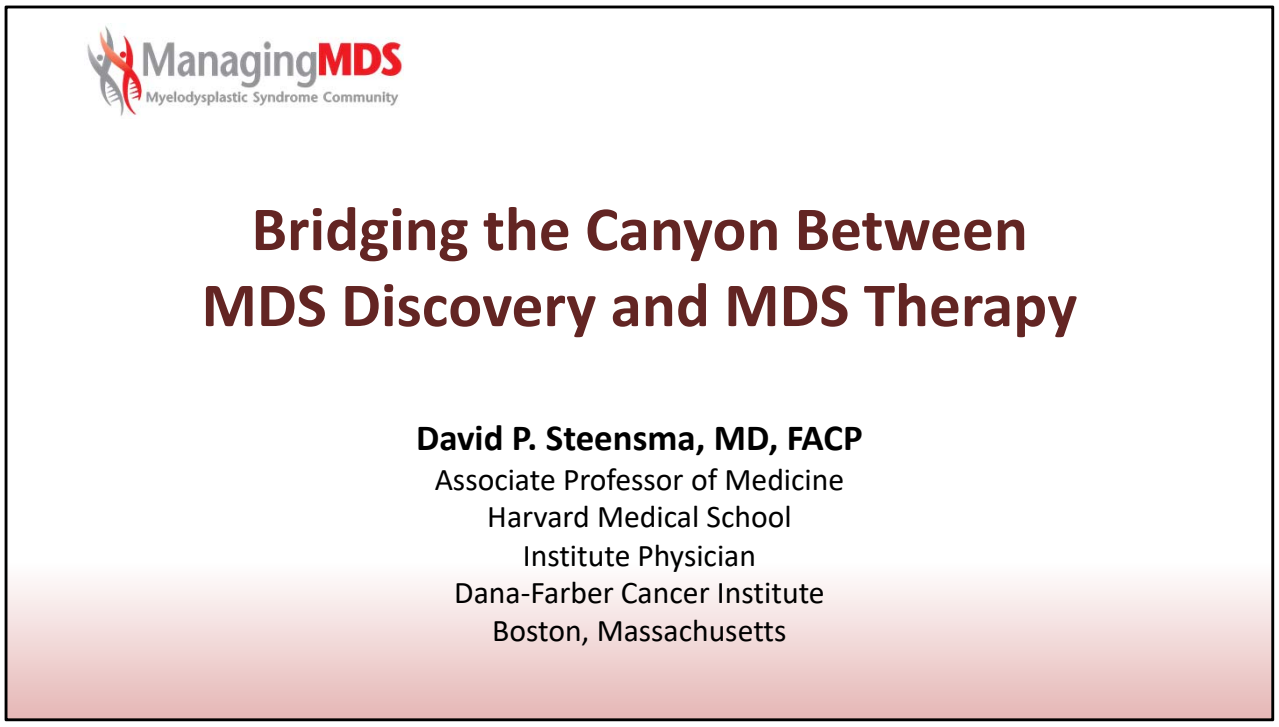
Bridging the Canyon Between MDS Discovery and MDS Therapy



Hello, I am David Steensma from the Dana-Farber Cancer Institute and Harvard Medical School in Boston, and I would like to speak with you today about bridging the canyon between myelodysplastic syndromes discovery and MDS therapy. This is a distillation of a presentation I recently gave at the MDS Foundation International Symposium in Copenhagen, Denmark in May of 2019.

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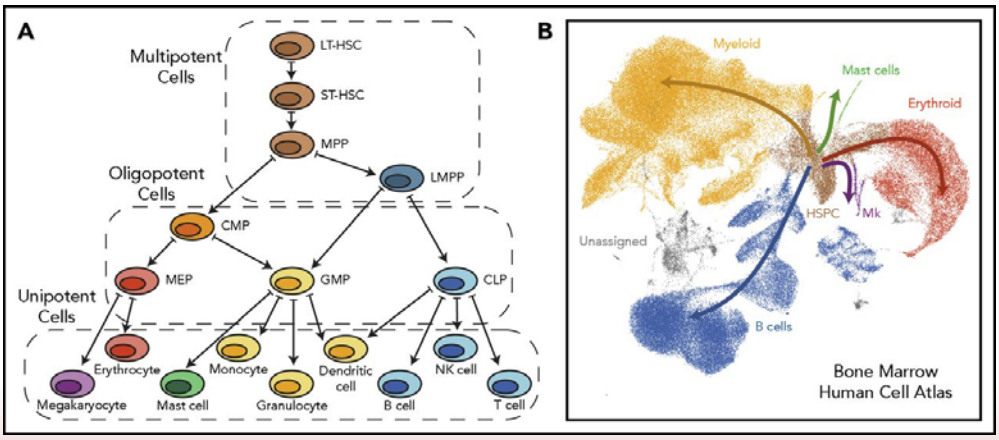
Comparison of a Hematopoietic Tree Diagram with a Single-cell Transcriptomic Landscape



Dimensionality reduction projection (UMAP algorithm) of marrow mononuclear cell single-cell transcriptomes

Watcham S, et al. *Blood*. 2019;133(13):1415-1426.

There have been tremendous advances in our understanding of hematopoiesis and of the biology of myelodysplastic syndromes specifically, and of hematologic disorders more generally. We can now do single cell analysis, and this has led to tremendous insights into how cells diversify and differentiate during hematopoiesis and how that goes wrong in various disease states.

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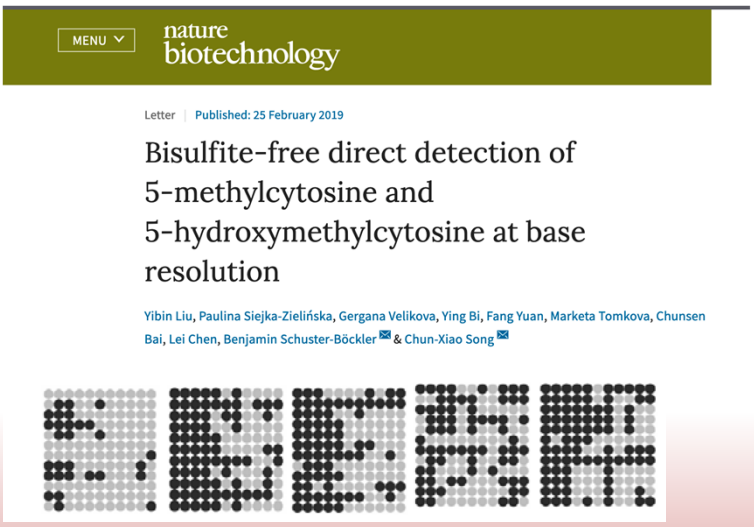
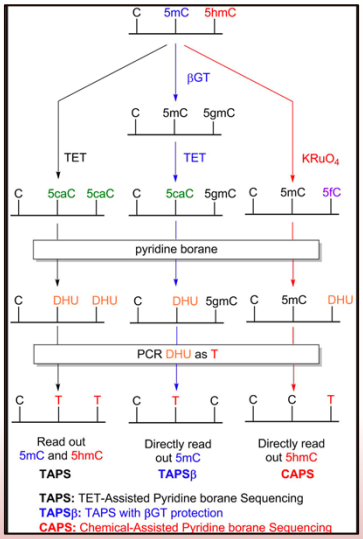
TET-assisted Pyridine Borane Sequencing (TAPS)





We can now do epigenetic and assessment without destroying the sample the way that it had to be done for many years with bisulfite sequencing.

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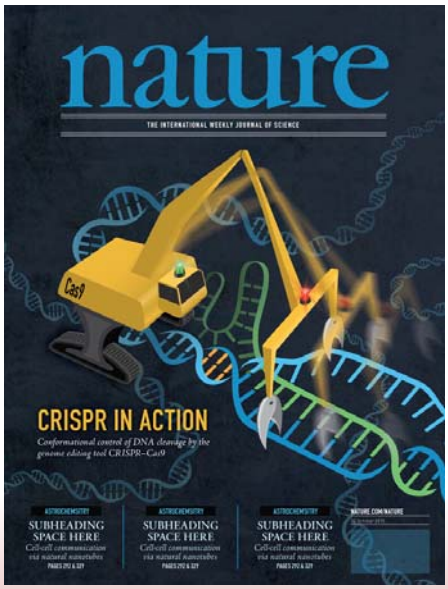

Using techniques such as the CRISPR-Cas9 system and other novel gene editing techniques we can gain better understanding of disease biology at the cellular and organismal level, and this has been a tremendous advance in the biotechnology tools.

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BROAD INSTITUTE

There are huge chemical libraries that can be used to screen for molecules that do what we want them to do and not what we do not want them to do, such as this large library at the Broad Institute across town here in Cambridge, Massachusetts and these libraries can then be the starting point for developing novel drugs.

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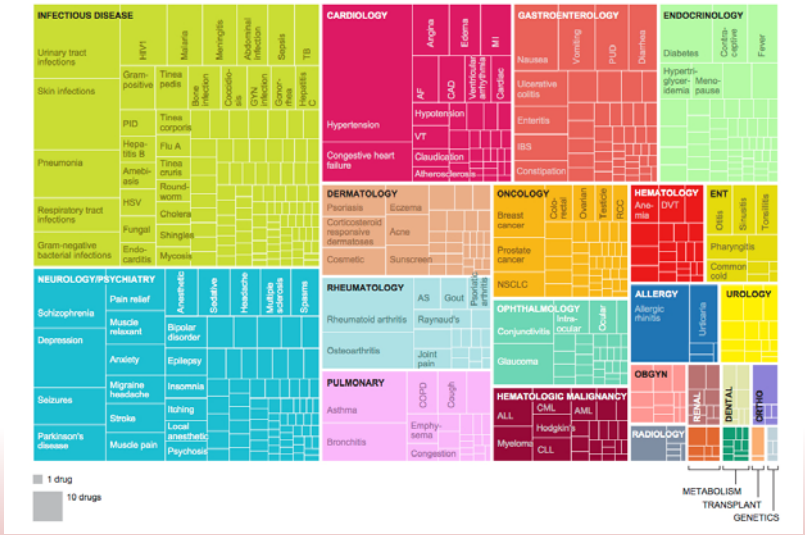
Broad Institute "Drug Repurposing Hub"



Corsello SM, et al. *Nat Med.* 2017;23(4):405-408.

There is also the possibility to use libraries to repurpose drugs to look at drugs that had been FDA approved for other indications and see if they might have a role in hematologic malignancies such as MDS.

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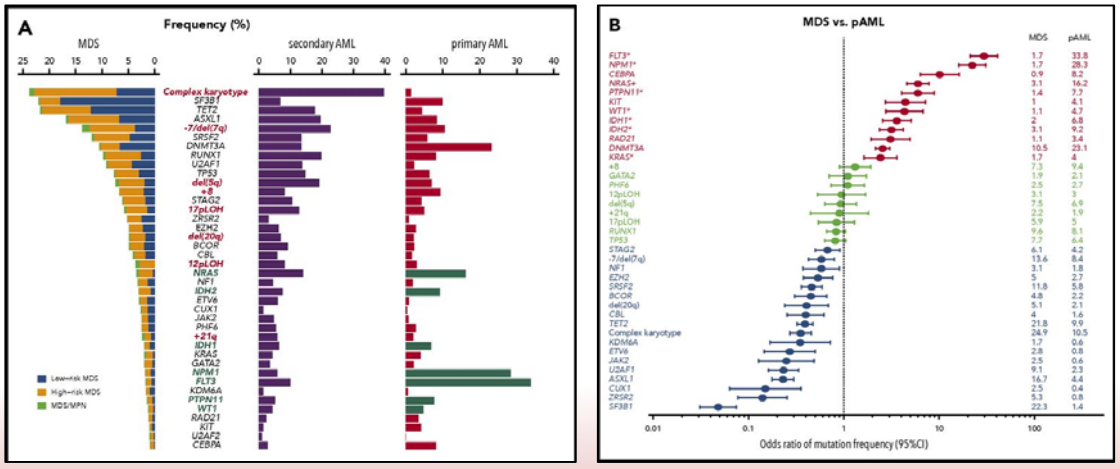
Common Putative Driver Alterations in MDS and Related Myeloid Neoplasms



1988: *NRAS/KRAS;* 1991: *TP53;* 2000: *RUNX1;* 2002: *ATRX*

Ogawa S, et al. *Blood.* 2019;133:1049-1059.

In 2002 we only knew about five different gene mutations in MDS with the advent of next-generation sequencing, we now know about more than 40,

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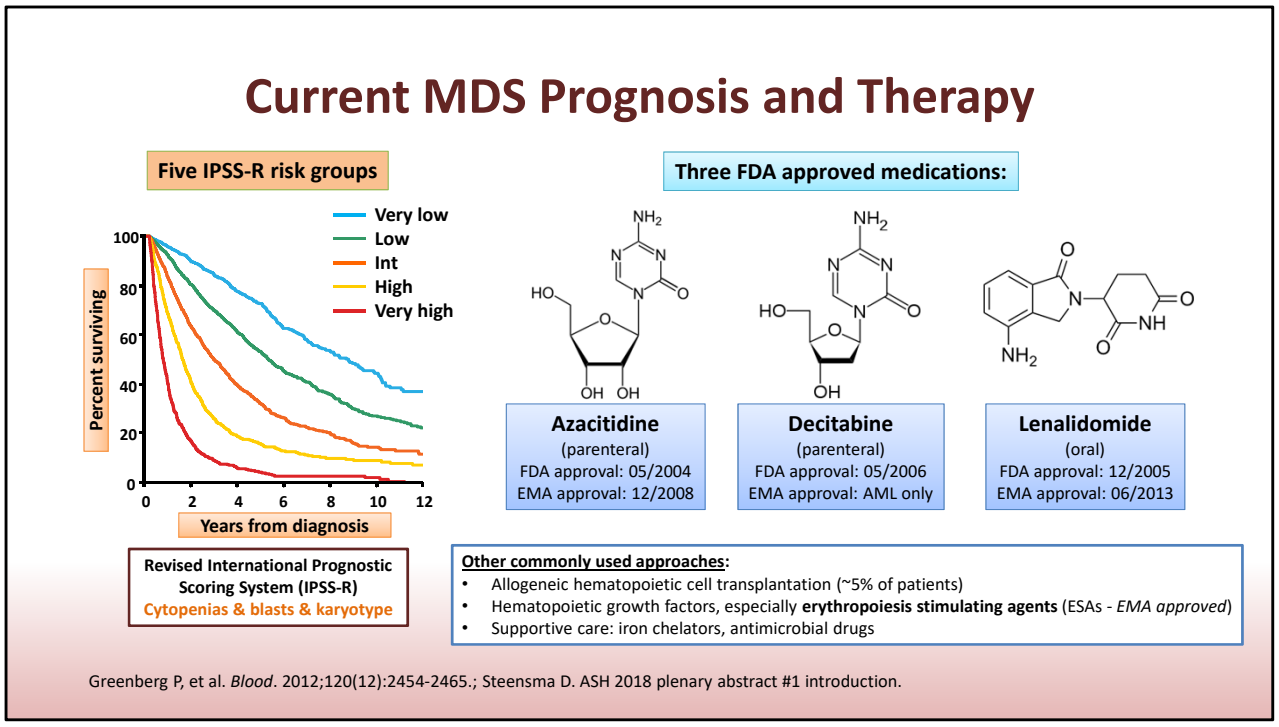

and yet we are still using quite ancient technology, chromosome assessment and blood counts for risk stratification of patients, and we have only three medications with an FDA approval: azacitidine, which was approved in 2004, decitabine in 2006, and lenalidomide in 2005.

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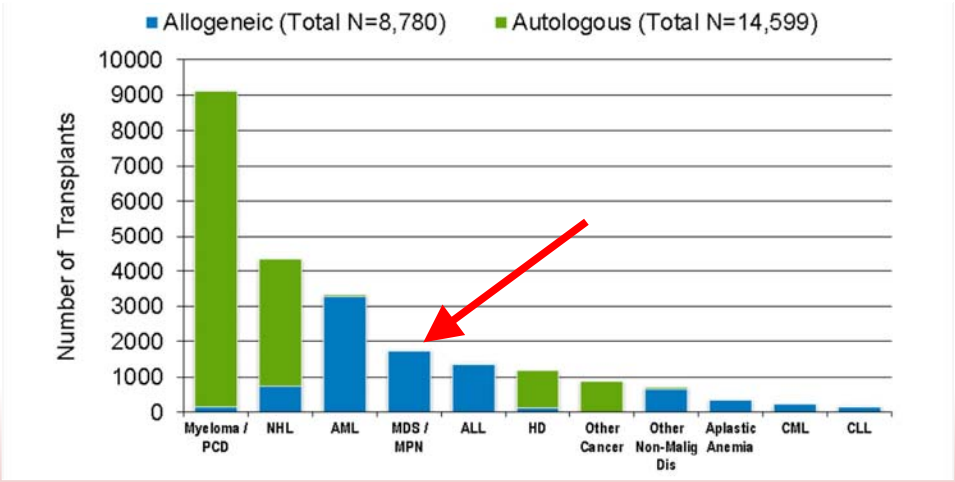
Indications for Hemopoietic Cell Transplant in the US in 2017



CIBMTR, downloaded May 2019.

The only potentially curative approach for MDS is allogeneic hematopoietic cell transplantation which is performed in only about 5% of patients. The most common used drug for MDS is erythropoiesis stimulating agents (ESAs) which had been with us since the 1980s but were only very recently approved for MDS in Europe and have not been approved by the FDA for MDS specifically. Most patients therefore are treated with supportive care with transfusion and antibiotics if they get infected and so on.

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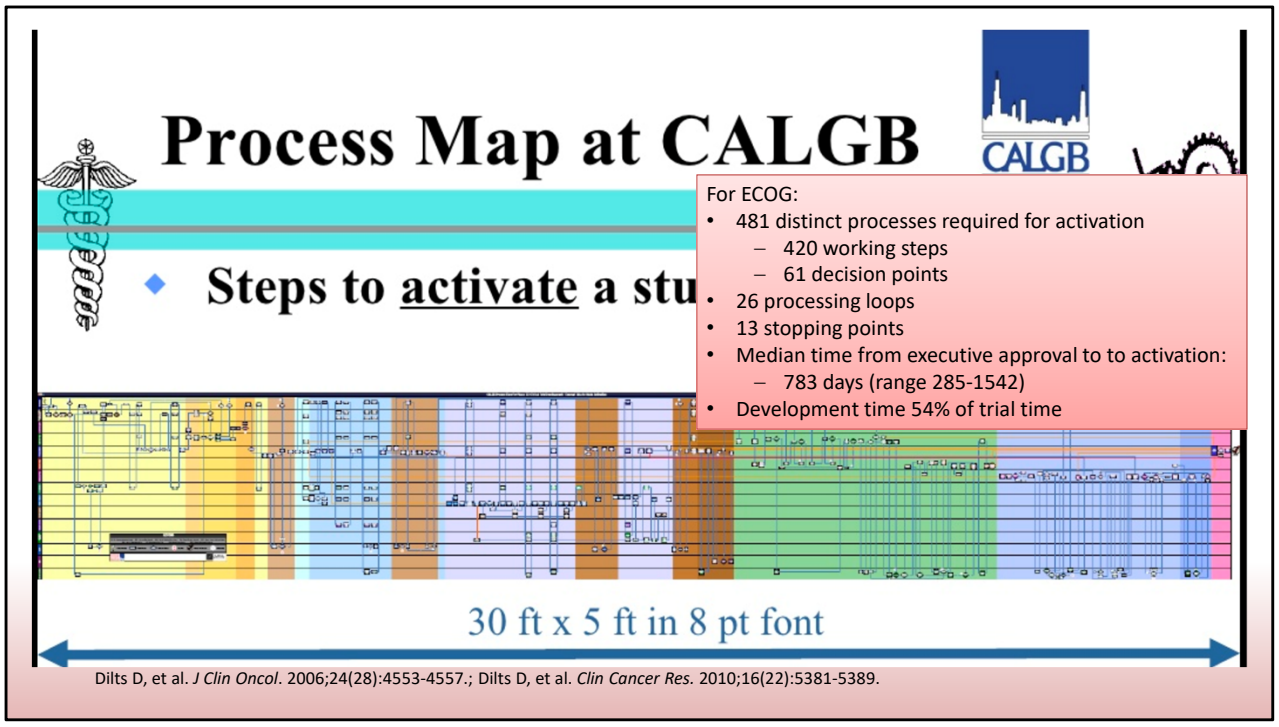

Dilts D, et al. *J Clin Oncol*. 2006;24(28):4553-4557.; Dilts D, et al. *Clin Cancer Res*. 2010;16(22):5381-5389.

Part of the reason why there had been so many scientific discoveries and yet the clinical trials have lagged behind and drug development has lagged behind is just the bureaucracy behind doing clinical trials today. There is so much red tape, particularly in the cooperative groups. About 10 years ago a process management expert assessed both CALGB, now Alliance, and ECOG and found hundreds of different processes were required for activation of trials, that there were numerous processing loops which could become infinite where committee A was waiting for committee B to act and committee B could not act until committee A had acted, and the median time from executive approval of the protocol to activation was more than two years. This has dropped a little bit with some aggressive action by the NCI and other organizations, but it is still far too long and the process is far too bureaucratic.

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Commentary

Contract Research Organizations in Oncology Clinical Research: Challenges and Opportunities

Daniel A. Roberts, MD[1]; Hagop M. Kantarjian, MD[2]; and David P. Steensma, MD[3]

Contract research organizations (CROs) represent a multibillion dollar industry that is firmly embedded in the contemporary clinical trial process. Over the past 30 years, and especially within the last decade, the reach of CROs has extended to service all phases of drug trials in an increasingly global research environment. The presence of CROs is particularly noticeable in medical oncology because of the large number of investigational compounds developed to treat cancer that are currently undergoing testing in human subjects. Although limited data are available with which to objectively define the effects that CROs have had on the clinical trial process, with the expansion of these organizations, several reports have called into question whether ethical and professional standards in research conduct are at times secondary to economic considerations. CROs can add considerable value to the clinical trial process, but difficulty communicating with CRO representatives and time spent answering trivial data queries generated by CROs are current obstacles for study site personnel interacting with CROs. Further study of the effect of the CRO industry on the clinical trial process is needed to ensure efficient data collection and patient safety while collaboratively developing novel therapies in an expedited fashion. ***Cancer*** **2016;122:1476-82.** *© 2016 American Cancer Society.*

KEYWORDS: clinical trial; contract research organizations; drug trial; ethics.

When it comes to industry trials, the advent of contract research organizations has led to a host of new steps and bureaucratic challenges with respect to opening trials. Contract research organizations are here to stay, but they often make the trials more difficult rather than expediting them.

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Lasagna's Law

Louis Lasagna
1923-2003

- "The incidence of patient availability sharply decreases when a clinical trial begins, and returns to its original level as soon as the trial is completed"
- **Paraphrase:** investigators systematically overestimate the number of patients they see who will be eligible for a trial

Lasagna LC. *Clin Pharmacol Ther*. 1975;18(5 Pt 2):629-633.

In addition, investigators who are interested in trials often sharply overestimate the number of patients that are available for clinical studies. In fact in the 1970s, Louis Lasagna, a pharmacologist coined Lasagna's Law, which is that the incidence of patient availability sharply decreases when the trial begins and returns to its original level as soon as the trial is completed. Basically, he was stating that investigators systematically overestimate the number of patients that we see who will be eligible for a trial.

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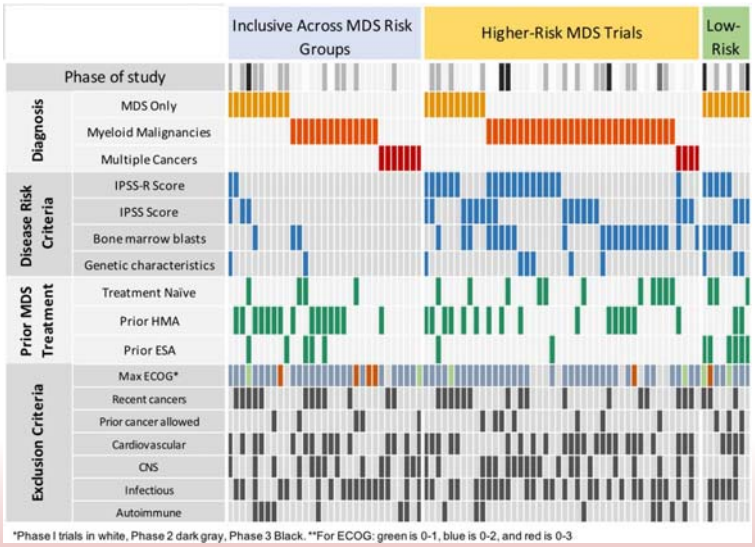
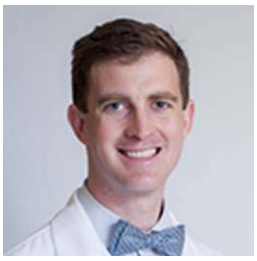
Variation in MDS Clinical Trial and Exclusion Criteria



Brunner AM, et al. *Blood.* 2018;132:4378.



Andrew Brunner
Massachusetts General Hospital

The inclusion and exclusion criteria for clinical trials often have no relationship to the expected toxicity of the drug being studied and are often copied forward from say solid tumor indications where the drugs have been assessed previously. My colleague, Andy Brunner at Massachusetts General Hospital here in Boston has done a formal assessment of MDS clinical trial inclusion and exclusion criteria and found that trials frequently exclude patients with CNS disease. Well if you have CNS disease, that is leukemia, that is no longer MDS and there are a host of other exclusion that just really seem unnecessary.

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Analysis of 141 Therapeutic MDS Clinical Trials from 1999-2017 Representation of t-MDS Patients

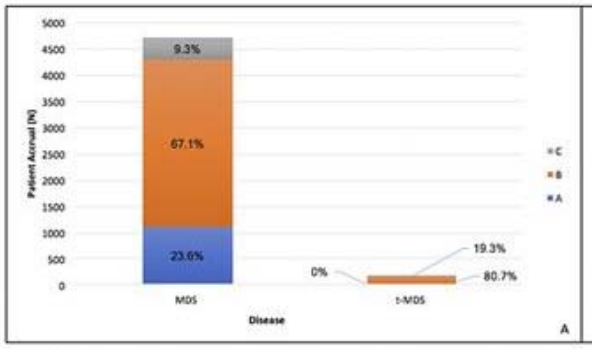

Figure 2: (A) MDS and t-MDS patient accrual for completed trials across Groups A, B, and C. actively recruiting clinical trials across Groups A, B, and C.

Uma Borate
Oregon Health Sciences U.

- t-MDS is 10-20% of all MDS but <3% of trial participants
- Rarely is t-MDS (hard to define anyway) a compelling reason to exclude patients
- More likely to be excluded in industry-sponsored trials

Borate U, et al. *Blood*. 2017;130:4250.

Uma Borate at Oregon Health Science University did an analysis of more than 140 therapeutic MDS clinical trials conducted over a 20-year period and found that therapy related MDS, which accounts for 10 to 20% of MDS, are particularly underrepresented subtype in clinical trials. They represent less than 3% of trial participants and although their prognosis is poor and their outcomes are poor, this is a group that really needs clinical trials. They are very often excluded from clinical trials especially industry sponsored trials.

Swarm Behavior: How Many HMA + New Drug, or Checkpoint Inhibitor Trials, Do We Need?

Finally, we have seen quite a bit of swarm behavior where a lot of clinical trials are studying very similar questions. For instance, there are at least half a dozen different checkpoint inhibitor trials even though this have shown quite limited activity in MDS to date.

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Entities Being Combined With Azacitidine in "Active" or "Recruiting" MDS Trials: May 2019

APR-246	Ipilimumab	FT-2102 (IDH1i)	Ibrutinib	CDX-1401 (DEC-205/NY-ESO-1 Fusion Protein)
Venetoclax	Pevonedistat	Glasdegib	Sirolimus	PDR001 (PD-1i)
Deferasirox	CB-839/telaglenastat	Milademetan	ARGX-110/cusatuzumab	MBG453 (TIM-1i)
Vitamin D	Omacetaxine	Tosedostat	Hu5F9-G4 (anti-CD47)	Sonidegib
Valproic acid	Vosaroxin	Enasidenib	Rigosertib	Selinexor
GSK2879552 (LSD1i)	Durvalumab	Ivosidenib	GSK3326595 (PRMT5i)	INCB053914 (PIMKi)
SL-401/tagraxofusp	Panobinostat	CX-01 (heparin-like adhesion inhibitor)	Selumetinib	INCB059872 (LSDi)
Pembrolizumab	Lenalidomide	SY-1425/tamibarotene	Avelumab	Bortezomib
Pracinostat	Idarubicin	Vitamin C	FT-1101 (BETi)	Atezolizumab
Nivolumab	Peptide vaccine	Quizartinib	Eltrombopag	Donor lymphocytes

Source: ClinicalTrials.gov

More than 50 different agents are being combined with azacitidine in trials. Many of these agents only because they failed as monotherapy and this is an attempt to salvage them. Now in some cases there is good reason. There is rationale for combining with a hypomethylating agent, but for a number of these agents there is not, and the combination is simply because the azacitidine is out there.

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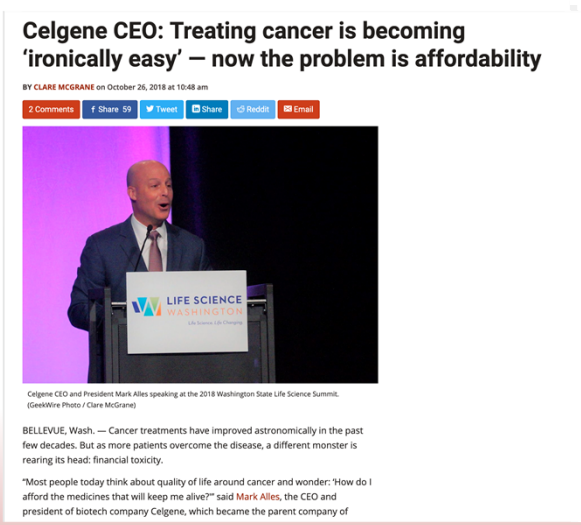
Some Scientists and Executives Seem Unaware (or Have Forgotten) How Difficult and Messy Clinical Medicine Is



Celgene CEO: Treating cancer is becoming 'ironically easy' — now the problem is affordability

BY CLARE MCGRANE on October 26, 2018 at 10:48 am

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Celgene CEO and President Mark Alles speaking at the 2018 Washington State Life Science Summit. (GeekWire Photo / Clare McGrane)

BELLEVUE, Wash. — Cancer treatments have improved astronomically in the past few decades. But as more patients overcome the disease, a different monster is rearing its head: financial toxicity.

"Most people today think about quality of life around cancer and wonder: 'How do I afford the medicines that will keep me alive?'" said Mark Alles, the CEO and president of biotech company Celgene, which became the parent company of

October 26, 2018

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Israeli scientists claim they will cure cancer within a year

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Israeli scientists have revealed that they might have found the first complete cure for cancer which will be affordable, quick, and have minimal side effects.

January 29, 2019

Even though this process is complicated, some scientists or particularly business executives who are far removed from the clinic seemed to have forgotten just how difficult and messy clinical medicine is. One CEO made headlines last year by stating that treating cancer is becoming ironically easy. His comments were about how affordability of drugs is an issue, but for those of us who really struggle with taking care of patients with MDS and other blood cancers, this was a hurtful comment. In addition, we often see quite a bit of cancer hype. Just a few months ago an Israeli group claimed that they will cure all cancer within a year, and this was published in the *Jerusalem Post* and many newspapers in the US and for several weeks every patient who saw us was asking about this. So, these sorts of things make matters difficult.

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Reasons for Optimism

Barriers not insurmountable

- Increased funding (Evans, Dresner, Taub, LLS, etc.)
- Many young investigators with new ideas/approaches
- Greater interactions between scientists and clinicians
- Eight drug approvals for AML 2017-2018
- Increasing use of single IRB and other streamlining tools
- Increasing use of and push for more open inclusion criteria by US NCI, etc.

Nevertheless, I am optimistic that we will do better in MDS. These barriers are not insurmountable. We are seeing increasing funding from various foundations, particularly the Edward Evans Foundation, but also the Taub Foundation and the Dresner Foundation, the Leukemia & Lymphoma Society, and so on. We have many young investigators coming into the field drawn by this funding who have new ideas and new approaches. There is increasing interaction between scientists and clinicians. After a long hiatus, there were eight approvals for AML between 2017 and 2018. The clinical trials are increasingly using single IRB, parallel processing and other streamlining tools, and the NCI is really pushing for more open inclusion criteria in clinical trials. I am hoping that this will be reflected in MDS trials in the future.

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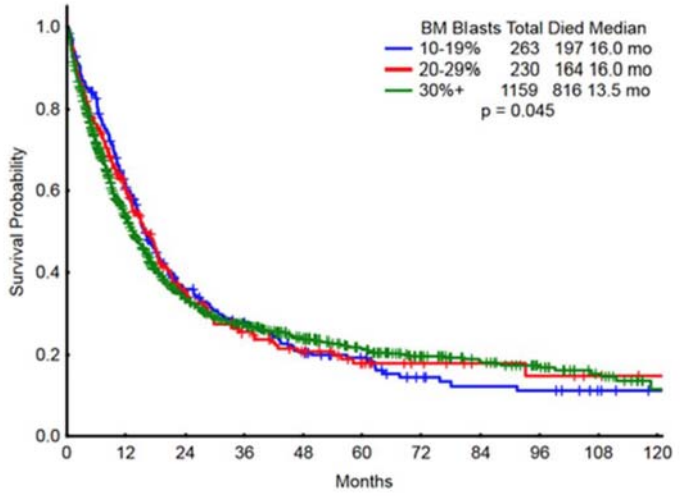
Inclusion of Patients with ≥10% Blasts in AML Trials?



1652 patients with MDS or AML and ≥10% blasts seen at MDACC 2000-2014

DiNardo C, et al. *Am J Hematol.* 2016;91(2):227-232.

We can in the short-term include patients with more than 10% blasts in AML trials since they have such a similar prognosis to AML.

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I also have to give a shout out to our colleagues at MD Anderson who have come up with a number of innovative ways of doing clinical trial designing conduct, including trials that allow patients to receive therapy locally, trials that have multiple arms that are covered by a single contract, and trials that are for patients who are not eligible for traditional clinical trials such as an azacitidine/vorinostat combination in MDS that required patients to have either poor kidney function, poor hepatic function, poor performance status, or not be eligible for other trials.

So, I think if we can cooperate then we will hopefully be able to bridge this canyon which right now is a very distressing one for those of us who care for patients with MDS and for our patients with these diseases and their families. Thank you for your attention.