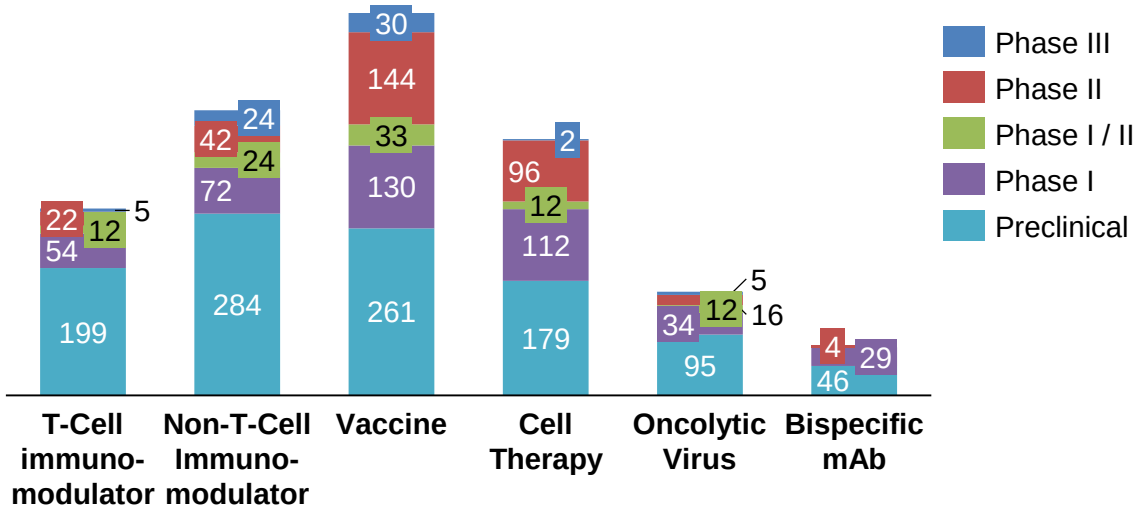
Develop the Landscape

KPMA Tools: MMRF Case Study

Updated: 2018

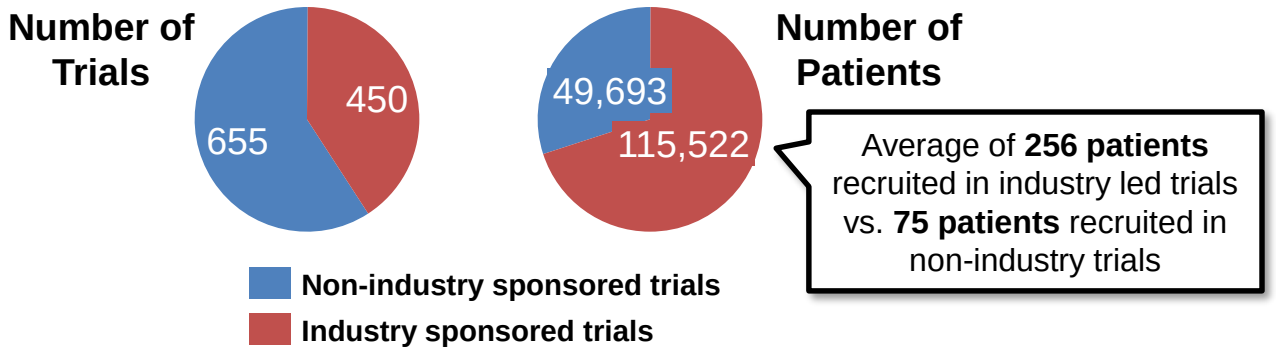
IMMUNO-ONCOLOGY ASSETS IN DEVELOPMENT

Immuno-oncology Drugs In Development



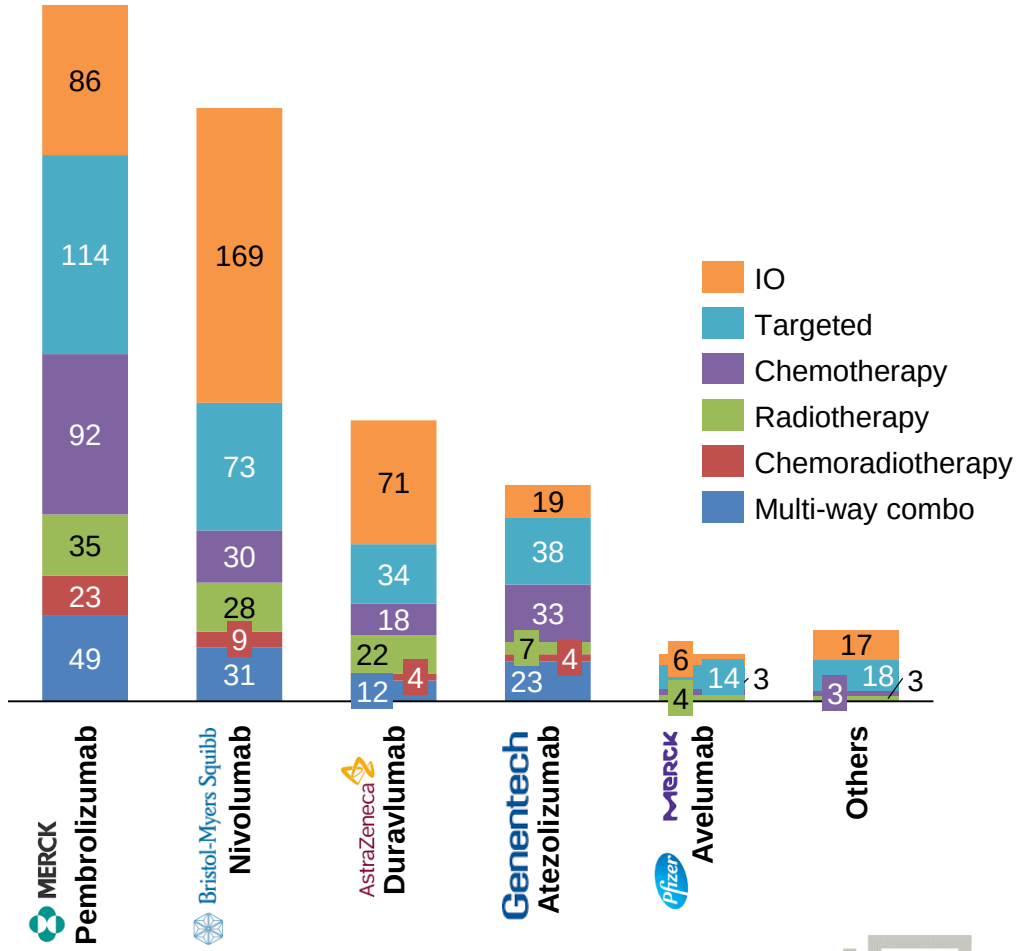
Total Trials and Planned Patient Enrollment

(Anti-PD-1/L1 combinations)



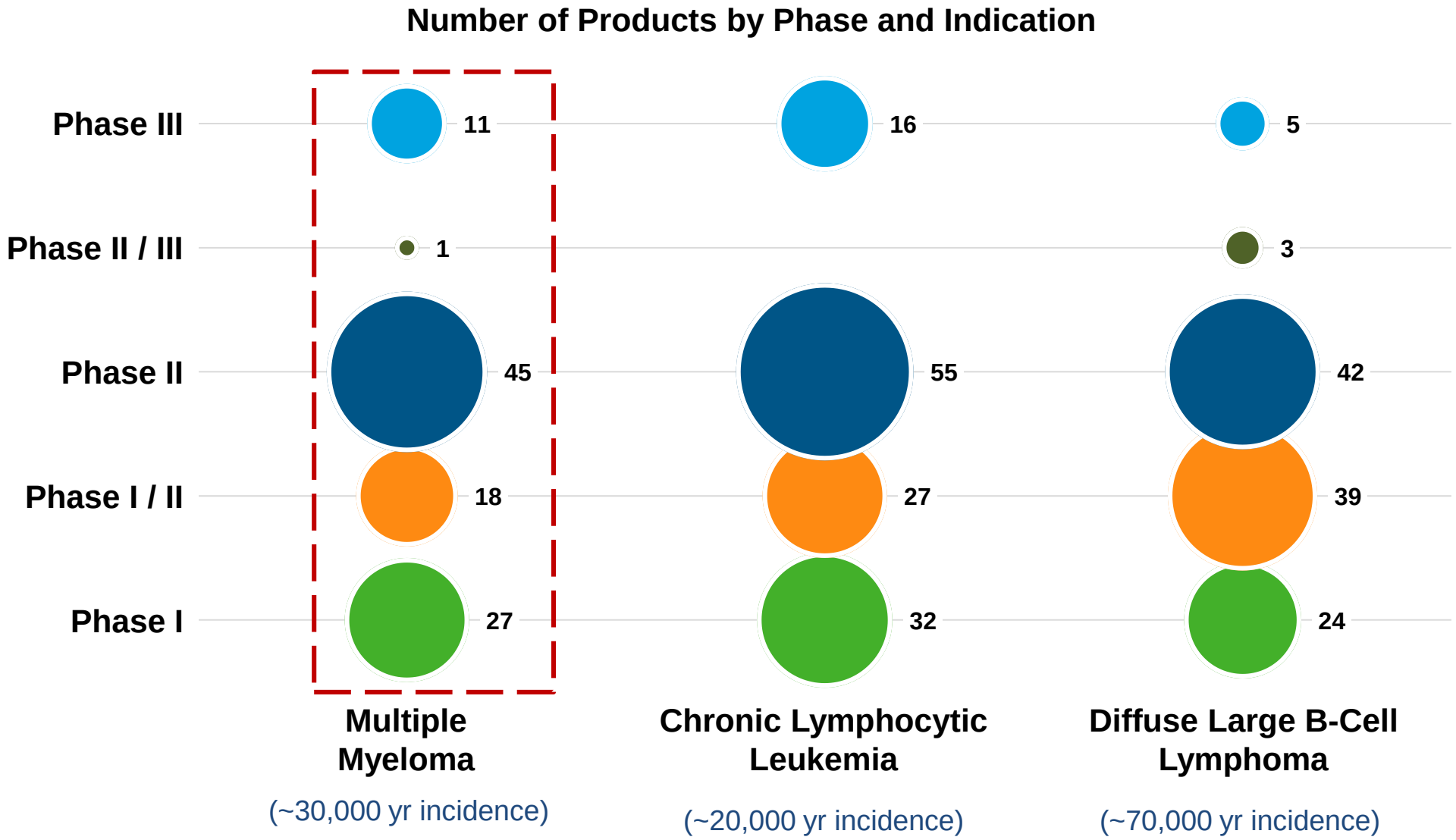
Average of **256 patients** recruited in industry led trials vs. **75 patients** recruited in non-industry trials

PD-1/L1 Combination Trials on 5 approved agents



Source: https://cancerresearch.org/scientists/clinical-accelerator/landscape-of-immuno-oncology-drug-development

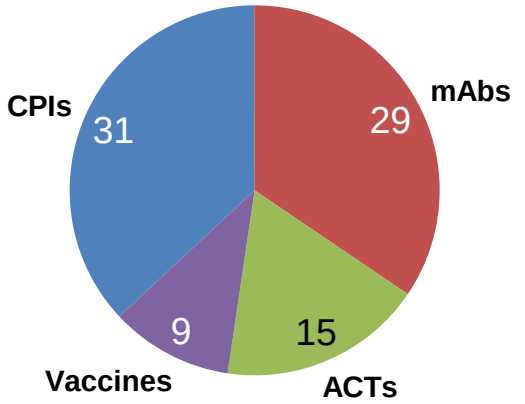
IMMUNO-ONCOLOGY RESEARCH IN MM



Source: TrialTrove, 2018

INVESTMENTS IN MM IMMUNO-ONCOLOGY RESEARCH

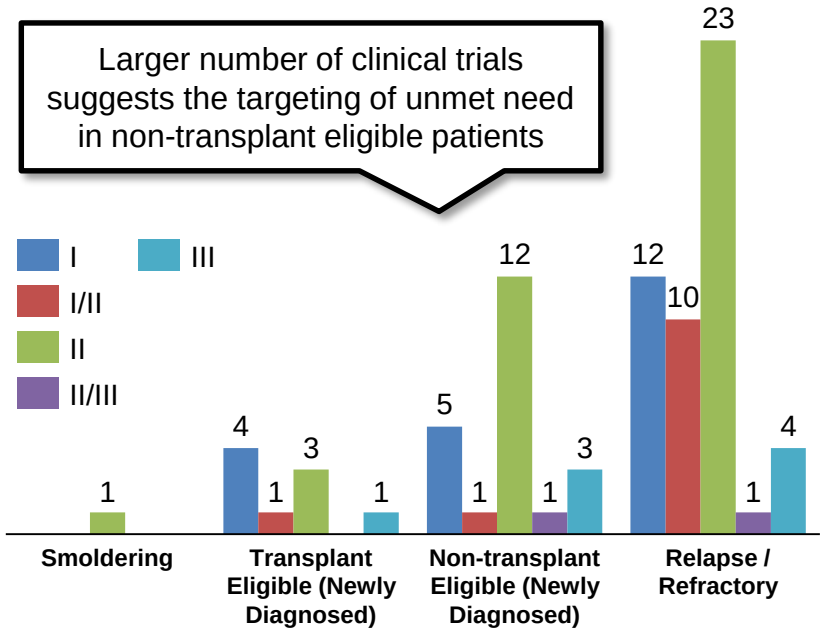
Current studies by MoA



In the past year, the number of multiple myeloma clinical trials have increased 40%

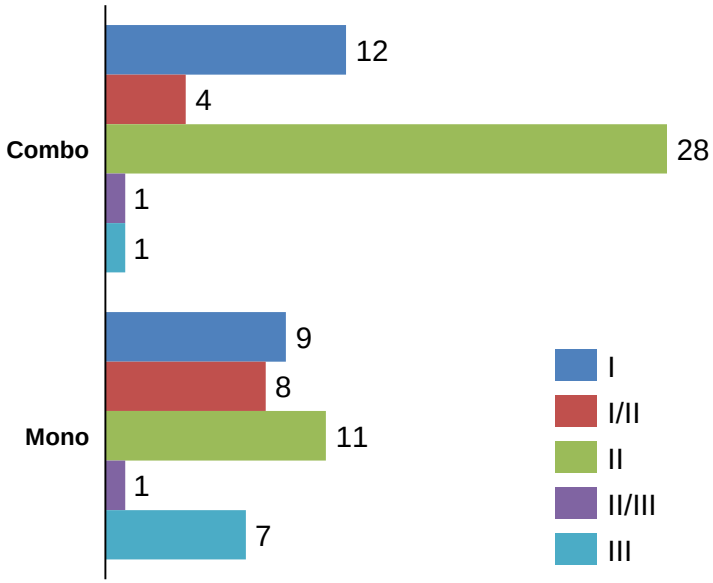
Among the 84 current IO studies in multiple myeloma, nearly half the activity focuses on checkpoint inhibitors

Current studies by phase and patient segment



The multiple myeloma IO activity is extremely active, especially in development for relapse / refractory patient segments

Current studies by intervention type



The majority of current trials are focused on combination therapy regimens

Source: Trialtrove, 2018; IQVIA Analysis

ADVANCED IMMUNO-ONCOLOGY ASSETS

Development activity – Study timeline and activities of key players

Company / Drug *(Molecule)*	Current Activity
MERCK **Keytruda** *(pembrolizumab)*	3 – Phase I; 2– Phase II; 2 – Phase I / II; 2 – Phase III
NOVARTIS **PDR001** *(spartalizumab)*	Phase I
janssen **JNJ-63723283** *(Janssen)*	Phase I; Phase I
Bristol-Myers Squibb **Opdivo** *(Nivolumab)*	4 – Phase I / II; 2 – Phase I / II; 8 – Phase II; Phase III

The FDA recently (Dec 2017) lifted 2 holds on a phase I and phase II nivolumab combination study after study protocols amendments;

A third study, the phase III CheckMate-602 trial still remains on hold

- FDA hold
- Combination therapy
- Monotherapy

Source: Trialtrove, 2018; IQVIA Analysis

EARLY STAGE IMMUNO-ONCOLOGY ASSETS

Target	Key Products *Sponsor*	Current Phase / Trial Name / Status *(Estimated completion)*	Other key products in development
LAG-3	**BMS-986016** *BMS*	• **Phase I/IIa** – Safety Study of Anti-LAG-3 in Relapsed or Refractory Hematologic Malignancies – *Actively recruiting (Jan 2020)*	**GSK2831781** (*GSK*) **REGN3767** *(Regeneron)*
CAR-T	**bb2121** *Bluebird*	• **Phase II** – KarMMa: Efficacy and Safety Study of bb2121 in Subjects With Relapsed and Refractory Multiple Myeloma – *Actively recruiting (Nov 2023)*	**ACTR087** *(Seattle Therap.)*
	LY3039478 *(Juno / Celgene / Lilly)*	• **Phase I** – A Study of LY3039478 in Participants With Advanced Cancer – *Active (2018)*	
Dendritic cell vaccine	**CT7, MAGE-A3, & WT1 mRNA-electroporated Langerhans cells** *MSKCC/ Rockefeller University*	• **Phase I –** Phase I Trial of Vaccination With CT7, MAGE-A3, and WT1 mRNA-electroporated Autologous Langerhans-type Dendritic Cells as Consolidation for Multiple Myeloma Patients Undergoing Autologous Stem Cell Transplantation – *Active (2018)*	
Bispecific	**PF-06863135** *Pfizer*	• **Phase I** – Phase 1 Study Of PF-06863135, A BCMA- CD3 Bispecific Ab, In Relapse/ Refractory Multiple Myeloma – Actively recruiting (Nov 2021)	

CHALLENGES TO PROGRESSING IMMUNO-ONCOLOGY RESEARCH

		Key Challenges Identified
	Overall challenges	• Poorly understood disease biology, mechanisms of immune suppression and drug MOA's especially with biologics • Lack of collaboration and standardization of immune correlative research data • Lack of understanding of resistance mechanisms and super responders • New biologics, bispecifics and ADC's also crowd the multiple myeloma research landscape and compete for patients
Mechanism of Action	**CPI**	• Current FDA hold on PD1/L1 studies without an accepted explanation for safety issues • Difficulty identifying effective combinations and most efficacious patient populations
	ACTs	• Early stage of clinical development of cellular therapy technologies • Lower likelihood of positive outcomes in relapse/refractory patients with poorly functioning immune systems • Uncertain duration of response with high safety risks, difficult access and high cost
	Vaccines	• Lack of good validated targets for vaccines • Poorly understood or tested vaccine combinations • Unsuccessful use of predictive biomarkers for vaccine development
Patient segments	**Smoldering**	• Inability to segment smoldering populations to high-risk and/or "immunologically hot" tumors • Unclear clinical trial endpoints and time to demonstrate statistically significant improvements
	Newly diagnosed	• Effective treatment available for many patients requires studies to focus on high risk segments • Unclear biomarkers to identify responders / super-responders
	Relapse / Refractory	• Unlikely that a therapy will be successful as a cure for multiple myeloma • Requirements of standardized adaptive trials / platform designs to assess IO/IO combinations

MMRF OPPORTUNITIES

✓Continue to invest in **basic and translational research** to better understand disease biology, immune suppression and resistance mechanisms to build on our understanding of baseline state of tumor interactions and treatment modalities that would allow you to mount an immune response

✓Close the gap on **immune assay and data standards** from research to diagnostics in the IO Initiative and by initiating strategic partnerships with organizations doing similar work

✓Build **longitudinal immune database** linking genomic and clinical data and outcomes in order to learn more about disease biology and patient phenotypes over the course of treatment to identify new IO targets and develop hypotheses as to which patient subgroups will respond to various IO therapies / combinations

✓Continue to invest in optimized **master protocols, platform studies, and other innovative trial designs** to efficiently test novel IO approaches and combinations which are thought to be the best approach to potential cures

✓Investigate opportunities to **accelerate CAR-T research and delivery models**, particularly in large medical centers to facilitate development of new technologies and patient access

✓Explore opportunities to **broker pre-competitive alliances** in cell therapy safety data registries, biomarker development, and assay standardization