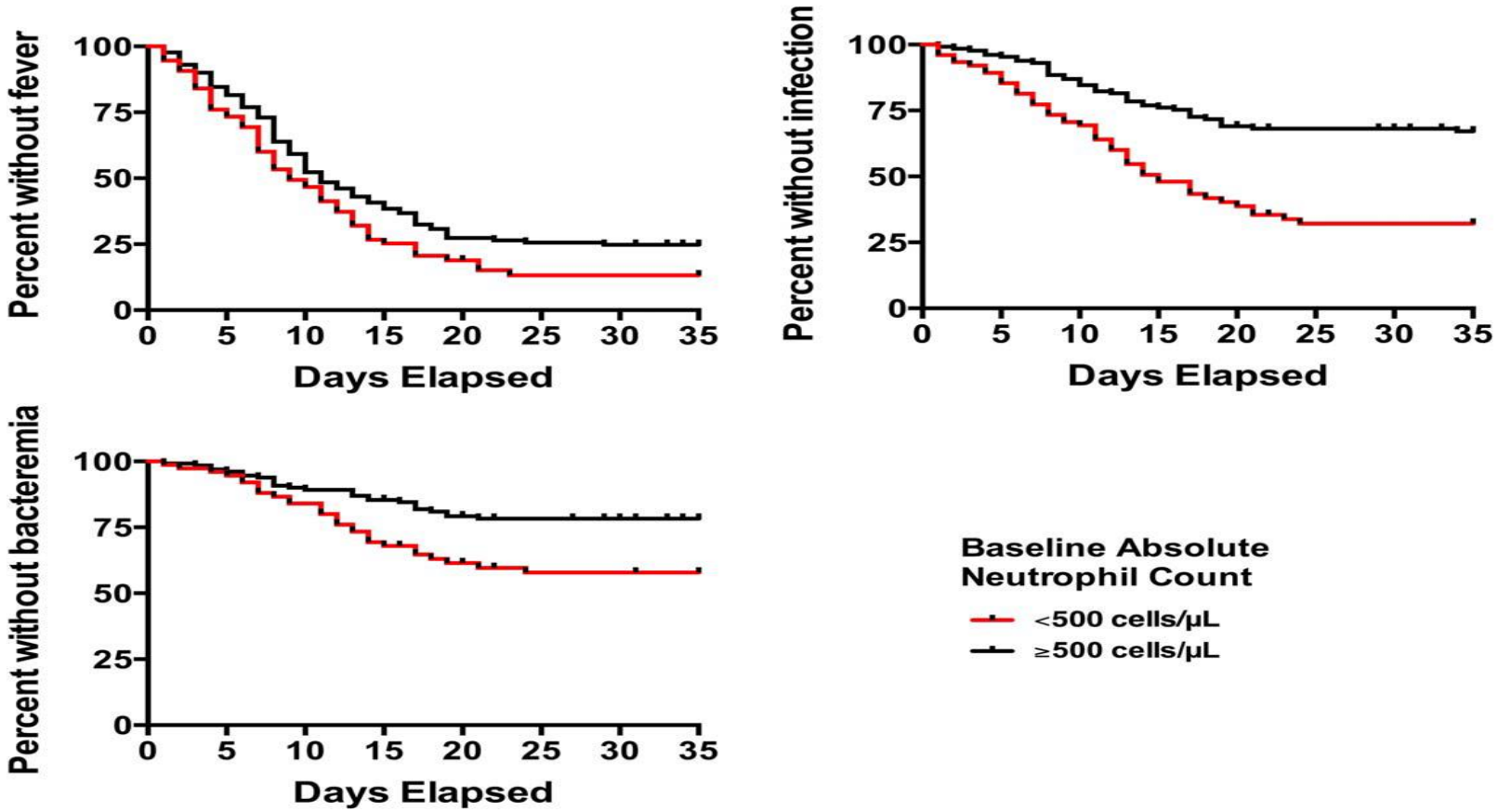
**Safety issue**

| Neulasta after chemotherapy | | |
|---|---|---|
| **Safety** | **Neulasta 6 mg[3] n=100** | **Neulasta 6 mg[4]** |
| Bone pain (score of 1-10) | 59% | 71% |
| **Severe bone pain (score of 6-10)** | **24%** | **27%** |

Note: [1] Masuda N et al., Support Care Cancer 23: 2891-2898 (2015). [2] Lee J et al., Annals of Surgical Treatment and Research 94(5): 223-238 (2018). [3] Kirshner et al., Comm Onc 4:455-459 (2007). [4] Xu et al., Support Care Cancer 24:723-730 (2016). [5] Lalami et al., Critical Reviews in Oncology / Hematology 120 163-179 (2017). ). [6] O'Regan et al., Clinical Breast Cancer 6(2): 163-168 (2005). [7] Vasey et al., British J Cancer 87: 1072-78 (2002). [8] Alba et al. JCO 22(13): 2587-93 (2002).

# Grade 4 neutropenia leads to development of fever, infection or bacteremia

Grade 4 neutropenia was associated with fever (p = 0.04), documented infection (p < 0.0001), and bacteremia (p = 0.002)[1]

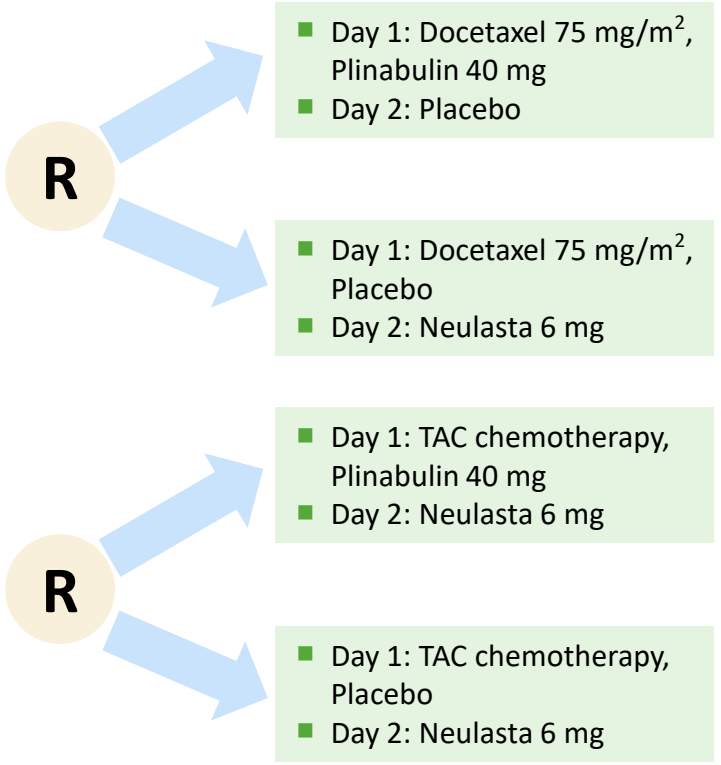



Note: [1]Buckley SA et al., "Prediction of adverse events during intensive induction chemotherapy for acute myeloid leukemia or high-grade myelodysplastic syndromes." American J. Hematology 2014; 89(4): 423-28.

# Potential for broad CIN label: for “all cancer”, with “all chemo”, can be combined with all “G-CSF”

- **PROTECTIVE-1 (Study 105, intermediate risk chemotherapy with high risk factors)**
  - Phase 3 interim analysis: primary endpoint met statistical significance

- **PROTECTIVE-2 (Study 106, high risk chemotherapy, G-CSF’s main market)**
  - Phase 2 top line analysis: efficacy and safety endpoints met statistical significance; recommended Phase 3 dose established
  - Phase 3 interim analysis: primary endpoint met p<0.01, secondary endpoints met p<0.05




**CIN is a problem of bone marrow suppression from chemotherapy**

# PROTECTIVE-2 (Phase 2): high risk chemo
# Efficacy and safety endpoints met at top line analysis

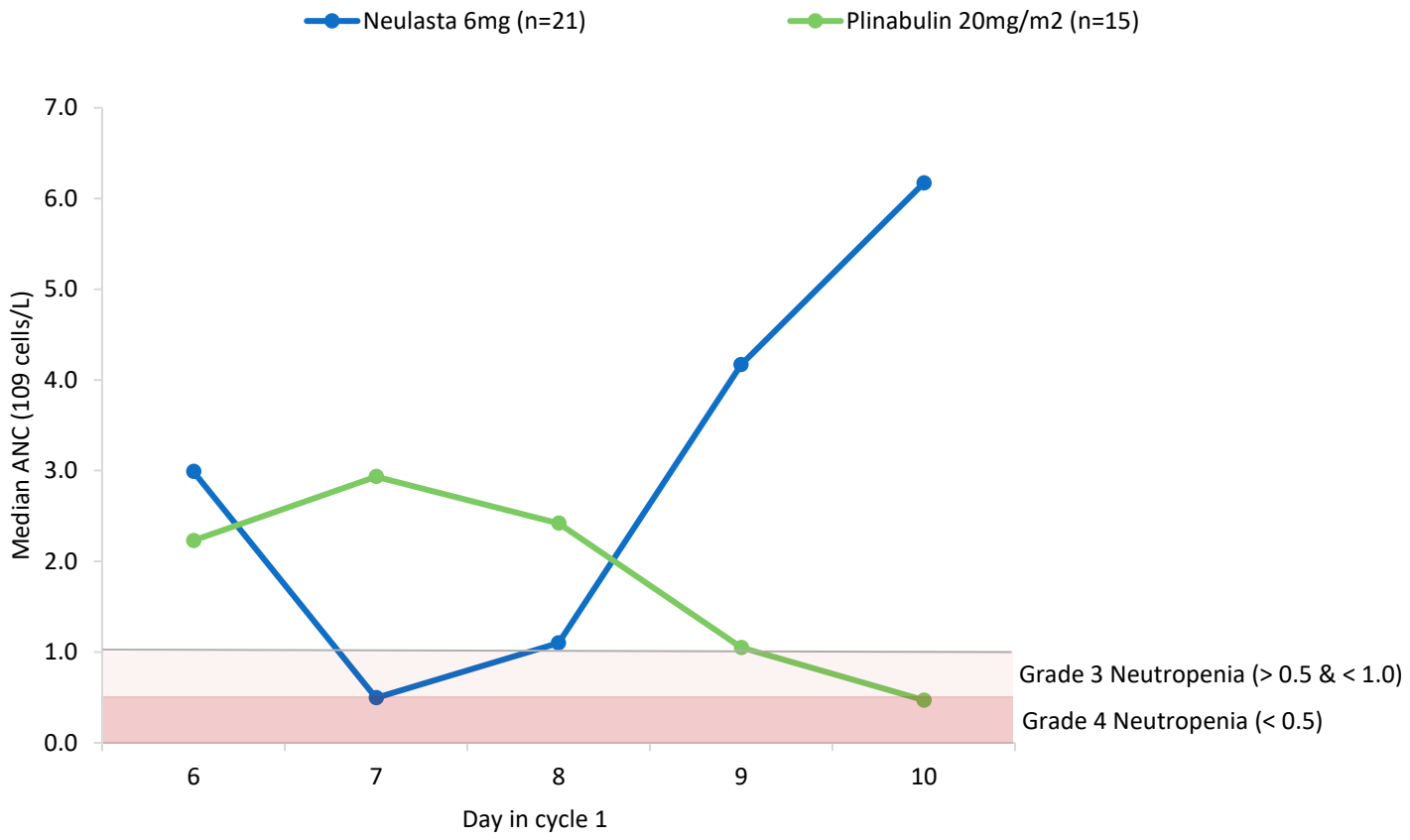
| Randomized, open label | |
|---|---|
| Patients & sites | 115 patients in 40+ sites |
| Patient eligibility | Patients with 1st line breast cancer |
| Primary endpoint | To establish the Recommended Phase 3 Dose (RP3D) based on PK/PD analysis |
| Dosing cohorts | ■ Arm 1 – TAC + Neulasta (pegfilgrastim) (6 mg), n=22<br>■ Arm 2 – TAC + Plinabulin (10 mg/m$^2$), n=15<br>■ Arm 3 – TAC + Plinabulin (20 mg/m$^2$), n=15<br>■ Arm 4 – TAC + Plinabulin (30 mg/m$^2$), n=12<br>■ Arm 5 – TAC + Plinabulin (20 mg/m$^2$) + Neulasta (pegfilgrastim) (1.5 mg), n=14<br>■ Arm 6 – TAC + Plinabulin (20 mg/m$^2$) + Neulasta (pegfilgrastim) (3 mg), n=21<br>■ Arm 7 – TAC + Plinabulin (20 mg/m$^2$) + Neulasta (pegfilgrastim) (6 mg), n=16 |
| Status | Efficacy and safety objectives met at interim analysis |

**One dose Plinabulin per cycle, 30 minutes after chemotherapy on day 1, 30 minute IV infusion**

Note: [1] Fixed dose, equivalent to 20 mg/m$^2$.

# PROTECTIVE-2 (phase 2): Plinabulin and Neulasta have complimentary absolute neutrophil count (ANC) profiles

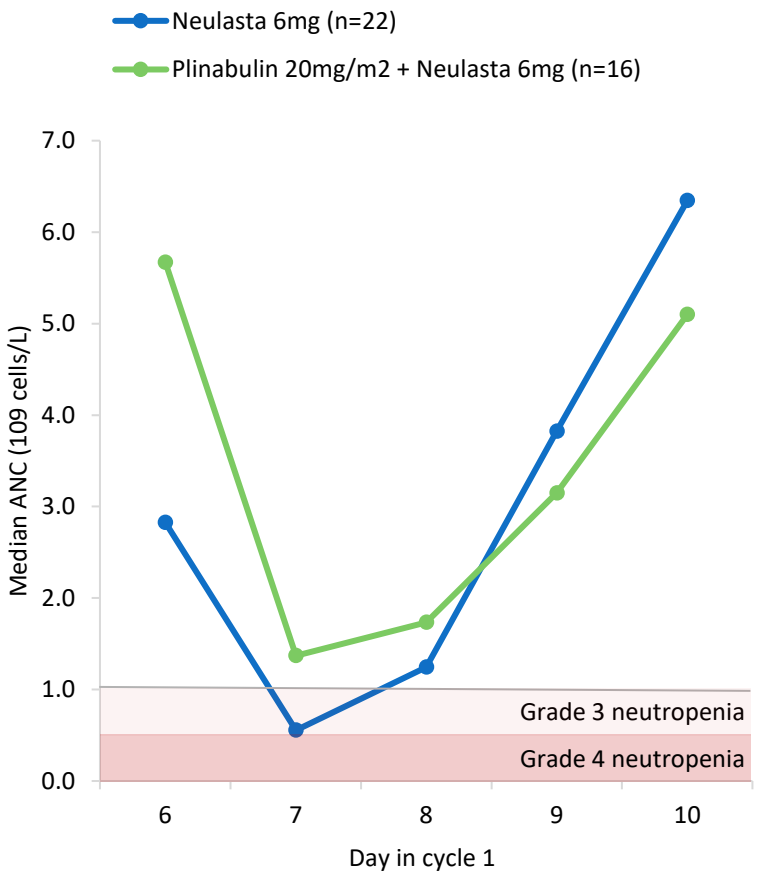
Median ANC in cycle 1 after TAC for breast cancer



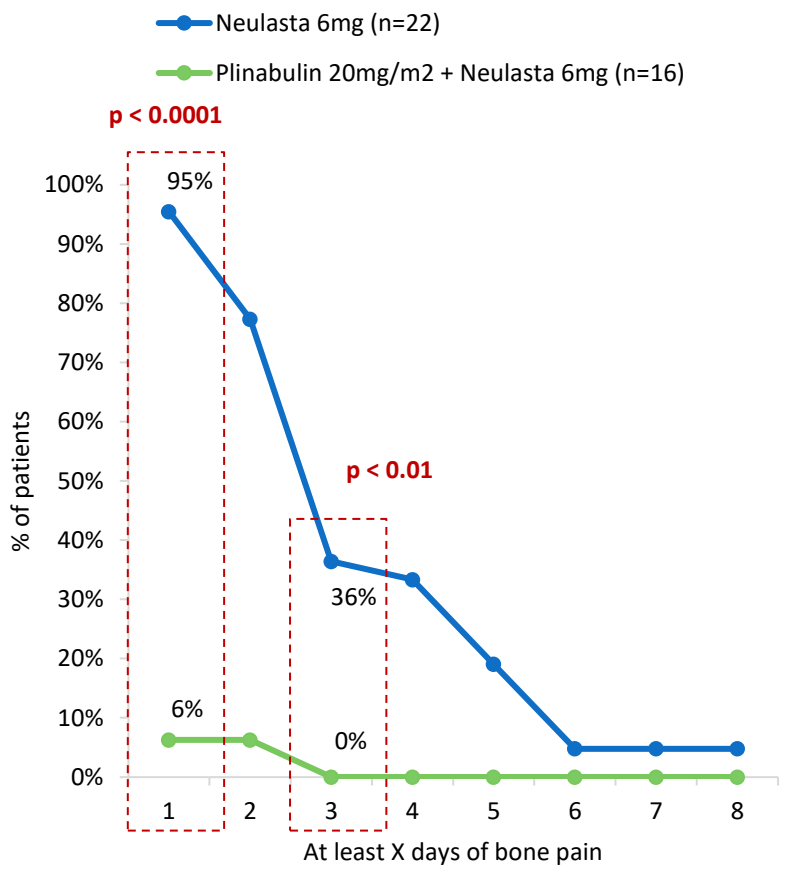

**Plinabulin CIN MOA: rapid onset of action in week 1, complimentary to G-CSF**

# PROTECTIVE-2 (Phase 2): Plinabulin / Neulasta Combo shows superior data in efficacy and safety analyses

Median ANC in cycle 1 after TAC for breast cancer

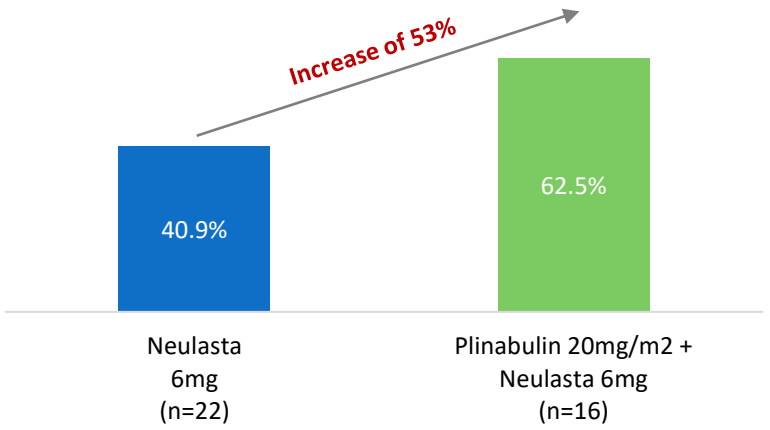



At lease X days of bone pain in cycle 1 after TAC for breast cancer

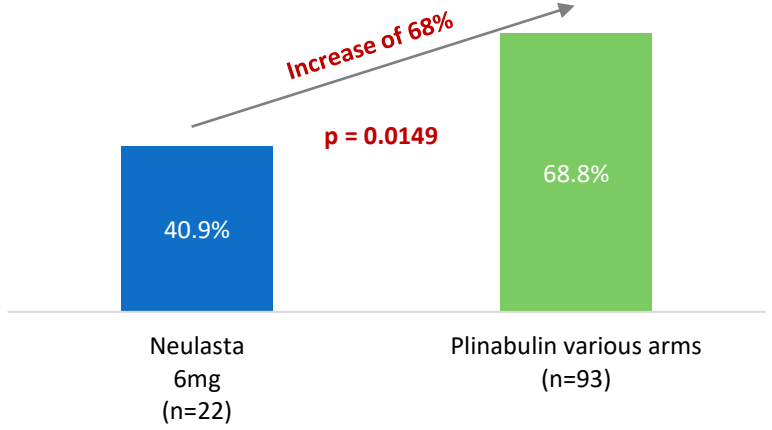


# PROTECTIVE-2 (Phase 2): Plinabulin / Neulasta Combo demonstrated positive efficacy and better chemo compliance

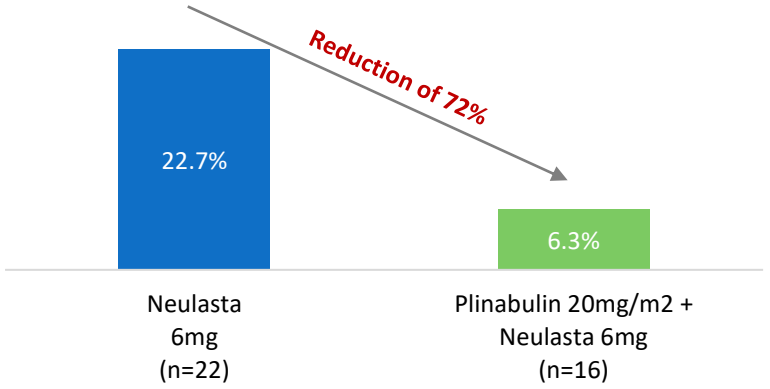
% of patients prevented grade 4 neutropenia in Cycle 1 after TAC



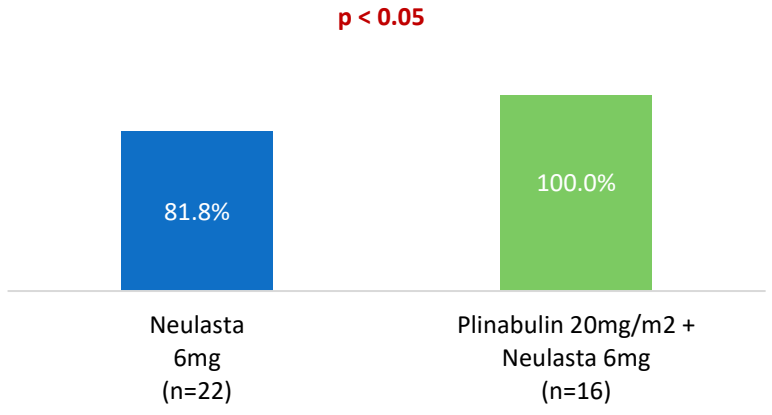

% patients prevented grade 4 neutropenia in Day 1-8 of Cycle 1 after TAC




% of patients with >15% decrease in chemotherapy dose after TAC




% of patients on TAC chemotherapy regimen[1] in breast cancer




Note: [1] Downgrade chemotherapy regimen from TAC (ORR = 83%) to TC (ORR = 42%).

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# PROTECTIVE-2 (Phase 3): high risk chemo
# Primary and key secondary endpoints met at interim analysis

| Randomized, double blind | |
|---|---|
| Patients & sites | 222 patients in 17 sites globally |
| Patient eligibility | 1st line breast cancer |
| Primary endpoint | % of prevention of grade 4 neutropenia (Cycle 1) |
| Secondary endpoints | ■ Mean DSN[1] (Cycle 1, Day 1-8)<br>■ Mean ANC[2] nadir (Cycle 1)<br>■ % of prevention of grade 3 and 4 neutropenia (Cycle 1)<br>■ DSN (Cycle 1)<br>■ % of bone pain (Cycle 1)<br>■ Composite risk<br>■ % of RDI[3] < 85% |
| Dosing cohorts | ■ Arm 1 – TAC[4] + Neulasta (pegfilgrastim) (6 mg)<br>■ Arm 2 – TAC + Plinabulin (40 mg[5]) + Neulasta (pegfilgrastim) (6 mg) |
| Status | Pre-specified interim analysis of approximately 120 patients completed |

**One dose Plinabulin per cycle, 30 minutes after chemotherapy on day 1, 30 minute IV infusion**

Note: [1] Duration of severe neutropenia. [2] Average neutrophil count. [3] Relative dose intensity. [4] Docetaxel, doxorubicin and cyclophosphamide. [5] Fixed dose, equivalent to 20 mg/m$^2$.

# PROTECTIVE-2 (Phase 3, pre-specified interim analysis): positive topline results

- **Chemotherapy regimen:** docetaxel, doxorubicin and cyclophosphamide (TAC) in breast cancer
- **Dosing cohorts:** Plinabulin (40 mg) + Neulasta® (6 mg) vs. Neulasta (6 mg)
- **Interim analysis:** at approximately 120 patients

| Endpoints | Results |
|---|---|
| **Primary endpoint:** | ■ p<0.01 |
| Rate of prevention of grade 4 neutropenia in Cycle 1 | ■ Higher prevention rate in Plinabulin-Neulasta combination |
| **Key secondary endpoint (#1):** | ■ p<0.05 |
| DSN in Cycle 1, Day 1-8 | ■ Plinabulin's MoA of early onset in Week 1 |
| **Key secondary endpoint (#2):** | ■ p<0.05 |
| DSN in Cycle 1 | ■ Plinabulin-Neulasta combination's better CIN benefit in Cycle 1 compared to Neulasta alone |

**Double blinded, active controlled, global trial**
**(CRO & central lab: Covance)**

Neulasta® is a registered trademark of Amgen, Inc.

# Plinabulin's regulatory strategy for CIN

**1** **Plinabulin + G-CSF combo in high risk chemo vs. G-CSF**

**MOA support:**
**Plinabulin early onset in Week 1**
**G-CSF effect in Week 2**

- **PROTECTIVE-2 Phase 3:** pre-specified interim analysis at around 60 pairs of patients (primary end point **p<0.01** and MOA of early onset)
- **PROTECTIVE-2 Phase 2:** early onset action for Plinabulin (**p=0.0149**)
- **PROTECTIVE-1 Phase 2 and Phase 3:** early onset action
- Prospectively grade 4 neutropenia linked to composite risk (FN, hospitalization, death and other negative consequences)

**2** **Plinabulin in intermediate risk chemo vs. placebo**

**Grade 4 reduction highly statistically significant**

- **Study 101:** Plinabulin reduced the incidence of grade 4 neutropenia from 33.8% in the docetaxel arm to less than 5% in the Plinabulin + docetaxel arms (p<0.0003) on Day 8 of Cycle 1
- **DUBLIN-3 138 patients:** Plinabulin reduced the incidence of grade 4 neutropenia from 27.4% in the docetaxel arm to 3.1% in the Plinabulin + docetaxel arm (p<0.0001) on Day 8 of Cycle 1

**3** **Plinabulin vs. G-CSF**

**Superior profile**

- **PROTECTIVE-1 Phase 2 and Phase 3 study:**
- **Non-inferior efficacy profile**
  - Plinabulin and Neulasta in CIN efficacy (non-inferiority)
- **Superior safety profile**
  - Thrombocytopenia (platelet decrease): yes for G-CSF; no for Plinabulin
  - Bone pain: yes for G-CSF; limited for Plinabulin
  - Immune suppression: yes for G-CSF; no for Plinabulin

**6 clinical trials (on 1,200+ patients) already proved Plinabulin's potential to statistically reduce grade 4 neutropenia**

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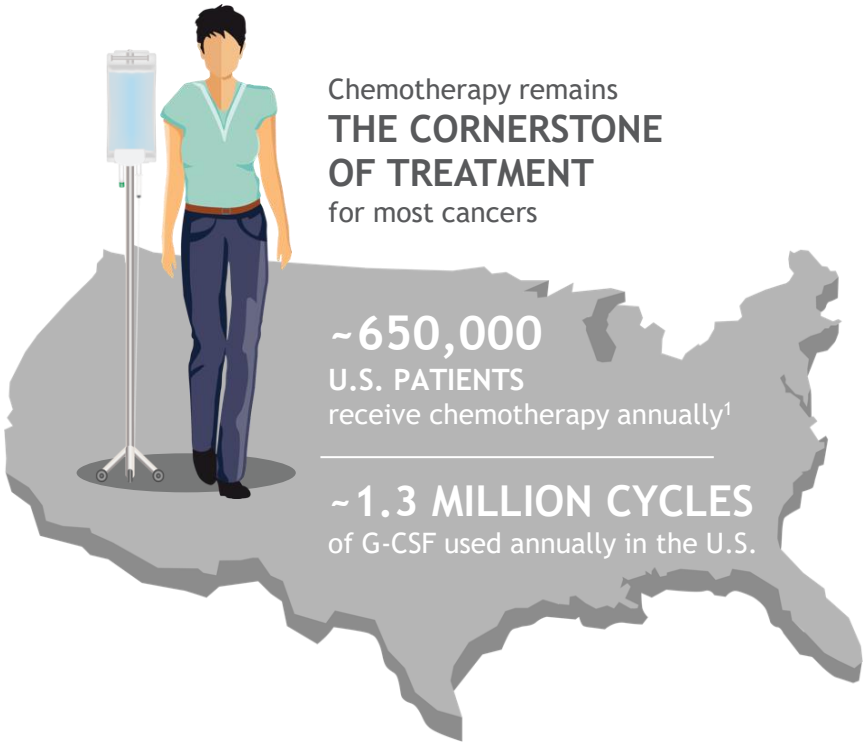
# Significant opportunities exist to improve the standard of care for patients on chemotherapy

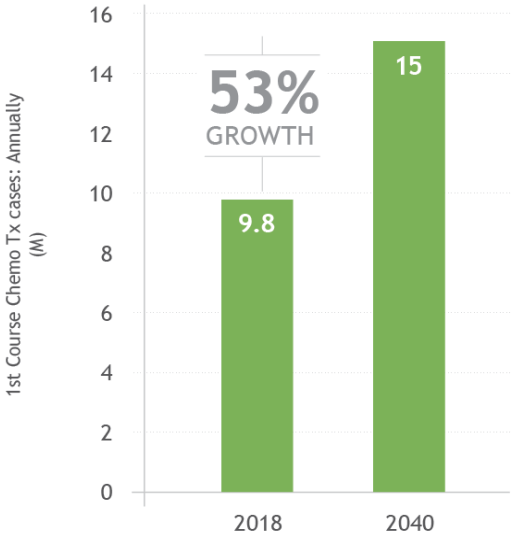


Chemotherapy remains
**THE CORNERSTONE OF TREATMENT**
for most cancers

**~650,000**
**U.S. PATIENTS**
receive chemotherapy annually[1]

**~1.3 MILLION CYCLES**
of G-CSF used annually in the U.S.

## 50%+ growth expected in use of first-line chemotherapy by 2040




- NCCN recently expanded recommended prophylaxis use of G-CSF to include both high risk and intermediate risk patients
- Increasing the addressable patient population from 32% of all chemotherapy patients to 69%

Note: [1] Centers for Disease Control and Prevention. Information for Health Care Providers. Available at: www.cdc.gov/cancer/preventinfections/providers.htm. Accessed February 21, 2020.

# $9+ billion opportunity in CIN global market

Plinabulin may potentially be used with each cycle of G-CSF in chemotherapy to provide improved protection from neutropenia



Plinabulin + G-CSF Addressable Market:

- US: 1.3M G-CSF cycles/year
- Global: 4M G-CSF cycles/year

Note: [1] https://onlinelibrary.wiley.com/doi/full/10.3322/caac.21338. G-CSF market growth based on IQVIA data (MIDAS for ex-U.S. and DDM MD for U.S.; Q3 '16 to Q2 '18. Standardized G-CSF units.

# G-CSF biosimilars: Plinabulin commercial accelerators

Combination therapy required to address unmet medical need

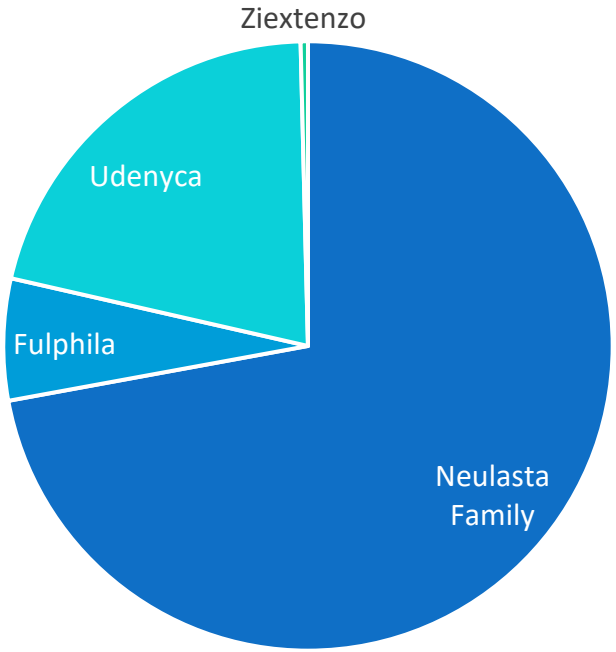
**Biosimilar success coming at Amgen's expense[1]**

Aligns with Plinabulin's combination strategy

- Increased choice
- Decrease price
  - Biosimilar list price ~33% below branded
  - Average selling price (ASP) continues to decline for all products
  - The gap shows no sign of slowing
    - Current difference between branded and biosimilar price is between $2,400 and $2,800/cycle

**All trends favor Plinabulin's combination strategy**

**Market Share YE '19[2]**



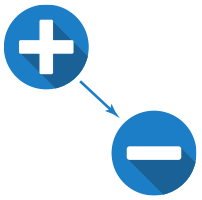

Source: [1] http://www.drugs.com/price-guide/. [2] Bloomberg

# Monotherapy G-CSF is not enough

Despite a broad use of monotherapy G-CSFs, the "4Ds" are a vexing clinical challenge for preventing neutropenia

**DECREASED**
recommended dose

**DELAYED**
cycles



**DOWNGRADE**
chemotherapy regimen

**DISCONTINUED**
chemotherapy

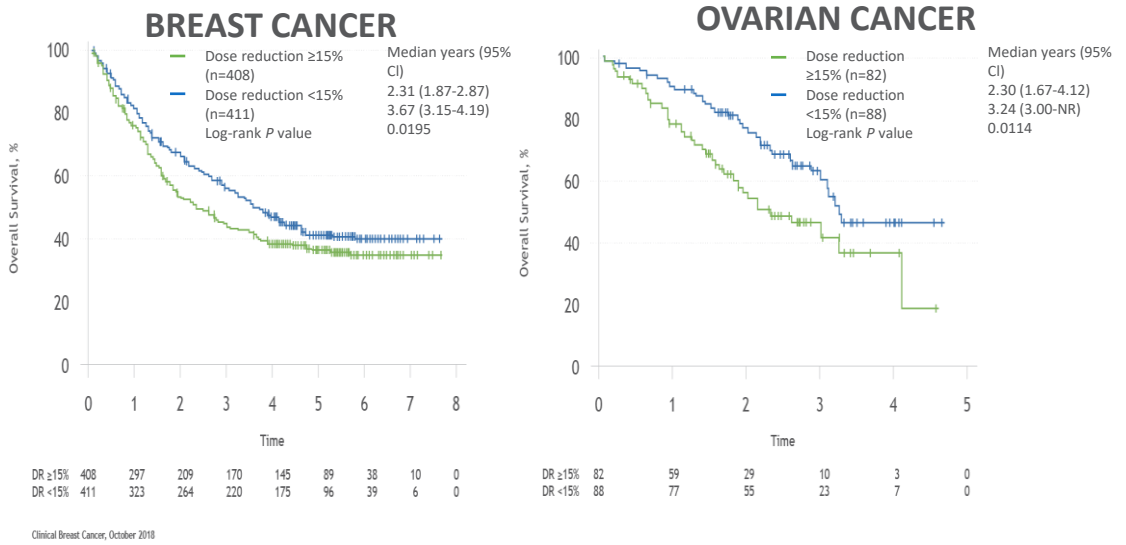
**…CIN and/or febrile neutropenia may have long-term effects with clinical impact on the overall chemotherapy treatment plan,** resulting in dose reductions and/or treatment delays, chemotherapy discontinuation, or a switch to less toxic alternatives, and potentially less effective regimens, leading finally to decreased response and survival rates[1].

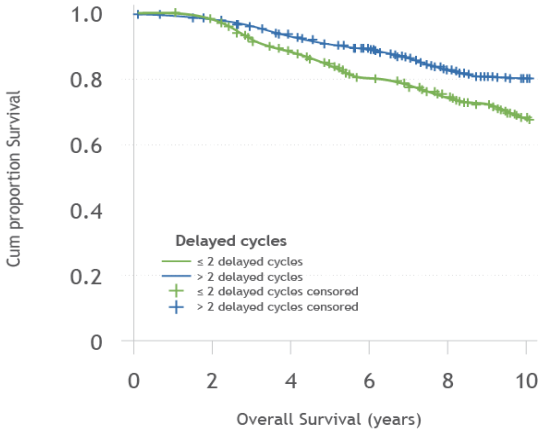
Source: [1] Segal et al., 2008; Schwenglenks et al., 2006

# Maintaining dose and dosing schedules are critical for survival

DOSE REDUCTIONS = DECREASED OVERALL SURVIVAL[1]

DELAYED CYCLES = DECREASED OVERALL SURVIVAL[2]



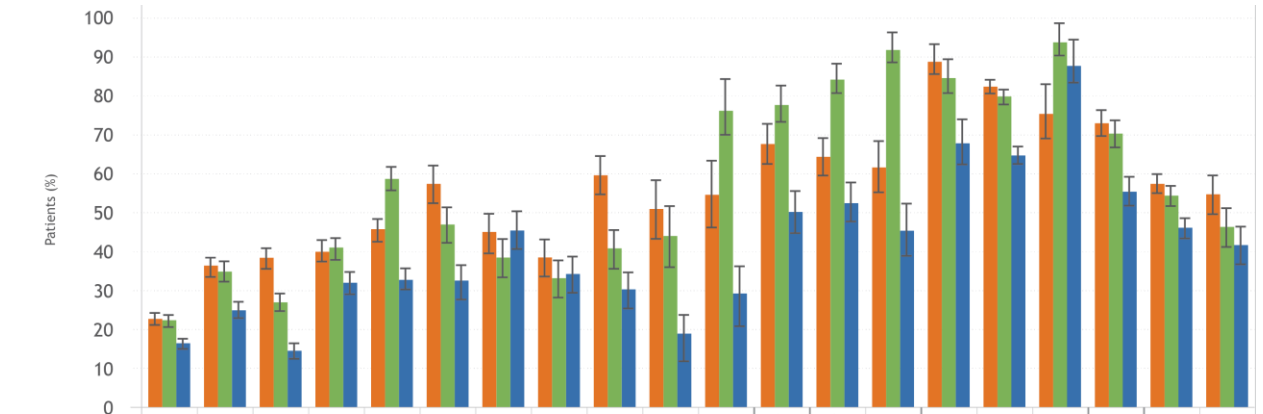




High grade 4 neutropenia rate leads to 4D's[3]:
decrease, delay, downgrade or discontinue chemotherapy treatment

Source: [1] Denduluri N et al., Clinical Breast Cancer 18(5): 380-386 (2018). [2] Chirivella I et al., *Breast Cancer Res Treat.* 2009; 114:479-484. [2] Lalami et al. Critical Reviews in Oncology / Hematology 120: 163-179 (2017).

# Universal challenge of maintaining therapy

**Dose reductions, delays, and missing doses by therapy (even with use of G-CSF)**




| | TC (4-cycle) | TAC | Dosedense AC → q2wk paclitaxel | TC (6-cycle) | TCH | AC → qwk paclitaxel | Dose-dense AC | AC | Dose-dense AC → qwk paclitaxel | AC → q3wk paclitaxel | AC → docetaxel | Carboplatin, paclitaxel | Carboplatin, paclitaxel | Cisplatin, vinorebine | FOLFOX4 | mFOLFOX6 | 5-FU (q6wk) | ABVD | R-CHOP/CHOP (q3wk) | RCVP/CVP |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | BREAST CANCER | | | | | | | | | | | OVARIAN CANCER | NSCLC | | CRC | | | HODGKINS LYMPHOMA | NHL | |
| Dose delay ≥7 days, % (95% CI) | 22.9 (21.5-24.3) | 36.1 (33.8-38.6) | 38.2 (35.6-40.9) | 40.2 (37.4-43.0) | 45.4 (42.6-48.3) | 57.0 (52.2-61.7) | 44.8 (40.0-49.9) | 38.5 (33.8-43.4) | 59.5 (54.5-64.3) | 50.6 (43.1-58.1) | 54.5 (46.0-62.7) | 67.2 (61.8-72.2) | 63.9 (59.1-68.5) | 61.5 (54.9-67.7) | 88.4 (84.0-91.8) | 82.1 (80.2-83.7) | 75.2 (67.6-81.5) | 72.6 (69.4-75.6) | 57.2 (54.6-59.7) | 54.5 (49.7-59.3) |
| Dose reduction ≥15 days, % (95% CI) | 22.3 (20.9-23.7) | 34.8 (32.5-37.2) | 27.0 (24.6-29.5) | 40.8 (38.0-43.6) | 58.5 (55.6-61.4) | 46.6 (41.8-51.3) | 38.4 (33.8-43.2) | 33.2 (28.7-38.0) | 40.5 (35.7-45.5) | 44.0 (36.6-51.6) | 76.1 (68.2-82.6) | 77.4 (72.5-81.7) | 83.6 (79.6-87.0) | 91.3 (86.8-94.4) | 84.2 (79.2-88.1) | 79.4 (77.4-81.1) | 93.1 (87.8-96.2) | 69.9 (66.6-73.0) | 54.1 (51.5-56.7) | 46.2 (41.4-51.1) |
| Missing dose, % (95 CI) | 16.5 (15.2-17.7) | 25.0 (22.9-27.2) | 14.7 (12.8-16.7) | 32.0 (29.4-34.7) | 32.9 (30.2-35.6) | 32.3 (28.0-36.9) | 45.3 (40.5-50.2) | 34.2 (29.7-39.0) | 30.3 (25.9-35.1) | 18.7 (13.5-25.3) | 29.1 (22.1-37.3) | 50.0 (44.5-55.5) | 52.4 (47.5-57.3) | 45.4 (38.9-52.0) | 67.6 (61.7-73.0) | 64.6 (62.4-66.8) | 87.6 (81.2-92.0) | 55.2 (51.6-58.6) | 45.9 (43.3-48.5) | 41.6 (36.9-46.4) |

**<u>16,000 patients</u>**

Despite broad-base use of monotherapy G-CSF, HCPs still ***struggle to deliver***

- On time doses
- Full dose chemotherapy
- Full course chemotherapy

***RESULT:***

- Chemotherapy is sub-optimized
- HCPs recognize the clinical gap

Source: Published, 2015. Per EMR review of 16,233 patients with 6 different tumor types 2007-2011. JNCCN—Journal of the National Comprehensive Cancer Network Volume 13 Number 11 November 2015

# Chemotherapy without compromise

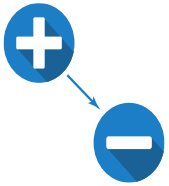
Plinabulin's differentiated clinical profile and the unmet market need enable us to pivot the discussion to improving the standard of care in chemotherapy

**DECREASED**
recommended dose

**STABLE DOSE**
maintaining ≥85%

**DELAYED**
cycles

**SUSTAINED CYCLES**
cycles on time



**DOWNGRADE**
chemotherapy regimen

**STRONGEST REGIMEN**
of chemotherapy

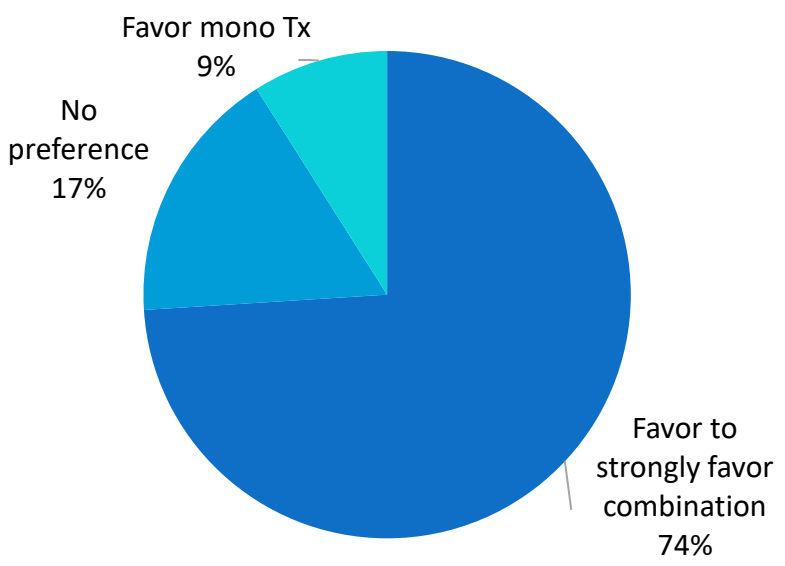
**DISCONTINUED**
**chemotherapy**

**STAY THE COURSE**
complete all cycles

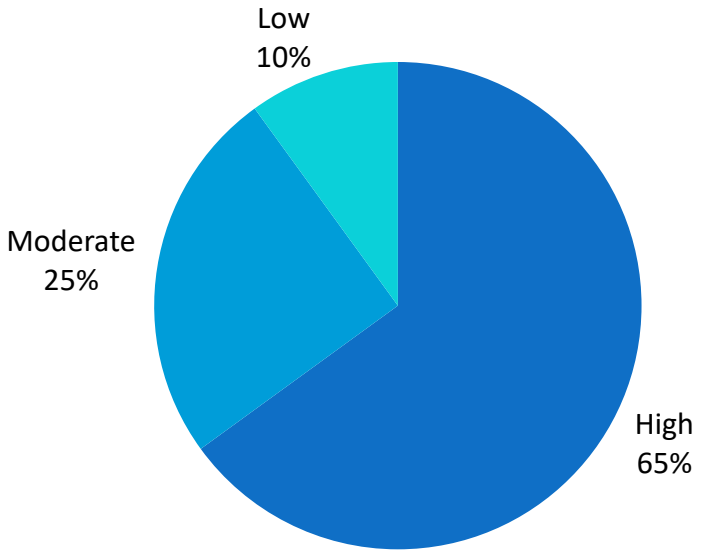
# Oncologist excitement for combination therapy with Plinabulin

Understanding the rationale for combination therapy: **high**
Likelihood to prescribe Plinabulin: **high**

Receptivity towards combination therapy[1]




Likelihood to use Plinabulin + G-CSF combination therapy[2]




Source: BeyondSpring market research
Note: [1] QB04: On a scale of 1-9, where 1 = Not at all likely to use and 9 = Extremely likely to use, please rate your likelihood to use PLIN + G-CSF combination therapy. [2] QB01: How would you characterize the overall clinical benefit of PLIN vs. G-CSFs?

# Plinabulin CIN summary

## Opportunity

- Market size +
- Market growth +
- NCCN guideline change +
- Managed care coverage +

## Unmet need

- CIN - #1 reason for therapy change (4Ds)
- Monotherapy G-CSF unable to address the CIN challenge
- 4Ds result in reduced overall survival

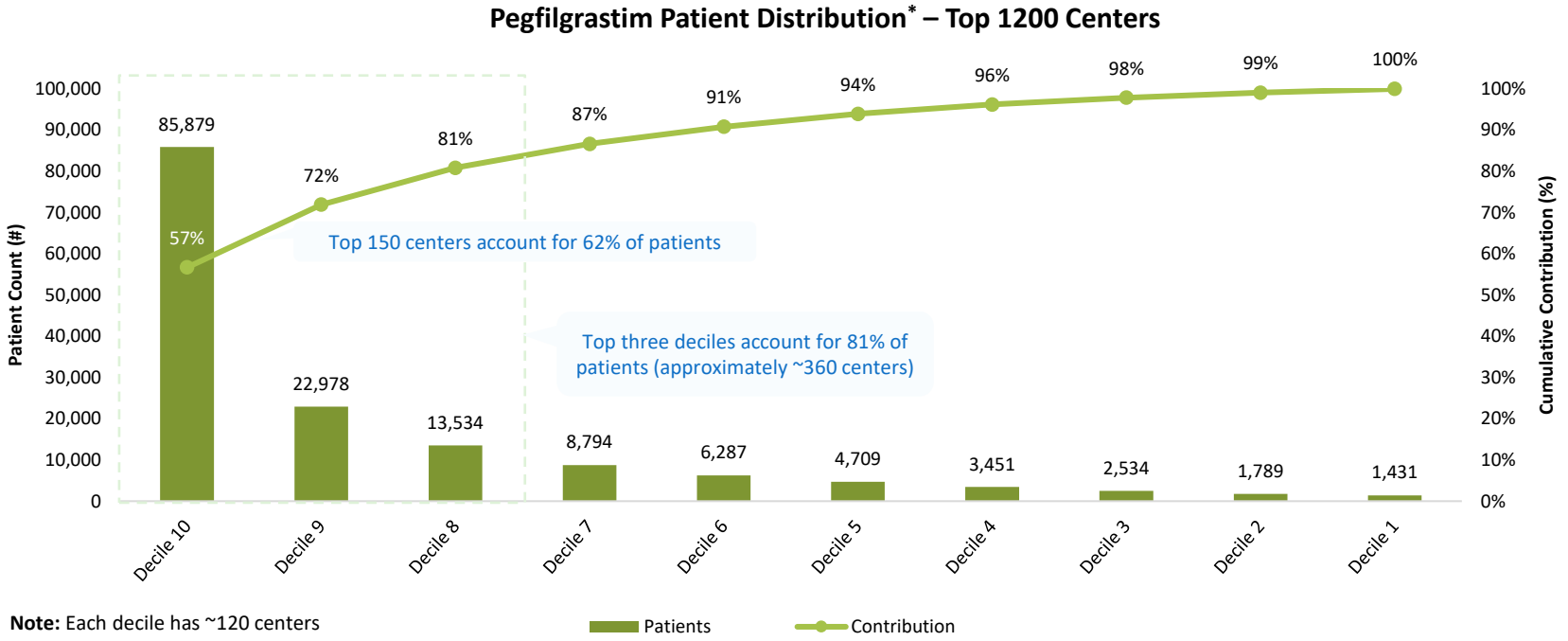
## Product differentiation

- Plinabulin + G-CSF addresses the oncologist three highest needs:
  - Maintains RDI +
  - Keeps ANC out of the danger zone +
  - Significantly reduces bone pain +

## Result – if approved, Plinabulin has the potential to

- Address the oncologist's desire for increased control
- Reduce patient anxiety and fears associated with interrupted therapy and adverse events
- Deliver improved chemotherapy care

# Market concentration favors Plinabulin's combination strategy




**Note:** Each decile has ~120 centers

- Komodo Health sample/analysis:
  - Conducted data analysis of pegfilgrastim / G-CSF patients by HCP and HCO (top ~1200 centers included in analysis)
  - Only centers with 10+ patients were included (~3000 HCOs with less than 10 patients excluded)
- Combination strategy:
  - Builds on the SOC and leverages the high concentration of accounts/patient
  - Supports efficient and effective use of commercial resources

Source: Komodo Health, Inc. Komodo Health, Inc. makes no representation or warranty as to the accuracy or completeness of the data ("Komodo Materials") set forth herein and shall have, and accept, no liability of any kind, whether in contract, tort (including negligence) or otherwise, to any third party arising from or related to use of the Komodo Materials by BeyondSpring Inc. Any use which BeyondSpring Inc.or a third party makes of the Komodo Materials, or any reliance on it, or decisions to be made based on it, are the sole responsibilities of BeyondSpring Inc. and such third party. In no way shall any data appearing in the Komodo Materials amount to any form of prediction of future events or circumstances and no such reliance may be inferred or implied.

# Agenda

Company Overview

Plinabulin Profile

CIN (Phase 3)

Commercial Opportunities

**NSCLC (Phase 3)**

I/O Combos

Summary

# 2nd/3rd line NSCLC (EGFR wild type): severely unmet clinical needs

## 2nd/3rd line NSCLC patients

| | EGFR mutant | EGFR wild type | In EGFR wild type patients |
|---|---|---|---|
| **% of 2L/3L NSCLC patients** (western) | 15% | 85% | Much larger population |
| **mOS** SoC | 18.3 months (TKI) | 6-8 months (docetaxel) | Much shorter OS |
| mOS TKI vs docetaxel[1] | | 5.4 vs 8.2 months | TKI worse than docetaxel |
| Currently available therapies | | PD-1<br>Pemetrexed<br>Ramucirumab + docetaxel<br>Docetaxel | All with significant limitations |

**Severely unmet clinical needs**

**For lung cancer patients infected by COVID-19, death rate is 55%![2]**

Note: [1] Lancet Oncol. 2013 Sep;14(10):981-8. [2] Mehta V et al., Cancer Discovery May 1, 2020 online; DOI: 10.1158/2159-8290.CD-20-0516.

# Approved therapies fail to address EGFR wild type NSCLC (85% of western patients) in 2nd/3rd lines

Only four therapies are currently approved: docetaxel, pemetrexed, ramucirumab and PD-1

| | Moving into 1st line | | 2nd & 3rd lines | |
|---|---|---|---|---|
| | **Nivolumab (PD-1) vs. docetaxel[1]** | **Pemetrexed vs. docetaxel[2]** | **Ramucirumab + docetaxel vs. docetaxel[3]** | **Plinabulin + docetaxel vs. Docetaxel[4]** |
| mOS | +2.8 months (12.2 vs. 9.4) HR = 0.73 | +0.4 months (8.3 vs. 7.9) HR = 0.99 | +1.4 months (10.5 vs. 9.1) HR = 0.86 | +4.6 months (11.3 vs. 6.7) HR < 0.75[5] |
| ORR | 19% vs.12% | 9.1% vs. 8.8% | 23% vs. 14% | 18.4% vs.10.5% |
| Grade 3/4 neutropenia | 0% vs. 27% | 5% vs. 40% | 49% vs. 39% | 7% vs. 26% |
| DOR | 17 vs. 6 months | 4.6 vs. 5.3 months | | 12.7 vs. 1 months |
| Conclusion | ▪ Introduces potential cytokine storm leading to inflammation<br>▪ Moved into 1st line | ▪ No efficacy improvement<br>▪ Approved based on low neutropenia rate | ▪ Modest efficacy benefit<br>▪ Higher severe neutropenia rate than docetaxel | ▪ Superior efficacy<br>▪ Superior ORR<br>▪ Superior CIN benefit<br>▪ Superior DOR |
| **COVID-19 implication** | ▪ Compounding inflammation caused by COVID-19 | | ▪ Severe neutropenia leads to infection and hospitalization | ▪ Limited severe CIN prevents infection and hospitalization |

Note: [1] NEJM 373: 1627-1639 (2015). [2] JCO 22(9): 1589-1597 (2004). [3] Lancet 384 (9944): 665-673 (2014). [4] Based on Study 101. [5] Based on first interim look of DUBLIN-3.

# DUBLIN-3 (Study 103): phase 3 in NSCLC – second interim analysis completed; DSMB recommended trial to continue

| Phase 3 study (randomized single blinded) | |
|---|---|
| # of patients & sites | 554 patients in 60 sites in U.S., Australia and China |
| Patient enrollment | ■ Patients with at least 1 measurable lung lesion; 2nd-/3rd-line NSCLC<br>■ PD-1/PD-L1 antibody failures (stratified)<br>■ EGFR wild type, mutations not eligible; no restriction on histology<br>■ One prior platinum-based chemotherapy; no restriction on biological therapy<br>■ SAP Plan: KRAS mutant subgroup; PD-L1 expression subgroup; tumor size subgroup; prior treatment include PD-1/PD-L1 or not |
| Primary objective | Overall survival |
| Secondary objective | Grade 4 neutropenia (C1D8), ORR, PFS, DOR, QoL |
| Dosing cohorts | ■ Arm 1 – docetaxel (75 mg/m$^2$)<br>■ Arm 2 – docetaxel (75 mg/m$^2$) + Plinabulin (30 mg/m$^2$) |
| Status | ■ First interim analysis completed in Q1 2019 at 1/3 patient mortality. DSMB recommended trial to continue without modification (HR < 0.75 based on mOS)<br>■ **Second interim analysis completed in Q2 2020 at 2/3 patient mortality. DSMB recommended trial to continue without modification**<br>■ Final analysis: 439 patient mortality, study succeeds if p < 0.046 for mOS |

# Agenda

Company Overview

Plinabulin Profile

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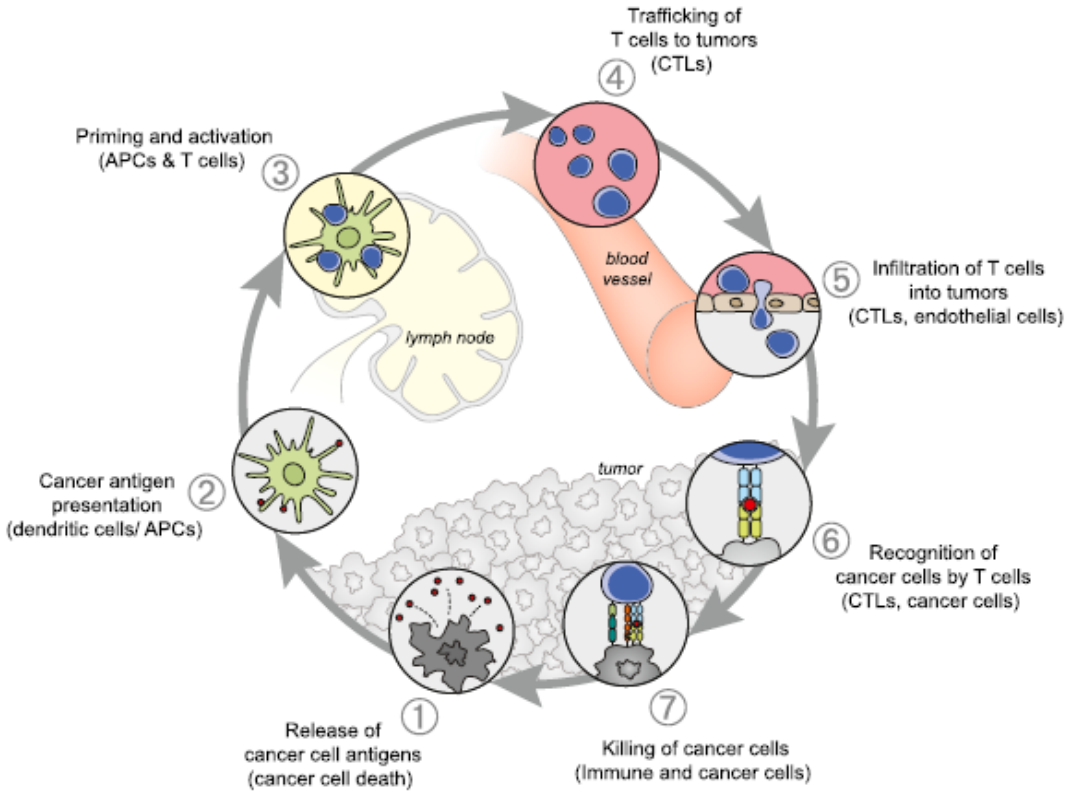
**I/O Combos**

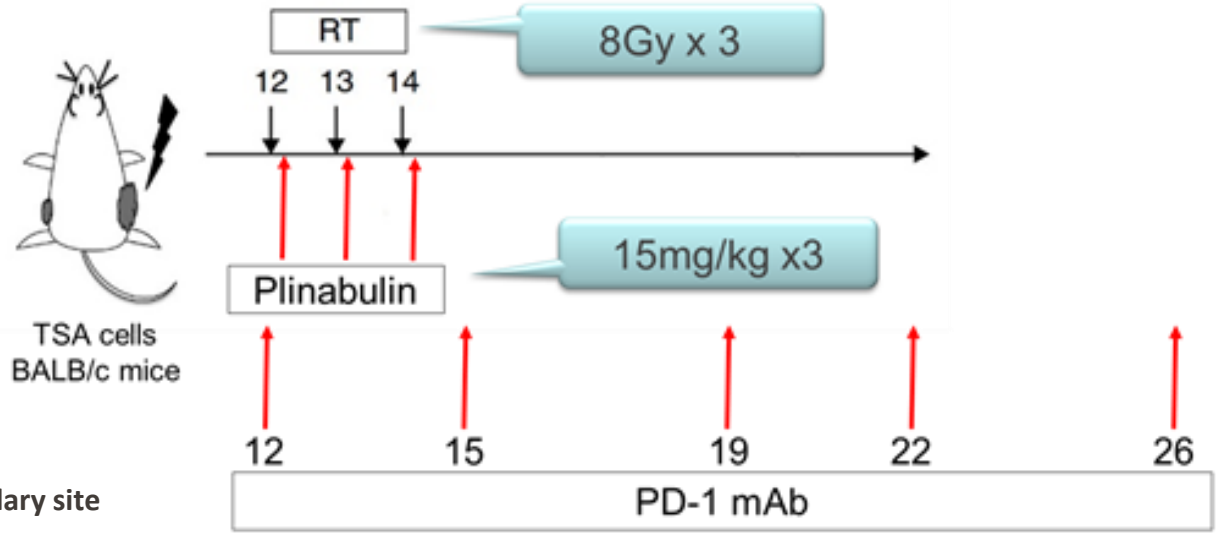
Summary

# Plinabulin induces dendritic cell DC maturation, a key step in initiating anti-cancer immunotherapy

- The generation of cancer immunity is a cyclic process. In principle, the response of T cells to tumor cells should be amplified and expanded
- Initiating anti-cancer immunity includes antigen release, presentation and activation of cancer antigen-specific T cells. Dendritic cells are the most important antigen-presenting cells

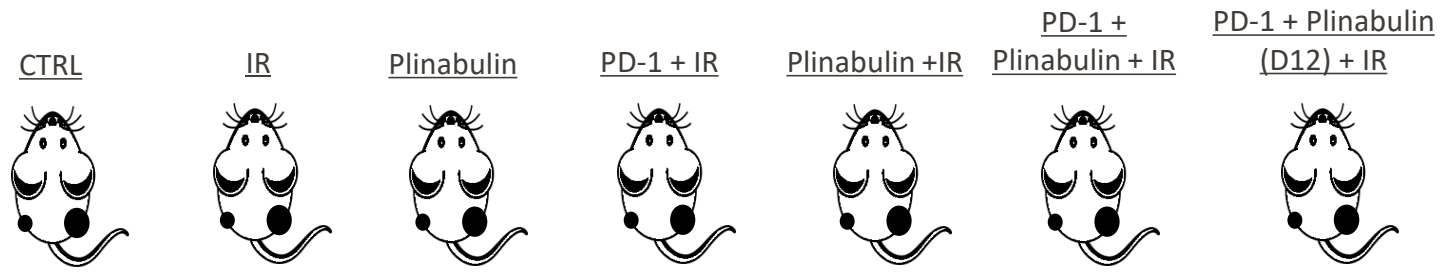


# In vivo model (MD Anderson)



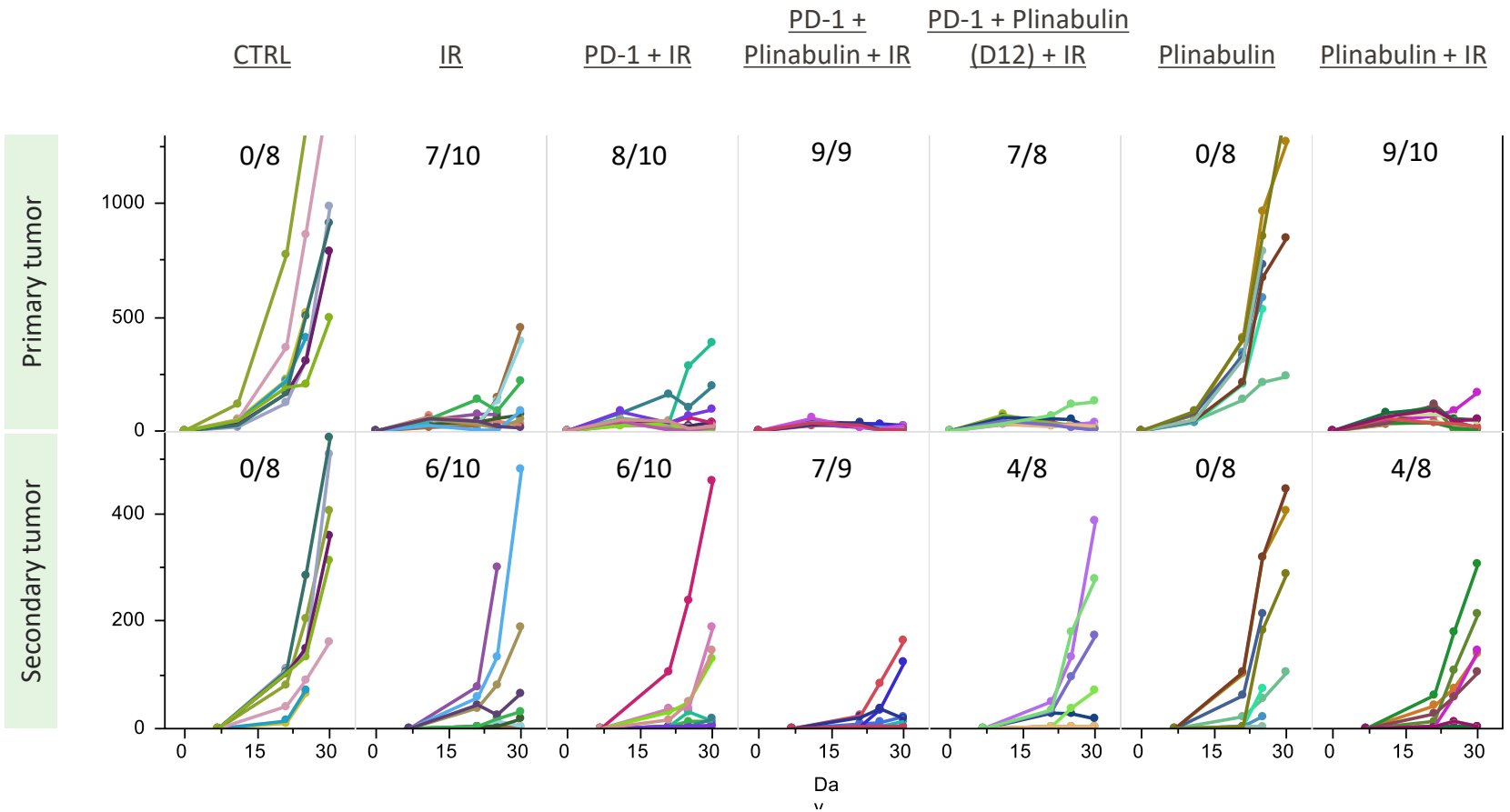

**Day0: primary site; Day8: secondary site**

**7 groups**




Note: Vanpouille-Box Nat Commun 2017, modified.

# Tumor size (MD Anderson)




- PD-1 + Plinabulin + IR: Plinabulin dose on D12, D13 and D14
- PD-1 + Plinabulin (D12) + IR: Plinabulin only dose on D12

# Plinabulin: "pipeline in a drug" for multiple cancer indications

| Foundation | Translation | Transformation |
|---|---|---|
| **CIN + NSCLC** | **+ chemo** | **+ IO agents + radiation/chemo** |
| ■ **CIN indication (broad label)**<br>■ 5 clinical trials confirm Plinabulin's CIN benefit with statistical significance<br>■ CIN benefit in multiple chemo with differentiated MOA in animal model<br>■ **NSCLC indication (+ docetaxel)**<br>■ 2 clinical trials show Plinabulin's durable anti-cancer benefit<br>■ **Milestones**<br>■ China NDA submission: Q1 2020 for CIN and H2 2020 for NSCLC<br>■ U.S. NDA submission: H2 2020 for CIN and H1 2021 for NSCLC | ■ Based on findings from Plinabulin studies (> 600-patient data), Plinabulin + chemo can potentially add OS benefit and reduce CIN of any chemo<br>■ Expand in cancer in combo with docetaxel<br>■ Breast cancer, prostate cancer etc.<br>■ Expand in cancer in combo with other chemo<br>■ e.g. colon cancer with irinotecan | ■ **The "attractive" triple combo**<br>■ MOA and pre-clinical data support combination approach and benefits from triple therapy<br>■ Radiation/chemo: generates tumor antigen<br>■ **Plinabulin: APC inducer, induces tumor antigen specific T cells and reduces CIN**<br>■ PD-1/PD-L1 Ab: release break for T cells to target and kill cancers<br>■ $100+ billion market opportunity for IO therapies by 2022[1] |

Note: [1] Based on data from Evaluate Pharma.

# Agenda

Company Overview

Plinabulin Profile

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NSCLC (Phase 3)

I/O Combos

**Summary**

# Plinabulin's potentially superior product profile is more evident in COVID-19 pandemic

- Death rate is 28% for cancer + COVID-19 patients and 55% for lung cancer + COVID-19 patients[1]
- Reduction of infection and hospitalization can save hospital resources and prevent patients from contracting COVID-19
- Avoids thrombocytopenia and therefore reduces blood transfusion needs
- NCCN guidelines for growth factor recently added G-CSF prophylaxis use for intermediate risk chemotherapy patients

## CIN (all cancer, all chemo, all G-CSF)

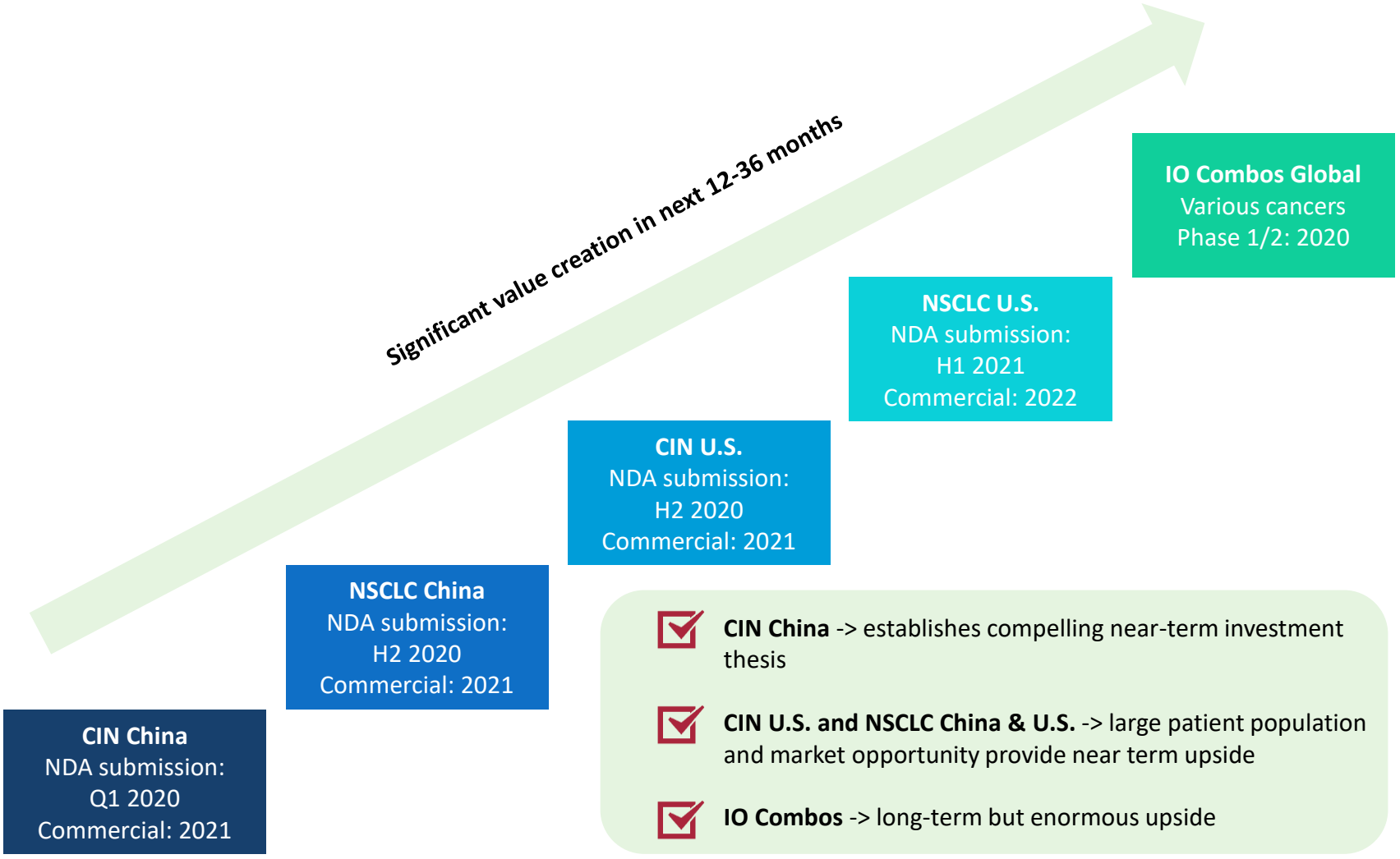
- Combo with G-CSF has lower grade 4 neutropenia rate vs. G-CSF alone, which would potentially reduce infection and hospitalization rate, and enable optimum dose of chemo for better anti-cancer clinical outcome
- First day dosing and rapid onset of action
- Good QoL with limited bone pain
- Does not introduce thrombocytopenia (platelet decrease), thus potentially avoiding blood transfusion
- Does not have pulmonary inflammation; Does not introduce immune suppression
- Potential anti-cancer agent
- Well tolerated, used in >600 cancer patients

**Plinabulin is the only agent which combines ANC protection (reduce infection) and potential anti-cancer benefit together**

**This is the "optimum" combination for cancer patients during COVID-19 pandemic**

Note: [1] Mehta V et al., Cancer Discovery May 1, 2020 online; DOI: 10.1158/2159-8290.CD-20-0516.

# Significant value creation for Plinabulin in next 12-36 months



# Agenda

## Appendix

# Study 101 (phase 2): Plinabulin safety summary

- As of now, Plinabulin generally well tolerated **(> 580 patients)**; no cardio adverse effects with two-year follow-up
- AEs are dose-dependent and manageable

| Grade 3/4 Adverse Event (AE) as % in patients | Plinabulin 30mg/m$^2$ (2 doses) + docetaxel 75mg/m$^2$ (n=50) | Docetaxel 75mg/m$^2$ (n=73) |
|---|---|---|
| Nausea (N) | 4 | 0 |
| Vomiting (V) | 4 | 1 |
| Diarrhea (D) | 8 | 6 |
| Constipation | 0 | 1 |
| Anorexia | 0 | 0 |
| Fatigue | 4 | 10 |
| Asthenia | 2 | 4 |
| Arthralgia | 0 | 0 |
| Myalgia | 2 | 0 |
| Headache | 0 | 0 |
| Dizziness | 0 | 0 |
| Dyspnea | 4 | 14 |
| Cough | 0 | 0 |
| Alopecia | 0 | 0 |
| Hypokalemia | 0 | 1 |
| Anemia | 8 | 2 |
| Leukopenia | 2 | 9 |
| Neutropenia | 8 | 26 |
| Pyrexia | 0 | 2 |
| Tachycardia | 0 | 0 |
| Transient Hypertension (TH) | 20 | 0 |

Increased AE  Reduced AE

# BeyondSpring's ubiquitination platform: "molecular glue"

## Reprogramming E3 ligases with molecular glue


**Others**

**PROTAC**

- Entail a bi-functional molecule
- Rely on high affinity on both ends
- Size might exceed >500 Da (may limit oral availability)
- Mostly limited to two E3s

**BeyondSpring**

**Molecular glue**

- Involves a regulator small molecule
- Does not need high affinity on both sides
- Three-way interactions (small enough to be drug-like compounds)
- Almost any E3 can be used

**The BeyondSpring team**

- RING E3 class – first solved by Prof. Ning Zheng in "Nature": Tan et al. Nature 446, 640-645 (2007)
- HECT E3 class – first solved by Dr. Lan Huang in "Science": Huang et al. Science 286, 1321-1326 (1999)
- Novel CRL E3 discoveries by Prof. Michele Pagano in "Nature Reviews Drug Discovery": Skaar et al. Nat Rev Drug Discov. 13, 889-903 (2014)