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Distribution Date: February 1, 2014
CTEP Submission Date: October 29, 2013

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swog.org

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS

FROM: Gilbert R. Carrizales, M.S., Protocol Coordinator

RE: **S0337,** "A Phase III Blinded Study of Immediate Post-TURBT Instillation of Gemcitabine Versus Saline in Patients with Newly Diagnosed or Occasionally Recurring Grade I/II Superficial Bladder Cancer." Study Chairs: Drs. E.M. Messing, D.M. Sahasrabudhe, T.M. Koppie, D.P. Wood, Jr., and P.C. Mack.

REVISION #7

Study Chair: Edward M. Messing, M.D.
Phone number: 585/275-3345
E-mail: edward_messing@urmc.rochester.edu

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

(√) Expedited review allowed

( ) No review required

REVISION #7

The above-referenced study has been updated as follows:

1. **Face page**: The version date of the protocol and model consent form have been updated (10/29/13).

2. **Page 25, Section 11.1, Primary Endpoint**: The 4th paragraph in this section has been revised in order to correct terms and assumptions for the statistical section specifications:

Original
"Two interim analyses of time-to-recurrence will be performed after 50% and 80% of the expected number of events have occurred (126 and 202 relapses, respectively, assuming the alternative treatment hypothesis) which will be approximately at the time accrual is completed and one year later. Consideration will be given to reporting early at either time if (1) TTR on the gemcitabine arm is

superior at the one-sided 0.005 level or if (2) the hypothesis λ=1.53 (where λ is the sterile water/gemcitabine hazard ratio) is rejected in favor of λ<1.53 at the one-sided 0.005 level (testing using a proportional hazards score test, an extension of the logrank test)."

New
"Two interim analyses of time-to-recurrence will be performed after 50% and 80% of the expected number of events have occurred (~~126~~ ***113*** and ~~202~~ ***181*** relapses, respectively, assuming the alternative treatment hypothesis) which will be approximately at the time accrual is completed and one year later. Consideration will be given to reporting early at either time if (1) TTR on the gemcitabine arm is superior at the one-sided 0.005 level or if (2) the hypothesis λ=1.53 (where λ is the sterile water/gemcitabine hazard ratio) is rejected in favor of λ<1.53 at the one-sided 0.005 level (testing using a proportional hazards score test, an extension of the logrank test)."

Please attach this memorandum to the front of your copy of the protocol.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Cathy M. Tangen, Dr.P.H.
Hongli Li, M.S.
Jean Barce
Austin Hamm
Brian Zeller
Steven Nicol, M.D. – Lilly
Barbra Podesta, R. Ph. – Lilly
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Distribution Date: October 15, 2013
CTEP Submission Date: August 29, 2013

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS

FROM: Gilbert R. Carrizales, M.S., Protocol Coordinator

RE: **S0337,** "A Phase III Blinded Study of Immediate Post-TURBT Instillation of Gemcitabine Versus Saline in Patients with Newly Diagnosed or Occasionally Recurring Grade I/II Superficial Bladder Cancer." Study Chairs: Drs. E.M. Messing, D.M. Sahasrabudhe, T.M. Koppie, D.P. Wood, Jr., and P.C. Mack.

REVISION #6

Study Chair: Edward M. Messing, M.D.
Phone number: 585/275-3345
E-mail: edward_messing@urmc.rochester.edu

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

(√) Expedited review allowed

( ) No review required

REVISION #6

The protocol has been reformatted and repaginated to meet the current requirements for electronic protocol submission. This includes addition of second level headings in instances where they were previously absent, reformatting the title page to include all second level headings, reformatting the protocol calendar into Microsoft® Word, removal of forms and form numbers, and removal of the consent document as Section 18.0. Additionally, cross-references have been corrected as needed.

1. **Face page (Page 1)**: The following changes have been made to this page:
   - The version date has been updated (8/29/13).
   - The heading "Study Coordinators" has been changed to "Study *Chairs*". The change from "Study Coordinator" to "Study *Chair"* was also made throughout the protocol in **Section 7.1** (page 18), **Section 8.5** (page 21), and **Section 11.3** (page 26).
   - The heading "*Biostatisticians"* has been added above the contact information for the biostatisticians.

2. **Page 22, Section 9.0**: References to Sections 15.4 and 15.3 have been corrected to *15.1* and *15.2*, respectively.

3. **Page 25, Section 11.1**: The following section has been revised in order to clarify terms and assumptions for the statistical section specifications:

Original
"If one assumes roughly equal numbers of patients with newly diagnosed and recurrent superficial bladder tumors, then we anticipate about 60% of patients will experience recurrences by 2 years. It is assumed that 14 eligible patients per month will be randomized. Patients will be stratified by disease status (first occurrence vs. recurrent disease), and number of tumors (one versus more than one). Assuming exponential time-to-recurrence (TTR) and 40% TTR at two years in the sterile saline group, then two years of accrual (340 eligible patients) and two additional years of follow-up will be required for a one-sided 0.025 level test to have power 0.89 for detecting a hazard ratio of 1.53 (equivalent to an improvement to a 55% TTR rate at two years on the gemcitabine arm). The primary test will be performed using the stratified logrank test. All eligible, randomized patients will be used in the primary analysis regardless of whether they actually receive the treatment to which they were assigned (intent-to-treat analysis).

Estimate of sample size: 340 eligible
Estimate of accrual rate: 170 eligible/year

Two interim analyses of time-to-recurrence will be performed after 50% and 80% of the expected number of events have occurred (126 and 202 relapses, respectively) which will be approximately at the time accrual is completed and one year later. Consideration will be given to reporting early at either time if (1) TTR on the gemcitabine arm is superior at the one-sided 0.005 level or if (2) the hypothesis $\lambda=1.53$ (where λ is the sterile water/gemcitabine hazard ratio) is rejected in favor of $\lambda<1.53$ at the one-sided 0.005 level (testing using a proportional hazards score test, an extension of the logrank test).

Assuming the study does not terminate early, the final analysis will occur when approximately 252 recurrences have been reported (estimated to be about two years after completion of accrual). The final analysis will be based on the stratified logrank test with stratification factors as specified in Section 6.0 with a one-sided 0.020 level to adjust for the two interim analyses, for an overall level of 0.025 (one-sided). In addition, the trial will be monitored for safety every six months."

New
"If one assumes roughly equal numbers of patients with newly diagnosed and recurrent superficial bladder tumors, then we anticipate about 60% of patients will experience recurrences by 2 years. It is assumed that 14 eligible patients per month will be randomized. Patients will be stratified by disease status (first occurrence vs. recurrent disease), and number of tumors (one versus more than one). Assuming exponential time-to-recurrence (TTR) and ~~40%~~ ***60%*** TTR ***(40% recurrence-free)*** at two years in the sterile saline group, then two years of accrual (340 eligible patients) and two additional years of follow-up will be required for a one-sided 0.025 level test to have power 0.89 for detecting a hazard ratio of 1.53 (equivalent to an improvement to a ~~55%~~ ***45%*** TTR ***(55% recurrence-free)*** rate at two years on the gemcitabine arm). The primary test will be performed using the stratified logrank test. All eligible, randomized patients will be used in the primary analysis regardless of whether they actually receive the treatment to which they were assigned (intent-to-treat analysis).

Estimate of sample size: 340 eligible
Estimate of accrual rate: 170 eligible/year

Two interim analyses of time-to-recurrence will be performed after 50% and 80% of the expected number of events have occurred (126 and 202 relapses, respectively***, assuming the alternative treatment hypothesis***) which will be approximately at the time accrual is completed and one year later. Consideration will be given to reporting early at either time if (1) TTR on the gemcitabine arm is superior at the one-sided 0.005 level or if (2) the hypothesis $\lambda=1.53$ (where λ is the sterile water/gemcitabine hazard ratio) is rejected in favor of $\lambda<1.53$ at the one-sided 0.005 level (testing using a proportional hazards score test, an extension of the logrank test).

Assuming the study does not terminate early ***and the alternative treatment hypothesis***, the final analysis will occur when approximately ~~252~~ ***226*** recurrences have been reported (estimated to be about two years after completion of accrual). The final analysis will be based on the stratified logrank test with stratification factors as specified in Section 6.0 with a one-sided 0.020 level to adjust for the two interim analyses, for an overall level of 0.025 (one-sided). In addition, the trial will be monitored for safety every six months ***and assuming the alternative hypothesis holds***."

4. **Page 29, Section 14.2, Master Forms**: The following section has been revised for editorial purposes as follows:

Original
"Master forms are included in Section 18.0 and (with the exception of the sample consent form and the Registration Form) must be submitted to the Data Operations Center in Seattle. Data from approved SWOG institutions must be submitted on-line via the Web; see Section 14.3a for details. Exceptions to online data submission are patient completed (e.g. Quality of Life) forms and source documents (e.g. pathology/operative/lab reports)."

New
"Master forms ~~are included in Section 18.0~~ ***can be found on the protocol abstract page on the SWOG website (www.swog.org)*** and (with the exception of the sample consent form and the Registration ~~Form~~***Worksheet***) must be submitted ~~to the Data Operations Center in Seattle~~ ***on-line via the Web***; ~~Data from approved SWOG institutions must be submitted on-line via the Web;~~ see Section 14.3a for details. ~~Exceptions to online data submission are patient completed (e.g. Quality of Life) forms and source documents (e.g. pathology/operative/lab reports)~~."

An entire replacement protocol is attached. Please discard any previous versions of the protocol, and attach this memorandum to the front of your copy of S0337.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Cathy M. Tangen, Dr.P.H.
Hongli Li, M.S.
Jean Barce
Austin Hamm
Brian Zeller
Steven Nicol, M.D. – Lilly
Barbra Podesta, R. Ph. – Lilly
Erin Fink – Lilly
Joseph J. Ashland - Lilly
Kathy Brown – Pharmagistics
Thomas King – Pharmagistics

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swog.org

July 15, 2012

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS

FROM: Jennifer I. Scott, Protocol Coordinator

RE: **S0337,** "A Phase III Blinded Study of Immediate Post-TURBT Instillation of Gemcitabine Versus Saline in Patients with Newly Diagnosed or Occasionally Recurring Grade I/II Superficial Bladder Cancer." Study Coordinators: Drs. E.M. Messing, D.M. Sahasrabudhe, T.M. Koppie, D.P. Wood, Jr., and P. C. Mack.

STATUS NOTICE

Study Coordinator: Edward M. Messing, M.D.
Phone number: 585/275-3345
E-mail: edward_messing@urmc.rochester.edu

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

(√) Expedited review allowed

( ) No review required

PERMANENT CLOSURE

The above-referenced protocol has met its accrual goal and will be permanently closed to accrual **effective 11:59 p.m. on August 15, 2012.**

Please attach this memorandum to the front of your copy of the protocol.

This memorandum serves to notify the NCI and SWOG Statistical Center.

cc: Cathy M. Tangen, Dr.P.H.
Hongli Li, M.S.
Jean Barce
Austin Hamm
Brian Zeller
Steven Nicol, M.D. – Lilly
Barbra Podesta, R. Ph. – Lilly
Erin Fink – Lilly
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swog.org

Distribution Date: July 15, 1012
CTEP Submission Date: June 19, 2012

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS

FROM: Jennifer I. Scott, Protocol Coordinator

RE: **S0337,** "A Phase III Blinded Study of Immediate Post-TURBT Instillation of Gemcitabine Versus Saline in Patients with Newly Diagnosed or Occasionally Recurring Grade I/II Superficial Bladder Cancer." Study Coordinators: Drs. E.M. Messing, D.M. Sahasrabudhe, T.M. Koppie, D.P. Wood, Jr., and P. C. Mack.

REVISION #5

Study Coordinator: Edward M. Messing, M.D.
Phone number: 585/275-3345
E-mail: edward_messing@urmc.rochester.edu

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

(√) Expedited review allowed

( ) No review required

REVISION #5

The above-referenced protocol has been revised as follows:

Face Page: The participants list was revised to delete "UCOP" as this program has been discontinued. The contact information for Dr. Koppie has been updated. Bryan Goldman is no longer with the Group. His name and contact information has been replaced with that for Hongli Li, M.S. The version date has been updated.

Page 1a: The contact information for Dr. Wood has been updated.

Section 7.0, page 15: The phone number for Dr. Wood has been revised.

Section 7.3, page 16: The form number for the **S0337** Cystoscopy and Urine Markers Form has been updated from Form #7491 to Form #42978.

Section 8.6, page 17: This section has been revised to reflect the Group's current standard language regarding reporting toxicities.

Section 13.3a, page 23: The phone number for the SWOG Operations Office has been updated.

Section 14.3a, page 24: The phone number for the SWOG Operations Office has been updated.

Sections 14.4 and 14.6, page 25: The form number for the **S0337** Cystoscopy and Urine Markers Form has been updated from Form #7491 to Form #42978.

Section 15.0, pages 25-27: This section has been updated so that the format is consistent the Group's current specimen submission instructions. The types of specimens collected, the frequency at which they are collected, and how they are collected has not changed.

Section 16.1, pages 28-30: This section has been updated to reflect the Group's current SAE reporting guidelines.

Section 18.2e, page 33: The **S0337** Cystoscopy and Urine Markers Form has been revised and the form number has been changed from Form # 7491 to Form #42798. The form itself was revised to add a check box for Month 42 which was inadvertently omitted.

Section 19.1, pages 59-60: This section has been revised to reflect the Group's current standard language regarding determination of expedited adverse event reporting requirements.

Section 19.3, page 63: The form number for the **S0337** Cystoscopy and Urine Markers Form has been updated from Form #7491 to Form #42978.

Please attach this memorandum to the front of your copy of the protocol.

This memorandum serves to notify the NCI and SWOG Statistical Center.

cc: Cathy M. Tangen, Dr.P.H.
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swog.org

February 1, 2012

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS

FROM: SWOG Operations Office

RE: IND Safety Reports for Gemcitabine hydrochloride (Gemzar®)

MEMORANDUM

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

(√) Expedited review allowed

( ) No review required

MEMORANDUM

The following revised safety report has been posted regarding an adverse event that occurred in association with the blinded drug gemcitabine hydrochloride/placebo. **This report downgraded the event previously reported such that the event is no longer reportable.** Please access this safety report via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

This safety report pertains to the following study:	Report:
S0337 Genitourinary	Dec. 27, 2011 AE #US201111007133 FU

A protocol amendment is not necessary at this time, but your consent form may be revised to include the information provided in this report if it is deemed necessary by your institution. Please append this notice and this report to your copy of the protocol and forward a copy to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding this adverse event be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Cathy M. Tangen, Dr.P.H.
Benjamin W. Ely, M.S.
Jean Barce
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Brian Zeller
Steven Nicol, M.D.–Lilly
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swog.org

January 1, 2012

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS

FROM: SWOG Operations Office

RE: IND Safety Reports for Gemcitabine hydrochloride (Gemzar®)

MEMORANDUM

IRB Review Requirements

( ) Full board review required. Reason:
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- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

(√) Expedited review allowed

( ) No review required

MEMORANDUM

The following new safety report has been posted regarding an adverse event that occurred in association with the drug gemcitabine hydrochloride. Please access this safety report via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

This safety report pertains to the following study:	Report:
S0337 Genitourinary	Dec. 1, 2011 AE #US201111007133

A protocol amendment is not necessary at this time, but your consent form may be revised to include the information provided in this report if it is deemed necessary by your institution. Please append this notice and this report to your copy of the protocol and forward a copy to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding this adverse event be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
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December 15, 2011

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS

FROM: Jennifer I. Scott, Protocol Coordinator

RE: **S0337,** "A Phase III Blinded Study of Immediate Post-TURBT Instillation of Gemcitabine Versus Saline in Patients with Newly Diagnosed or Occasionally Recurring Grade I/II Superficial Bladder Cancer." Study Coordinators: Drs. E.M. Messing, D.M. Sahasrabudhe, T.M. Koppie, D.P. Wood, Jr., and P. C. Mack.

MEMORANDUM

Study Coordinator: Edward M. Messing, M.D.
Phone number: 585/275-3345
E-mail: edward_messing@urmc.rochester.edu

IRB Review Requirements

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- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

( ) Expedited review allowed

(√) No review required

MEMORANDUM

The purpose of this memorandum is to inform sites of the Holiday closure of Pharmagistics/Knipper. They will be **closed Friday, December 23, 2011 through Monday, December 26, 2011**. Regular business hours and shipping will resume on Tuesday, December 27, 2011.

As a reminder, if a patient consents to the optional specimen submission, you must contact Dr. Jay Reeder's lab as noted in Section 15.3 of the protocol after the patient is registered and the Month 3 visit is scheduled to order a Paxgene blood tube well in advance of the Month 3 blood draw.

Please attach this memorandum to the front of your copy of the protocol.

This memorandum serves to notify the NCI and SWOG Statistical Center.

cc: Cathy M. Tangen, Dr.P.H.
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swog.org

Distribution Date: December 1, 2010
CTEP Submission Date: November 19, 2010

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP, AFFILIATE, AND UCOP MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS

FROM: Jennifer I. Scott, Protocol Coordinator

RE: **S0337,** "A Phase III Blinded Study of Immediate Post-TURBT Instillation of Gemcitabine Versus Saline in Patients with Newly Diagnosed or Occasionally Recurring Grade I/II Superficial Bladder Cancer." Study Coordinators: Drs. E.M. Messing, D.M. Sahasrabudhe, T.M. Koppie, D.P. Wood, Jr., and P. C. Mack.

REVISION #4

Study Coordinator: Edward M. Messing, M.D.
Phone number: 585/275-3345
E-mail: edward_messing@urmc.rochester.edu

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

(√) Expedited review allowed

( ) No review required

REVISION #4

The above-referenced protocol has been revised as follows:

1. Title Page: The version date has been updated.

2. Pages 16-16a, Section 8.1: The criteria for reporting Adverse Events have been updated. Effective January 1, 2011 the CTCAE Version 4.0 will be utilized for SAE reporting. The CTCAE Version 3.0 will continue to be utilized for routine toxicity reporting. Page 16a was added to prevent extensive repagination.

Please append this notice to the front of your protocol and insert the replacement pages referenced above.

This memorandum serves to notify the NCI and Southwest Oncology Group Statistical Center.

cc: Cathy M. Tangen, Dr.P.H.
Bryan Goldman, M.S.
Benjamin W. Ely, M.S.
Jean Barce
Janice Leaman
Brian Zeller
Steven Nicol, M.D. – Lilly
Barbra Podesta, R. Ph. – Lilly
Erin Fink – Lilly
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Oncology Group
A National Clinical Research Group

Distribution Date: November 15, 2009
CTEP Submission Date: October 21, 2009

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP, AFFILIATE, AND UCOP MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS

FROM: Jennifer I. Scott, Protocol Coordinator

RE: **S0337,** "A Phase III Blinded Study of Immediate Post-TURBT Instillation of Gemcitabine Versus Saline in Patients with Newly Diagnosed or Occasionally Recurring Grade I/II Superficial Bladder Cancer." Study Coordinators: Drs. E.M. Messing, D.M. Sahasrabudhe, T.M. Koppie, D.P. Wood, Jr., and P. C. Mack.

REVISION #3

Study Coordinator: Edward M. Messing, M.D.
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IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

(√) Expedited review allowed

( ) No review required

REVISION #3

The above-referenced protocol has been revised as follows:

Face Page: The version date of the protocol has been updated.

Section 3.1c, page 12: Two sentences have been added to the "Supplier" paragraph of Section 3.1c to provide logistical information for Saturday drug delivery for patients registered on Thursday after 2 p.m. Eastern time, but prior to 2. p.m. Eastern time on Friday.

Section 5.1, page 13: This section has been revised as follows: The bullet point "have had no prior bladder cancer for ≥ 9 months before the index tumor resection" has been deleted. The now second bullet point has been revised to indicate that patient must have had no more than 2 recurrences in the 18 months (versus 3 years) preceding index tumor's TURBT. Additionally this bullet point has been revised to indicate allowable stages of these recurrences.

Section 5.2, page 13: This section has been revised to indicate that there must be plans for the patient to receive a TURBT within 28 working days rather than ten working days after randomization.

Section 5.3, page 13: This section has been revised to indicate that patients must not have received previous intravesical therapy within 145 days rather than 180 days.

Section 5.4, page 13: This section has been revised to clarify to define negative urine analysis for infection.

Section 5.8, page 14: This section has been revised to allow patients free of disease for three years rather than five years.

Section 7.1g, page 15: This section has been revised to indicate that patient should have negative upper tract imaging studies obtained within 365 days prior to registration rather than within 180 days.

Section 7.2, page 15: This section has been revised to be consistent with the revision made in Section 5.2 as noted above.

Section 13.1, page 22: This section has been revised to be consistent with the revision made in Section 5.2 as noted above.

Prestudy Form: The Prestudy Form has been revised to be consistent with the changes made in Section 5.0 of the protocol. **Section 5.0, page 13, Section 14.4, page 25,** and **Section 18.2b, page 33** have been revised to cross reference the new form number (#19450) instead of Form #23033.

Please append this notice to the front of your protocol and insert the replacement pages referenced above.

This memorandum serves to notify the NCI and Southwest Oncology Group Statistical Center.

cc: Cathy M. Tangen, Dr.P.H.
Bryan Goldman, M.S.
Benjamin W. Ely, M.S.
Jean Barce
Janice Leaman
Brian Zeller
Steven Nicol, M.D. – Lilly
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Southwest
Oncology Group
A National Clinical Research Group

Distribution Date: June 1, 2009
CTEP Submission Date: May 15, 2009

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP, AFFILIATE, AND UCOP MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS

FROM: Jennifer I. Scott, Protocol Coordinator

RE: **S0337,** "A Phase III Blinded Study of Immediate Post-TURBT Instillation of Gemcitabine Versus Saline in Patients with Newly Diagnosed or Occasionally Recurring Grade I/II Superficial Bladder Cancer." Study Coordinators: Drs. E.M. Messing, D.M. Sahasrabudhe, T.M. Koppie, D.P. Wood, Jr., and P. C. Mack.

REVISION #2

Study Coordinator: Edward M. Messing, M.D.
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IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

(√) Expedited review allowed

( ) No review required

REVISION #2

The above-referenced protocol has been revised as follows:

Face Page: The version date of the protocol has been revised.

Section 3.1c, page 12: The last sentence of the "Supplier" section has been revised to more accurately reflect that each investigator must be linked to an active pharmacy in the SWOG database.

Section 5.4, page 13: For clarification, this section has been revised to move the end parenthesis in the second line; capitalize, underline and bold the text "**OR**"; and replace the word "and" with "with". Additionally, the third line of this section has been revised to indicate that patients must have WBC/HPF of ≤ 10 instead ≤ 2.

Please append this notice to the front of your protocol and insert the replacement pages referenced above.

This memorandum serves to notify the NCI and Southwest Oncology Group Statistical Center.

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Southwest
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A National Clinical Research Group

Distribution Date: February 1, 2009
CTEP Submission Date: December 30, 2008

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP, AFFILIATE, AND UCOP MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS

FROM: Jennifer I. Scott, Protocol Coordinator

RE: **S0337,** "A Phase III Blinded Study of Immediate Post-TURBT Instillation of Gemcitabine Versus Saline in Patients with Newly Diagnosed or Occasionally Recurring Grade I/II Superficial Bladder Cancer." Study Coordinators: Drs. E.M. Messing, D.M. Sahasrabudhe, T.M. Koppie, D.P. Wood, Jr., and P. C. Mack.

REVISION #1

Study Coordinator: Edward M. Messing, M.D.
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IRB Review Requirements

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(√) Expedited review allowed

( ) No review required

REVISION #1

The above-referenced protocol has been revised as follows:

Face Page: Dr. Theresa M. Koppie has been added as a Secondary Study Coordinator and her contact information included. The version date has been revised.

Section 3.1c, page 12: Two sentences have been added to the “Supplier” section of Section 3.1c to clarify drug shipping and delivery timeframes. The last sentence of the "Supplier" section has been revised to clarify that the pharmacist will need the patient number in order to identify the correct package from the drug distributor.

Sections 5.3 and 5.4, pages 13-14: Sections 5.3 and 5.4 have been moved to the Good Medical Practice Section (Section 7.1, page 15) and the remainder of Section 5.0 renumbered accordingly. A sentence was added to Section 5.4 (now Section 7.1g) to indicate that the imaging studies may be performed after registration, but prior to TURBT on the day of the treatment.

Section 7.1f&g, page 15: These sections have been added as indicated above and the text "must" has been revised to "should."

Section 7.3, page 16: The second sentence of this section has been revised to indicate that the BTA Stat and NMP-22 Bladder Check are commercially available tests. The last sentence of this section has been revised to replace the text “specimen kits” with “tests.”

Section 9.0, page 18: The "£"footnote has been added to the Study Calendar.

Section 11.2, page 20: The text “sterile water” has been replaced with “saline” in the second paragraph of this section.

Section 15.3, page 26: This section has been revised to update the phone number for Dr. Reeder (Lab #135) and clarify the blood submission procedure.

Page 1a was added to prevent extensive repagination of the protocol.

Please append this notice to the front of your protocol and insert the replacement pages referenced above.

This memorandum serves to notify the NCI and Southwest Oncology Group Statistical Center.

cc: Cathy M. Tangen, Dr.P.H.
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Southwest
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September 1, 2007

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP, AFFILIATE, AND UCOP MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS

FROM: Jennifer I. Scott, Protocol Coordinator

RE: **S0337,** "A Phase III Blinded Study of Immediate Post-TURBT Instillation of Gemcitabine Versus Saline in Patients with Newly Diagnosed or Occasionally Recurring Grade I/II Superficial Bladder Cancer." Study Coordinators: Drs. E.M. Messing, D.M. Sahasrabudhe, D.P. Wood, Jr., and P. C. Mack.

MEMORANDUM

Study Coordinator: Edward M. Messing, M.D.
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IRB Review Requirements

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( ) Expedited review allowed

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MEMORANDUM

Please note that the intellectual property terms applicable to participation in this trial, as partially funded by an industry collaborator, are different from the terms set forth in the Purchase Service Agreement (PSA) signed by registering members. Specifically, participation in this trial requires agreement and compliance with allowing the industry collaborator a non-exclusive license to any intellectual property resulting from this trial, including use for commercial purposes. This is in contrast to the standard intellectual property terms in the PSA which restricts the industry collaborator to a non-exclusive license for research purposes only. This exception to the standard intellectual property terms has been approved by the NCI. You are required to inform your site's appropriate grants and contracts office about this modification to the PSA. Please direct any questions related to this modification to the legal department at Group Headquarters Office at 734-998-7173.

Please attach this memorandum to the front of your copy of the protocol.

This memorandum serves to notify the NCI and Southwest Oncology Group Statistical Center.

cc: Cathy M. Tangen, Dr.P.H.
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Barbra Podesta, R. Ph. – Lilly
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Southwest
Oncology Group
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July 15, 2007

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP, AFFILIATE, AND UCOP MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS

FROM: Jennifer I. Scott, Protocol Coordinator

RE: **S0337,** "A Phase III Blinded Study of Immediate Post-TURBT Instillation of Gemcitabine Versus Saline in Patients with Newly Diagnosed or Occasionally Recurring Grade I/II Superficial Bladder Cancer." Study Coordinators: Drs. E.M. Messing, D.M. Sahasrabudhe, D.P. Wood, Jr., and P. C. Mack.

STATUS NOTICE

Study Coordinator: Edward M. Messing, M.D.
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IRB Review Requirements

(√) Full board review required. Reason:
- (√) Initial activation (should your institution choose to participate)
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- ( ) Study closure due to new risk information

( ) Expedited review allowed

( ) No review required

ACTIVATION

The study referenced above is now open for participation. An entire copy of the protocol is enclosed for your use.

This memorandum serves to notify the NCI and Southwest Oncology Group Statistical Center.

cc: Cathy M. Tangen, Dr.P.H.
Bryan Goldman, M.S.
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Janice Leaman
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PRIVILEGED COMMUNICATION
FOR INVESTIGATIONAL USE ONLY

Activated July 15, 2007

SWOG

A PHASE III BLINDED STUDY OF IMMEDIATE POST-TURBT INSTILLATION OF GEMCITABINE VERSUS SALINE IN PATIENTS WITH NEWLY DIAGNOSED OR OCCASIONALLY RECURRING GRADE I/II SUPERFICIAL BLADDER CANCER

PARTICIPANTS: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, AFFILIATE AND CCOP MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS

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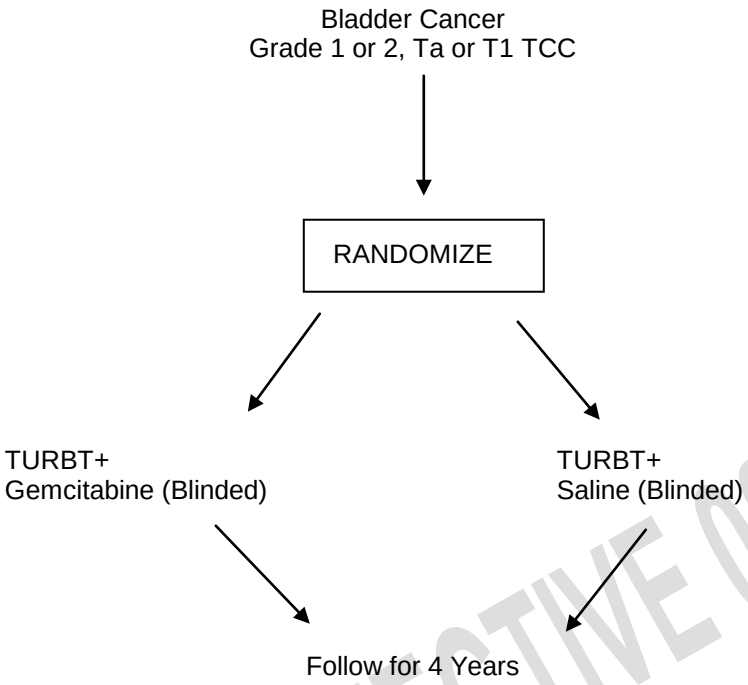
TABLE OF CONTENTS

SCHEMA



1.0 OBJECTIVES

1.1 Primary Objective

The primary objective of this study is to determine the efficacy of a single post-transurethral resection of the bladder (TURBT) intravesical instillation of gemcitabine versus saline in preventing recurrence of completely resected Grade 1 or 2, Ta or T1 transitional cell cancer (TCC) of the bladder at two years.

1.2 Secondary Objectives

a. To test whether a single instillation of intravesical gemcitabine can improve the time to progression to muscle invasive disease compared to saline in this patient population.

b. To compare the qualitative and quantitative toxicities between the arms.

c. To determine if effective post TURBT instillation therapy results in reduced long term morbidity as determined by patients randomized to gemcitabine requiring fewer TURBTs, courses of traditional intravesical therapies, and surveillance cystoscopies over four years compared with those randomized to intravesical saline.

1.3 Translational Medicine Objectives

a. The correlative studies will evaluate whether performing a combination of molecular/cytologic diagnostic marker tests including NMP-22 Bladder Chek and BTA Stat every three months can predict recurrence as accurately as cystoscopy alone.

b. To acquire blood and tissue specimens from patients on this clinical trial for banking for genotyping.

2.0 BACKGROUND

Overview

While well- and moderately-differentiated recurring superficial bladder cancer rarely progresses to a life threatening condition, repeated resections represent considerable morbidity for patients and expense for both patients and the healthcare system as a whole. In several European studies, immediate post-TURBT instillations of chemotherapeutic agents including epirubicin, mitomycin-C, doxorubicin, and thiotepa have been shown to decrease the likelihood of recurrence and to be well-tolerated. *(1-5)* Despite these data, this type of therapy has not been embraced by American urologists as part of standard care for the management of low-grade superficial bladder cancer.

Superficial Bladder Cancer

Natural History: Bladder cancer is the fifth most common solid malignancy diagnosed annually in the United States. *(6)* Between 75 - 80% of these cancers will be superficial (Stage TIS, Ta, T1), greater than 90% transitional cell carcinomas (urothelial cancer), and the majority well (Grade 1) or moderately (Grade 2) differentiated (roughly equivalent to tumors of low malignant potential and low-grade carcinoma by 1998 AJCC criteria, respectively). *(7)* If one eliminates patients with Grade III (high-grade) cancer or carcinoma-in-situ (CIS), the risk of recurrence after endoscopic resection alone, is quite high, but that of progression to muscle invasion, relatively

low. *(2-4)* Based upon a recently completed NCI/ILEX Corporation chemoprevention study (CN-26534), roughly 60% of patients eligible for **S0337** (assuming most patients have prior histories of bladder cancer), will be expected to experience a tumor recurrence within two years, as detected upon every three month cystoscopy. Fewer than 20% of patients eligible for this study would be expected to experience grade progression upon first failure, and far less than this stage progression to T2+. *(2-4,8)*

The population eligible for this trial will be patients who have low (Stage Ta, low malignant potential [LMP]) to moderate (Stage T1, low grade) risk urothelial cancer of the bladder and whose primary urologist believes are not candidates for more prolonged courses of intravesical or more aggressive therapies based upon preoperative cystoscopic inspection, bladder cancer history, and other factors (e.g. upper tract evaluation, cytology results, tumor size, multifocality, etc.). Although cystoscopic inspection for experienced urologists is usually a reliable predictor of tumor grade and stage, it is estimated that roughly 10% of cases will be eliminated after randomization and drug/placebo instillation, because high grade cancer, TIS or muscle invading cancer (Stage T2+) is documented on final histology, mandating more aggressive therapies. *(9)* Additionally, another 5-10% of patients would be expected to have sufficiently deep, large or bloody resections that urologists would be hesitant to perform immediate post TURBT instillations.

Mechanisms of Superficial Bladder Cancer Recurrence: Particularly for LMP and low grade superficial bladder cancers, data would indicate that recurrences of seemingly completely resected tumors occur because of new tumor development at other regions of the urothelium (field effect), implantation of tumor cells derived from the original tumor in other sites of urothelium (presumably occurring spontaneously as well as because of perturbations induced by instrumentations such as cystoscopy and transurethral resection [TUR]), and because of failure to resect the original malignancy. *(5,10)* Evidence to support implantation includes differences in locations of primary tumors compared to recurrences with the former primarily located on the lateral bladder walls (70%) and trigone (20%); while recurrences frequently arise on the dome and anterior bladder wall. *(11)* Animal models also indicate that both spontaneous and mechanically facilitated implantation occurs. Sites of urothelial injury are preferential sites of recurrence. *(12-13)* A single, immediately post TURBT intravesical instillation of chemotherapy is primarily directed at reducing the rate of implantation, although it may have a beneficial effect on eliminating field effect tumors or persistent (incompletely resected) ones, as well.

Intravesical Therapy: To reduce the frequency of recurrences in these individuals at low risk for bladder cancer progression and at high risk for recurrence, intravesical therapy with a variety of chemo- and immunotherapeutic agents have been used. Agents have included BCG, mitomycin-C, doxorubicin, and thiotepa in the United States, as well as epirubicin and epodyl in Europe. Courses of instillation therapy starting days and weeks after the TURBT can reduce recurrences by 17 to 44% compared with controls. *(14-16)* These treatments, however, are not without considerable inconvenience, expense, and morbidities for patients with side effects including thrombocytopenia and leukopenia with thiotepa in 9% of patients, genital rash due to mitomycin in 6% of patients, and bladder contracture in as many as 16% of those treated with doxorubicin and a smaller percentage of those treated with mitomycin. Side effects from BCG therapy occur in 20 - 45% of patients and can include high fever, granulomatous prostatitis, pneumonitis, and hepatitis.

To reduce these sources of morbidity, inconvenience and expense immediately following TURBT, intravesical instillations of a variety of chemotherapeutic agents have been tested in prospective randomized studies. These studies are summarized in Table 1. The agents have included thiotepa, mitomycin-C, epirubicin, doxorubicin, and epodyl. While patients, drug dosages, times of instillation after TURBT, and durations of follow-up have varied, most studies have shown a 40 - 50% reduction in tumor recurrences with active agents (see Table 1).

Table 1

	AGENT DOSE CONTROL	# Pts	STAGE	NEW VS RECURRENT	RECURRENCE RATE 2 YR
MRC, Br J Urol 57:6810, 1985	Ttp 30 mg/50 ml vs obs	256	TaT1	N only	41.3% 35.4% p=.7
MRC, Br J Urol 73:632, 1994	Long term f/u – 8.75 → no diff time to 1st recurrence, recurrence rate, or failure free interval				
Solsona, et al Br J Urol 161:1120, 1999	MMC 30mg/50ml NS vs obs	121	TaT1	90% new 10% recurrent	RR 1yr 22% 59% p<.005 no diff in recurrences after 1 yr
Oosterlinck, et al J Urol 149:749, 1993	Epirub 80 mg in 50cc NS vs 50 ml H_2O	399	TaT1	80% new 20% recurrent	RR 1yr 17% 32% p<.0001 10-15% 31% p<.0001 Recurrent 26% 35% p = .38 but after 12-18 mo recurrences were = & continued in each arm after 18 mo → 4yr
Burnand, et al Br J Urol 48:55, 1976	Ttp 90 mg/100cc	51	TaT1	Unknown	Recurrences (2-5 yr f/u) 57.9%* 96.8% p<.005 *no recurrence at vault alone vs 21.9% at vault alone for control
Ali-el-dein, et al Br J Urol 79:731, 1997	Epirub 50 mg/50ml NS vs obs	109 (19% G3)	TaT1	55% new 45% recurrent (24% interval to tumor recur)	RR at mean 2.5 yr 52% p<.002 16 mo 7 mo p<.05
Rajala, et al J Urol 161:1133, 1999	Epirub 100 mg vs Ifα2b 50 M unit (3 arm) vs obs	200 (12% G3)	TaT1	All new Single tumor Multiple tumors	RR at 2 year Epi Ifα Cont 32% 62% 60% p<.05 27% 63% 55% 56% 67% 74%
Tolley, et al J Urol 155:1233, 1996	MMC 40 mg/40 ml H_2O vs obs	306	TaT1	All new After 18 mo no further improvement from MMC hazard rate MMC .66 control for recurrent	RR at 2 year MMC Cont 42% 55% p = .05
Zincke, et al J Urol 129:505, 1983	Ttp 60 mg/60ml Dox 50 mg/60ml H_2O 60 ml	45 (roughly)	Ta, T1, TIS	21% new 79% recur new recurrent	RR at 3 mo – 4 mo Ttp Dox H_2O 30% 32% 71% 43% 0 43% 26% 38% 81%

In some studies, patients with newly diagnosed cancers were particularly advantaged, while in others those with recurrent tumors were advantaged. *(3,17)* The largest of the studies is that reported by Oosterlinck et al, carried out by the EORTC. *(3)* In this study, 80 mg of epirubicin in 50 cc of saline was compared to 50 ml of sterile H_20 immediately after TURBT of Stage Ta and T1 completely resected tumors in 399 patients. Roughly 80% had new tumors and experienced a reduction of recurrence by over 50% from 31% recurrences per year in control patients to less than 15% in treated patients. Patients whose index tumors were recurrent cancers experienced a non-significant reduction of recurrence rates compared to controls (p=.38). The differences in recurrences were primarily achieved during the first 12 months, but these differences continued in each arm up to the four years of follow-up reported.

Gemcitabine in Urothelial Cancer

Gemcitabine 2^1, 2^1-difluoro-2^1-deoxycytidine is incorporated by dividing cells into DNA and will inhibit further DNA synthesis. It may also inhibit ribonucleotide reductase and cytidine deaminase activity. *(18)* This drug has been shown to be active against unresectable and metastatic cancers in several sites including bladder cancer. In a variety of reports, single agent systemic gemcitabine for metastatic or unresectable TCC has had objective response rates ranging from 22.5% to 28%. *(18)* When gemcitabine is used in "doublets" with cisplatin, carboplatin, or paclitaxel, response rate in the 24%-78% range, mostly 40% - 60% have been seen. *(17)* When used in "triplets" with cisplatin or carboplatin plus paclitaxel, objective response rates in Phase II studies have been in the 68% - 77% range. *(19)* Additionally, in a randomized prospective study of gemcitabine plus cisplatin versus methotrexate, vinblastine, adriamycin, cisplatin (MVAC) chemotherapy for unresectable or metastatic TCC, equivalence of the two regimens was found with less toxicity for the gemcitabine plus cisplatin arm. *(20)* Thus, this agent has efficacy both alone and in combination in advanced urothelial cancer.

Intravesical Gemcitabine: Based on these observations, Dalbagni and colleagues have in a Phase I study tested various concentrations of this agent in an intensive regimen (biweekly instillations for three weeks followed by a one week hiatus in which patients were cystoscoped, and then received three more weeks of biweekly instillations in dosages ranging from 500 to 2,000 mg of gemcitabine in 100 ml of buffered water). *(21)* The 18 patients taking part in this Phase I study were at very high risk, having highly refractory TIS or more advanced superficial TCC. Thirty-nine percent of the patients achieved complete pathologic and cytologic responses and another 22% had mixed responses (negative biopsies but positive cytologies). The responses were not clearly dose related when dosages of $\geq$ 10 mg/ml were administered. There was no response seen, however, at the lowest dose, 5 mg/ml. At the 10 mg/ml dose, 3 of 6 patients experienced a complete response, 2 of 6 had a mixed response as defined above and 1 of 6 had persistent tumor. Encouraged by these findings in an extremely high risk group of patients, Dalbagni, et al, are carrying out a Phase II trial of this regimen in highly refractory high risk superficial bladder cancer patients.

Gemcitabine when dissolved in water or saline reduces the pH of the solution to the 2 to 3 range. Because at least in in vitro studies, acidification to this degree alone has toxic effects on human urothelial cells in culture, some authors have suggested buffering the solution with sodium bicarbonate to reach a pH of 5-6, which is physiologic in the bladder. *(O'Donnell, personal communication, (22)* In the clinical study performed by Dalbagni, et al, such buffering was performed. *(21)* However, in no other studies (described below) has buffering been used.

In a separate Phase I study, Laufer, et al, studied 15 patients with recurrent superficial bladder cancer (heavily pretreated with intravesical therapies) with six weekly instillations of gemcitabine dissolved in 0.9% saline beginning 2-4 weeks after TURBT. *(23)* Three patient cohorts were enrolled sequentially, receiving doses of 500, 1,000 and 1,500 mg in 100 ml 0.9% saline. An additional six patients received 2,000 mg in 100 ml or 50 ml. Nine of 13 evaluable patients had complete responses at six weeks after completion of therapy – all responders receiving ≥ 1,000

mg doses. Pharmacokinetic studies demonstrated gemcitabine or its metabolite, 2^1 2^1 difluorodeoxyuridure in plasma of patients transiently in doses ≥ 1,500 mg/100ml. No Grade 4 toxicities were seen but one patient receiving 2,000 mg/100 ml experienced reversible significant urinary frequency (stopped treatment). While these patients received six weekly instillations, none were started for at least two weeks after TURBT. Two other presentations of Phase I studies of escalating doses of gemcitabine in 50 ml 0.9% NaCl have been presented, using six weekly instillations starting 2-4 weeks after TURBT. *(24-25)* Each had a minimal intensity of side effects, primarily minor dysuria in 7 of 10 and 1 of 12 patients, respectively.

Tolerability of Post TURBT Instillations of Gemcitabine

Germane to the above comments, which are the rationale for this large proposed study, is that there have been several reports about tolerability of various dosages of gemcitabine. In one study not yet reported, O'Donnell from the University of Iowa instilled immediate post-TURBT gemcitabine – five patients received 1,500mg/100ml 0.9% saline and five received 2,000mg/100ml for 60 minutes. Hematuria occurred in 2 of 10 and 10 of 10 respectively. All other side effects were mild, transient, and unrelated to dose. *(22)*

In a separate study, Buettner and Boehle performed a small Phase I study of immediate post-TURBT instillations of gemcitabine in dosages of 500 mg/50ml, 800 mg/50 ml, 1,000 mg/50 ml, 1,000 mg/100 ml, 1,500 mg/100 ml and 2,000 mg/100 ml of 0.9% NaCl. *(26)* No systemic absorption of the drug was found for any of the dosages yet tested (based on pharmacokinetic data). Moreover, all dosages were well tolerated except for 1,000 mg/50 ml which appeared to cause considerable bladder irritative symptoms that were relieved as soon as the fluid was drained from the bladder by unclamping the catheter. Since this was not found at similar concentrations with higher volumes, even the authors are perplexed by these results. Mild (Grade 1 or 2) hematuria and/or dysuria that was quite transient were the only other side effects (in 9 of 26 patients). *(26)* In addition, Maddineni and colleagues from the University of Manchester, England administered similar dosages of gemcitabine, again finding no systemic absorption in 15 patients with frequently recurrent superficial bladder cancer. They found the instillations to be quite tolerable, although at doses above 1,000 mg/ml dwell times exceeding 40 minutes became difficult to tolerate due to bladder spasms. However these investigators were choosing 20 - 24 hours post TURBT for instillations, not three hours when anesthetic effects are likely to permit greater drug retention. Ten of the 15 patients have been evaluated for recurrence, five of whom were tumor free. *(27)*

In a separate study, Palou, et al, treated five patients each with 1,500 or 2,000 mg/100 ml 0.9% NaCl, within three hours of TURBT. No significant toxicities were seen, with only one patient at the 2,000 mg dose experiencing only self-limited minor urinary irritation and two patients at the 1,500 mg dose experiencing transient Grade 1 hypogastric discomfort. *(28)* Mean maximum serum concentrations of gemcitabine were 1.8 ug/ml, and no systemic toxicity was seen. Four of the ten patients were found to have recurrences on reevaluation. A summary of these pilot data on intravesical gemcitabine appear in Table 2.

Table 2. Phase I Clinical Experience

Reference	Number of Patients	Gemci-tabine Dose (mg)	Dilution (Normal Saline) (mL)	Dwell Time (hr)	Dosing Schedule	Buffering	Grade 3/4 Systemic Toxicity (Patients)
Dalbagni, et al, 2002	18	500-2000	100	1	Twice weekly	Yes	2*
Laufer, et al, 2003	15	500-2000	50-100	2	1x week	No	0
Witjes, et al, 2004	10	1000-2000	50	1	1x week	No	0
DeBerardinis, et al, 2004	12	500-2000	50	2	1x week	No	0
Buettner, et al, 2003	26	500-2000	50-100	0.5	Single dose adjuvant	No	0
Palou, et al, 2004	10	1500-2000	100	1	Single dose adjuvant	No	0
Maddineni, et al, 2003	15	500-1000	100	1-2	Single dose adjuvant	No	0

* One Grade 3 neutropenia and thrombocytopenia was reported at the 2,000 mg level, and one Grade 3 "hand/foot syndrome" was reported at the 1,000 mg level.

Proposed Clinical Trial – Efficacy and Morbidity of Therapy:

Reducing the recurrence rate of superficial bladder cancer has benefit in terms of reduced morbidity and expense, and possibly reduces serious morbidity and mortality. Immediate post-transurethral resection (TUR) instillation therapy is standard treatment in Europe, but has not been popular in North America. The publication of a North American study showing efficacy is likely to change practices of North American urologists. The use of gemcitabine will not only confirm the benefits of post TURBT instillation therapy, but also will test the efficacy of this agent, which has promising effects against high risk urothelial cancer in topical and systemic applications. Since this is preventing recurrence in a somewhat mixed group of patients whose composite populations have a range of recurrence rates, designs other than randomized prospective trials have no realistic chance of establishing efficacy, and use of saline control is valuable to make certain that active agent is more efficacious than diluent alone. We propose to determine if gemcitabine in a dosage and volume that appear to be well tolerated (2,000 mg in 100 ml of 0.9% NaCl) when instilled intravesically immediately after TURBT (within 3 hours), is more effective than instillation of sterile saline in preventing recurrences of newly diagnosed or occasionally recurrent low grade superficial bladder cancer that has been endoscopically resected in its entirety. Additionally, by preventing short-term recurrences, we believe this therapy will also reduce longer term recurrences, and the need for frequent TURBTs, more traditional courses of intravesical therapy, and very frequent surveillance cystoscopies.

Proposed Correlative Studies:

The follow-up of patients with superficial bladder cancer is a subject of great interest because of the inconvenience, expense and morbidity of frequent cystoscopies. Use of a non-invasive technique which has equal accuracy to cystoscopy would be desirable, but currently no commercially available noninvasive test is believed to have sufficient sensitivity in itself to replace cystoscopy. In this study, two commercially available, point-of-care, non-invasive tests will be used in addition to cystoscopy to see if any, alone or in combination, can equal the sensitivity of a cystoscopy. This will provide compelling information on each test (data on combined tests are not available) and are likely, if a positive result is found, to significantly change standard urologic practice. Additionally, this will provide necessary background information for a bladder cancer screening trial which may be proposed in the future.

Summary

In summary, we propose that immediate (within three hours) post TURBT intravesical gemcitabine will significantly improve the recurrence free survival occurring with intravesical saline, from 40% (with saline) to 55% (with gemcitabine) at two years post TURBT in patients with newly diagnosed or occasionally recurrent Grade 1 or 2, Ta or T1 bladder cancer that has been endoscopically resected in its visible entirety.

Inclusion of Women and Minorities:

Women and Minorities

Based on a previous Southwest Oncology Group superficial bladder cancer trial, the expected breakdown by race and sex would be:

	White	Black	Asian/Pacific Islander	Native American	Total
Male	289	7	1	0	297
Female	40	3	0	0	43
Total	329	10	1	0	340

Treatment interactions are not anticipated, so the trial has not been powered to address specific race or gender questions. However, we will do exploratory analyses of treatment by race and treatment by gender interactions at the end of the study.

3.0 DRUG INFORMATION

3.1 Gemcitabine hydrochloride (Gemzar®) (NSC-613327) (IND-73,058)

a. DESCRIPTION

2'-Deoxy-2', 2'-difluorocytidine monohydrochloride (Gemcitabine hydrochloride or Gemcitabine®) is a white to off-white or translucent solid with a molecular weight of 299.66.

Mechanism of Action: Gemcitabine, like ara-C, is an analog of deoxycytidine. This antimetabolite, a pyrimidine analog inhibiting both DNA and RNA viruses, is cell-cycle-specific in blocking the cells at the G1/S and is retained in human tumor cells for long periods. Studies suggest that gemcitabine is activated by deoxycytidine kinase. Deoxycytidine has been shown to reverse the growth inhibitory activity of gemcitabine.

b. TOXICOLOGY

Human Toxicology: Phase I clinical experiences with intravesical gemcitabine have been reported in seven studies where dose ranges of 500 to 2,000 mg at concentration of 20 - 40 mg/ml with 1 to 2 hours of indwelling time were used. Four of these studies were performed in patients who had intact bladder mucosa. The most common side effects reported were urinary frequency and hematuria. At 2,000 mg dose level, Grade 3 urinary frequency and local irritation were the most common complaints. *(21,23,25)* Grade 3 thrombocytopenia and neutropenia without infection was reported in one out of six patients. *(21)* The remaining three Phase I studies were performed in patients immediately after, within three hours after, and up to 24 hours after transurethral resection. *(26-28)* No additional adverse events were noted in these patients. A few cases of renal failure of uncertain etiology have been reported with intravenous gemcitabine administration. While on study, one patient who received prior mitomycin developed hemolytic uremic syndrome requiring dialysis. The relationship of this event to intravenous gemcitabine is not known.

Pregnancy and Lactation: Gemcitabine may cause fetal harm when administered to a pregnant woman. This agent has produced teratogenic effects in mice and rabbits when administered at a dose of < 2 mg/m^2. Adverse effects included decreased fetal viability, weight and morphologic defects. There is no data on gemcitabine administration during human pregnancy, and it is not currently known if metabolites are excreted in human milk. However, many drugs are excreted in human milk, and there is a potential for adverse effects in nursing infants. Therefore, the use of gemcitabine should be avoided in pregnant or nursing women because of the potential hazard to the fetus or infant.

c. PHARMACOLOGY

Kinetics: Gemcitabine is metabolized intracellularly to form active gemcitabine di- and tri-phosphates. Additional metabolites have not been identified in either plasma or urine. The gemcitabine di- and tri-phosphates do not appear to circulate in plasma in measurable amounts. The compound is metabolized principally by the liver to form an inactive uridine derivative (dFdU or 2'-deoxy-2',2'-difluorouridine). The plasma protein binding of gemcitabine is negligible. Following a single 1,000 mg/m^2/30 min [^{14}C]-gemcitabine infusion, 92% to 98% of the dose was recovered within one week after gemcitabine administration. Urinary excretion of parent and dFdU accounted for 99% of the excreted dose, and less than 1% of the dose was excreted in feces. The renal clearance of gemcitabine is less than 10%; therefore, the parent drug appears to be almost completely metabolized to the inactive dFdU.

Half-life ranged from 11 to 26 minutes for patients receiving single dose infusions (1,000 mg/m^2 to 2,500 mg/m^2) of 1.1 hours or less. Following longer duration infusions (3.6 to 4.3 hours), the half-life ranged between 18.5 and 57.1 minutes for single gemcitabine doses between 2,500 mg/m^2 and 3,600 mg/m^2. The increase in half-life may relate to the appearance of a possible third exponential phase (representing a deep compartment) that is not observed following the shorter infusions.

The population pharmacokinetic analyses of the effect of patient specific characteristics showed that clearance normalized for BSA was affected by gender. The clearance obtained for the female patient for all studies was 46.2 L/hr/m^2 and the male's was 66.8 L/hr/m^2. These moderate to high gemcitabine values suggest that gemcitabine may be metabolized by various tissues, including the liver. The renal clearance for gemcitabine is less than 10% of the systemic clearance.

The maximum dFdU plasma concentrations were achieved from 0 to 30 minutes after the discontinuation of the gemcitabine infusions, ranging from 0.4 to 4.75 hours. The apparent formation of dFdU (determined from the fraction of the gemcitabine dose excreted as dFdU) ranged from 91.2% to 98.2% of gemcitabine clearance in a single-dose study. Based on the imputed formation rate of dFdU, the mean dFdU volume of distribution at steady-state was 150.4 L/m^2, indicating that dFdU was extensively distributed into tissues. The metabolite was excreted in urine without undergoing further biotransformation. The mean apparent clearance of dFdU was 2.5 L/hr/m^2.

Pharmacokinetics (PK) of intravesical gemcitabine and its metabolite, dFdU, were studied in plasma and urine by Laufer, et al. (*23*) Plasma samples for PK were collected before the instillation and 15, 30, 60, 90, and 120 minutes after the instillation. Gemcitabine was observed in plasma of the 4 patients treated with 40 mg/mL in 50 mL normal saline, but not in the patients treated with 20 mg/mL in 100 mL normal saline. Peak concentrations in this and several other studies were below 1 µg/mL, which were significantly lower than the 10 to 30 µg/mL observed after a single intravenous (IV) dose of 1,000 mg/m^2 (Lilly 2002). The plasma gemcitabine concentrations declined rapidly, even during the 120-minute dwell time, and no gemcitabine was detectable in patient plasma beyond 60 minutes after the instillation of the drug. DFdU was also not detected in patients treated with 500 or 1,000 mg of gemcitabine. In the 1,500 mg and 2,000 mg groups, plasma concentrations of dFdU increased progressively during the first 60 to 90 minutes of dwell time, after which they remained constant during the observation period.

The authors estimated that based on their PK results and the 120-minute dwell time, the predicted amounts of gemcitabine absorbed from the bladder ranged from 10 to 110 mg, corresponding to 0.52% to 5.52% of the total gemcitabine dose instilled. No dFdU was measured in voided urine, and 61% to 100% of the gemcitabine was accounted for in the voided urine. The authors also studied the in vitro decomposition at 37°C with gemcitabine incubated with three control urine samples. They found no reduction in the concentration of gemcitabine, nor was any production of dFdU observed. Minimal systemic absorption based on measured serum gemcitabine levels following intravesical gemcitabine administration was confirmed by the other six Phase I studies. *(21,24-28)*

Formulation; Storage and Stability; and Reconstitution: Gemcitabine is supplied as a lyophilized powder in sterile vials containing 1,000 mg of gemcitabine as the hydrochloride salt (expressed as the free base), mannitol, and sodium acetate. The lyophilized product should be stored below 30°C.

The drug will be reconstituted with 25 mL of 0.9% Sodium Chloride Injection to the 1 gram vial. The vial will be shaken to dissolve. This dilution yields a gemcitabine concentration of 38 mg/mL which includes accounting for the displacement volume of the lyophilized powder (1.3 mL for the 1 gram vial). The total volume upon reconstitution will be 26.3 mL. Complete withdrawal of the vial contents will provide 1 gram of gemcitabine. The procedure will be repeated with a second 1 gram vial to reach the 2 gram dose for treatment. The appropriate amount of drug may be administered as prepared or further diluted with 0.9% Sodium Chloride Injection to concentrations as low as 0.1 mg/mL. For this trial, gemcitabine will be reconstituted according to above guidelines and the 2 gram treatment dose volume (approximately 52.6mL) will be loaded into a syringe and additional 0.9% Sodium Chloride for injection will be added to reach a 100 mL volume. Rationale for the 100 mL volume is addressed in Section 2.0 of the protocol.

Control drug will consist of 0.9% sodium chloride solution. Since it is not possible to use a placebo powder in intravesical therapy without inadvertent alteration of the bladder epithelium, the pharmacist will be unblinded in this trial.

Reconstituted gemcitabine is a clear, colorless to light straw-colored solution. After reconstitution with 0.9% Sodium Chloride Injection, the pH of the resulting solution lies in the range of 2.7 to 3.3. The solution should be inspected visually for particulate matter and discoloration, prior to administration, whenever solution or container permits. If particulate matter or discoloration is found, do not administer. When prepared as directed, gemcitabine solutions are stable for 24 hours at controlled room temperature 20° to 25°C (68° to 77°F) [*See* USP]. Unused portions will be discarded. Solutions of reconstituted gemcitabine should not be refrigerated, as crystallization may occur.

Administration: Intravesical.

Handling Precautions: Gemcitabine is a toxic material which could cause skin and eye irritation. Ingestion or inhalation exposure of sufficient quantities could result in decreased white and red blood cells, hypospermatogenesis, gastrointestinal disturbances, and other signs of toxicity. The compound was positive in one of three tests for mutagenicity. Laboratory animal studies indicate that compounds in this therapeutic class may be reproductive toxins and may induce fetal malformations. Contact or inhalation should be avoided. The urine and solution drained after the foley catheter is unclamped should be discarded as hazardous waste according to local, state and federal policies.

Supplier: Gemcitabine is considered investigational for this study and will be supplied by Lilly. The study drug will be distributed by Pharmagistics. Pharmagistics will be notified automatically after each new randomization. Study drug and a letter outlining the treatment preparation will be shipped via overnight delivery to the pharmacist to arrive within 2 business days. For patients registered Monday through Thursday prior to 2 p.m. Eastern time, drug will be delivered the next day. For patients registered Friday through Sunday, or on a holiday, drug will be shipped the next business day for arrival the following day. For patients registered Thursday after 2:00 p.m. Eastern time or Friday prior to 2:00 p.m. Eastern time, shipment on Friday for Saturday delivery may be arranged only if the pharmacy is prepared to receive shipment on Saturday. If Saturday delivery is required, this MUST be communicated to Bryan Goldman (bgoldman@fhcrc.org) or in his absence Cathy Tangen (ctangen@fhcrc.org) at the Southwest Oncology Group Statistical center PRIOR to registration. Each investigator MUST be linked to an active pharmacy in the SWOG database.

Important: you must record the patient identification number, which is assigned at the time of randomization, for each patient you register. Your pharmacist will need this patient number in order to identify the appropriate package from the drug distributor for each of your patients.

Emergency Unblinding: See Appendix 18.2 for emergency unblinding instructions.

4.0 STAGING CRITERIA (AJCC Sixth Edition, 2002)

BLADDER PRIMARY TUMOR (T)

Ta Non-invasive papillary carcinoma.

T1 Tumor invades subepithelial connective tissue.

HISTOPATHOLOGIC TYPE

The histologic types are: Urothelial (transitional cell) carcinoma.

HISTOPATHOLOGIC GRADE (G)

Grade 1 Well differentiated (papillary urothelial tumor of low malignant potential).

Grade 2 Moderately differentiated (low grade urothelial cancer).

5.0 ELIGIBILITY CRITERIA

Each of the criteria in the following section must be met in order for a patient to be considered eligible for registration. Use the spaces provided to confirm a patient's eligibility. For each criterion requiring test results and dates, please record this information on the Prestudy Form and submit to the Data Operations Center in Seattle (see Section 14.0). Any potential eligibility issues should be addressed to the Data Operations Center in Seattle at 206/652-2267 prior to registration.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday one week later would be considered Day 7. This allows for efficient patient scheduling without exceeding the guidelines. **If Day 7, 28, 56, 145 or 365 falls on a weekend or holiday, the limit may be extended to the next working day.**

SWOG Patient No. _____

Patient's Initials (L, F, M) _____

5.1 Disease Related Criteria

_____ a. Patients must:

- clinically appear to have newly diagnosed or recurrent Grade 1 or 2, Ta or T1 urothelial (transitional cell) cancer of the bladder,
- have had no more than 2 recurrences (other than the index tumor) in the 18 months preceding the index tumor's TURBT which are also Grade 1 or 2, Stage Ta or T1 without any previous TIS or Grade 3 cancers within 2 years preceding the index tumor TURBT or any history of muscularis propria invading (Stage ≥ T2),
- in their urologist's opinion not currently be a candidate for treatment other than a TURBT (e.g., a series of BCG instillations).

Central pathology review is not required.

5.2 Prior Therapy Criteria

_____ a. There must be plans for the patient to receive a TURBT within 28 working days after randomization. There must be plans for treatment to be given within three hours of TURBT.

_____ b. Patients must not have received previous intravesical therapy within 145 days prior to registration. Patients must not be considered by their treating physician to be candidates for more intensive treatments such as a series of instillations of intravesical immunotherapy (e.g. BCG) or intravesical chemotherapy, or for cystectomy or partial cystectomy.

5.3 Clinical/Laboratory Criteria

_____ a. Patients must have a negative urine culture (including ≤ 10,000 col/ml or "mixed flora-likely contamination") or a negative urine analysis for infection with (either a microscopic urinalysis with negative nitrates and no organisms on reagent strip and < 10 wbc/hpf OR an automated or visual reagent strip urinalysis which is negative for leukocytes and nitrates) within 28 days prior to registration.

_____ b. Patients must have a Zubrod performance status of 0 - 1 (see Section 10.5).

SWOG Patient No. _____

Patient's Initials (L, F, M) _____

(5.3 Clinical/Laboratory Criteria contd.)

_____ c. Patients must not be pregnant or nursing. Women/men of reproductive potential must have agreed to use an effective contraceptive method.

_____ d. Except as outlined in Section 5.1, no other prior malignancy is allowed except for the following: adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, adequately treated Stage I or II cancer from which the patient is currently in complete remission, or any other cancer from which the patient has been disease-free for 3 years.

5.4 Specimen Submission Criteria

_____ a. Patients must be offered the opportunity to participate in specimen banking as outlined in Section 15.0 of the protocol.

5.5 Regulatory Criteria

_____ a. All patients must be informed of the investigational nature of this study and must sign and give written informed consent in accordance with institutional and federal guidelines.

_____ b. At the time of patient registration, the treating institution's name and ID number must be provided to the Data Operations Center in Seattle in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered into the data base.

6.0 STRATIFICATION FACTORS

Patients will be centrally randomized at the Southwest Oncology Group Statistical Center. At the time of registration, patients will be randomly assigned to either Arm 1 or Arm 2 in a blinded fashion according to a dynamic allocation scheme. *(29)* The treatment arms will be balanced with respect to the following factors:

a. Disease status: first occurrence versus recurrent disease,

b. One tumor site versus two or more tumor sites.

7.0 TREATMENT PLAN

For treatment or dose modification-related questions, please contact Dr. Edward M. Messing at 585/275-3345 or Dr. David P. Wood, Jr. at 248/551-0678. For dosing principles or questions, please consult the Southwest Oncology Group Policy #38 "Dosing Principles for Patients on Clinical Trials" at http://swog.org (then click on "Policies and Manuals" under the "Visitors" menu and choose Policy #38).

7.1 Good Medical Practice

The following pre-study tests should be obtained within 28 days prior to registration in accordance with good medical practice. Results of these tests do not determine eligibility and minor deviations would be acceptable if they do not impact on patient safety in the clinical judgment of the treating physician. The Study Chair must be contacted if there are significant deviations in the values of these tests.

a. WBC ≥ 3,000/mcL,

b. Hematocrit > 35 and < 52 and Hemoglobin > 10 and < 16,

c. Serum creatinine < 2.2 mg%,

d. Platelet count > 75,000/mcL and < 500,000/mcL,

e. SGOT or SGPT, Alkaline phosphatase, and total bilirubin ≤ 2 x institutional upper limit of normal.

f. Patients should be believed based upon endoscopic inspection not to have urothelial cancer of the prostate or more distal urethra (or urethra at all in women). Endoscopy should be performed within 56 days prior to registration.

g. Patients should have negative upper tract imaging studies obtained within 365 days prior to registration. Imaging studies may be performed after registration, but prior to TURBT on the day of treatment.

7.2 Treatment

Within 28 working days after randomization, patient will have a complete resection of all visible index bladder tumors (TURBT). The investigator, treating urologist and patient will be blinded to treatment, but the local institutional pharmacist will not.

Patients will be randomized to one of two treatment groups.

Arm 1 - Within three hours following complete TURBT of index tumor(s) patients will receive intravesical gemcitabine – 2,000 mg in 100 ml of 0.9% NaCl. Solution is to be held in the bladder for one hour by clamping foley catheter. If this is not tolerable based on pain or other signs or symptoms, the duration of time held, and reason for premature release must be reported on the **S0337** Treatment Summary Form. After one hour, the catheter will be unclamped and allowed to drain. Irrigation of the bladder will not be performed immediately after unclamping (unless as is clinically indicated to assure catheter patency).

Arm 2-within 3 hours following complete TURBT of index tumor(s), patients will receive 100 ml of sterile 0.9% NaCl. Solution is to be held in the bladder for one hour by clamping foley catheter. If this is not tolerable based on pain or other signs or symptoms, the duration of time held, and reason for premature release must be reported on the **S0337** Treatment Summary Form. After one hour, the catheter will be unclamped and allowed to drain. Irrigation of the bladder will not be performed immediately after unclamping (unless as is clinically indicated to assure catheter patency).

For both groups, if immediate post TURBT bleeding is considered too brisk by the treating urologist to permit catheter clamping and intravesical instillation of study drug, continuous or intermittent irrigation via a 3-way catheter of 0.9% NaCl or sterile water is permitted up to 3 hours post operatively.

Patients will be followed with cystoscopies every three months for two years and then every 6 months for an additional two years. Positive cystoscopies should be biopsied and pathology reports submitted to the Data Operations Center. Tissue from the first positive biopsy should be submitted per Section 15.0 if the patient has consented.

Because non-malignant lesions can be mistaken for recurrence, suspected recurrences must be biopsied.

7.3 NMP-22 Bladder Chek and BTA Stat Testing

Urine samples will be collected pre-treatment and then every three months for two years for NMP-22 Bladder Chek and BTA Stat testing. These tests are commercially available and the tests must be performed at the local site and the results reported to the Data Operations Center in Seattle on the **S0337** Cystoscopy and Urine Markers Form. Instructions for sample processing are included in each of the tests.

7.4 Criteria for Removal from Protocol Treatment

a. Completion of intravesical instillation.

b. Unacceptable toxicity - however, patients will be analyzed for outcome and toxicity even if the instillation is ended in less than 1 hour because of side effects/intolerability.

c. Delay of instillation more than three hours post-TURBT.

d. Urologist believes at the end of the TURBT, because of depth of tumor resection, degree of bleeding, medical instability, etc. that instillation is contraindicated.

e. The patient may withdraw from the study at any time for any reason.

7.5 Emergency Unblinding

Procedures for emergency unblinding of the gemcitabine/saline treatment assignment are outlined in Appendix 18.2.

7.6 Discontinuation of Treatment

All reasons for discontinuation of treatment must be documented in the study forms.

7.7 Follow Up Period

All patients will be followed for a maximum of 4 years after registration.

8.0 DOSAGE MODIFICATIONS

8.1 NCI Common Terminology Criteria for Adverse Events.

Two different versions of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be used on this study.

a. Serious Adverse Event (SAE) reporting

The CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 4.0 will be utilized **for SAE reporting only**. The CTCAE Version 4.0 is identified and located at the CTEP website at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTCAE Version 4.0.

b. Routine toxicity reporting

This study will utilize the CTCAE Version 3.0 for routine toxicity reporting. A copy of the CTCAE Version 3.0 can be downloaded from the CTEP home page (http://ctep.cancer.gov). All appropriate treatment areas should have access to a copy of the CTCAE Version 3.0.

8.2 General Dose Modification Considerations

a. There will be no dose modifications. Duration of retention of drug/control can be shortened if medically indicated (e.g. bleeding, pain or bladder spasm uncontrollable by symptomatic medications, feared bladder perforation, etc.).

b. Toxicity measurements include a CBC. This will be done somewhere between 7 and 14 days post instillation. If white blood count is below 3,000/mcL or platelet below 75,000/mcL, these tests must be repeated at least on a weekly basis until they reach pre-treatment levels.

8.3 Gemcitabine Dose Modifications.

a. Pulmonary toxicity: If pneumonitis Grade 2 or higher develops and is related to gemcitabine, gemcitabine should be promptly discontinued and the patient should be removed from protocol treatment. Treatment with corticosteroids should be given according to established guidelines**.**

b. Hemolytic uremic syndrome (HUS) toxicity: The diagnosis of hemolytic uremic syndrome should be considered if the patient develops anemia with evidence of microangiopathic hemolysis as indicated by elevation of bilirubin or LDH, reticulocytosis, severe thrombocytopenia, and/or evidence of renal failure

(elevation of serum creatinine of BUN). Gemcitabine therapy should be discontinued immediately. Renal failure may not be reversible even with discontinuation of therapy and dialysis may be required.

8.4 Dose Modification Contacts

For treatment or dose modification related questions, please contact Dr. Edward M. Messing at 585/275-3345 or Dr. David P. Wood, Jr. at 248/551-0678.

8.5 Adverse Event reporting

Toxicities (including suspected reactions) that meet the expedited reporting criteria as outlined in Section 16.0 of the protocol must be reported to the Operations Office, Study Chair and NCI via AdEERS, and to the IRB per local IRB requirements.

9.0 STUDY CALENDAR

REQUIRED STUDIES	PRE STUDY	PRE TREATMENT	Wk 1	Wk 2	Wk 3	Wk 4	Mo 3	Mo 6	Mo 9	Mo 12	Mo 15	Mo 18	Mo 21	Mo 24	Mo 30	Mo 36	Mo 42	Mo 48
PHYSICAL																		
History and Physical Exam	X			X			X	X	X	X	X	X	X	X	X	X	X	X
Weight and Performance Status	X																	X
Disease Assessment	X¥						X	X	X	X	X	X	X	X	X	X	X	X
Toxicity Notation £			X	X		X												
LABORATORY																		
CBC/Differential/Platelets å	X			Xµ														
Serum Creatinine å	X																	
Urine Analysis	X																	
SGOT/SGPT å	X			Xµ														
Alkaline Phosphatase å	X			Xµ														
Bilirubin å	X			Xµ														
NMP-22 Bladder Check		X					X	X	X	X	X	X	X	X				
BTA Stat		X					X	X	X	X	X	X	X	X				
OPTIONAL SPECIMEN SAMPLES (BANKING)																		
Tissue (see Section 15.1) Ω			X															
Whole blood (see Section 15.2)							X											
X-RAYS & SCANS																		
IVP for Retrogrades or CT with IV Contrast	X¥																	
Cystoscopy ¶	X						X	X	X	X	X	X	X	X	X	X	X	X
TREATMENT																		
TURBT & Blinded Treatment			X															

Click here for Footnotes.

Note: Forms submission guidelines are found in Section 14.0.

Footnotes

å These tests are suggested prestudy for Good Medical Practice (see Section 7.1), but are required during treatment and follow-up as indicated above, or more frequently as clinically indicated.

¥ To be performed within 6 months before registration.

¶ Histologic confirmation of recurrence required.

µ CBC/Platelets must be obtained between 7 and 14 days post instillation. Blood counts may be performed more often at the discretion of the treating investigator. If cytopenias or liver function test abnormalities are observed, patients should be followed weekly until these laboratory test abnormalities have resolved.

Ω With the patient's additional consent, it is strongly recommended that tissue be submitted per Section 15.1 from TURBT **and at time of first recurrence and/or progression**.

£ A toxicity assessment should be made 7-14 days after the TURBT. Only if adverse events are noted during this earlier period (Week 1-2) should a Week 4 assessment also be done.

10.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

10.1 Recurrence

Histological confirmation of recurrence is required. Cystoscopic and cytologic evidence alone is not satisfactory – although will be noted.

10.2 Time to Recurrence

From date of registration to date of first observation of recurrent disease subsequently confirmed by biopsy. Patients without recurrence are censored at the time of their last cystoscopy.

10.3 Progression

Recurrence of urothelial cancer to Stage ≥ T2, or other diagnosis of N+ or M+ disease.

10.4 Time to Progression

From date of registration to date of diagnosis of progressive disease. Censor at date of last disease assessment for those without progression.

10.5 Performance Status

Patients will be graded according to the Zubrod Performance Status Scale.

POINT	DESCRIPTION
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of self-care but unable to carry out any work activities; up and about more than 50% of waking hours.
3	Capable of limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair.

10.6 Worsening-free Survival

From date of registration to date of first observation of subsequently confirmed recurrent disease (as defined in Section 10.2), progression (as defined in Section 10.3), start of systemic chemotherapy, radiation or cystectomy, or death due to any cause. Patients who experience none of these events will be censored at date of last disease assessment.

10.7 Time to Death

From date of registration to date of death due to any cause. Patients last known to be alive are censored at date of last contact.

11.0 STATISTICAL CONSIDERATIONS

11.1 Primary Endpoint

The primary objective of this study is to compare the efficacy of a single post-TURBT intravesical instillation of gemcitabine versus saline in preventing recurrence of completely resected Grade 1 or Grade 2, Ta or T1 transitional cell carcinoma of the bladder. The endpoint of interest is time to recurrence which is defined (see Section 10.2) as time from date of registration to date of first observation of recurrent disease subsequently confirmed by biopsy. Those without recurrence are censored at the date of last cystoscopy. Patients who die without any evidence of disease recurrence, will be censored at time of death.

If one assumes roughly equal numbers of patients with newly diagnosed and recurrent superficial bladder tumors, then we anticipate about 60% of patients will experience recurrences by 2 years. It is assumed that 14 eligible patients per month will be randomized. Patients will be stratified by disease status (first occurrence vs. recurrent disease), and number of tumors (one versus more than one). Assuming exponential time-to-recurrence (TTR) and 60% TTR (40% recurrence-free) at two years in the sterile saline group, then two years of accrual (340 eligible patients) and two additional years of follow-up will be required for a one-sided 0.025 level test to have power 0.89 for detecting a hazard ratio of 1.53 (equivalent to an improvement to a 45% TTR (55% recurrence-free) rate at two years on the gemcitabine arm). The primary test will be performed using the stratified logrank test. All eligible, randomized patients will be used in the primary analysis regardless of whether they actually receive the treatment to which they were assigned (intent-to-treat analysis).

Estimate of sample size: 340 eligible
Estimate of accrual rate: 170 eligible/year

Two interim analyses of time-to-recurrence will be performed after 50% and 80% of the expected number of events have occurred (113 and 181 relapses, respectively, assuming the alternative treatment hypothesis) which will be approximately at the time accrual is completed and one year later. Consideration will be given to reporting early at either time if (1) TTR on the gemcitabine arm is superior at the one-sided 0.005 level or if (2) the hypothesis $\lambda=1.53$ (where λ is the sterile water/gemcitabine hazard ratio) is rejected in favor of $\lambda<1.53$ at the one-sided 0.005 level (testing using a proportional hazards score test, an extension of the logrank test).

Assuming the study does not terminate early and the alternative treatment hypothesis, the final analysis will occur when approximately 226 recurrences have been reported (estimated to be about two years after completion of accrual). The final analysis will be based on the stratified logrank test with stratification factors as specified in Section 6.0 with a one-sided 0.020 level to adjust for the two interim analyses, for an overall level of 0.025 (one-sided). In addition, the trial will be monitored for safety every six months and assuming the alternative hypothesis holds.

11.2 Secondary Endpoints

A sample of 170 patients per arm is sufficient to estimate the probability of a specific toxicity to within at worst = ± 0.077. There is power of 0.81 for a one-sided 0.025 level test to detect a 0.16 difference in a specific toxicity probability between the two arms.

The logrank test will be used to evaluate whether worsening-free survival (see Section 10.0 for definition) is better on the gemcitabine arm relative to the saline arm. Descriptive statistics will be used to evaluate the number of diagnostic tests required for individuals on each treatment arm.

11.3 Sensitivity and Specificity of Assays for Predicting Recurrence

Sensitivity and specificity of the BTA Stat and the NMP-22 Bladder Chek alone and in combination are the primary endpoints of this correlative study. The gold standard to define a recurrence is a positive biopsy prompted by a cystoscopy. Absence of recurrence will be confirmed by a negative complete diagnostic work-up. Disease status will be evaluated every three months for two years and then every six months for an additional two years. Recurrence information over time is not independent within an individual. To account for this correlation, a GEE approach will be used to estimate sensitivity and specificity. GEE accounts for correlation within participants when estimating parameters and the corresponding standard errors are adjusted. Logistic regression using general estimating equation methodology (to account for repeated evaluations of an individual) will be used to assess and compare sensitivity and specificity of accurately classifying recurrence status using information from each individual urinary marker.

The BTA Stat test and the NMP-22 Bladder Chek test will have responses positive, negative or invalid. Invalid tests at a given time will not be used in the GEE analyses. Two types of analyses will be performed using these urine markers.

The following information was obtained from the Early Detection Research Network (EDRN) protocol entitled, "Detection of bladder cancer by microsatellite analysis of urinary sediment: Multi-Institutional Study, Version 1.5" with Mark Schoenberg, M.D. as the Study Chair and Mark Thornquist, Ph.D., as the study statistician.

In that EDRN study, they assumed that 270 patients will have follow-up data, and 81 of the 270 would have a recurrence during the two year surveillance period. Those numbers are lower than the 300 patients and 120 recurrences that we would expect during the same period if we assume 10% loss to follow-up and a 40% recurrence rate at two years. So the estimates that they simulated would be expected to be conservative.

They generated 250 datasets for each sensitivity and specificity pair. The data are summarized by looking at the distribution of sensitivities and specificities. The table below shows the result when the simulations assumed exchangeable correlation between observations within a patients.

Table from Section 7.2 of EDRN Superficial Bladder Protocol: Simulations

Sensitivity	Specificity	Std Error Sensitivity	Std Error Specificity	95% CI Sensitivity	95% CI Specificity
0.95	0.95	0.020	0.005	0.89, 0.97	0.94, 0.96
0.90	0.90	0.028	0.007	0.81, 0.92	0.89, 0.91
0.85	0.85	0.033	0.009	0.75, 0.88	0.83, 0.86
0.80	0.80	0.035	0.010	0.70, 0.82	0.78, 0.82

This table shows that the EDRN study, with a slightly smaller sample size and lower expected event rate, will have ample power to detect relevant values of sensitivity and specificity while ruling out unacceptable low values. We, therefore, would expect **S0337** to have at least as much power if not more to estimate the properties of the BTA Stat and NMP-22 urine markers individually and in combination.

a. Surveillance estimates of sensitivity and specificity

These analyses will evaluate the performance of each of the markers, alone and in combination, every three months for the first two years of the study. At each follow-up time t, cases will be those who are biopsy positive at time t, and controls will be those with negative cystoscopy exams or positive cystoscopy exams but biopsy-negative. All patients will have a cystoscopy every three months, regardless of urine marker results.

Sensitivity and specificity will be defined based on the concurrent marker status.

M+ = positive marker
M - = negative marker
D+ = biopsy confirmed bladder cancer
D- = no disease indicated

Sensitivity = Prob(M+ | D+)
Specificity = Prob(M− | D−)

When evaluating the properties of both markers together, sensitivity will be the probability that either of the urine markers is positive given that a patient has a positive biopsy, and specificity will be the probability that both of the markers are negative given that the patient is without recurrence. In order to test the differences between the area underneath the curves (AUCs) for the single marker versus combined marker approach, we will compute the U-statistic of DeLong et. al. *(30)*

b. A second type of analysis will be the anticipatory estimate of sensitivity and specificity of each of the urine markers and the combination. It has been hypothesized that the BTA Stat or NMP-22 Bladder Chek may be able to detect the presence of cancer earlier than cystoscopy. If this is true, then we'd expect a fair number of false positives since the clinical diagnosis might not follow for several months. To evaluate whether this hypothesis is true, an analysis will be performed on the time course of the follow-up BTA Stat and NMP-22 tests and cystoscopy. In this case, sensitivity and specificity will not be based on concurrent disease status but instead disease status at a future time t. The anticipatory period can be varied to assess the lead-time provided by each of the tests.

11.4 Data and Safety Monitoring Committee Oversight

a. Regular study monitoring (described in more detail below) includes an assessment of accrual, adverse events and study outcome. In particular, the SWOG Data and Safety Monitoring Committee monitors accrual, and studies with accrual concerns are targeted for discussion at the bi-annual meetings. In addition, NCI guidelines for study monitoring will be followed, recognizing that it often takes approximately 6 months for regulatory approvals at the institutions before an accrual rate can accurately be assessed. During quarters 5 and 6, if the accrual is less than 20% of projected, the study will be considered infeasible, and closure will be recommended to the Data and Safety Monitoring Committee. If accrual is between 20% and 50% of projected, then attempts will be made to improve accrual in the next six month period. By quarter 8 (at the latest), if accrual is below 50% of projected, the trial will be assessed for an amendment to reflect actual accrual, with implications on study relevance and feasibility to be discussed with the Data and Safety Monitoring Committee, the study committee, and the National Cancer Institute.

b. A Data and Safety Monitoring Committee will oversee the conduct of the study. The Committee consists of the four members from outside of the Southwest Oncology Group, three Southwest Oncology Group members, three non-voting representatives from the National Cancer Institute (NCI), and the Group Statistician (non-voting). The members of this Committee will receive confidential reports every 6 months from the Southwest Oncology Group Statistical Center, and will meet at the Group's bi-annual meetings as necessary. The Committee will be responsible for decisions regarding possible termination and/or early reporting of the study.

12.0 DISCIPLINE REVIEW

There will be no formal discipline review in conjunction with this study.

13.0 REGISTRATION GUIDELINES

13.1 Registration Timing

Patients must be registered prior to initiation of treatment (no more than 28 working days prior to planned start of treatment).

13.2 Phone or Web Registration

For either phone or web registration, the individual registering the patient must have completed the appropriate Southwest Oncology Group Registration Form. The completed form must be referred to during the registration but should not be submitted as part of the patient data.

The individual registering the patient must also be prepared to provide the treating institution's name and ID number in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered into the data base. Patients will not be registered if the IRB approval date has not been provided or is > 365 days prior to the date of registration.

13.3 Registration procedures

a. You may register patients from Member, CCOP, UCOP and approved Affiliate institutions to a therapeutics study using the SWOG Registration program. To access the Registration program go to the SWOG Web site (http://swog.org) and click on the *Logon* link to go to the SWOG Members Area logon page (https://swog.org/visitors/logon.asp). This Web program is available at any time except for periods listed under *Down Times*. Log on as an Individual User using your SWOG Roster ID Number and individual web user password. Help for the logon process may be found at https://swog.org/visitors/logonhelp.asp. After you have logged on, click on the *Clinical Trials* link and then the *Patient Reg* link to go to the Entry Page for the Patient Registration program. If you are a Registrar at an institution with Internet access you are encouraged to register this way. For new users, the link to a "Starter Kit" of help files may be found by clicking on Starter Kit link at the logon page.

To register a patient the following must be done (in order):

1. You are entered into the Southwest Oncology Group Roster and issued a SWOG Roster ID Number,

2. You are associated as an investigator or CRA/RN to the institution where a registration is occurring, and

3. You are granted permission to use the Patient Registration program at that institution.

For assistance with points 1 and 2 call the SWOG Operations Office at 210/614-8808. For point 3 you must contact your Web User Administrator. Each SWOG institution has one or more Web User Administrators who may set up Web Users at their institution and assign permissions and passwords to these users. For other password problems or problems with the Patient Registration program, please e-mail webreghelp@crab.org. Include your name, Roster ID Number, and telephone number, when the problem occurred, and exactly what you were doing.

b. If the Web Reg program is not used, the registration must be done by phone.

Member, Affiliate, CCOP, and UCOP Institutions

Registration by phone of patients from Member, Affiliate, CCOP, and UCOP institutions must be done through the Southwest Oncology Group Data Operations Center in Seattle by telephoning 206/652-2267, 6:30 a.m. to 4:00 p.m. Pacific Time, Monday through Friday, excluding holidays.

13.4 For either method of registration, exceptions to Southwest Oncology Group registration policies will not be permitted.

a. Patients must meet all eligibility requirements.

b. Institutions must be identified as approved for registration.

c. Registrations may not be cancelled.

d. Late registrations (after initiation of treatment) will not be accepted.

14.0 DATA SUBMISSION SCHEDULE

14.1 Data Submission Requirements

Data must be submitted according to the protocol requirements for ALL patients registered, whether or not assigned treatment is administered, including patients deemed to be ineligible. Patients for whom documentation is inadequate to determine eligibility will generally be deemed ineligible.

14.2 Master Forms

Master forms can be found on the protocol abstract page on the SWOG website (www.swog.org) and (with the exception of the sample consent form and the Registration Worksheet) must be submitted on-line via the Web; see Section 14.3a for details.

14.3 Data Submission Procedures

a. Southwest Oncology Group institutions must submit data electronically via the Web by using the SWOG CRA Workbench. To access the CRA Workbench, go to the SWOG Web site (http://swog.org) and logon to the Members Area. After you have logged on, click on the *CRA Workbench* link to access the home page for CRA Workbench website. Next, click on the *Data Submission* link and follow the instructions. For new users, the link to a "Starter Kit" of help files may be found by clicking on the **Starter Kit** link at the Members' logon page.

To submit data via the web the following must be done (in order):

1. You are entered into the Southwest Oncology Group Roster and issued a SWOG Roster ID Number,
2. You are associated as an investigator or CRA/RN at the institution where the patient is being treated or followed, and
3. Your Web User Administrator has added you as a web user and has given you the appropriate system permissions to submit data for that institution.

For assistance with points 1 and 2 call the Operations Office at 210/614-8808. For point 3, contact your local Web User Administrator (refer to the "Who is my Web User Administrator?" function on the swog.org Members logon page). For other difficulties with the CRA Workbench, please email *technicalquestion@crab.org*.

b. If you need to submit data that are not available for online data submission, the only alternative is via facsimile. Should the need for this occur, institutions may submit data via facsimile to 800/892-4007 or 206/342-1680 locally. Please do not use cover sheet for faxed data.

14.4 Data Submission Overview and Timepoints

a. WITHIN 28 DAYS OF REGISTRATION:

Submit copies of the following:

S0337 Prestudy

Pathology Reports

S0337 Treatment Summary Form

S0337 Adverse Event Summary Form

S0337 Cystoscopy and Urine Markers Form

Submit materials outlined in Section 15.0 to the SWOG Repository in Colorado.

b. AT MONTH 3 CYSTOCOPY:

Submit materials outlined in Section 15.2 to Lab #135.

c. EVERY 3 MONTHS FOR 2 YEARS AND THEN EVERY SIX MONTHS UNTIL 4 YEARS AFTER REGISTRATION:

Submit a copy of the **S0337** Disease Assessment and Follow-Up Form and **S0337** Cystoscopy and Urine Markers Form.

d. WITHIN 14 DAYS OF RECURRENCE OR PROGRESSION TO MUSCLE INVASIVE DISEASE:

Submit a copy of the **S0337** Disease Assessment and Follow-Up Form and pathology report. For those agreeing to banking, submit tissue per Section 15.0 at first recurrence.

e. WITHIN 4 WEEKS OF KNOWLEDGE OF DEATH:

Submit copy of the Notice of Death.

15.0 SPECIAL INSTRUCTIONS

15.1 Tissue Specimens for Banking for Future Studies of As Yet To Be Determined Molecular Markers

a. With patient's consent, a representative bladder tumor tissue paraffin-embedded block must be submitted at the following times (see Section 9.0): prestudy from the TURBT for the index tumor and at first recurrence.

b. Specimen collection and submission instructions can be accessed on the SWOG Specimen Submission webpage: (**http://swog.org/Members/ClinicalTrials/Specimens/STSpecimens.asp**), or via the link on the **S0337** protocol abstract page on the SWOG website (www.swog.org).

c. Specimen collection kits are not being provided for the tissue submission; sites will use institutional supplies.

15.2 Whole Blood Specimens for Banking for Genotyping

a. With patient's consent, whole blood specimens must be submitted at the timepoints listed below. Collection instructions are outlined in Section 15.2c and submission instructions are outlined in Section 15.2e.

b. With patient's consent, whole blood specimens must be submitted at the following times (see Section 9.0): at Month 3 cystoscopy.

c. On the day of the 3 month cystoscopy, draw the blood sample into the Paxgene blood tube (8.5 mL). Invert 5 times to mix. Place upright in a sealed plastic bag in a 4°C refrigerator. On the next Monday, Tuesday, or Wednesday, ship the specimen to Dr. Reeder's laboratory (Lab #135) in the infectious substance container with the provided shipping label following the Federal guidelines for shipment described above. Blood should be shipped on ice packs by overnight carrier Monday through Wednesday only.

d. Specimen collection kits may be ordered as follows: After patient is registered and the Month 3 visit is scheduled, contact Dr. Jay Reeder's laboratory at the University of Rochester (585/275-1191) to obtain Paxgene blood tube for the blood draw at the Month 3 visit. The Paxgene blood tube will be shipped to you in an infectious substance shipping container which is to be used to ship the specimen to Dr. Reeder's laboratory.

e. SHIPPING SAMPLES

1. SWOG Specimen Tracking System (STS)

All specimen submissions for this study must be entered and tracked using the SWOG online Specimen Tracking system. SWOG members may log on the online system via the CRA Workbench. To access the CRA Workbench, go to the SWOG Web site (http://swog.org) and logon to the Members Area. After you have logged on using your SWOG roster ID number and password, click on the *CRA Workbench* link to access the home page for CRA Workbench website. First time non- SWOG users must refer to start-up instructions located at https://gill:crab.org/SpecTrack/.

A copy of the Shipment Packing List produced by the online Specimen Tracking system should be printed and placed in the pocket of the specimen bag if it has one, or in a separate resealable bag. The Specimen Submission Form is NOT required when the online system is used.

ALL SPECIMENS MUST BE LOGGED VIA THIS SYSTEM; THERE ARE NO EXCEPTIONS.

To report technical problems with Specimen Tracking, such as database errors or connectivity issues, please send an email to technicalquestion@crab.org. For procedural help with logging and shipping specimens, there is an introduction to the system on the Specimen Tracking main page (http://dnet.crab.org/SpecTrack/Documents/Instructions.pdf); or contact the Data Operations Center at 206/667-2267 to be routed to the Data Coordinator for further assistance.

In the online specimen tracking system, the appropriate Southwest Oncology Group laboratory for submission of bone marrow, serum, and peripheral blood samples for Southwest Oncology Group Repository Submission and SNP testing is identified as follows:

Lab #135: Dr. Reeder's Laboratory
Phone: 585/275-1191
Contact: Sue Schoen

2. Federal guidelines for the shipment of blood products:

a. The tube must be wrapped in an absorbent material.

b. The tube must then be placed in an AIRTIGHT container (like a resealable bag).

c. Pack the resealable bag and tube in a Styrofoam shipping container.

d. Pack the Styrofoam shipping container in a cardboard box.

e. Mark the box "Biohazard".

16.0 ETHICAL AND REGULATORY CONSIDERATIONS

The following must be observed to comply with Food and Drug Administration regulations for the conduct and monitoring of clinical investigations; they also represent sound research practice:

Informed Consent

The principles of informed consent are described by Federal Regulatory Guidelines (Federal Register Vol. 46, No. 17, January 27, 1981, part 50) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46). They must be followed to comply with FDA regulations for the conduct and monitoring of clinical investigations.

Institutional Review

This study must be approved by an appropriate institutional review committee as defined by Federal Regulatory Guidelines (Ref. Federal Register Vol. 46, No. 17, January 27, 1981, part 56) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46).

Drug Accountability

For each drug supplied for a study, an accountability ledger containing current and accurate inventory records covering receipt, dispensing, and the return of study drug supplies must be maintained. Drug supplies must be kept in a secure, limited access storage area under the recommended storage conditions. During the course of the study, the following information must be noted on the accountability ledger; the identification code of the subject to whom drug is dispensed, the date(s) and quantity of drug dispensed to the subject, and the date(s) and quantity of drug returned by the subject; subjects should return empty containers to the investigator, with the return noted on the ledger. These Accountability Forms must be readily available for inspection and are open to FDA or NCI inspection at any time.

Monitoring

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31.

16.1 Adverse Event Reporting Requirements

a. Purpose

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial.

(Directions for routine reporting are provided in Section 14.0.) Additionally, certain adverse events must be reported in an expedited manner to allow for more timely monitoring of patient safety and care. The following guidelines prescribe expedited adverse event reporting for this protocol. Also see Appendix 18.1 for general and background information about expedited reporting.

b. Reporting method

This study requires that expedited adverse event reporting use the NCI's Adverse Event Expedited Reporting System (AdEERS). The NCI's guidelines for AdEERS can be found at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adeers.htm

c. When to report an event in an expedited manner

Some adverse events require 24-hour notification (refer to Table 16.1) via AdEERS. When Internet connectivity is disrupted, a 24-hour notification is to be made to the SWOG Operations Office by telephone at 210-614-8808 or by email at adr@swog.org. Once Internet connectivity is restored, a 24-hour notification that was made by phone or using adr@swog.org must be entered electronically into AdEERS by the original submitter at the site.

When the adverse event requires expedited reporting, submit the report within the number of calendar days of learning of the event, as specified in Table 16.1.

d. Other recipients of adverse event reports

The SWOG Operations Office will forward reports and documentation to the appropriate regulatory agencies and drug companies as required.

Adverse events determined to be reportable to the Institutional Review Board responsible for oversight of the patient must be reported according to local policy and procedures.

e. **Expedited reporting for investigational agents**

Expedited reporting is required if the patient has received at least one dose of the investigational agent as part of the trial. Reporting requirements are provided in Table 16.1. The investigational agent used in this study is gemcitabine. If there is any question about the reportability of an adverse event or if on-line AdEERS cannot be used, please telephone or email the SAE Specialist at the Operations Office, 210/614-8808 or adr@swog.org, before preparing the report.

Table 16.1:
Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under a Non-CTEP IND within 30 Days of the Last Administration of the Investigational Agent Gemcitabine.

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via AdEERS within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">10 Calendar Days</td><td rowspan="2">24-Hour 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Section 16.1f.

Expedited AE reporting timelines are defined as:

- o "24-Hour; 5 Calendar Days" - The AE must initially be reported via AdEERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.

- o "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

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f. **Additional Instructions or Exceptions to AdEERS Expedited Reporting Requirements for Late Phase 2 and Phase 3 Studies Utilizing an Agent under a non-CTEP-IND:**

1. **Group-specific instructions**

Supporting Documentation Submission - Within 5 **calendar days** submit the following to the SWOG Operations Office by fax to 210-614-0006 or mail to the address below:

- Printed copy of the first page of the AdEERS report
- Copies of clinical source documentation of the event
- If applicable, and they have not yet been submitted to the SWOG Data Operations Center, copies of Off Treatment Notice and/or Notice of Death.

2. For this study, the adverse event listed below does **not** require expedited reporting via AdEERS:

- Grade 4 myelosuppression.

g. **Reporting Secondary Malignancy, including AML/ALL/MDS**

1. A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

SWOG requires all secondary malignancies that occur following treatment with an agent under a Non-NCI IND to be reported via AdEERS. Three options are available to describe the event.

- Leukemia secondary to oncology chemotherapy (e.g., Acute Myelocytic Leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

For more information see:
http://ctep.cancer.gov/protocolDevelopment/default.htm#adverse_events_adeers

2. Supporting documentation should be submitted to CTEP in accordance with instructions provided by the AdEERS system. A copy of the report and the following supporting documentation must also be submitted to SWOG Operations Office within 30 days:

- a copy of the pathology report confirming the AML/ALL /MDS diagnosis
- (if available) a copy of the cytogenetics report

SWOG
ATTN: SAE Program
4201 Medical Drive, Suite 250
San Antonio, Texas 78229

NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the report must be submitted for the most recent trial.

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18.0 APPENDIX

18.1 Determination of Expedited Adverse Event Reporting Requirements

18.2 Emergency Unblinding Guidelines

18.3 Correlative Studies for **S0337**

18.1 Determination of Expedited Adverse Event Reporting Requirements

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. (Directions for routine reporting are provided in Section 14.0.) Additionally, certain adverse events must be reported in an expedited manner to allow for more timely monitoring of patient safety and care. Expedited adverse event reporting principles and general guidelines follow; specific guidelines for expedited adverse event reporting on this protocol are found in Section 16.1.

All serious adverse events determined to be reportable to the Institutional Review Board responsible for the oversight of the patient must be reported according to local policy and procedures. Documentation of this reporting should be maintained for possible inspection during quality assurance audits.

Steps to determine if an adverse event is to be reported in an expedited manner (*This includes all events that occur while on treatment or within 30 days of the last dose of protocol treatment.*)

Step 1: Determine whether the patient has received an investigational agent, commercial agent, or a combination of investigational and commercial agents.

An investigational agent is a protocol drug administered under an Investigational New Drug Submission (IND). In some instances, the investigational agent may be available commercially, but is actually being tested for indications not included in the approved package label.

Commercial agents are those agents not provided under an IND but obtained instead from a commercial source. The NCI, rather than a commercial distributor, may on some occasions distribute commercial agents for a trial.
When a study includes both investigational and commercial agents, the following rules apply.

- ***Concurrent administration*:** When an investigational agent(s) is used in combination with a commercial agent(s), the combination is considered to be investigational and expedited reporting of adverse events would follow the guidelines for investigational agents.
- ***Sequential administration*:** When a study includes an investigational agent(s) and a commercial agent(s) on the same study arm with sequential administration all expedited reporting of adverse events should follow the guidelines for the type of agent being given. For example, if the patient begins the study on the investigational agent(s), then all expedited reporting of adverse events should follow guidelines for the investigational agent(s). Once the patient begins receiving the commercial agent(s) then all expedited reporting of adverse events should follow the guidelines for commercial agent(s).

Step 2: Identify the type of event using the NCI Common Terminology Criteria for Adverse Events (CTCAE). The CTCAE provides descriptive terminology and a grading scale for each adverse event listed. A copy of the CTCAE can be downloaded from the CTEP home page (http://ctep.cancer.gov). Additionally, if assistance is needed, the NCI has an Index to the CTCAE that provides help for classifying and locating terms.

Step 3: Grade the event using the NCI CTCAE version specified in the protocol for reporting serious adverse events.

Step 4: Determine if the adverse event is Expected or an Exception to Expedited Reporting. **Expected** events are those that have been previously identified as resulting from administration of the agent and are listed in one of the following:

- The current NCI SPEER (Specific Protocol Exceptions to Expedited Reporting) for treatments using agents provided under an NCI-held IND, or an equivalent listing for treatments using agents provided under a Non-CTEP-held IND; located in Section 3.0 of the protocol.
- For treatments using commercial agents, the current CAEPR (Comprehensive Adverse Event and Potential Risks), ASAEL (Agent Specific Adverse Event List), or other list of expected toxicities located in Section 3.0 of the protocol, or the drug package insert.
- Exception to Expedited reporting located in Section 16.1f of the protocol.

An adverse event is considered **unexpected,** for expedited reporting purposes only, when either the type of event or the severity of the event is **not** listed in one of the areas outlined above.

Step 5: Determine whether the adverse event involved hospitalization or a prolongation of hospitalization (≥ 24 hours).

Step 6: Additionally, for commercial drugs, determine whether the adverse event is related to the protocol therapy. Attribution categories are as follows: Unrelated, Unlikely, Possible, Probable, and Definite. Consult the appropriate table for expedited reporting criteria for commercial agent(s).

NOTE: Any event that occurs more than 30 days after the last dose of study agent and is attributed (possible, probable, or definite) to the study agent(s) must be reported according to the instructions above and as outlined in the appropriate table in Section 16.1.

18.2 Emergency Unblinding Guidelines

a. **General Considerations**

The randomized regimen for this study includes a blinded drug, which is either gemcitabine or placebo. During the course of this study it may become necessary to identify (or unblind) a patient's treatment assignment. The circumstances that will warrant unblinding and the procedure for unblinding are described in this Appendix.

b. **Criteria for Emergency Unblinding**

In general, treatment assignments will not be unblinded unless there is a compelling medical or ethical reason that the treatment should be identified. In most circumstances it will be appropriate to treat the patient or person who received blinded drug as though he or she received gemcitabine, irrespective of the drug actually received. Therefore, unblinding should seldom be necessary.

The following events MAY require unblinding of treatment assignments in this study:

1. A compelling medical need as determined by a physician, e.g., existence of a condition for which knowledge of the patient's treatment assignment is necessary for the selection of appropriate care.

2. Administration of blinded drug to a person other than the patient.

c. **Procedure for Emergency Unblinding**

Emergency unblinding of treatment assignments for patients on this study will be performed by the Washington Poison Center (WPC), upon approval from a designated physician (either one of the WPC's resource physicians or Dr. Edward Messing). The procedure for emergency unblinding the treatment assignment for a patient on this study is as follows:

1. All requests for emergency unblinding must be made by the registering physician or his/her designee.

2. Call the WPC collect at 206/526-2121 from outside Washington State or toll free at 800/222-1222 from within Washington State. The WPC is accessible 24 hours per day, 365 days per year.

3. The person calling the WPC must be prepared to provide the following information:

   Study number (**S0337**)

   SWOG Patient Number (e.g., "999999")

   Patient Initials

   Name and telephone number of the caller

   Reason emergency unblinding is thought to be required

4. The WPC will contact one of its resource physicians and provide the information received from the caller. If none of the WPC's resource physicians can be contacted, then the WPC will contact Dr. Edward Messing. The contacted physicians will evaluate the need for emergency unblinding and provide the WPC either approval to unblind or a recommendation for treatment, if any, while maintaining blinding. The WPC will then call the person who initiated the unblinding request and tell him/her either the treatment assignment or the resource physician's treatment recommendation.

5. If the WPC is unable to contact any of its resource physicians or Dr. Messing within three hours after receiving the request for emergency unblinding, then the WPC will notify the person who initiated the unblinding request that treatment assignment will not be unblinded at that time and treatment of the patient or person who received blinded drug should proceed as if the blinded drug is gemcitabine. In such cases, the WPC will continue to attempt to contact the resource physicians, and when one of them is contacted, will proceed as in #4 above.

6. Any patient whose treatment assignment is emergency unblinded will receive no further blinded drug, but should continue all other protocol treatment if his/her medical condition permits.

7. Unblinding of treatment assignments for any reason must be documented on the **S0337** Treatment Summary Form.

   Questions regarding the unblinding may be directed to any of the following resource physicians:

Edward M. Messing, M.D.
University of Rochester
Strong Memorial Hospital
601 Elmwood Avenue, Box 656
Rochester, NY 14642-0001
Phone: 585/275-3345

Bruce G. Redman, D.O.
Southwest Oncology Group
24 Frank Lloyd Wright Drive
P.O. Box 483
Ann Arbor, MI 48106
Phone: 734/998-7154

Washington Poison Center
Phone: 206/526-2121

18.3 Correlative Studies for **S0337**

Urinary Markers

Hypothesis

The sensitivity of no single test will be as good as that of cystoscopy and cytology to detect recurrences of these tumors during monitoring. However, a combination of non or minimally invasive markers will be as sensitive as cystoscopy.

Rationale

The point-of-service bladder cancer marker tests, BTA Stat and NMP-22 Bladder Chek have been approved by the FDA as aids to cystoscopy in the diagnosis of bladder cancer. Depending on the populations studied, each test has been reported to have sensitivities of 35-80% in the detection of bladder cancer, and specificities of 65-90%. *(1-3)* However, combined performance is not known and the performance of each of the two tests in a large population of patients with low risk bladder cancer has only been partially defined. In the current study, each test will be performed prestudy and then every three months with each surveillance cystoscopy for 2 years (or until recurrence). This information is needed to determine the relative safety with which one or both tests could replace some surveillance cystoscopies in this population. Additionally, based on the pattern of recurrences in the placebo arm in **S0337**, and from other studies, the optimal way for using these markers in monitoring superficial bladder cancer can be modeled. *(4)* For instance, if the initial recurrence is most likely to happen at the first or second surveillance cystoscopy, these tests might be best suited for use after those examinations.

Methods

BTA Stat and NMP-22 Bladder Chek will each be performed prior to the TURBT of the index tumor and with each surveillance cystoscopy for 2 years, or until first histologically confirmed recurrence (whichever is sooner). Each test will be performed as per manufacturer's instructions by the research nurse with each institution's investigators and results will be reported to the Southwest Oncology Group Data Operations Office on the **S0337** Urine Markers Form.

Interpretation of Data

Statistical considerations appear in Section 11.0. With this information, the ability of each test (or combination of tests) to replace any surveillance cystoscopy during the 2 years following TURBT will be ascertained. Performance characteristics of the tests will be determined. Sensitivities, specificities, positive and negative predictive values, and accuracy of each test and the combination (either test positive = a positive test) will be calculated. Additionally, the anticipation rate of each marker, independently and combined, in this longitudinal study (i.e. what proportion of "false positive" results predict future tumor appearance and how long after the first positive test result tumors become cystoscopically apparent), and how consistently that marker remains positive before cancer is diagnosed, will be determined.

Additionally, how best to use each or both tests instead of cystoscopy, will be compared with published recommendations (e.g. alternating one marker with cystoscopy) in terms of benefit and cost effectiveness. *(5)*

References:

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3. Grossman et al. JAMA 293:810, 2005.

4. Messing et al, J Urol 173:249a, 2005.

5. Lotan Y, Roehborn, CG. J Urol 167:75-79, 2002.

Informed Consent Model for S0337

*NOTES FOR LOCAL INSTITUTION INFORMED CONSENT AUTHORS:

This model informed consent form has been reviewed by the DCT/NCI and is the official consent document for this study. Local IRB changes to this document are allowed. (Institutions should attempt to use sections of this document that are in bold type in their entirety.) Editorial changes to these sections may be made as long as they do not change information or intent. If the institutional IRB insists on making deletions or more substantive modifications to the risks or alternatives sections, they may be justified in writing by the investigator and approved by the IRB. Under these circumstances, the revised language, justification and a copy of the IRB minutes must be forwarded to the Southwest Oncology Group Operations Office for approval before a patient may be registered to this study.

Please particularly note that the questions related to banking of specimens for future study are in bolded type and may not be changed in any way without prior approval from the Southwest Oncology Group Operations Office.

Readability Statistics:	
Flesch Reading Ease	61.6 (targeted above 55)
Flesch-Kincaid Grade Level	8.8 (targeted below 8.5)

- Instructions and examples for informed consent authors are in *[italics]*.
- A blank line, _____, indicates that the local investigator should provide the appropriate information before the document is reviewed with the prospective research participant.
- The term "study doctor" has been used throughout the model because the local investigator for a cancer treatment trial is a physician. If this model is used for a trial in which the local investigator is not a physician, another appropriate term should be used instead of "study doctor".
- The dates of protocol updates in the header and in the text of the consent is for reference to this model only and should not be included in the informed consent form given to the prospective research participant.
- The local informed consent must state which parties may inspect the research records. This includes the NCI, the drug manufacturer for investigational studies, any companies or grantors that are providing study support (these will be listed in the protocol's model informed consent form) and the Southwest Oncology Group.

  The "Southwest Oncology Group" must be listed as one of the parties that may inspect the research records in all protocol consent forms for which patient registration is being credited to the Southwest Oncology Group. This includes consent forms for studies where all patients are registered directly through the Southwest Oncology Group Data Operations Office, all intergroup studies for which the registration is being credited to the Southwest Oncology Group (whether the registration is through the SWOG Data Operations Office or

directly through the other group), as well as consent forms for studies where patients are registered via CTSU and the registration is credited to the Southwest Oncology Group.

- When changes to the protocol require revision of the informed consent document, the IRB should have a system that identifies the revised consent document, in order to preclude continued use of the older version and to identify file copies. An appropriate method to identify the current version of the consent is for the IRB to stamp the final copy of the consent document with the approval date. The stamped consent document is then photocopied for use. Other systems of identifying the current version of the consent such as adding a version or approval date are allowed as long as it is possible to determine during an audit that the patient signed the most current version of the consent form.

*NOTES FOR LOCAL INVESTIGATORS:

- The goal of the informed consent process is to provide people with sufficient information for making informed choices. The informed consent form provides a summary of the clinical study and the individual's rights as a research participant. It serves as a starting point for the necessary exchange of information between the investigator and potential research participant. This model for the informed consent form is only one part of the larger process of informed consent. For more information about informed consent, review the "Recommendations for the Development of Informed Consent Documents for Cancer Clinical Trials" prepared by the Comprehensive Working Group on Informed Consent in Cancer Clinical Trials for the National Cancer Institute. The Web site address for this document is http://cancer.gov/clinicaltrials/understanding/simplification-of-informed-consent-docs/
- A blank line, _____, indicates that the local investigator should provide the appropriate information before the document is reviewed with the prospective research participant.
- Suggestion for Local Investigators: An NCI pamphlet explaining clinical trials is available for your patients. The pamphlet is titled: "If You Have Cancer…What You Should Know about Clinical Trials". This pamphlet may be ordered on the NCI Web site at *http://cissecure.nci.nih.gov/ncipubs* or call 1-800-4- CANCER (1-800-422-6237) to request a free copy.
- Optional feature for Local Investigators: Reference and attach drug sheets, pharmaceutical information for the public, or other material on risks. Check with your local IRB regarding review of additional materials.

*These notes for authors and investigators are instructional and should not be included in the informed consent form given to the prospective research participant.

S0337, "A Phase III Blinded Study Of Immediate Post-TURBT Instillation Of Gemcitabine Versus Saline In Patients With Newly Diagnosed Or Occasionally Recurring Grade I/II Superficial Bladder Cancer"

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

You are being asked to take part in this study because you have newly diagnosed superficial bladder cancer or superficial bladder cancer that has come back.

Who is doing this study?

The Southwest Oncology Group (SWOG) is sponsoring this trial. SWOG is an adult cancer clinical trials organization. SWOG is funded through the National Cancer Institute, and its network consists of almost four thousand physicians at almost three hundred institutions throughout the United States. Your study doctor has met all requirements to be a member of SWOG and to perform National Cancer Institute-funded research through this Group.

Why is this study being done?

The type of bladder tumor that you have has a relatively high chance of coming back in your bladder after it has been removed. It usually comes back in a different spot of your bladder than where it was originally.

The purpose of this study is to determine if gemcitabine, a chemotherapy drug that is effective against very advanced bladder cancer when given through a vein (intravenously) is also effective against earlier stage bladder cancers when given into your bladder (intravesically). Specifically, the study will determine whether gemcitabine is more likely than saline (salt water) to lower the chances of your tumor recurring if given into the bladder within 3 hours after your tumor is removed.

In this study, the drug gemcitabine is being used in a new (investigational) way.

Since the final pathology will not be available until after you receive treatment, there is a possibility that you may not have cancer, but still may undergo treatment. The likelihood of this is extremely small in view of known data that indicates that experienced urologists are capable of accurately assessing the presence of tumor.

How many people will take part in the study?

About 340 people will take part in this study.

What will happen if I take part in this research study?

Before you begin the study …

You will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- Your doctor will review your medical history and perform a physical examination.
- Your doctor will perform a cystoscopy (looking into the bladder with a flexible or rigid endoscope, usually in the clinic under local anesthesia) to look inside your bladder, with the collection of urine for cytology (a laboratory evaluation for cancer cells in the urine).
- An x-ray of your kidneys (intravenous pyelogram or CAT scan) will be performed if you have not had that done within the last six months.
- Your urine will be collected for urinalysis and urine culture. If you have a urinary tract infection you cannot participate on this study. Tell your doctor if you believe you have developed a urinary tract infection since the urine culture was collected.
- Routine blood tests will be performed to evaluate your white cells, red cells and platelets, and the function of your liver and kidneys.

During the study:

If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will need the following tests and procedures.

You will be "randomized" into one of the study groups described below. Randomization means that you are put into a group by chance. Neither you nor your doctor will either know or choose the group you will be in. You will have an equal chance of being placed in either group.

- After you agree to take part in the study but before you receive treatment, your urine will be collected for research studies. The tests performed will be the NMP-22 Bladder Chek and BTA Stat test. Part of this study is to see whether these tests can predict recurrence as well as cystoscopy alone. Your urine will be collected once every three months for the first two years for these tests.
- The study involves one intravesical instillation treatment of either gemcitabine or saline (salt water) into the bladder immediately following the TURBT (trans-urethral resection of bladder tumor) procedure. Saline (salt water) is a placebo, not a form of treatment for superficial bladder cancer. It does not contain any medication. You will have a catheter tube inserted in your bladder through the urethra. About ¼ cup of liquid containing either the study drug (gemcitabine 2,000 mg in 100 mL of saline) or saline alone (100 mL) will be instilled into your bladder after all the urine has been drained out. You will be asked to hold

the liquid in your bladder for about 1 hour. After about 1 hour the liquid will be drained from the bladder through the catheter. If you experience discomfort while the liquid is in your bladder, you should notify your urologist who may choose to drain your bladder earlier than the 1 hour dwell time. Similarly, if you wish the liquid to be drained earlier than planned, notify your urologist and the infusion will be stopped and the bladder drained. Additionally, if immediately after your surgery your urine is found to be quite bloody, your urologist may choose to irrigate your bladder with liquid. If the urine becomes clear within 3 hours, the liquid could still be instilled at the time.

- If your urologic surgeon believes for any number of reasons, including that there is too much post-operative bleeding, or that removal of the tumor went so deep into the bladder wall that instilling the liquid might be dangerous, he/she will not place the liquid into your bladder.
- You will be asked to keep track of any side effects you have during the treatment, and will be asked about them by your doctor or the study nurse.
- Between 7 and 14 days after you receive the intravesical treatment, routine blood tests will be performed to evaluate your white cells and platelets and to test your liver function.
- Every 3 months for the first two years, then every 6 months for the next two years, your doctor will review your medical history and perform a physical examination.
- Every 3 months for the first two years, then every 6 months for the next two years, your doctor will perform a cystoscopy (looking into the bladder with a flexible or rigid endoscope, usually in the clinic under local anesthesia) to look inside your bladder, with the collection of urine for cytology (a laboratory evaluation for cancer cells in the urine). At each evaluation, if either test is abnormal your doctor will arrange for you to have a bladder biopsy performed. If the cancer comes back, your doctor will discuss with you other options for treatment of your cancer at that point. We will continue to follow you to see how you are doing for up to 4 years after you start the study.

How long will I be in the study?

You will continue as detailed above for up to 4 years from the start of the study. You will need routine follow-up evaluations (cystoscopy and urinary cytology) every 3 months the first and second year and every 6 months for the next two years.

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from the intravesical gemcitabine/saline can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The study doctor may end your participation in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

What side effects or risks can I expect from being in the study?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after the gemcitabine/saline instillation. In some cases, side effects can be serious, long lasting, or may never go away.

You should talk to your study doctor about any side effects that you have while taking part in the study.

Risks and side effects related to the bladder tumor resection (TURBT) and intravesical gemcitabine include:

Likely

- **Bladder irritation causing urinary frequency or burning**
- **Hematuria (blood in the urine)**
- **Bladder spasms**

Less Likely

- **Bladder perforation (a hole in your bladder). This usually will require you to have a draining catheter for several days longer than normal after your surgery, and rarely might require you to undergo an operation to repair your bladder.**
- **If gemcitabine is put into your bladder, there might be other risks including the risk of the drug getting into your blood stream. If this happens, you may also experience low white blood cell or platelet counts, which could cause increased susceptibility to infection or bleeding. Very rarely anemia (low red blood cell count) causing fatigue and sometimes requiring transfusions may occur.**

Rare but Serious

In a few patients who received gemcitabine through a vein, the following rare, but serious side effects were seen:

- **Fluid in your lungs, which could make you short of breath, wheeze or cough**
- **Kidney stress or damage as shown by abnormal kidney function tests. You may notice blood and/or protein in your urine.**

Risks and side effects related to the bladder tumor resection (TURBT) and intravesical saline include:

Likely

- **Bladder irritation causing urinary frequency or burning**
- **Hematuria (blood in the urine)**
- **Bladder spasms**

Less Likely

- **Bladder perforation (a hole in your bladder). This usually will require you to have a draining catheter for several days longer than normal after your surgery, and rarely might require you to undergo an operation to repair your bladder.**

Reproductive risks: You should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important you understand that you need to use birth control while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study.

For more information about risks and side effects, ask your study doctor.

Are there benefits to taking part in the study?

Taking part in this study may or may not make your health better. While doctors hope intravesical gemcitabine will be more useful against cancer compared to the usual treatment, there is no proof of this yet. We do know that the information from this study will help doctors learn more about intravesical gemcitabine as a treatment for cancer. This information could help future cancer patients.

What other choices do I have if I do not take part in this study?

Your other choices may include:

- **Getting treatment or care for your cancer without being in a study. This may include other intravesical treatments, surgery to remove the bladder, radiation therapy to the bladder, or systemic chemotherapy,**
- **Taking part in another study,**
- **Getting no treatment.**

Talk to your doctor about your choices before you decide if you will take part in this study.

Will my medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people
- The Southwest Oncology Group
- Lilly Pharmaceuticals

What are the costs of taking part in this study?

You and/or your health plan/ insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment. Because instillation of chemotherapy immediately after surgery is frequently done for bladder cancer, you and/or your insurance company may need to pay for this as well. If there are complications of the surgery or the drug instillation, you or your health insurance may be required to pay for the expenses created by caring for/or correcting these complications.

Administration of the drug will be (*provided free of charge/charged in the usual way*). The parts of the research consisting of keeping research records will be paid by those organizing and conducting the research. The research requires that you receive certain standard medical tests and examinations. These standard tests and examinations will be *(charged in the usual way/provided at a reduced rate). (local institutions must choose the option that best fits the hospital's situation).* Lilly Pharmaceuticals has agreed to pay (up to a defined amount per test) for the NMP-22 Bladder Chek and BTA Stat tests.

Lilly Pharmaceuticals will provide you with the investigational agent gemcitabine or saline at no cost to you.

You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage . You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

What happens if I am injured because I took part in this study?

It is important that you tell your study doctor, _____ *[investigator's name(s)],* if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at _____ *[telephone number].*

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

A Data Safety and Monitoring Board, an independent group of experts, will be reviewing the data from this research throughout the study. We will tell you about important new information from this or other studies that may affect your health, welfare, or willingness to stay in this study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the study?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor _____ *[name(s)]* at _____ *[telephone number].*

For questions about your rights while taking part in this study, call the _____ *[name of center]* Institutional Review Board (a group of people who review the research to protect your rights) at _____ *(telephone number). [Note to Local Investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here.]*

*You may also call the Operations Office of the NCI Central Institutional Review Board (CIRB) at 888-657-3711 (from the continental US only). *[*Only applies to sites using the CIRB.]*

Please note: This section of the informed consent form is about additional research studies that are being done with people who are taking part in the main study. You may take part in these additional studies if you want to. You can still be a part of the main study even if you say 'no' to taking part in any of these additional studies.

You can say "yes" or "no" to each of the following studies. Please mark your choice for each study.

Future Contact

I agree to allow my study doctor, or someone approved by my study doctor, to contact me regarding future research involving my participation in this study.

Yes **No**

Consent Form for Use of Specimens for Research

About Using Specimens for Research

Prior to receiving gemcitabine or placebo, you will have a biopsy (TURBT) to remove your bladder cancer. In addition, if your cancer recurs in the future, additional biopsies will be performed at that time. We would like to obtain some of the tissue that was removed both before and after the treatment so that we can do some research tests on the tissue. We would also like to collect a sample of your blood 3 months after you receive gemcitabine or placebo. The goal of these research tests it to improve our understanding of your type of bladder cancer and its response to the intravesical gemcitabine treatment.

Your tissue will be kept at:

Southwest Oncology Group Tumor Tissue Bank:
University of Colorado HSC at Fitzsimons
Department of Pathology
RC-1 South, Room L18-5104
12801 East 17th Avenue
Aurora, CO 80010
Phone: 303/724-3086

We would like to keep some of the tissue and blood that is left over for future research. If you agree, these specimens will be kept and may be used in research to learn more about cancer and other diseases. Please read the information sheet called "How are Specimens Used for Research" to learn more about tissue research.

The research that may be done with your specimens is not designed specifically to help you. It might help people who have cancer and other diseases in the future.

Reports about research done with your specimens will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

Things to Think About

The choice to let us keep the left over specimens for future research is up to you. No matter what you decide to do, it will not affect your care.

If you decide now that your specimens can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your specimens. Then any specimens that remain will no longer be used for research.

In the future, people who do research may need to know more about your health. While the Southwest Oncology Group may give them reports about your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Sometimes specimens are used for genetic research (about diseases that are passed on in families). Even if your specimens are used for this kind of research, the results will not be put in your health records.

Your specimens will be used only for research and will not be sold. The research done with your specimens may help to develop new products in the future.

Benefits

The benefits of research using specimens include learning more about what causes cancer and other diseases, how to prevent them, and how to treat them.

Risks

The greatest risk to you is the release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small.

Making Your Choice

Please read each sentence below and think about your choice. After reading each sentence, circle "Yes" or "No." If you have any questions, please talk to your doctor or nurse, or call our research review board at IRB's phone number.

No matter what you decide to do, it will not affect your care.

1. **My specimens may be kept for use in research to learn about, prevent, treat or cure cancer.**

   Yes No

2. **My specimens may be kept for use in research about other health problems (for example: diabetes, Alzheimer's disease, or heart disease).**

   Yes No

3. **Someone may contact me in the future to ask me to allow other uses of my specimens.**

   Yes No

If you decide to withdraw your specimens from a Southwest Oncology Group Specimen Repository in the future, a written withdrawal of consent should be submitted through your treating physician to the Southwest Oncology Group Operations Office. Please designate in the written withdrawal whether you would prefer to have the specimens destroyed or returned to the treating physician.

Where can I get more information?

You may call the National Cancer Institute's Cancer Information Service at:

1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

You may also visit the NCI Web site at http://cancer.gov/

- For NCI's clinical trials information, go to: http://cancer.gov/clinicaltrials/
- For NCI's general information about cancer, go to http://cancer.gov/cancerinfo/

You will get a copy of this form. If you want more information about this study, ask your study doctor.

Signature

I have been given a copy of all _____ *[insert total of number of pages]* pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Participant _____

Date _____

Specimen Consent Supplemental Sheets

How are Specimens Used for Research?

Where do specimens come from?

A specimen may be from a blood sample or from bone marrow, skin, toenails or other body materials. People who are trained to handle specimens and protect donors' rights make sure that the highest standards of quality control are followed by the Southwest Oncology Group. Your doctor does not work for the Southwest Oncology Group, but has agreed to help collect specimens from many patients. Many doctors across the country are helping in the same way.

Why do people do research with specimens?

Research with specimens can help to find out more about what causes cancer, how to prevent it, how to treat it, and how to cure it. Research using specimens can also answer other health questions. Some of these include finding the causes of diabetes and heart disease, or finding genetic links to Alzheimer's.

What type of research will be done with my specimen?

Many different kinds of studies use specimens. Some researchers may develop new tests to find diseases. Others may develop new ways to treat or even cure diseases. In the future, some of the research may help to develop new products, such as tests and drugs. Some research looks at diseases that are passed on in families (called genetic research). Research done with your specimen may look for genetic causes and signs of disease.

How do researchers get the specimen?

Researchers from universities, hospitals, and other health organizations conduct research using specimens. They contact the Southwest Oncology Group and request samples for their studies. The Southwest Oncology Group reviews the way that these studies will be done, and decides if any of the samples can be used. The Southwest Oncology Group gets the specimen and information about you from your hospital, and sends the specimen samples and some information about you to the researcher. The Southwest Oncology Group will not send your name, address, phone number, social security number or any other identifying information to the researcher.

Will I find out the results of the research using my specimen?

You will not receive the results of research done with your specimen. This is because research can take a long time and must use specimen samples from many people before results are known. Results from research using your specimen may not be ready for many years and will not affect your care right now, but they may be helpful to people like you in the future.

Why do you need information from my health records?

In order to do research with your specimen, researchers may need to know some things about you. (For example: Are you male or female? What is your race or ethnic group? How old are you? Have you ever smoked?) This helps researchers answer questions about diseases. The information that will be given to the researcher may include your age, sex, race, diagnosis, treatments and family history. This information is collected by your hospital from your health record and sent to the Southwest Oncology Group. If more information is needed, the Southwest Oncology Group will send it to the researcher.

Will my name be attached to the records that are given to the researcher?

No. Your name, address, phone number and anything else that could identify you will be removed before they go the researcher. The researcher will not know who you are.

How could the records be used in ways that might be harmful to me?

Sometimes, health records have been used against patients and their families. For example, insurance companies may deny a patient insurance or employers may not hire someone with a certain illness (such as AIDS or cancer). The results of genetic research may not apply only to you, but to your family members too. For disease caused by gene changes, the information in one person's health record could be used against family members.

How am I protected?

The Southwest Oncology Group is in charge of making sure that information about you is kept private. The Southwest Oncology Group will take careful steps to prevent misuse of records. Your name, address, phone number and any other identifying information will be taken off anything associated with your specimen before it is given to the researcher. This would make it very difficult for any research results to be linked to you or your family. Also, people outside the research process will not have access to results about any one person which will help to protect your privacy.

What if I have more questions?

If you have any questions, please talk to your doctor or nurse, or call our research review board at (Insert IRB's Phone Number).