CheckMate-8HW: Nivolumab/Ipilimumab in MSI-H/dMMR mCRC

Results from the phase 3 CheckMate-8HW trial show improved outcomes with nivolumab plus ipilimumab versus standard therapies in metastatic colorectal cancer (mCRC) with high-level microsatellite instability or deficient mismatch repair (MSI-H/dMMR).

Key Findings

First Phase 3 Trial

Comparing dual- vs single-agent immunotherapy in MSI-H/dMMR mCRC

Risk Reduction

38% reduction in disease progression or death risk with combo vs nivolumab alone

Toxicity Increase

Higher incidence of treatment-related adverse events with combination therapy

Study Design

1 **Patient Population**

Adults with unresectable or metastatic CRC with MSI-H/dMMR status

2 **Randomization**

2:2:1 ratio to nivolumab+ipilimumab, nivolumab alone, or chemotherapy

3 **Treatment Duration**

Until disease progression, toxicity, or maximum 2 years for immunotherapy arms

Efficacy Results

47.0

Median Follow-up

Months of follow-up for efficacy analysis

68%

3-Year PFS Rate

For nivolumab+ipilimumab combination

51%

3-Year PFS Rate

For nivolumab monotherapy

Response Rates

Nivolumab + Ipilimumab

71% overall response rate across all lines of therapy

Nivolumab Alone

58% overall response rate across all lines of therapy

Safety Profile

Grade 3/4 TRAEs

22% with nivolumab+ipilimumab vs 14% with nivolumab alone

Treatment Discontinuation

9% vs 4% due to grade 3/4 TRAEs in combo vs mono arms

Treatment-Related Deaths

2 in nivolumab+ipilimumab arm, 1 in nivolumab arm

Expert Commentary

> "With these results...the combination of nivolumab and ipilimumab could become a new standard of care in the first-line [setting] for patients with mCRC MSI-H/dMMR."

- Dr. Thierry André, Sorbonne University and Saint-Antoine Hospital

Implications for Practice

1

New Standard of Care

Nivolumab+ipilimumab as first-line for MSI-H/dMMR mCRC

2

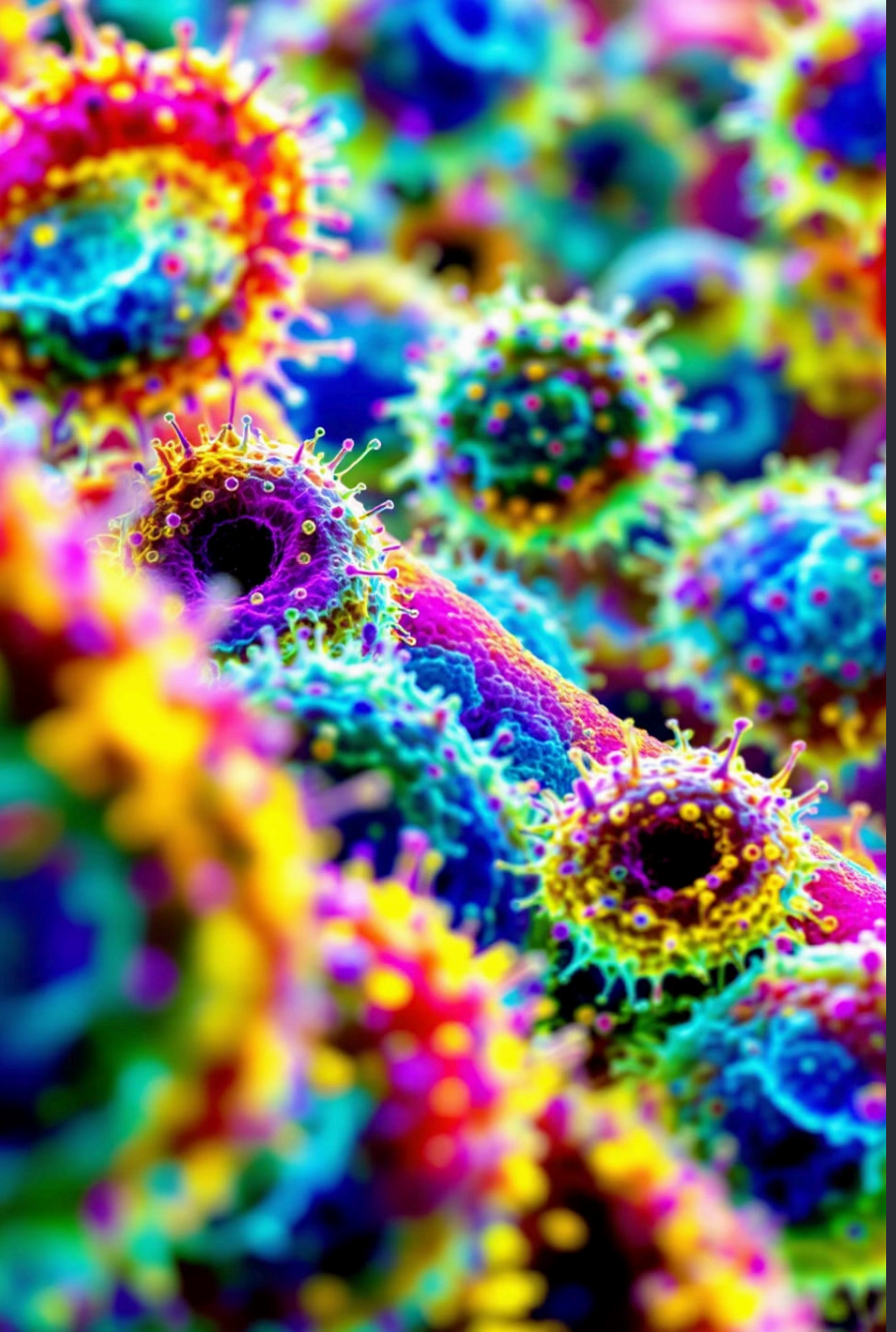
Patient Selection

Consider dual immunotherapy for most patients without contraindications

3

Chemotherapy Role

Reserve for patients with autoimmune diseases or other contraindications



Background on MSI-H/dMMR mCRC

Poor Chemotherapy Response

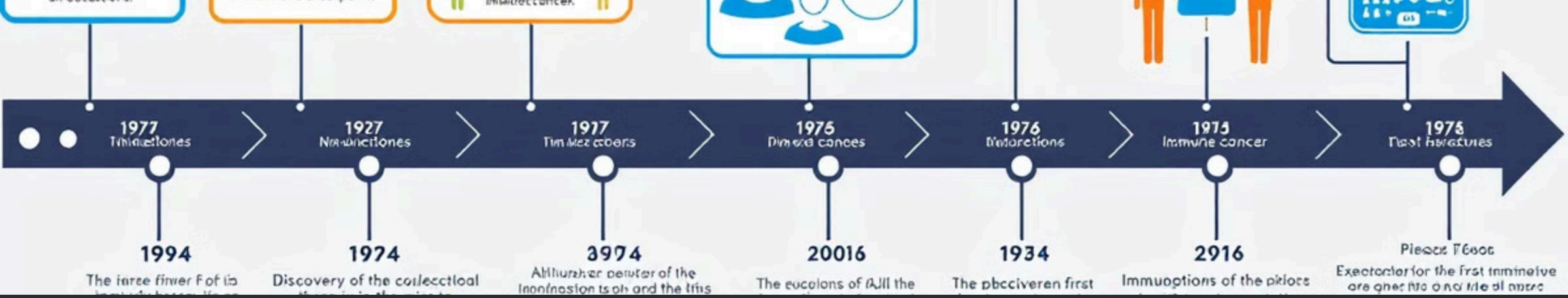
Patients typically respond poorly to conventional chemotherapy

Immunotherapy Rationale

Defects in DNA mismatch repair lead to increased tumor neoantigens

Immune Cell Infiltration

Higher levels of immune cells in tumor microenvironment



Previous Immunotherapy Studies

1

2015

PD-1 blockade shows efficacy in MSI-H tumors (Le et al.)

2

2017-2020

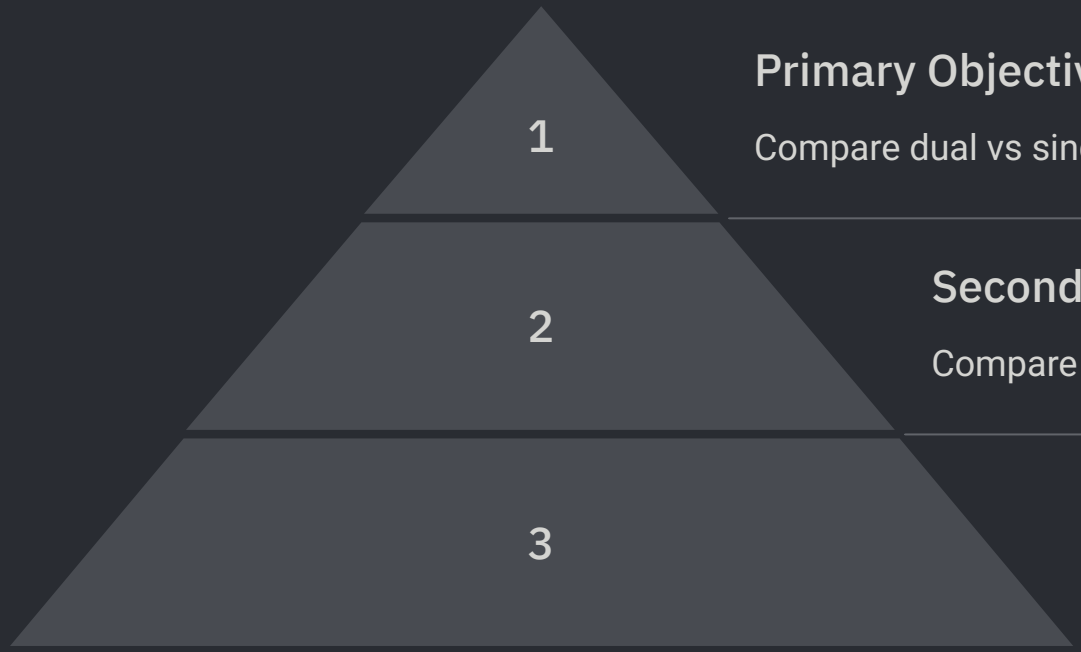
Nivolumab, pembrolizumab show benefit in MSI-H/dMMR mCRC

3

2022

Nivolumab+ipilimumab combination shows promise in phase 2 study

CheckMate-8HW Objectives



Primary Objective

Compare dual vs single immunotherapy efficacy

Secondary Objective

Compare immunotherapy vs standard chemotherapy

Exploratory Objective

Assess biomarkers and long-term outcomes

Treatment Arms

Nivolumab + Ipilimumab

Combination immunotherapy every 3 weeks for 4 doses, then nivolumab maintenance

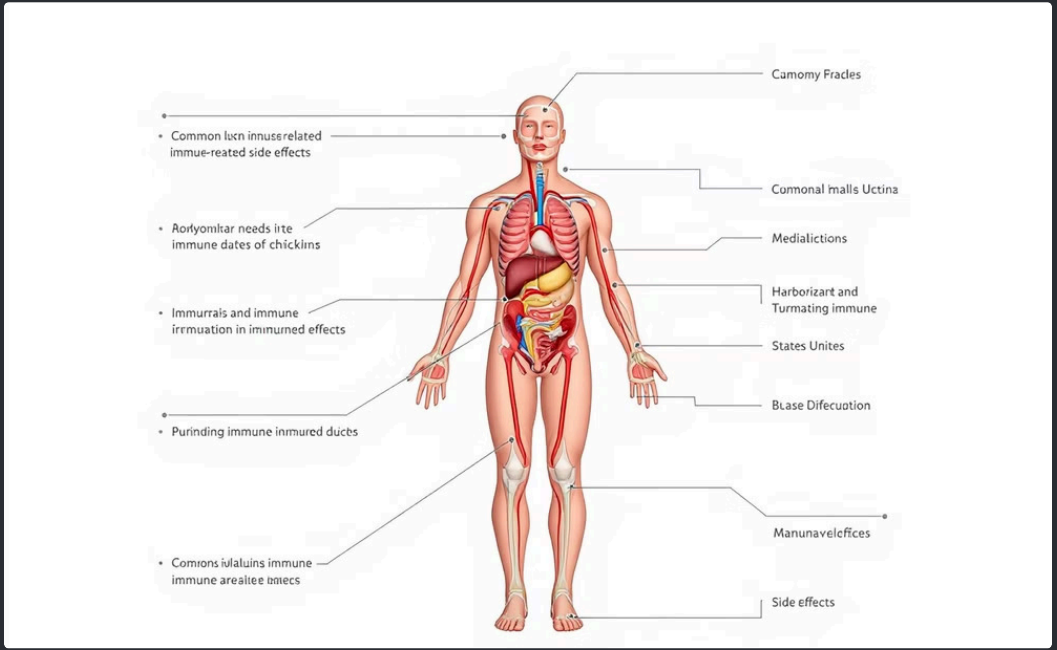
Nivolumab Alone

Single-agent immunotherapy every 2 weeks for 6 doses, then every 4 weeks

Chemotherapy

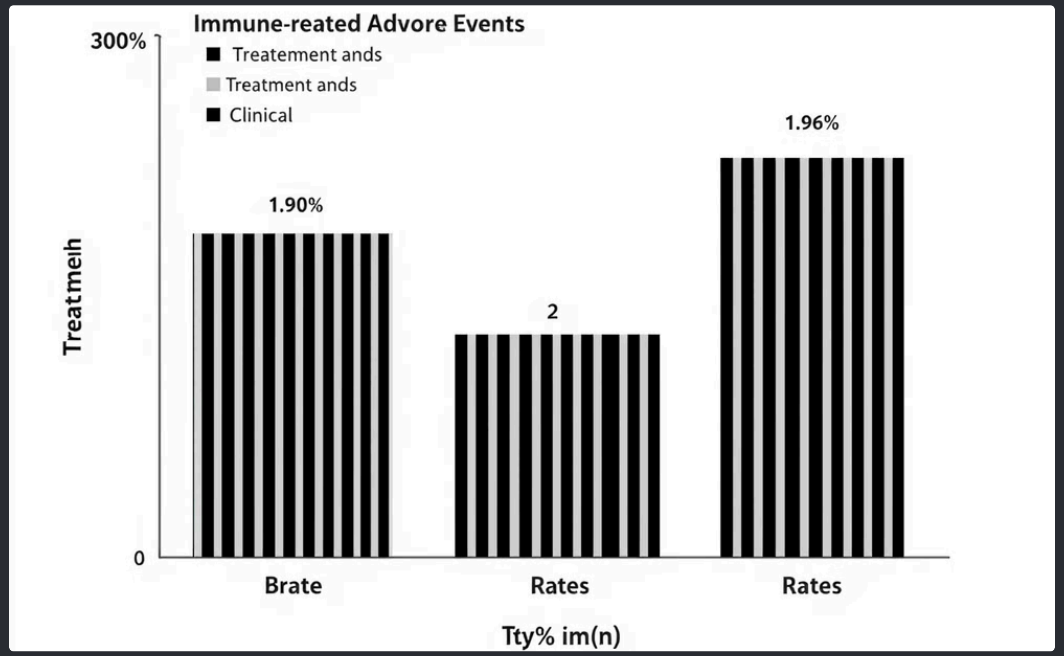
FOLFOX or FOLFIRI +/- bevacizumab or cetuximab

Immune-Mediated Adverse Events



Common IMAEs

Skin reactions, colitis, hepatitis, endocrinopathies were most frequent



Comparison Between Arms

Marginal differences in IMAE rates between nivolumab+ipilimumab and nivolumab alone

Next Steps

1

Regulatory Submissions

Marketing authorization initiated in Europe

2

Reimbursement Discussions

Engage payers on value of dual immunotherapy

3

Clinical Practice Updates

Incorporate findings into treatment guidelines

Conclusions

Practice-Changing Results

Nivolumab+ipilimumab shows superior efficacy in MSI-H/dMMR mCRC

New Standard of Care

Dual immunotherapy emerging as first-line option

Toxicity Management

Close monitoring needed for immune-related adverse events

Patient Selection

Consider patient factors when choosing between mono- and dual therapy