ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

ICMJE Form for Disclosure of Potential Conflicts of Interest

Instructions

The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. The form is designed to be completed electronically and stored electronically. It contains programming that allows appropriate data display. Each author should submit a separate form and is responsible for the accuracy and completeness of the submitted information. The form is in six parts.

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4. Intellectual Property.

This section asks about patents and copyrights, whether pending, issued, licensed and/or receiving royalties.

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Hagop
2. Surname (Last Name): Kantarjian
3. Date: 08-December-2016

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Jan Burger and Nicholas Chiorazzi

5. Manuscript Title: Leukemia cell proliferation and death in chronic lymphocytic leukemia patients on therapy with the BTK inhibitor ibrutinib

6. Manuscript Identifying Number (if you know it): 89904-INS-CMED-RV-3

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Dr. Kantarjian has nothing to disclose.

Evaluation and Feedback

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Section 1. Identifying Information

1. Given Name (First Name): Ahmed
2. Surname (Last Name): Amer
3. Date: 08-December-2016

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Jan Burger and Nicholas Chiorazzi

5. Manuscript Title: Leukemia cell proliferation and death in chronic lymphocytic leukemia patients on therapy with the BTK inhibitor ibrutinib

6. Manuscript Identifying Number (if you know it): 89904-INS-CMED-RV-3

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Dr. Amer has nothing to disclose.

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Section 1. Identifying Information

1. Given Name (First Name): Shih-Shih
2. Surname (Last Name): Chen
3. Date: 08-December-2016

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Jan Burger and Nicholas Chiorazzi

5. Manuscript Title: Leukemia cell proliferation and death in chronic lymphocytic leukemia patients on therapy with the BTK inhibitor ibrutinib

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Section 1. Identifying Information

1. Given Name (First Name): Marc
2. Surname (Last Name): Hellerstein
3. Date: 08-December-2016

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Jan Burger and Nicholas Chiorazzi

5. Manuscript Title: Leukemia cell proliferation and death in chronic lymphocytic leukemia patients on therapy with the BTK inhibitor ibrutinib

6. Manuscript Identifying Number (if you know it): 89904-INS-CMED-RV-3

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Are there any relevant conflicts of interest? ☑ Yes ☐ No

If yes, please fill out the appropriate information below. If you have more than one entity press the "ADD" button to add a row. Excess rows can be removed by pressing the "X" button.

Name of Institution/Company	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments	
KineMed	☐	☐	☐	☑	Employee/consultants	

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Dr. Hellerstein reports being an employee/consultant from KineMed, during the conduct of the study; .

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Section 1. Identifying Information

1. Given Name (First Name): Naveen
2. Surname (Last Name): Garg
3. Date: 08-December-2016

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Jan Burger and Nicholas Chiorazzi

5. Manuscript Title: Leukemia cell proliferation and death in chronic lymphocytic leukemia patients on therapy with the BTK inhibitor ibrutinib

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Dr. Garg has nothing to disclose.

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4. Intellectual Property.

This section asks about patents and copyrights, whether pending, issued, licensed and/or receiving royalties.

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Definitions.

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Personal Fees: Monies paid to you for services rendered, generally honoraria, royalties, or fees for consulting , lectures, speakers bureaus, expert testimony, employment, or other affiliations
Non-Financial Support: Examples include drugs/equipment supplied by the entity, travel paid by the entity, writing assistance, administrative support, etc.
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Royalties: Funds are coming in to you or your institution due to your patent

ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Alessandra
2. Surname (Last Name): Ferrajoli
3. Date: 08-December-2016

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Jan Burger and Nicholas Chiorazzi

5. Manuscript Title: Leukemia cell proliferation and death in chronic lymphocytic leukemia patients on therapy with the BTK inhibitor ibrutinib

6. Manuscript Identifying Number (if you know it): 89904-INS-CMED-RV-3

Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 3. Relevant financial activities outside the submitted work.

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 5. Relationships not covered above

Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

☐ Yes, the following relationships/conditions/circumstances are present (explain below):

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Section 6. Disclosure Statement

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Dr. Ferrajoli has nothing to disclose.

Evaluation and Feedback

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Claire
2. Surname (Last Name): Emson
3. Date: 08-December-2016

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Jan Burger and Nicholas Chiorazzi

5. Manuscript Title: Leukemia cell proliferation and death in chronic lymphocytic leukemia patients on therapy with the BTK inhibitor ibrutinib

6. Manuscript Identifying Number (if you know it): 89904-INS-CMED-RV-3

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Are there any relevant conflicts of interest? ☑ Yes ☐ No

If yes, please fill out the appropriate information below. If you have more than one entity press the "ADD" button to add a row. Excess rows can be removed by pressing the "X" button.

Name of Institution/Company	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments	
KineMed	☐	☐	☐	☑	Employee/consultant	

Section 3. Relevant financial activities outside the submitted work.

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

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Dr. Emson reports being an employee/consultant from KineMed, during the conduct of the study; .

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Royalties: Funds are coming in to you or your institution due to your patent

ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Jan
2. Surname (Last Name): Burger
3. Date: 07-December-2016

4. Are you the corresponding author? ☑ Yes ☐ No

5. Manuscript Title: Leukemia cell proliferation and death in chronic lymphocytic leukemia patients on therapy with the BTK inhibitor ibrutinib

6. Manuscript Identifying Number (if you know it): 89904-INS-CMED-RV-3

Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☑ Yes ☐ No

If yes, please fill out the appropriate information below. If you have more than one entity press the "ADD" button to add a row. Excess rows can be removed by pressing the "X" button.

Name of Institution/Company	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments
Pharmacyclics	☑	☐	☐	☐	research funding from Pharmacyclics
Janssen	☐	☑	☐	☐	J.A.B. received speaking fees from Janssen Pharmaceuticals
Cancer Center Support Grant	☑	☐	☐	☐	NCI Grant P30 CA016672
MD Anderson's Moon Shot Program in CLL	☑	☐	☐	☐	

Section 3. Relevant financial activities outside the submitted work.

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

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Dr. Burger reports grants from Pharmacyclics, personal fees from Janssen, grants from Cancer Center Support Grant, grants from MD Anderson's Moon Shot Program in CLL, during the conduct of the study; .

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Royalties: Funds are coming in to you or your institution due to your patent

ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Nicholas
2. Surname (Last Name): Chiorazzi
3. Date: 08-December-2016

4. Are you the corresponding author? [✓] Yes [ ] No

5. Manuscript Title: Leukemia cell proliferation and death in chronic lymphocytic leukemia patients on therapy with the BTK inhibitor ibrutinib

6. Manuscript Identifying Number (if you know it): 89904-INS-CMED-RV-3

Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? [✓] Yes [ ] No

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Name of Institution/Company	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments
National Cancer Institute	✓				CA081554
Pharmacyclics	✓				

Section 3. Relevant financial activities outside the submitted work.

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Are there any relevant conflicts of interest? [ ] Yes [✓] No

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Do you have any patents, whether planned, pending or issued, broadly relevant to the work? [ ] Yes [✓] No

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Dr. Chiorazzi reports grants from National Cancer Institute , grants from Pharmacyclics, during the conduct of the study; .

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Shih-Shih
2. Surname (Last Name): Chen
3. Date: 08-December-2016

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Jan Burger and Nicholas Chiorazzi

5. Manuscript Title: Leukemia cell proliferation and death in chronic lymphocytic leukemia patients on therapy with the BTK inhibitor ibrutinib

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

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Dr. Chen has nothing to disclose.

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4. Intellectual Property.

This section asks about patents and copyrights, whether pending, issued, licensed and/or receiving royalties.

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Royalties: Funds are coming in to you or your institution due to your patent

ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Ahmed
2. Surname (Last Name): Amer
3. Date: 08-December-2016

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Jan Burger and Nicholas Chiorazzi

5. Manuscript Title: Leukemia cell proliferation and death in chronic lymphocytic leukemia patients on therapy with the BTK inhibitor ibrutinib

6. Manuscript Identifying Number (if you know it): 89904-INS-CMED-RV-3

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 5. Relationships not covered above

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Section 6. Disclosure Statement

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Dr. Amer has nothing to disclose.

Evaluation and Feedback

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Michael
2. Surname (Last Name): Keating
3. Date: 08-December-2016

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Jan Burger and Nicholas Chiorazzi

5. Manuscript Title: Leukemia cell proliferation and death in chronic lymphocytic leukemia patients on therapy with the BTK inhibitor ibrutinib

6. Manuscript Identifying Number (if you know it): 89904-INS-CMED-RV-3

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

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Dr. Keating has nothing to disclose.

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Kelvin
2. Surname (Last Name): Li
3. Date: 08-December-2016

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Jan Burger and Nicholas Chiorazzi

5. Manuscript Title: Leukemia cell proliferation and death in chronic lymphocytic leukemia patients on therapy with the BTK inhibitor ibrutinib

6. Manuscript Identifying Number (if you know it): 89904-INS-CMED-RV-3

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Are there any relevant conflicts of interest? ☑ Yes ☐ No

If yes, please fill out the appropriate information below. If you have more than one entity press the "ADD" button to add a row. Excess rows can be removed by pressing the "X" button.

Name of Institution/Company	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments	
KineMed Inc.	☐	☐	☐	☑	Employee	

Section 3. Relevant financial activities outside the submitted work.

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

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Dr. Li reports being an employee from KineMed Inc., during the conduct of the study; .

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Susan
2. Surname (Last Name): O'Brien
3. Date:

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Jan Burger and Nicholas Chiorazzi

5. Manuscript Title: Leukemia cell proliferation and death in chronic lymphocytic leukemia patients on therapy with the BTK inhibitor ibrutinib

6. Manuscript Identifying Number (if you know it): 89904-INS-CMED-RV-3

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Are there any relevant conflicts of interest? ☑ Yes ☐ No

If yes, please fill out the appropriate information below. If you have more than one entity press the "ADD" button to add a row. Excess rows can be removed by pressing the "X" button.

Name of Institution/Company	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments	
Pharmacyclics	☑	☐	☐	☐	received research funding	

Section 3. Relevant financial activities outside the submitted work.

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Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

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Dr. O'Brien reports grants from Pharmacyclics, during the conduct of the study; .

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Mariela
2. Surname (Last Name): Sivina
3. Date: 08-December-2016

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Jan Burger and Nicholas Chiorazzi

5. Manuscript Title: Leukemia cell proliferation and death in chronic lymphocytic leukemia patients on therapy with the BTK inhibitor ibrutinib

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Dr. Sivina has nothing to disclose.

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Royalties: Funds are coming in to you or your institution due to your patent

ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Scott
2. Surname (Last Name): Turner
3. Date: 08-December-2016

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Jan Burger and Nicholas Chiorazzi

5. Manuscript Title: Leukemia cell proliferation and death in chronic lymphocytic leukemia patients on therapy with the BTK inhibitor ibrutinib

6. Manuscript Identifying Number (if you know it): 89904-INS-CMED-RV-3

Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☑ Yes ☐ No

If yes, please fill out the appropriate information below. If you have more than one entity press the "ADD" button to add a row. Excess rows can be removed by pressing the "X" button.

Name of Institution/Company	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments	
KineMed	☐	☐	☐	☑	Employee/consultant	

Section 3. Relevant financial activities outside the submitted work.

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the "Add +" box. You should report relationships that were **present during the 36 months prior to publication**.

Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

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ICMJE Form for Disclosure of Potential Conflicts of Interest

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☐ Yes, the following relationships/conditions/circumstances are present (explain below):

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Section 6. Disclosure Statement

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Dr. Turner reports being an employee/consultant from KineMed, during the conduct of the study; .

Evaluation and Feedback

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): William
2. Surname (Last Name): Wierda
3. Date: 08-December-2016

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Jan Burger and Nicholas Chiorazzi

5. Manuscript Title: Leukemia cell proliferation and death in chronic lymphocytic leukemia patients on therapy with the BTK inhibitor ibrutinib

6. Manuscript Identifying Number (if you know it): 89904-INS-CMED-RV-3

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 3. Relevant financial activities outside the submitted work.

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

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Section 6. Disclosure Statement

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Dr. Wierda has nothing to disclose.

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Dominik
2. Surname (Last Name): Wodarz
3. Date: 08-December-2016

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Jan Burger and Nicholas Chiorazzi

5. Manuscript Title: Leukemia cell proliferation and death in chronic lymphocytic leukemia patients on therapy with the BTK inhibitor ibrutinib

6. Manuscript Identifying Number (if you know it): 89904-INS-CMED-RV-3

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Dr. Wodarz has nothing to disclose.

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Xuelin
2. Surname (Last Name): Huang
3. Date: 08-December-2016

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Jan Burger and Nicholas Chiorazzi

5. Manuscript Title: Leukemia cell proliferation and death in chronic lymphocytic leukemia patients on therapy with the BTK inhibitor ibrutinib

6. Manuscript Identifying Number (if you know it): 89904-INS-CMED-RV-3

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Dr. Huang has nothing to disclose.

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Xiao-Jie
2. Surname (Last Name): Yan
3. Date: 08-December-2016

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Jan Burger and Nicholas Chiorazzi

5. Manuscript Title: Leukemia cell proliferation and death in chronic lymphocytic leukemia patients on therapy with the BTK inhibitor ibrutinib

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Dr. Yan has nothing to disclose.

Evaluation and Feedback

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Item	Description	Reported on line number
Title	A Pilot Study to determine the effects of the Bruton's tyrosine kinase (Btk) inhibitor PCI-32765 on leukemia cell kinetics and trafficking, using Heavy Water Labeling in subjects with Chronic Lymphocytic Leukemia (CLL) and Small Lymphocytic Lymphoma (SLL).	
Authors *	Jan A. Burger, M.D., Ph.D., Kelvin W. Li, Ph.D., Michael J. Keating, M.D., Mariela Sivina, Ph.D., Ahmed M. Amer, M.D., Naveen Garg, M.D., Alessandra Ferrajoli, M.D., Xuelin Huang, Ph.D., Hagop Kantarjian, M.D., William G. Wierda M.D., Ph.D., Susan O'Brien, M.D., Marc K. Hellerstein, M.D., Ph.D., Scott M. Turner, Ph.D., Claire L. Emson, Ph.D., Shih-Shih Chen, Ph.D., Xiao-Jie Yan, Ph.D., Dominik Wodarz, Ph.D., and Nicholas Chiorazzi, M.D.	
Trial design	Pilot Study	
Methods		
Participants	**Subject Eligibility** **Inclusion Criteria:** Subjects will be eligible for inclusion in the study if they meet all of the following criteria: 1) A diagnosis of CLL/ SLL and have not been previously treated. 2) An indication for treatment by 2008 IWCLL Criteria 3) Male and female subjects of age ≥ 65 years at the time of signing informed consent and requiring treatment within the next 2 to 6 months. 4) Understand and voluntarily sign an informed consent, and be able to comply with study procedures and follow-up examinations. 5) Platelet counts at study entry must be greater than 50,000/μL and absolute neutrophil counts at study entry must be greater than 750/μL 6) Free of prior malignancies for 3 years with exception of currently treated basal cell, squamous cell carcinoma of the skin, or carcinoma "in situ" of the cervix or breast. 7) Subjects must be able to contribute the required amount of blood and/or tissue without compromising their well-being or care and must weigh at least 110 pounds 8) Adequate renal and hepatic function as indicated by all of the following: total bilirubin </=1.5 x institutional Upper Limit of Normal (ULN); AST or ALT </=2.5 x ULN; and estimated creatinine clearance (CrCl) of > 30 mL/min, as calculated by the Cockroft- Gault equation 9) Participants must be willing to be contacted again for consideration of additional studies in the future, such as a blood draw or another action (e.g., bone marrow aspiration and/or biopsy) that would be associated with their standard of care, unless they consented to such for research purposes.	

10) An ECOG/WHO performance status of 0-2.
11) Males and females of child bearing potential must have adequate birth control protection while on study and for 30 days after the last dose of study drug.

Exclusion Criteria:

1) Subjects less than 65 years of age
2) A lymphocyte doubling time of < 3 months, or other clinical or laboratory signs indicating that a treatment delay of 2 months or longer (due to heavy water labeling and resting period) would result in a significant progression of the disease and be detrimental to the subject, as determined by the treating physician
3) Any prior treatment for CLL including chemotherapy, chemoimmunotherapy, monoclonal antibody therapy, radiotherapy, or high-dose corticosteroid therapy (Prednisone > 60 mg daily or equivalent), or immunotherapy prior to enrollment or concurrent with this trial.
4) Concomitant use of agents that have been described to affect the biology and/or proliferation rate of CLL cells such as: PDE-inhibitors (e.g., sildenafil, theophylline), immunosuppressive agents (e.g., prednisone, cyclosporin-A, rapamycin), green tea extract, itraconazole, ketoconazole, clarithromycin, bupropion, and Cox-2 inhibitors
5) Investigational agent received within 30 days prior to the first dose of study drug. If received any investigational agent prior to this time point, drug-related toxicities must have recovered to Grade 1 or less prior to first dose of study drug.
6) Systemic fungal, bacterial, viral, or other infection not controlled (defined as exhibiting ongoing signs/symptoms related to the infection and without improvement, despite appropriate antibiotics or other treatment).
7) Subjects with uncontrolled autoimmune hemolytic anemia (AIHA) or autoimmune thrombocytopenia (ITP)
8) Any other severe concurrent disease, or have a history of serious organ dysfunction or disease involving the heart, kidney, liver or other organ system that may place the subject at undue risk to undergo therapy with PCI-32765.
9) Any serious medical condition, laboratory abnormality, or psychiatric illness that places the subject at unacceptable risk if he/she were to participate in the study.
10) History of intracranial hemorrhage or stroke within 6 months prior to the study
11) Evidence of bleeding diathesis or coagulopathy
12) Major surgical procedure, open biopsy, or significant traumatic injury, within 28 days prior to Day 1, anticipation of need for major surgical procedure during the course of the study. (Minor surgical procedures, fine needle aspirations or core biopsies within 7 days prior to Day 1. Bone

marrow aspiration +/- biopsy is allowed).

13) Serious, non-healing wound, ulcer, or bone fracture.
14) Subjects receiving anticoagulation (for example heparin, Coumadin, low-molecular-weight heparin (LMWH, such as Lovenox), and anti-platelet drugs (except for low-dose aspirin) will be ineligible to participate in this study. Subjects who recently received drugs for anticoagulation must be off those medications for at least 7 days prior to start of the study.
15) Subjects who are known to be anemic, with hemoglobin <8.0g/dl.
16) Weight less than 110 pounds
17) Subjects who are known to be infected with HIV, or have signs of active Hepatitis B or Hepatitis C
18) Biliary obstruction, acute hepatitis, severe liver failure, or severely impaired renal function

Interventions

Treatment Plan

Heavy Water Protocol: Labeling phase.

After enrollment and a baseline blood draw (60ml), subjects will start to consume heavy water (^2H_2O). Subjects will be given 50 mL of 70% ^2H_2O 3 times a day for the first 5 days followed by 60ml daily for a total of 4 weeks (labeling phase). Lightheadedness or dizziness may occur for some subjects (~15%) with the initial doses; therefore subjects will be given their first dose in clinic and asked to avoid driving or performing potentially hazardous activities for one hour. If such symptoms occur, they usually abate within 2-3 hours. Subjects will then be given individual doses of ^2H_2O to consume at home; after the 5-day loading period, a 60 mL maintenance dose of ^2H_2O will be drunk at bedtime to obviate any problems with dizziness. Compliance with ^2H_2O ingestion will be documented using a heavy water ingestion diary (intake logs). Unused ^2H_2O will be returned for disposal.

Subjects will be seen at weeks 1 (+/- 3 days), 2 (+/- 3 days), and 4 (+/- 3 days) after beginning ^2H_2O ingestion for follow-up visits with clinical and laboratory assessment, which will include determining if there have been any problems with ^2H_2O ingestion, analysis and discussion of intake logs, and blood sampling (60ml) for CLL cell kinetic measurements (heavy water testing).

Heavy Water Protocol: Resting phase.

At the end of the 4th week, subjects will stop drinking ^2H_2O (washout phase) and be followed for 6-12 weeks until beginning treatment with PCI-32765. During the period until initiation of therapy, subjects will be seen every 2 weeks (+/- 3 days) for follow-up visits with clinical and laboratory assessment. Blood will be drawn at the same time every 2 weeks (+/- 3 days), to determine a disappearance rate (death plus re-distribution into solid tissue) of CLL cells containing ^2H-labeled DNA. Only those subjects that have not imbibed ^2H_2O for at least 6 weeks from the end of the labeling period until starting on treatment with PCI-32765 will be included in further ^2H_2O

	kinetic studies, although they will receive PCI-32765 as a part of the response to therapy studies. After start of treatment with PCI-32765, there will be blood sampling (60ml) for CLL cell kinetic measurements (heavy water testing) on days 1, 3, and then at weeks 1 (+/- 3 days), 2 (+/- 3 days) and every 2 weeks (+/- 3 days) thereafter for a period of at least equal in duration to that of the initial ^2H_2O washout phase (6 to 12 weeks). Patients will continue to return or be seen by a local physician or clinical laboratory each month for an additional 3 months for blood drawing (60ml). Data obtained from these blood samples will permit a determination of CLL birth rate as well as a slope of labeled cell emergence from solid tissue into the peripheral blood. **Treatment with PCI-32765** PCI-32765 will be administered with 8 ounces (~240mL) of water at a dose of 420 mg (3 x 140mg capsules) orally once daily and will be continued daily. Each dose of PCI-32765 should be taken at least 30 minutes before eating and at least 2 hours after a meal at approximately the same time each day. Subjects will be instructed to avoid grapefruit juice due to CYP450 3A4 inhibition. Compliance with PCI-32765 ingestion will be documented using a diary. Treatment duration will be 12 cycles, with each cycle consisting of 28 days. Response will be evaluated after 3, 6 and 12 cycles. It will be possible for subjects to continue taking the drug beyond 12 cycles if there is a significant benefit such as an ongoing PR or CR. Unused PCI-32765 will be returned for disposal per institutional policy.
Objective	**Objectives** The primary objective is to assess the impact of the Bruton's tyrosine kinase (Btk) inhibitor PCI-32765 on leukemia cell trafficking and death using heavy water (^2H_2O) labeling of newly-born malignant cells in subjects with Chronic Lymphocytic Leukemia (CLL) and Small Lymphocytic Lymphoma (SLL). The secondary objective is to determine the percent of recently born versus older leukemia cells mobilized into the blood by PCI-32765 treatment. The tertiary objective is to compare the kinetic biomarker measurements in CLL subjects to other established prognostic tests and response to therapy with PCI-32765.
Outcome	This is a one center, open label pilot study to evaluate the impact of the Btk inhibitor PCI-32765 on leukemia cell trafficking and death, using heavy water labeling in subjects with Chronic Lymphocytic Leukemia (CLL) and Small Lymphocytic Lymphoma (SLL). The study objectives are described above.
Randomization	Not applicable
Blinding (masking)	Not applicable

Results	
Numbers randomized	Not applicable
Recruitment	Closed to new patient entry
Numbers analysed	30 patients total
Outcome	The primary objectives of the statistical analysis will be (1) to demonstrate that there is a population of CLL cells that do not leave or take sanctuary outside of the peripheral blood system in solid lymphoid tissues, (2) to describe the longitudinal pattern in observed labeled cells and (3) to estimate rates of cell death. For purposes of statistical analysis, the experiment will be divided into two periods (with each period, itself, being divided into two subperiods): Period 1 corresponds to the non-interventional period when heavy water is consumed for 4 weeks (Period 1a) and then discontinued (Period 1b) so that a CLL cell disappearance rate can be tracked over time. Period 2 corresponds to the interventional period when Btk inhibitor (PCI-32765) is administered to subjects. Assuming that the observed percentage of labeled cells (LC) reaches a peak at some point in time, T, then Period 2a is defined as the “pre-peak” sub-period (i.e., all times t ≤ T) and Period 2b is the “post-peak” sub-period (t >T). Strictly speaking, Period 1 does not enter into any statistical analysis, as it only serves to provide labeling for the cells that allegedly remain and return and are retained in solid tissues. However, Period 1 will permit definition of CLL cell birth rate and disappearance rate (death and permanent return to solid tissue from blood). An important part of the statistical analysis in Period 2 is characterization of the pattern of LC over time. Patterns will be analyzed both visually and using more formal statistical methods in an exploratory manner. First, the pattern will be smoothed using a cubic spline interpolation (SAS Graph, SAS Institute, Cary, NC). This will facilitate the determination of shape and numbers and patterns of peaks by eliminating “noise” in the data. Second, based on the patterns observed after smoothing, the data will be fit to candidate regression models (e.g., parabolas, mixtures of parabolas, piecewise curves, etc.) and the best fitting model will be identified using common statistical methods such as R^2, Akaike’s information, etc. All curves will be fit on individual subjects, thereby permitting subjects to vary in the pattern of their LC response curves. For example, one possible pattern would be an inverted-U parabola (Figure 1), where LC initially increases (presumably, as previously labeled CLL cells are simultaneously retrieved from solid tissue sanctuaries) and then declines (as the solid tissue sanctuaries have been depleted). Another example would be a mixture of two inverted-U parabolas (Figure 2), whereby there are

	two distinct peaks, suggesting that retrieval of cells from solid tissue may take place at two distinct times. Clearly, many other patterns are possible; however, the most likely candidate patterns are those with some form of initial upward slope, followed by a global peak, followed by a downward slope. In order to monitor study progress and success, interim analyses will be done after the first 5 and the first 10 patients have been labeled and treated for 3 months. At that time, the investigators together with the sponsor will determine whether the data indicate that the objectives of the study can be met, or whether substantial changes to the protocol or data analyses would become necessary. This interim analysis will, however, not place the patient accrual on hold, unless the interim analyses would come to the conclusion that the study needs to be modified.
Harms	At the time of analysis, median follow-up for all patients was 26 months and median treatment duration was 24 months. Twenty-seven of 30 patients (90%) continued on therapy without disease progression, 20 (67%) achieved partial remission, 9 (30%) complete remission, and 1 (3%) had stable disease, yielding an overall response rate (ORR) of 97%. Three patients came off study: one after 186 days due to suicide (ibrutinib-unrelated), and two after 575 and 658 days, respectively, due to toxicity (Grade 3 gastrointestinal hemorrhage and grade 2 joint aches and pains).
Conclusions	The measured average CLL-cell proliferation (“birth”) rate before ibrutinib therapy was 0.39% of the clone per day (range 0.17–1.04%); this decreased to 0.05% per day (range 0-0.36%) with treatment. Death rates of blood CLL cells increased from 0.18% per day (average, range 0–0.7%) prior to treatment to 1.5% per day (range 0–3.0%) during ibrutinib therapy, and were even higher in tissue compartments. This study provides the first direct *in vivo* measurements of ibrutinib’s anti-leukemia actions, demonstrating profound and immediate inhibition of CLL-cell proliferation and promotion of high rates of CLL-cell death.
Trial registration	NCT01752426
Funding	Source of funding

**this item is specific to conference abstracts*