

PANEL PRESENTATION

SYNERGO SB-TS 101.1 HYPERTHERMIA DEVICE

PMA NO. P010045

MEL - MEDICAL ENTERPRISES LTD.

Presenters

- ◆ **Prof. Michael O'Donnell**, *Director of Urologic Oncology, University of Iowa Hospitals & Clinics*
- ◆ **Prof. Fred Witjes**, *Dept of Urology, Radboud University Nijmegen Medical Center, The Netherlands*
- ◆ **Prof. H. Barton Grossman**, *Dept of Urology, University of Texas MD Anderson Cancer Center*
- ◆ **Ms. Ahava Stein**, *Regulatory Consultant for Medical Enterprises Ltd.*
- ◆ **Dr. Yagel Koren**, *Medical Director, Medical Enterprises Ltd.*

Outline of Presentation

- ◆ Introduction..... *Dr. Yagel Koren*
- ◆ Treatment Options..... *Prof. Michael O'Donnell*
- ◆ Device Description and
Pre-Clinical Studies..... *Ms. Ahava Stein*
- ◆ Overview of Clinical Studies..... *Prof. Fred Witjes*
- ◆ Overall Summary..... *Prof. Barton Grossman*
- ◆ Post Approval Study..... *Prof. Michael O'Donnell*

Introduction

Dr. Yagel Koren

Medical Director, Medical Enterprises

Synergo Development

- ◆ Intravesical chemotherapy (incl. MMC) has been widely used for decades to decrease recurrence of Non Muscle Invasive Bladder Cancer (NMIBC)
- ◆ Methods to improve the efficacy of MMC were needed
- ◆ This led to the development of the Synergo hyperthermia device at San Raffaele Hospital, Italy in the early 1990's

Synergo SB-TS 101.1 Device



- ◆ Hyperthermia device to heat bladder walls for synergic effect with MMC in bladder cancer

Synergo Development

- ◆ 1994 - Study 101.1 (pivotal study) began as a collaborative investigator initiated study in 3 academic centers.
- ◆ 1997
 - Medical Enterprises formed and acquired Synergo to commercialize promising technology, and assumed the responsibility for continuation of study 101.1
 - CRFs formed and previous data transcribed
- ◆ Thereafter ALL data filled prospectively to end of study (2001)

Synergo Development (cont'd)

- ◆ 2000 – Synergo received CE mark and Israeli Ministry of Health approval
- ◆ Medical Enterprises:
 - A small company
 - Has Synergo as its only product

Bladder Cancer: Clinical Overview of the Disease and its Treatment

Michael O'Donnell, MD

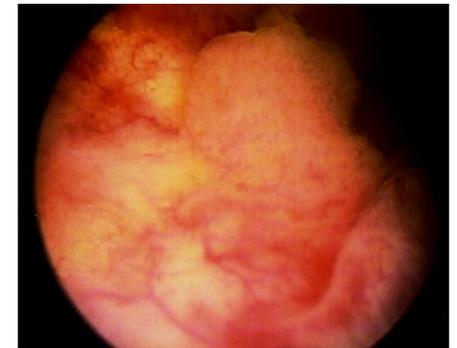
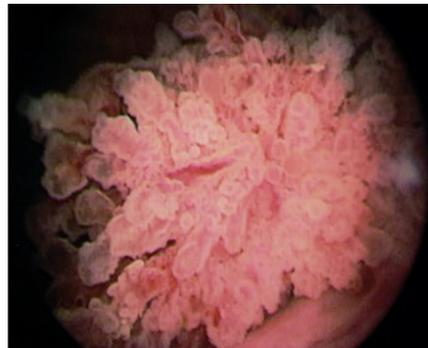
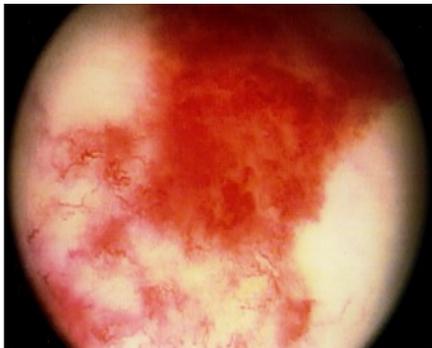
Professor and Director of Urologic Oncology,
University of Iowa, Carver College of Medicine

Past Director, Bladder Cancer Subcommittee-CALGB

Peer Reviewer, AUA Bladder Cancer Guidelines Panel

The Disease

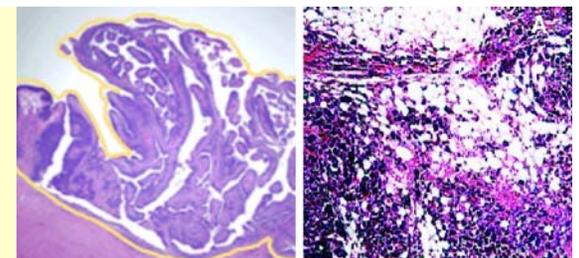
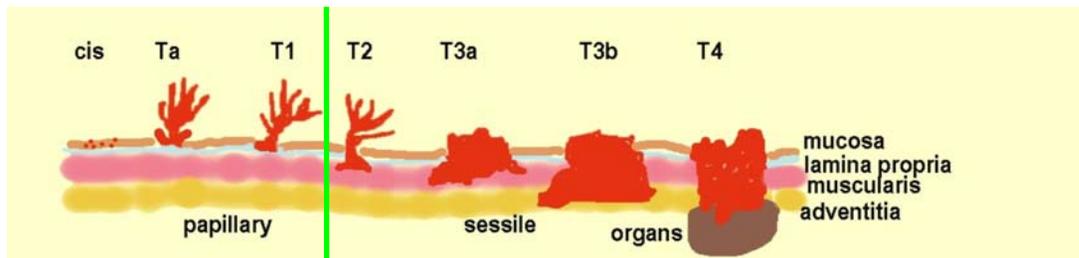
Malignant growth originating from the surface epithelium of the bladder



Distinguished functionally by the STAGE (depth of invasion: superficial vs. muscle invasive) and GRADE (G1, G2, G3 or low/high)

STAGE

GRADE



75% Superficial

25% Muscle Invasive

Low

High

Bladder Cancer Demographics

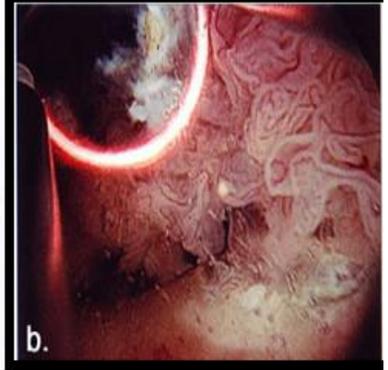
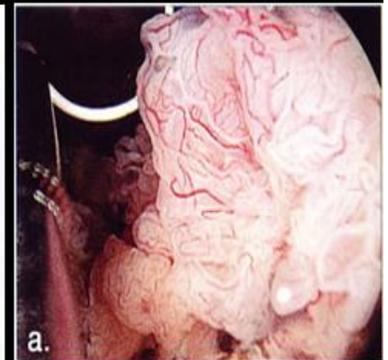
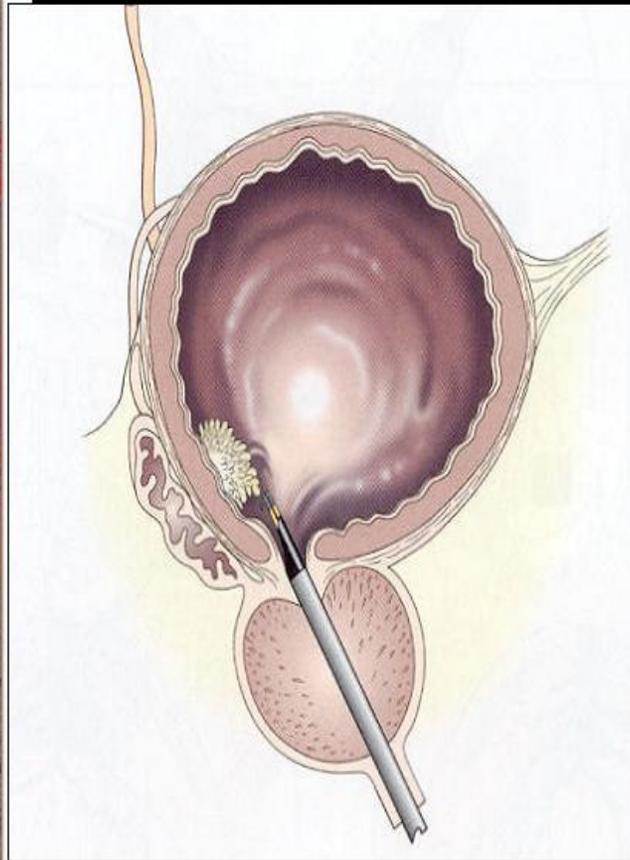
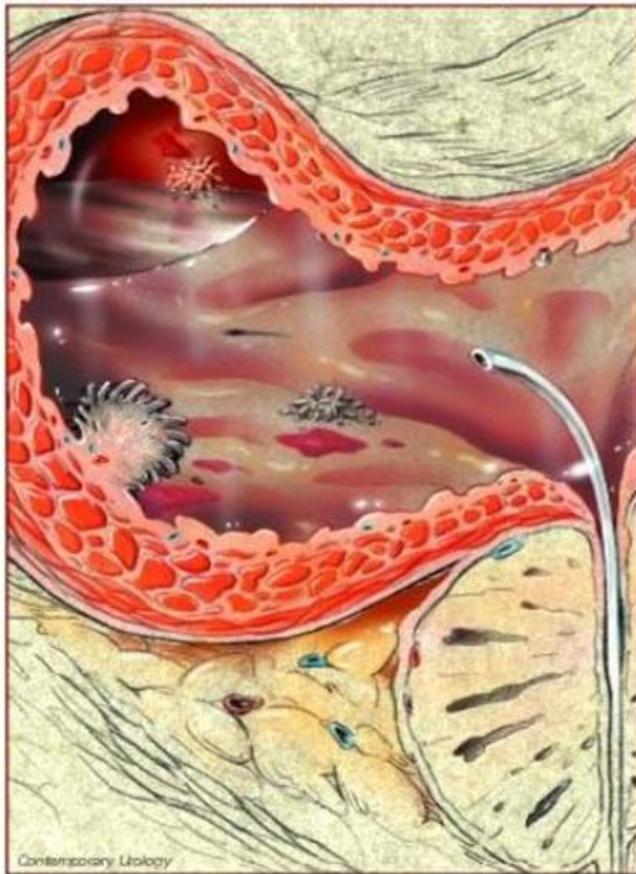


World Wide Incidence of Bladder Cancer is Similar Throughout the “Western World”

Similarity of US and Europe

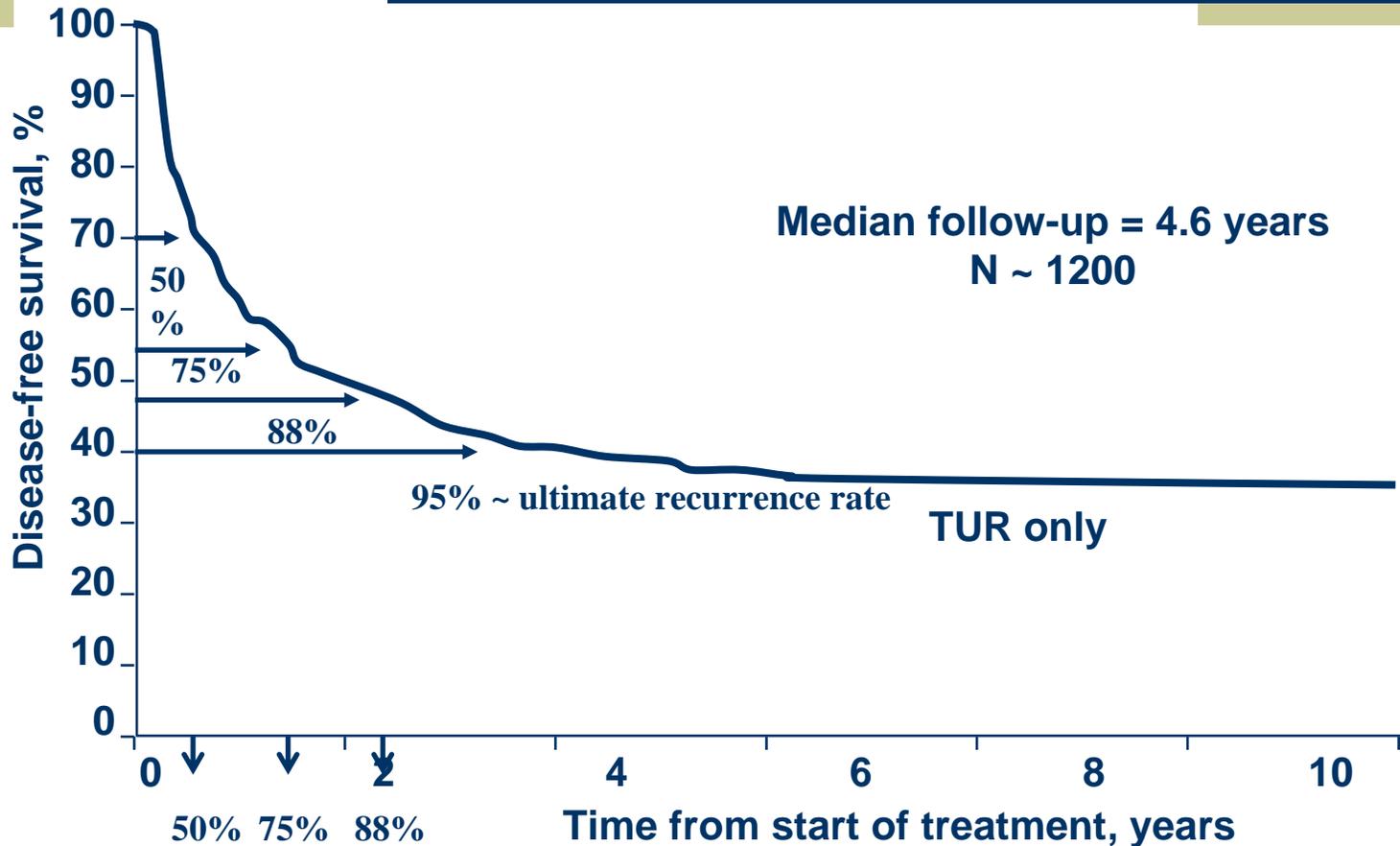
- ◆ Disease characteristics are universal
- ◆ Treatment program is highly similar
- ◆ Guidelines of AUA and EAU reflect similar consensus for management

Cystoscopy with Transurethral Resection (TUR) is the Gold Standard for Diagnosis and Initial Treatment



BUT.....

A Very High Percent Recur with TUR Alone (usually within 2 years)



Composite results of EORTC and MRC studies—Meta-analysis.

Adapted with permission from Pawinski A, et al. *J Urol*. 1996;156:1934-1940.

High Recurrence Rate is the Problem

For this reason, additional (adjuvant) intravesical therapy is advocated by both the AUA (2007) and EAU (2008) guidelines panels according to a risk-adapted policy

Low-Risk (~40% recurrence*)	Intermediate-Risk (~60% recurrence*)	High-Risk (>70% recurrence*)
Single G1Ta, < 3 cm	Multifocal G2Ta, G1T1, solitary G2T1, > 3 cm	Multifocal G2T1, G3Ta-T1, CIS

*2 yr recurrence rates with TUR surgery alone

Intravesical Treatment

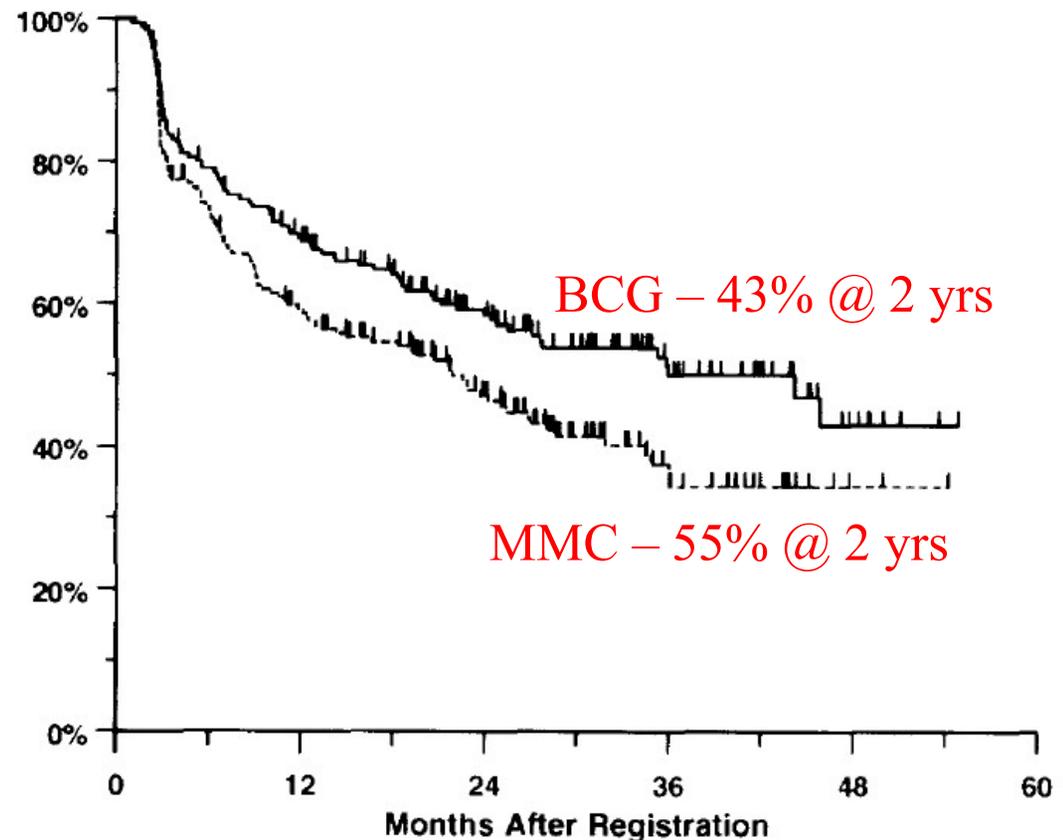
- ◆ Guideline recommendations:
 - In low-risk (50%) one immediate instillation of chemotherapy, usually MMC, is recommended and sufficient
 - In intermediate-risk (35%) one immediate chemotherapy instillation is recommended but insufficient
 - Additional 6-12 months chemo (e.g., MMC) or > 1 yr BCG immunotherapy
 - In high-risk (15%) >1yr BCG or cystectomy is recommended due to added risk of progression

Current Intravesical Treatments Have Serious Limitations

- ◆ Both treatments had high relapse rates
- ◆ Trial was stopped at interim analysis

KM of Disease free survival
BCG Vs MMC
BCG NDA pivotal study

Lamm D. et al 1995 (SWOG), J.Oncol;1,119-126



Toxicity Remains Problem

Toxicity	MMC	BCG
Local		
Frequency/Nocturia	42% (26-59%)	63% (48-76%)
Dysuria	35% (30-41%)	75% (64-84%)
Irritative Symptoms	18% (12-26%)	Too varied
Pain/Cramps	10% (6-14%)	12% (7-18%)
Hematuria	16% (7-28%)	29% (22-36%)
Incontinence	1% (0.4-4%)	4% (3-6%)
Bladder Contracture	5% (2-11%)	3% (2-5%)
Systemic		
Flu-like	20% (4-48%)	24% (18-31%)
Fever/Chills	3% (1-7%)	27% (22-32%)
Arthalgias	9% (0.1-47%)	5% (1-13%)
Myelosuppression	2% (0.3-7%)	1% (0.1-4%)
Nausea/Vomiting	9% (1-26%)	9% (6-14%)
Skin Rash	13% (8-19%)	6% (3-10%)
Other	3% (0.5-8%)	23% (19-27%)
Infectious		
Bacterial Cystitis	20% (17-23%)	20% (13-8%)
Epid/Prost/Urethral	4% (2-9%)	5% (4-8%)
Pneumonia	0.2% (0-2%)	1% (0.2-3%)
Systemic	NR	4% (2-5%)
Treatment Continuation		
Incomplete	9% (2-14%)	8% (5-10%)
Interruption	11% (8-16%)	7% (5-11%)

American Urological Association Guidelines (1999) toxicity table of BCG and MMC

Added toxicity of BCG*:
5% serious + rare lethal sepsis

*(Lamm DL, et al. Prog Clin Biol Res 1989).

US Bladder Cancer Vital Statistics

Annual Incidence	68,810
Cancer Deaths	14,100
Cancer Cost (Dx → Death)	#1 (\$100-200 K/patient)
TUR procedures estimate	334,000
Prevalence estimate	522,000
# instillations, estimate	2,650,000

Why We Need New Treatments

For intermediate risk - neither MMC nor BCG provide reliable long term relapse free rates

For High risk - BCG is the only currently acceptable option but at the cost of significant risk of toxicity

Device Description and Preclinical Studies

Ahava Stein

A. Stein-Regulatory Affairs Consulting
Regulatory Consultant for Medical Enterprises

Indications for Use

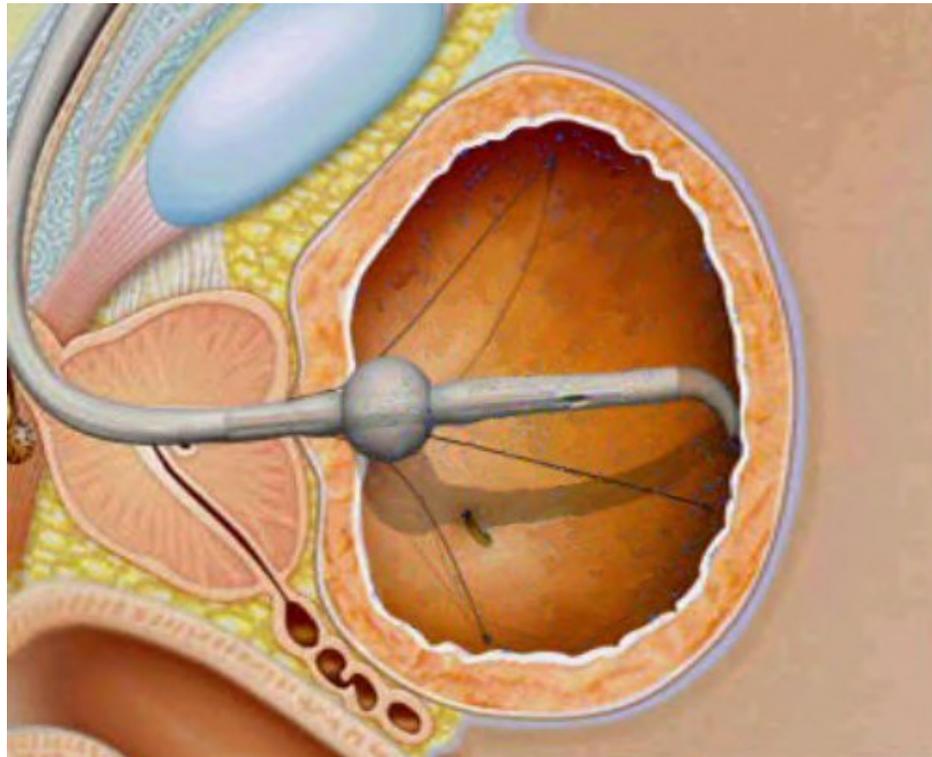
- ◆ Synergo and Mitomycin C is intended for prophylactic treatment of recurrence in patients following endoscopic removal of Ta-T1 and G1-3, superficial transitional cell carcinoma of the bladder (STCCB)
- ◆ Synergo and Mitomycin C treatment is clinically indicated for STCCB patients of intermediate and high risk

Synergo SB-TS 101.1 Device

- ◆ The Synergo SB-TS 101.1 device delivers heat intravesically by means of radio frequency (RF) energy to the urinary bladder **wall**
- ◆ Synergo hyperthermia is delivered concomitantly with **cooled** intravesical instillation of Mitomycin C

Synergo Catheter

- ◆ Catheter System applied in the bladder



Synergo Catheter Functions

- ◆ The Synergo catheter performs three main functions:
 - Uniform heating of the bladder **wall** via a small antenna emitting RF (microwave) radiation
 - Temperature monitoring of bladder wall by thermocouples, and
 - Circulation of the **cooled** chemotherapeutic drug into and out of the bladder

Pharmacology/Toxicology, Bioavailability and Pharmacokinetic Studies

- ◆ Pharmacology/Toxicology, Bioavailability and Pharmacokinetic Studies for MMC
 - Letter of Authorization from Bedford Laboratories™ to reference approved MMC NDA; and
 - Letter of Authorization from Bristol Myers Squibb to reference approved MMC NDA

Pharmacology/Toxicology, Bioavailability and Pharmacokinetic Studies (Cont'd)

- ◆ Paroni et al. Study - Assessed the effect of local hyperthermia on the systemic absorption of MMC during intravesical chemotherapy
 - Result: Highest MMC plasma concentration (67.9 ng/ml) is well below critical toxic systemic level of 400 ng/ml

Degradation Studies of Synergo with Mitomycin C

- ◆ Degradation of MMC dissolved in intravenous (I.V.) fluids, at 50°C (temperature higher than Synergo device hyperthermia treatment)
- ◆ Results: MMC did not degrade below the approved Gensia Sicor Pharmaceutical bulk drug specification limits

Safety Testing (Electrical, EMC, SWV)

- ◆ IEC 60601-1 Mechanical and Electrical safety standard
- ◆ IEC 60601-1-2 EMC standard
- ◆ IEC 60601-1-4 and FDA Guidelines for Software Validation

All tests passed according to international standards

Catheter Standards and Bench Testing

- ◆ ASTM F 623-89 standard for Foley Catheters
- ◆ ISO 10993 standard for biocompatibility
- ◆ Bench testing of electromagnetic field generated by the antenna and its interaction with simulated biological tissues

Animal Study

◆ Purpose

- Demonstrate that during normal treatment conditions there are no risks of damage to the bladder or adjacent organs

◆ Methods

- Sheep model - temperature mapping of the bladder walls and adjacent organs during treatment with Synergo device
- Pathological evaluation of the organs after the treatment, in comparison with control animals

Animal Study – Conclusions

- ◆ Synergo thermocouple temperature measurements verified using an independent temperature measuring system
- ◆ No risks of irreversible damage to the urinary bladder or adjacent tissues even under “worst-case” conditions, (i.e., at temperatures higher than intended for use)

Summary of Clinical Studies

Fred Witjes, MD, PhD

- ◆ Chairman of the EORTC STCCB committee
- ◆ Professor and Chairman of oncological urology, Radboud University hospital, Nijmegen, The Netherlands
- ◆ Vice Chairman of the European bladder cancer guideline committee

Overview of Clinical Studies

(Valid Scientific Evidence)

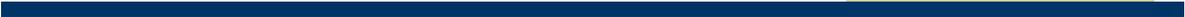
Study		Design	Support PMA
101.1	Synergo vs. MMC Pivotal Study	Controlled, Randomized	Safety & Efficacy
102.1	Synergo vs. BCG	Controlled, Randomized, Ongoing	Safety & Efficacy
EPP	European Prophylactic Patients – Synergo	Uncontrolled, commercial use	Safety & Efficacy
BS	Bladder Salvage – Synergo	Uncontrolled, commercial use	Safety
EAP	European Ablation Patients – Synergo	Uncontrolled, commercial use	Safety
101.4	Synergo Ablation	Controlled, one arm	Safety



PMA Pivotal Study 101.1



Study 101.1: Objectives



To compare the safety and effectiveness of Synergo vs. MMC for prophylactic treatment of STCCB

Study 101.1: Endpoints

- ◆ Primary endpoint
 - Comparison of recurrence rates at 2 years
- ◆ Secondary endpoints
 - Comparison of progression of stage and grade
 - Comparison of occurrence of CIS
 - Comparison of occurrence of urothelial cell carcinoma in the upper tract or in the prostatic urethra
 - Comparison of occurrence of distant metastasis

Study 101.1: Sample Size Calculation

Sample size calculation based on primary endpoint of 2 year recurrence

Assumptions for Calculation:

- 2 year recurrence rate in MMC Control group is 40% based on scientific literature
- Study is designed to detect a reduction of 50% in the recurrence rate of the Synergo group versus the MMC group, with a power of 80% and a 5% level of significance

Sample Size: N=158

Study 101.1: Interim Analysis

- ◆ Originally, N=158 patients
- ◆ Protocol called for Interim Analysis when 80 patients complete 1-year follow-up
- ◆ Interim Analysis performed earlier than planned due to ethical reasons
- ◆ Interim Analysis recurrence rates:
 Synergo 11% vs. MMC 62%
- ◆ Recalculated Sample Size: N=84 patients

Study 101.1: Randomization errors

- 5 pairs of administrative/clerical randomization errors at the central randomization office
- Clinical sites and sponsor were unaware of errors
- Total numbers of pts. in each group unchanged
- Results re-analyzed: randomization error patients assigned to groups as randomized:
Similar Kaplan-Meier and statistical significance (P=0.0097)

Study 101.1: Protocol Deviations and Withdrawals

- 5 Synergo patients withdrawn from study
 - 3 withdrew consent prior to receiving any treatment
 - 1 physician withdrawn due to deteriorating health
 - 1 skin allergy to MMC
- 1 MMC patient withdrawn from study
 - 1 skin allergy to MMC
- 2 additional Synergo patients were not included in Per Protocol cohort due to major protocol deviations

Study 101.1: Patient Accountability

Analysis Population	Treatment Group		Total
	Synergo	MMC	
All Study Patient: Randomized as Treated¹	42	41	83
Evaluable: Randomized as Intended²	36	41	77
Evaluable: Randomized as Treated³	37	40	77
PP (Per Protocol)	35	40	75

¹All study patients grouped according to actual treatment given, for baseline and safety evaluations

²Patients having follow-up data, grouped according to intended randomization assignment

³Patients having follow-up data, grouped according to actual treatment given

Study 101.1 Procedures

- ◆ Randomization
- ◆ Synergo or MMC (2 x 20mg) in 8 weekly, 4 monthly treatment sessions
- ◆ Follow-up every 3 months up to 2 years
- ◆ Endpoint assessment – tumor recurrence confirmed with positive histology

Study 101.1: Clinical Sites

Clinical Center	Geographical Location	Principal Investigator
San Raffaele Hospital	Milan, Italy	Prof. Rigatti
University Hospital of Palermo	Palermo, Italy	Prof. Pavonne
Rabin Medical Center, Belinson Campus	Petach Tikva, Israel	Prof. Servadio

Study 101.1 – Clinical Data

- ◆ Monitoring of 100% of CRFs according to GCP requirements was performed
- ◆ FDA audit (2005) of all sites confirmed “CRFs were an adequate reflection of source documentation”
- ◆ Safety and efficacy data adequately captured on CRFs
 - Consistent reporting of AEs throughout study

Study 101.1: Baseline Characteristics

	Total N (%)	Synergo N=42	MMC N=41
Age < 65	41 (49%)	25	16
Age ≥ 65	42 (51%)	17	25
First episode	31 (37%)	15	16
Recurrent	52 (63%)	25	27
Prior therapy	18 (42%)	18	17
Ta	33 (40%)	15	17
T1	50 (60%)	26	24
G1	5 (6%)	4	1
G2	60 (72%)	27	33
G3	18 (22%)	11	7
Low Risk	0	0	0
Int. Risk	43 (52%)	19	24
High Risk	40 (48%)	23	17

Study 101.1: Blinding

- ◆ Investigator blinding not typically performed in intravesical therapy trials published in scientific literature
- ◆ Pivotal studies submitted for FDA approval were not blinded (e.g., BCG NDA, Valrubicin)
- ◆ Blinding is not possible with Synergo treatment:
 - Patients aware of heat
 - Thermal effects easily observed in cystoscopy
- ◆ Synergo long term follow-up confirms that study results were not biased by lack of blinding

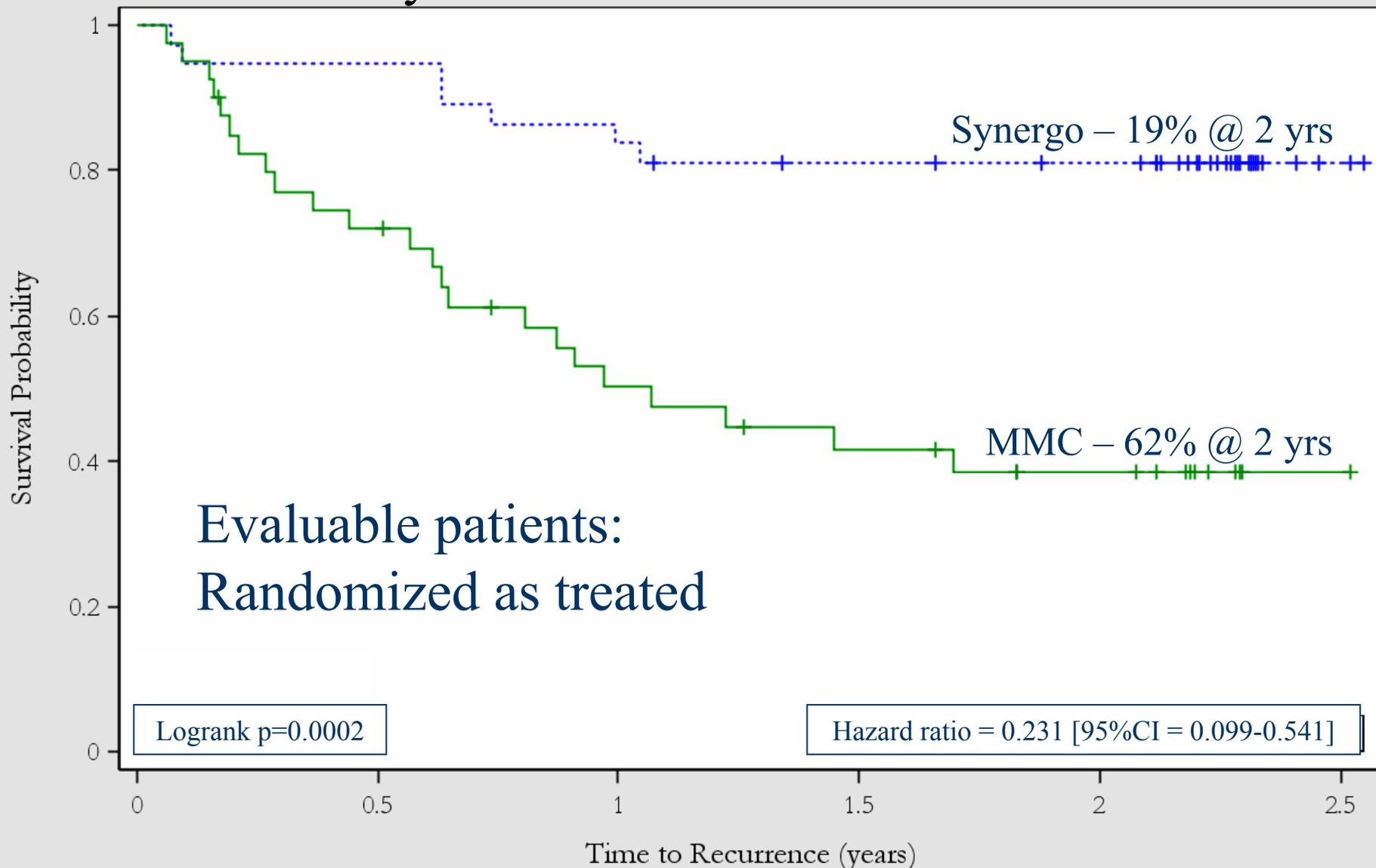
Study 101.1: Efficacy Results of Different Cohorts

Recurrence Rate: 2 yr K-M estimates

Patient Population	Synergo	MMC	Log-Rank
Evaluable: Randomized As Treated (N=77)	18.9%	61.6%	P=0.0002
Evaluable: Randomized As Intended (N=77)	25.0%	54.4%	P=0.0097
Per-Protocol (N=75)	17.1%	61.6%	P=0.0002

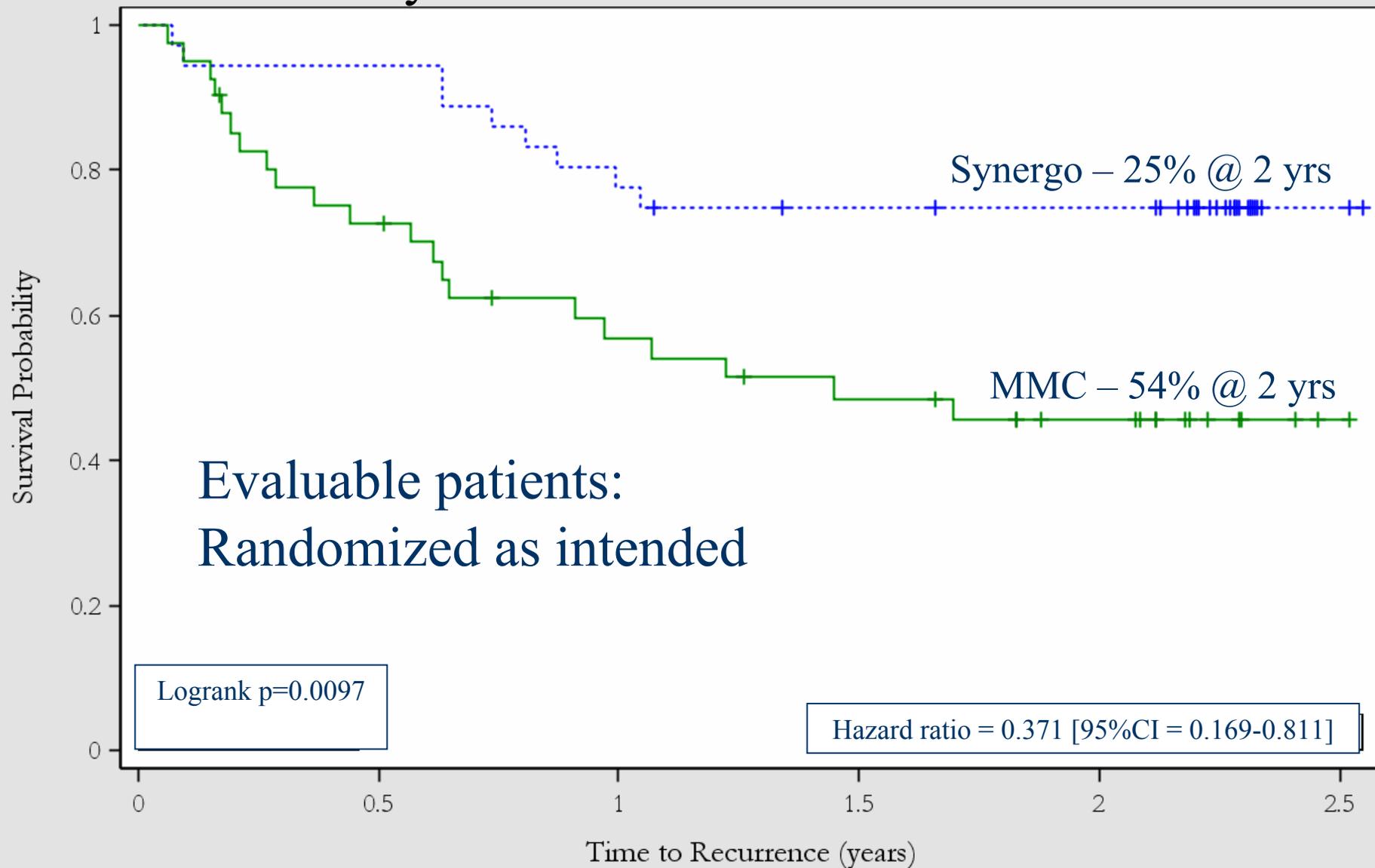
Synergo treatment was consistently significantly better than MMC in these patient populations

Study 101.1: K-M Time to Recurrence



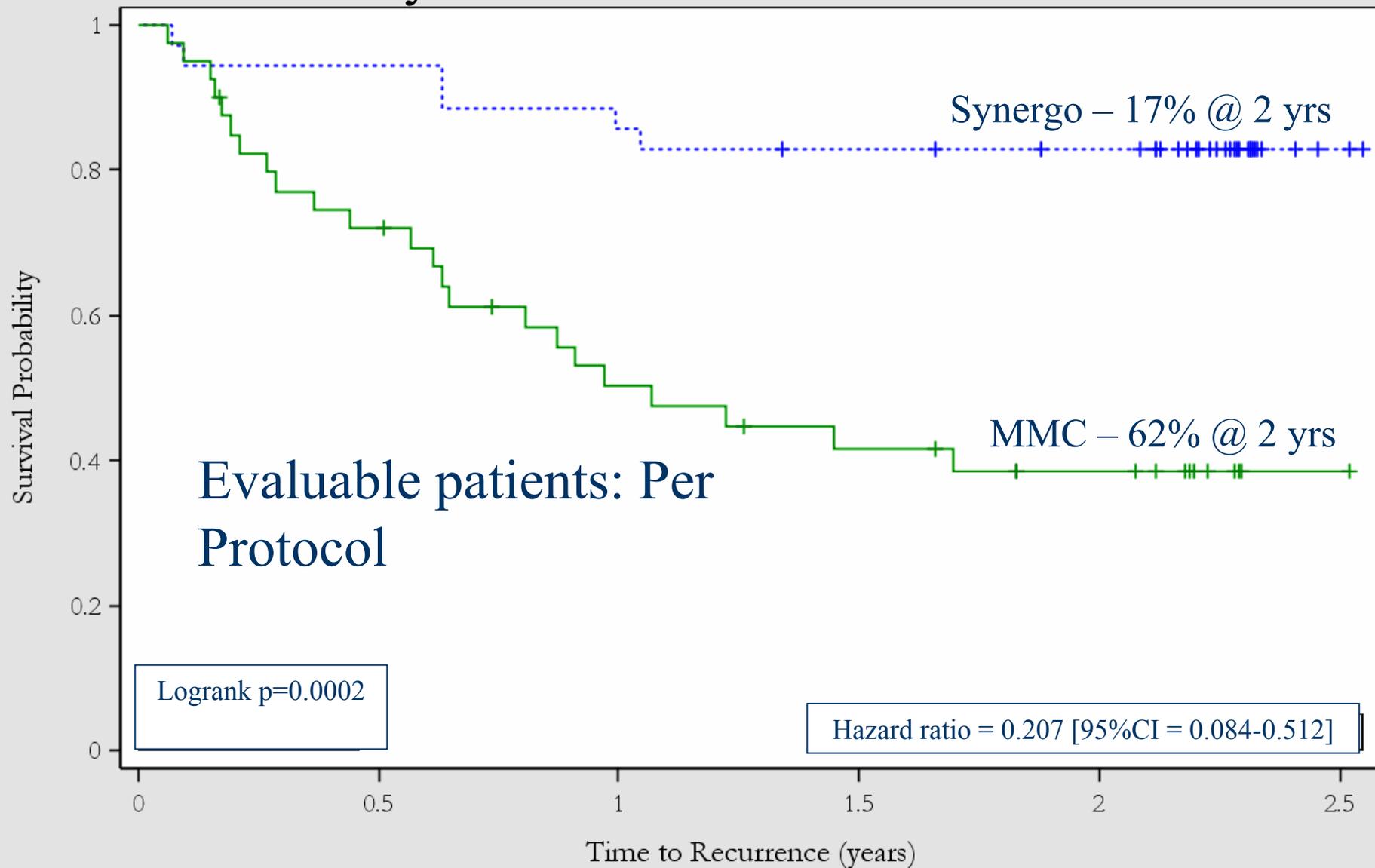
	No. of Subjects	Event	Censored	Median Survival (95% CL)
Synergo	37	19% (7)	81% (30)	NA (NA NA)
MMC	40	58% (23)	43% (17)	1.070 (0.632 NA)

Study 101.1: K-M Time to Recurrence



	No. of Subjects	Event	Censored	Median Survival (95% CL)
Synergo	36	25% (9)	75% (27)	NA (NA NA)
MMC	41	51% (21)	49% (20)	1.448 (0.646 NA)

Study 101.1: K-M Time to Recurrence



	No. of Subjects	Event	Censored	Median Survival (95% CL)
Synergo	35	17% (6)	83% (29)	NA (NA NA)
MMC	40	58% (23)	43% (17)	1.070 (0.632 NA)

Study 101.1: Efficacy Results of Different Cohorts

Recurrence Rate: 2 yr K-M estimates

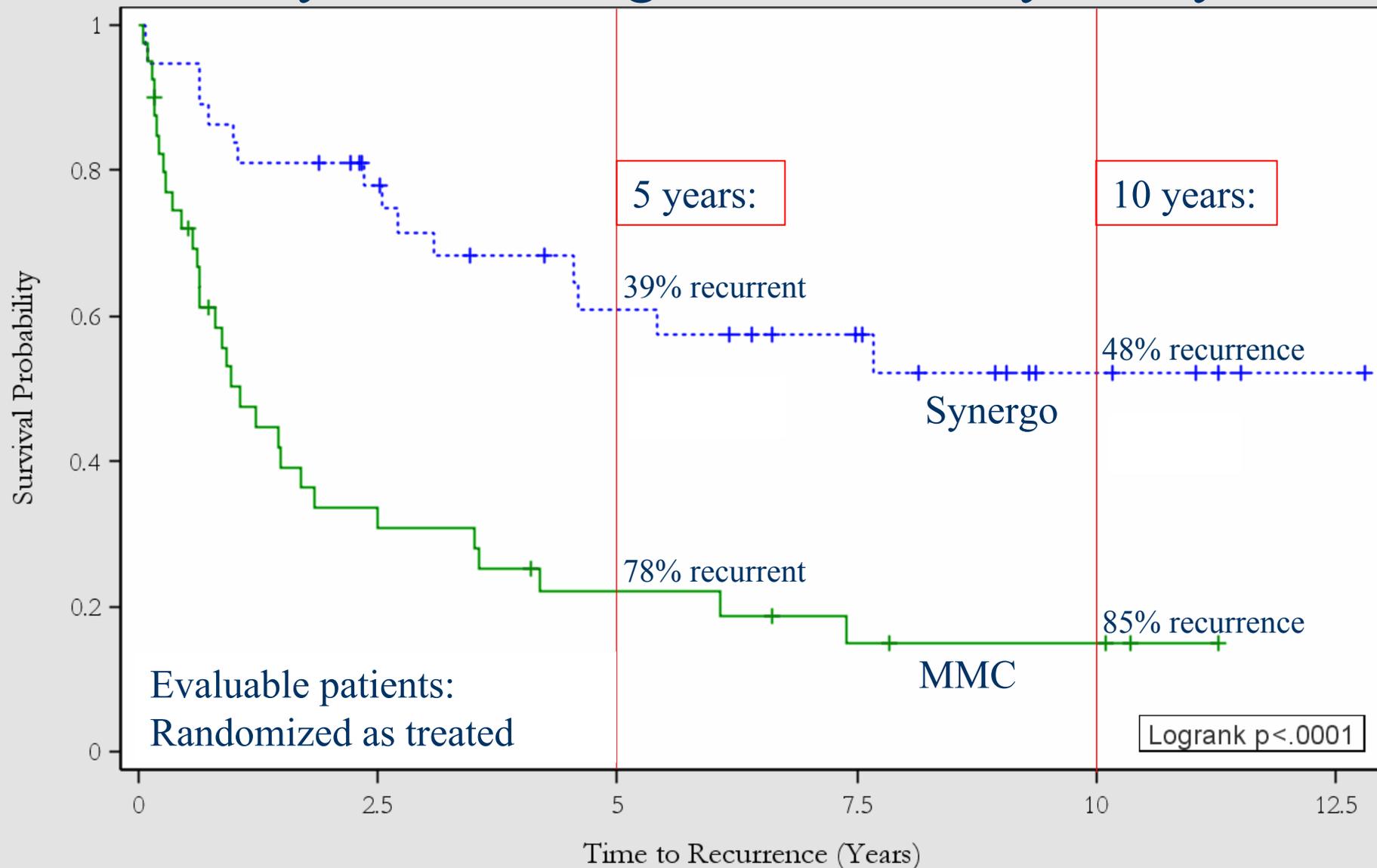
Patient Population	Synergo	MMC	Log-Rank
Worst Case Scenario 1*: All Study Patients, As Treated	30.9%	59.9%	P=0.0219
Worst Case Scenario 2* (FDA): All Study Patients, As Intended	38.1%	54.4%	P=0.225

* Assumes for drop-outs: 1 control patient was recurrence-free at 2 yrs and 5 Synergo patients had disease-recurrence at first follow-up

Study 101.1: Secondary Endpoint Analysis

- ◆ No patients with progression of tumor stage or grade in Synergo group
- ◆ No patients with occurrence of CIS in Synergo group
- ◆ No patients with carcinoma in the upper tract or prostatic urethra in Synergo group
- ◆ No patients with occurrence of distant metastasis in Synergo group (3 in control group at long term f/u)

Study 101.1: Long-Term Efficacy Analysis



	No. of Subjects	Event	Censored	Median Survival (95% CL)
Synergo	37	41% (15)	59% (22)	NA (4.542 NA)
MMC	40	78% (31)	23% (9)	1.071 (0.633 1.827)

Study 101.1: Long Term Follow-up

	Synergo	MMC
Radical Cystectomy	2 (5%)	5 (12%)
Overall Mortality	5 (14%)	9 (23%)

Study 101.1: Efficacy Subgroup Analysis

◆ No significant effects of:

- Age
- Gender
- Number of previous occurrences
- Previous tumor stage (T)
- Previous tumor grade (G)
- Previous tumor size (<2 cm vs. ≥2 cm)
- Previous multifocal tumor (≤5 vs. >5)
- Current number of tumor sites (single tumor vs. multiple tumors)
- Previous prophylactic treatments (with different chemotherapeutic agents; MMC or other drugs), and first episode patients
- Clinical center

Study 101.1: Efficacy Subgroup Analysis

- ◆ **Significant effect:**
 - History of recurrence (first episode, recurrent or high recurrent)
 - EAU risk category
- ◆ In multivariate analysis the Synergo treatment effect remains highly statistically significant

Treatment Effect for Recurrence	Synergo vs. MMC Hazard Ratio (95% CI)	P-Value*
Unadjusted	0.231 [0.099-0.541]	0.0007
Adjusted for type of recurrence	0.174 [0.073-0.417]	<0.0001
Adjusted for EAU risk group	0.160 [0.066-0.386]	<0.0001

Study 101.1: Expected Adverse Events

Adverse Events	Synergo N=42		MMC N=41		P-Value (Fisher's exact test)
	N	%	N	%	
Dysuria	10	23.8	4	9.8	0.141
Hematuria	3	7.1	2	4.9	1.000
Tissue Reaction (hyperemia, inflammation, etc.)	21	50	20	48.8	1.000
Urethral Stenosis	3	7.1	2	4.9	1.000
Skin Allergy	5	11.9	2	4.9	0.433
Pain	17	40.5	0	0	<0.0001
Posterior Wall Tissue Reaction	27	64.3	1	2.4	<0.0001
Urinary Tract Infection	3	7.1	0	0	0.241
Bladder Wall Necrosis	2	4.8	2	4.9	1.000

Study 101.1: Other Adverse Events

Adverse Events	Synergo N=42		MMC N=41		P-Value
	N	%	N	%	
Anxiety	1	2.4%	0	0	1.000
Amnesia	1	2.4%	0	0	1.000
Hypotonic bladder	1	2.4%	0	0	1.000
Reduced bladder capacity	2	4.8%	0	0	0.494
False passage	1	2.4%	0	0	1.000
Fever & Urgency	0	0	1	2.4%	1.000
General weakness	0	0	1	2.4%	1.000

Study 101.1: Pain

- ◆ Includes bladder spasms, intolerability to treatment, pain in general and urethral pain
- ◆ Small number of Synergo treatment sessions were shortened (10/425) or skipped (7/425) due to pain
- ◆ Transient during treatment, usually managed with medications

Study 101.1: Posterior Wall Tissue Reaction

- ◆ Asymptomatic and detected only on cystoscopy
 - Visually scored as mild, moderate, severe
 - “Severe” PWTR (10%) were still asymptomatic
- ◆ Resolved without medical intervention
- ◆ Due to RF antenna in the bladder
- ◆ Superficial (no muscle involvement)
- ◆ Minor or no residual effect (hyperemia)

Study 101.1: Adverse Events

No significant difference between groups for these AEs:

- ◆ Reduced bladder capacity
 - Known to occur after intravesical treatment
- ◆ Urethral stenosis and stricture
 - Occasionally observed in patients undergoing multiple catheterizations, TURs and cystoscopy procedures
 - Larger size of Synergo catheter (20F) will identify less significant stenosis/stricture earlier
- ◆ Dysuria
 - Majority of patients did not require treatment
 - No patients shortened or terminated treatment

Study 101.1: Serious Adverse Events

- ◆ Serious adverse events in Synergo group
 - bronchial bleeding (n=1)
 - suspected Myocardial Infarction (n=1)
 - nephrolithiasis (n=1)
- ◆ Serious adverse events in MMC group
 - hydronephrosis (n=1)
 - CVA (n=1)
 - leukemia (n=1)

No serious adverse events were considered to be treatment related

101.1 Study Conclusions

◆ Efficacy

- Highly significant reduction in 2 year recurrence rate in Synergo group
- Compelling study results even with relatively small sample size
- Durable results over time

◆ Safety

- Synergo was well tolerated
- Toxicity comparable to literature for intravesical therapy

102.1 Study – Synergo vs. BCG

Study 102.1: Overview

- ◆ Purpose: RCT comparing Synergo treatment to BCG immunotherapy, for prophylactic treatment in patients with intermediate or high risk superficial transitional cell carcinoma of the bladder (STCCB)
- ◆ Anticipated end of study: 2013
- ◆ Supportive Data:
 - NOT to statistically compare study endpoints
 - To demonstrate the consistency of results for the Synergo treatment in another randomized controlled clinical study

Study 102.1: Endpoints

- ◆ Primary Endpoint: compare the 2 year recurrence rate between groups (same as 101.1)
- ◆ Secondary Endpoint
 - compare progression rate (to disease stage>T1) and/or
 - compare metastatic disease
- ◆ Additional Endpoint
 - local and systemic adverse events

Study 102.1: Procedures

- ◆ Treatments:
 - Synergo & MMC (2 x 20mg) in 6 weekly & 6 monthly treatment sessions; or
 - BCG in 6 weekly & 3 x 3 weekly at 3, 6 and 12 months.
- ◆ Follow-up every 3 months up to 2 years
- ◆ Endpoint assessment – tumor recurrence based on positive biopsy histology

Study 102.1: Analysis Population

	Number	By Treatment Group	
		Synergo	BCG
All Study Patients*	104 (100%)	51 (49%)	53 (51%)
Evaluable Patients (for efficacy analysis)	90 (100%)	42 (47%)	48 (53%)

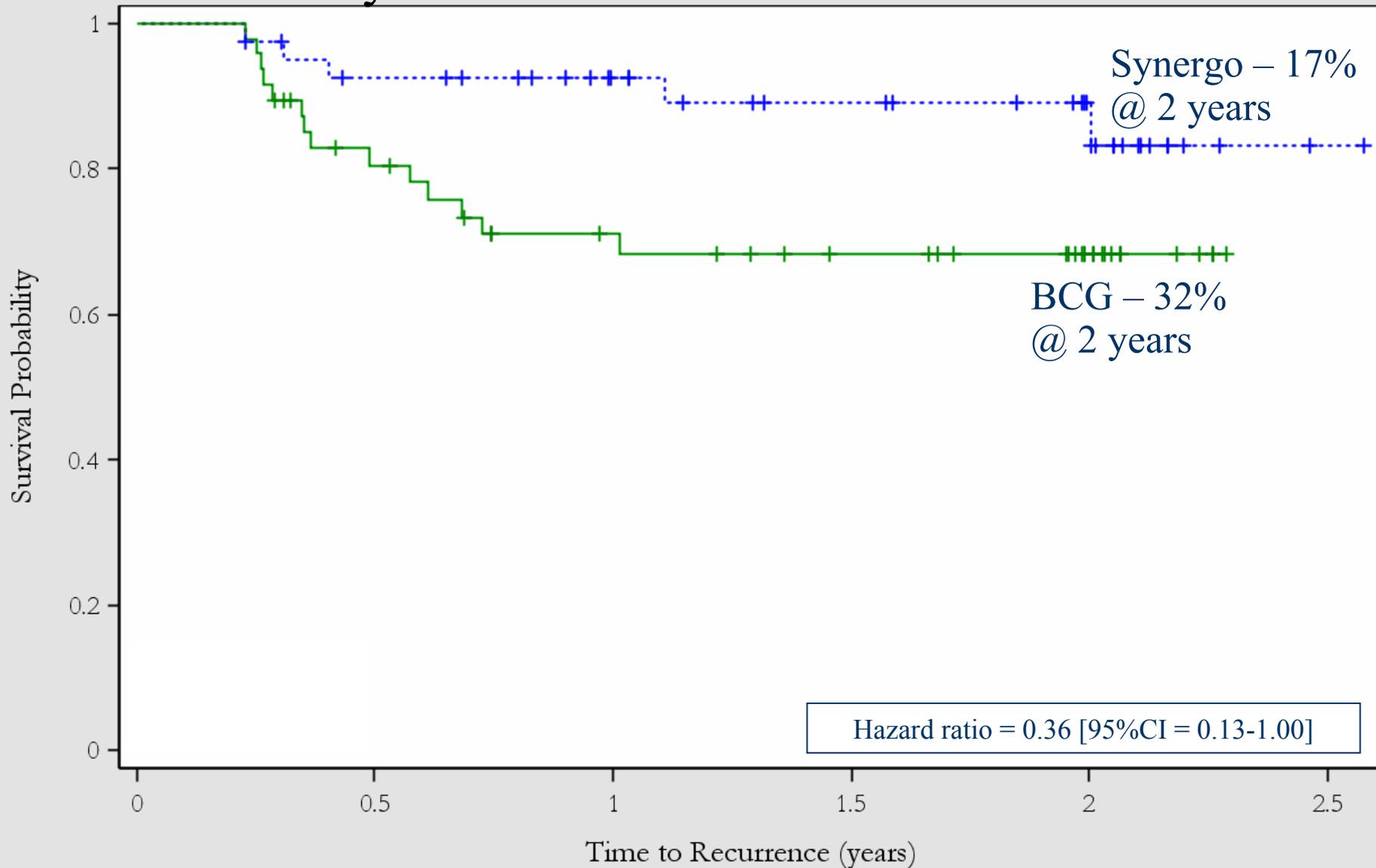
* At data lock in April 2007

Study 102.1: Baseline Characteristics

Baseline demographics and tumor characteristics were comparable between study arms:

- Age and gender
- History of tumor recurrence
- Number of previous tumor occurrences
- Previous tumor stage and grade
- Previous tumor size
- Previous number of tumors
- Previous prophylactic treatments
- EAU risk group
- Center

Study 102.1: K-M Time to Recurrence

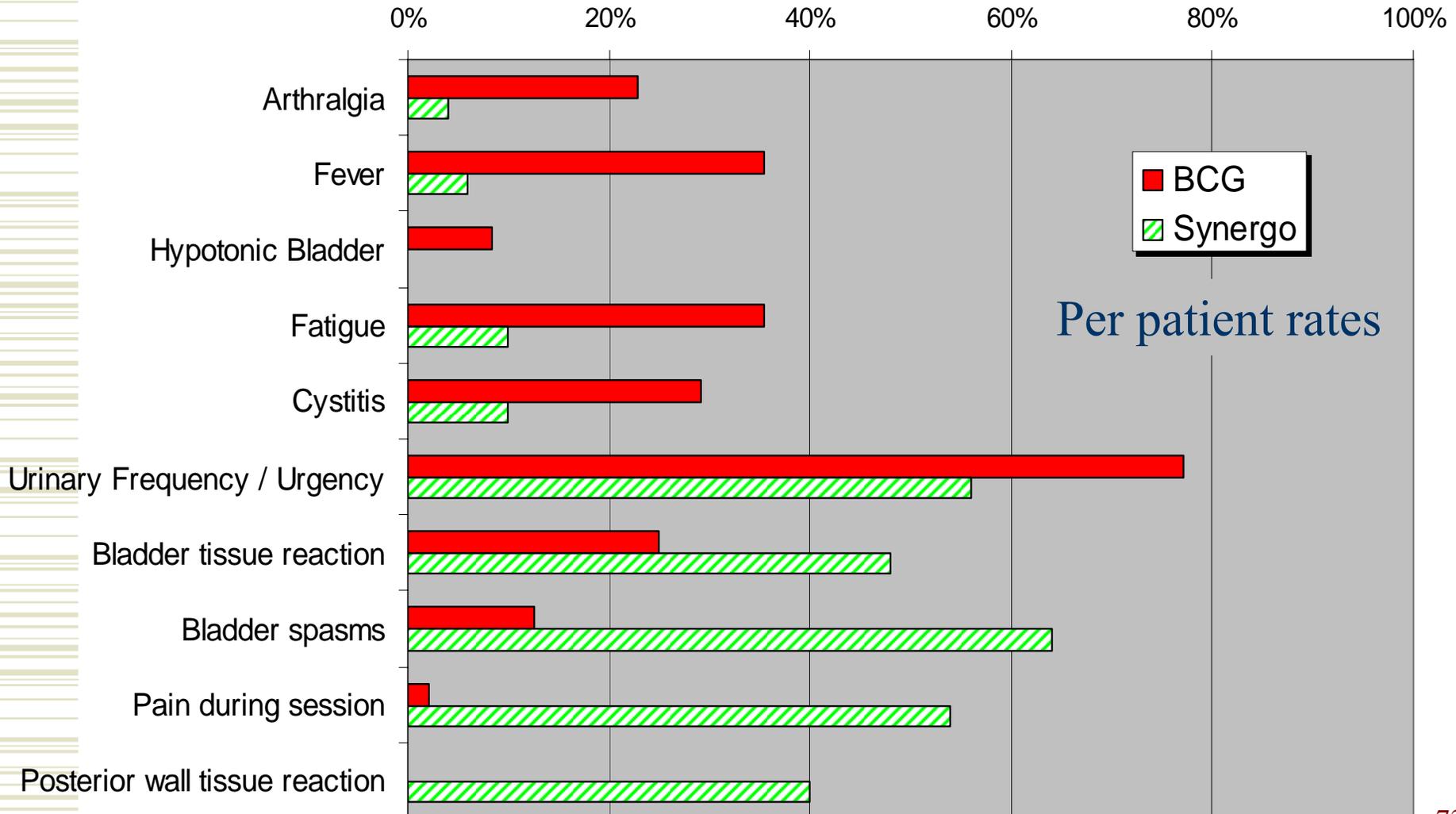


	No. of Subjects	Event	Censored	Median Survival (95% CL)
Synergo	42	12% (5)	88% (37)	NA (NA NA)
BCG	48	29% (14)	71% (34)	NA (NA NA)

Study 102.1: Secondary Endpoints

No progression in tumor Stage or Grade in Synergo patients (based on limited follow-up)

Study 102.1: Adverse Events (significantly different between study arms)



Study 102.1 – Adverse Events (similar in both study arms)

Rates of the following adverse events were **similar** in both BCG and Synergo groups

- ◆ Urethral Stricture / Stenosis
- ◆ Allergic Reaction / Hypersensitivity
- ◆ Pain between sessions
- ◆ Incontinence
- ◆ Residual urine ($\geq 100\text{cc}$)
- ◆ Urinary tract infection
- ◆ Dysuria
- ◆ Hematuria
- ◆ Nocturia
- ◆ Urinary retention
- ◆ Vomiting
- ◆ Hypotonic Bladder
- ◆ Granulomatous Changes of Bladder Wall

Study 102.1: Serious Adverse Events

- ◆ Serious Adverse Events related to Synergo device (and/or MMC)
 - Urethral stricture (n=1)
 - Contracted bladder (patient underwent cystectomy, although recurrent free, n=1)
 - Urethral bleeding (patient withdrew consent, n=1)
 - Dysuria, urinary urgency and fever (transient event, n=1)

Study 102.1: Serious Adverse Events

- ◆ Serious Adverse Events related to BCG treatment
 - Macrohematuria and Urinary Retention (treated with catheter and antibiotics, n=1)
 - Fever, conjunctivitis and Urinary Tract Infection (resolved with antibiotic treatment, n=1)

Study 102.1: Safety Conclusions

- ◆ Expected Adverse Events, same as study 101.1 (dysuria, hematuria, tissue reaction, urinary tract infection, pain, posterior wall tissue reaction and bladder wall necrosis)
- ◆ Other Adverse Events, similar nature to study 101.1
- ◆ Synergo treatment was well tolerated



Studies 101.1 & 102.1

Studies 101.1 & 102.1

- ◆ 93 Synergo patients at 12 unique sites
 - Study 101 – 42 patients at 3 sites
 - Study 102 – 51 patients at 10 sites
- ◆ Consistent 2 year recurrence rate
- ◆ Consistent results across sites
- ◆ Consistent safety profile

Studies 101.1 & 102.1: Results

	Synergo 2 yr estimated r.r. (95% CI)	MMC 2 yr estimated r.r. (95% CI)	BCG 2 yr estimated r.r. (95% CI)
Study 101.1*	18.9% (6.3-31.5%)	61.6% (45.7-77.5%)	--
Study 102.1	16.9% (2.1-31.7%)	--	31.7% (17.8-45.6%)
Meta-Analysis of Literature	--	41.5% (36.8-46.3%)	35.6% (32.4-38.7%)

*Based on evaluable patients: Randomized As Treated cohort.



European Prophylactic Patients

European Prophylactic Patients (EPP)

- ◆ Single arm, uncontrolled, commercial use
- ◆ Patient selection, treatment sessions and follow-up examinations similar to Study 101.1 and Study 102.1 procedures
 - EAU High Risk: 58% in EPP vs. 55% in 101.1 and 102.1
- ◆ N=168 patients (1598 Synergo treatments)

EPP: Efficacy Results

- ◆ More prior highly recurrent tumors in EPP relative to 101.1 & 102.1
 - 60% in EPP vs. 36% in 101.1 and 22% in 102.1
- ◆ 32.2% estimated recurrence rates - Kaplan Meier (2 year)
- ◆ Synergo estimated 2-year recurrence rate of 32.2% is far better than MMC treatments and at least as good as BCG treatment.



Bladder Salvage Patients

Bladder Salvage Patients

- ◆ Extremely high-risk patients:
 - highly recurrent (≥ 3 recurrences in last 24 months) and
 - Failed prior BCG treatment(s)
 - Candidates for cystectomy
- ◆ N=82 patients (845 Synergo treatments)
- ◆ Presented for Safety

Study 101.4

Study 101.4

- ◆ Controlled, monitored clinical study
- ◆ Ablative Indication for Use - STCCB patients for whom TUR was not possible or not recommended
- ◆ N=42 patients (394 Synergo treatments)
- ◆ Presented for Safety



European Ablation Patients

European Ablation Patients: EAP

- ◆ Ablative Indication for Use - STCCB patients for whom TUR was not possible or not recommended
- ◆ N=104 patients (764 Synergo treatments)
- ◆ Presented for Safety

Supportive Studies: Safety Results

EPP, Bladder Salvage, 101.4 & EAP:

- ◆ Expected Adverse Events, same as 101.1 & 102.1 studies (dysuria, hematuria, tissue reaction, urinary tract infection, pain, posterior wall tissue reaction and bladder wall necrosis)
- ◆ Other Adverse Events, similar nature to 101.1 & 102.1 studies
- ◆ No serious adverse events related to Synergo device

Overall Summary

H. Barton Grossman, MD

- ◆ W.A. “Tex” and Deborah Moncrief, Jr.
Distinguished Chair in Urology
- ◆ Professor and Deputy Chairman, Department of
Urology, MD Anderson Cancer Center, Houston,
Texas

Clinical Need

- ◆ In the US, patients with intermediate or high risk STCCB continue to be a significant treatment problem
- ◆ MMC and BCG are recommended by the AUA and commonly used for STCCB
- ◆ BCG is characterized by high initial efficacy but a significant recurrence rate over time
- ◆ BCG has a significant local and systemic toxicity
- ◆ There is a need for a more effective and less toxic treatment

Overall Summary: Safety

- ◆ Safety data on **4502** Synergo treatment sessions in **506** patients
- ◆ Similar toxicities reported in the pivotal 101.1 study and across all five supportive clinical studies
- ◆ Most common toxicity is posterior wall tissue reaction and pain due to the nature of the hyperthermia treatment
 - Posterior wall tissue reaction:
 - Asymptomatic and resolved without medical intervention.
 - Non-healing ulcers as a result of MMC are well recognized
 - Transient pain - only 4% of Synergo treatments were shortened or skipped due to transient pain during the session

Overall Summary: Safety (Cont'd)

- ◆ Adverse events observed in the Synergo studies commonly occur with other forms of intravesical chemotherapy and/or immunotherapy
- ◆ Very few serious adverse events were treatment related
- ◆ Overall Synergo was well-tolerated

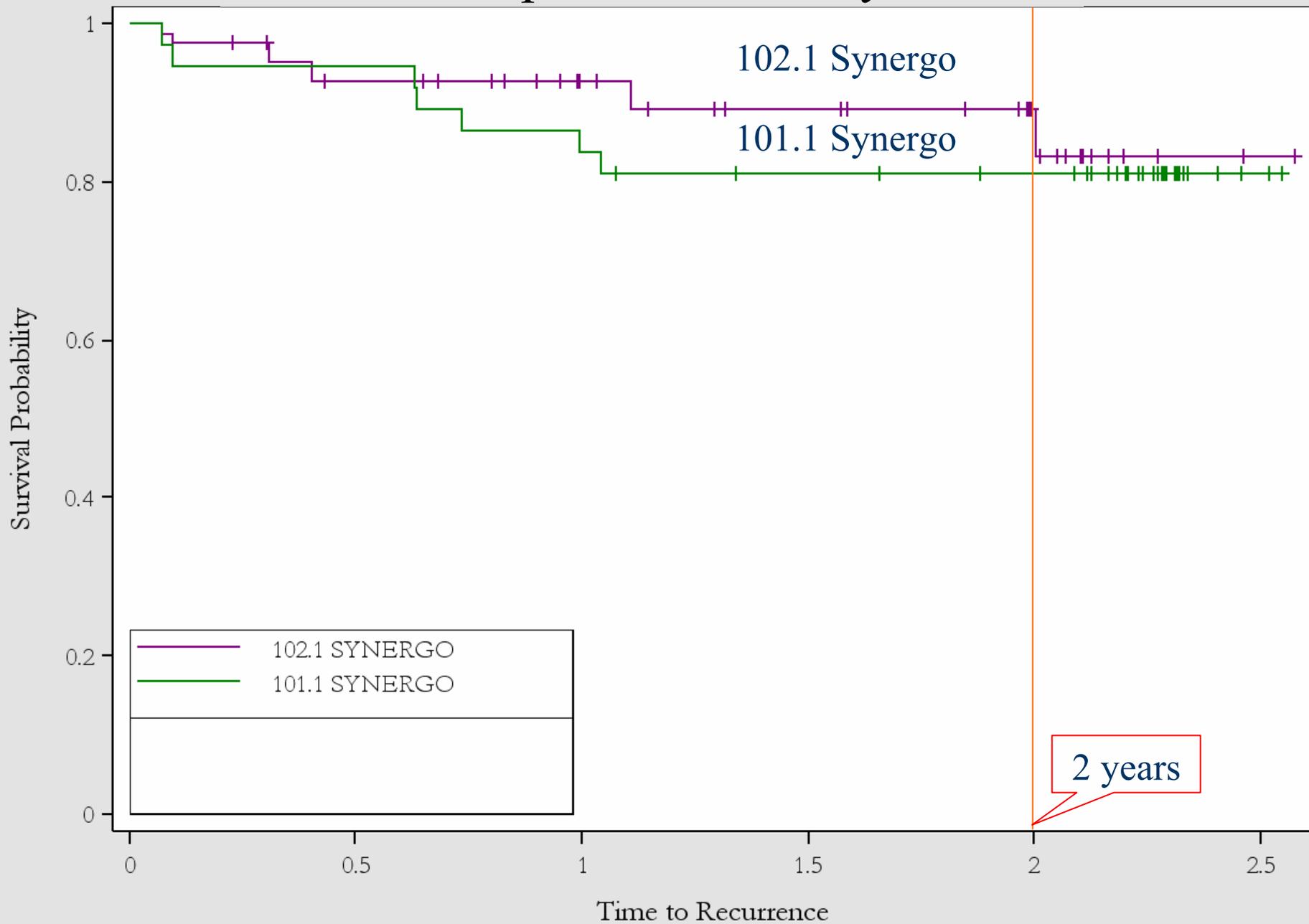
Overall Summary: Efficacy

Study 101.1:

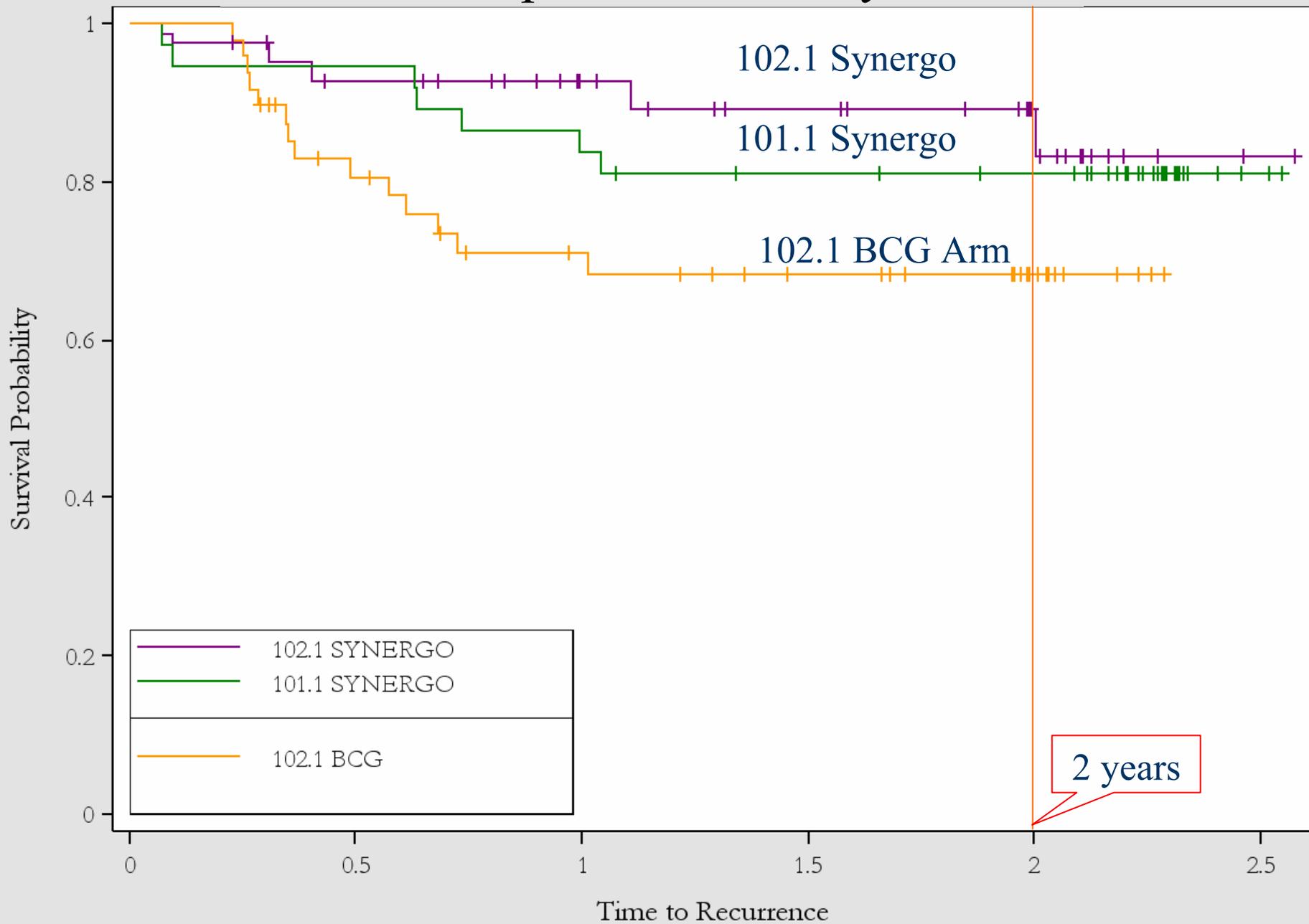
- ◆ Evaluable Patients: Randomized As Treated - 80% reduction in rate of recurrence with Synergo compared to Control (HR=0.23)

Synergo treatment was consistently better than MMC in ALL patient analyses

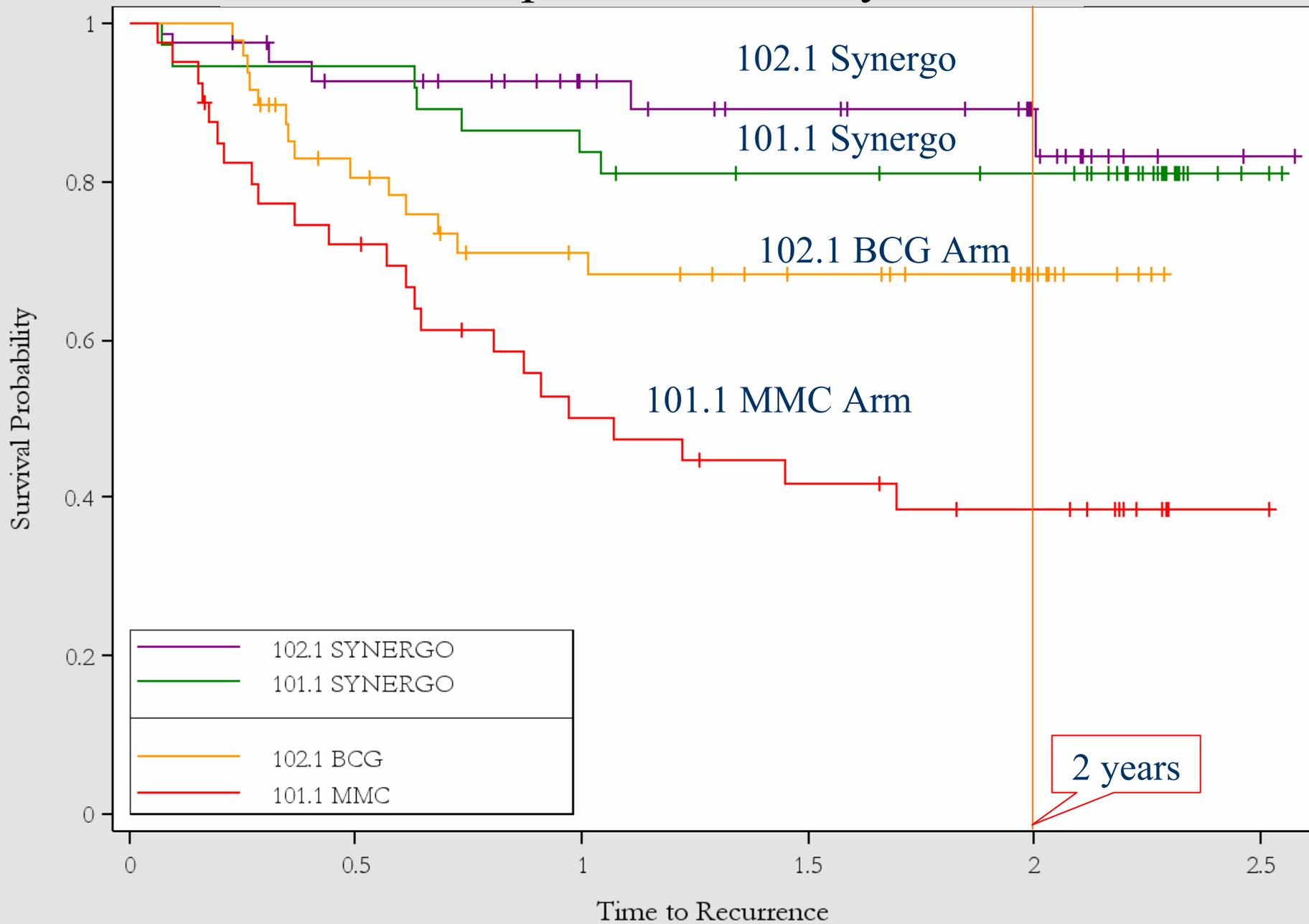
Comparative Efficacy



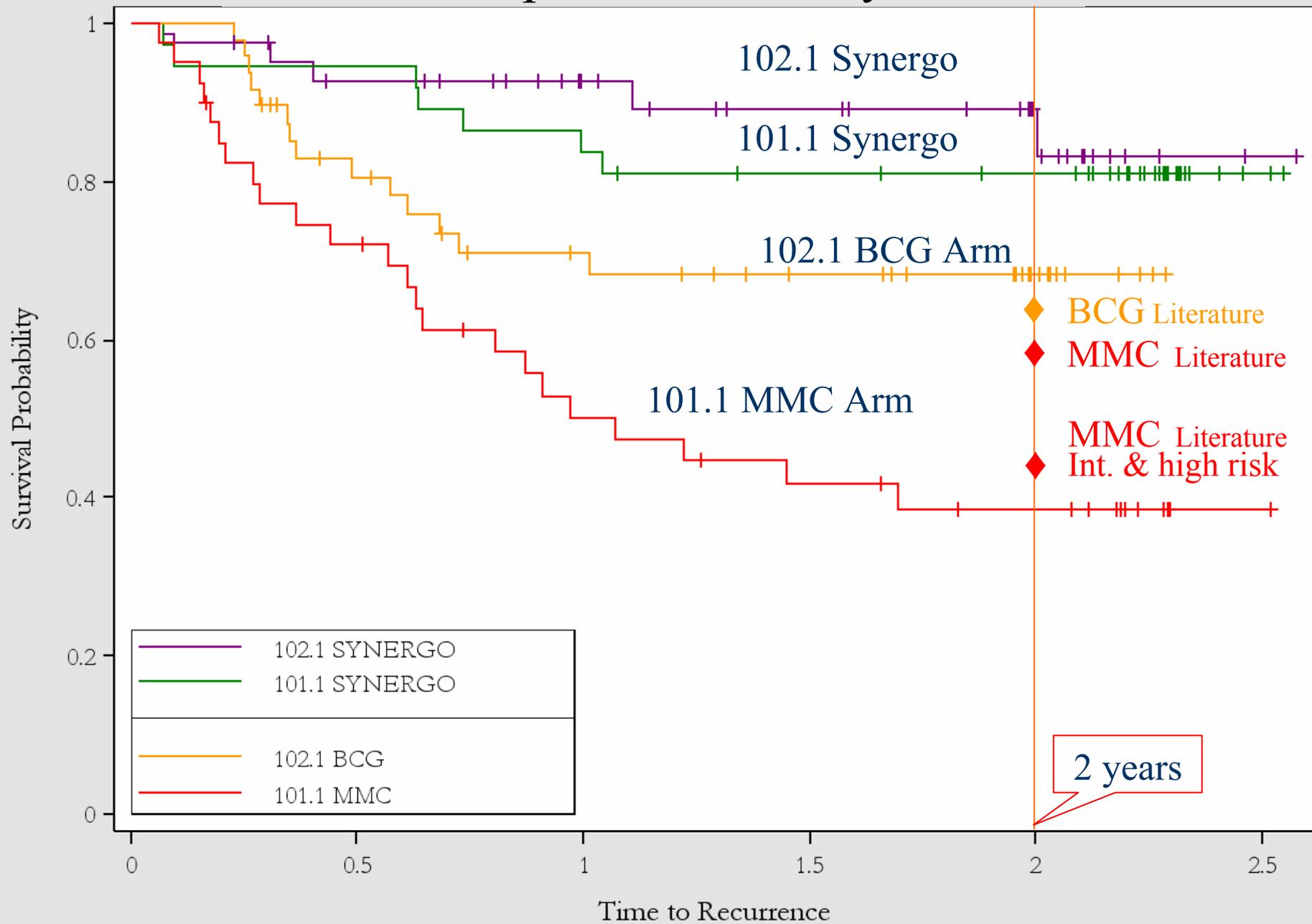
Comparative Efficacy



Comparative Efficacy



Comparative Efficacy



Recurrence Rates - Study 101.1

Long Term Kaplan-Meier Estimates

	Recurrence rate [95%CI]	
Time	Synergo	MMC
5-year	39% [22.4%-56.5%]	78% [64.5%-91.7%]
10-year	48% [29.6%-66.8%]	85% [72.7%-97.2 %]

Differences still notable at 5 & 10 years

Valid Scientific Evidence

- ◆ Regulatory Standard (21 CFR 860.7(c)(2)):
 - Adequate and controlled investigations
 - Partially controlled studies
 - Studies without matched controls
 - Well documented case histories
 - Significant human experience with a marketed device

Valid Scientific Evidence

Study		Type of VSE	Efficacy	Safety
101.1	Synergo vs. MMC Pivotal Study	Adequate and controlled investigations	37	42
102.1	Synergo vs. BCG	Adequate and controlled investigations	42	50
EPP	European Prophylactic Patients – Synergo	Significant human experience with a marketed device	122	186
BS	Bladder Salvage – Synergo	Significant human experience with a marketed device		82
101.4	Synergo Ablation	Adequate and controlled investigations		42
EAP	European Ablation Patients – Synergo	Significant human experience with a marketed device		104
		Total:	201	506

Risk Benefit Summary

- ◆ Synergo treatment demonstrated to be far better than MMC for prophylactic treatment of STCCB in intermediate and high-risk patients
- ◆ Data suggest Synergo may be comparable to, if not better than, BCG treatments
- ◆ Synergo has low, acceptable and predictable toxicity, without potentially life threatening AEs reported with BCG
- ◆ Patients treated with Synergo are virtually identical to the intermediate and high risk patient in the US today

Conclusions

- ◆ Study 101.1 results are compelling and consistent across studies
- ◆ Long term results show that there was no assessment bias
- ◆ Synergo fills an important need for additional treatment for STCCB patients
- ◆ Study 101.1 & supportive data provide *reasonable assurance* of safety and effectiveness based on valid scientific evidence

Post Approval Study

Michael O'Donnell, MD

Professor and Director of Urologic Oncology,
University of Iowa, Carver College of Medicine

Past Director, Bladder Cancer Subcommittee-
CALGB

Peer Reviewer, AUA Bladder Cancer
Guidelines Panel

Post Approval Study Design

- ◆ **Objective:**
 - To evaluate the safety of the Synergo system in the U.S. population
- ◆ **Study Group:**
 - Single arm study of Synergo treatment
- ◆ **Treatment Regimen:**
 - 8 weekly sessions + 4 monthly sessions
- ◆ **Follow-up:**
 - 3, 6, 9 & 12 months follow-up, including evaluation exams for recurrence (i.e., cystoscopy, cytology and biopsies, as appropriate)

Post Approval Study: Eligibility Criteria

◆ **Key Inclusion Criteria:**

- Subjects with resected Stage Ta or T1 and Grade G1-G3, STCCB, intermediate or high risk (according to the EAU definitions)
- Complete tumor eradication must be possible

◆ **Key Exclusion Criteria:**

- Subjects with Ta, G1 single transitional tumors at first episode of disease
- Subjects with tumor stage $> T1$
- Subjects with Tis transitional tumor

Post Approval Study: Endpoints

◆ **Safety Endpoints:**

- Treatment-related adverse events
 - Posterior wall tissue reaction
 - Pain
 - Dysuria (including frequency and urgency)
 - Urethral stenosis / stricture
 - Hematuria
 - False passage
 - Hypotonic bladder
 - Reduced bladder capacity
 - Urinary tract infection
 - Bladder wall necrosis
- All other reported adverse events

Post Approval Study: Sample Size

◆ **Prior Proposal**

- Based on NI hypothesis testing for individual AEs
- Not clinically meaningful

◆ **Number of Subjects now proposed:**

- A total of ~120 subjects to be enrolled at 5-10 U.S. sites, with a goal of ~100 completed subjects

◆ **Statistical Analysis**

- Proportion of patients with each adverse event & the number of adverse events per treatment session will be reported.
- Point estimates and 95% confidence intervals will be reported.

Training Program

- ◆ Didactic training
- ◆ Written training program
- ◆ Mentorship for physicians and technical staff
- ◆ On-site training
- ◆ Assessment of proficiency



THANK YOU