



Full Science and Business Deck

Tumor Specific (TS) Cell Cycle Synchronous Chemotherapy (CCSC) Protocols

Overview

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The Problem

Best in Class S-Phase Cytotoxics can kill 100% of cells in the S-Phase

- However, less than a third of cancer cells are in the S-Phase

The Opportunity

A Market Transforming Opportunity exists from Best in Class S-Phase Protocols

- Boosting the S-Phase fraction from <33% to an eventual 100% ceiling

The Product : TS-CCSC Protocols

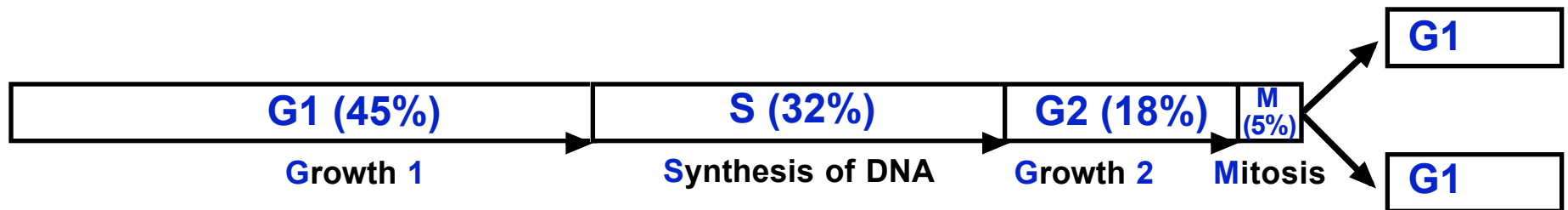
Modulate tumor specific mutations or characteristics for:

- S-Phase enrichment / synchronization
- Preventing tumor regrowth between administrations of cytotoxic

Science Background

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- All dividing cells go through 4 distinct phases

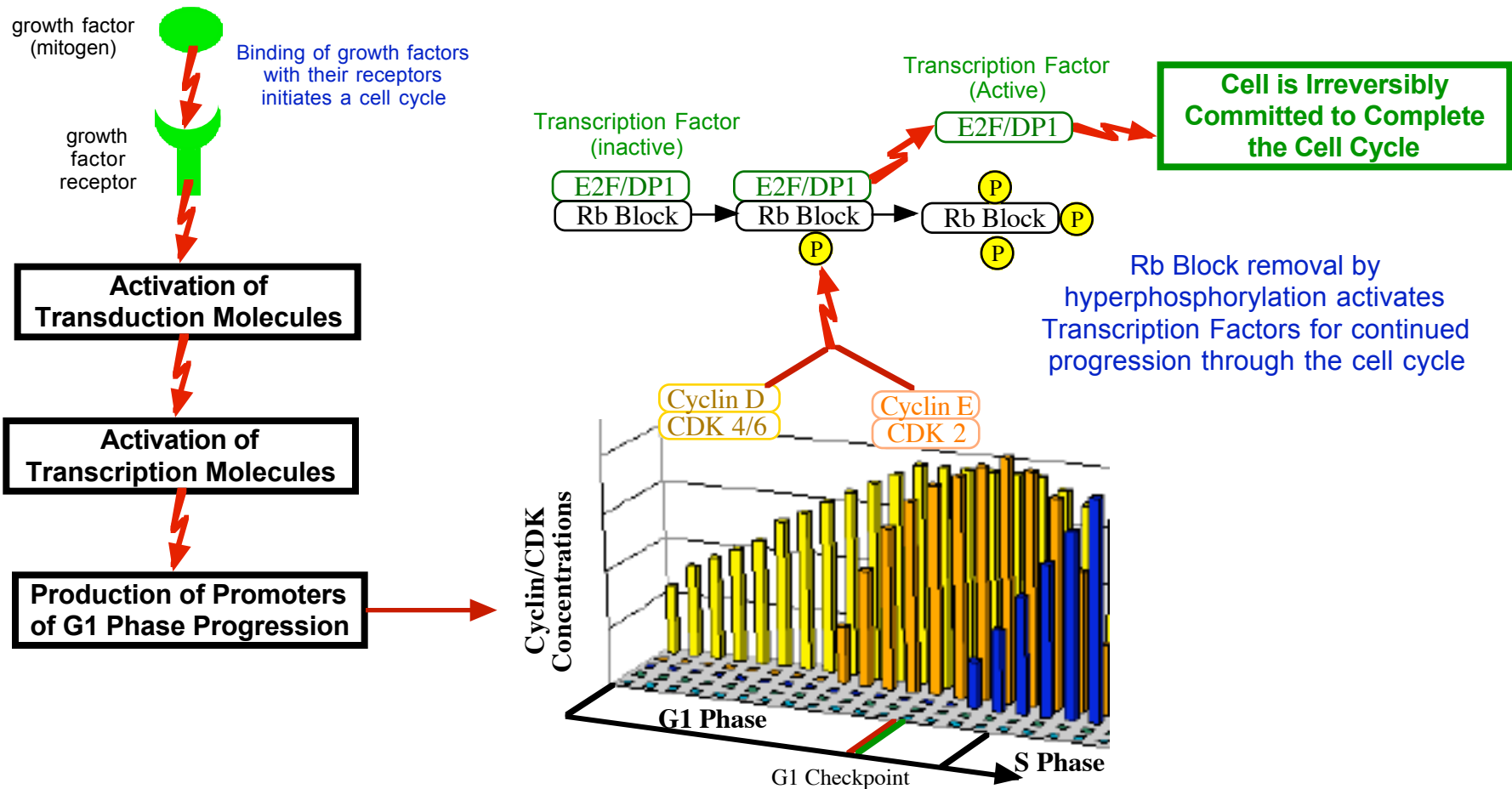


- Good S-Phase cytotoxics can kill all cells that are in the S-Phase
 - However less than a third of cells are in the S-Phase

Science Background

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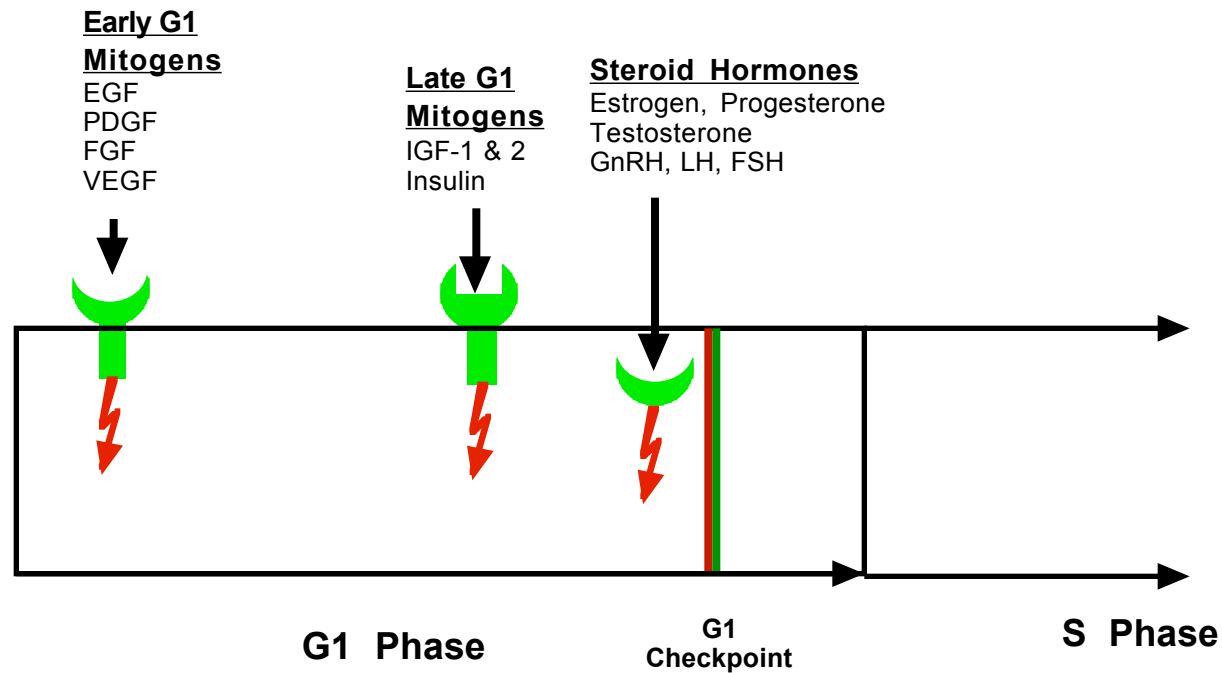
- Binding of growth factors with receptors initiates a cell cycle in normal cells



Science Background

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- Different cells possess different combinations of receptors
- Multiple receptor activation is typically required prior to S-Phase entry



CCSC Targeted Mutations

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- Overexpression of growth factor receptors is a common mutation
- Overexpressed receptors preferentially take up more ambient mitogens
- Mimic elevated levels of mitogens, inappropriately initiating a cell cycle

HER1 (EGF) Receptor

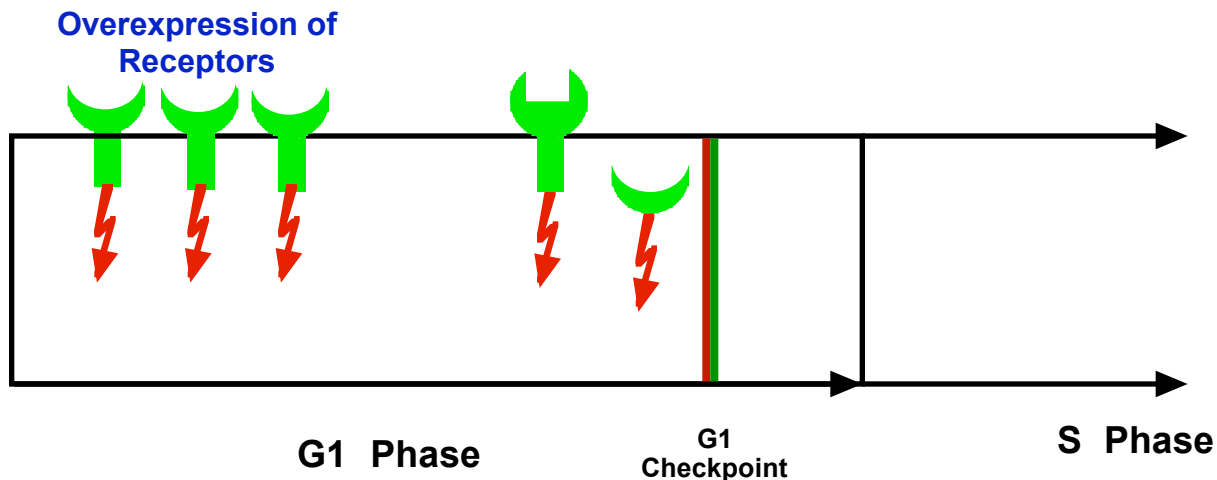
Overexpression:

80+% Head / Neck Cancers
55% of NSCLC Lung Cancers
50% of Prostate Cancers
50% of Glioblastomas (brain)
35 - 70% Ovarian
30 - 50% Pancreatic
25 - 77% Colorectal
15 - 90% Breast

HER2 Overexpression:

(HER2 Potentiates HER1 Activation)

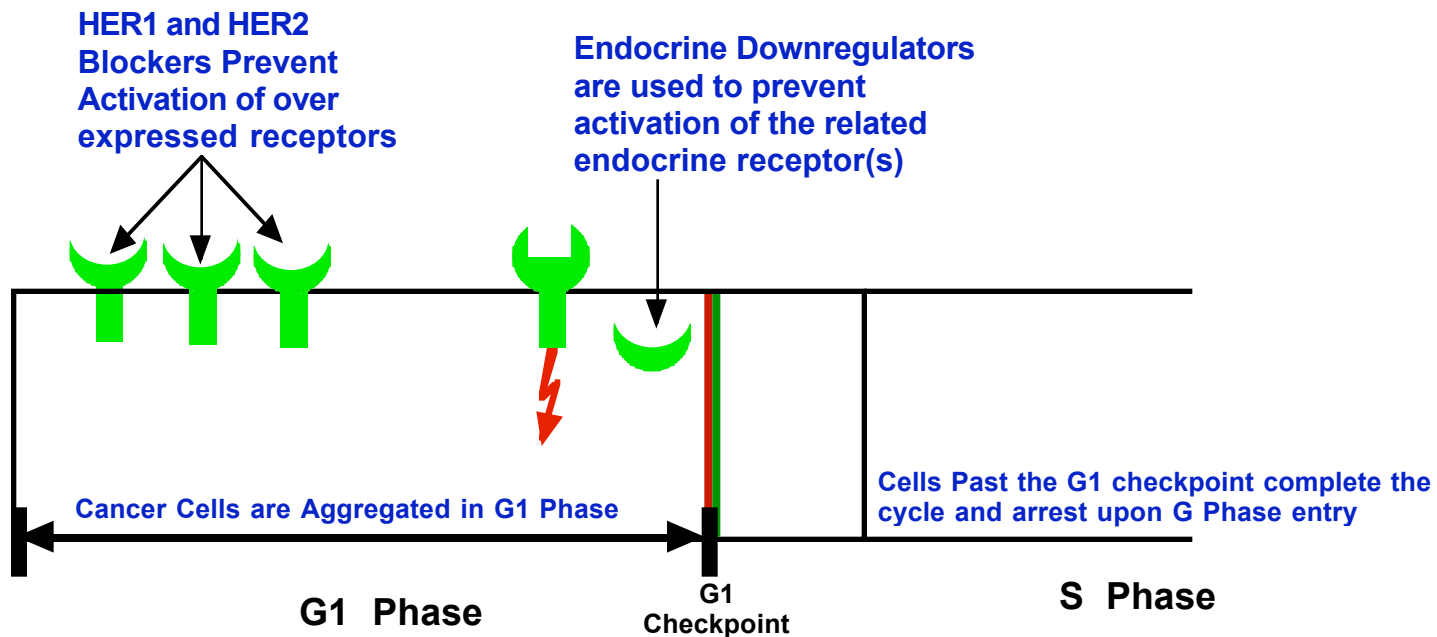
20 - 25% Breast Cancers
20 - 30% of NSCLC Lung Cancers
Ovarian



CCSC Targeted Mutations

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- Our TS-CCSC protocols target HER1 and HER2 overexpression mutations
- Our TS-CCSC protocols target endocrine dependent cancers
- Preventing receptor activation is used to aggregate cancer cells in the G Phase



The TS-CCSC Protocol Approach

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- TS-CCSC aggregates the cancer cells over several weeks
- The cancer cells are then released into the S-Phase to be killed by the cytotoxic

0) Start with Randomly Distributed Cancer Cells



1) Aggregate



2) Release



3) Kill



TS-CCSC - HER 1 & 2 Overexpression

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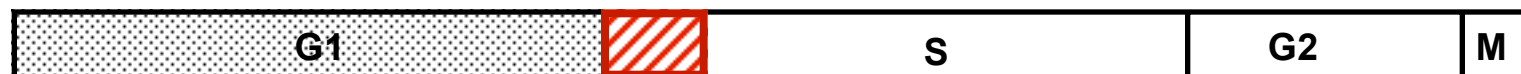
- Reversible HER blockers are preferred

G1 Phase Oncostatic: Reversible HER Blocker

Subtype	Name	Company
HER1	Erlotinib-Tarceva®	Genentech / OSI / Roche
HER1/ 2	Lapatinib - Tykerb®	GalaxoSmithKlein
HER1	Gefitinib - Iressa®	Astra Zeneca (efficacy ?)
HER1, VEGF	Vandetanib - Zactima™	Astra Zeneca (ZD6474)
HER2	CP-724714	OSI-Pfizer
HER2	CP-654577	OSI-Pfizer
HER1	AG1478	Academic
HER1,2,4	Arry-334543	Array Biopharma
HER1/ 2	AEE-788	Novartis
HER1	CGP-59326A	Novartis
HER1/ 2	PKI-166, CGP-75166	Novartis
HER1/ 2	BMS-599626	Bristol Myers Squibb

1) Aggregate

G1 Phase
Oncostatic



Anti-Oncostatic: CYP3A4 Inducer / HER Blocker Inactivator

Drug	Trade Name	Company
Rifampicin	Rifadin® Rimactan®	Sanofi-Aventis Sandoz
Carbamazepine	Tegretol®	Novartis
Phenytoin	Dilantin® Phenytek®	Parke Davis/Pfizer Mylan Labs.
Hyperforin	Amoryn®	BioNeurix

2) Release

Anti-
Oncostatic



TS-CCSC: Endocrine Dependent Cancers

- The big 3 targeted: Estrogen, Progesterone, Testosterone dependent cancers

1) Aggregate

G1 Phase
Oncostatic

Drug Type	Name	Company
GnRH Agonist	Goserelin / Zoladex®	AstraZeneca
	Luprolide / Lupron®	Abbott Labs
	Viadur®	Bayer
	Eligard®	Sanofi-Aventis
GnRH Antagonist	Histrelin / Suprelin®	Indevus
	Cetorelix / Cetrotide®	Merck Serono
	Ganirelix / Antagon®	Schering (Organon)
Aromatase Inhib.	Exemastane/Aromasin®	Pfizer
	Anastrozole/Arimidex®	Astra Zeneca
	Letrozole/ Femara®	Novartis
Testosterone Inhib.	Abiraterone	Cougar/J&J



2) Release

Anti-
Oncostatic

Drug Type	Name	Company
Estrogen	Estradiol	Various Generic
	Climara®	Bayer/3M, Berlex, Mylan gen.
	Alora®	Watson
	Estraderm®, Vivelle®	Novartis
	Esclim®	Women's First Health
	Premarin®	Pfizer (Wyeth)
Progesterone	Cenestin®	Teva (Duramed)
	Provera®	Pfizer
	Aygestin®	Teva (Barr/Duramed)
Testosterone	Megace®	Bristol-Myers Squibb
	Generic	Various
	Androderm®	Watson
	AndroGel®	Solvay

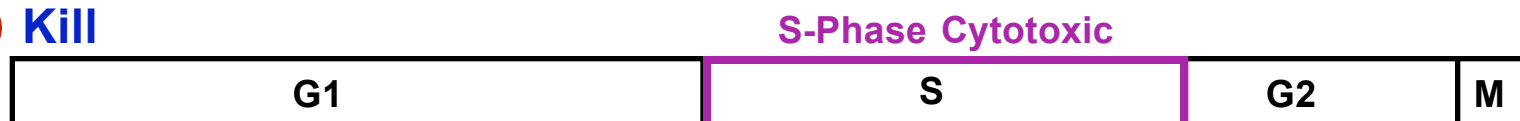


TS-CCSC S-Phase Cytotoxics

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- High S-Phase kill rate cytotoxics are required in step 3

3) Kill



Known Good

<u>Name</u>	<u>Company</u>
Irinotecan - Camptosar®	Generic (Hospira, Sandoz), Camptosar® - Pfizer
Gemcitabine - Gemzar®	Eli Lilly

Potential New

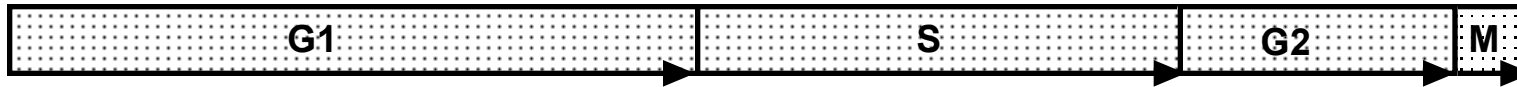
<u>Name</u>	<u>Company</u>
SN-38 Pro Drug SN2310	OncoGenex
DNA Terminator Triapine	Vion

CCSC vs. Single Agent Cytotoxic Protocol

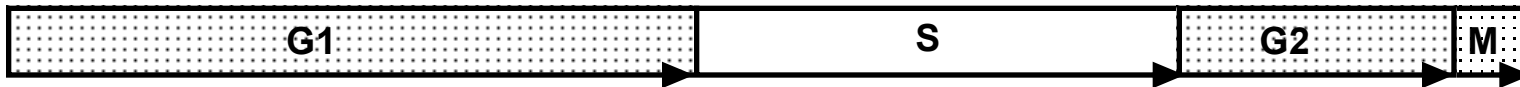
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- A Legacy Protocol kills less than a third of cancer cells per administration

0) Start with Randomly Distributed Cancer Cells



1) Killing S-Phase cells translates into less than a third of cancer cells killed per administration



- TS-CCSC Cancer Kill Rate is limited only by the amount of S-Phase Enrichment

0) Start with cancer cells aggregated in the S-Phase



1) Killing S-Phase cells translates into cancer cell kill rates equal to S-Phase fraction percentages



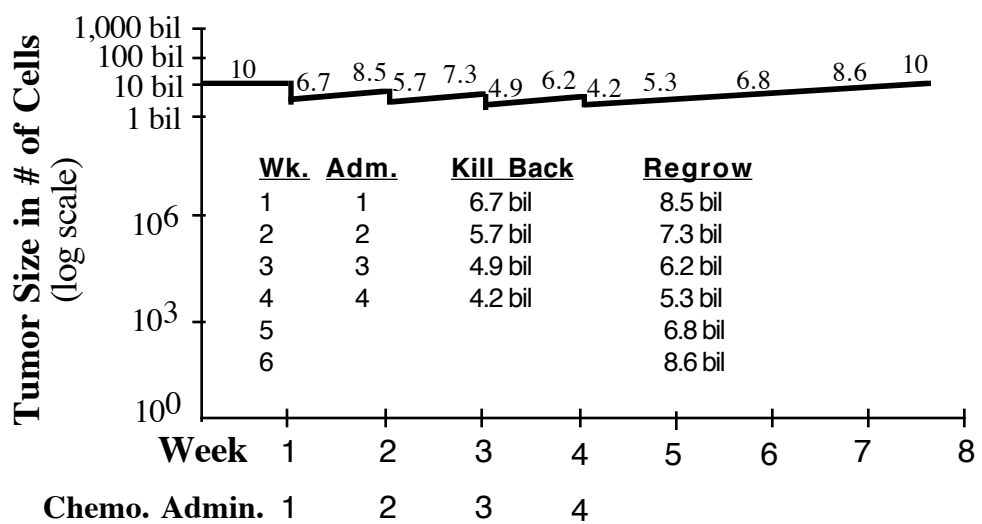
TS - CCSC vs. Single Agent Cytotoxic Protocol

- Legacy Protocols use 7 or 21 day administration intervals
 - Do not prevent regrowth between administrations, hence kill back is not cumulative

Asynchronous Tumor Kill Back / Regrowth

Skipper Log Cell Kill Model Matches Clinical Observations

(10 bil. cell tumor, 4 admin. cycles, 7 day administration intervals, 20 day PDT, 33% TKR/adm.)



- CCSC inhibits tumor regrowth between administration of S-Phase cytotoxic
 - This makes kill back cumulative
 - Downward staircase pattern vs. legacy saw tooth pattern

CCSC vs. Single Agent HER Blockers

- **A HER Blocker is mechanistically a G1 Phase Cytostatic** (slides 4 and 7)
 - “G1 cell cycle arrest and growth inhibition” corroborated ex-vivo by Bunn et. al.⁽¹⁾

0) Start with randomly cycling cells



1) Preventing receptor activation results in G1 Phase cell cycle arrest and inhibition of growth



- **Cytostatics can shrink tumors by preventing replacement of normal attrition**
 - Example: Normal attrition / replacement rate of breast epithelial cells is 0.7% per day⁽²⁾
 - Skipper model predicts 100 days to achieve 50% tumor reduction at 0.7% daily attrition rate
- **TS-CCSC would easily outperform stand alone cytostatics**
 - In contrast, CCSC would achieve a much higher tumor reduction in one 30 day CCSC cycle
 - Even a really bad CCSC that only boosted S-Phase fractions to 50% each 30 day CCSC cycle would achieve an 87.5% tumor reduction in 90 days (3 CCSC cycles)

1) Paul A. Bunn Jr. et. al., Clinical Cancer Research, Vol. 7, 3239 - 3250, October 2001

2) Lisa M. Misell et. al., Breast Cancer Research and Treatment, 89; 257-264, 2005

CCSC vs. Cytostatic/Cytotoxic Combinations

- **Concurrent use of Cytostatics and Cytotoxics in Full Prescribing Information**

- HER1 blocker cetuximab concurrent with S-Phase Cytotoxic Irinotecan regimen
- HER1 blocker erlotinib concurrent with S-Phase Cytotoxic Gemcitabine regimen
- HER1 blocker gefitinib concurrent with S-Phase Cytotoxic Gemcitabine regimen
- HER2 blocker trastuzumab concurrent with S-Phase Cytotoxic Anthracycline regimen

- **Concurrent use is mechanistically antagonistic**

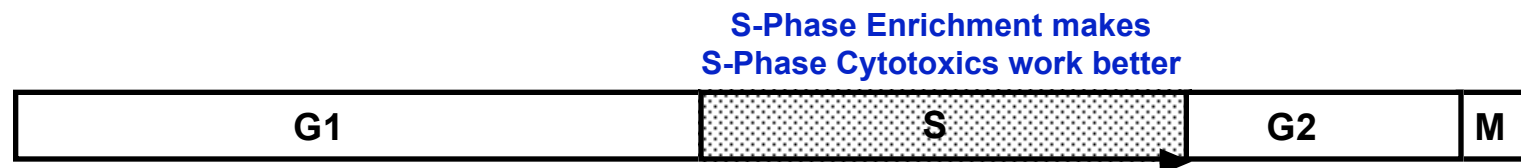
- Corroborated in US 7,507,704 using Skipper model applied to Trastuzumab Phase III data

- **G1 Phase arrest = S Phase Depletion**

- Successive administrations of S Phase cytotoxic have no cancer cells to kill
- Provide no therapeutic benefit only systemic toxicity



- **In Contrast, CCSC's Interlaced Protocols result in S Phase enrichment**



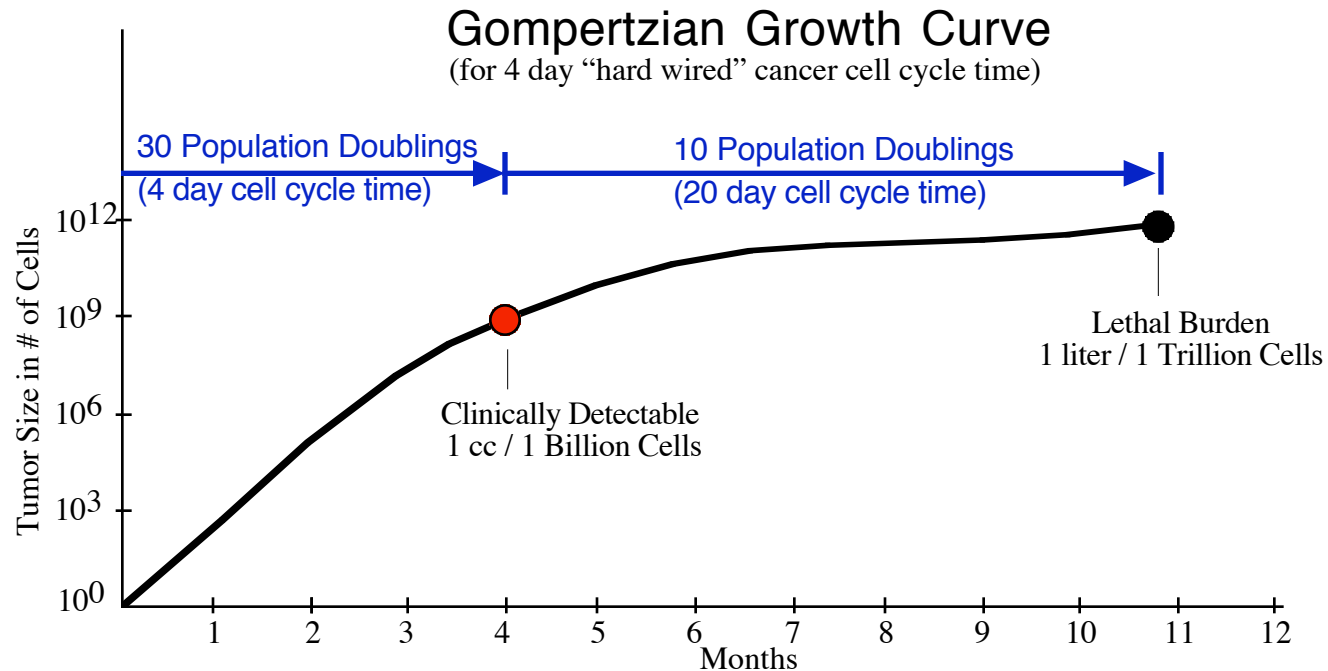
TS - CCSC vs. Failed Prior Art CCSC

- The enormous therapeutic potential of CCSC is commonly acknowledged
- However, failed prior art attempts at CCSC had a chilling effect
- Understanding why prior art failed is necessary for understanding why TS-CCSC will succeed and realize the enormous therapeutic potential
- The two biggest reasons for prior art failures:
 - Aggregation periods were too short
 - Lack of Targeted (tumor specific) aggregation

Failure Reason 1: Aggregation periods were too short

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- Tumor growth kinetics radically alter cell cycle times and S-Phase fractions
- From the first malignant cell, cancer growth is logarithmic and follows a Gompertzian Growth Curve
 - It only takes 10 population doublings from 1 cc to avg. lethal burden
 - i.e. from 1 Bil. cells to 2, 4, 8, 16, 32, 64, 128, 256, 512, 1,024 Bil. = lethal burden
 - Fortunately, cell cycle times slow as tumors grow



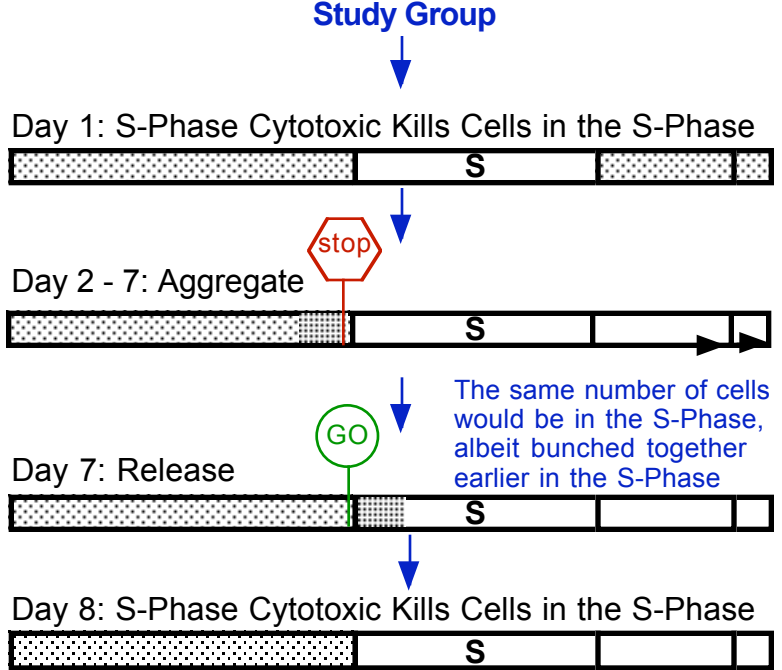
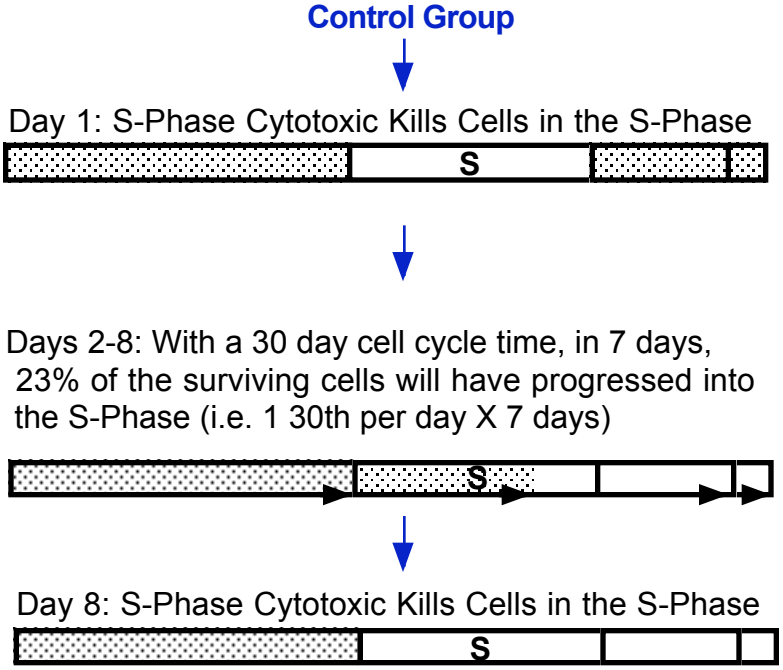
Failure Reason 1: Aggregation periods were too short

- **Several Density Related Stasis Mechanisms Slow Growth**
 - Density restricts blood and oxygen delivery = slowed growth across all phases
 - Upregulation of density dependent pathways (e.g. p27) favors G1 stasis / low S-Phase fractions
 - Ratio of ambient growth factors to cells drops = G1 stasis/low S phase for HER+ mutations
 - Density restricted blood = restricted endocrine delivery = G1 stasis / low S-Phase fractions
- **Cancer Cell Cycle Times are much longer than most researchers realized**
- **10 population doublings from 1 cc to lethal burden yields an ~avg. cycle time**
 - Colon Cancer BSC Median Survival of 194 days \div 10 population doublings = ~ 19 day cycle time
 - Breast Cancer, untreated, under ideal conditions is ~ 30 days⁽¹⁾
 - Breast Cancer, treated with anti-estrogens, is ~ 90 days
 - Anastrozole Median Survival of 913 days \div 10 population doublings = ~ 91 days
 - Faslodex Median Survival of 844 days = ~ 84 days
 - Menopause and Chemo. ablation of Ovaries drops endocrine levels, mimics anti-estrogens

1) Disclosed in US 6,486,146 from BSC survival data and also corroborated by assay data of Misell et. al. 2005, summarized in US 7,507,704)

Failure Reason 1: Aggregation periods were too short

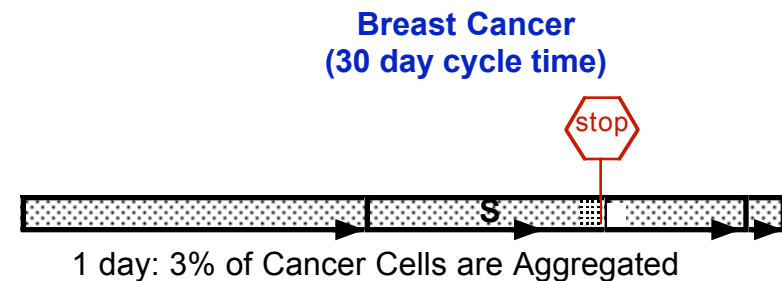
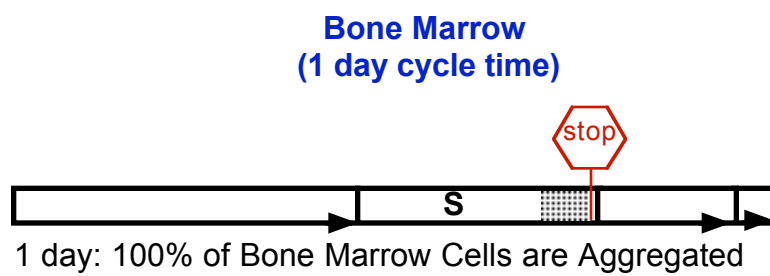
- **Lippman et. al. Failed Attempt at estrogen modulated synchronization**
 - S-Phase cytotoxic on days 1 and 8, Aggregation on days 2 - 6, Release on day 7
- **Even using a 30 day breast cancer cell cycle time, the number of cells in the S-Phase would have been the same in both the control and study group**



- **Exactly the same number of cells would be killed in both groups**
(provided no preexisting endocrine deficit related stasis)

Failure Reason 2: Lack of Targeted (Tumor Specific) Aggregation

- **Non Targeted CCSC preferentially aggregates normal 1 day cyclers**
 - Non tumor specific aggregating agents include vincristine, methionase, hydroxyurea, etc...
- **One Day of Non Targeted Aggregation:**



- **Typical Result: High hematologic toxicity, Low increase in tumor response**

The TS - CCSC Patents

The TS-CCSC Patents Overcome the Prior Art Failures

- They are Targeted
- They use Adequate Aggregation Periods

Categorized By Mutation or Characteristic Modulated for S-Phase Enrichment:

- **HER1 Cancers** (US 7,507,704)
- **HER2 Cancers** (US 7,309,486)
- **Endocrine Dependent Cancers** (US 6,486,146)

Scope of Patent Coverage

- 900,000 Prospective US Patients Annually for TS - CCSC

Cancer	New Cases	Deaths	Prevalence			TS-CCSC Prospects			CCSC Total
			HER1	HER2	ED	HER1	HER2	ED	
Lung	219,440	159,390	55%	30%		120,692	65,832		186,524
Breast	194,280	40,610	15%	20%	60%	29,142	38,856	116,568	184,566
Prostate	192,280	27,360	60%		70%	115,368		134,596	249,964
Colon/Rectum	146,970	49,920	50%			73,485			73,485
Lymphoma	74,490	20,790							
Bladder	70,980	14,330	40%			28,392			28,392
Melanoma	68,720	8,650							
Renal	57,760	12,980	70%			40,432			40,432
Uterine	53,430	27,310	50%		30%	26,715		16,029	42,744
Leukemia	44,790	21,870							
Pancreatic	42,470	35,240	40%			16,988			16,988
Thyroid	37,200	1,630							
Oral/Pharynx	35,720	7,600	80%			28,576			28,576
Liver	22,620	18,160							
Brain/nerve	22,070	12,920	45%			9,932			9,932
Ovary	21,550	14,600	5%		80%	1,078		17,240	18,318
Stomach	21,130	10,620							
Myeloma	20,580	10,580							
Esophagus	16,470	14,530	75%			12,353			12,353
Other	116,400	53,250							
Total	1,479,350	562,340				503,152	104,688	284,433	892,273

Est. Cancer Cases and Deaths, US, 2009 (per American Cancer Society)

ED = Endocrine Dependent: estrogen / progesterone for breast and uterine, testosterone / estrogen for prostate, GnRH for ovarian
Receptor Prevalence (HER1, HER2, ED) applied to new cases

TS- CCSC Market Potential

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- **900,000 Prospective Patients for the mutations covered by the 3 patents**
- **225,000 CCSC Patients for plan purposes (@ 25% of Prospective Patients)**
- **~ \$ 50,000 Full Regimen Cost = \$ 11 Bil. Revenue potential**

Value Proposition Totem Pole

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Value Proposition is “Best Standard of Care” for these 225,000 patients

Using a \$50,000 Full Regimen Cost Breakdown of:

- ~ \$ 30,000 Drug Package Cost to Patient
- ~ \$ 10,000 Drug Administration, Tests, Pathology, etc...
- ~ \$ 10,000 Physician Visits / CCSC Protocol Monitoring and Evaluation

Value Proposition To Full Service Oncology Provider:

- 225,000 Patients X \$ 50,000 Full Regimen Price = \$ 11 Bil. Annual Revenue
 - Full Service Providers include US Oncology, Cancer Treatment Centers of America, etc...

Value Proposition To Drug Manufacturers:

- 225,000 Patients X \$ 30,000 Drug Package = \$ 6.75 Bil. Annual End User Revenue
 - Drug Manufacturers include S-Phase Cytotoxics, HER 1/2 Blockers, Endocrine Downregulators, etc...

Value Proposition To Personalized Medicine Service Provider:

- CCSC Test Panel and Personalized Protocol at \$ 2,500
- 900,000 Prospective Patients X \$ 2,500 CCSC Personalized Protocol Price = \$ 2.25 Bil. / yr
 - Personalized medicine providers include McKesson Specialty Care Solutions, Proventys, etc...

Value Proposition Summary

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Value Proposition to Full Service Oncology Provider

- Our IP offers a large potential for revenue growth over competitors

Value Proposition to New S-Phase Cytotoxic Manufacturer

- New drugs not likely to outperform existing 100% S-Phase kill rate cytotoxics
- New S-Phase cytotoxic + legacy protocol \leq Irinotecan or Gemcitabine efficacy
- NexGen's Protocol Advantage would easily change that
- Comparable S-Phase cytotoxic + NexGen protocol = Best Standard of Care

Value Proposition to reversible HER1 / HER2 Blocker Manufacturer

- Numerous HER1 / HER2 blockers currently under development
- Protocol advantage would put the collaborator at the front of the pack

Value Proposition to Personalized Medicine Solutions

- Expands cost saving solutions to life saving and revenue generating solutions
- Novel Protocols that boost median survival boost commercial client revenues
- Novel Life Saving protocols bring large publicity benefit