10th Anniversary

Sumitomo Dainippon Pharma

R&D Meeting

December 9, 2015

Sumitomo Dainippon Pharma Co., Ltd.

Today's Agenda

◆ Quest for Further Innovation

Hiroshi Noguchi, Ph.D.

Representative Director, Senior Executive Vice President, Chief Scientific Officer

◆ Development products topics

Nobuyuki Hara, Ph.D.

Executive Officer, Deputy Executive Director, Drug Development

- ✓**Obeticholic acid (Nonalcoholic steatohepatitis (NASH))** **Phase II study results**
- ✓**Ranirestat (Diabetic neuropathy)** **Phase III study results**
- ✓**Lurasidone hydrochloride (Schizophrenia)** **Phase III study plan**

◆ Oncology

Chiang J. Li, MD, FACP

Executive Officer, Head of Global Oncology for Sumitomo Dainippon Pharma Group

President, Chief Executive Officer and Chief Medical Officer, Boston Biomedical, Inc.

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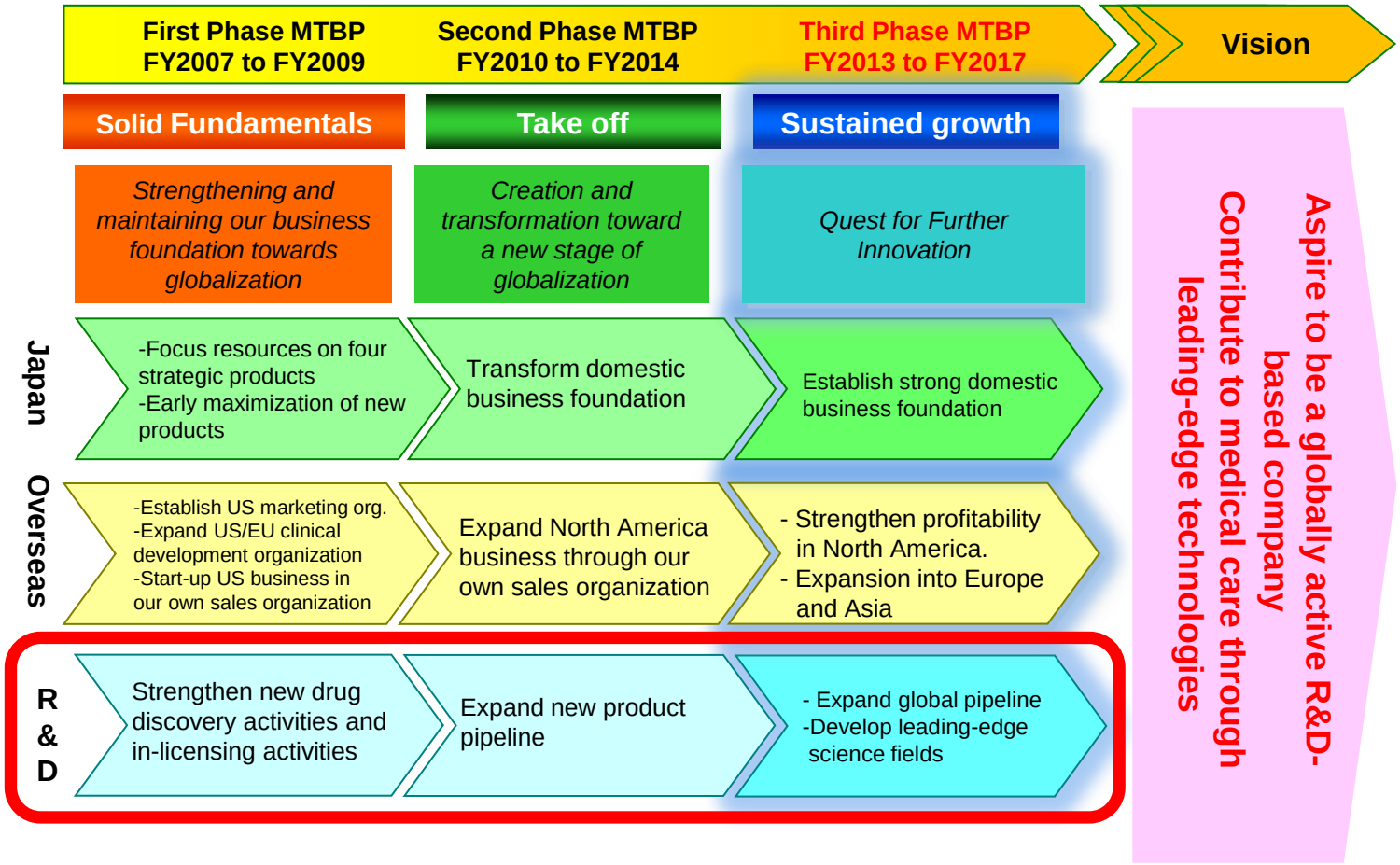
Quest for Further Innovation

Hiroshi Noguchi, Ph.D.
Representative Director,
Senior Executive Vice President
Chief Scientific Officer
Executive Director, Drug Research; Global R&D Office;
Global Oncology Office

Vision

- **Aim to global, R&D-based company**
- **Venture into leading-edge Science and Technology**



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R&D: Accomplishments in the past 10 years

- **Own development of LATUDA in the U.S.**

  Acquisition of Sepracor (’09), LATUDA approved (’10)

  Enhanced capacities for clinical studies and regulatory science

- **R&D strategy redefined to take the U.S. market in consideration: Entry into Oncology Area**

  In-licensing of BBI608 (’11) and Acquisition of Boston Biomedical, Inc. (’12)

- **Focus on innovative drugs**

  R&D organizations and management restructured

  In-licensing team realigned

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R&D Strategy-1: Basic Approach

Discover first-in-class drugs or drugs that can make the difference

Innovative Drug Discovery Laboratories has been created

Take on the challenge of unmet medical needs; “from point to plane” (from one rare disease solution to broader indication additions)

Implant and nurture a new R&D culture and mindset; a new human resource management scheme

- **Early POC demonstration and prompt application for late-stage development**

  Focus on Killer Experiments (minimum required experiments and tests to move on to the next R&D stage)

  Enhance the success ratio of late-stage development products

- **Focus on priority areas and venturing into new areas**

  Adopt business unit structure (oncology area and regenerative/cell therapy area)

- **Strategies according to the development stage**

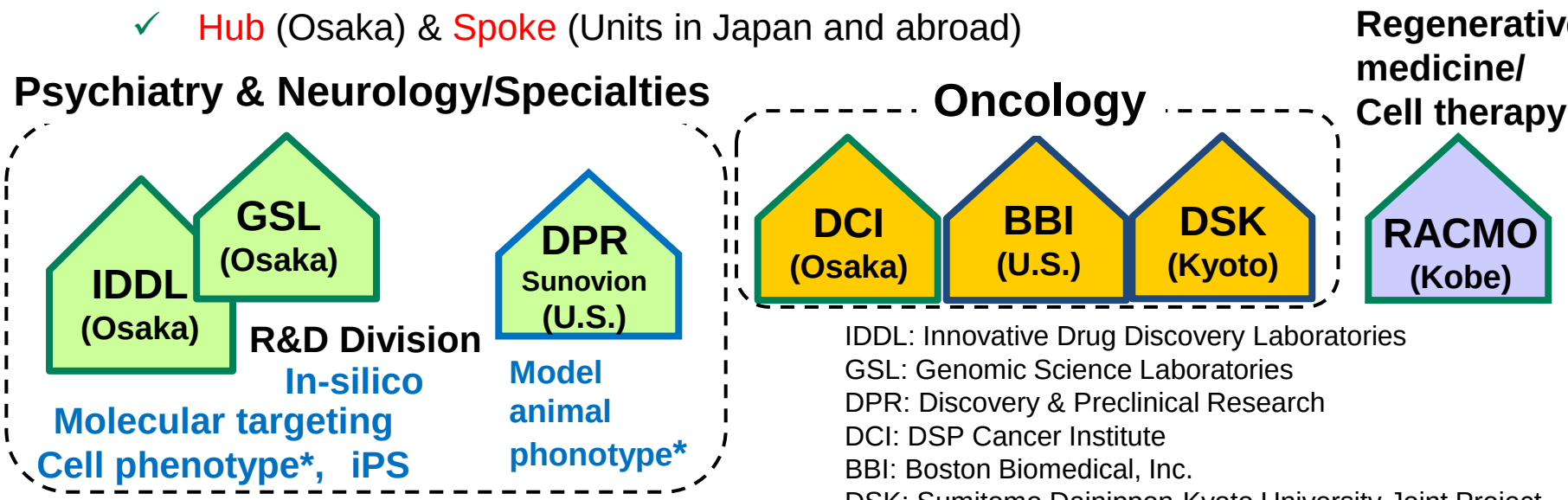
  Early-stage: focus on innovation, individual strengths, from out to in

  Late-stage: team strength, collaboration

R&D Strategy-2: Early-stage drug discovery

Build up "autonomous" units

- ✓ Innovative Drug Discovery Laboratories: Concentrate on **"Delivering 1 from 0"**
- ✓ Multiple arrows: multiple units compete with respective strengths
- ✓ Venture capital-like management
- ✓ Hub (Osaka) & Spoke (Units in Japan and abroad)



IDDL: Innovative Drug Discovery Laboratories
GSL: Genomic Science Laboratories
DPR: Discovery & Preclinical Research
DCI: DSP Cancer Institute
BBI: Boston Biomedical, Inc.
DSK: Sumitomo Dainippon-Kyoto University Joint Project
RACMO: Regenerative & Cellular Medicine Office

Pursue originality (make use of original technologies)

- ✓ In-silico drug discovery, iPS drug discovery, nucleic acid medicine (aiRNA)
- ✓ Introduce most leading-edge Science and Technology (mitochondria drug discovery, cerebral DDS, etc.)

* A drug discovery strategy to use phenotype as screening index

R&D Strategy-3:
Late-stage drug discovery and clinical studies

- **Show team strength through collaboration, seek speed and quality**
  - ✓ Collaboration among drug discovery, clinical studies, CMC as well as among division headquarters
  - ✓ Collaboration with Sunovion Pharmaceuticals Inc. and Boston Biomedical, Inc. Established of development integrated organization GCD (Global Clinical Development)
  - ✓ Develop products efficiently and quickly
  - ✓ Improve thematic quality by portfolio management
- **Intensify translational research (TR) approaches**
  - ✓ Make use of non-human primates (NHP)
  - ✓ Translational research using EEG (brain waves), PET and other non-invasive methods
  - ✓ Promote biomarker research with clinical samples
- **Use novel techniques**
  - ✓ Get pharmacologic/pharmacodynamics signals by f-MRI (functional MRI) (non-clinical and clinical)
  - ✓ Improve success ratio by pharmacokinetic/pharmacodynamics modelling and simulation
- **Re-positioning & PLCM**

R&D organization

Japan

- CEO
  - Board of Directors
- Global Oncology Office (GOO)
  DSP Cancer Institute (DCI)
- Global R&D Office
- Drug Research Division (include External Innovation Development Office)
- Drug Development Division*
- Techonology Research & Development Division
- Regenerative & Cellular Medicine Office (RACMO)
- Global Corporate Planning
- Global Business Development
- ・
- ・
- ・

*GCD：Global Clinical Development

- ✓ 3 Divisions: Research, Development, Technology R&D
- ✓ Established GCD* regarding Clinical Development
- ✓ Oncology and Regenerative medicine / Cell therapy independent of the 3 divisions
- ✓ R&D bases in group companies in the U.S., China
- ✓ R&D personnel: approx.1,360 (consolidated)

Overseas

- Sunovion Pharmaceuticals Inc. (Research・Development*・CMC)
- Boston Biomedical, Inc. (R&D&CMC in the Oncology area)
- Sumitomo Pharmaceuticals (Suzhou) Co., Ltd (Development)

Area strategy and R&D investment strategy

Priorities: Innovation, Competition, Market, Growth potential

- **Take on the challenge to unmet medical needs**
  From point to plane
- **Timespan**
  Needs of the time
  Rapid advance of
  Science and Technology
- **Own strengths**
  Past accomplishments & experiences
- **Toward the future**
  High-growth areas

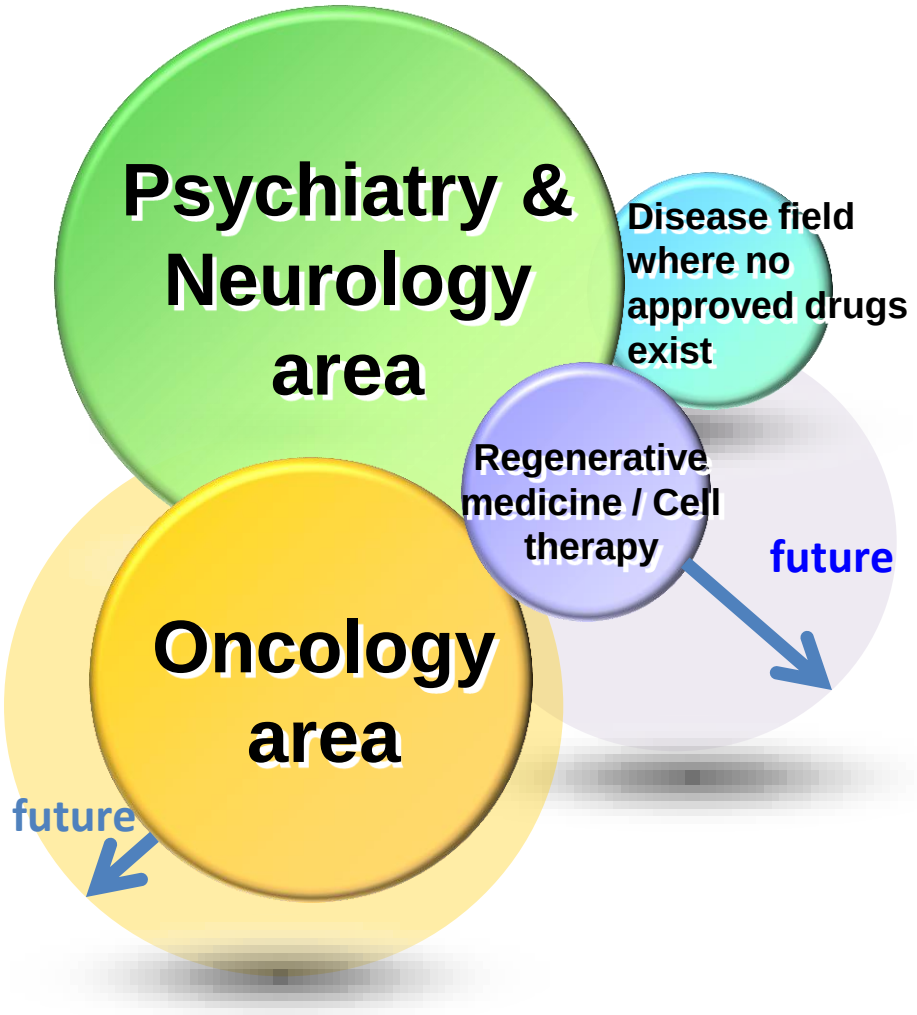


Image of R&D investment

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R&D activity making use of our strengths

Psychiatry & Neurology	Oncology	Disease field where no approved drugs exist	Regenerative medicine / Cell therapy
EXCEGRAN/TRERIEF DOPS, SEDIEL, LULLAN, LONASEN	SUMIFERON CALSED MIRIPLA	GENOTROPIN／GROWJECT REPLAGAL	Research of nerve regeneration Cell mass culture technology Cell culture techniques, QC/QA

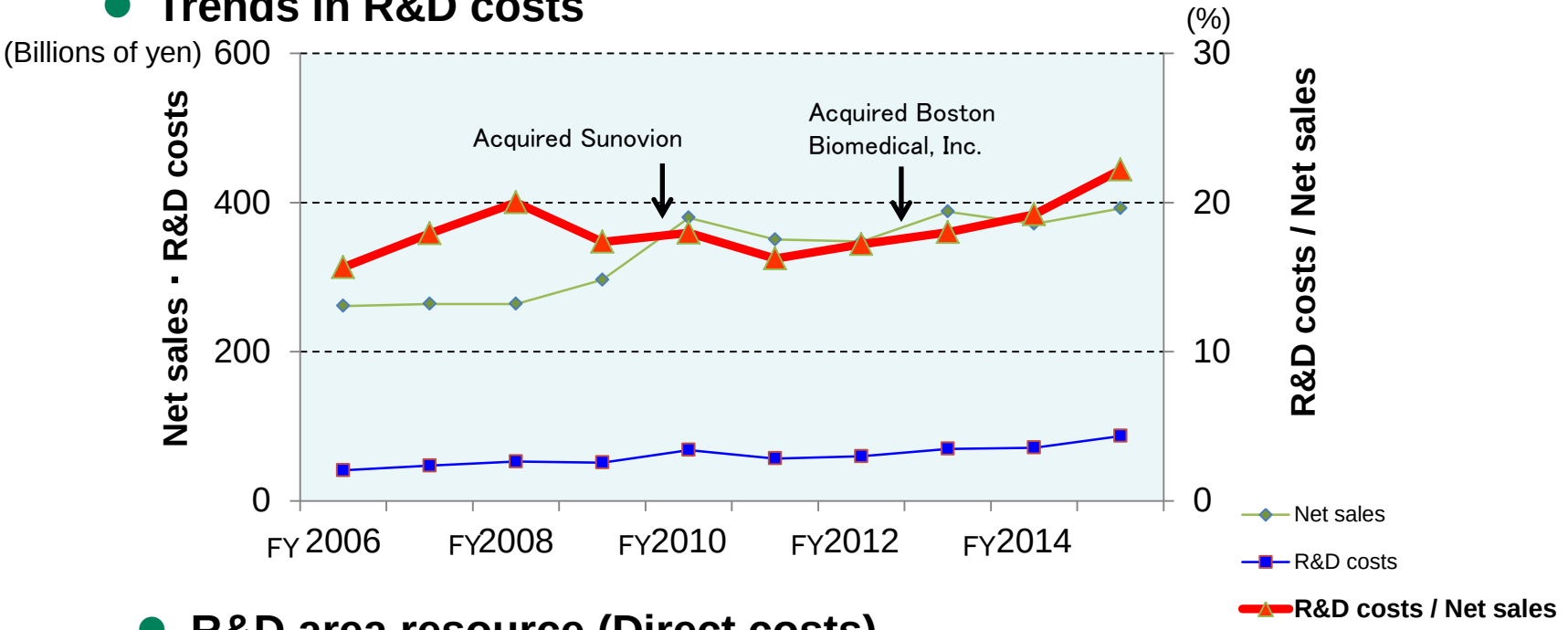
Sumitomo Dainippon Pharma created in 2005

Acquired Sepracor Inc. (current Sunovion) (2009)	Acquired Boston Biomedical, Inc. (2012)	In-license and alliance with venture companies	Partnerships with academia and venture (SanBio, Healios)
LATUDA			
Post LATUDA (Development in-house) **SEP-225289** (Ph3) ADHD*1, BED **SEP-363856** (Ph1) Schizophrenia **DSP-2230** (Ph1) Neuropathic pain **DSP-3748** (Ph1) CIAS*2	**Post LATUDA (Development in-house)** **BBI608** (Ph3) Gastric and GEJ Colorectal cancer **BBI503** (Ph2) Solid tumors **DSP-7888** (Ph1) Solid tumors, Hematologic malignancies	**Development products** **EPI-743/EPI-589** Neurodegenerative disease **DSP-1747** Nonalcoholic steatohepatitis (NASH)	**Development products** **iPS cell-derived RPE cells** Age-related macular degeneration **SB623** (Ph2b) Chronic stroke

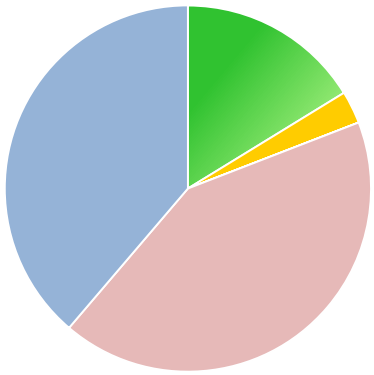
*1 ADHD: Attention-deficit hyperactivity disorder
*2 CIAS: Cognitive impairment associated with schizophrenia

Trends in R&D costs and allocation to therapeutic areas

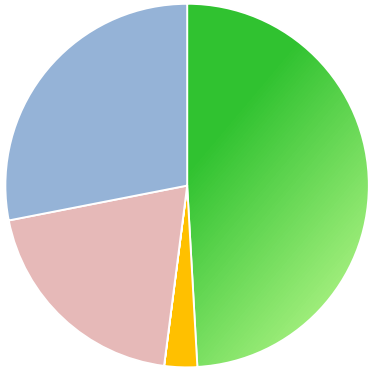
Trends in R&D costs



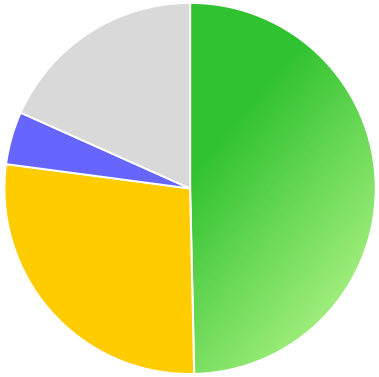
R&D area resource (Direct costs)



<FY2006>
17.6 Billion yen



<FY2010>
41.1 Billion yen

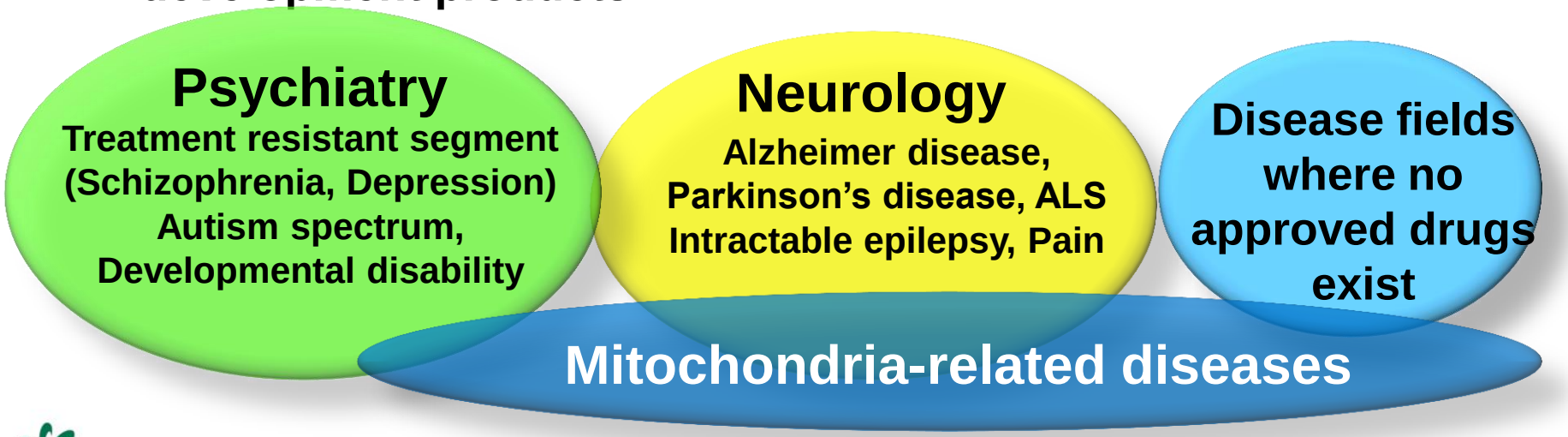


<FY2015> (Forecast)
53.9 Billion yen

Psychiatry & Neurology
Oncology
Regenerative medicine / Cell therapy
Cardiovascular and diabetes Area
Others (Exclude cardiovascular and diabetes area)
Others (Including cardiovascular and diabetes area)

Activities in Psychiatry & Neurology and Disease fields where no approved drugs exist

- Psychiatry/neurology: Capitalize on our strengths, take in leading-edge Science and Technology
  - ✓ Monoamine drug discovery, disease iPS, in-silico, phenotype
  - ✓ Channel technique, omics technology
  - ✓ Non-human primate (NHP)
- More weight on diseases of higher unmet medical needs
- Promote research cooperation with other companies
- Early POC demonstration for early-stage development products and early application for approval of late-stage development products



Targeted diseases

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Development Pipeline: Psychiatry & Neurology and Disease fields where no approved drugs exist

- **Invest in high priority late-phase products to seek fastest approval**
  - ✓ Dasotraline (SEP-225289)： ADHD (Ph3)・BED (Ph2/3)／U.S.
  - ✓ TRERIEF： Parkinsonism in Dementia with Lewy Bodies (DLB) (Ph3)／Japan
  - ✓ Obeticholic acid (DSP-1747)： NASH／Japan (Ph2)
- **Aim to obtain early POC of early-phase products**
  - ✓ EPI-589： Parkinson's disease, ALS
  - ✓ DSP-2230： Neuropathic pain
  - ✓ SEP-363856： Schizophrenia
  - ✓ DSP-3748： Cognitive impairment associated with schizophrenia (CIAS)

＜Products under consideration of development strategy ＞

- ✓ Ranirestat： Diabetic neuropathy／Japan
  ⇒Development strategy to be determined after additional data analysis
- ✓ Lurasidone： Schizophrenia／Japan ⇒ Another Ph3 study to be implemented
- ✓ Vatiquinone (EPI-743)： Leigh syndrome／Japan
  ⇒ development strategy under consideration

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Oncology area: Background of full entry and challenges

Consistent with Management Mission and Strategy

- ✓ Cancer drug development is a mission of R&D-based pharmaceuticals company
- ✓ Not always determined by company size; medium-sized company could be successful
  - Highly competitive market but product-driven
- ✓ A typical specialty area
  - No heavy sales force required

Externals: opportunities, market attractiveness

- ✓ High unmet medical needs, drugs based on innovative concept are required
- ✓ Rapid science and technology advances in the area, the time is calling for change from an incurable disease to curable
- ✓ Market growing medium- to long-term

- ➢ Very competitive market (over 800 compounds being developed, rush for patients recruit), speed is critical
- ➢ Complex indication strategy (cancer type X line X combined drug), unprecedented development strategy and emergent design are necessary

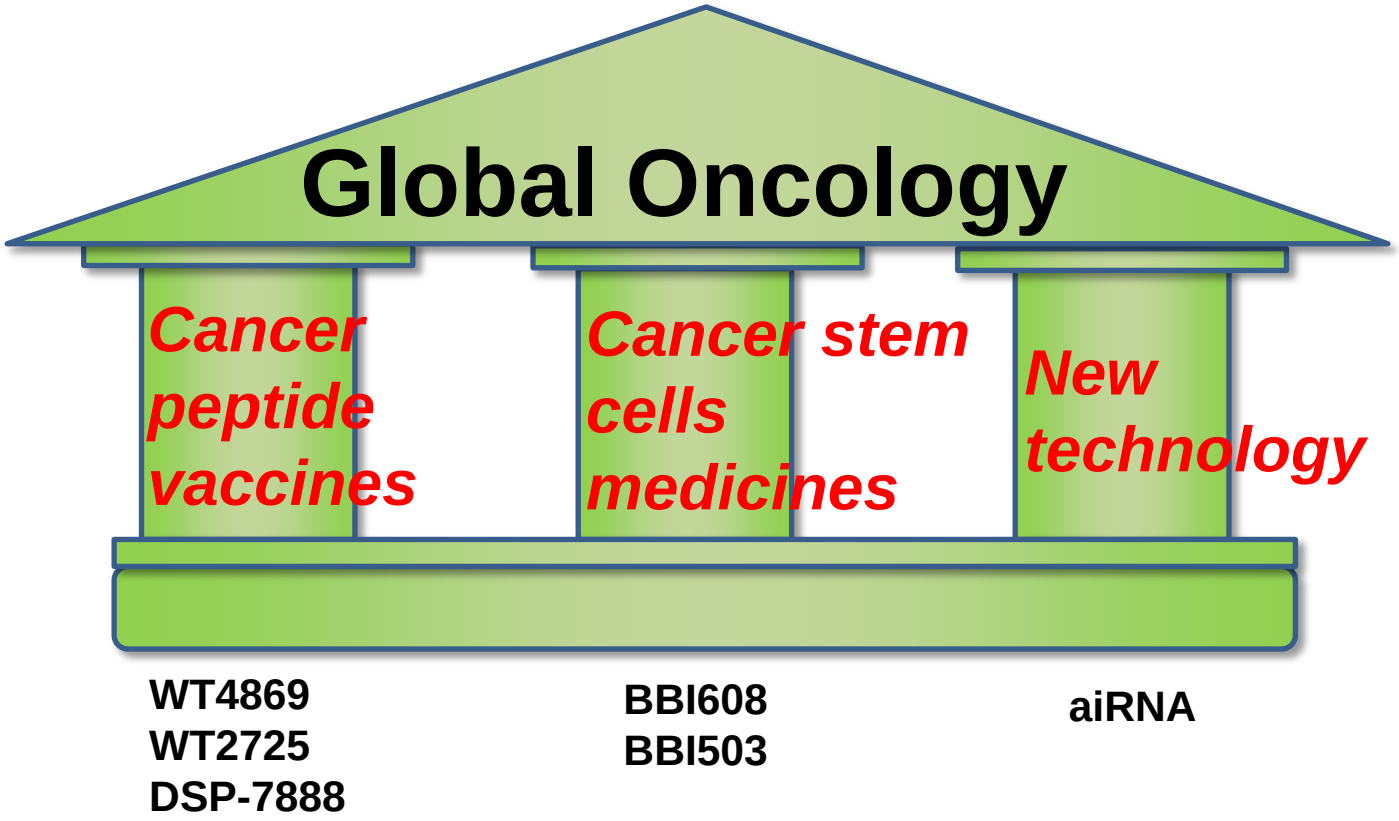
Internals: Change in business climate

- ✓ US market became accessible (2009)
- ✓ The next step following LATUDA launch (2011), post LATUDA strategy, pipeline enrichment

- ➢ A pillar for Sumitomo Dainippon Pharma Group on a long-term basis
- ➢ Limited management resources

Oncology area：R&D strategy

- **Advanced technology to capitalize on our strengths**
  - ✓ Cancer stem cells medicine
  - ✓ Cancer peptide vaccines
  - ✓ New technology (aiRNA, etc.)
- **Boston Biomedical, Inc. and DSP cancer institute together expand drug discovery activities through cooperation and competition**



Oncology area: Development pipeline

●Napabucasin (BBI608)

Phase 3 :

- ✓ Colorectal cancer (Monotherapy) (CO.23 study)
- ✓ Gastric and Gastro-esophageal junction adenocarcinoma (Combination therapy) (BRIGHTER study)

→ **Approval application planned for FY2017**

Candidate for new pivotal studies:

- ✓ Colorectal cancer (Combination therapy) (from 246 study)
- ✓ Solid tumors (Non-small cell lung cancer, Pancreatic cancer, Ovarian, Breast cancer) (Combination therapy) (from 201study)
- ✓ Pancreatic cancer (Combination therapy) (from 118 Study)

● BBI503:

- ✓ Plan pivotal study in FY2016

→ **Approval application planned for FY2018**

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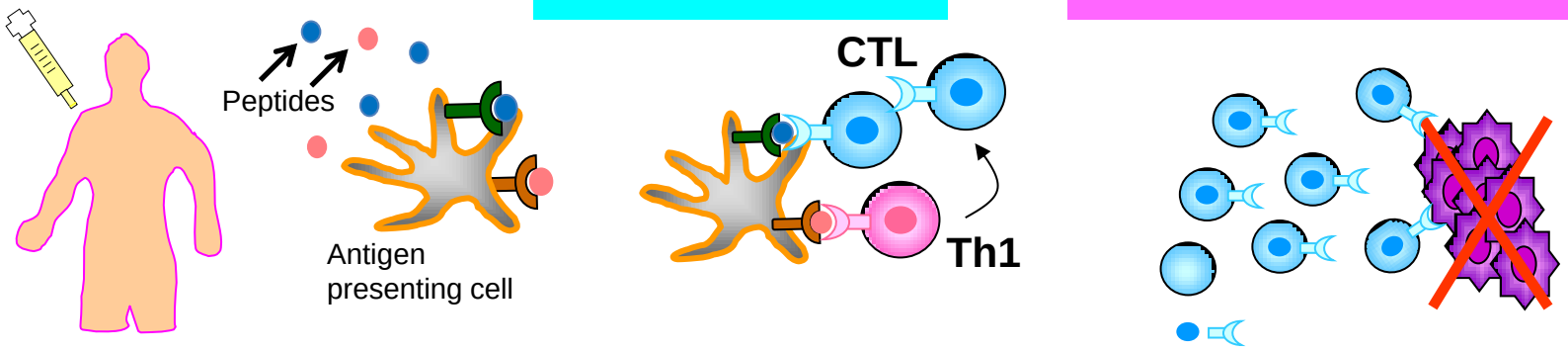
Cancer peptide vaccine (DSP-7888)

Product code	Characteristics	Indications
DSP-7888	Therapeutic peptide vaccine candidate containing peptides which induce WT1-specific cytotoxic T lymphocytes (CTLs) and helper T cells	Myelodysplastic syndromes (MDS), Solid tumors, Hematologic malignancies

- **MOA of DSP-7888**

DSP-7888 = CTL- inducing peptide + Helper T cell- inducing peptide



Injection of DSP-7888 ▶ Peptides are presented on antigen presenting cell ▶ CTLs and helper T cells are induced. Helper T cell enhance the activity of CTL ▶ Clonally expanded WT1-specific CTLs attack WT1-expressing cancer cells **Cancer cell killing**

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Cancer peptide vaccine (WT4869/WT2725)

Product code	Characteristics	Indications
WT4869	Therapeutic cancer peptide vaccine candidate derived from Wilms' tumor gene 1 (WT1) protein	Myelodysplastic syndromes (MDS), Solid tumors
WT2725	Therapeutic cancer peptide vaccine candidate derived from WT1 protein	Solid tumors, Hematologic malignancies

- **Phase 1/2 study of WT4869 in Patients with Myelodysplastic Syndromes (MDS)**

Clinical response (N=22, evaluable)

ORR*	18.2% (4/22)
DCR	59.1% (13/22)

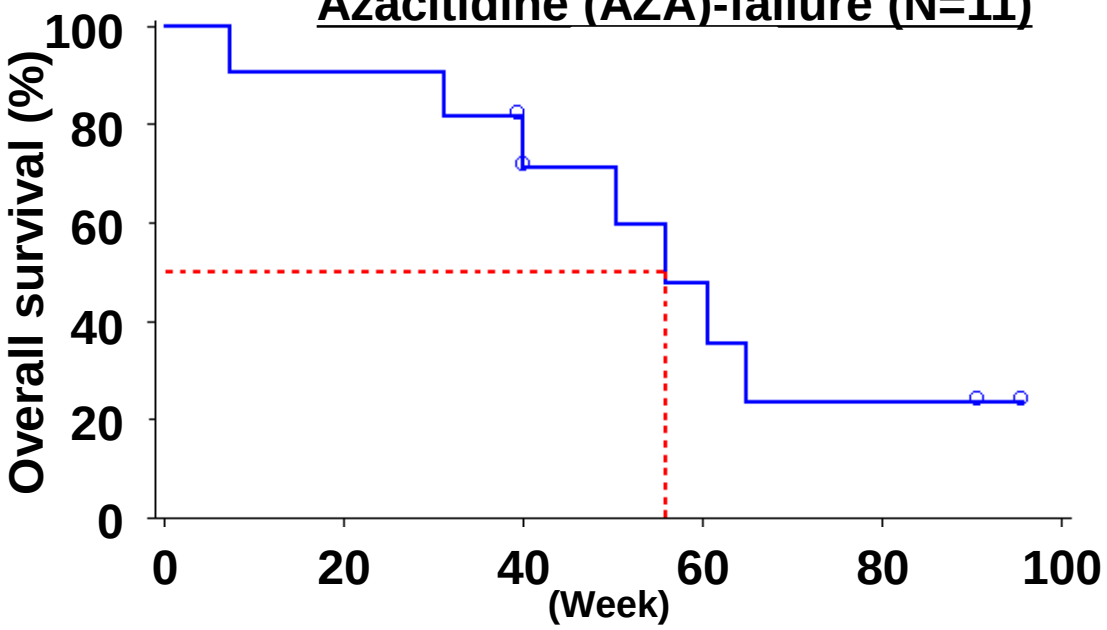
* included hematological improvement

Median OS of higher risk AZA failure

WT4869 (N=11): 55.71 week (aprox. 13 months)[1)]

Historical data (N=435): 5.6 months[2)]

Overall survival (OS) of higher risk Azacitidine (AZA)-failure (N=11)



1) ASH 2015 (Abstract 2868) Suzuki T et. al.
2) J Clin Onclol 2011;29:3322-7 Prebet T et. al.

WT1: Wilms' tumor gene 1
CTL: Cytotoxic T lymphocyte

Regenerative medicine / Cell therapy: R&D strategy

- **High unmet medical needs and incurable diseases**
- **An area of big market potential**
- **Our longstanding R&D expertise and our group strengths can be utilized in this area**

  ⇒ Cooperate with regulatory authority, academia and venture firms to promote development

- **Progress & change in the last 12 months**
  - ✓ Pharmaceuticals and Medical Devices Act became effective
  - ✓ SB623 (for chronic stroke)： A Ph2b study begun in the U.S. [156 patients (3-group double-blinded test)]
  - ✓ Age-related macular degeneration: suspension chosen as formulation
  - ✓ Parkinson's disease: Study begun on evaluation method of auto-culture (selected as an AMED project)
  - ✓ iPS cells: Production begun of master cell bank for clinical iPS cells
  - ✓ A cell production center (CPC) under construction in Kobe (estimated investment: 2.2 billion yen)

Regenerative medicine / Cell therapy of Business Plan

(Updated December 2015)

	Partnering	Region (planned)	Cell type	Schedule for practical use (Calendar year)					
				2015	2016	2017	2018	2019	2020
Chronic Stroke	**SanBio**	North America	Allo MSC	Ph2b			Ph3		Approval Target
AMD (age-related macular degeneration)	**Healios RIKEN**	Japan	Allo iPS cell	Clinical research (autologous / allogeneic)		Investigator initiated clinical trial			Approval Target
Parkinson's disease	**Kyoto Univ CiRA**	global	Allo iPS cell		Clinical research or clinical trial				
Retinitis pigmentosa	**RIKEN**	global	Allo iPS cell				Investigator initiated clinical trial		
Spinal Cord Injury	**Keio Univ, Osaka National Hospital**	global	Allo iPS cell				Clinical research (allogeneic)		

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Product Launch Plan (Updated December 2015)

Area	FY2015 (Launched)	FY2016	FY2017	FY2018	FY2019～FY2021	
Japan	REMITCH® (Pruritus (chronic liver disease) (Promotion) Trulicity® (GLP-1 recepter agonist) (Marketing)	※ EPI-743 (Leigh syndrome)	ranirestat (Diabetic neuropathy) napabucasin (Gastric and Gastro-esophageal junction adenocarcinoma)	LONASEN® (Schizophrenia / Transdermal patch) TRERIEF® (Parkinsonism in Dementia with Lewy Bodies)	Lurasidone (Schizophrenia / Bipolar I depression / Bipolar maintenance) napabucasin (Colorectal cancer, etc.) BBI503 (Solid tumors) DSP-7888 (Solid tumors/ Hematologic cancer)	DSP-1747 (NASH) DSP-6952 (IBS with constipation, Chronic idiopathic constipation iPS cell-derived RPE cells (Age-related macular degeneration)
U.S.	APTIOM® (Epilepsy-monotherapy)		napabucasin (Gastric and Gastro-esophageal junction adenocarcinoma) SUN-101 (COPD)	dasotraline (ADHD)	SB623 (Chronic stroke) DSP-2230 (Neuropathic pain) SEP-363856 (Schizophrenia) dasotraline (BED)	napabucasin (Colorectal cancer, etc.) BBI503 (Solid tumors) DSP-7888 (Solid tumors/ Hematologic cancer)
China		LONASEN® (Schizophrenia) CALSED® (Small cell lung cancer)		lurasidone (Schizophrenia)		

: P&N
: Oncology
: Liver/ Digestive
: Respiratory

New Chemical Entities
New Indication , etc.

※ Development strategy under consideration

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Summary

Serve medical community with most leading-edge technology, and grow to be an R&D-based and globally operating pharmaceuticals group

- **Concentrate to the target disease and research area**

  Identify targets to fill unmet medical needs

Focus Therapeutic Areas

- Psychiatry & Neurology
- Oncology

New fields

- Disease fields where no approved drugs exist
- Regenerative medicine / Cell therapy

- **Stage-focused R&D strategy and management**

Early drug discovery
Value creation (0 → 1)
Venture approach
Individuality-focused
Innovation-oriented

+

Late discovery, development
Value enhancement (1→10)
Medium-sized pharma approach
Team strength-focused
Speed/POC-oriented

=

Emphasis on speed and quality

✓Contribute to medicine by preempting science and technology advances and commercializing them

✓ Take on the challenge of first-in-class drug discovery

✓ Promote open innovation and collaboration (joint R&D, in-licensing)

Looking ahead...

Venture into new areas by the application of most advanced science and technology

- Era of nucleic acid medicine and cell therapy is sure to come
- Small molecule drug discovery will make progress

- Cancer will no longer be an incurable disease in near future
- Population aging and stressful life will increase cases of psychiatric diseases as well as Alzheimer's and other neurological diseases, causing a serious social problem

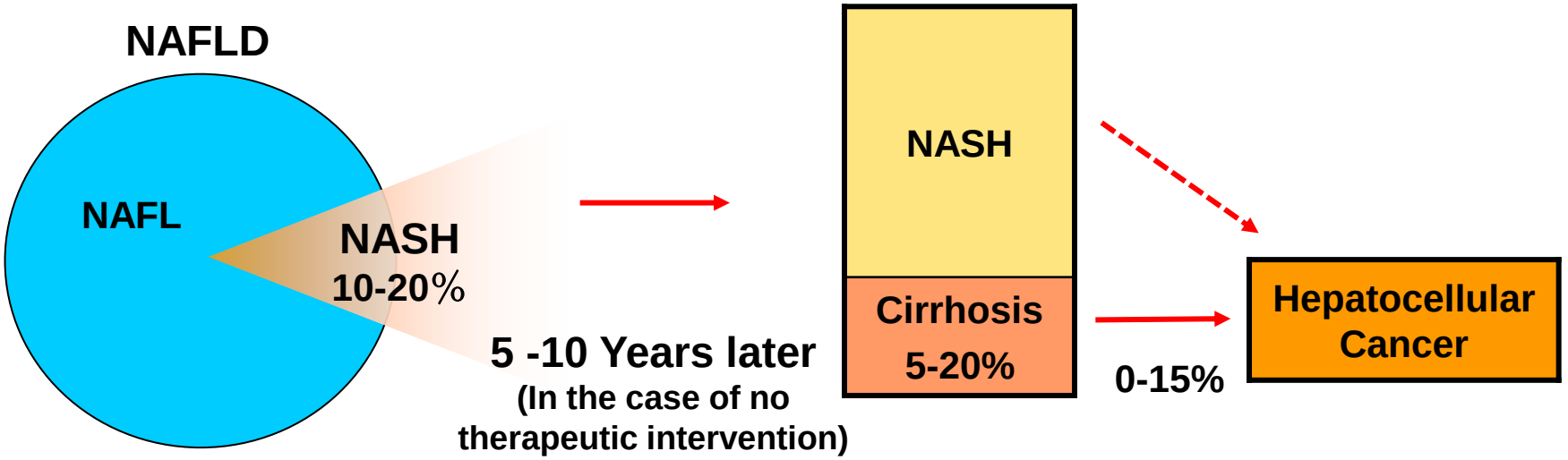
- Treatment of rare or segmented diseases will advance
- Integration technologies will improve diagnosis, prevention and treatment

Development products topics

Nobuyuki Hara, Ph.D.
Executive Officer
Deputy Executive Director, Drug Development

Obeticholic acid (DSP-1747) and NASH

- **Mode of Action for DSP-1747: FXR agonist**
  - ✓ **Improvement on NASH is expected by improvement of liver accumulation, anti-inflammatory effect, and anti-fibrosis effect**
- **Prognosis of NASH/NAFLD[1)]**



NASH

- **Number of NASH patients in Japan: approximately 200 to 300 millions (estimate 2 to 3% of adult population)[1)]**
- **Five to 20 % of NASH progress to cirrhosis in 5 to 10 years.**
- **The 5-year survival rates of NASH cirrhosis is comparable to that of Hepatitis C[2)]**

NAFLD: Non-Alcoholic Fatty Liver Disease
NAFL: Non- Non-Alcoholic Fatty Liver
NASH: Non-Alcoholic Steatohepatitis

1) Japan Society of Hepatology : NASH/NAFLD practice guideline 2015
2) The Journal of the Japan Medical Association: 2010; 139(9); 1880

DSP-1747 Phase II study

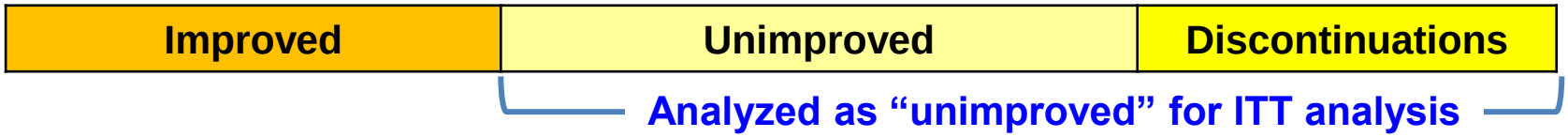
- **Study Design**
  - ✓ Randomized, Double-blind, Parallel-group, Placebo-controlled Study of DSP-1747 in Patients with NASH
  - ✓ The number of dosed subjects: 200 (50 subjects/arm)
  - ✓ Arms: DSP-1747 10mg/day, 20mg/day, 40mg/day, and Placebo
  - ✓ Primary endpoint: Improvement of liver pathological findings from baseline to week 72
    The improvement was defined as: a) No worsening of Kleiner's fibrosis staging, and b) Decrease in NAFLD activity score (NAS) by 2 or more points.
    - Factors of NAS are steatosis (3 points), inflammation (3 points) and ballooning (2 points); total NAS is 8 points at maximum
    - Evaluating liver fibrosis with Kleiner's fibrosis staging (stage 0-4). Stage 4 was excluded from the study because stage 4 is liver cirrhosis.

DSP-1747 Phase II study: Results

- **Efficacy: The percentages of improvement increased dose dependently**
  [Primary analysis with Stratified Cochran-Armitage test with multiple contrast coefficients: p=0.053]

＜Primary endpoint＞

Arms（ITT）	Placebo（N=50）	10mg/day（N=50）	20mg/day（N=50）	40mg/day（N=50）
Improved[*1]	10（20%）	11（22%） p=0.807[*2]	14（28%） p=0.338[*2]	19（38%） p=0.0496[*2]
Decrease in NAS by 2 or more points	12	13	17	20
No worsening of liver fibrosis	31	30	29	28
Unimproved ( ): number of discontinuations	40（5）	39（6）	36（6）	31（13）



< Analyzed with the subjects who conducted 2nd biopsy at 72 W >

Arms	Placebo	10mg/day	20mg/day	40mg/day
Improved	10/45 (22.2%)	11/44 (25.0%) P=0.764[*2]	14/44 (31.8%) P=0.291[*2]	19/37 (51.4%) P=0.006[*2]

[*1] The subjects for whom the fibrosis stage or NAS or both at Week 72 were missing were classified as “unimproved”
[*2] vs placebo, CMH test stratified by baseline fibrosis stage, There is no adjustment for multiplicity.

DSP-1747 Phase II study：Efficacy (liver fibrosis)

Arms (ITT)	Placebo	10mg/day	20mg/day	40mg/day
No worsening of liver fibrosis	**31/50 (62%)**	**30/50 (60%)**	**29/50 (58%)**	**28/50 (56%)**
Fibrosis improvement (1 stage or more improvement of liver fibrosis)*1	**12/50 (24.0%)**	**12/44 (27.3%)**	**15/49 (30.6%)**	**10/49 (20.4%)**

＜Analyzed with the subjects who conducted 2nd biopsy at 72 W*2＞

Arms	Placebo	10mg/day	20mg/day	40mg/day
No worsening of liver fibrosis	31 / 45 (68.9)	30 / 44 (68.2%)	29 / 44 (65.9%)	28 / 37 (75.7%)
Fibrosis improvement (1 stage or more improvement of liver fibrosis)*3	12 / 45 (26.7%)	12 / 38 (31.6%)	15 / 43 (34.9%)	10 / 36 (27.8%)

*1 Percentages are based on the number of ITT subjects for whom the Kleiner's fibrosis stage at baseline are not stage 0.
*2 Post-hoc analyses.
*3 Percentages are based on the number of the subjects, who conducted 2nd biopsy at 72 W , for whom the Kleiner's fibrosis stage at baseline are not stage 0.

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DSP-1747 Phase II study：Efficacy (NASH resolution, ITT)

Arms (ITT)	Placebo (N=50)	10mg/day (N=50)	20mg/day (N=50)	40mg/day (N=50)
Non-NASH in Matteoni classification*1	0 (0%)	1 (2%)	3 (6%)	3 (6%)
p value (vs placebo)*2		p=0.317	p=0.075	p=0.079
Resolution of hepatocyte ballooning and residual inflammation (0-1)*3	2 (4%)	2 (4%)	4 (8%)	7 (14%)
p value (vs placebo)*2		p=1.000	p=0.379	p=0.082
Resolution of hepatocyte ballooning	3 (6%)	4 (8%)	7 (14%)	9 (18%)
p value (vs placebo)*2		p=0.694	p=0.163	p=0.064*4

*1 NASH diagnosis method which is used in Japan widely. NAFLD (Non-Alcoholic Fatty Liver Diseases) patients are classified in type 1 to 4 and type 3 and 4 are diagnosed as NASH.

*2 vs placebo, CMH test stratified by baseline fibrosis stage. There is no adjustment for multiplicity.

*3 As a part of surrogate histological primary endpoint of pivotal Phase 3 study planned by Genfit, NASH resolution is defined as “ballooning = 0, inflammation = 0-1” (press release by Genfit on Nov.16, 2015)

*4 Analyzed with the subjects who conducted 2nd biopsy at 72 W as post-hoc analysis: placebo 3/45 (6.7%) vs 40mg/day 9/37 (24.3%), p=0.030 (vs placebo, CMH test stratified by baseline fibrosis stage. There is no adjustment for multiplicity)

DSP-1747 Phase II study: Safety

Adverse events reported more than 10% incidence in any DSP-1747 arms

Adverse events (PT; Preferred Terms)	Placebo N=50 n (%)	10 mg/day N=50 n (%)	20 mg/day N=50 n (%)	40 mg/day N=50 n (%)
Constipation	3 (6%)	3 (6%)	5 (10%)	2 (4%)
Dental caries	1 (2%)	1 (2%)	1 (2%)	5 (10%)
Nasopharyngitis	27 (54%)	21 (42%)	23 (46%)	21 (42%)
Influenza	4 (8%)	2 (4%)	8 (16%)	4 (8%)
Diabetes mellitus	2 (4%)	3 (6%)	6 (12%)	3 (6%)
Insomnia	2 (4%)	0	5 (10%)	0
Pruritus	4 (8%)	10 (20%)	12 (24%)	25 (50%)

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NASH Diagnostic Marker：Exploratory Study

- **Original article "Identification of novel noninvasive markers for diagnosing nonalcoholic steatohepatitis and related fibrosis by data mining" ("Hepatology" accepted on Sep. 21)**
  http://onlinelibrary.wiley.com/doi/10.1002/hep.28226/abstract;jsessionid=42FA284E0BD5D00BE38F2B50947DB3BC.f01t03

  - ✓ **Collaborative study with Saiseikai Suita Hospital**
  - ✓ **The purpose of the study was to identify noninvasive diagnosing marker differentiating NASH or NASH-related liver fibrosis from NAFLD patients.**
  - ✓ **261 blood molecules were examined for 132 Japanese NAFLD patients.**
  - ✓ **The two markers by using combinations of a few molecules respectively appropriate to diagnosing NASH and NASH-related liver fibrosis were established.**
  - ✓ **Reproducibility of diagnosis by the NASH-related liver fibrosis marker has been confirmed by examinations of an independent validation group at the same hospital consisting of 62 Japanese NAFLD patients.**
  - ✓ **While the novel markers seem promising, the study has several limitations due to single institution and limited number of subjects => Additional multicenter study is needed**

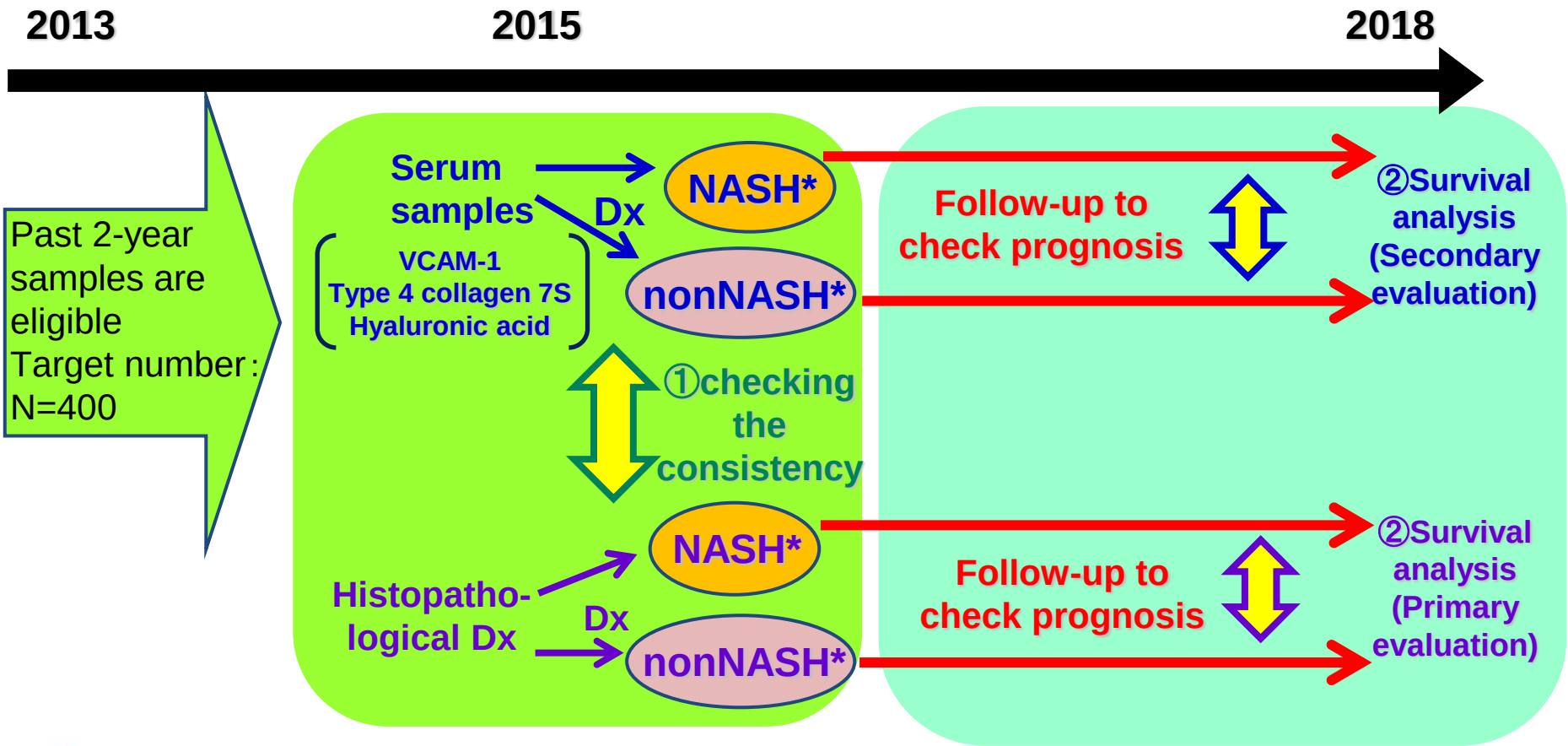
Markers for diagnosing NASH related liver fibrosis	Clinical Parameters/Blood molecules	AUROC of Exploratory Group	AUROC of Validation Group
FM-fibro Index (Novel)	VCAM1, Type IV collagen 7S	**0.896**	**0.852**
	VCAM1, Hyaluronic acid	**0.867**	**0.878**
	Hyaluronic acid, Type IV collagen 7S	**0.917**	**0.892**
FIB4 Index (Existing)	Age, AST, ALT, Platelet	**0.809**	**0.831**

AUROC: Area Under the Receiver Operator Characteristic curve; which is used as a basis for evaluation of diagnostic markers.
If the value is closer to "1" , it means more sensitive marker for diagnosis.

Clinical Research on NASH diagnosis markers

① External validation study of diagnostic accuracy for NASH by the serum biomarkers vs histopathological Diagnosis (Dx): cross-sectional, retrospectively collected samples

② Investigation on the prognosis of NASH/NAFLD

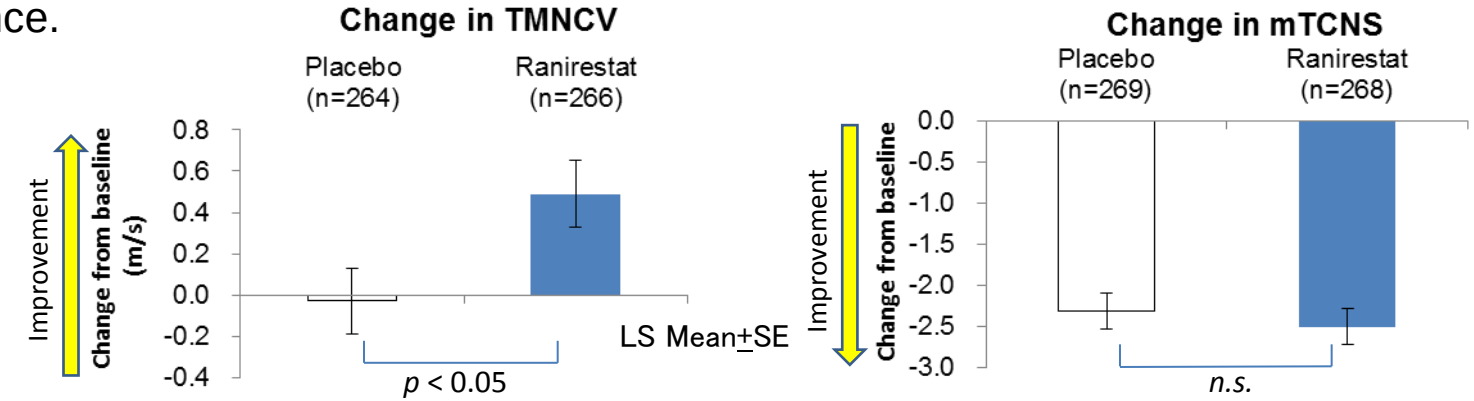


* NASH here means “NASH with fibrosis (type 4 patients of Matteoni’s classification)”

Ranirestat (AS-3201) Phase III study top-line results

- **Study design**
  - ✓ Randomized, double-blind, parallel-group, placebo-controlled study with diabetic neuropathy patients
  - ✓ Arms and subject number: Ranirestat 40 mg/day: 277 pts, Placebo: 278 pts
  - ✓ Treatment period:1 year treatment
  - ✓ Co-primary endpoints: Changes in tibial motor nerve conduction velocity (TMNCV) and modified Toronto Clinical Neuropathy Score (mTCNS)
- **Study results**

  Efficacy: In comparison with placebo treatment, ranirestat 40 mg/day treatment significantly improved the TMNCV although did not improve the mTCNS with statistical significance.



  - ✓ Safety: The incidences of TEAEs and treatment-related TEAEs in 40mg/day treatment group were comparable to those in placebo treatment group, respectively.

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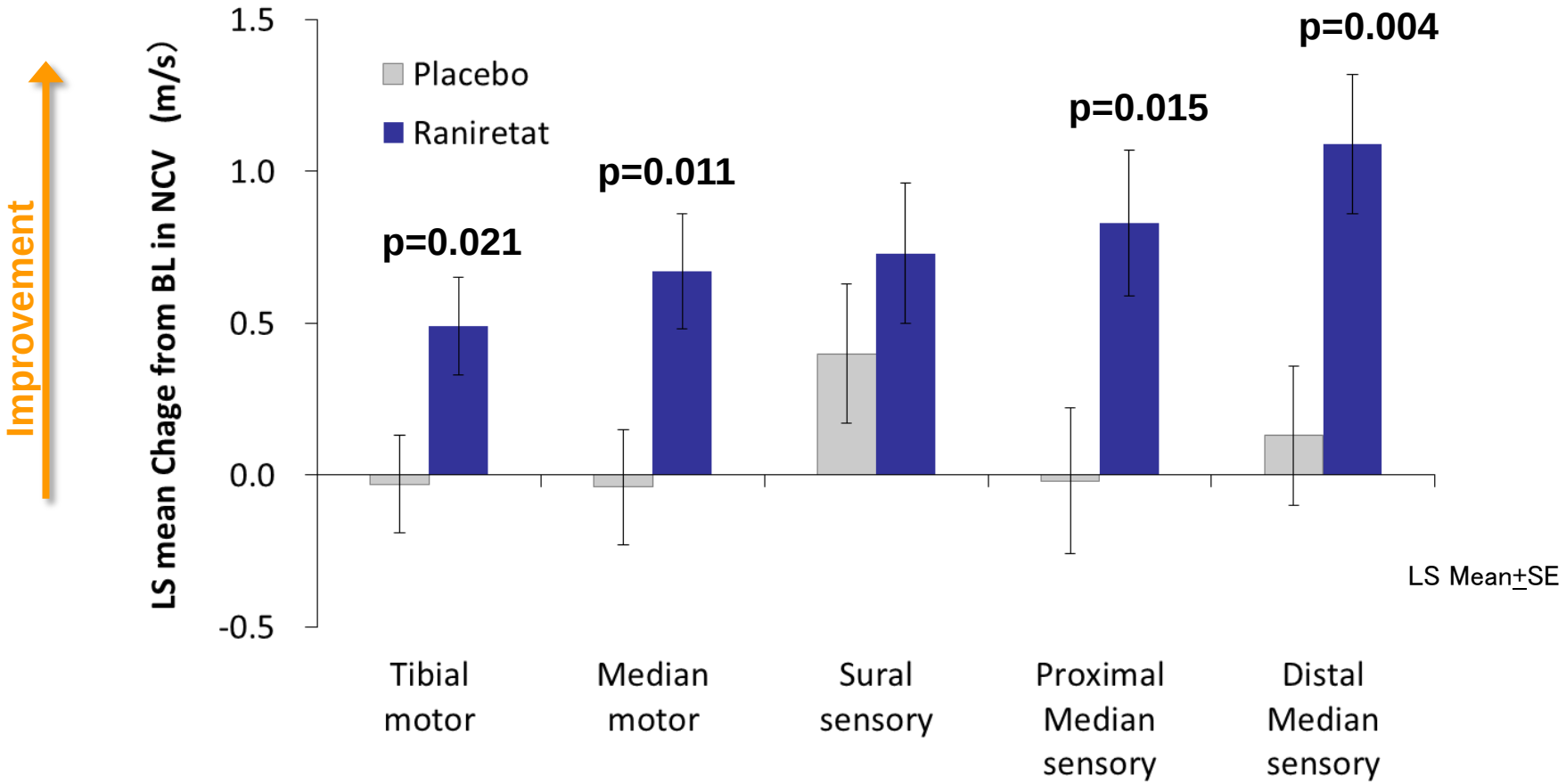
p-value were calculated using ANCOVA with the baseline value as a covariate

Ranirestat (AS-3201) Phase III study results



- In comparison with placebo, ranirestat 40 mg/day treatment significantly improved not only NCV of tibial motor nerve, but also other motor and sensory nerves
- Additional data analysis ongoing, development strategy under consideration

p-value were calculated using ANCOVA with the baseline value as a covariate

Lurasidone: Schizophrenia
New Phase III study plan

Study Design	Randomized, double-blind (6 weeks) , placebo-controlled, parallel-group study in patients with Schizophrenia
Countries	Multinational study including Japan
Primary efficacy variable	Change from baseline in PANSS total score at week 6
Target sample size	About 450 – 550 subjects
Study period	About 2.5 years from Clinical trial notification (FY2015) to Data base lock (FY2018)

- Target Doses: 40mg/d and 80mg/d
- Simultaneous J-NDA submission with Bipolar I depression and Schizophrenia is planned (To avoid the off label use when BP indication would be approved prior to Schizophrenia)
- The first study collaborated with Sunovion since GCD establishment
- Based on the past experiences, the study will be conducted in the countries which can be expected speedy enrollment with high quality

Development products topics: Summary

- **DSP-1747**
  - ✓ NASH Phase II study results:
    - Efficacy: Improvements of histological findings were shown in 40mg/day
    - Safety: Incidences of reported adverse events of DSP-1747 groups were generally similar to placebo group except pruritus
  - ✓ Tolerability against pruritus needs to be improved at Phase 3
- **Ranirestat**
  - ✓ Phase III study with diabetic neuropathy patients results: in comparison with placebo treatment, ranirestat 40 mg/day treatment significantly improved the TMNCV although did not improve the mTCNS with statistical significance.
  - ✓ Development strategy under consideration
- **Lurasidone hydrochloride**
  - ✓ New Phase III study with schizophrenia patients will be initiated in FY 2015

Oncology

Chiang J. Li MD FACP

Executive Officer, Head of Global Oncology for
Sumitomo Dainippon Pharma Group
President, Chief Executive Officer and Chief Medical Officer,
Boston Biomedical, Inc.

GLOBAL ONCOLOGY

A LEADER IN MEDICAL INNOVATION FOR TARGETING CANCER STEM CELLS

OUR TEAM, SCIENCE, AND STRATEGY

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Location and Organization in Global Oncology

- Oncology Clinical Development Unit (OCU)
- Oncology Marketing Unit (OMU)
- Global Oncology Office (GOO) (Tokyo)

- DSP Cancer Institute (DCI)
- Global Oncology Office (GOO) (Osaka)

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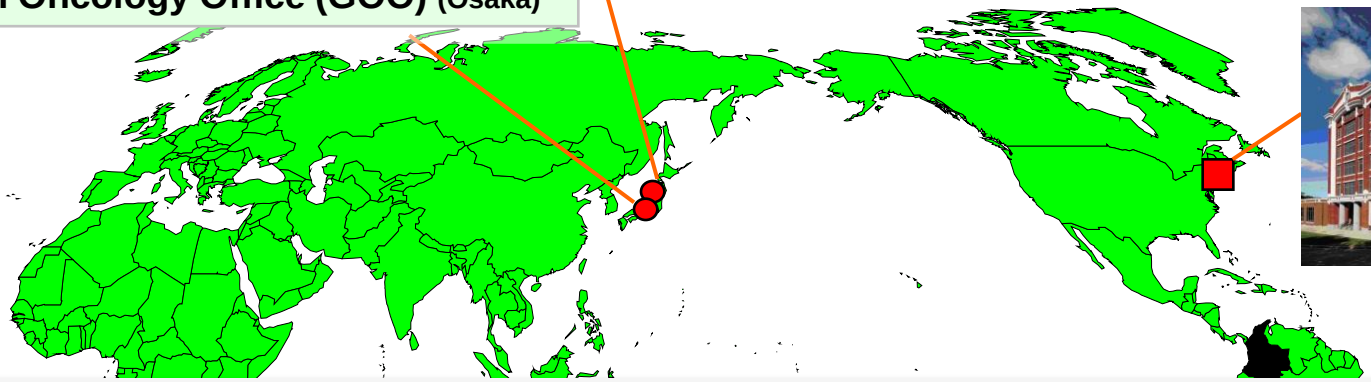
- Boston Biomedical, Inc. (BBI)
- Boston Biomedical Pharma, Inc. (BBP)
- Global Oncology Office (GOO)



	Japan	USA
Planning	GOO: Tokyo, Osaka	GOO: Cambridge
R&D	DCI: Osaka OCU: Tokyo	BBI: Cambridge
MA & Commercial	OMU: Tokyo	BBP: Cambridge

Challenges in Cancer Therapy

- **Chemotherapy/XRT**

  Mainstay for over 50 years…still so!

  Toxicity, very limited efficacy

- **Targeted Therapy (1998-)**

  Efficacy is limited for most cancer types and patients

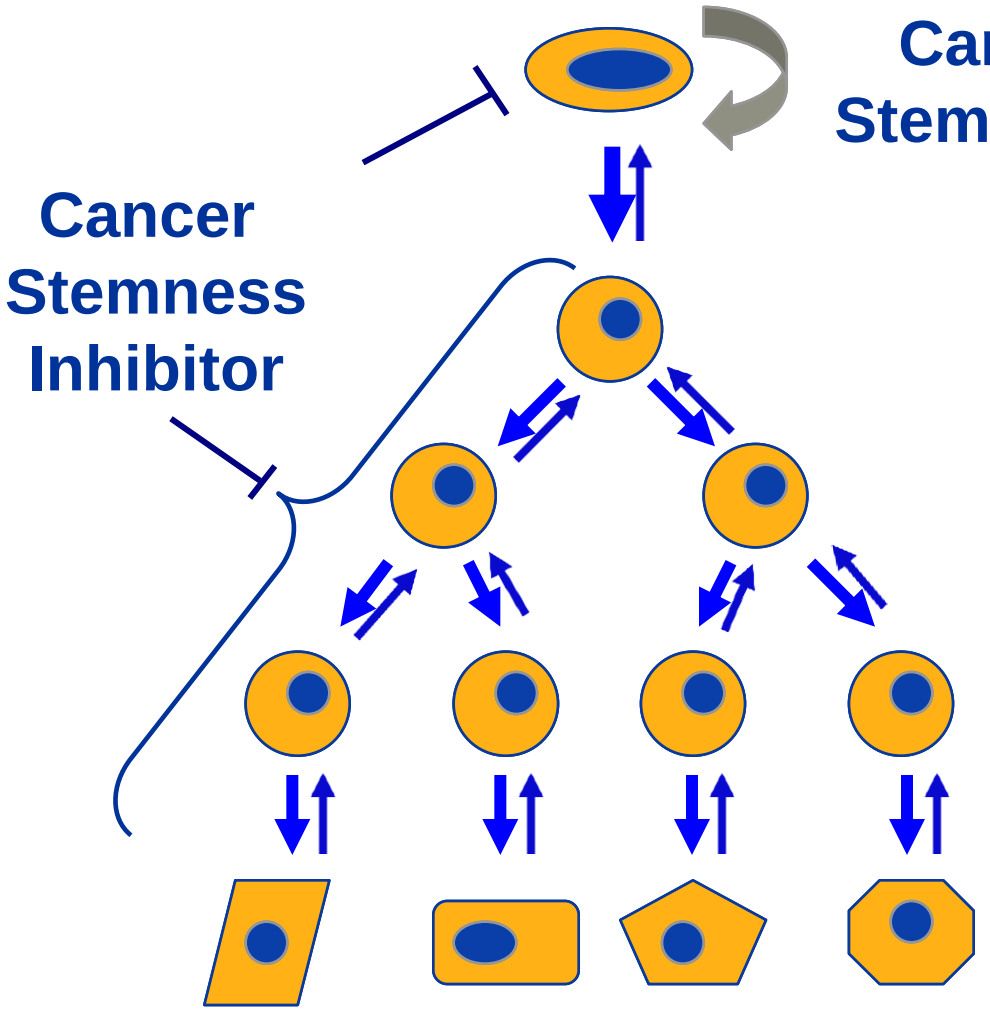
- **Cancer Immunotherapy Therapy (2015-)**

  Unprecedented prolonged disease control in about 20-30% in responding tumor types

Relapsed Cancer Enriched with CSC and Stemness Phenotype

CSC Science Update I

Targeting Cancer Stemness



Cancer Stem Cells (CSC)

Fundamentally responsible for

malignant growth

recurrence

metastasis

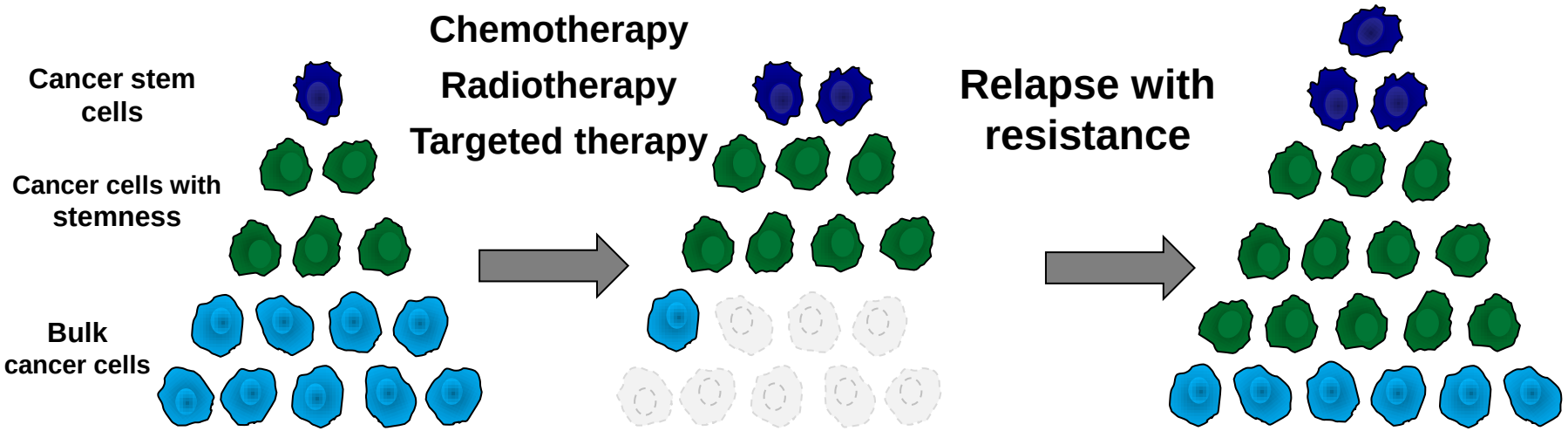
resistance

Hitron M, et al. *J Clin Oncol*. 2014;32(5 suppl), ASCO 2014 (Abstract 2530)

CSC Science Update II

Cancer Stemness Mediates Drug Resistance

- Cancer stem cells and cancer cells with stemness are resistant to current therapies
- Conventional therapies can induce cancer stemness
- Relapsed cancer, after initial response to current therapies, display stemness phenotypes



CSC Science Update III

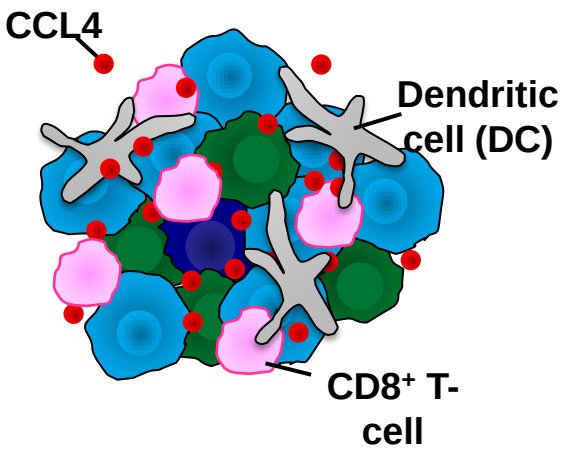
Cancer Stemness Gene Mediates Resistance to Immune Checkpoint Inhibitors

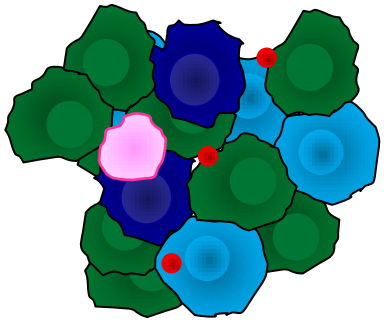
β-catenin

Chemoattractant

Infiltration

Tumor





β-catenin

Chemoattractant

Infiltration

NO active β-catenin signaling		Active β-catenin signaling
+++	Chemoattractant (CCL4)	+/-
+++	T-cell / DC infiltration	+/-

T cell-inflamed phenotype
Immune Checkpoint Inhibitors-**sensitive**

Non-T cell-inflamed phenotype
Immune Checkpoint Inhibitors-**resistant**

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Ref: S. Spranger et al Nature (2015)

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Clinical Development Strategy For Cancer Stemness Inhibitors

Quality, Timeline, and Cost

- **Novel and Efficient Clinical Trial Design and Conduct**
  - **Adaptive multi-arms Ph1/2 studies**
    - **Efficient and economical way to enrich or to kill an indication**
    - **Data-driven selection and prioritization of indications**
  - **Multiple pivotal Ph2/3 studies in parallel**
    - **"Built-in" flexibility for quality, speed and cost-efficiency**
    - **Capture broad potential of cancer stemness inhibitors**

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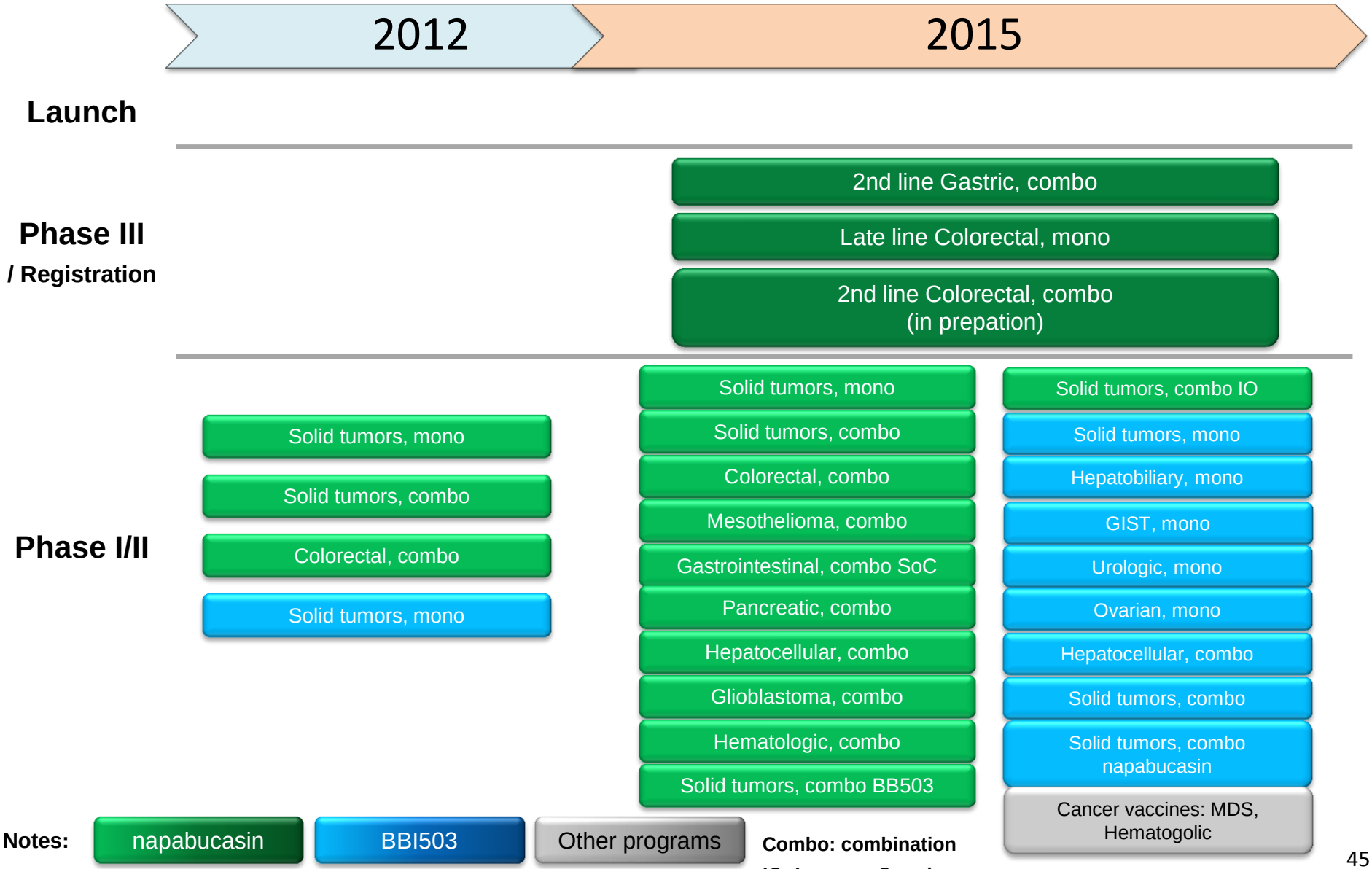
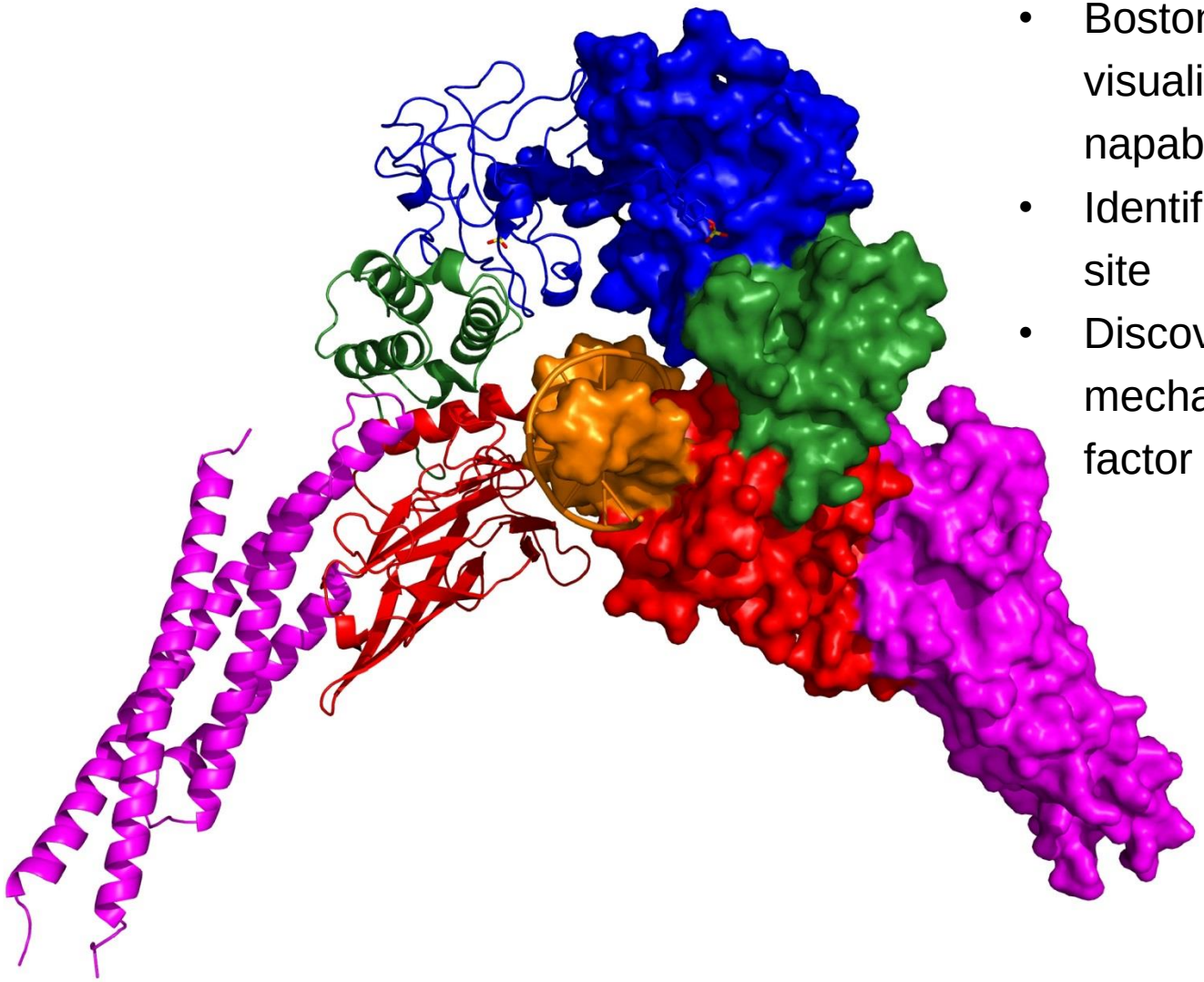
Pipeline Growth



Napabucasin

First-in-Class inhibitor of Stat3, a critical pathway in cancer stemness

Napabucasin Targets Stat3

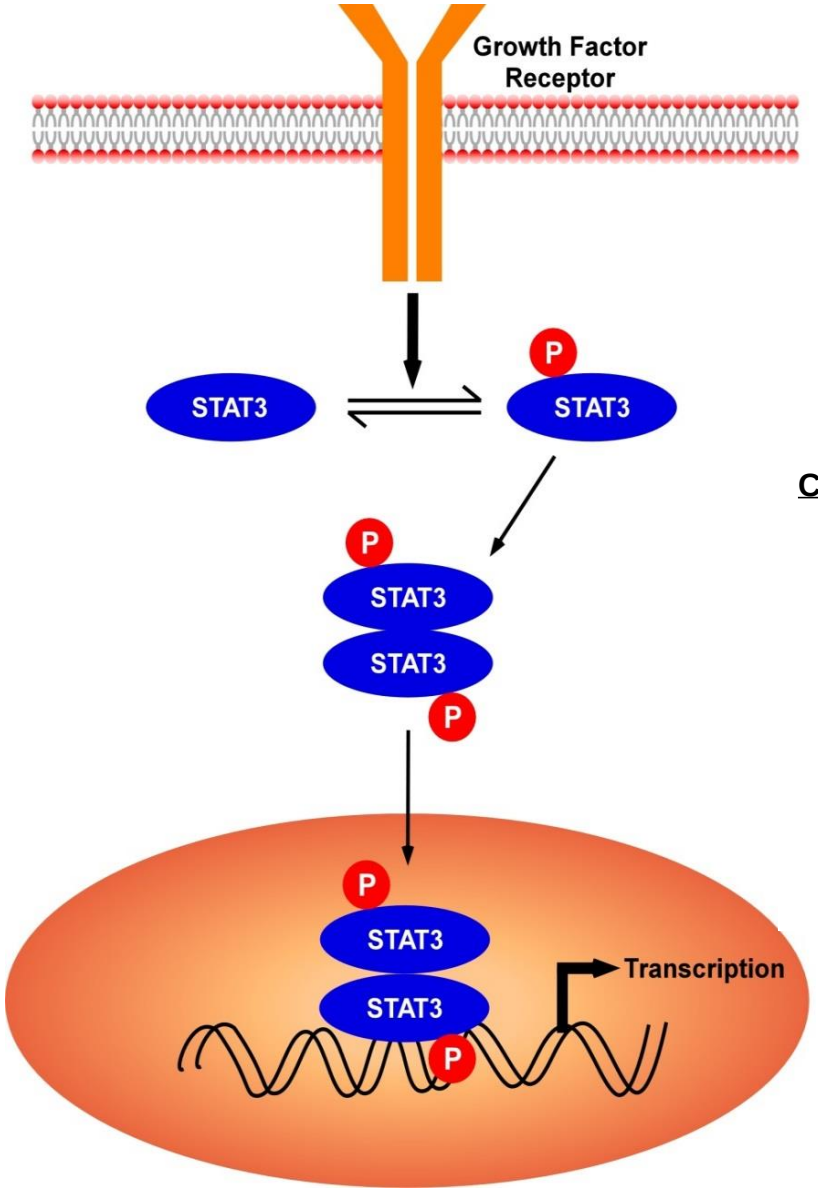


- Boston Biomedical successfully visualized the direct binding of napabucasin to p-Stat3
- Identification of a novel binding site
- Discovery of a novel mechanism of transcription factor inhibition

Stat3 is a Key Regulator of Cancer Stemness

<u>Tumor Types with Activated Stat3</u>

Breast Cancer
Head and Neck Cancer
Ovarian Cancer
Lung Cancer
Colorectal Carcinoma
Prostate Cancer
Renal Cell Carcinoma
Melanoma
Hepatocellular Carcinoma
Cervical Cancer
Sarcoma
Brain Tumors
Gastric Cancers
Multiple Myeloma
Leukemia
Lymphoma



<u>Cancer stemness</u>	<u>Immune checkpoint</u>
Nanog	**IDO1**
Sox2	**PD-L1**
c-Myc	**MHC class II**
CD133	**IL-10 (Th1 response)**
β-Catenin	**Effector T cell infiltrate**
Twist	
Zeb1	

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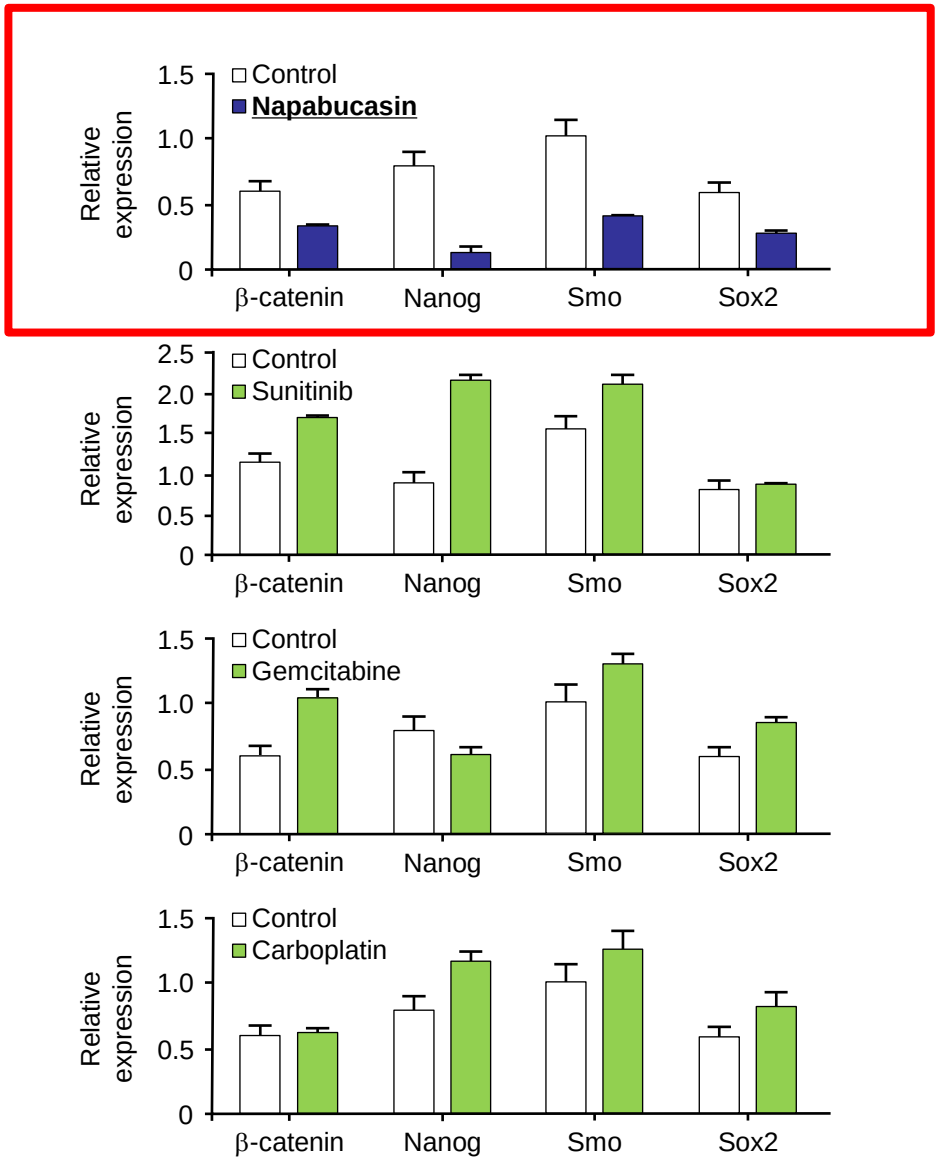
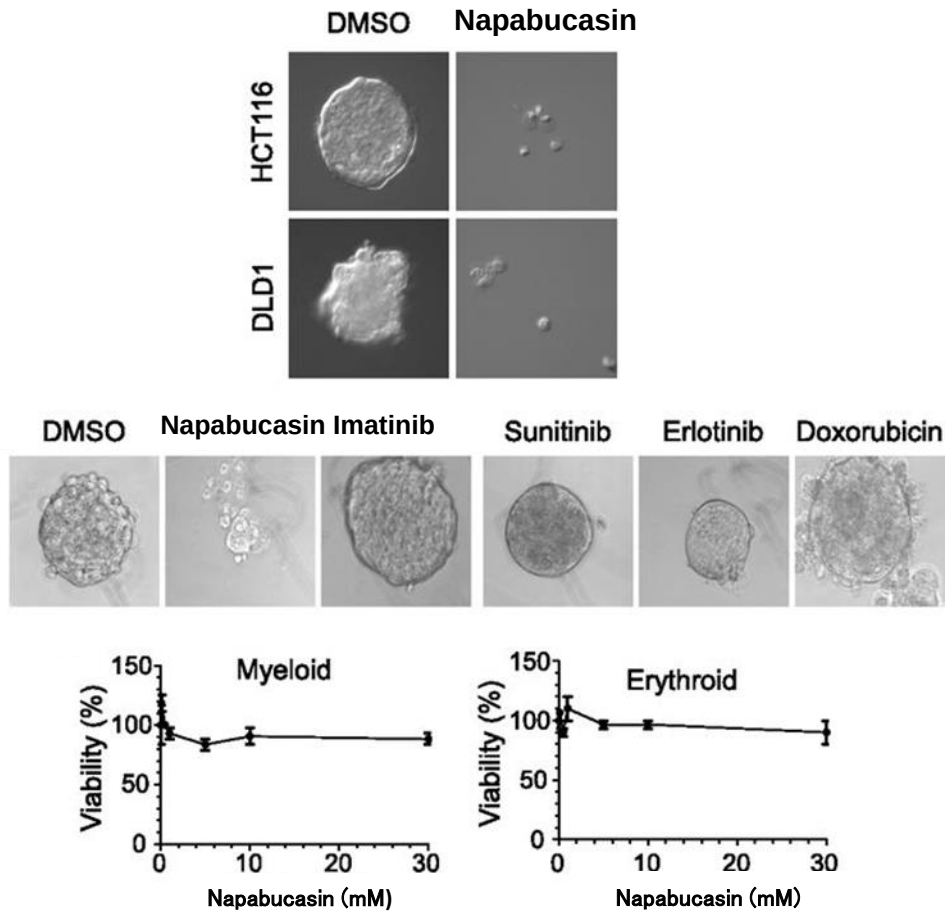
Unlike Current Therapeutics, Napabucasin Suppresses CSC Gene Expression



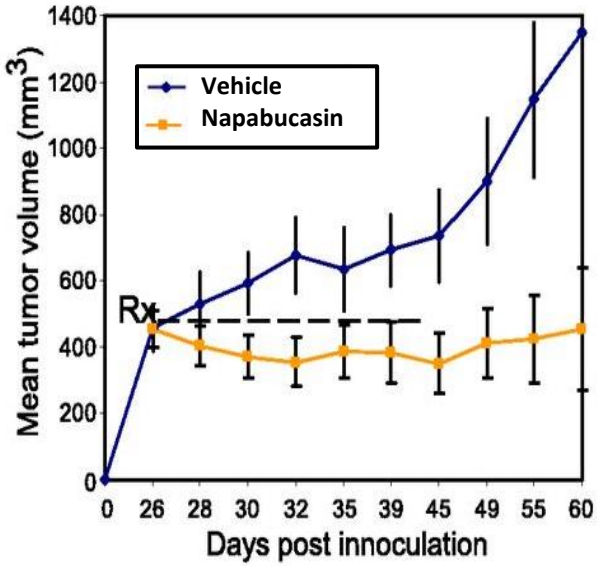
Li Y, et al. *Proc Natl Acad Sci U S A.* 2015;112(6):1839-1844.

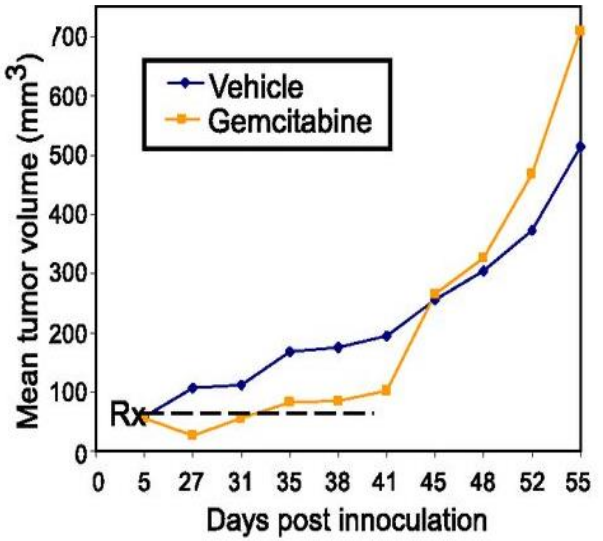
Napabucasin Targets CSC and Spares Normal Stem Cells

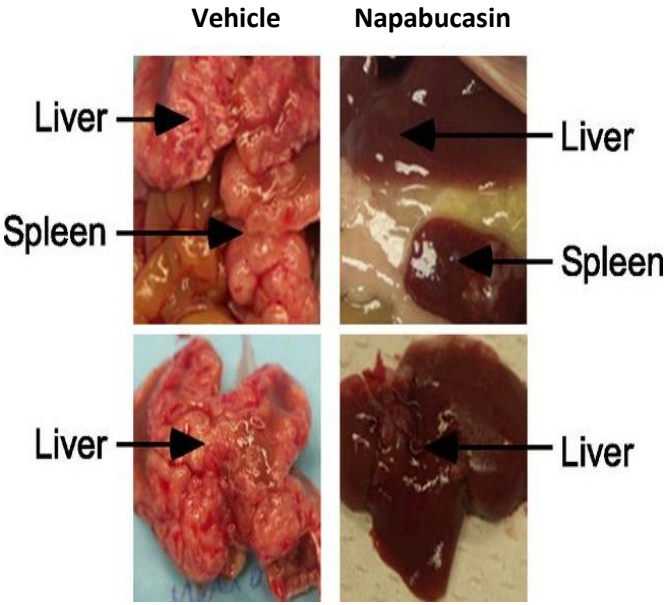


Li Y, et al. *Proc Natl Acad Sci U S A.* 2015;112(6):1839-1844.

Napabucasin Inhibits Cancer Relapse and Metastasis in Mice



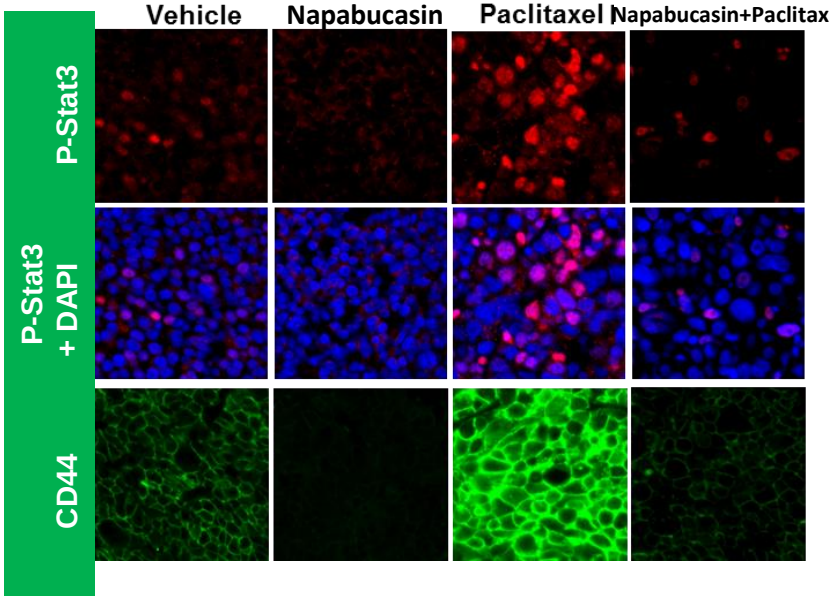




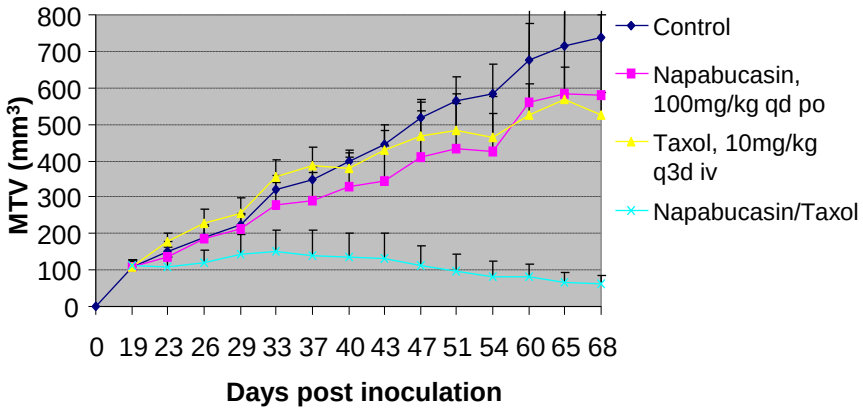
Li Y, et al. *Proc Natl Acad Sci U S A.* 2015;112(6):1839-1844.

Napabucasin Enhances Efficacy of Current Therapies (Paclitaxel as an Example)

***In-Vivo* Biomarker Response in Xenograft Tumo**



Human lung cancer xenograft, A549



Hitron M, et al. *J Clin Oncol*. 2014;32(5 suppl), ASCO 2014 (Abstract 2530)

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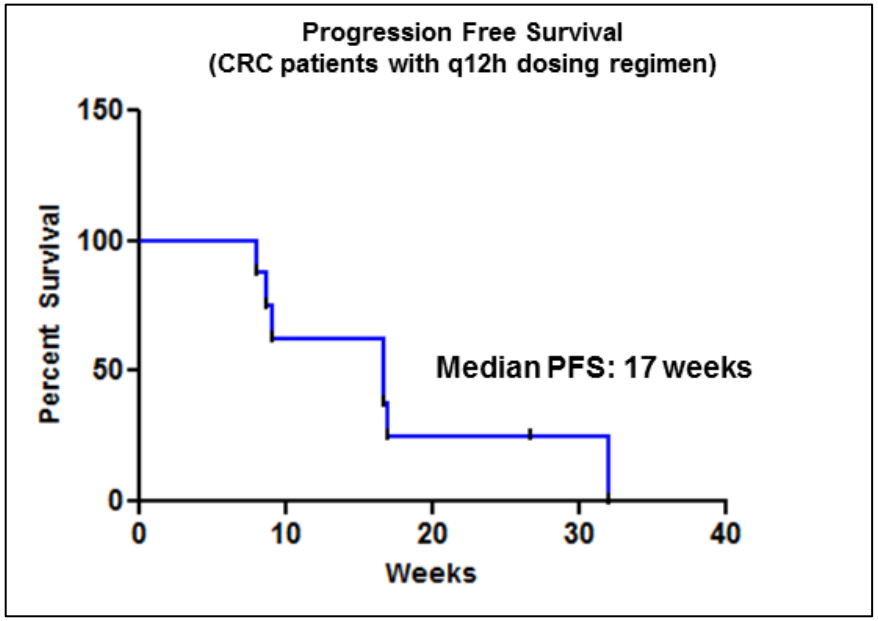
Napabucasin

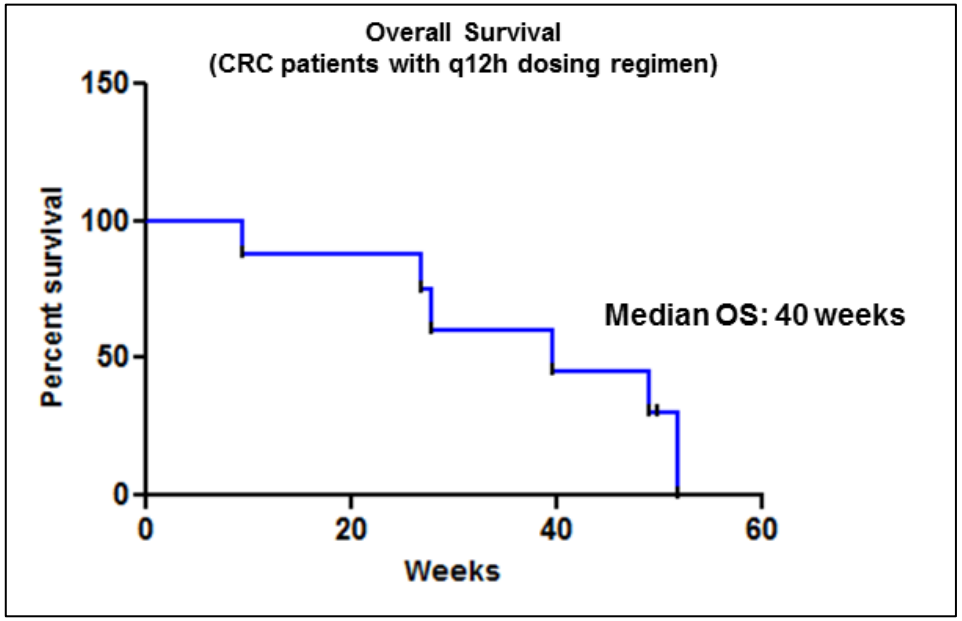
First-in-Class inhibitor of Stat3, a critical pathway in cancer stemness

― Colorectal Cancer (CRC) ―

Colorectal Cancer: Napabucasin as Monotherapy

Signs of Clinical Activity in CRC





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Jonker D, et al. *J Clin Oncol.* 2014;32(5 suppl), ASCO 2014 (Abstract 2546)

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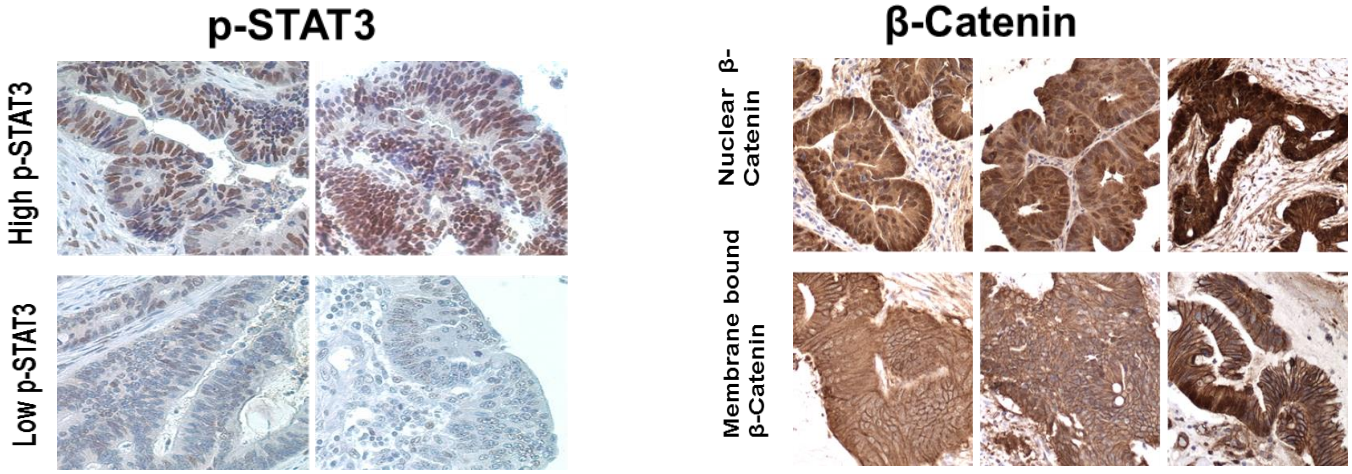
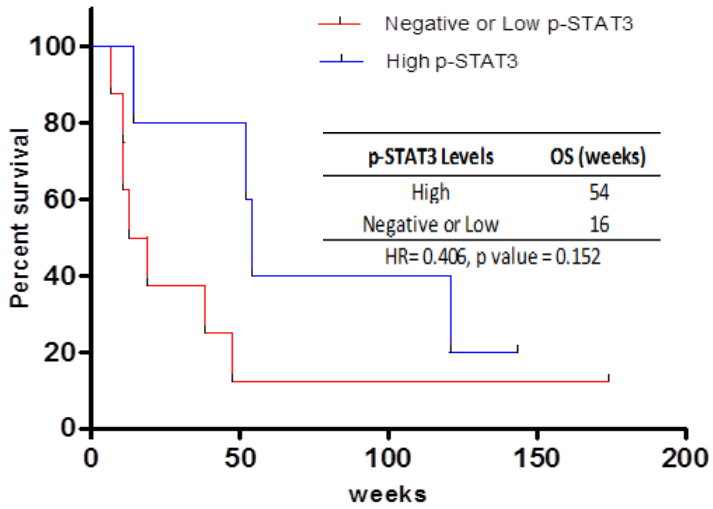
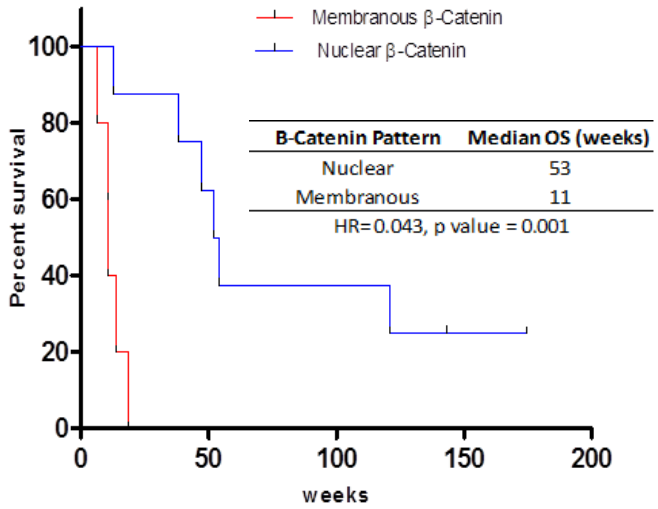
Predictive Biomarkers







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Adrian Langleben, et al. *J Clin Oncol.* 31, 2013
ASCO 2013 (Abstract 2542)

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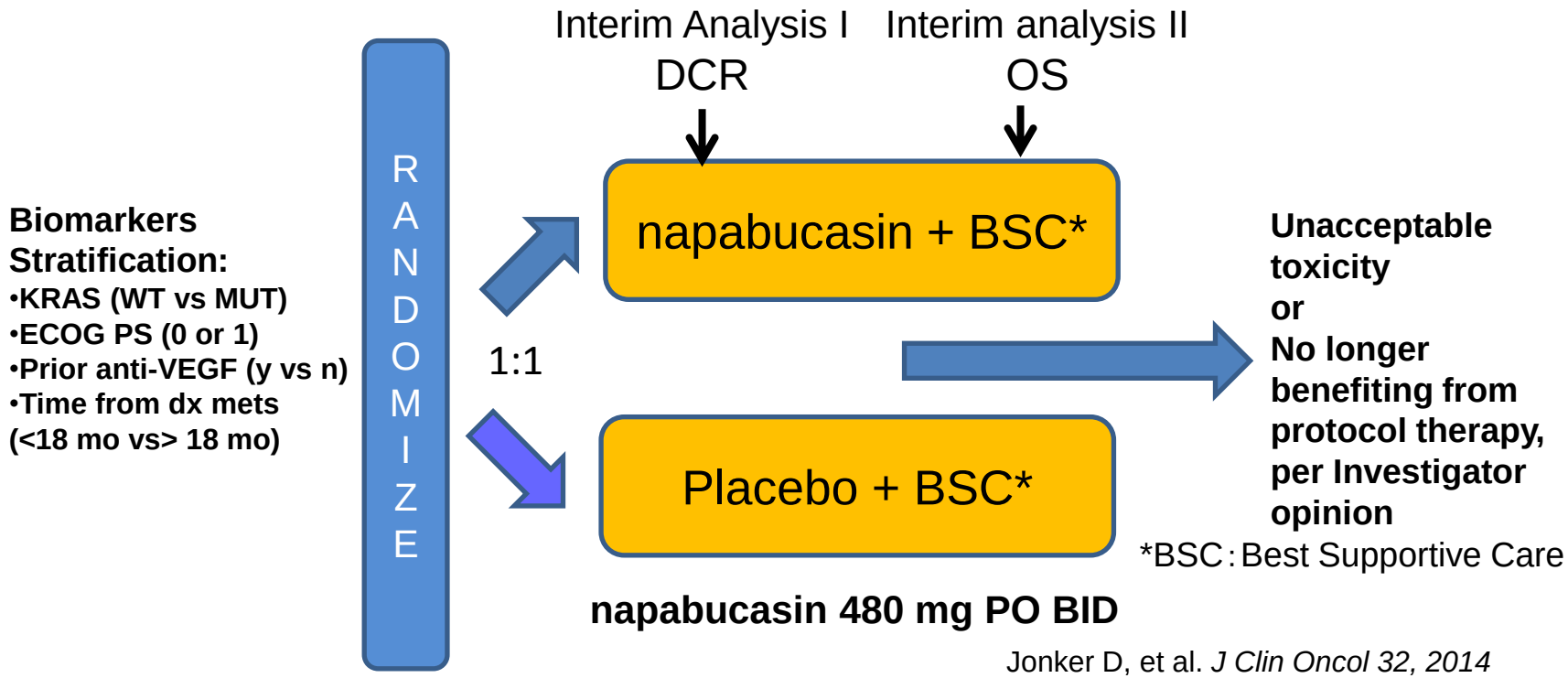
Colorectal Cancer: Napabucasin as Monotherapy CO.23 Study

The analysis results including Overall Survival and Biomarker have not been obtained yet.

Sponsor: National Cancer Institute of Canada - Clinical Trial Group (NCIC-CTG)
Patients：Failed or intolerant to all recommended therapies
(TS inhibitor, Oxaliplatin, Irinotecan + EGFR inhibitor if KRAS WT)



Jonker D, et al. *J Clin Oncol 32, 2014*
ASCO 2014 (Abstract TPS3660)

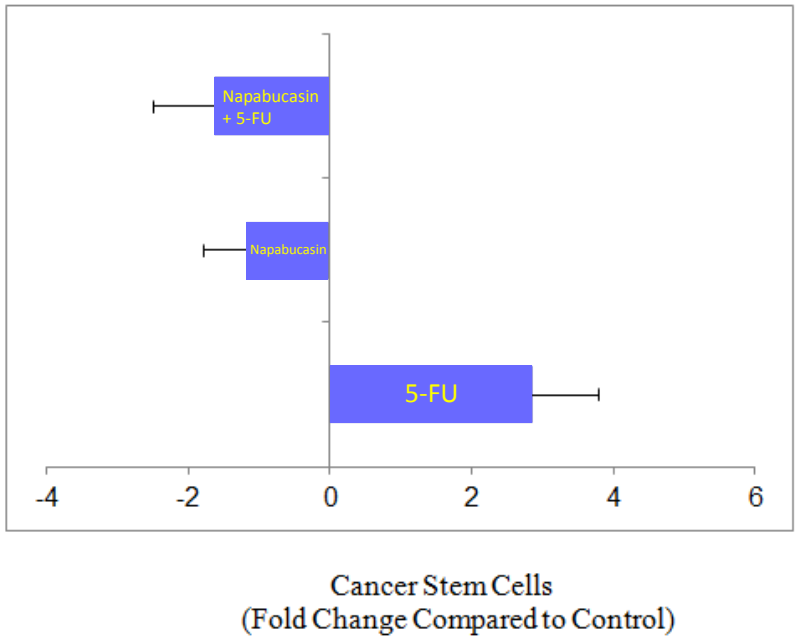
- **Primary Objective: Overall Survival (5% alpha, 90% power, HR=0.75)**
- **Secondary: Progression Free Survival, Disease Control Rate, Safety, Quality of Life, Health Economics, PK, Correlative Biomarkers**

Note: Further enrollment of new patients was stopped and all patients discontinued study therapy in May 2014.

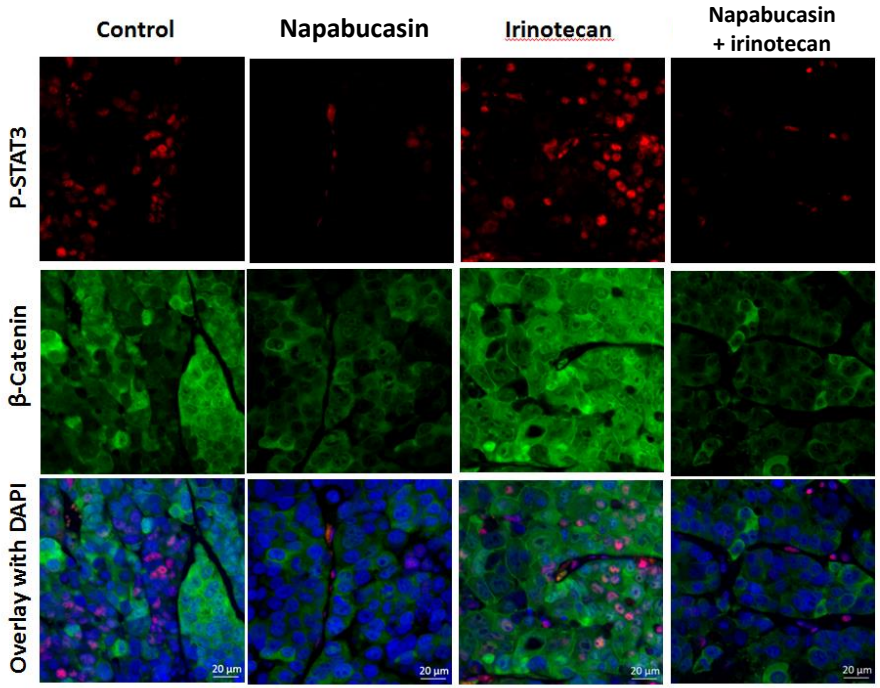
Colorectal Cancer: Preclinical Rationale for Napabucasin in Combo with Chemo

The combination of napabucasin with Chemo showed strong synergy in-vitro and in-vivo.

Effect of Treatments on Cancer Stem Cells



Effect of Treatments on Cancer Stemness Biomarker Response in Xenograft Tumor

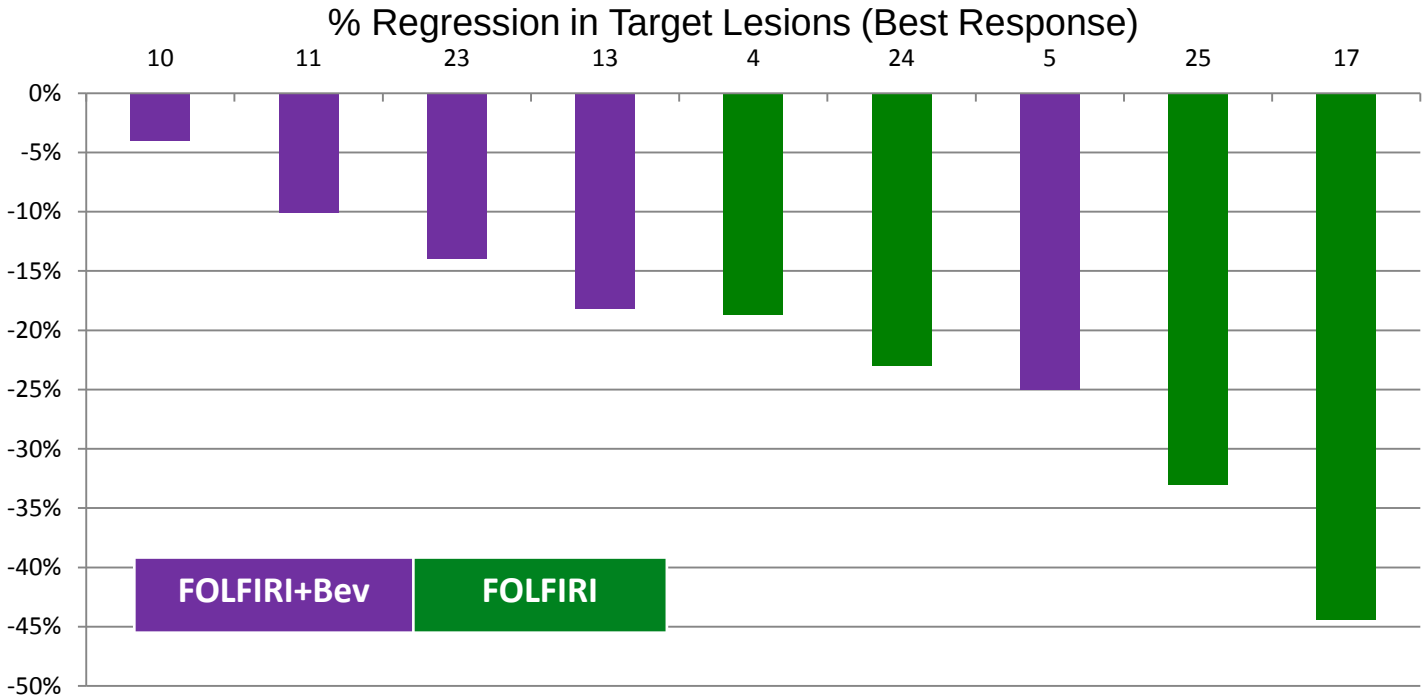


Hubbard JM, et al. *J Clin Oncol 33, 2015*
ASCO 2015 (Abstract 3616)

Colorectal Cancer: Signs of Activity for Napabucasin in Combo with FOLFIRI

FOLFIRI +/- bevacizumab as the second line treatment of CRC has DCR ~50 to 68%, and ORR ~ 5% in FOLFIRI-naive patients. Phase Ib study has been conducted to use napabucasin plus FOLFIRI in CRC patients (Total 9 Patients, 6 patients had failed FOLFIRI)

- Signs of tumor regression observed in every patient (**100%**)
- Disease control (Partial Regression and Stable Disease) achieved in all patients (**100%**)
- **56%** (5 of 9 evaluable pts) had prolonged SD (≥ 6 months).



Hubbard JM, et al. *J Clin Oncol 33, 2015 (ASCO 2015 suppl; abstr 3616)*
ASCO 2015 (Abstract 3616), data of BBI608-246 study

Further data update: ASCO-GI 2016 (Abstract 569) First Author: Joleen Hubbard

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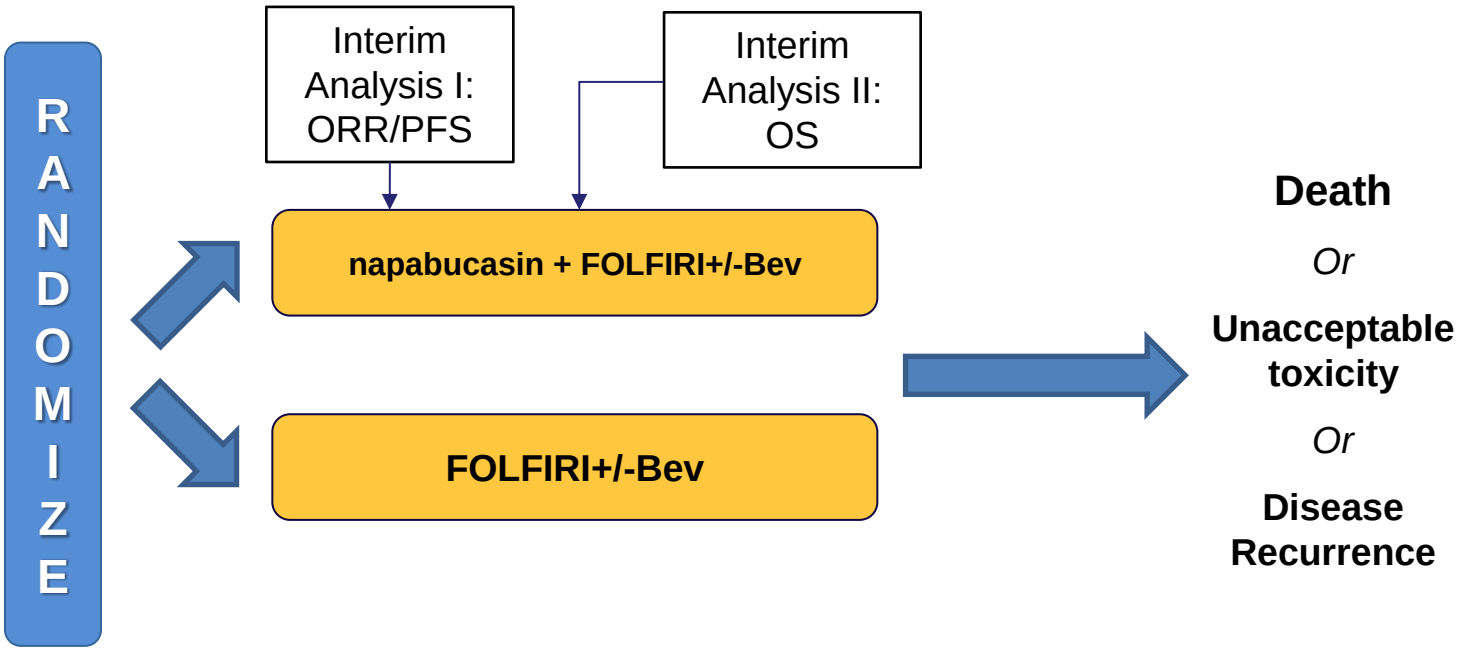
Colorectal Cancer: BBI608-303CRC Study in Advanced Colorectal Cancer

Phase III study of BBI608 in combination with FOLFIRI with or without bevacizumab in patients with advanced colorectal cancer who have failed first line chemotherapy



Primary Endpoint: **Overall Survival**

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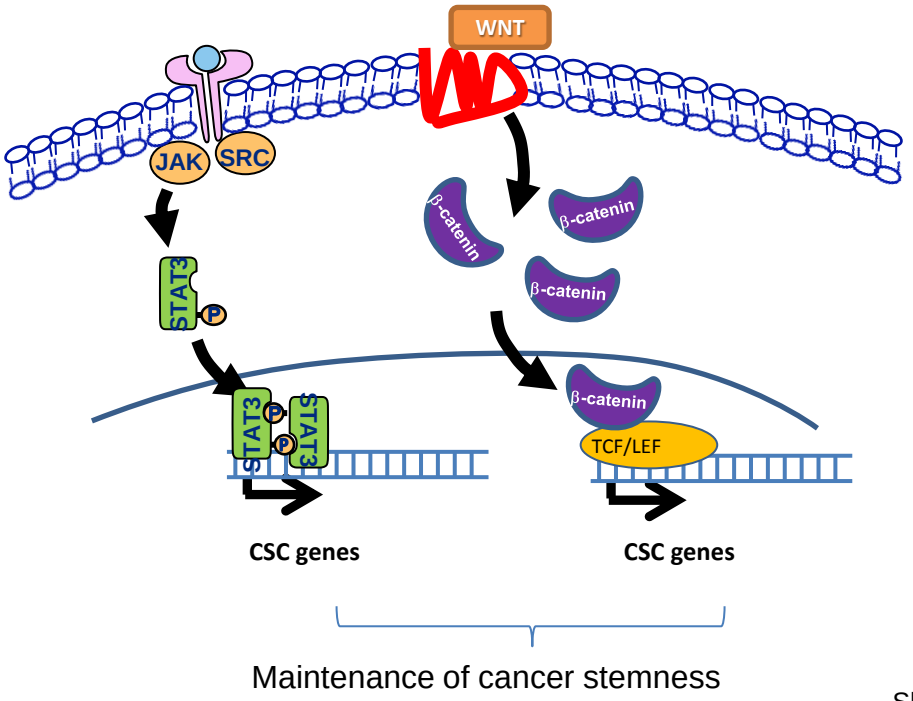
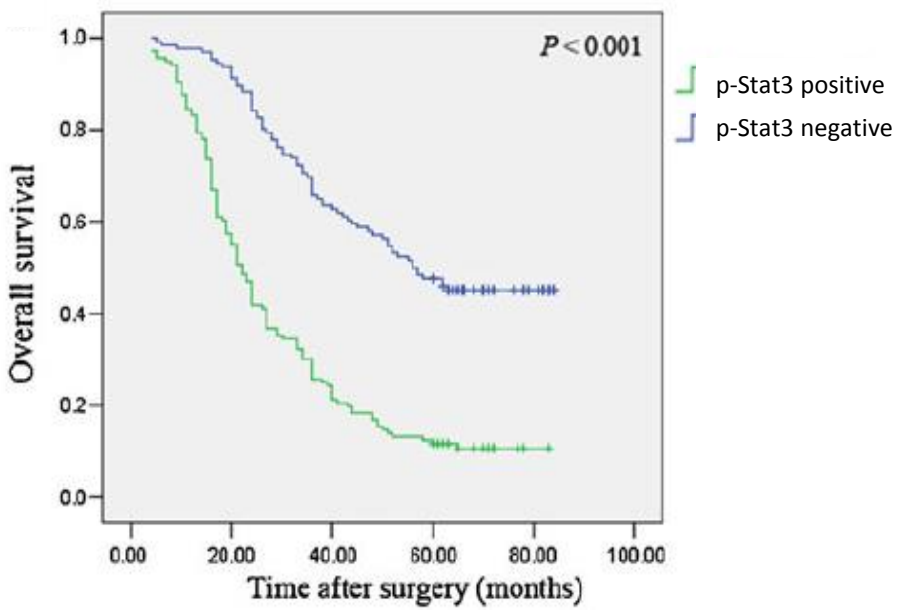
Napabucasin

First-in-Class inhibitor of Stat3, a critical pathway in cancer stemness

— Gastric/GEJ Cancer —

Gastric/GEJ Cancer: Preclinical Rationale





Shah MA, et al. *J Clin Oncol 33, 2015 (ASCO 2015 suppl; abstr TPS4139)*.
Xiong H, et al. *J Mol Med (Berl). 2012;90(9):1037-46.*

Stat3 and β-catenin in gastric cancer

- Elevated expression p-Stat3 and nuclear β-catenin associated with advanced disease
- Gastric cancer patients with positive p-Stat3 expression have a poorer overall survival

Gastric/GEJ Cancer: Signs of Activity of Napabucasin

BBI608-201: A Phase Ib/II Clinical Study of BBI608 Administered With Paclitaxel in Adult Patients With Advanced Malignancies

Patient Summary

Total Daily Dose (mg)	Diagnosis	Weeks on Study	Best Response (RECIST 1.1)	Comment
400	Small Cell Lung Cancer	8	PD	Lesion growth
400	**Gastric adenocarcinoma**	**25**	**SD**	**24% regression, 90% CEA decrease**
400	**Non-small cell lung cancer**	**7**	**SD**	**Minimal change in target lesions**
1000	**Bladder cancer**	**17**	**SD**	**Minimal change in target lesions, PFS 16 weeks**
1000	**Ovarian cancer**	**20**	**PR**	**40% regression, 40% CA-125 decrease**
1000	**Melanoma**	**4**	**SD**	**11% regression, elected to receive vemurafenib**
1000	Melanoma	8	PD	Brain metastases not previously imaged
1000	Ovarian cancer	5	PD	Pathologic fractures
1000	**Melanoma**	**25**	**SD**	**0% lesion change, prolonged stable disease**
1000	**GEJ adenocarcinoma**	**9**	**PR**	**44% regression**
1000	**GEJ adenocarcinoma**	**21**	**PR**	**48% regression**
1000	**GEJ adenocarcinoma**	**21**	**SD**	**0% lesion change, prolonged stable disease**
1000	Bladder cancer	8	PD	Lesion growth
1000	Bladder cancer	8	PD	Lesion growth
1000	**GEJ adenocarcinoma**	**23**	**SD**	**60% CEA decrease, prolonged stable disease**

- 5 patients total with gastric/GEJ adenocarcinoma enrolled:
  all 5 responded to treatment
  - 3 patients had tumor regression (44%, 48%, 24%)
  - 2 patients who failed prior taxane had prolonged stable disease (>5 months)

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Hitron M, et al. *J Clin Oncol*. 2014;32(5 suppl). ASCO 2014 (Abstract 2530)

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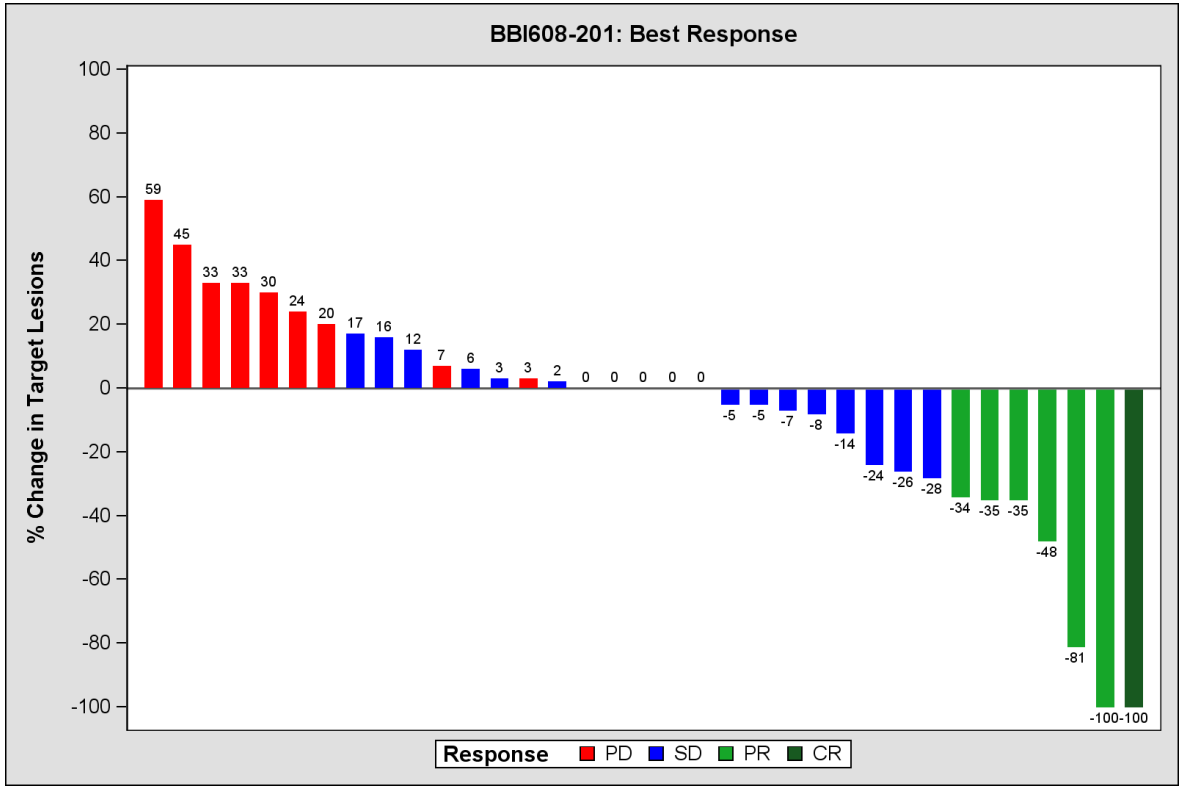
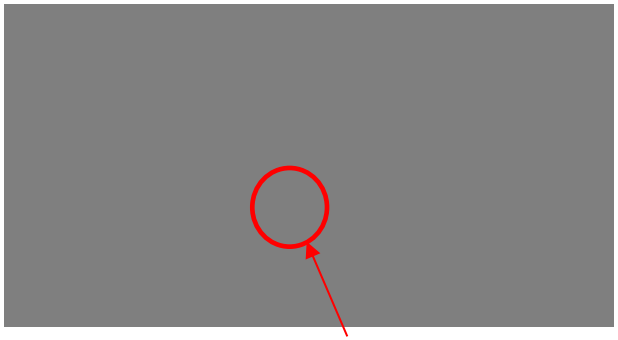
Gastric/GEJ Cancer: Early Signs of Clinical Activity

Early signs of anti-cancer activity in patients with gastric/GEJ adenocarcinoma were confirmed in an expansion cohort of heavily pre-treated gastric/GEJ patients

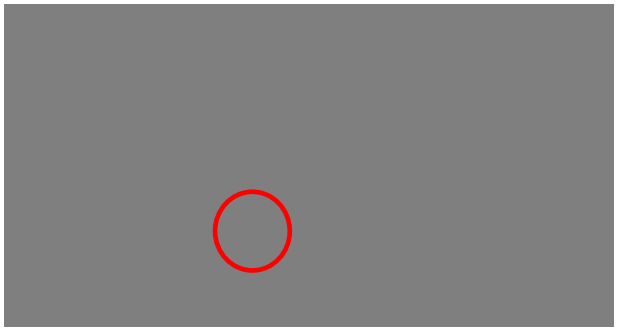


Baseline



2.2 cm RLL metastasis

8 weeks



Resolved

Revised on December 28th, 2015 : deleted the images of CT-scan

Becerra C, et al. *J Clin Oncol 33, 2015*
ASCO 2015 (Abstract 4069)

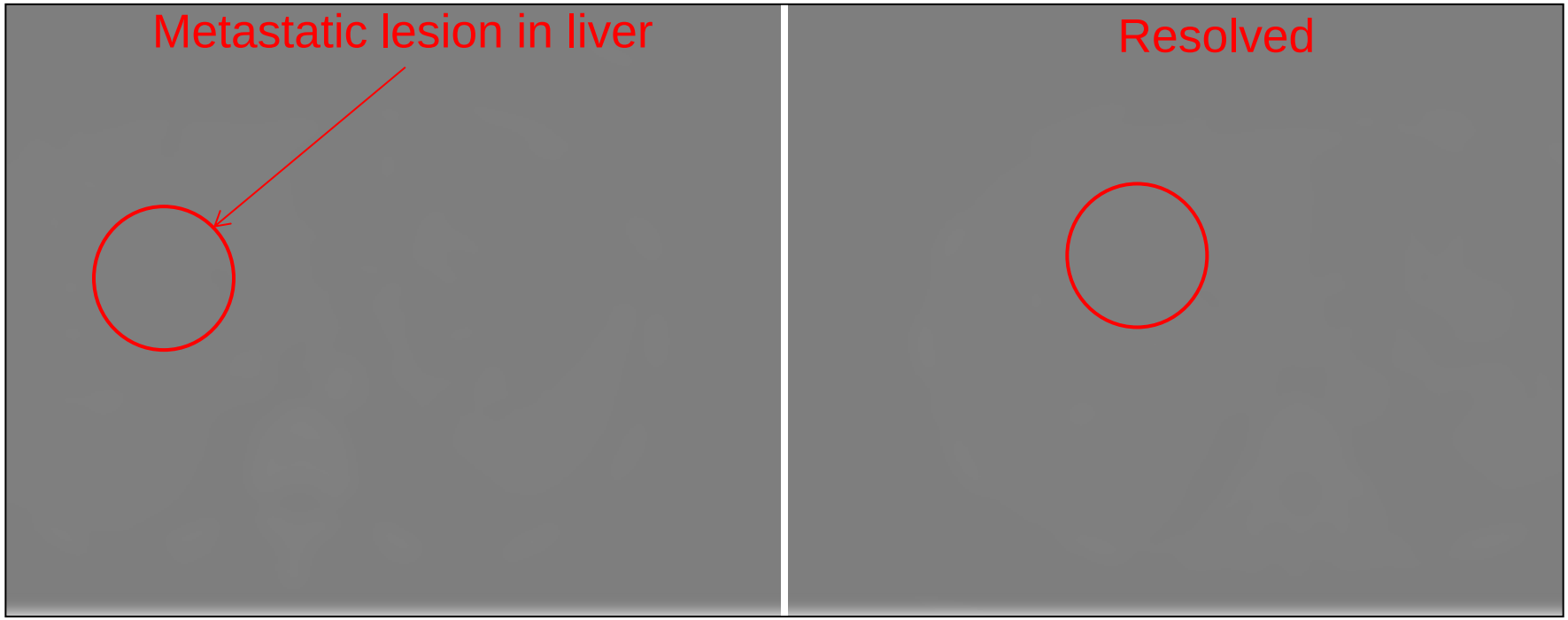
BB608-201 (Gastric/GEJ adenocarcinoma) Patient

- Gastric Adenocarcinoma, metastatic to liver
- Failed first line therapy

100% regression of hepatic lesion
Complete Response per RECIST

BASELINE

8 Weeks



Revised on December 28th, 2015 : deleted the images of CT-scan

Gastric/GEJ Cancer: Signs of Clinical Activity

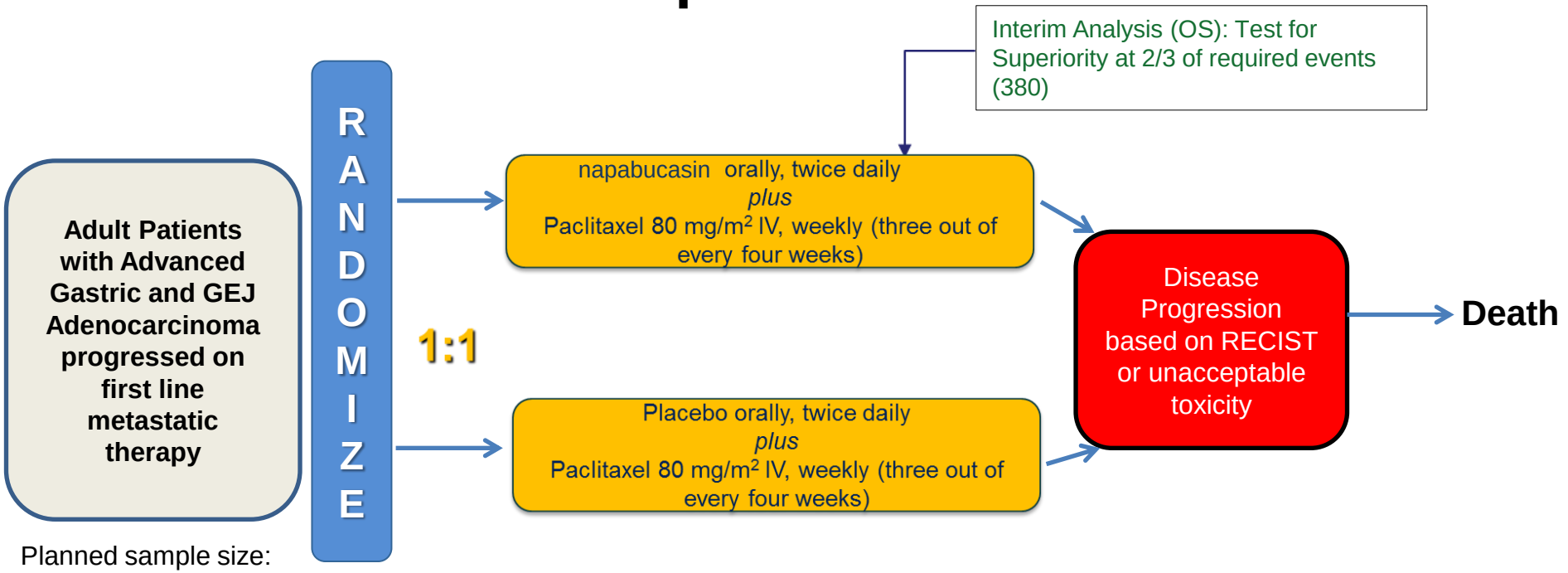
Efficacy-Summary (BBI608-201)

Group	N	Prior lines (ave.)	ORR (%)	DCR (%)	mPFS (weeks)	mOS (weeks)
All patients	46	2.4	15%	54%	13.0	31.6
Total Evaluated Per-Protocol	35	2.4	20%	71%	14.6	34.0
Received Taxane in Metastatic Setting	19	2.6	11%	68%	12.6	33.1
No Taxane in Metastatic Setting	16	2.1	31%	75%	20.6	39.3

Becerra C, et al. *J Clin Oncol 33, 2015*
ASCO2015 (Abstract 4069)

- **In 6 patients evaluated who received 1 prior line of therapy that did not include a taxane, an objective response rate of 50% was observed.**
- Napabucasin plus weekly paclitaxel for the treatment of patients with gastric/GEJ adenocarcinoma who have failed first line platinum-based therapy is being evaluated in a phase III randomized controlled trial, the BRIGHTER study.

Gastric/GEJ Cancer: BRIGHTER Study of Napabucasin



Planned sample size:
700 patients
(350 pts on napabucasin arm and 350 pts on Placebo arm)

Primary

- Overall survival (OS) in general study population

Secondary

- Overall survival in predefined biomarker-positive sub-population
- Progression-Free Survival (PFS) in general study population
- Progression-Free survival in predefined biomarker-positive sub-population
- Objective response rate (OR) in general study population
- Disease Control Rate (DCR)
- Safety profile

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Adapted from Shah MA, et al. *J Clin Oncol 33, 2015*
ASCO 2015 (Abstract TPS4139)

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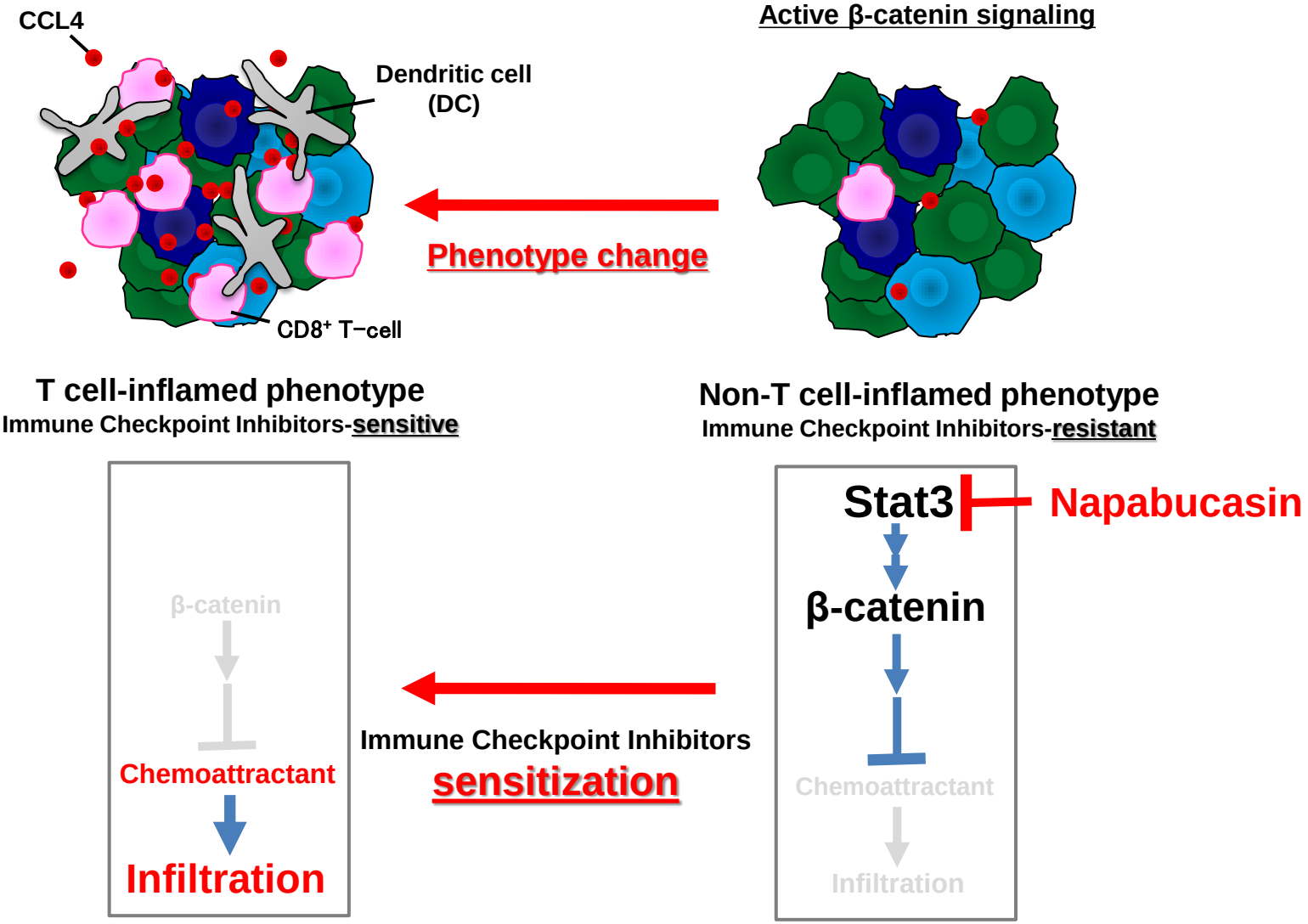
Napabucasin

First-in-Class inhibitor of Stat3, a critical pathway in cancer stemness

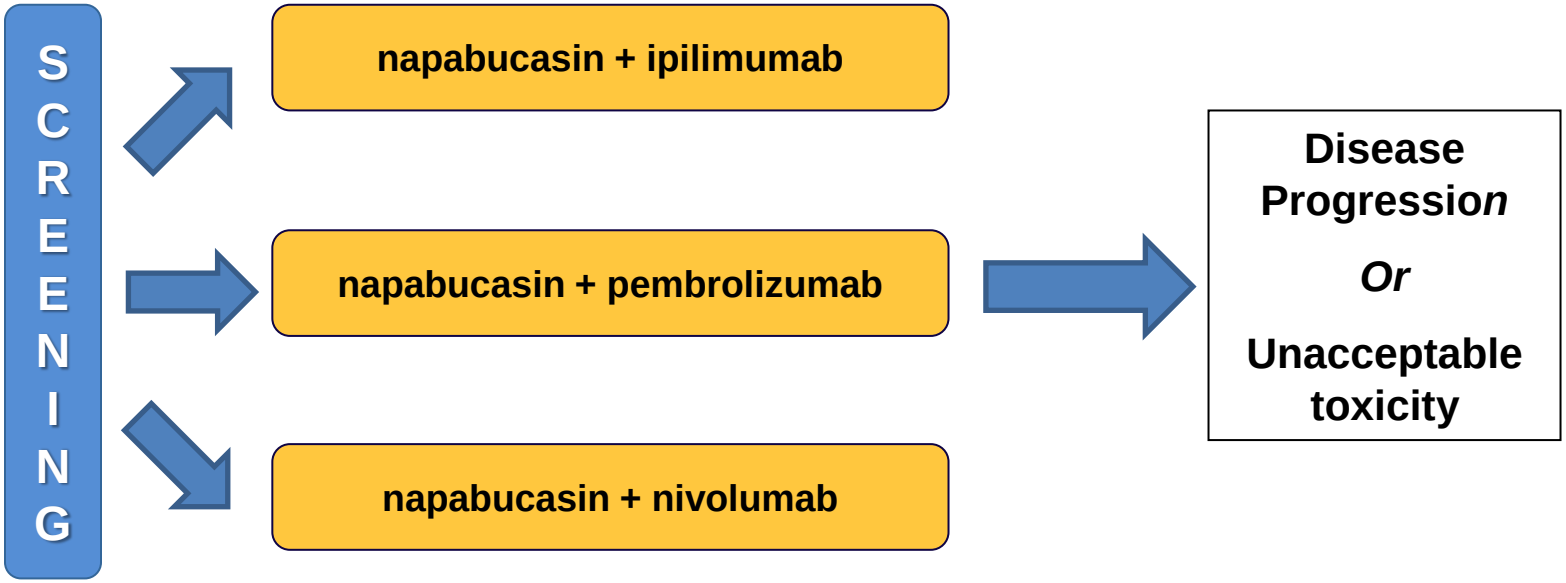
— Combination with Immune Checkpoint Inhibitors —

Napabucasin Inhibits Cancer Immune Evasion



Targeting Stemness May Sensitize Cancer to Immune Checkpoint Drugs

BBI608-201CIT: A Phase Ib/II Clinical Study of BBI608 Administered in Combination with Immune Checkpoint Inhibitors to Adult Patients with Advanced Cancers



Primary objective : Safety, Tolerability, RP2D
Secondary objective : PK profile, preliminary anti-tumor activity

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(Clinical Trial .gov NCT02467361)

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Clinical Strategy to Develop Cancer Stemness Inhibitors

Phase1/2
（Each study tests multiple tumor types and/or regimens）

BBI608-101
Explore tumor types in monotherapy

BBI608-224 (3-arm)
Explore best combination regimens in CRC

BBI608-246 (6-arm)
Explore best combination regimens in GI cancers

BBI608-201
Explore tumor types in combination w paclitaxel

BBI608-201CIT
Explore tumor types in combination w ICIs

+
+
+

Pancreatic Cancer Data Presentations
ASCO-GI, 2016

Phase 2/3
（Multiple pivotal studies run in parallel）

CO.23
CRC, monotherapy

BBI608-336 (BRIGHTER)
Gastric/GEJ, combo w paclitaxel

BBI608-303CRC
Combo w FOLFIRI+/-bev

To be selected

- NSCLC
- Breast Cancer
- Ovarian Cancer
- Pancreatic Cancer

+
+
+

Napabucasin – Clinical Trials

Napabucasin is an orally- administered investigational agent designed to inhibit cancer stem cell pathways by targeting Stat3

Proposed indication	Development Location	Phase 1	Phase 2	Phase 3
Colorectal cancer (Monotherapy)	Global			
Gastric / GEJ adenocarcinoma (Combination therapy)	Global			
Colorectal Cancer (Combination therapy)	North America			
Multiple solid tumors (NSCLC, ovarian, breast, melanoma) (Combination therapy)	North America			
Malignant pleural mesothelioma (Combination therapy)	Japan			
Gastrointestinal cancer (Combination therapy)	North America			
Pancreatic cancer (Combination therapy)	U.S.			
Hepatocellular carcinoma (Combination therapy)	U.S.			
Glioblastoma (Combination therapy)	Canada			
Hematologic malignancies (MM, lymphoma, AML, MDS, CML) (Monotherapy / Combination therapy)	U.S.			
Multiple solid tumors (Combination with BBI503)	U.S.			
Multiple solid tumors (Combination with immune checkpoint inhibitors)	U.S.			
Hepatocellular carcinoma (Combination therapy)	Japan			

Napabucasin is investigational agent and not approved by the U.S. FDA.

Upcoming Presentation

Gastrointestinal Cancers Symposium (ASCO-GI)
Jan 21-23, 2016, San Francisco, CA

(Pancreatic Cancer)

Poster Session B: Cancers of the Pancreas, Small Bowel, and Hepatobiliary Tract
Friday, January 22, 2016: 12:30 PM–2:00 PM and 5:30 PM–7:00 PM

A phase Ib study of cancer stem cell (CSC) pathway inhibitor BBI-608 in combination with gemcitabine and nab-paclitaxel (nab-PTX) in patients (pts) with metastatic pancreatic ductal adenocarcinoma (mPDAC). (Abstract 284) First Author: Safi Shahda

A phase Ib/II study of BBI608 combined with weekly paclitaxel in advanced pancreatic cancer. (Abstract 196) First Author: Tanios Bekaii-Saab

(Colorectal Cancer)

Poster Session C: Cancers of the Colon, Rectum, and Anus
Saturday, January 23, 2016: 7:00 AM–7:55 AM and 12:30 PM–2:00 PM

Phase Ib study of cancer stem cell (CSC) pathway inhibitor BBI-608 administered in combination with FOLFIRI with and without bevacizumab (Bev) in patients (pts) with advanced colorectal cancer (CRC). (Abstract 569) First Author: Joleen Hubbard

BBI503

First-in-Class Kinase Inhibitor of Cancer Stem Cell Pathways, including Nanog

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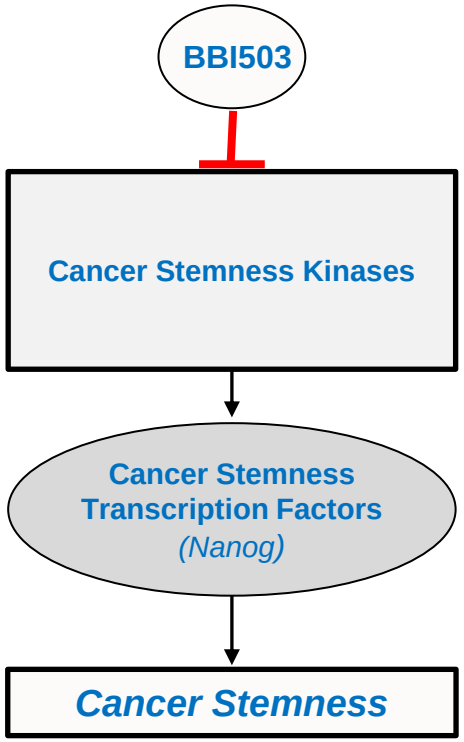
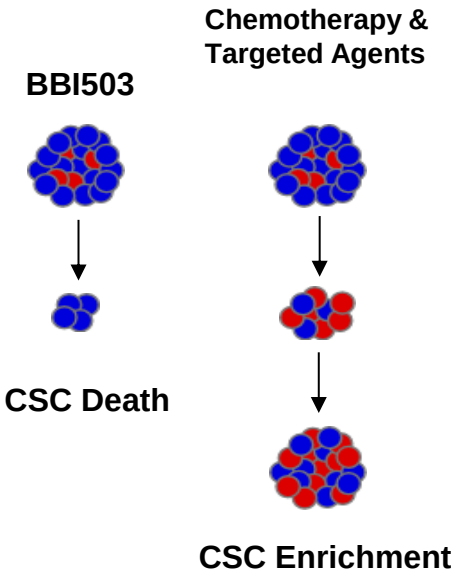
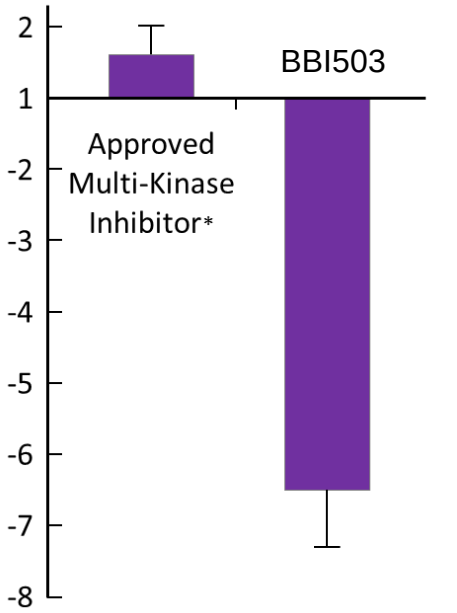
BBI503: First-in-Class Kinase Inhibitor of Cancer Stem Cell Pathways

Cancer stem cells

- Highly tumorigenic
- Responsible for continued malignant growth
- Initiators of metastases
- Chemoresistant







*Similar data obtained with other chemotherapeutics

BBI503

- Inhibits multiple kinases responsible for cancer cell stemness
- Has demonstrated inhibitory activity in cancer stem cell assays
- Has demonstrated antitumor activity in preclinical models

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Jonker D, et al. *J Clin Oncol 33, 2015*
ASCO 2015 (Abstract 3615)

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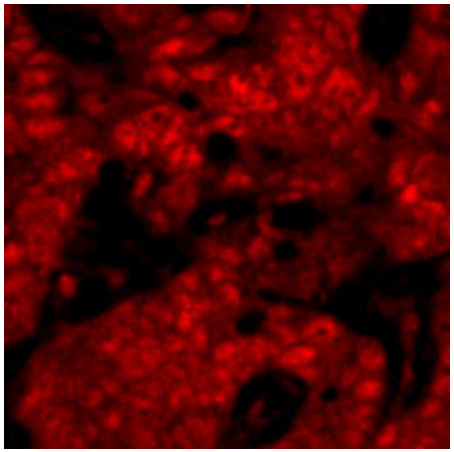
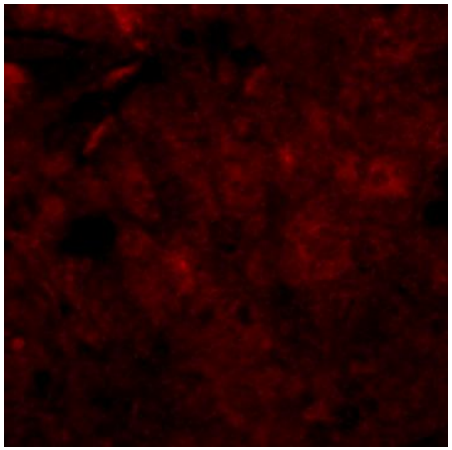
BBI503 Inhibits Cancer Stemness Pathways in Patients

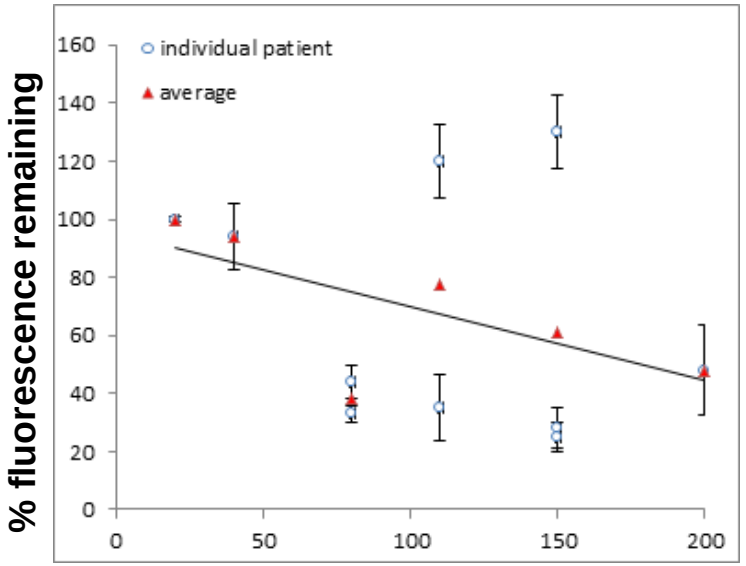
Nanog in Pre-Treatment and On-Treatment Tumor Biopsies

Baseline Biopsy



On-Treatment Biopsy





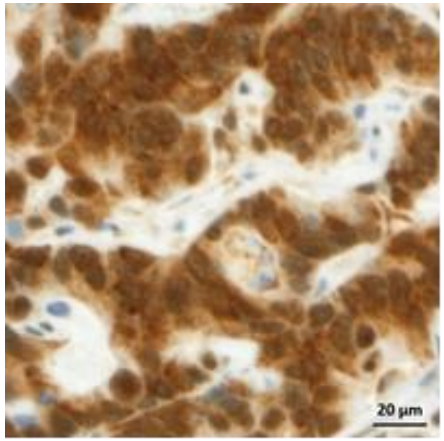
% fluorescence remaining plotted as function of total daily dose

Jonker D, et al. *J Clin Oncol 33, 2015*
ASCO 2015 (Abstract 3615)

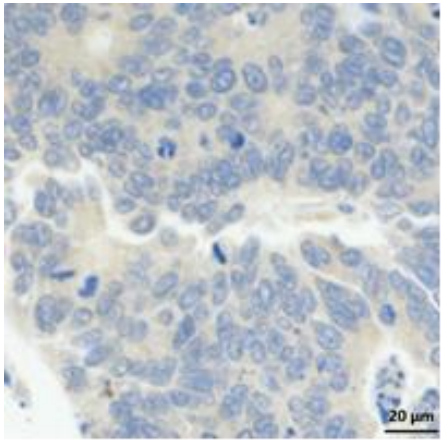
Cancer Stemness Gene Nanog as a Predictive Biomarker for BBI503

Nanog Staining of Archival Tissue

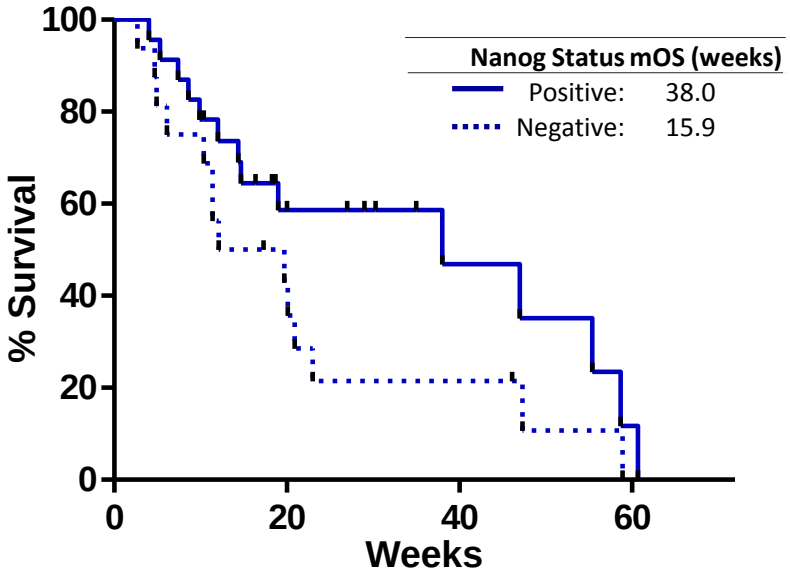
Positive



Negative



Overall Survival Stratified by Nanog Status



Tissue considered positive if ≥ 20% of tumor cells have 2+ Nanog staining or ≥ 5% tumor cells have 3+ intensity of Nanog staining.

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Jonker D, et al. *J Clin Oncol 33, 2015*
ASCO 2015 (Abstract 3615)

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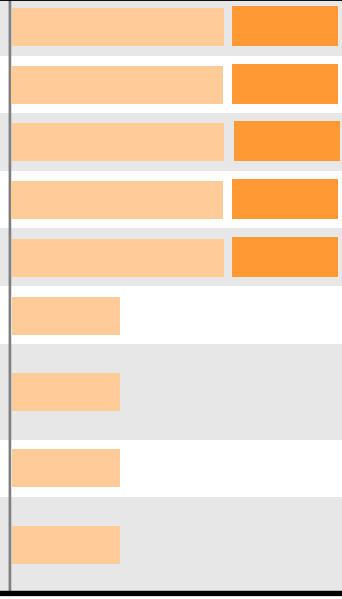
BBI503 – Clinical Trials

BBI503 is an orally-administered investigational agent designed to inhibit cancer stem cell pathways, including Nanog by targeting kinases

Proposed indication	Development Location	Phase 1	Phase 2	Phase 3
Multiple solid tumors (Monotherapy)	North America			
Hepatobiliary cancer (Monotherapy)	Canada			
Gastrointestinal stromal tumors (Monotherapy)	Canada			
Urologic malignancies (Monotherapy)	Canada			
Ovarian cancer (Monotherapy)	U.S.			
Hepatocellular carcinoma (Combination therapy)	U.S.			
Multiple solid tumors (Combination therapy with napabucasin)	U.S.			
Multiple solid tumors (Combination therapy)	North America			
Multiple solid tumors (Monotherapy) (Combination therapy in Hepatocellular carcinoma)	Japan			



BBI503 is investigational agent and not approved by the U.S. FDA.

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New Product Development Opportunities

Major Product Platform Technologies

- Small Molecules (1950s-1980s)
  - 1000 products
- Antibody/Protein (1980s-2000s)
  - 200 products
- **RNA Interference <Gene-Targeted Platform>**
  - Major Therapeutic Product Platform of the 21st century

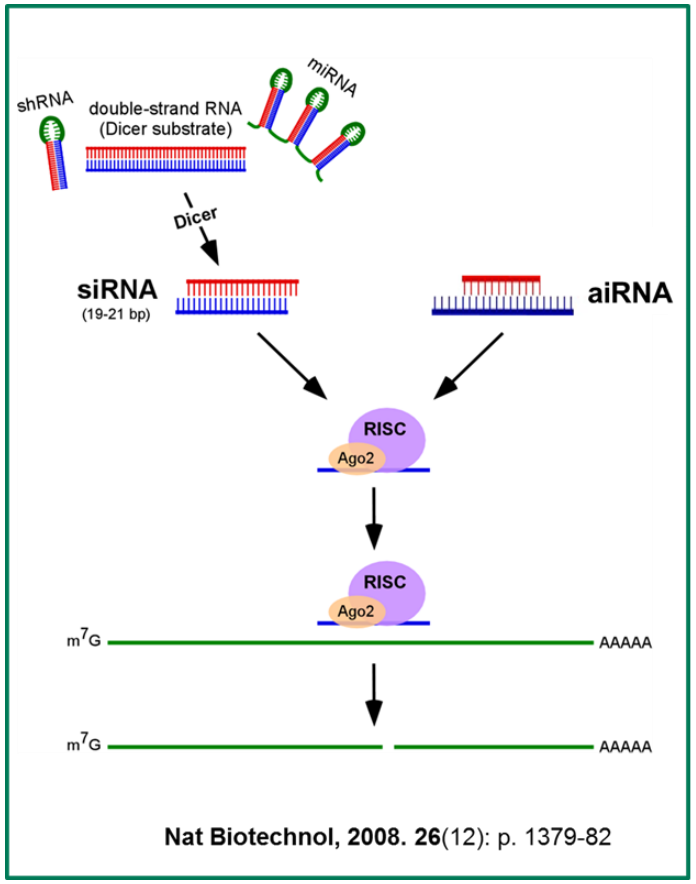
RNA interference discovered in 1998.

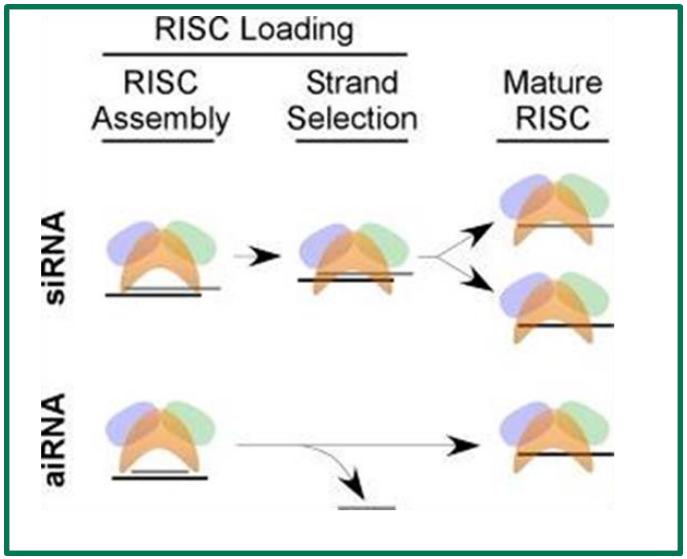
Can potentially target any disease gene, including "non-druggable" targets.

Over 20 clinical trials had launched.

	RNAi	Small molecule
Specificity	**High, sequence driven**	**Low-medium, conformation driven**
Potency	**Typically pM-nM**	**Variable**
# of accessible targets	**>>1000**	**500 to 1,000**
Lead discovery timeline	**4 to 8 weeks**	**2 to 4 years**
Manufacturing	**Common, rapid, scalable methods**	**Variable, can be complex**

aiRNA – The Next Generation of Gene Silencing Technology





Effective RISC loading of aiRNA. Sense strands and anti-sense strands from siRNA are incorporated into RISC and off-target silencing derived from sense strands is induced. By contrast, only antisense strands from aiRNA are incorporated into the RISC increasing specific target gene silencing.

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J.Oishi, et al. *Cancer Res 75, August 1, 2015*
AACR 2015 (Abstract LB-14)

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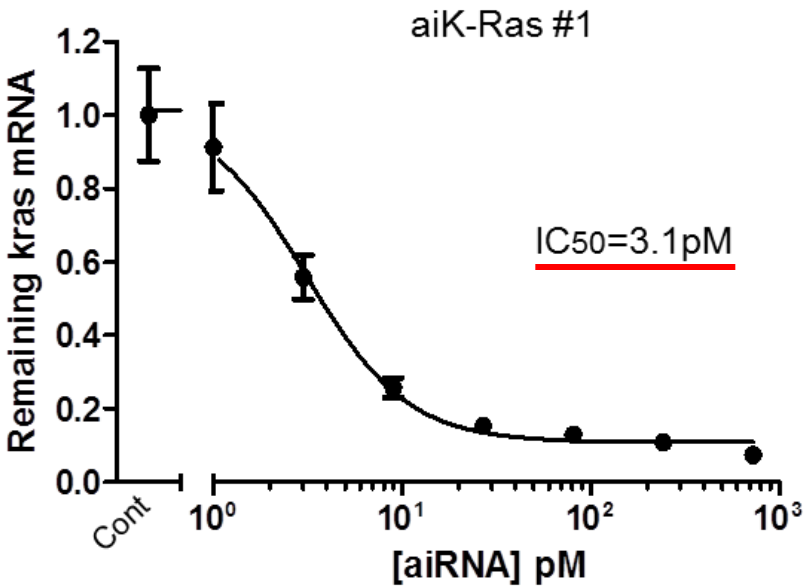
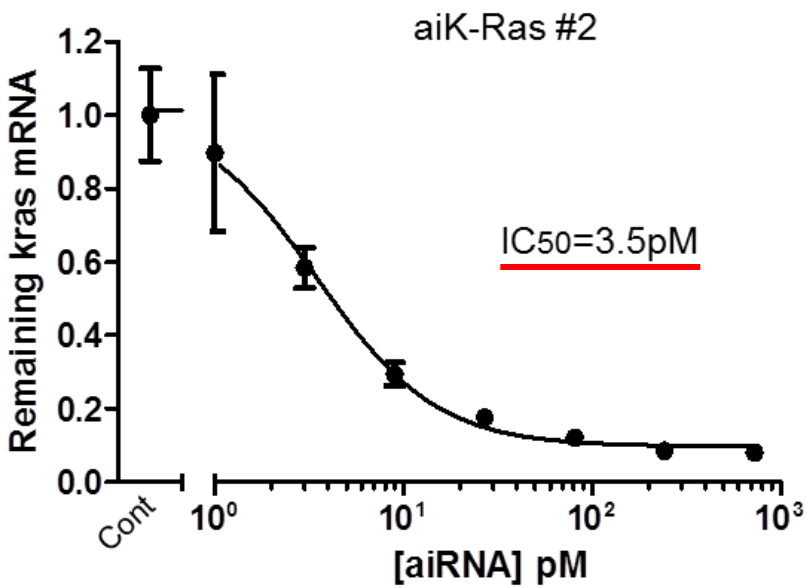
aiRNA Enables Superior Gene Silencing Efficiency





- Super aiRNA shows **pico-molar** activity.
- **20 fold potent** more than siK-Ras used in the recent clinical trials.
  (siG12D RODER trial, NCT01188785)

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J.Oishi, et al. *Cancer Res 75, August 1, 2015*
AACR 2015 (Abstract LB-14)

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Global Oncology Discovery Research Perspective

Targeting cancer stem cells with diverse approaches

Small mole-cules

aiRNA

Peptide

Cancer tissues

Bulk tumor cells

Stroma cells

Immune cells

Cancer stem cells

Stem cell pathways

Stemness kinases

Pipeline

Research	Preclinical	Phase 1
aiRNA		
CSC Kinase Inhibitors		
Stemness Inhibitor		
Epigenetic targets		
Cancer Vaccine		
Immune Response Enhancers		

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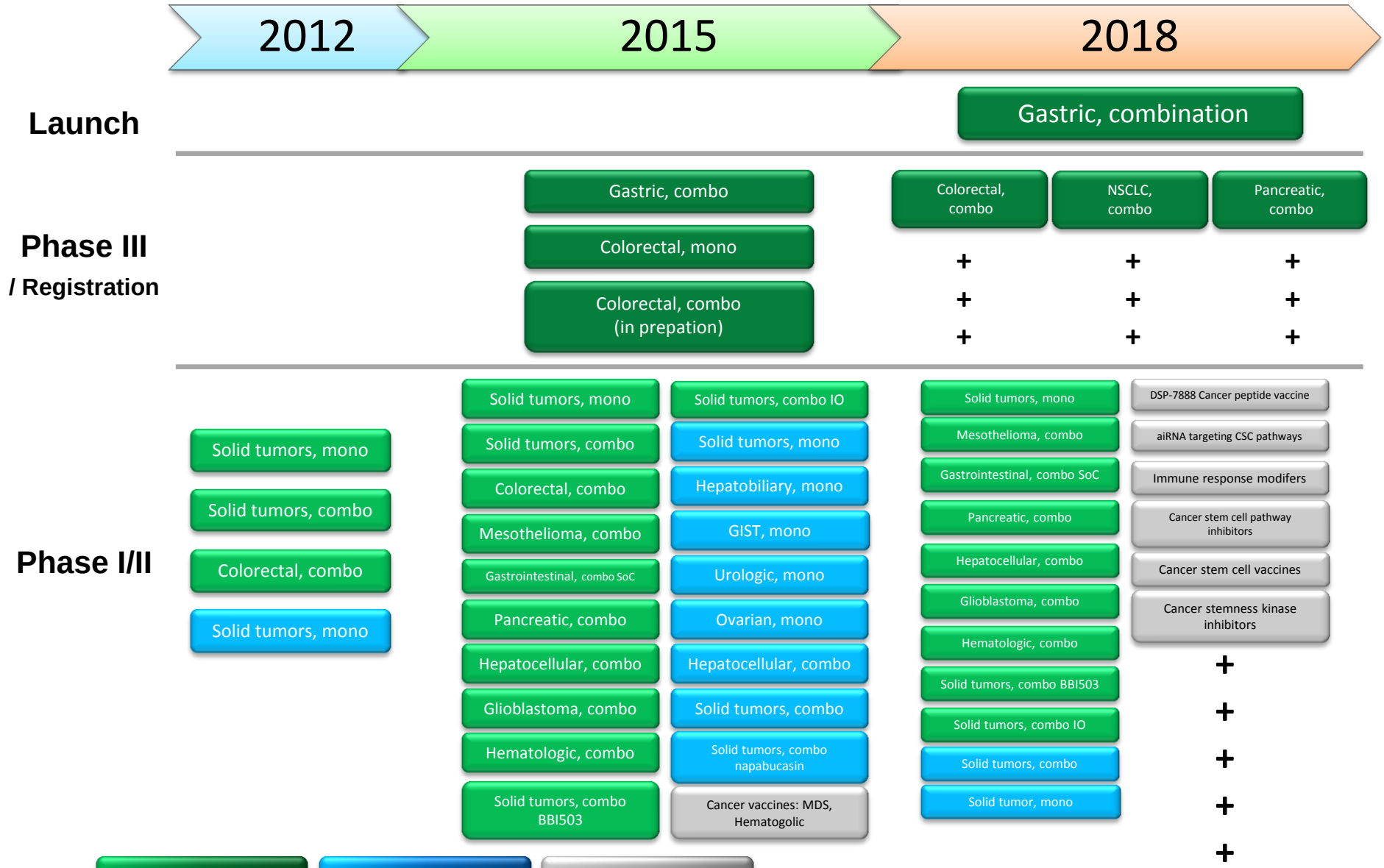
Global Oncology Clinical Development Perspective



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Innovation today, healthier tomorrows