NASDC
NCI Awardee Skills Development Consortium

Introduction to Oncology Clinical Trials for the Non-Clinician

Katherine Panageas, DrPH
Dept. of Epidemiology and Biostatistics

Margaret Callahan, MD PhD
Dept. of Medicine

Memorial Sloan Kettering Cancer Center

Objectives

» Familiarize a non-clinical audience with the basic concepts related to clinical trial design, execution and interpretation.

» Introduce and define relevant common terms in clinical trial design.

» Introduce and define basic concepts in clinical trial endpoints & review common methods to present data.

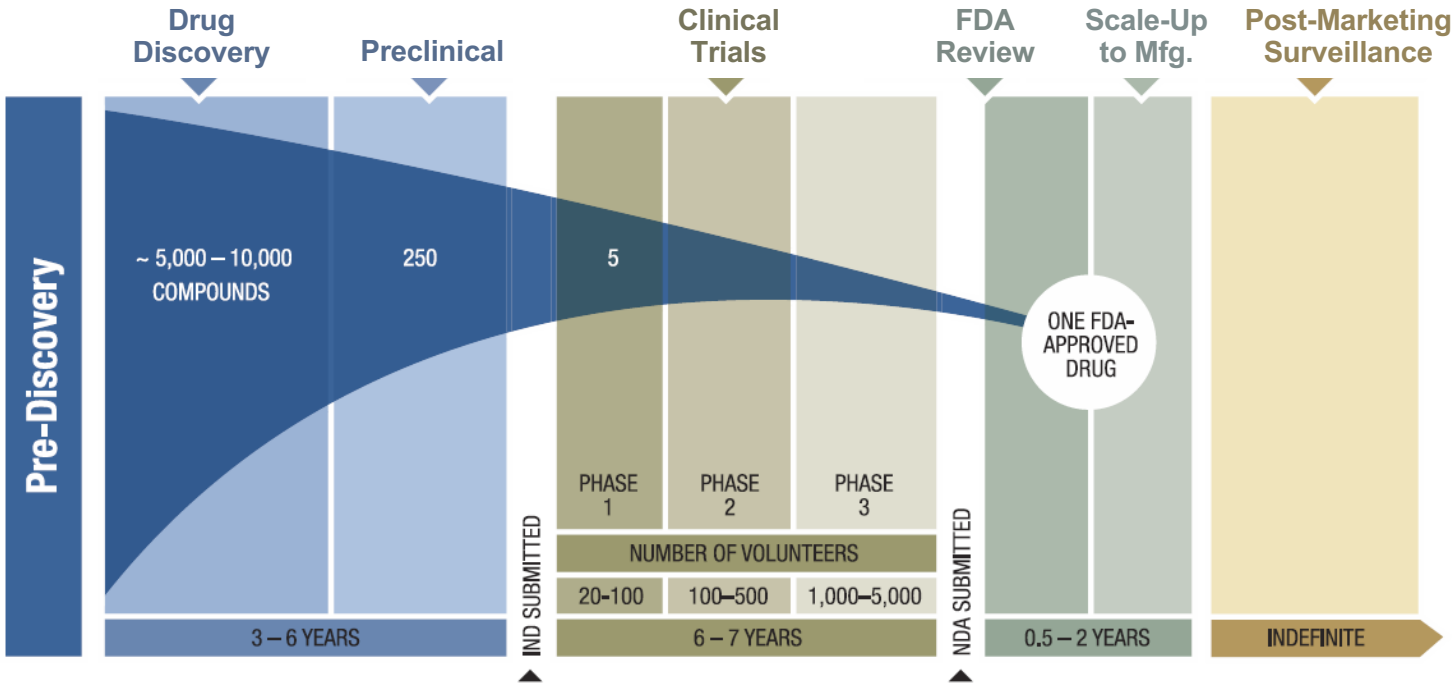
Clinical Trial Phases

Evaluation of novel agents typically progresses through a three-phase system of clinical trials

- » Phase I
- » Phase II
- » Phase III

A new treatment that is successful in one phase will continue to be tested in subsequent phases

Drug Discovery & Development Timeline



American Association of Cancer Research 2011 Cancer Progress Report

Clinical Trial Designs in Oncology

Phase I

- Determine drug safety
- Characterize toxicity profile
- Determine maximum tolerated dose (MTD)
- Determine dose for further study
- Pharmacokinetics

Phase II

- Assess initial signal of efficacy
- Disease Specific Tumor Response
  - ~25-50 patients

Phase III

- Gold standard
- Definitive studies
- Randomized Controlled
- Compared with standard of Care (superiority)
- Change clinical practice
- Large sample size

Therapeutic Clinical Trial Design Considerations: Study Objectives

Foundation of your clinical trial is the research objective.

Objectives should:

- be concrete and clearly defined
- include measurable outcomes and relevant patient population

Bad Examples:

- To evaluate the effect of flavopiridol on cancer.
- To see if flavopiridol improves cancer outcomes
- To determine the safety of flavopiridol

What is wrong with these aims?

- what does “effect” mean? what kind of cancer, in what patients?
- “Improves” compared to what? what is the outcome of interest?
- How is “safe” defined?

Therapeutic Clinical Trial Design Considerations: Study Objectives

Better example:

» **To evaluate the efficacy of flavopiridol** administered by two different schedules followed by ara-C and mitoxantrone in adults with newly diagnosed AML with poor-risk features

Keywords for AIMS:

» estimate, evaluate, assess, describe, identify, compare

» efficacy, safety, toxicity, recommended dose

Therapeutic Clinical Trial Design Considerations

Clearly defined patient population

- » Who do you want to treat?
- » What disease?
- » What stage?
- » Where in the course of disease (e.g., neoadjuant, adjuvant, first or second line)?
- » How will this population compare to other study-populations or populations that may serve as a reference ?

Choosing Your Patient Population – Knowing the Lingo

Patient selection is a key element of study design – this will help you best address the aims of your study, allow comparison with similar studies and will define how (and if) your study results are applied to clinical practice.

	Definition
Inclusion Criteria	As defined by the protocol, characteristics a prospective study participant must have to be included in the trial. i.e. type and stage of disease
Exclusion Criteria	As defined by the protocol, characteristics a prospective study participant may have that would exclude them from the trial. i.e. co-morbidities
Eligible Patients	Prospective study participants that fulfill inclusion and exclusion criteria.
Evaluable Patients	As defined by the protocol, study participants that will be included in the analysis of specific study endpoints.

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Therapeutic Clinical Trial Design Considerations

Clearly defined therapeutic details?

- » Will you be evaluating different schedule or route of administration?
- » Will you be evaluating different doses?
- » Will be experimental therapy be given alone or in combination with another therapy?

Therapeutic Clinical Trial Design Considerations

Clearly defined endpoints

- » Will you be evaluating measures of safety or clinical activity?
- » How will you define toxicity?
- » How will you define clinical benefit?
- » How often will you measure clinical endpoint(s)?

Memorial Sloan Kettering
Cancer Center

Clinical Trial Endpoints – Knowing the Lingo

For early studies, assessing the safety of the drug is often the main objective and here are some of the endpoint used commonly.

	Definition
Maximum Tolerated Dose (MTD)	The highest dose of a drug or treatment that does not cause unacceptable side effects, as defined by the protocol.
Dose Limiting Toxicity (DLT)	A side effects of a drug or other treatment that is serious enough to prevent an increase in dose or level of that treatment, as defined by the study protocol.
Pharmacokinetics (PK)	The activity of drugs in the body over a period of time, including the processes by which drugs are absorbed, distributed in the body, localized in the tissues, and excreted. “What the body does to the drug”.
Pharmacodynamics (PD)	The biochemical and physiologic effects of drugs. “What the drug does to the body”.

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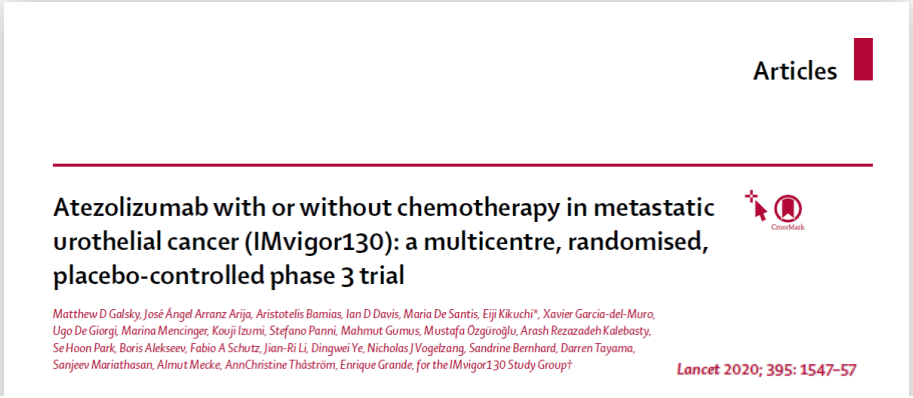
Clinical Trial Endpoints – Toxicity



Articles

Atezolizumab with or without chemotherapy in metastatic urothelial cancer (IMvigor130): a multicentre, randomised, placebo-controlled phase 3 trial

Matthew D Galsky, José Ángel Arranz Arija, Aristotelis Bamias, Ian D Davis, Maria De Santis, Eiji Kikuchi*, Xavier Garcia-del-Muro, Ugo De Giorgi, Marina Mencinger, Kouji Izumi, Stefano Panni, Mahmut Gumus, Mustafa Özgüroğlu, Arash Rezazadeh Kalebasty, Se Hoon Park, Boris Alekseev, Fabio A Schutz, Jian-Ri Li, Dingwei Ye, Nicholas J Vogelzang, Sandrine Bernhard, Darren Tayama, Sanjeev Mariathasan, Almut Mecke, AnnChristine Thåström, Enrique Grande, for the IMvigor130 Study Group†

Lancet 2020; 395: 1547–57

	Group A (n=453)	Group B (n=354)	Group C (n=390)
Total deaths	236 (52%)	190 (54%)	223 (57%)
Adverse events regardless of attribution			
Any grade adverse events	451 (>99%)	329 (93%)	386 (99%)
Grade 3 or 4 adverse events	383 (85%)	148 (42%)	334 (86%)
Grade 5 adverse events	29 (6%)	28 (8%)	20 (5%)
Treatment-related adverse events	434 (96%)	211 (60%)	373 (96%)
Treatment-related grade 3 or 4 adverse events	367 (81%)	54 (15%)	315 (81%)
Treatment-related grade 5 adverse events	9 (2%)	3 (1%)	4 (1%)
Serious adverse events			
Regardless of attribution	234 (52%)	152 (43%)	191 (49%)
Treatment-related serious adverse events	144 (32%)	44 (12%)	101 (26%)
Adverse events leading to any treatment discontinuation	156 (34%)	22 (6%)	132 (34%)
Adverse events leading to discontinuation of atezolizumab or placebo	50 (11%)	21 (6%)	27 (7%)
Adverse events leading to discontinuation of cisplatin	53 (12%)	0	52 (13%)
Adverse events leading to discontinuation of carboplatin	90 (20%)	1 (<1%)*	79 (20%)
Adverse events leading to discontinuation of gemcitabine	117 (26%)	1 (<1%)*	100 (26%)
Adverse events leading to any dose reduction or interruption	363 (80%)	112 (32%)	304 (78%)
Any grade adverse events of special interest	227 (50%)	132 (37%)	135 (35%)
Grade 3 or 4 adverse events of special interest	34 (8%)	29 (8%)	17 (4%)
Grade 5 adverse events of special interest	3 (1%)	2 (1%)	1 (<1%)

Data are n (%). *This patient was randomly assigned to group A and received atezolizumab; they had an adverse event of pyrexia that day, and gemcitabine and carboplatin were marked as drug withdrawn. Since no chemotherapy was given, this patient was included in group B for safety analysis.

***Table* 3: Safety summary**

Clinical Trial Endpoints – Knowing the Lingo

For later studies, assessing the clinical activity of the drug is often the main objective and here are some of the endpoint used commonly.

	Definition
Response	In medicine, an improvement related to treatment. In oncology, radiographic and clinical evidence of tumor(s) shrinking.
Duration of Response (DOR)	The period of time of a continued response.
Overall survival (OS)	The length of time from the start of treatment for a disease, such as cancer, that patients diagnosed with the disease are still alive.
Progression free survival (PFS)	The length of time during and after the treatment of a disease, such as cancer, that a patient lives with the disease but does not progress radiographically or otherwise, as defined by study criteria.

RECIST definitions for tumor response categories

Complete Response (CR):	Disappearance of all lesions
Partial Response (PR):	At least a 30% decrease in the sum of the diameters of target lesions
Stable disease (SD):	Disease other than progressive disease, complete response, or partial response
Progressive Disease (PD):	A 20% increase in the sum of the longest diameters of target lesions, unequivocal progression of nontarget lesions, and/or the development of new lesions. [10,11,14]

RECIST guidelines are not applicable to all types of cancer. Separate criteria are available for other cancers, such as lymphomas, brain tumors

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Clinical Trial Endpoints – Response

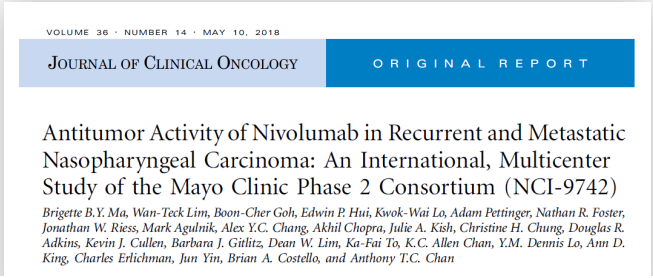
Table 2. Clinical Activity of Anti–PD-1 Antibody in the Efficacy Population.*

Dose of Anti–PD-1 Antibody	Objective Response†	Objective-Response Rate‡	Duration of Response§	Stable Disease ≥24 wk		Progression-free Survival Rate at 24 wk¶
	no. of patients/ total no. of patients	*% (95% CI)*	*mo*	*no. of patients/ total no. of patients*	*% (95% CI)*	*% (95% CI)*
Melanoma						
0.1 mg/kg	4/14	29 (8–58)	7.5+, 5.6+, 5.6, 5.6	1/14	7 (0.2–34)	40 (13–66)
0.3 mg/kg	3/16	19 (4–46)	3.8+, 2.1+, 1.9+	1/16	6 (0.2–30)	31 (9–54)
1.0 mg/kg	8/27	30 (14–50)	24.9+, 22.9, 20.3+, 19.3+, 18.4+, 7.6+, 5.6+, 5.3+	3/27	11 (2–29)	45 (26–65)
3.0 mg/kg	7/17	41 (18–67)‖	22.4+, 18.3+, 15.2+, 12.9, 11.1, 9.3, 9.2+	1/17	6 (0.1–29)	55 (30–80)
10.0 mg/kg	4/20	20 (6–44)	24.6+, 23.9+, 18.0+, 17.0	0/20	0	30 (9–51)
All doses	26/94	28 (19–38)		6/94	6 (2–13)	41 (30–51)

Topalian SL et al. N Engl J Med 2012;366:2443-2454.

Clinical Trial Endpoints – Response

Fig 4. Spider plot of changes in the sum of unidimensional tumor measurements over time. The dotted blue line represents responders (according to Response Evaluation Criteria in Solid Tumors); solid gold line represents non-responders. CR, complete response; PR, partial response.


VOLUME 36 · NUMBER 14 · MAY 10, 2018
JOURNAL OF CLINICAL ONCOLOGY
ORIGINAL REPORT

Antitumor Activity of Nivolumab in Recurrent and Metastatic Nasopharyngeal Carcinoma: An International, Multicenter Study of the Mayo Clinic Phase 2 Consortium (NCI-9742)

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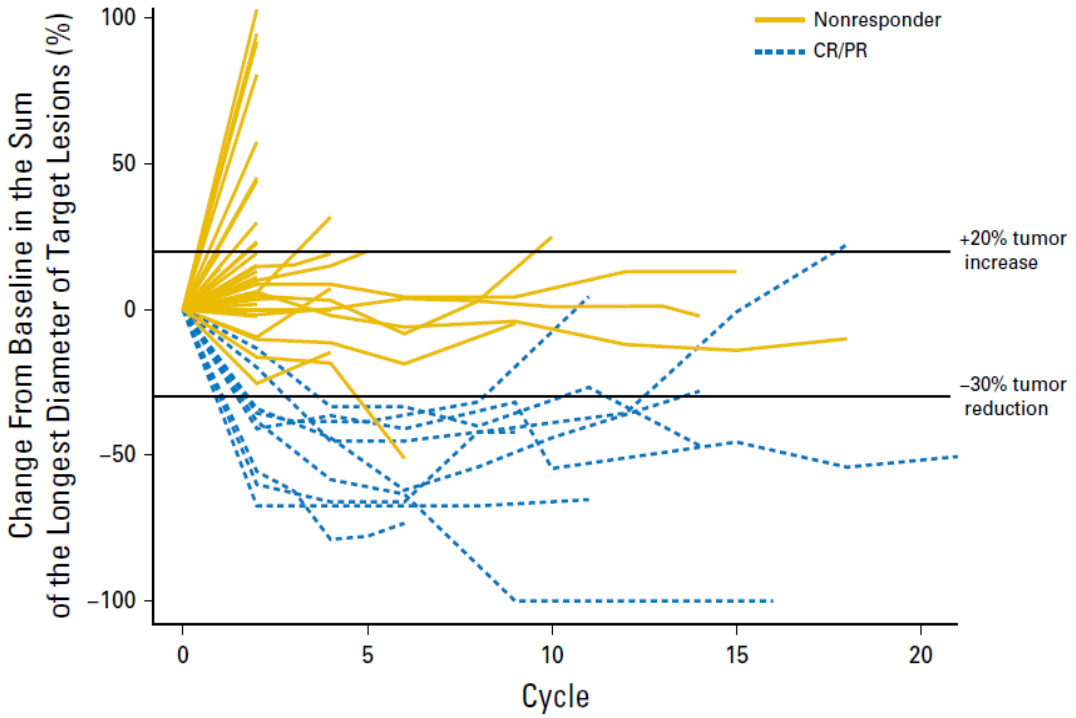
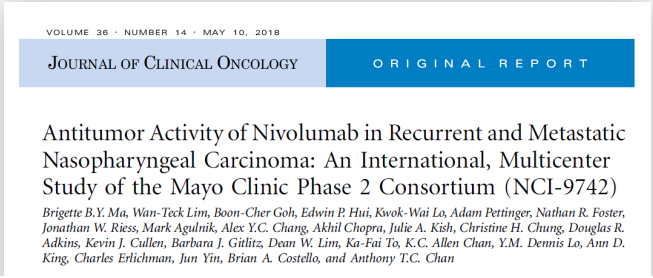


Ma, B et al. JCO 2018.

Clinical Trial Endpoints – Response

Fig 1. Waterfall plot. Changes in sum of unidimensional tumor dimension from baseline and Response Evaluation Criteria in Solid Tumors response in individual patients. Partial response was defined as ≥ 30% decline in tumor dimension. Progressive disease was defined as a > 20% increase in tumor dimensions.



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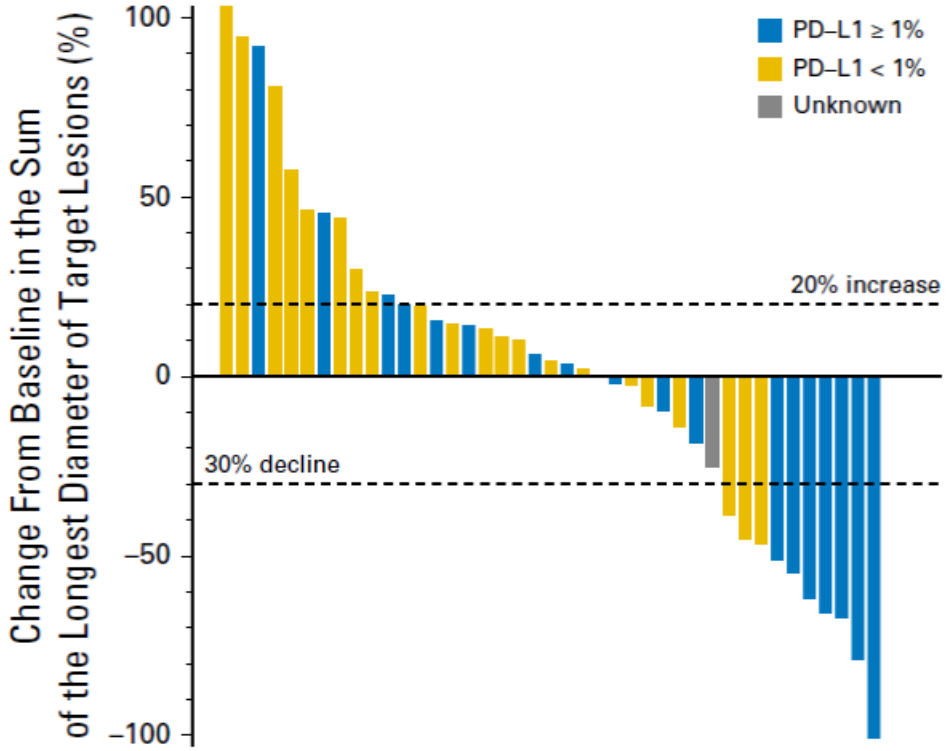
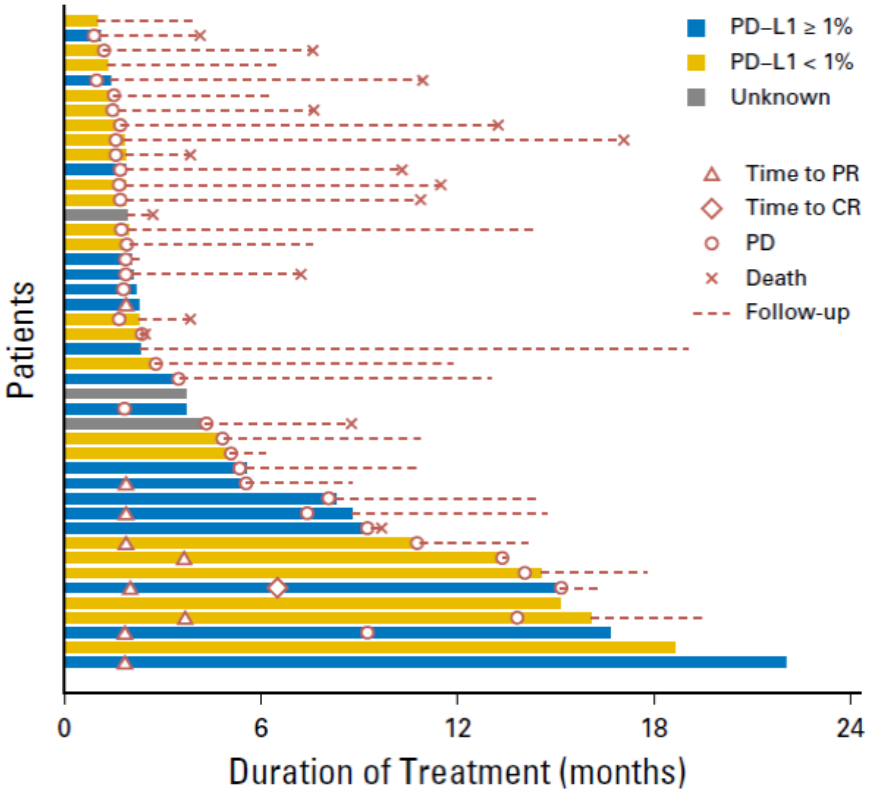
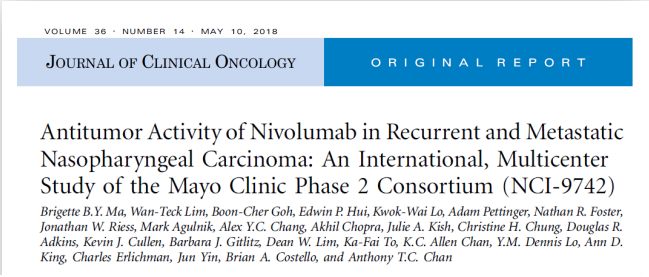


Ma, B et al. JCO 2018.

Clinical Trial Endpoints – Response

Fig 2. Swimmer plot. Duration of response and time to response in patients receiving nivolumab. CR, complete response; PD, progressive disease; PR, partial response.





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Clinical Trial Endpoints – OS

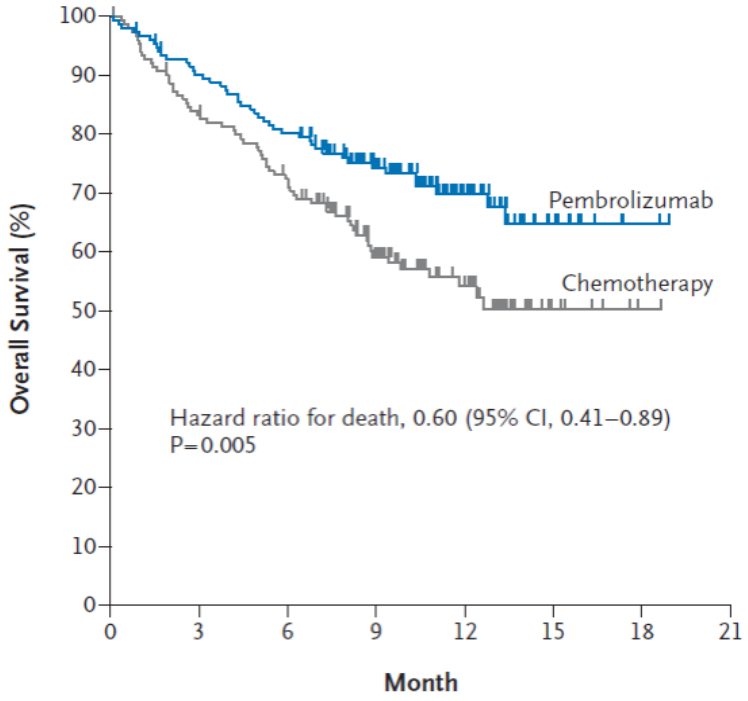
The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 NOVEMBER 10, 2016 VOL. 375 NO. 19

Pembrolizumab versus Chemotherapy for PD-L1–Positive Non–Small-Cell Lung Cancer

Martin Reck, M.D., Ph.D., Delvys Rodríguez-Abreu, M.D., Andrew G. Robinson, M.D., Rina Hui, M.B., B.S., Ph.D., Tibor Csőszi, M.D., Andrea Fülöp, M.D., Maya Gottfried, M.D., Nir Peled, M.D., Ph.D., Ali Tafreshi, M.D., Sinead Cuffe, M.D., Mary O'Brien, M.D., Suman Rao, M.D., Katsuyuki Hotta, M.D., Ph.D., Melanie A. Leiby, Ph.D., Gregory M. Lubiniecki, M.D., Yue Shentu, Ph.D., Reshma Rangwala, M.D., Ph.D., and Julie R. Brahmer, M.D., for the KEYNOTE-024 Investigators*

Figure 2. Overall Survival in the Intention-to-Treat Population.

Shown are Kaplan–Meier estimates of overall survival, according to treatment group. Tick marks represent data censored at the last time the patient was known to be alive. The intention-to-treat population included all patients who underwent randomization.



No. at Risk

Pembrolizumab	154	136	121	82	39	11	2	0
Chemotherapy	151	123	106	64	34	7	1	0

Reck, M et al. NEJM 2016.

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Clinical Trial Endpoints – PFS

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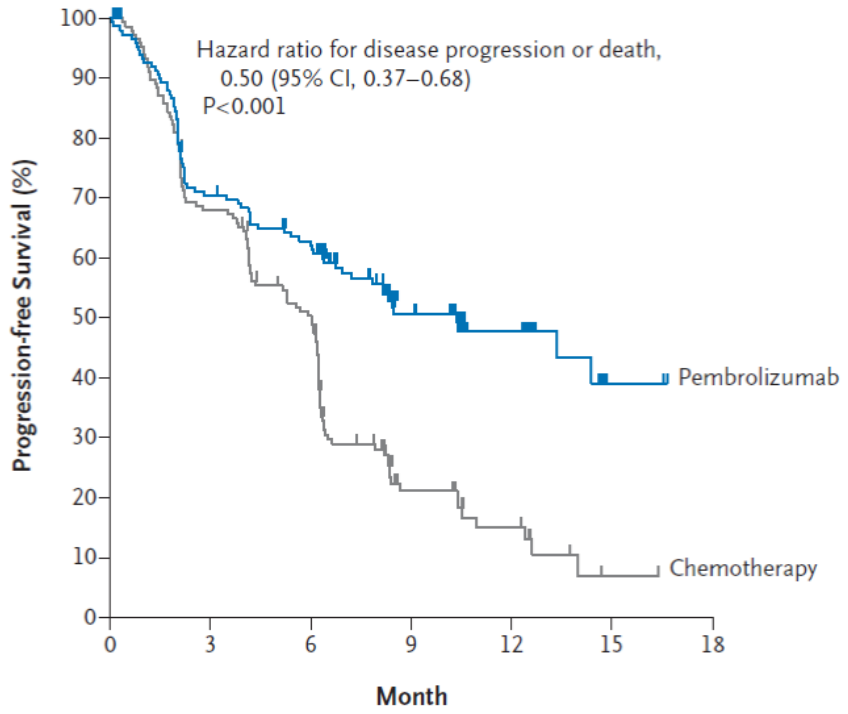
Figure 1 (facing page). Progression-free Survival in the Intention-to-Treat Population.

Panel A shows Kaplan–Meier estimates of progression-free survival, according to treatment group. Tick marks represent data censored at the last time the patient was known to be alive and without disease progression.



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Other Considerations:

» Analysis of data

» QC

» Biomarkers or correlatives

» Randomization methods

» Stratification methods

» Approaches to dose escalation