



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
- FDA approved drugs to do this already exist for many cancers

The Product : TS-CCSC Protocols

Modulate tumor specific mutations or characteristics for:

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

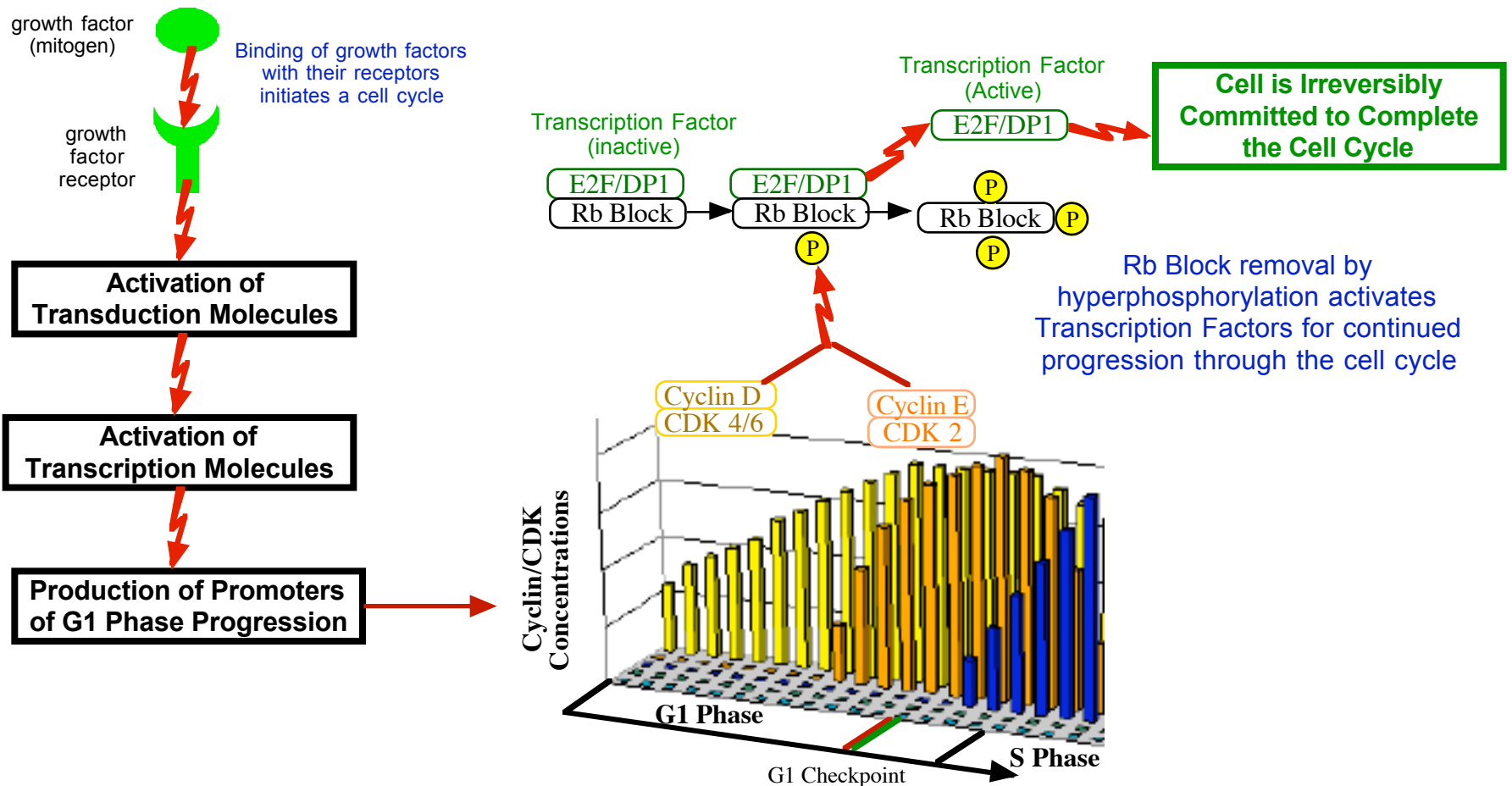
Value Proposition

- “Best Standard of Care” at a fraction of the cost of proprietary drug regimens

Science Background

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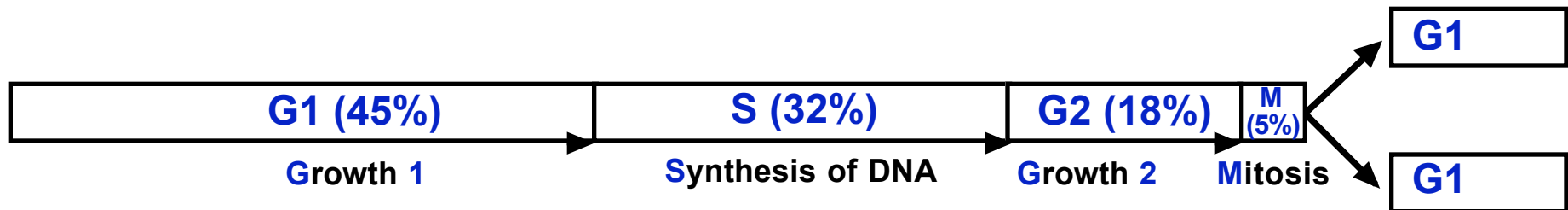
- Binding of growth factors with receptors initiates a normal cell division cycle
- Mutations in growth control pathways cause cancer
 - Growth Factor Receptor Overexpression / Inappropriate Expression (our target market)
 - Inappropriate Expression of Transduction Molecules (RAS “active”)
 - Rb Block Deletion Mutations



Science Background

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- All dividing cells go through 4 distinct phases



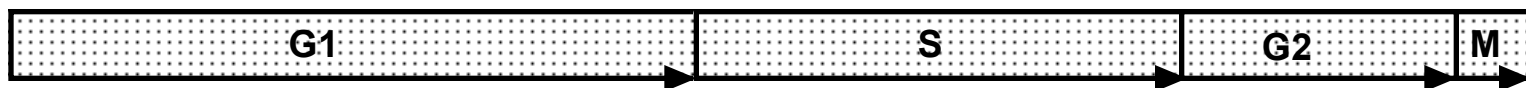
- Good S-Phase cytotoxics (gemcitabine, irinotecan) can kill all cells in the S-Phase
 - However less than a third of cells are in the S-Phase

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

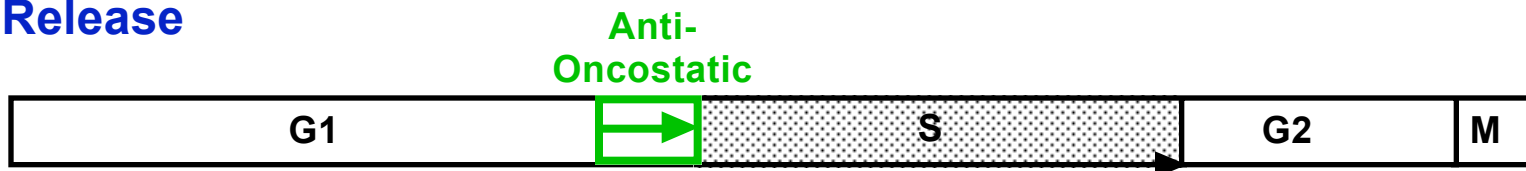
0) Start with Randomly Distributed Cancer Cells



1) Aggregate



2) Release



3) Kill



Example: Endocrine Dependent Cancer ⁶

- A Cornell study found ~ half of prostate cancers are driven by an estrogen activated cell surface receptor (fusion mutation)
- After an initial S-Phase Cytotoxic admin. to depopulate the tumor:

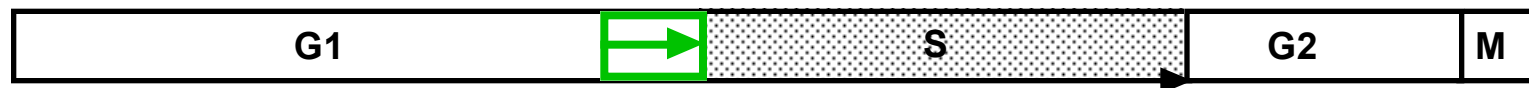
1) Aggregate

G1 Phase Oncostatic
GnRH Antagonist + Aromatase Inhibitor



2) Release

Anti-Oncostatic
Estrogen



3) Kill

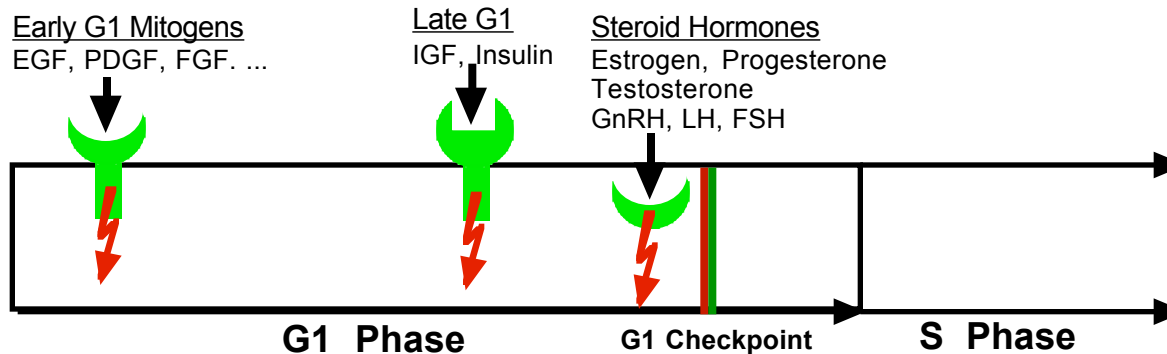
S-Phase Cytotoxic
gemcitabine or irinotecan



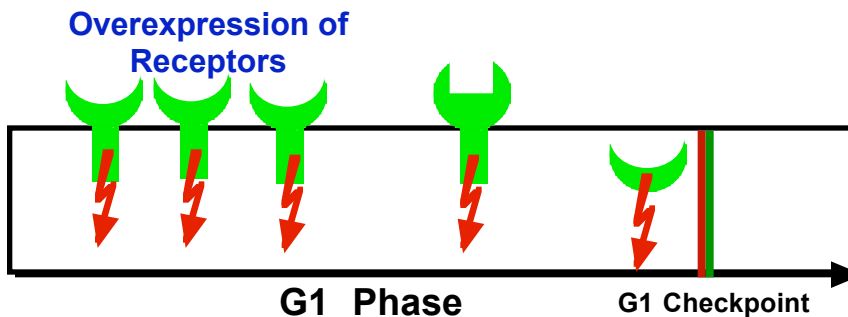
TS-CCSC Targeted Mutations

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- Multiple receptor activation is typically required prior to S-Phase entry



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



HER1 (EGF) Receptor:

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

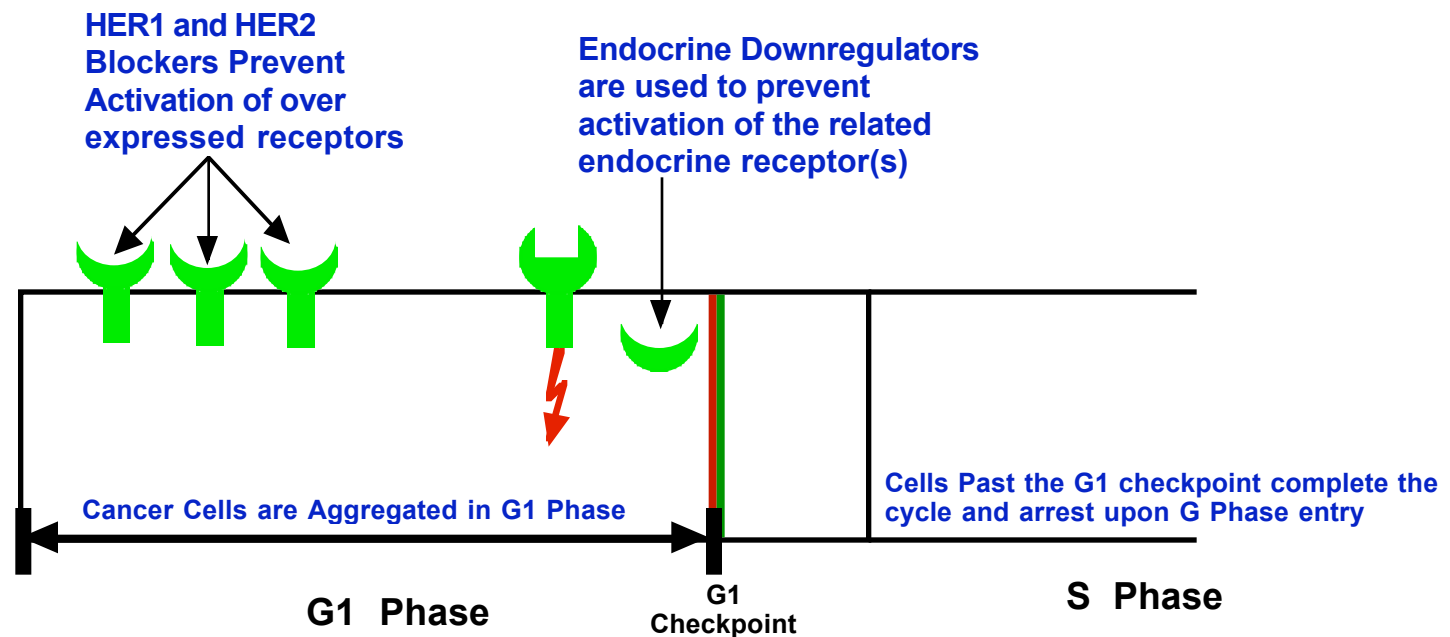
HER2 Receptor (potentiates HER1):

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

TS-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



TS-CCSC - HER 1 & 2 Overexpression

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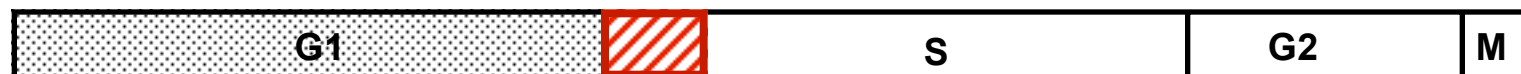
- Reversible HER blockers are preferred

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®	Sanofi-Aventis
	Rimactan®	Sandoz
Carbamazepine	Tegretol®	Novartis
Phenytoin	Dilantin®	Parke Davis/Pfizer
	Phenytek®	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 Cytotoxic

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- High S-Phase kill rate cytotoxics required in step 3 already exist:

3) Kill



Known Good

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

Potential New

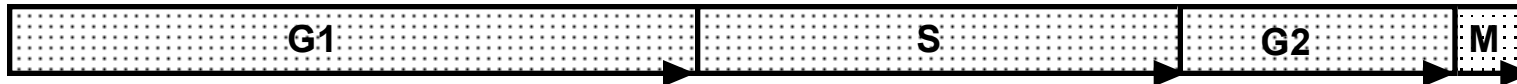
<u>Name</u>	<u>Company</u>
SN-38 Pro Drug SN2310	OncoGenex
DNA Terminator Triapine	Vion

TS-CCSC vs. Single Agent Cytotoxic Protocol

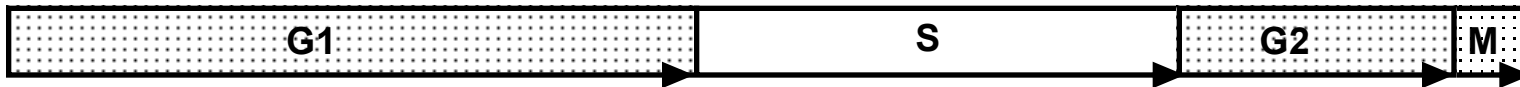
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- A Legacy Protocol kills less than a third of cancer cells per administration

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

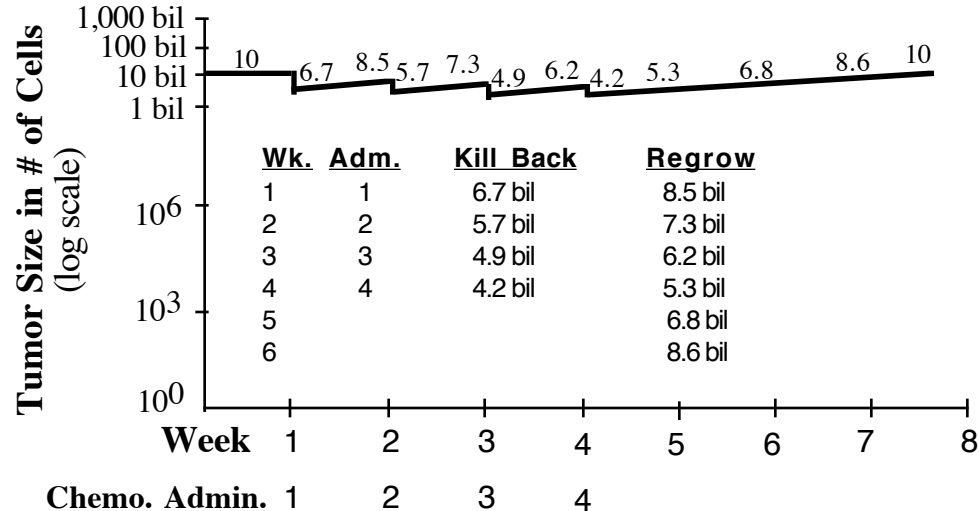
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- Legacy Protocols use 7 or 21 day administration intervals
 - Do not prevent regrowth between administrations, hence kill back is not cumulative

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.)



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

TS-CCSC vs. Single Agent HER Blockers

- **A HER Blocker is mechanistically a G1 Phase Cytostatic**
 - “G1 cell cycle arrest and growth inhibition” corroborated ex-vivo by Bunn et. al.⁽¹⁾
 - Consistent with MOA of preventing receptor activation
- **Cytostatics stop, but do not kill cancer**
- **TS-CCSC would easily outperform stand alone cytostatics**
 - HER blockers with 90% efficacy rates could theoretically achieve 90% aggregation
 - S-Phase fractions of 90% would result in 99.9% tumor reduction in 3 TS-CCSC cycles (90 days)
 - >8 TS-CCSC cycles meet the theoretical requirements for curative outcome (Skipper Model)

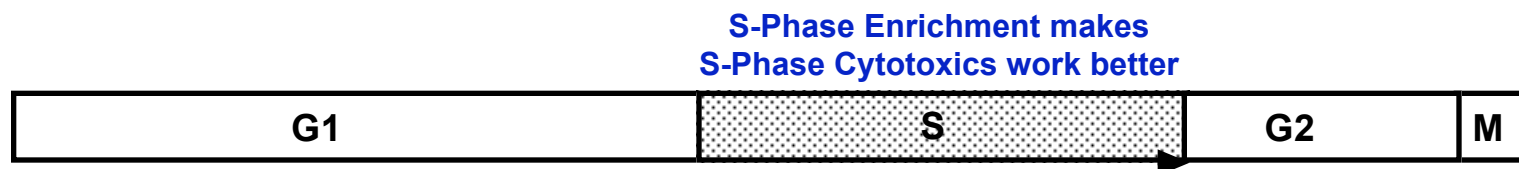
1) Paul A. Bunn Jr. et. al., Clinical Cancer Research, Vol. 7, 3239 - 3250, October 2001

TS-CCSC vs. Cytostatic/Cytotoxic Combinations

- **Concurrent use of Cytostatics and S-Phase Cytotoxics** (per 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, TS-CCSC's Interlaced Protocols result in S Phase enrichment**

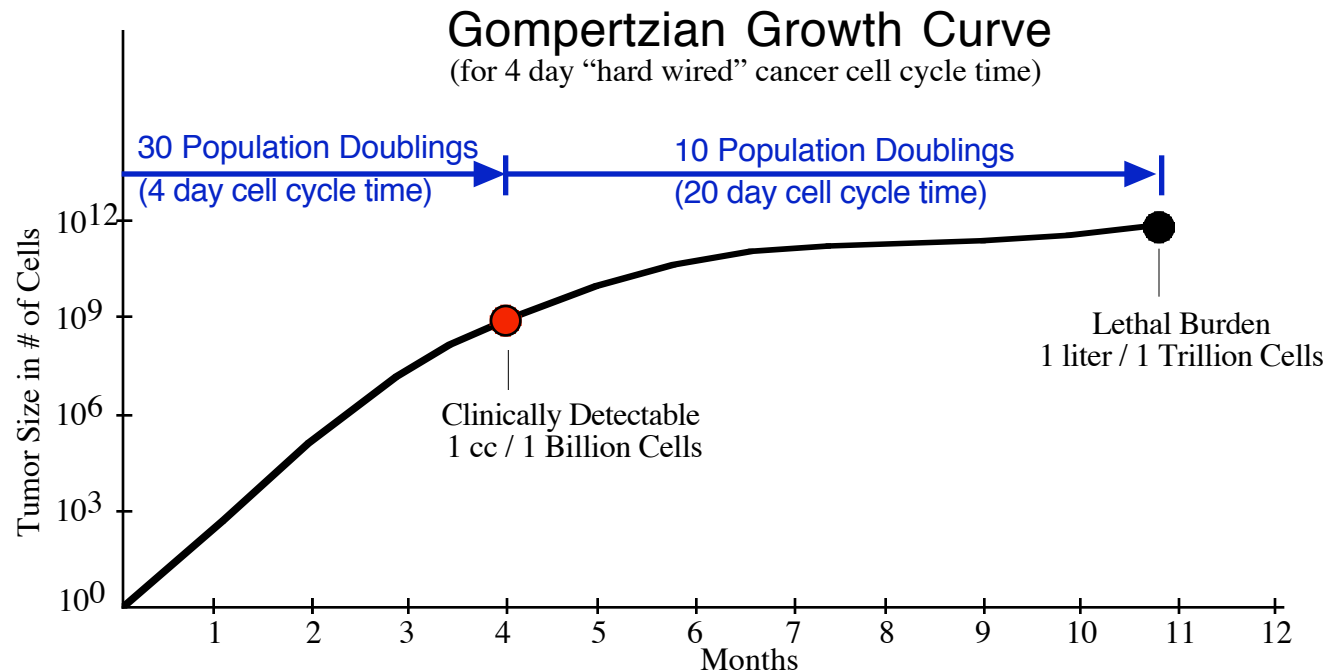


TS-CCSC vs. Failed Prior Art CCSC

- 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

Aggregation periods were too short versus Cancer Cell Cycle Times

- Cancer growth is logarithmic and follows a Gompertzian Growth Curve
 - Cell cycle times slow as tumors grow



- **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

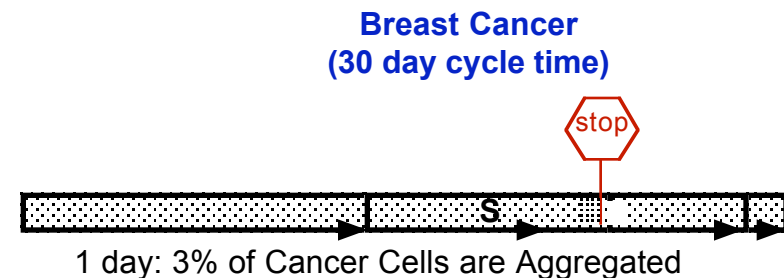
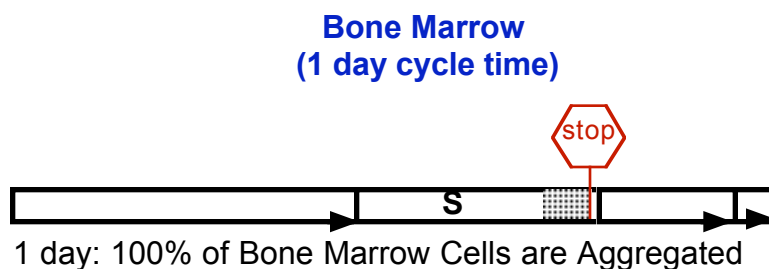
Aggregation periods were too short versus Cancer Cell Cycle Times

- **Cancer Cell Cycle times: 20 - 90 days**
- **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 Chemotherapeutic Ablation of the Ovaries mimics anti-estrogens
- **In contrast, Normal Active Cyclers : 1 day cell cycle time**

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: Lack of Targeted (Tumor Specific) Aggregation

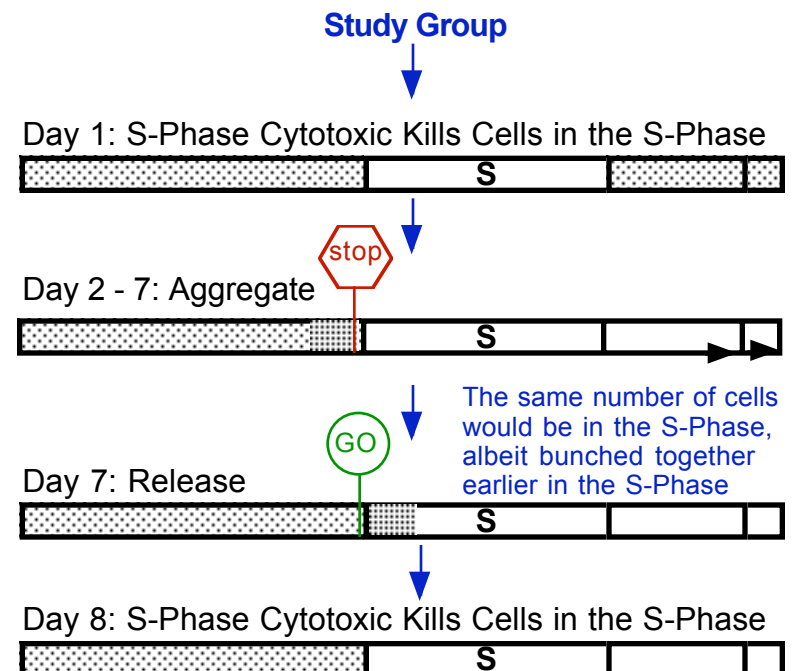
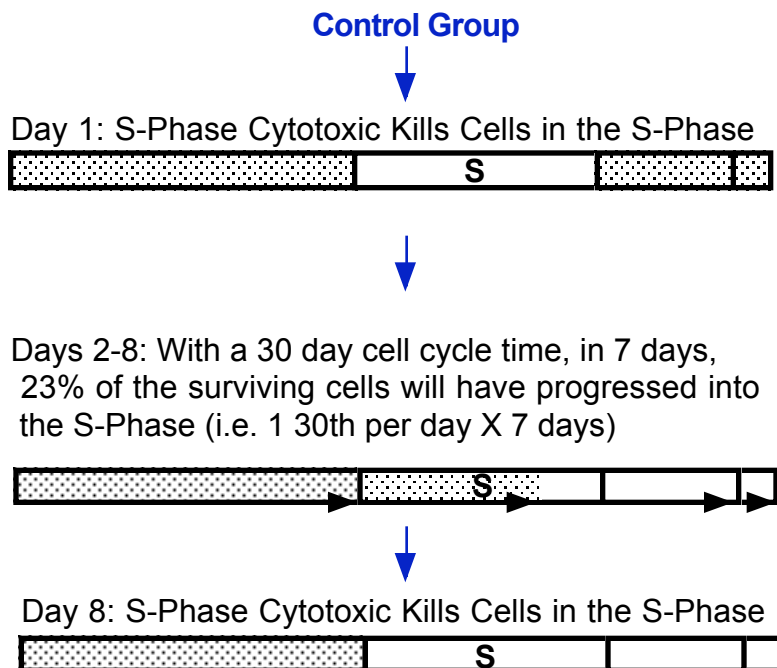
- **Non Targeted CCSC preferentially aggregates normal 1 day cyclers**
 - Non tumor specific aggregating agents include vincristine, methionase, hydroxyurea, etc...
- **One Day of Non Targeted Aggregation:**



- **Typical Result: High hematologic toxicity, Low increase in tumor response**
- **Effectively human proof of concept, in reverse**
 - **Prior Art preferentially aggregated and obliterated bone marrow cells**
 - **We preferentially aggregate and obliterate tumor cells (hence TS-CCSC)**

Failure Reason: Targeted (not really) and 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
 - **Randomized Patients - not selected for estrogen dependence**
- **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**



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/yr for the mutations covered by the 3 patents**
- **225,000 Ideal Responders for plan purposes (@ 25% of Prospective Patients)**
- **~ \$ 50,000 Annual Regimen Cost = \$ 11 Bil. Revenue potential per year**

Service Business Model

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

- At a fraction of the cost of expensive proprietary drug regimens

Business Model: Service Model that allows oncologists to make more money

- Effectively usurping money from expensive proprietary drug regimens
- **TS-CCSC Chemotherapy Centers:**
 - Ongoing new TS-CCSC clinical trials for continued growth
 - Publication and promotion of TS-CCSC clinical results
 - Patient recruitment
- **TS-CCSC Chemotherapy Centers - Working with Physicians to:**
 - Provide physician with prospective TS-CCSC patients
 - Participating oncologist services built into regimen price
 - Validated drug packages and TS-CCSC administration services

Funding and Exit Points

Seeking \$ 2 Mil. / \$ 25 Mil.

First \$ 2 Mil. :

- **Addition of Human Data to Patents to make IP commercially fundable**
- **Obtain 10 Phase II data points in 3 defined cancer patient populations**
 - **US CRO Expenses: \$ 1.8 mil. (@ \$ 60K per data point X 30 data points)**

Next \$ 25 Mil. :

- **Expansion of clinical data**
- **Infrastructure for service model business (\$ 11 Bil. Revenue Potential)**
 - **“Chemotherapy Only” has low capital requirement (unlike surgery or radiation)**
 - **Main infrastructure cost is for market control**
- **Exit possible in 3-5 yrs. by sale of growing, profitable business or by IPO**

Potential Purchasers:

 - **Oncology Service Provider (e.g. US Oncology, Cancer Treatment Center of America)**
 - **S-Phase Cytotoxic Drug Manufacturer (either proprietary or generic)**
 - **Personalized Medicine Service Provider (e.g. McKesson, Proventys)**

Summary

- **Market and Cancer Treatment Transforming Technology**
- **Significant Addressable Markets in Several Cancer Indications**
- **Low risk - uses only existing FDA approved drugs**
- **Short time to value inflection, revenue generation, and possible exit point**
 - **Can be started in Phase II setting**
- **Alternatively, potential for long term, high growth service business**
 - **TS-CCSC Chemotherapy Centers**
 - **US Revenue potential of \$ 11 Bil./yr.**