# Clinical Trials:
# From idea to practice change

**BRENDON STILES, MD**
**PROFESSOR, CHIEF OF THORACIC SURGERY AND SURGICAL ONCOLOGY**
**MONTEFIORE HEALTH SYSTEM – ALBERT EINSTEIN COLLEGE OF MEDICINE**


Montefiore Einstein
Cancer Center

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Consulting/advisory fees: AstraZeneca, Pfizer, Genentech, Bristol Myers Squibb, Galvanize Therapeutics, Flame Biosciences

Research support:  BMS Foundation, BMS, Mark Foundation for Cancer Research

Board:  Lung Cancer Research Foundation (pharma support)

# How I do it?

I asked those who *have* changed practice.

*“Would you be able to share what you think are some of the most important things for surgeons to consider when designing or running a clinical trial?”*

# David Jones

- **Significance:** Important problem or critical barrier? Strong scientific premise? Will it change the field?
- **Investigators:** Investigators well suited w/ appropriate experience and training? Complementary or integrated experience? Governance?
- **Innovation:** Novel approach and/or methodology?
- **Approach:** Are strategy, methodology, and analyses well reasoned and appropriate? Robust and unbiased approach?
- **Environment:** Institutional, financial, and statistical support?

**1999**
-ACOSOG Z0030
(1999-2004)

# Valerie Rusch

- Make sure question worth asking (large trials take lots of time and money, make sure it will have major impact)
- Make sure you know literature (fundamental principle)
- Interface with biostatistician early (too long of a wait for results may render trial irrelevant)
- Ask clear questions with clean endpoints.  Keep it simple.
- Don’t overestimate ability to accrue patients (lots of physicians express enthusiasm, but reality is often harder)
- Always include meaningful secondary endpoints (especially tissue correlatives)
- Give appropriate credit (biostatisticians, scientific thought leaders, lead accruers)
- From inception think multidisciplinary, multidisciplinary, multidisciplinary

**2006**
SWOG 9416
(2007)

# Nasser Altorki

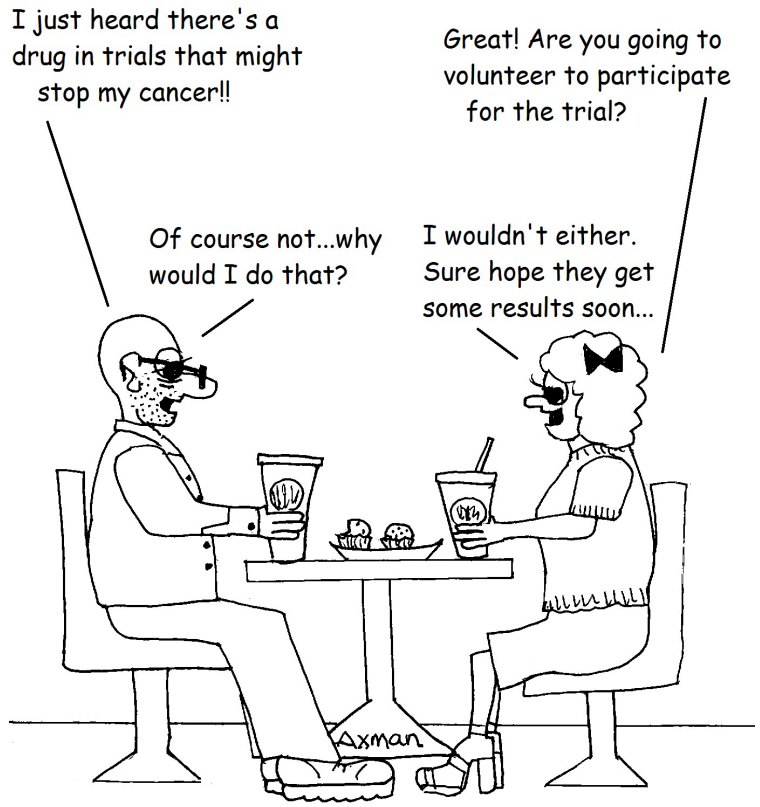
- Understand basic trial design
- Testable hypothesis with good rationale
- Close work with biostatistician to adequately power primary outcome
- Resources for data collection in real time and study coordinators to monitor compliance and ensure follow-up and documentation
- Money, “more than you think”

- *“CALGB 140503 took 2 years to design and activate, 10 years to accrue, and 7 years of follow-up”*

**2007**
CALGB 140503
(2007-2017)
RADIANT (2007-2010)
MAGRIT (2007-2012)

# Common themes

- Ask important questions
- Understand and pay attention to methodology
- Design with clean and realistic endpoints
- Build in secondary and correlative endpoints that are meaningful
- Ensure adequate financial and human resources
- Take a multidisciplinary approach
- *Make it easy and appealing for patients*



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# Thoracic surgeons can't do it alone

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Overall Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC

S.J. Antonia, A. Villegas, D. Daniel, D. Vicente, S. Murakami, R. Hui, T. Kurata, A. Chiappori, K.H. Lee, M. de Wit, B.C. Cho, M. Bourhaba, X. Quantin, T. Tokito, T. Mekhail, D. Planchard, Y.-C. Kim, C.S. Karapetis, S. Hiret, G. Ostoros, K. Kubota, J.E. Gray, L. Paz-Ares, J. de Castro Carpeño, C. Faivre-Finn, M. Reck, J. Vansteenkiste, D.R. Spigel, C. Wadsworth, G. Melillo, M. Taboada, P.A. Dennis, and M. Özgüroğlu, for the PACIFIC Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 29, 2020 VOL. 383 NO. 18

## Osimertinib in Resected *EGFR*-Mutated Non–Small-Cell Lung Cancer

Yi-Long Wu, M.D., Masahiro Tsuboi, M.D., Jie He, M.D., Thomas John, Ph.D., Christian Grohe, M.D., Margarita Majem, M.D., Jonathan W. Goldman, M.D., Konstantin Laktionov, Ph.D., Sang-We Kim, M.D., Ph.D., Terufumi Kato, M.D., Huu-Vinh Vu, M.D., Ph.D., Shun Lu, M.D., Kye-Young Lee, M.D., Ph.D., Charuwan Akewanlop, M.D., Chong-Jen Yu, M.D., Ph.D., Filippo de Marinis, M.D., Laura Bonanno, M.D., Manuel Domine, M.D., Ph.D., Frances A. Shepherd, M.D., Lingmin Zeng, Ph.D., Rachel Hodge, M.Sc., Ajlan Atasoy, M.D., Yuri Rukazenkov, M.D., Ph.D., and Roy S. Herbst, M.D., Ph.D., for the ADAURA Investigators*

## Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB–IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase 3 trial

*Enriqueta Felip, Nasser Altorki, Caicun Zhou, Tibor Csőszi, Ihor Vynnychenko, Oleksandr Goloborodko, Alexander Luft, Andrey Akopov, Alex Martinez-Marti, Hirotsugu Kenmotsu, Yuh-Min Chen, Antonio Chella, Shunichi Sugawara, David Voong, Fan Wu, Jing Yi, Yu Deng, Mark McCleland, Elizabeth Bennett, Barbara Gitlitz, Heather Wakelee, for the IMpower010 Investigators**

AACR American Association for Cancer Research



## Nivolumab + platinum-doublet chemotherapy vs chemotherapy as neoadjuvant treatment for resectable (IB-IIIA) non-small cell lung cancer in the phase 3 CheckMate 816 trial

Patrick M. Forde,[1] Jonathan Spicer,[2] Shun Lu,[3] Mariano Provencio,[4] Tetsuya Mitsudomi,[5] Mark M. Awad,[6] Enriqueta Felip,[7] Stephen Broderick,[1] Julie Brahmer,[1] Scott J. Swanson,[6] Keith Kerr,[8] Changli Wang,[9] Gene B. Saylors,[10] Fumihiro Tanaka,[11] Hiroyuki Ito,[12] Ke-Neng Chen,[13] Cecile Dorange,[14] Junliang Cai,[14] Joseph Fiore,[14] Nicolas Girard[15]

[1]Johns Hopkins Kimmel Cancer Center, Baltimore, MD, USA; [2]McGill University Health Center, Montreal, Québec, Canada; [3]Shanghai Chest Hospital, Shanghai, China; [4]Hospital Universitario Puerta de Hierro, Madrid, Spain; [5]Kindai University Faculty of Medicine, Ohno-Higashi, Osaka-Sayama, Japan; [6]Dana-Farber Cancer Institute, Boston, MA, USA; [7]Vall d'Hebron Institute of Oncology, Barcelona, Spain; [8]Aberdeen Royal Infirmary, Aberdeen, UK; [9]Tianjin Lung Cancer Center, Tianjin Medical University Cancer Institute and Hospital, Tianjin, China; [10]Charleston Oncology, Charleston, SC, USA; [11]University of Occupational and Environmental Health, Kitakyushu, Japan; [12]Kanagawa Cancer Center, Yokohama, Japan; [13]Peking University School of Oncology, Beijing Cancer Hospital, Beijing, China; [14]Bristol Myers Squibb, Princeton, NJ, USA; [15]Institut du Thorax Curie-Montsouris, Institut Curie, Paris, France

*Presentation Number CT003*

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# Cooperative group or industry?

- 259 physicians surveyed
- 77% in participated in co-op led and 88% in pharma-led clinical research
- Preferred participating in both (49%), pharma only (22%), or co-op only (11%)
- Co-op considered more prestigious to lead (86%) and less likely to imply COI (59%)
- But…not financially sustainable (69%) and slower to accrue (85%)
- Pharma trials perceived to have better compensation (61%) and superior efficacy (48%)

Journal of Clinical Oncology > List of Issues > Volume 39, Issue 15_suppl >

Meeting Abstract | 2021 ASCO Annual Meeting I

CARE DELIVERY AND REGULATORY POLICY

Cooperative group and pharmaceutical sponsored clinical trials: Perceptions of U.S. community oncologists.



Richard Scott Swain, Marjorie E. Zettler, Yolaine Jeune-Smith, Bruce A. Feinberg, Ajeet Gajra

Show Less

Cardinal Health, Dublin, OH

**But…45% of NCTN trials are practice influential at a cost of $16.6 million/PI trial -Unger JM et al, *JAMA Network Open*, 2019;2(9):e1910593**

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# Surgeons working with industry

- Advisory boards
  - Trial specific
  - Multidisciplinary care
  - Biomarker testing
  - Lung cancer screening
  - Surgical quality
- Satellite symposium
  - Genentech, AstraZeneca, Medtronic
- AATS “Think Tanks” and other society collaborations
  - Surgeon’s role in preparing the patient for upcoming treatment and surgical plan
  - Decision for surgery, surgical approach, and extent of resection
  - Role of surgeon beyond surgery
  - Early diagnosis and screening

# When planning a trial:  Read the tea leaves

- Things are moving so fast, you must look ahead
- What is coming next and why is it important?
- Is there forthcoming data that will amplify (or negate) your trial?
- What are the critical endpoints?
- Focus on patient selection and recruitment

# One piece of advice: Pay attention to twitter

**H. Jack West, MD** @JackWestMD · Mar 5

Replying to @StephenVLiu

Here, DFS & pCR benefit, assoc'd w/OS diff in other settings, plus magnitude of diff. I'm satisfied w/DFS in IMpower010 for high PD-L1. My concern re: DFS on ADAURA is based on ongoing Rx making no pretense of eradicating disease. In **CM816** & IM-010, DFS is long after end of Rx.

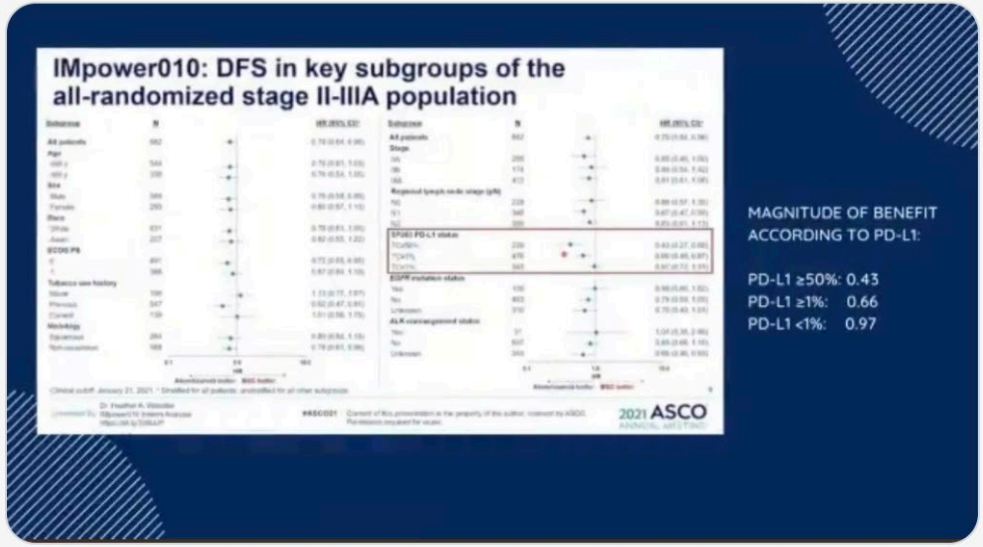
**Jonathan Spicer MD PhD** @DoctorJSpicer · 10h

The #thoracicsurgery community is aware of this and it's important for centres to share and publish their outcomes. **CM816** however demonstrates a high degree of safety related to surgery for these stages of disease - cf forthcoming manuscript. Look at 30- and 90-day EFS outcomes...

> **H. Jack West, MD** @JackWestMD · 10h
>
> Replying to @DoctorJSpicer
>
> Fair. But TBH, I think we must acknowledge painfully variable (i.e., often low) quality of lung surgery (at least in US). So often not done by thoracic surgeons specifically, quality measures are humbling. W/lung surgery so skill/volume dependent, IMO we need to be wary of this.

**Sandip Patel MD** @PatelOncology · Mar 5

And if PD-L1 neg (& EGFRwt) only opportunity to use aPD(L)1 immunotherapy is with **CM816**, as IMP010 approved for >1% with efficacy driven particularly by >50%. So **CM816** could be preferred for PD-L1 neg (though need to see data, other neoadjuvant IO had benefit even in PD-L1 neg)




**Balazs Halmos** @DrSteveMartin · Dec 11, 2021

Replying to @n8pennell @BrendonStilesMD and 8 others

But - IO synergy with concurrent chemo seems really highlighted by **CM816**, no? Analogous to benefit w chemoIO in st 4

I personally think we will favor it for

➡️the higher the T
➡️the higher the N
➡️the lower the TPS

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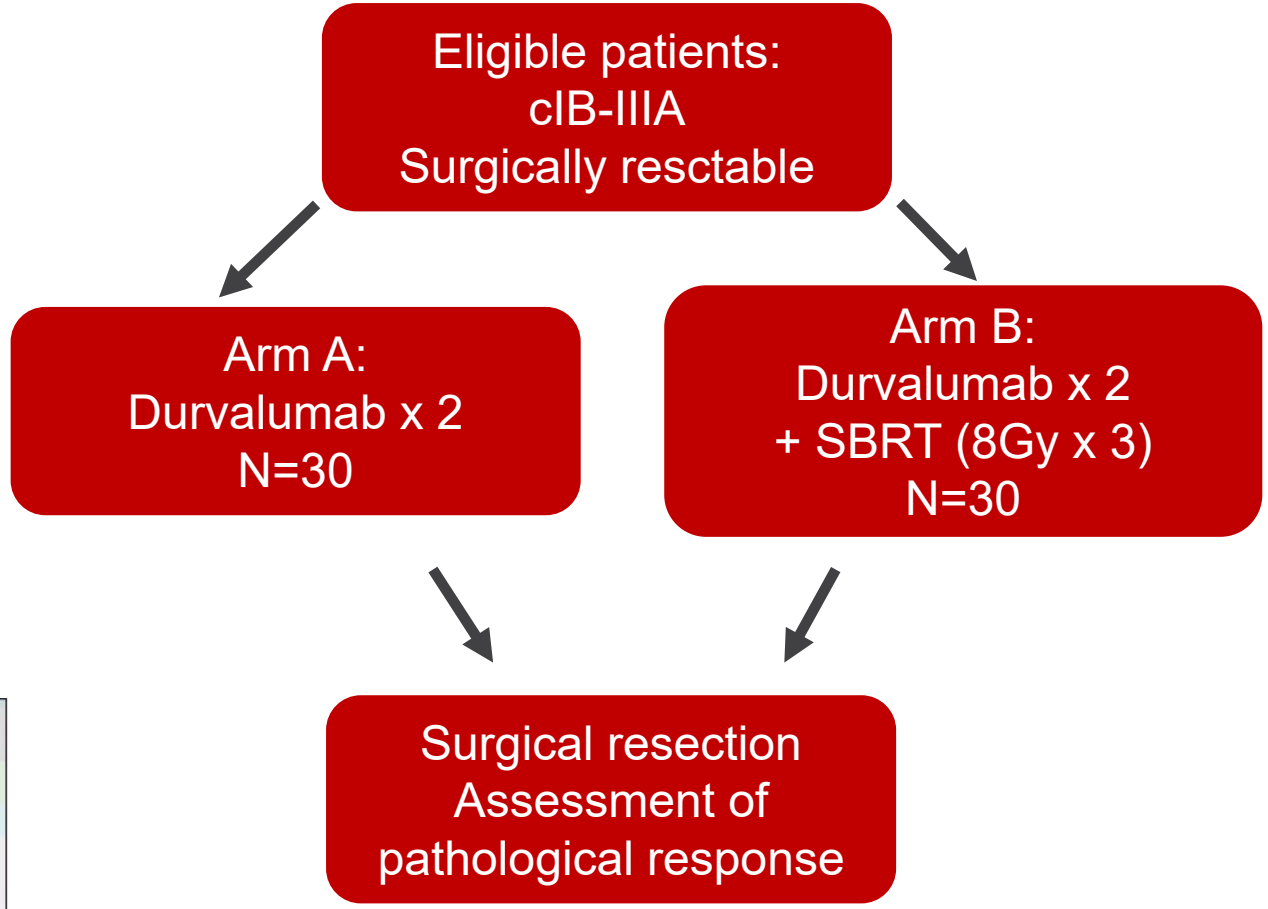
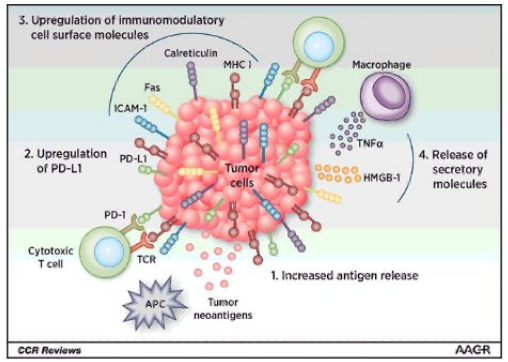
# Design a trial that meets the current needs and leverages translational opportunities and local expertise

**Weill Cornell Investigator- initiated neoadjuvant trial (NCT02904954) MEDI4736 2016-2020**




**Non-ablative SBRT to activate tumor immune responses**




Ko, Clin Can Research, 2018

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# Neoadjuvant durvalumab with or without stereotactic body radiotherapy in patients with early-stage non-small-cell lung cancer: a single-centre, randomised phase 2 trial

*Nasser K Altorki, Timothy E McGraw, Alain C Borczuk, Ashish Saxena, Jeffrey L Port, Brendon M Stiles, Benjamin E Lee, Nicholas J Sanfilippo, Ronald J Scheff, Bradley B Pua, James F Gruden, Paul J Christos, Cathy Spinelli, Joyce Gakuria, Manik Uppal, Bhavneet Binder, Olivier Elemento, Karla V Ballman, Silvia C Formenti*

Lancet Oncol 2021

Published Online May 17, 2021 https://doi.org/10.1016/S1470-2045(21)00149-2

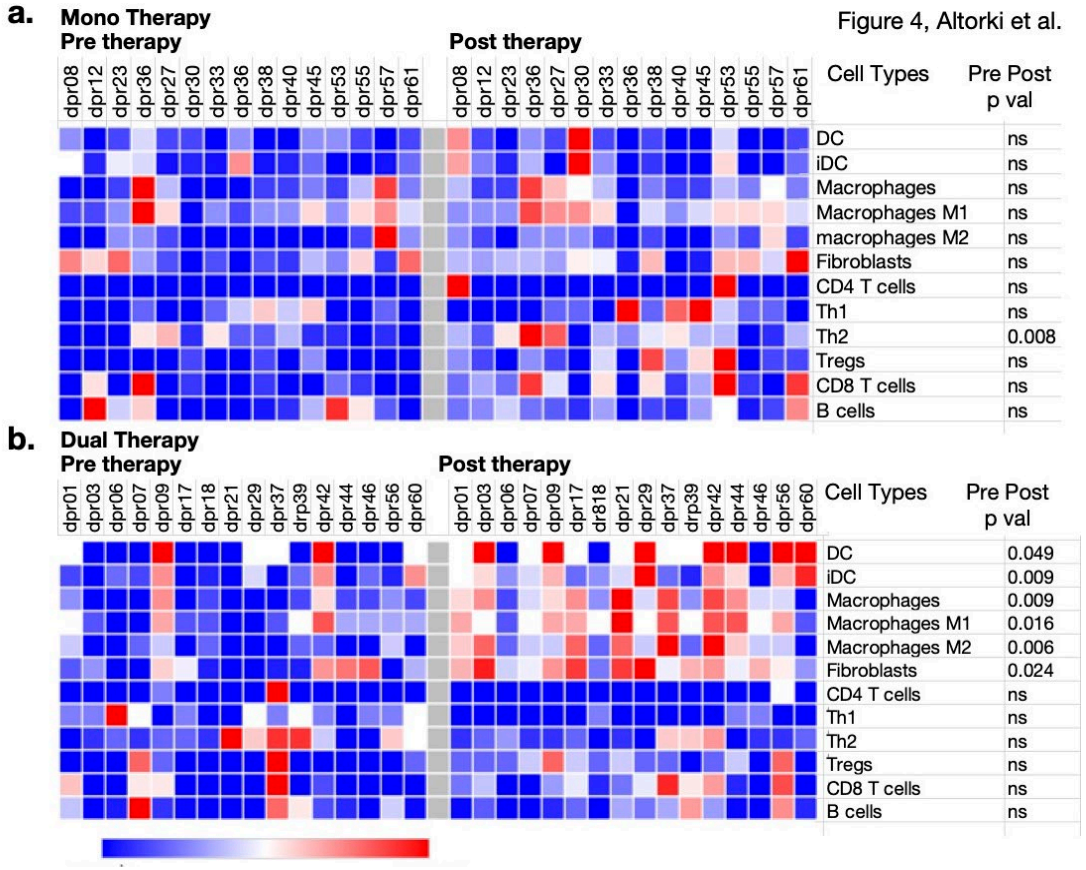


Figure 4, Altorki et al.

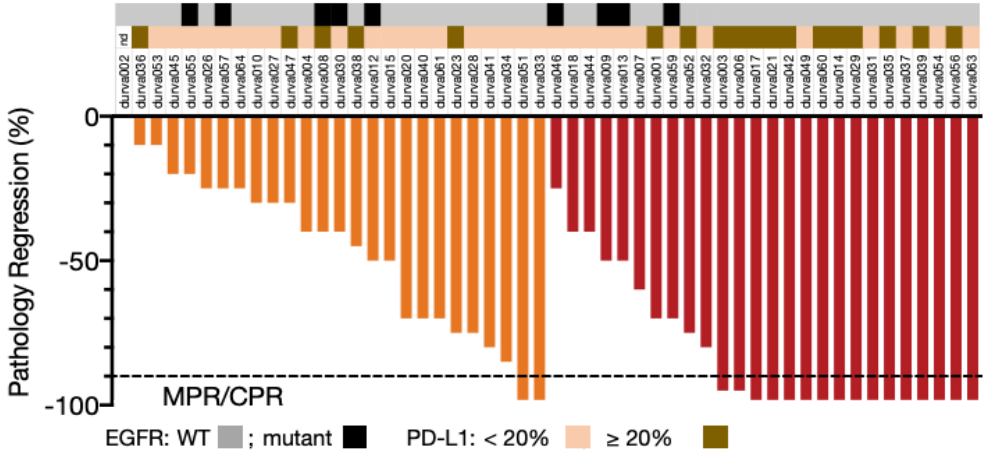


*Figure 2.* **Waterfall plot of pathology regression.** Pathology regression was determined as the negative of 100 minus the residual tumor percentage. Difference between arms for response, measured by MPR/CPR, was p <0.0001, Fisher's exact test. Mono therapy arm n = 26 and dual therapy arm n = 26. EGFR status and percent PD-L1 positive cancer cells are noted.

| | Major pathological response | Complete pathological response |
|---|---|---|
| Durvalumab monotherapy (n=30) | 2 (6.7%) | 0 |
| Durvalumab + SBRT (n=30) | 16 (53.3%) | 8 (26.7%) |

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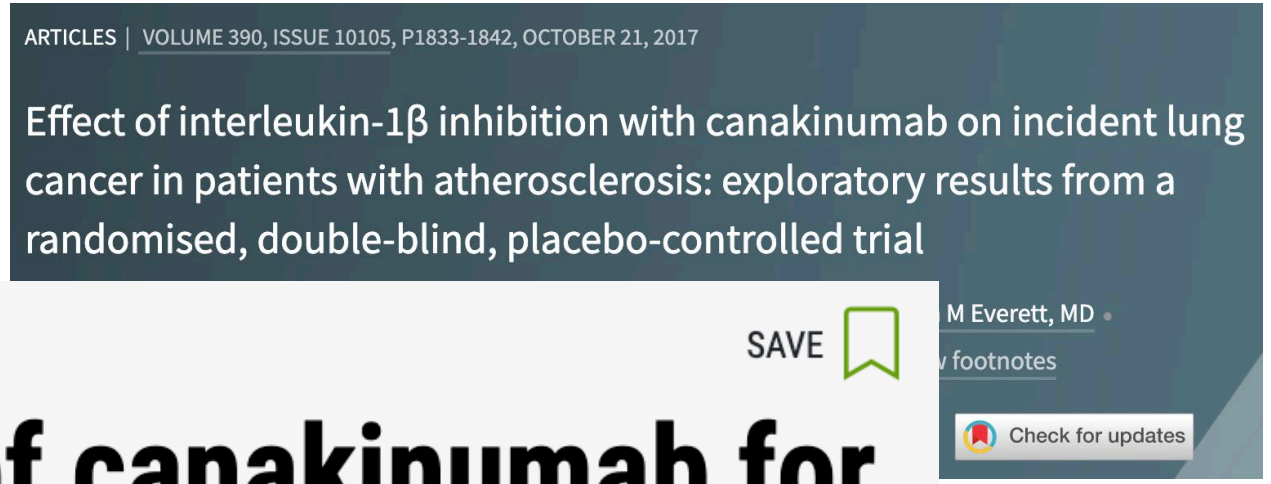
# My Montefiore-Einstein Cancer Center experience: A “brilliant” plan…

- IL-1B inhibitor
- Shown to decrease lung cancer incidence and death in patients with cardiac di
- Extensive
- Flame Bic follower” c
- More pote population
- Great adv Paul Bunn, Paul Ridker
- Translational interest
- Lots of work….




October 26, 2021 | 1 min read SAVE

**Phase 3 trial of canakinumab for lung cancer misses primary endpoints**

e NSCLC

A randomized, open-label, Phase II study of canakinumab or pembrolizumab as monotherapy or in combination as neoadjuvant therapy in adult patients with resectable non-small cell lung cancer (NSCLC) (CANOPY-N)[1,2]



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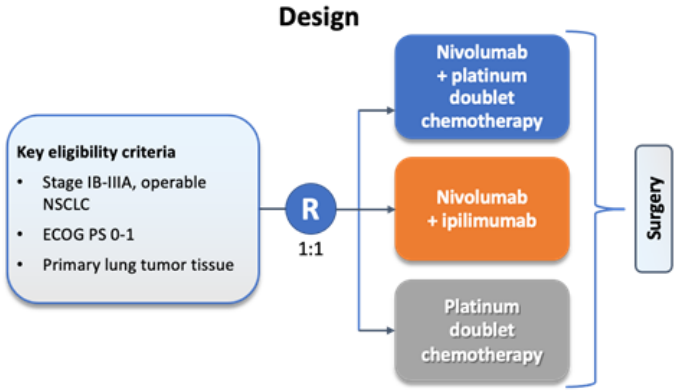
# Second take: Neoadjuvant chemo-IO and CM 816 trial

## CheckMate -816: Design and Baseline Characteristics[1]



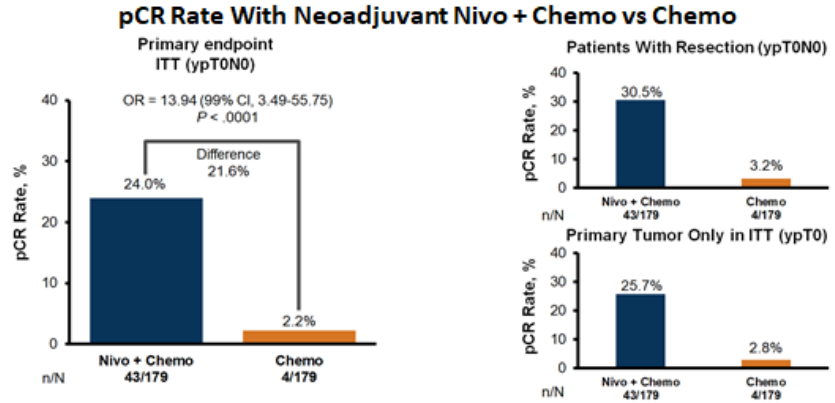

**Primary outcome measures**
- EFS (time frame: up to 69 mo)
- pCR (time frame: at the time of surgery)

**Secondary outcome measures**
- OS, MPR, TTDM

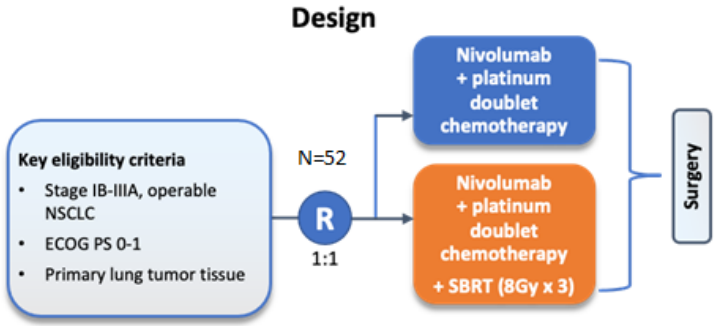
1. Forde PM et al. American Association for Cancer Research Annual Meeting 2021 (AACR 2021). Abstract CT003.

## CheckMate -816: pCR Rate (Primary Endpoint)[1]

- The addition of nivo to chemo increased pCR from 2.2% with chemo alone to 24% with chemo + nivo ($P < .0001$)
- pCR was assessed by central pathologists who were blinded to trial arms




## Proposed Montefiore-Einstein Investigator Initiated Trial
## PIs: Brendon Stiles, Balazs Halmos, Nitin Ohri




**Primary outcome measures**
- pCR (time frame: at the time of surgery)
- Assume >55% with addition of SBRT

**Secondary outcome measures**
- EFS, DFS, MPR, Pathologic downstaging of biopsy confirmed lymph nodes, OS, clearance of ctDNA

**Translational endpoints:**
-ctDNA clearance
-Whole tumor RNAseq pre- and post treatment
-Immune phenotype pre- and post-treatment

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# MECC IIT (BMS): Neoadjuvant Chemo + Nivo +/- low dose SBRT

- Built on backbone of CheckMate 816
- Remarkably multidisciplinary approach with buy-in from medical oncology and radiation oncology
- Focuses on quick endpoint currently of interest: pCR
- Rationale scientific design to meet endpoint
- Excellent opportunity for translational science

Bristol Myers Squibb

news.bms.com

U.S. Food and Drug Administration Approves Opdivo® (niv...

Approval marks the first-and-only immunotherapy-based treatment for use before surgery for non-small cell lung ...


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# Another focus:
# Compelling need for diversity in clinical trials

FDA STATEMENT

## FDA Offers Guidance to Enhance Diversity in Clinical Trials, Encourage Inclusivity in Medical Product Development

Share | Tweet | Email

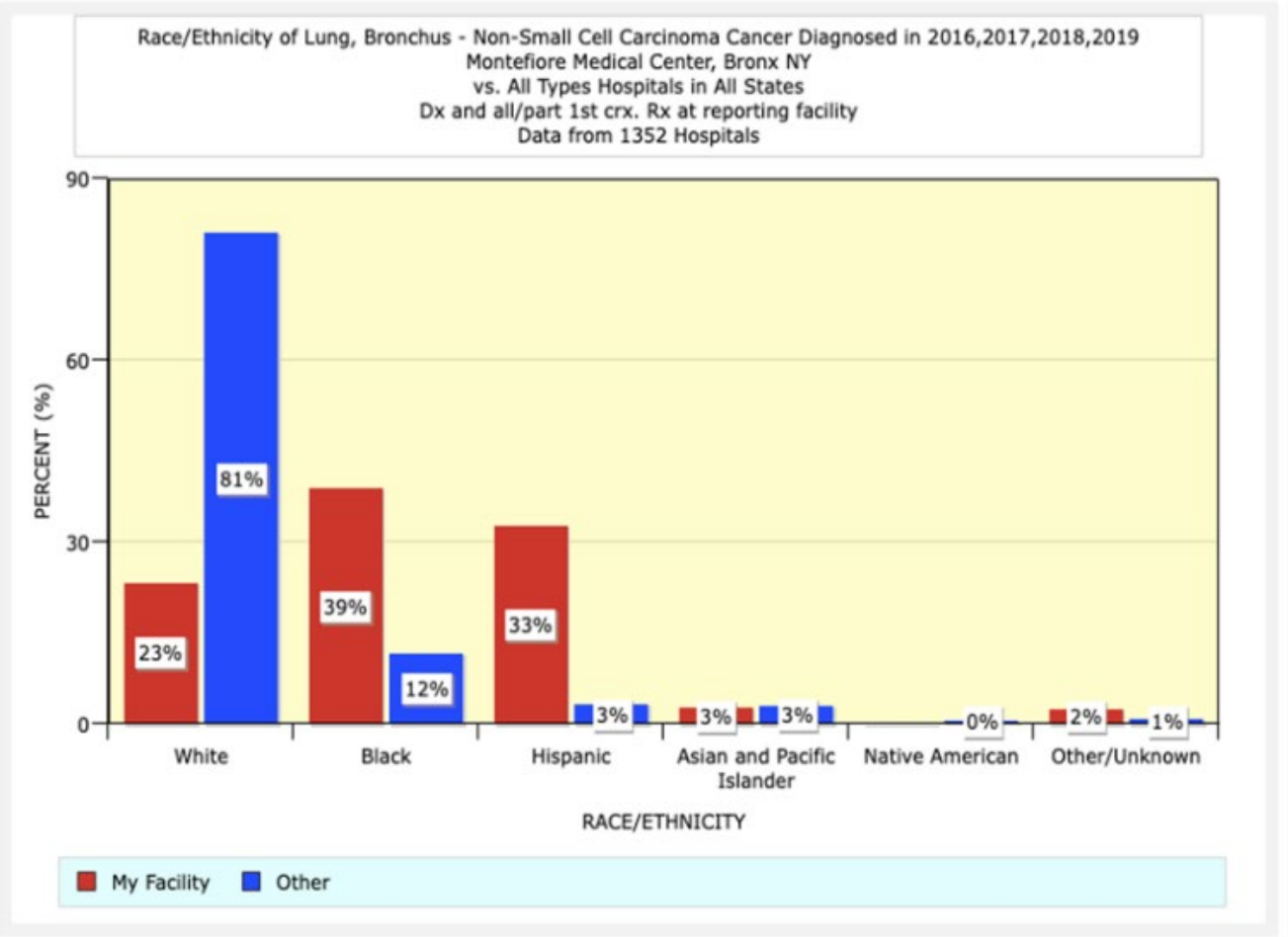
**For Immediate Release:**

November 09, 2020

## Making cancer research more inclusive

*John D. Carpten, Lola Fashoyin-Aje, Levi A. Garraway and Robert Winn*

We have been aware for some time that cancer research, from careers to clinical trials, is not as inclusive as it should be. The Black Lives Matter movement and protests against racism have emphasized that the time has come to stop talking about the lack of diversity, health inequities and structural racism in cancer research and instead work towards solutions. In that spirit, and on the basis of a virtual discussion during the American Association for Cancer Research 2020 Annual Meeting, we asked several scientists actively working to increase representation of Black American populations in cancer research how they are addressing these issues.

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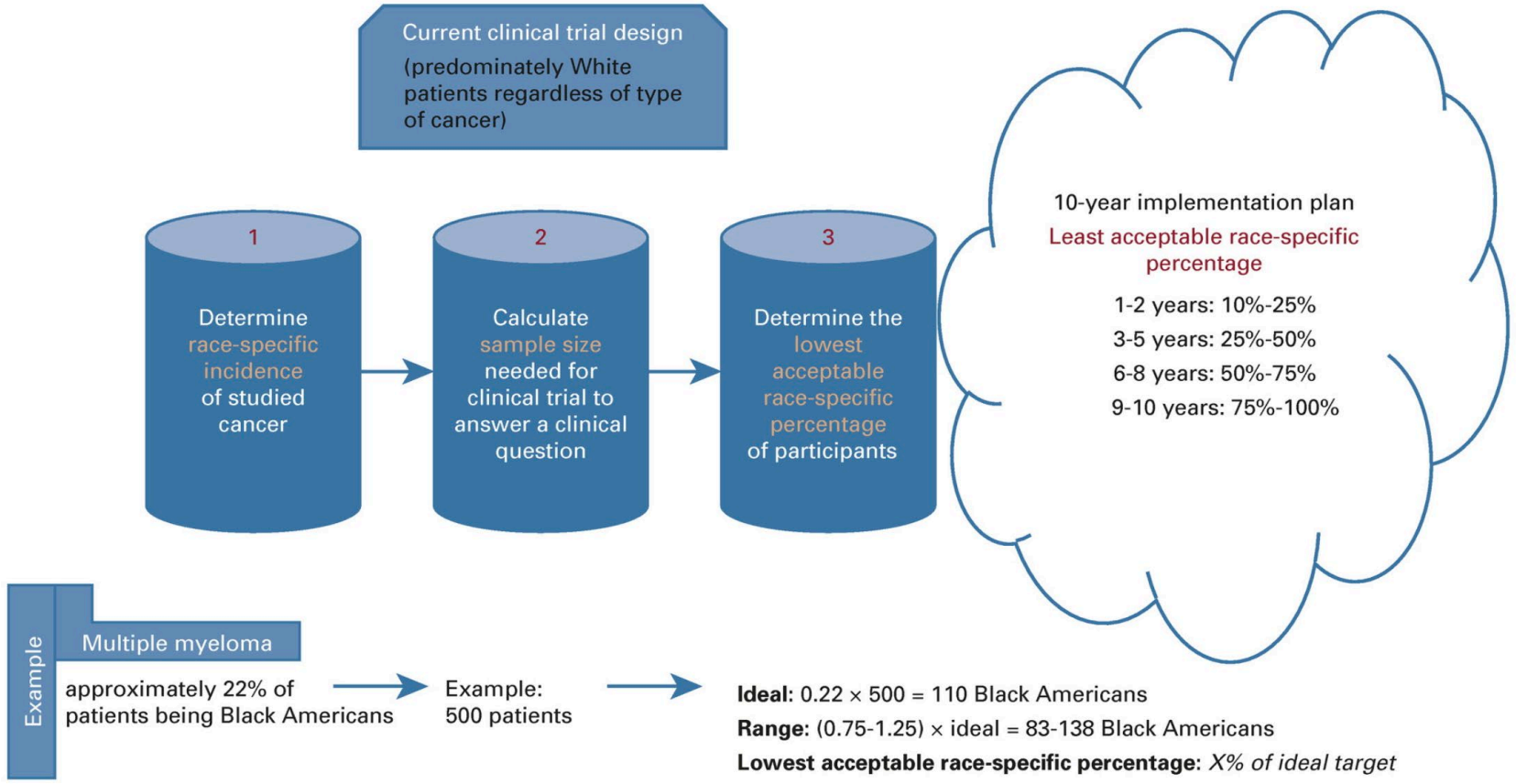
SPECIAL SERIES: DISPARITIES IN CANCER CARE FOR BLACK PEOPLE IN THE UNITED STATES

# Participation of Black Americans in Cancer Clinical Trials: Current Challenges and Proposed Solutions

Muhammad Awidi, MD[1] and Samer Al Hadidi, MD, MS[2]

JCO Oncol Pract 17:265-271. © 2021 by American Society of Clinical Oncology

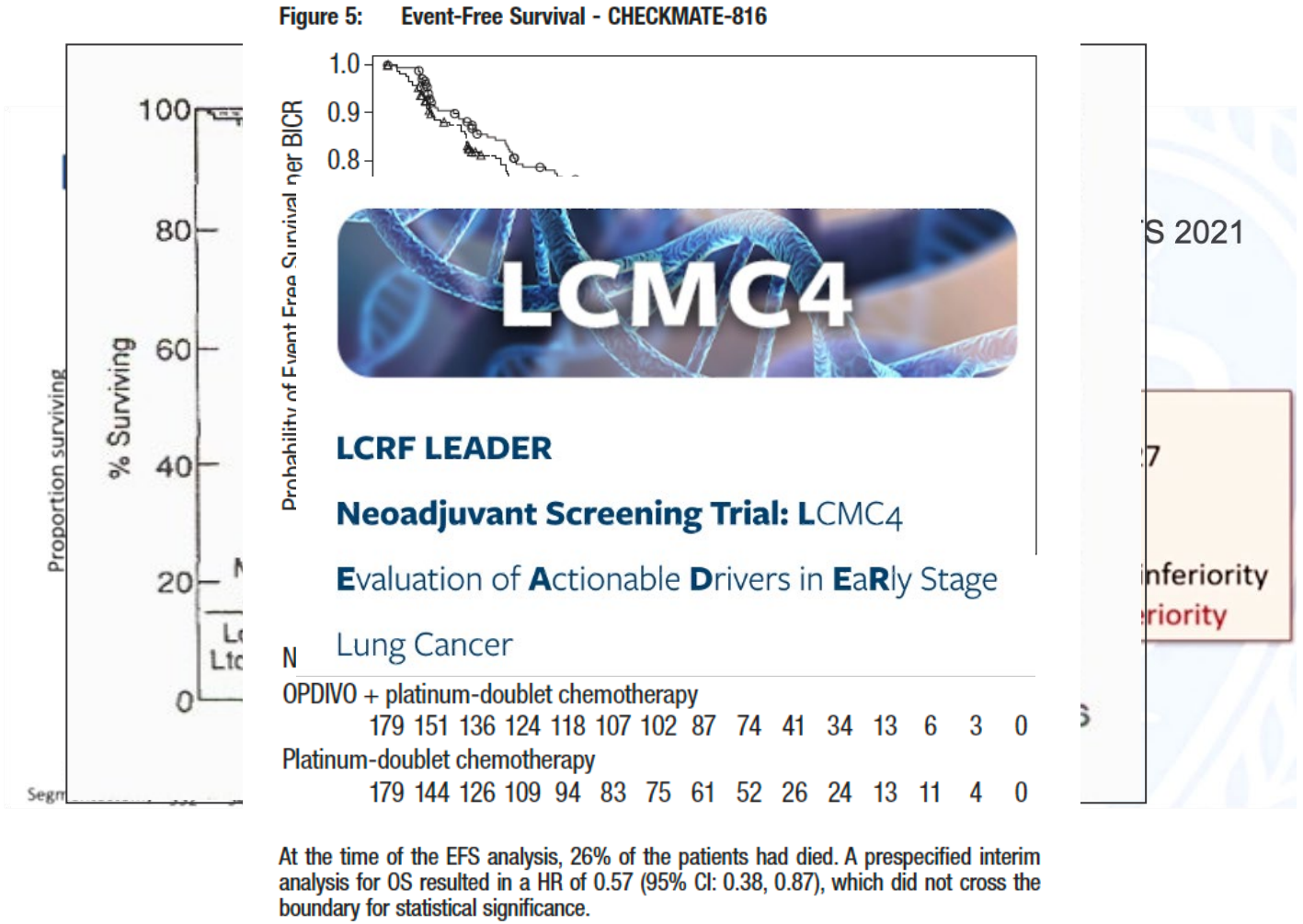


# Trial opportunities:
# Play to my institutional strengths (or weaknesses)

- Underserved populations
- Locally advanced disease:  Neoadjuvant therapy
- High rate of incidental nodule patients lost to follow up
  - Neel Chudgar (Lungevity award)
  - Cluster randomized trial of management strategies:  Proportion of patients with follow up, % of lung cancers diagnosed among IPNs, stage at diagnosis
- High rate of patients with chronic pain, substance abuse, or poor pulmonary function
  - Marc Vimolratana
  - Post operative cryotherapy vs. Standard ERAS
  - Randomized trial with morphine equivalents as primary endpoint and secondary endpoints including postop complications, LOS, readmission

# In conclusion: Practice changing trials on the horizon

- JCOG 0802
- CALGB 140503
- VALOR
- CheckMate 816
- LCRF Leader



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# Key take away messages

- Clinical trial planning is complex
- Industry partnerships are useful
- Critical to assemble the right team and to develop a deliberate and thoughtful strategy
- Know the field, but take some risks
- Recruit diverse patient populations
- Find your niche

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