TSC Treats GBM by Reducing Hypoxia

a Novel Approach

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the problem

GBM is the most common and deadly type of primary malignant brain tumor

If the patient cannot have an initial surgery, median survival rate is from 9–10 months. Because of such dire prognosis, these patients are frequently excluded from GBM clinical trials.

Hypoxia has been implicated as a factor reducing the effectiveness of both radiation and chemotherapy

Even so, little research has been directed to lessening its effects.

the need

well oxygenated tumor cells are

2–3X more likely

to be eliminated by radiation[1]

Little research has been done concerning hypoxia and chemotherapy, but it may be related to the effect of hypoxia on cell cycles.

Is there a way to improve oxygenation in cancerous tumors?

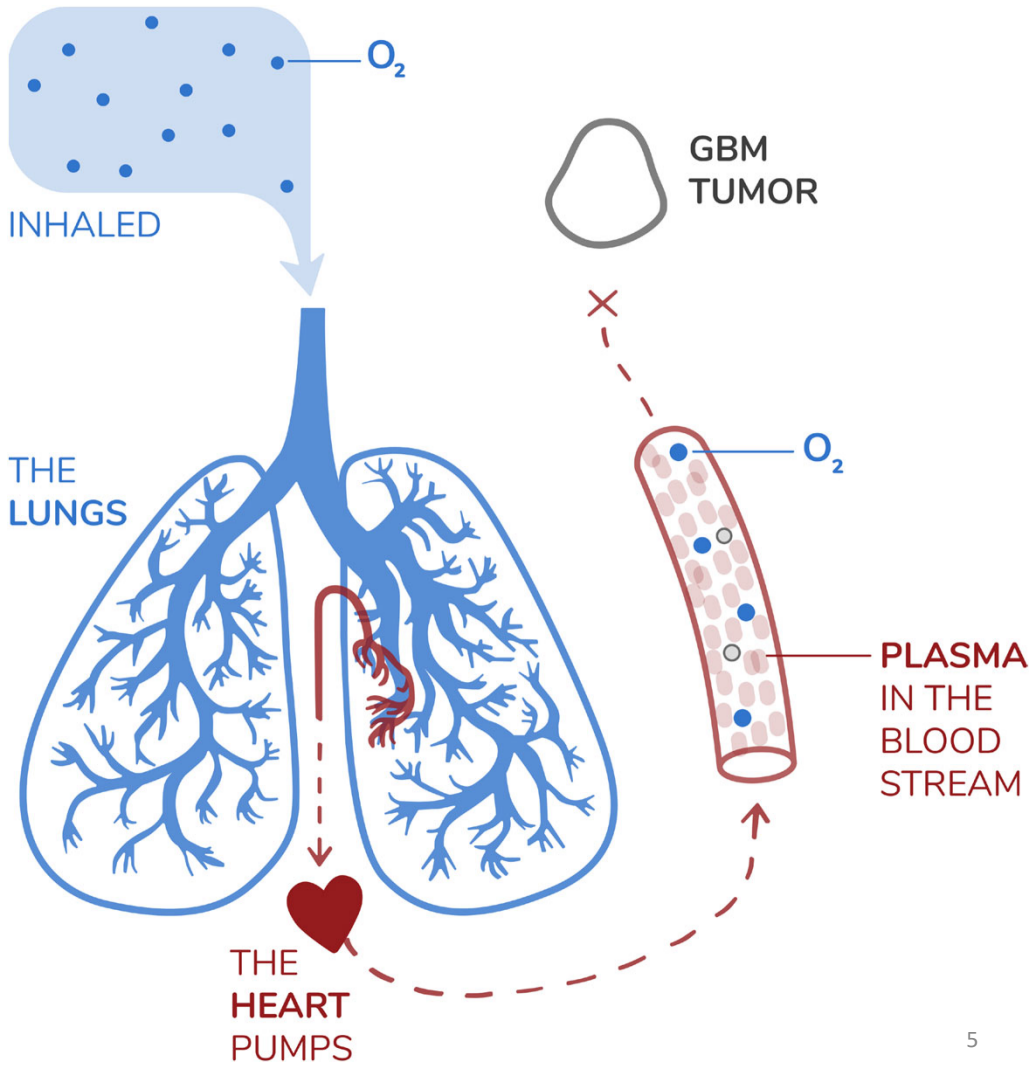
[1] *Radiobiology for the Radiologist.* Hall and Giaccia, Chapter 6, Oxygenation Effect and Reoxygenation, Pgs 85 - 105

reducing hypoxia

Brute force methods:

- increase concentration of O2 in inspired gas
- increasing solubility of O2 in plasma by adding fluorocarbons or other chemicals

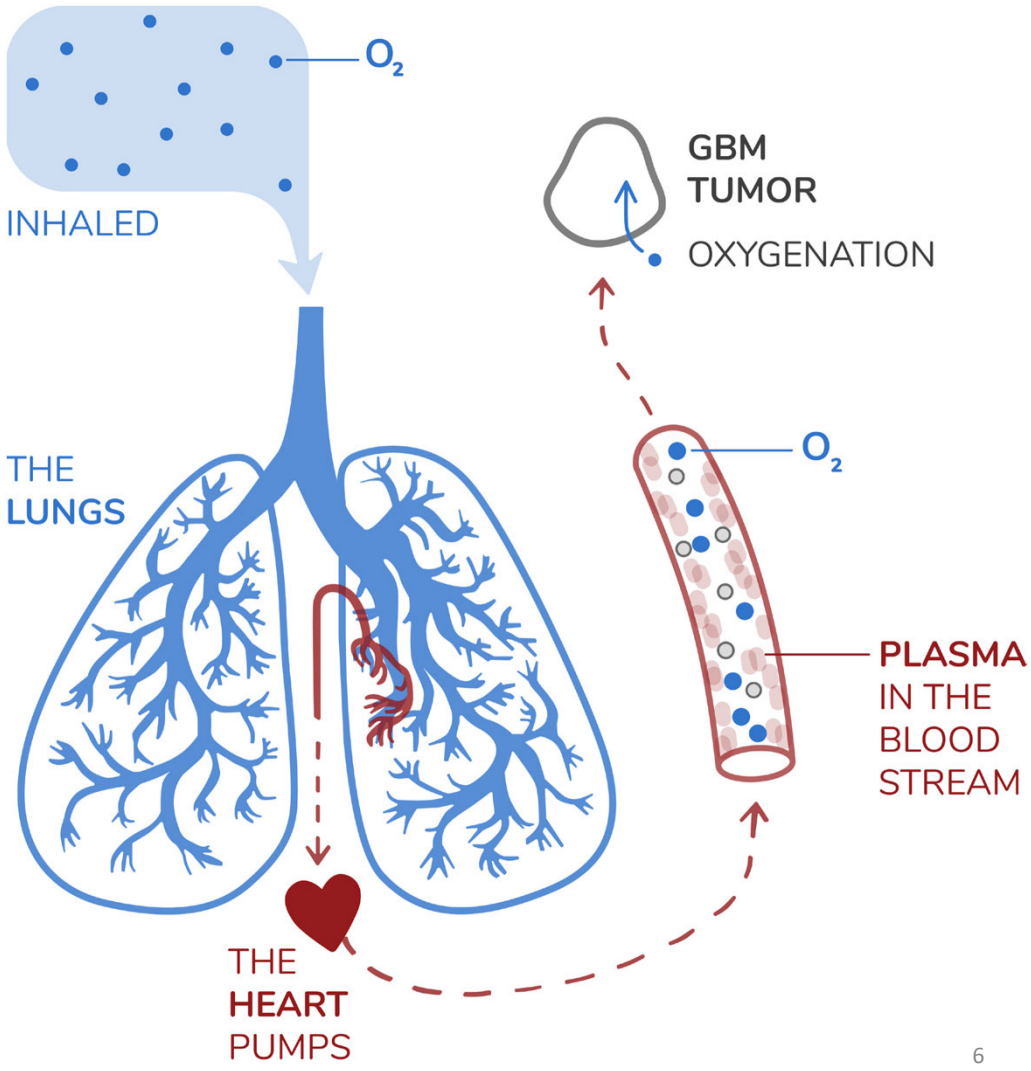
but none of these have proven to extend survival



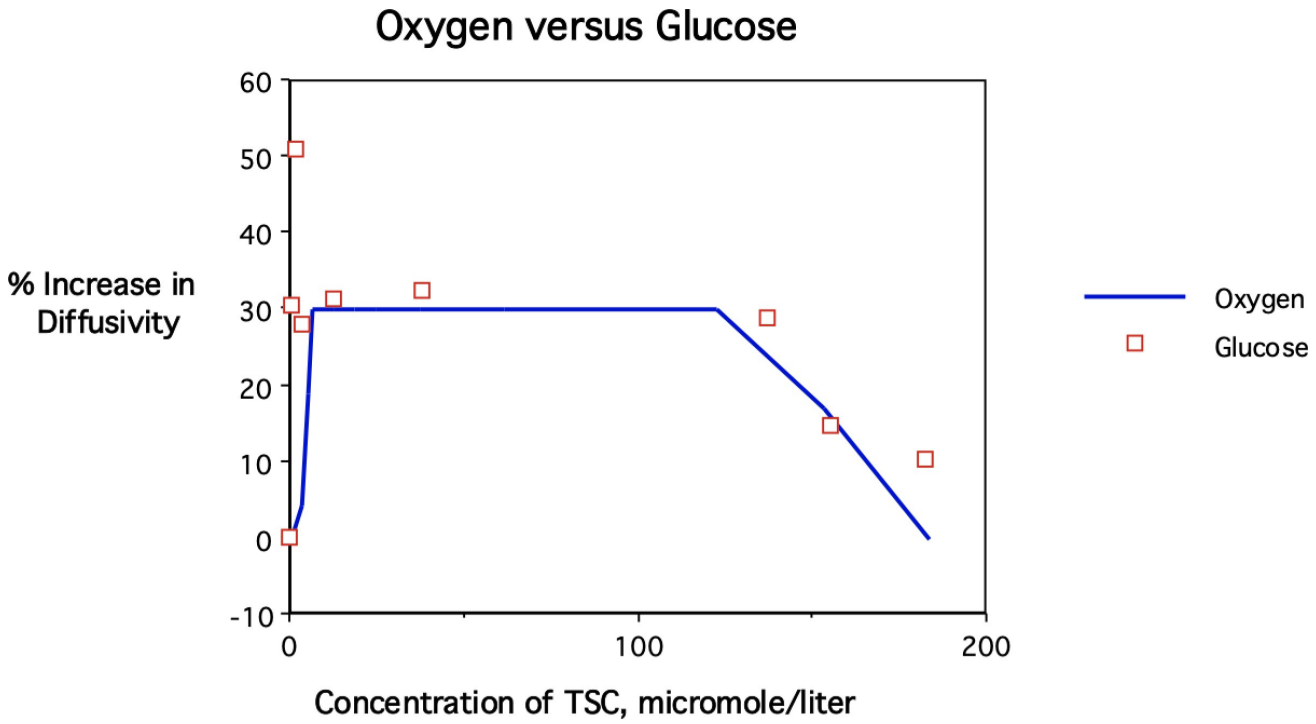
A solution from Chemistry: TSC

TSC promotes the formation of additional hydrogen bonds among the water molecules of the blood plasma.

This allows increased diffusional movement of small molecules like oxygen and glucose.



TSC



Over-oxygenation does not occur because oxygen and glucose transport rates increase by the same percentage.[1]

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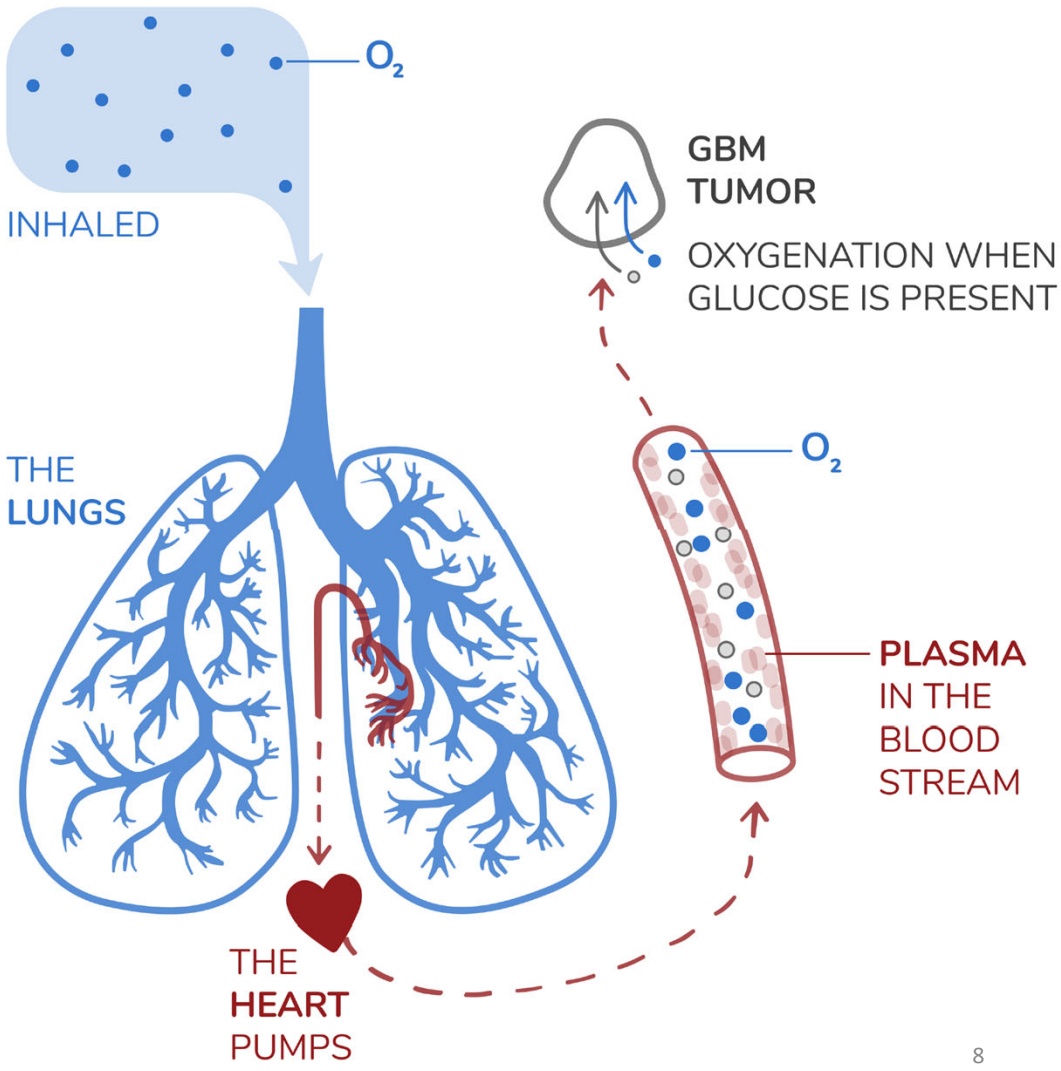
Gainer, Expert Opinion, *Trans-sodium crocetinate for treating hypoxia/ischemia*, 2008 Informa UK [1]

A solution from Chemistry: TSC

30% increase of **O2** paired with a

30% increase of **glucose**

keeps metabolism “in balance”[1]



Gainer, Expert Opinion, *Trans-sodium crocetinate for treating hypoxia/ischemia*, 2008 Informa UK [1]

TSC

“White Label" Drug: all safety studies in humans indicate that TSC has

No known serious adverse effects.

Easily administered by IV injection or IM injection.

Oral administration in development phase.

TSC: Progress

Phase 2 Clinical Trial

TSC for Treatment of Acute Stroke

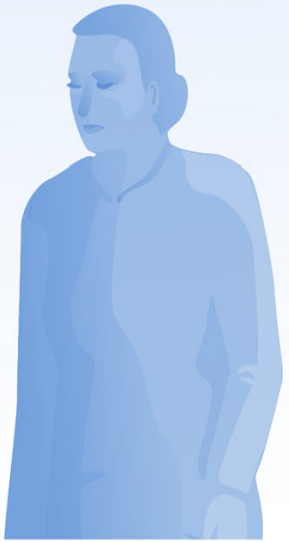
Researchers at UCLA and UVA are cooperating on this trial involving the on-ambulance administration of TSC to 160 patients within 2 hours of the onset of stroke symptoms.

Phase 3 Clinical Trial

TSC for Inoperable GBM Patients

Lead-in portion completed – described later.

TSC: Greater Implications



Hypoxia is the common denominator in
over 23,000,000 patient cases per year

HEMORRHAGIC SHOCK

100,000

CASES / YEAR

Battlefield Casualties (Office of Naval Research)

Kauvar and Charles E Wade, *The epidemiology and modern management of traumatic hemorrhage*: Crit Care. 2005; 9(Suppl 5): S1–S9

TSC: Greater Implications

Hypoxia is the common denominator in
over 23,000,000 patient cases per year

HEMORRHAGIC SHOCK	TRAUMA	MULTIPLE ORGAN FAILURE	STROKE	ONCOLOGY	HEART ATTACK / CHF	RESPIRATORY DISEASES
100,000	**100,000**	**100,000**	**800,000**	**900,000**	**6,000,000**	**15,000,000**
CASES / YEAR	CASES / YEAR	CASES / YEAR	CASES / YEAR	CASES / YEAR	CASES / YEAR	CASES / YEAR

Centers for Disease Control and Prevention, https://www.cdc.gov/datastatistics/index.html

TSC: Greater Implications

Example: Stroke

TSC supports immediate treatment of stroke symptoms without waiting for the in-clinic hemorrhagic v. ischemic determination.

GBM Clinical Trials by Diffusion Pharmaceuticals

Phase 2 (100-202): Open-trial, 56 patients (all comers including biopsy-only).

Surgery: if possible.

Chemo-radiation Therapy: 0.25 mg/kg TSC IV on M,W,F 45-60 minutes prior to 2 Gy radiation. Radiation given 5 days/week for 6 weeks. Temozolomide, 7 days/week 75 mg/m².

Adjunct Chemotherapy: Temozolomide, 150-200 mg/m² given on days 1-5 of six 4-week cycles (nothing on other days). No TSC.

Phase 2 Trial (100-202) Results

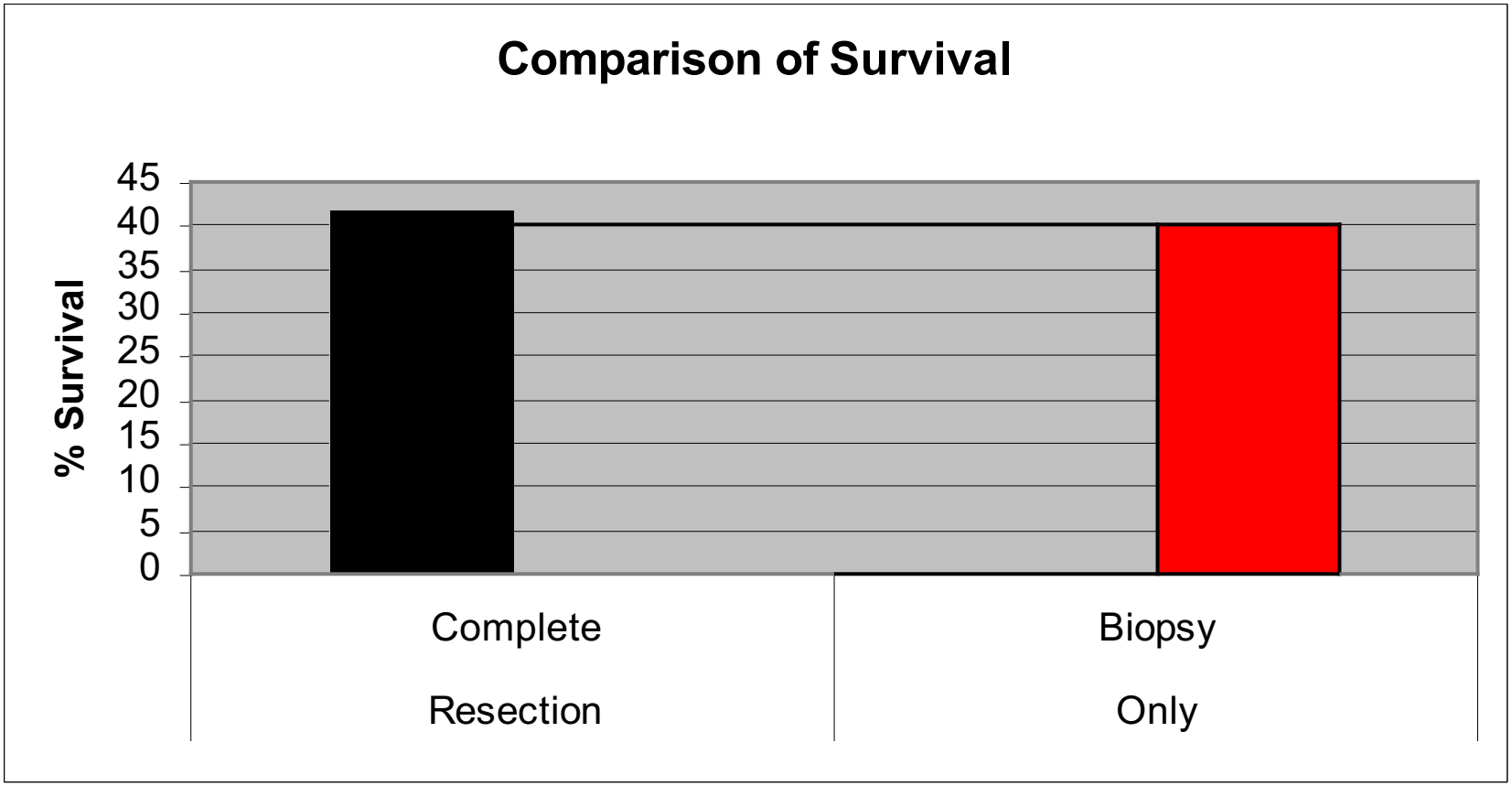
(Published in J Neurosurg, 126:460-416, 2017)

2-Year Overall Survival: 36% versus 27% for SOC
3-Year Overall Survival: 22 % versus 16% for SOC

However for Biopsy-Only Patients:

2-Year Overall Survival: 40% versus 10% for SOC

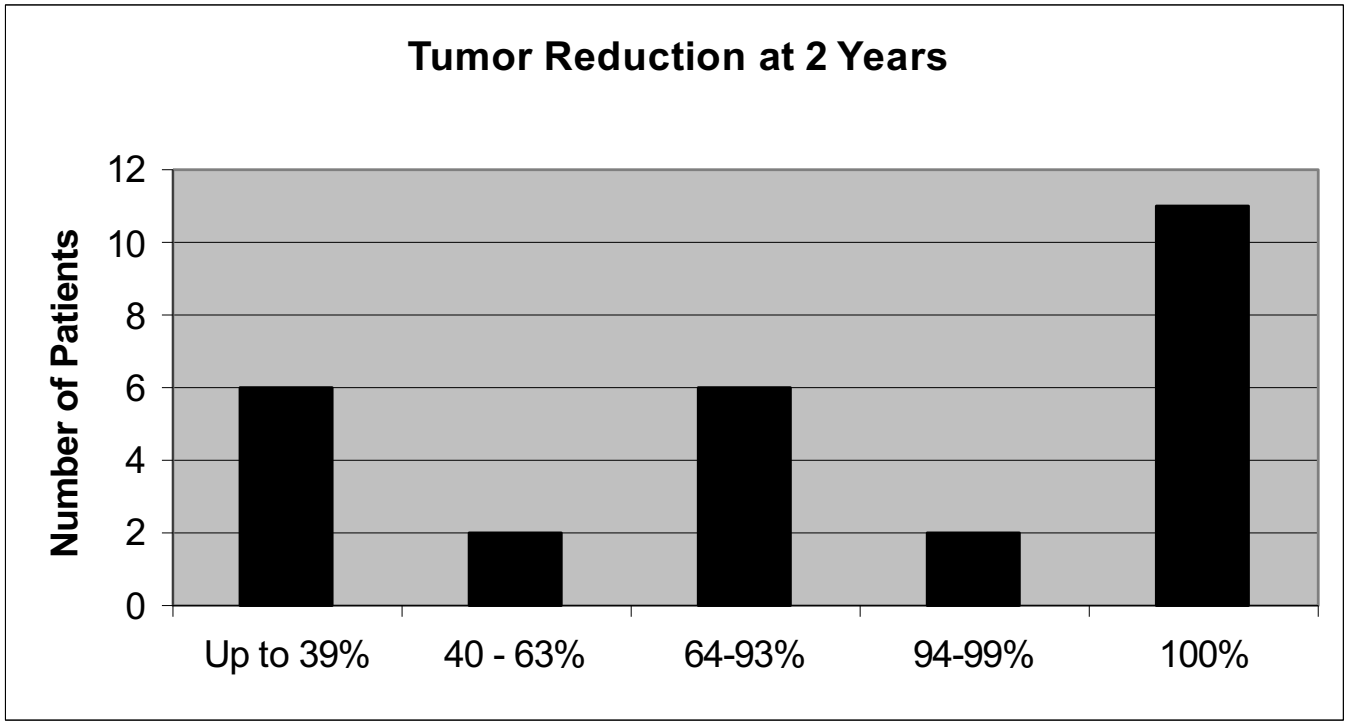
Results from Trial 100-202



Biopsy only patients treated with TSC had the same survival outcome as fully resected patients at 2 years.

Trial 100-202 Tumor Control

Size reduction in 37/41 tumor-bearing patients.



Phase 3 (100-206): Open-label, Randomized, Controlled, 236 patients, biopsy-only.

Chemoradiation Therapy. 0.25 mg/kg TSC given as in Phase 2 trial.

Adjunct Chemotherapy: Temozolomide, 150-200 mg/m², given for days 1-5 of six 4-week cycles. TSC, 1.5 mg/kg, given on Days 1,3,5 one to two hours prior to temozolomide.

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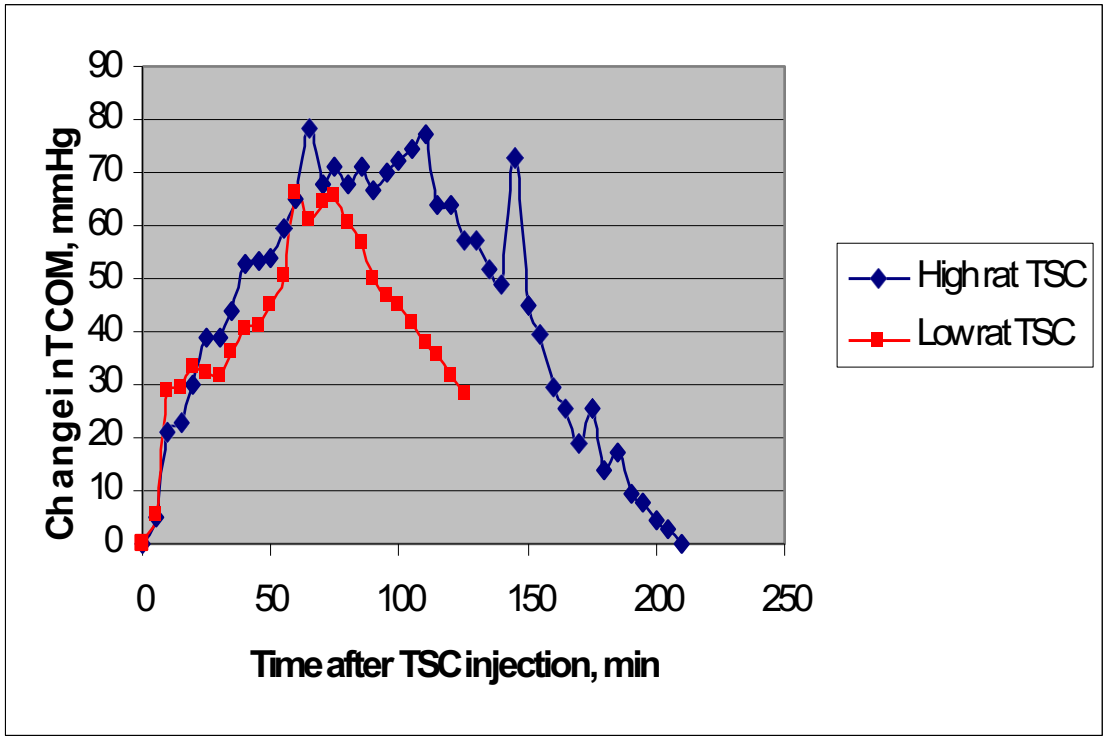
Why a Different Dose for Chemotherapy?

One study in the literature suggested that oxygen and the chemo-therapeutic agent need to be administered at the exact same time to kill tumor cells.



Diffusion internal study verified that chemotherapy was far more efficient with high dose TSC when given 1-2 hours after IV injection --so escalation to high human dose (1.5 mg/kg) was selected for clinical study.

Since this dose is higher than that used during radiation therapy, FDA suggested the following lead-in study:

Each patient would do same radiation therapy as in Phase 2 study.

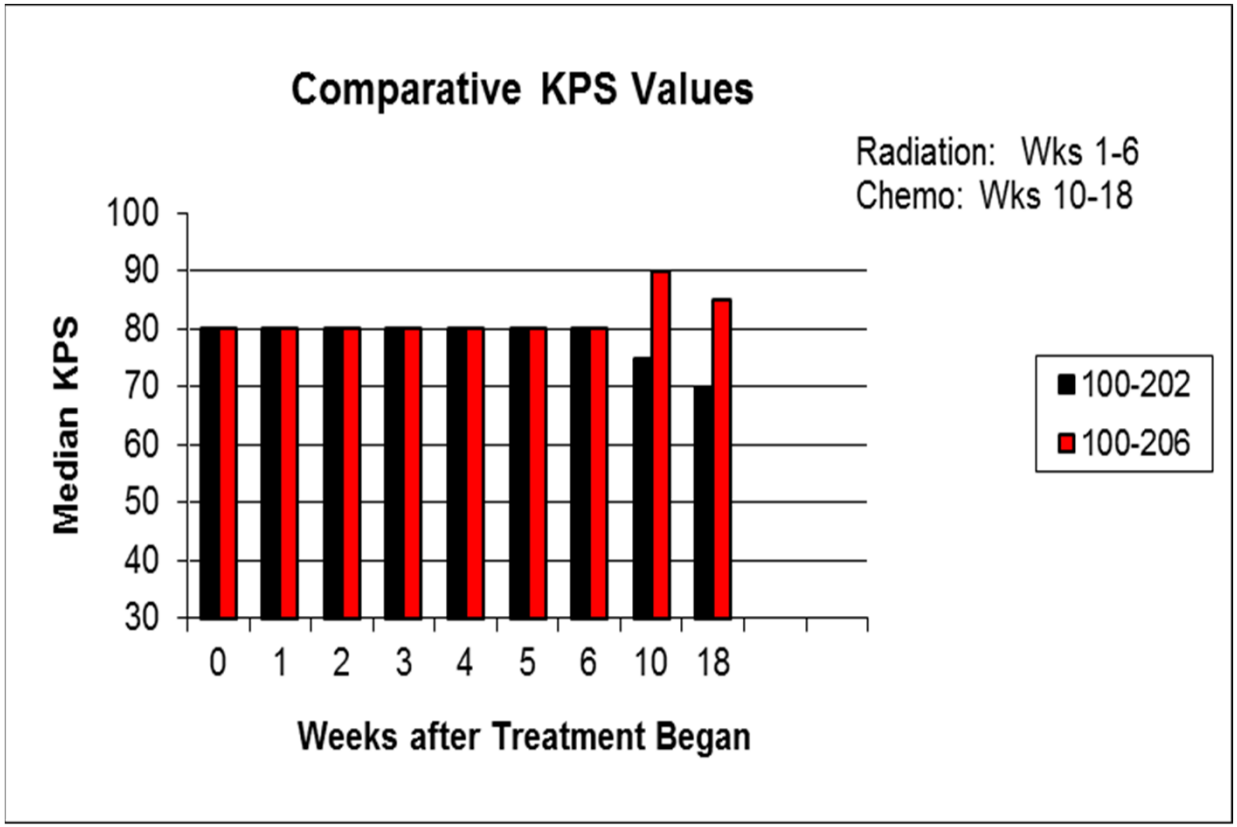
2 patients, each receiving escalating doses of TSC ranging from 0.25 mg/kg to 1.5 mg/kg during chemotherapy cycle. Two such cycles required. DSMB to determine safety and recommend TSC chemo dose.

LEAD-IN

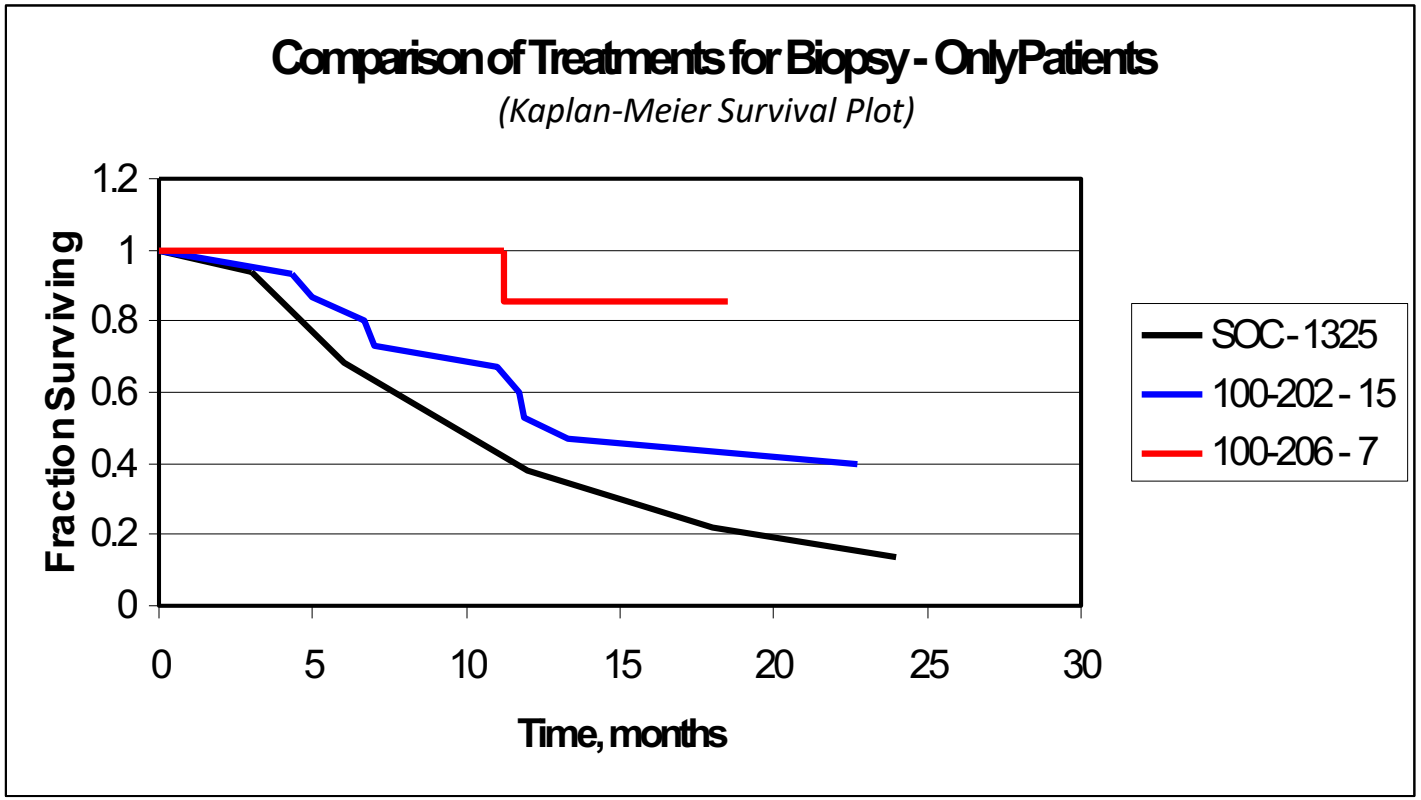
19 patients enrolled in Lead-In Study. 11 patients completed the FDA-required protocol. Of those, 4 received a low dose (0. 25 or 0.5 mg/kg) of TSC while 7 received a high dose (1.0 or 1.5 mg/kg) of TSC. DSMB found no serious adverse events attributable to TSC for any TSC dose, and recommended 1.5 mg/kg to be used for randomized portion of trial.

All 7 high dose patients were alive at end of required protocol, and have been followed up to current time.

Comparison of Karnofsky Performance Scores (KPS) at end of 18 weeks (FDA period)



Currently: 6/7 high dose patients are still alive.



DIFFUSION SEEKING PARTNERS

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