Daring to Believe in a Cure... And Why the Belief is Justified

October 15, 2020
Cancer: An Insidious Disease

Worldwide:
- 14,000,000 New Cases
- 8,100,000 Deaths per year

17 People Die Every Minute

Worldwide:
- 1 Out of 3 People will develop cancer in their lifetime

In the US Alone:
- 1,735,000 Diagnosed
- 610,000 Die per year
Daring to Believe in a Cure, and Why the Belief is Justified

Why is cancer such a hard problem?

How are we doing in the fight against cancer?

Is a cure realistic?
Oldest case of cancer found in Sudan in 2013

Skelton of 25-35 year old male

Laid to rest in 1200 BC

Metastatic cancer throughout his body
The Potential for Cancer in Within Everyone

40% of women age 40-56 have microscopic cancer in their breasts.

50% of men age 50-60 have microscopic cancer in their prostate.

100% of people age 70+ have microscopic cancer in their thyroids.

Given the effectiveness of our immune systems most will never become dangerous “Cancer without Disease”
Cancer Develops When Cancer Cells Corrupts the Immune System to Escape Attack and Create its own Supportive Ecosystem

**Elimination**
Healthy immune systems routinely and effectively eliminating cancer cells and stop the spread of cancer

**Escape**
Cancer occurs when the immune system fails to do its job allowing rouge cells to establish a beach head and promote their own existence at the expense of healthy cells
Cancer Develops Slowly over many Years, Is Often Asymptomatic and not Diagnosed Until very Advanced Stages Making Treatment too Late

Distribution of Lung Cancer Diagnoses by Stage at Diagnosis, 2000-2017
~Half of Patients are Diagnosed with Metastatic Stage III/IV Disease

SEER National Cancer Institute.
How Are We Doing in the 50 Year War on Cancer?
Unequivocal Progress!!

THE OVERALL CANCER DEATH RATE IN THE UNITED STATES FELL BY 20%
Prevention! Lung Cancer

Trends in Tobacco Use and Lung Cancer Death Rates in the U.S.

- Per capita cigarette consumption
- Male lung cancer death rate


Screening, Prevention, Early Detection and Treatment
Decreased Colorectal Cancer Incidence and Mortality Rates

Colorectal test use rates’ for adults aged 50-75 years, Both Sexes, 2000-2018¹

Centers for Disease Control and Prevention, National Center for Health Statistics. National health Interview Survey.

Colorectal Incidence and Mortality²

¹Centers for Disease Control and Prevention, National Center for Health Statistics. National health Interview Survey.
²https://seer.cancer.gov
Screening, Prevention, Early Detection and Treatment in Breast Cancer
Decreased Mortality Rate in the US

Breast Cancer Diagnoses by Stage, Women, US*

Five Year Survival Rate, Women, US†

Trend in Breast Cancer Death Rate, Women, US‡

*SEER Program, National Cancer Institute. Incidence data are from the SEER 9 areas seer.cancer.gov/registries/terms.html
† BreastCancer.Org/symptoms/diagnosis/prognosis
Survival with CML Over Time – The German CML-Study Group Experience 9/2014*

Survival Probability

Year After Diagnosis

HU = hydroxyurea; IFN = interferon; SCT = stem cell transplantation. Survival with chronic myeloid leukaemia (CML) as observed in five consecutive randomised treatment options studies of the German CML Study Group 1983-2014. Kindly authorized by R Hehlmann.

Nov 2019 Analysis of Nilotinib vs Imatinib showed over 40% improvement in molecular response at 10 years**

Newer Therapies Ibrutinib and Venetoclax expected to further change treatment paradigms in CLL

Projected Growth in Prevalence of CML†

Number of Cases

Year

2020

2025

2030

2035

2040

2045

2050

2000

2005

2010

2015

2020

2025

2030

2035

2040

2045

2050

180,000

160,000

140,000

120,000

100,000

80,000

60,000

40,000

20,000

100,000

80,000

60,000

40,000

20,000

10,000

0

Treatment Advances Leverage Successes in Prevention and Detection

In the last 20 years, over 80 targeted therapies have been approved for over 30 cancers.
Unequivocal Progress
Over 2.9 M Cancer Deaths Averted in US in 25 Years From 1990 to 2017
Despite Successes, We Have a Very Long Way to Go
Minimal Progress Against Many Cancers

Based on data from SEER 18 2010-2016. Gray figures represent those who have died from pancreatic cancer. Green figures represent those who have survived 5 years or more.

† SEER 9 Incidence & U.S. Mortality 1975-2014, All Races, Both Sees, Rates are Age Adjusted.

Pancreas Cancer 5 Year Survival in 2016*

New Cases and 5-Year Survival over 40 Years†
AND, Global Cancer Outlook Is Grim

WORLDWIDE CANCER CASES
ARE PROJECTED TO INCREASE BY
50%
FROM 14 million TO 21 million

WORLDWIDE CANCER DEATHS
ARE PROJECTED TO INCREASE BY
60%
FROM 8 million TO 13 million

World Population 1750-2050 (in Billions)†

Global Rise in Aging Population (in Billions)‡

The number of people in the world aged 60 and older is expected to grow past 2 billion by the year 2050.

† World Bank, Development Education Program
‡ Source: United Nations Population Fund
**Unhealthy Lifestyle Changes in Developing Countries**

**Significant Increase in Smokers**

<table>
<thead>
<tr>
<th>Countries with Biggest Reduction in Smokers</th>
<th>Change in millions of smokers, 1980-2012</th>
</tr>
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<tbody>
<tr>
<td>United States</td>
<td>-13.9</td>
</tr>
<tr>
<td>Japan</td>
<td>-9.3</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>-6</td>
</tr>
<tr>
<td>Germany</td>
<td>-3.9</td>
</tr>
<tr>
<td>Canada</td>
<td>-3</td>
</tr>
<tr>
<td>Poland</td>
<td>-2.5</td>
</tr>
<tr>
<td>Italy</td>
<td>-2.2</td>
</tr>
<tr>
<td>Ukraine</td>
<td>-1.9</td>
</tr>
<tr>
<td>Mexico</td>
<td>-1.6</td>
</tr>
<tr>
<td>Sweden</td>
<td>-0.8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Countries with Biggest Increase in Smokers</th>
<th>Change in millions of smokers, 1980-2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>China</td>
<td>99.6</td>
</tr>
<tr>
<td>India</td>
<td></td>
</tr>
<tr>
<td>Indonesia</td>
<td></td>
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<tr>
<td>Bangladesh</td>
<td></td>
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<td>Pakistan</td>
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<td>Turkey</td>
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<td>Philippines</td>
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<tr>
<td>Egypt</td>
<td></td>
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<tr>
<td>Vietnam</td>
<td></td>
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<tr>
<td>Brazil</td>
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</tbody>
</table>
Incredible Acceleration in Advances Over Just Last 20 Years!

Three Pillars of Cancer Therapy Since Advent of Chemotherapy in 1940:
- Surgery
- Radiation
- Chemotherapy

Pace of Ongoing Innovation is Critical to Tackling the Global Challenges Ahead
Immunotherapy Has Transformed the Treatment of Many Cancers, Advances From 2010+ Will Drive Progress for the next 25+ Years

New drug 'doubles survival rates for lung cancer patients' by helping the body detect and attack tumour cells
- New study shows immunotherapy could be better than chemotherapy
- Early results show it could double survival rates for common lung cancer
- Drug works by interfering with a protein that is found on tumour cells
- Itreactivates the ability of the immune system to detect and kill disease

By LIZZIE PARRY FOR MAILONLINE

2018 Nobel Prize in Medicine
1500 Trials now underway
Annual revenue >$7B

Long-term survival rates double for melanoma patients getting immunotherapy

By Laurie McGinley April 17, 2016 Email the author
The Power of Harnessing the Immune System!
Checkpoint Inhibitors Can Generate an Effective Anti-Tumor Immune Response in Some Patients Across a Broad Range of Cancers


- NSCLC
- Gastric
- Liver
- Head and neck
- Bladder
- Kidney
- Breast (TN)
- Ovarian
- Melanoma
- CRC MSI hi
- Breast HR+
- CRC non-MSI hi
- Prostate
- NSCLC (EGFR Mu, ALK+)

Patients Responsive to PD-1/PD-L1 Inhibitors (~1 M patients)
But an Effective Immune Response is Not Generated in Most Patients

Growing Evidence that BOTH ‘Enabling’ Effectors and ‘Suppressing’ Suppressors Are Necessary to Generate Clinically Meaningful Immune Responses

Estimation of the Percentage of US Patients With Cancer Who Are Eligible for and Respond to Checkpoint Inhibitor Immunotherapy Drugs (2011-2018)

- As of 2019, only 13% of US cancer patients are eligible to receive and are likely to respond to Checkpoint inhibitor therapy (CPI)
- Characteristics of responders vs non-responders MUST be identified to develop better treatment options for the 87% not currently benefitting from CPI

Analysis based on 6 approved checkpoint inhibitors in 14 approved indications between 2011 and 2018
Why Aren’t Checkpoint Inhibitors Effective in More Patients?
Tumor Associated Macrophages/MDSCs Supress Anti-Tumor T Cell Immune Responses

"Pro-tumor (M2) Macrophages/MDSCs Supressed T cells"

- Macrophage mediated suppression of T Cells reduces expansion and activated of T Cells and dampens \( \gamma \)-IFN Mediated Immune Response

- Results in “Cold” Tumor Microenvironment characterized by low levels of tumor PDL1 expression and less responsiveness to checkpoint inhibitor therapy

Post Platinum Metastatic Bladder Cancer Patients with Low PDL1 Expression Levels Do Not Respond As Well to Checkpoint Inhibitors

Notes:
From Biomarkers of Immunotherapy in urothelial and renal cell carcinoma: PD-L1, tumor mutational burden, and beyond
Assays used for Atezo: SP142 (Ventana); assay used for Nivo: 28-8 (Dako); assay used for Durval: SP263 (Ventana) and assay used for Avel: 73-10 (Dako)
## CheckMate 275: Opdivo Patient Benefit According to PDL1 Status in 2L Platinum-Treated mUC Patients

<table>
<thead>
<tr>
<th></th>
<th>ORR</th>
<th>DCR</th>
<th>Median OS (mo.)</th>
<th>Median PFS (mo.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All (n=270)</td>
<td>21% (16-26)</td>
<td>41% (36-48)</td>
<td>8.6 (6.1–11.3)</td>
<td>1.94 [1.87, 2.33]</td>
</tr>
<tr>
<td>PDL1 ≥1%</td>
<td>26% (18-34)</td>
<td>52% (42-61%)</td>
<td>11.9 (9.1–19.1)</td>
<td>3.45 [1.91, 3.71]</td>
</tr>
<tr>
<td>PDL1 &lt;1%</td>
<td>16% (11-23%)</td>
<td>33% (25-41%)</td>
<td>6.0 (4.4–8.1)</td>
<td>1.87 [1.74, 2.00]</td>
</tr>
</tbody>
</table>

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**Invigor210: Atezolizumab in Platinum-treated mUC Overall survival according to PD-L1 status**
How to Address the Problem Pro-Tumor Macrophages Suppressing Immune Responses and Limiting the Effectiveness of Checkpoint Inhibitors

- Macrophage mediated suppression of T Cells reduces expansion and activated of T Cells and dampens \( \gamma \)-IFN Mediated Immune Response

- PI3K-\( \gamma \) signaling plays a key role in programming macrophages to the pro-tumor M2 phenotype driving the immunosuppressive function of these cells\(^1\)

- Targeting PI3K-\( \gamma \) in myeloid cells shown to re-program macrophages; relieving suppression, activating T cells, generating an immune response that can then be enhanced by checkpoint inhibitors\(^1\)

New Discoveries on The Role of PI3K-γ in Programming Macrophages

LETTER

PI3K-γ is a molecular switch that controls immune suppression

Megan M. Kanesha, Karen S. Messer1,2, Natacha Ratulairina1, Hongying Li1,2, Glyngwri W. Nolley, Abraham V. Nguyen1, Camila C. Ferrerdo3, Philippe Fontaine, David G. Weikler4, Matthew Rausch4, Vito J. Palombett5, Jeffery Kufok6, Ki-Min Kwon7, Roman Szepek8, Ezra E. W. Cohen1,9 & Judith A. Varner1,9,10

Macrophages play critical, but opposite, roles in acute and chronic inflammation and cancer1–3. In response to pathogens or injury, inflammatory macrophages express cytokines that stimulate cytotoxic T cells, whereas macrophages in neoplastic and parasitic diseases express anti-inflammatory cytokines that induce immune suppression and may promote resistance to T cell checkpoint inhibitors1–7. Here we show that macrophage PI 3-kinase-γ controls a critical switch between immune stimulation and suppression during inflammation and cancer. PI3K-γ signalling through Akt and mTOR inhibits NFkB activation while stimulating C/EBPα activation, thereby inducing a transcriptional program that promotes immune suppression during inflammation and tumour growth. By contrast, selective inactivation of macrophage PI3K-γ stimulates and reloaxes)

Recent clinical trials using immunotherapy have demonstrated its potential to control cancer by downregulating the immune system. Immune checkpoint blocking (ICB) antibodies against cytotoxic-T-lymphocyte-associated protein 4 or programmed cell death protein 1/programmed death-ligand 1 have displayed durable clinical responses in various cancers4. Although these new immunotherapies have had a notable effect on cancer treatment, multiple mechanisms of immune resistance exist in tumours. Among the key mechanisms, myeloid cells have a major role in limiting effective tumour immunoactivity5–4. Growing evidence suggests that high infiltration of immune-suppressive myeloid cells correlates with poor prognosis and ICB resistance5–6. These observations

 nature
 doi:10.1038/nature19834

Overcoming resistance to checkpoint blockade therapy by targeting PI3K-γ in myeloid cells

Olivier De Hena1, Matthew Rausch2, David Winkler2, Luis Fidel Campesarato1, Cadien Liu3, Daniel Hirschhorn-Cymerman4, Sadia Budu4, Armanda Ghos1,5,6, Melina Pink7, Jeremy T. Tsuchida2, Mark Douglas8, Thomas Tibbitts9, Sujata Sharma1, Jennifer Proctor2, Nicole Kosmider2, Kerry White1, Howard Stern3, John Soglia3, Julian Adams3, Vito J. Palombetta5, Karen McGovern6, Jeffery L. Kufok6, Jed D. Wolchol6,7 & Tahar Mergoub8

but contain more activated CD8+ T cells (Fig. 1d, c). Additionally, CD8+ T cells express more granzyme B in the B16-F10 model. They also express higher levels of PD-1 and CTLA4 (Fig. 1c, data not shown), which might explain their sensitivity to ICB. Furthermore, myeloid cells from 4T1 tumours or spleens suppress proliferation of T cells to a greater extent compared to myeloid cells from B16-F10 models (Fig. 1d and Extended Data Fig. 1b). These data suggest that TAMs have varying phenotypes and are more suppressive in ICB-resistant tumours. Tumour-derived soluble factors such as granulocyte-macrophage colony-stimulating factor (GM-CSF) help shape the tumour microenvironment by promoting myelopoiesis and recruitment of suppressive myeloid cells10–13. To directly assess the ability
PI3K-γ Inhibition Reprograms Macrophages, Turning Tumor MicroEnvironment (TME) from “Cold” To “Hot”

1. Eganelisib Inhibition of PI3K γ Re-programs Pro-tumor (M2) Macrophages/MDSCs to Anti-Tumor (M1) Function

2. Relieves Macrophage Suppression, Expands Activated T Cells and Generates γ-IFN Mediated Immune Response

3. Up-Regulates PDL1 to Blunt T Cell Response

4. Enhances Response to CPI, Overcomes CPI Resistance
1. Eganelisib Inhibition of PI3K-γ Re-programs Pro-tumor (M2) Macrophages/MDSCs to Anti-Tumor (M1) Function Which:

- Decrease in Blood Myeloid-Derived Suppressor Cells (N=15)
- Relieves Macrophage Suppression of T Cells
- Expands Activated T Cells and Generates γ-IFN Mediated Immune Response

C=cycle (28 days), D=days; Sullivan et al., ASCO 2018.
2. Eganelisib Reduces Macrophage Suppression, Expands Activated T Cells and Generates \( \gamma \)-IFN Mediated Immune Response Which:

3. Upregulates PDL1 Expression, Increasing Importance of Check Point Inhibitors to Enhance Responses

<table>
<thead>
<tr>
<th>IFN-( \gamma ) - responsive genes</th>
<th>Fold increase at C2D1</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD274 (PDL1)</td>
<td>2.4</td>
<td>3.5 \times 10^{-5}</td>
</tr>
<tr>
<td>FCGR1B</td>
<td>1.8</td>
<td>1.5 \times 10^{-3}</td>
</tr>
<tr>
<td>GBP2</td>
<td>1.5</td>
<td>5.6 \times 10^{-4}</td>
</tr>
<tr>
<td>GBP5</td>
<td>2.3</td>
<td>1.3 \times 10^{-4}</td>
</tr>
<tr>
<td>GBP1</td>
<td>2.0</td>
<td>1.9 \times 10^{-4}</td>
</tr>
<tr>
<td>GBP4</td>
<td>1.7</td>
<td>9.4 \times 10^{-4}</td>
</tr>
</tbody>
</table>

The above interferon-\( \gamma \)-responsive genes were among the top 30 most significantly differentially expressed genes.

RNA Seq peripheral blood across all dose levels

Hong et al., SITC 2017.
3. Eganelisib Mediated Relief of Immune Suppression Activates an Immune Response Which:

4. Enhances Responses to Checkpoint inhibitors, Overcomes CPI Resistance

- Patient A: 71 yo male with stage I BRAF WT Melanoma
  - Single lung metastasis after 3 doses of Opdivo, continued on nivolumab therapy
  - Subsequent progression with new lung and liver lesions
- Extensive disease in lungs and liver at study start
- Normalization of LDH 528 → 211 (ULN 256) and PR (-40% tumor reduction of target lesions) observed at C7D1
- Remains on study after > 8 months with confirmed PR as best response
4. Eganelisib Overcomes Resistance to Checkpoint Inhibitors, On-Mechanism Activity

Melanoma Patient A progressing with new liver and lung lesions after 3 Opdivo cycles

Eganelisib Macrophage Re-programming Relieves Macrophage Suppression of T Cells

Expands Activated T Cells

Generates γ-IFN Mediated Immune Response

High levels of immunosuppressive M2 macrophages (CD163+ in purple) and adjacent cytotoxic T cells (CD8+ in yellow) in tumor observed at baseline.
MARIO-275: Global, Randomized, Blinded Trial of Eganelisib in mUC

Designed to Show Benefit of Adding Eganelisib to Improve Outcomes for Patients Currently Underserved by Standard of Care

Advanced Platinum Refractory 2nd Line Urothelial Cancer Patients

- Incl/excl criteria per CheckMate-275
- MDSC all comers (stratified)
- PDL1 status all comers (non-stratified)

Primary objective: ORR in MDSC High

Secondary objectives: DOR, PFS, OS, ORR in Total population + MDSC subset

CheckMate-275: ORR 20.7%, mPFS 1.9 months mOS (8.6 months)

Tremendous Opportunity to Take Immuno-Oncology Therapy to the Next Level

• Studies Must Identify Those Patients Most/Less Likely to Benefit, and to Experience Side Effects, From Specific Therapies
  – Tumor Biopsies and Translational Medicine Are Essential

• The Evolutionary Nature of Cancer and the Heterogeneity of Tumors Increases this Challenge

• There is a Significant Effort Across Academia and Industry to Identify Accurate, Predictive Biomarkers to Meet This Challenge

• Outputs from Genomics, Transcriptomics, Proteomics, Metabolomics, as well as Exploring Discreet Blood Niches and Circulating Tumor Cells, Will Be Extremely In Realizing the Full Value of Immuno-Oncology and Increasing the Effectiveness of Drug Development
Dramatic Scientific and Medical Advances Are Further Leveraging the Bodies Immune System to Win the Evolutionary Battle Against Cancer

• Vaccines
  – Two vaccines approved Provenge (prostate) and Imlygic (melanoma) and many more in development

• Gene Editing: Addressing the Root Cause of Diseases Caused by Mutations in Our DNA and Repairing Broken Genes: Multiple Gene Editing Programs in Clinical Studies

• Cell Therapy
  – CAR-T (Chimeric Antigen Receptor T-cells): Using Your own Cells to Identify Cancer and Activate a T Cell Response
  – First Induced Pluripotent Stem Cells Derived Therapies for ‘Off the Shelf’ Delivery of T Cell and NK Therapies to Large Number of Patients Now in Clinical Studies

Source: Editas Medicine Website
Incredible Acceleration in Advances Over Just Last 20 Years! Pace of Ongoing Innovation is Critical to Tackling the Global Challenges Ahead

- Vaccines
- Immunotherapy
- Targeted Drugs
- Gene Editing
- Cell Therapy
- Radiation
- Chemotherapy
- Surgery
Daring to Believe in a Cure, and Why the Belief is Justified

- **Why is cancer such a hard problem?**
  *Very complex, evolutionary problem*

- **How are we doing in the fight against cancer?**
  *Unequivocal progress…. with a long way to go!*

- **Is a cure realistic?**
  *Absolutely! Enabled by unprecedented technological advances*
Daring to Believe and Committed to Finding a Cure for all!