Benefit of Dual Immunotherapy in GI Cancers

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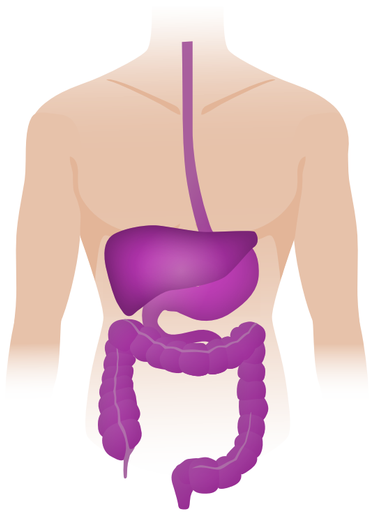
Immunotherapy in GI Cancers

Immunotherapy with standard PD(L)-1 or CTLA-4 ICIs has transformed the treatment of melanoma and NSCLC. However, until recently, this approach has shown limited benefit in GI cancer.[1]



Recent and ongoing studies demonstrate the benefit of dual immunotherapy combination therapy compared with conventional therapy in GI cancers, including CRC and HCC.[2-8]

Abbreviations
chemo: chemotherapy; CI: confidence interval; CR: complete response; CRC: colorectal cancer; ctDNA: circulating tumor DNA; CTLA: cytotoxic T lymphocyte–associated antigen-4; dMMR: deficient DNA mismatch repair; GI: gastrointestinal; HCC: hepatocellular carcinoma; HR: hazard ratio; ICI: immune checkpoint inhibitor; IPI: ipilimumab; LEN: lenvatinib; mCRC: metastatic colorectal cancer; mo: months; MRD: minimal residual disease; MSI-H: microsatellite instability-high; NE: not evaluable; NIVO: nivolumab; NR: not reported; NSCLC: non-small cell lung cancer; OS: overall survival; PD(L): programmed cell death protein (ligand) 1; PFS: progression-free survival; Q3W: once every 3 weeks; Q4W: once every 4 weeks; SOR: sorafenib; TRAE: treatment-related adverse event.

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CRC: CheckMate 8HW (NCT04008030)

Randomised Phase III study: NIVO + IPI versus NIVO or chemo in MSI-H/dMMR mCRC.[2,3]

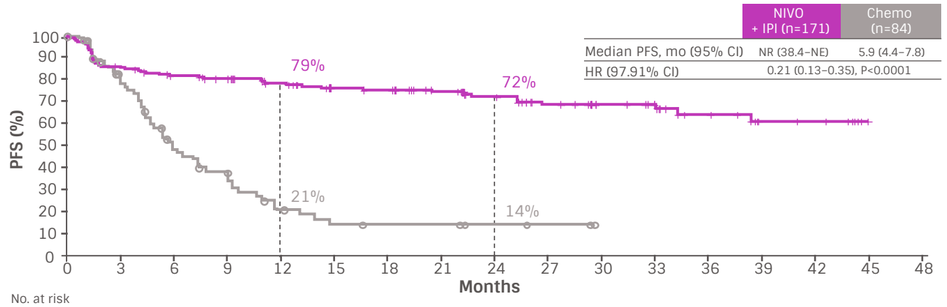
79% — NIVO + IPI showed a **79% reduction** in risk of disease progression or death (**median follow-up: 31.5 months**).[2,3]

PFS benefit with NIVO + IPI was seen across all prespecified patient subgroups, including *KRAS* or *NRAS* mutations, and liver, lung, or peritoneal metastases.[2,3]

Overall safety profile favoured NIVO + IPI: Patients receiving NIVO + IPI had fewer Grade 3–4 TRAEs **23%** versus **48%** for chemotherapy.[2,3]

PFS in the centrally confirmed population (median follow-up: 31.5 months)[2]

Clinically meaningful and statistically significant improvement in PFS (NIVO + IPI versus chemo)



Previously untreated patients were randomised 2:2:1 to NIVO (240 mg) + IPI (1 mg/kg) Q3W (four doses, then NIVO 480 mg Q4W), NIVO (240 mg) Q2W (six doses, then NIVO 480 mg Q4W), or chemo ± targeted therapies; treatments continued until disease progression or unacceptable toxicity, or a maximum of 2 years (NIVO ± IPI arms).

CRC: NICHE-2 (NCT03026140)

Single-group Phase II study: Neoadjuvant NIVO + IPI in nonmetastatic, locally advanced, previously untreated dMMR colon cancer.[4,5]

Unprecedented 3-year disease-free survival of 100% (**median follow-up: 36.6 months**).[4]

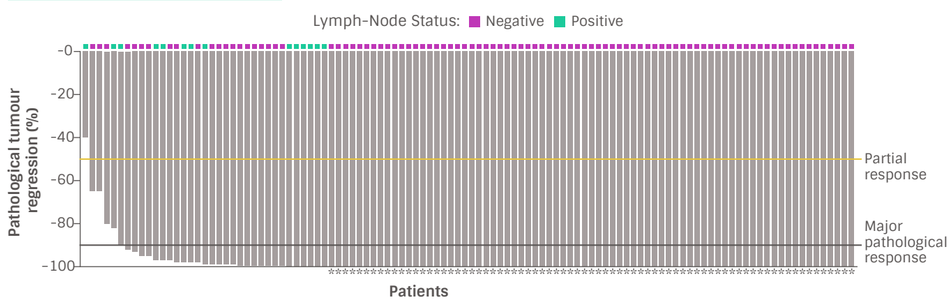
All patients were ctDNA negative at MRD timepoint (3 weeks after surgery).[4]

68% — Pathologic response was observed in 98% of 111 patients in efficacy analysis, with a major pathologic response (≤10% residual viable tumour) in 95% and a complete pathologic response in **68% of patients**.[4,5]

Neoadjuvant NIVO + IPI had an acceptable safety profile.[5]

Pathological response[5]

Pathological response in 98% of patients after 4 weeks of treatment.



*Patients with a pathological CR in both the primary tumour and the lymph nodes.
Black line: threshold for major pathological response (≥90% tumour regression).
Yellow line: threshold for partial response (≥50% regression).

HCC: CheckMate 9DW (NCT04039607)

Open-label, randomised Phase III study: NIVO + IPI versus LEN or SOR as first-line therapy for patients with unresectable HCC. >85% LEN was used,[6,7] compared to competitors who used SOR only.

Longer median OS and long-term survival benefit with **higher OS rates at 24 and 36 months** for NIVO + IPI versus LEN or SOR.[7]

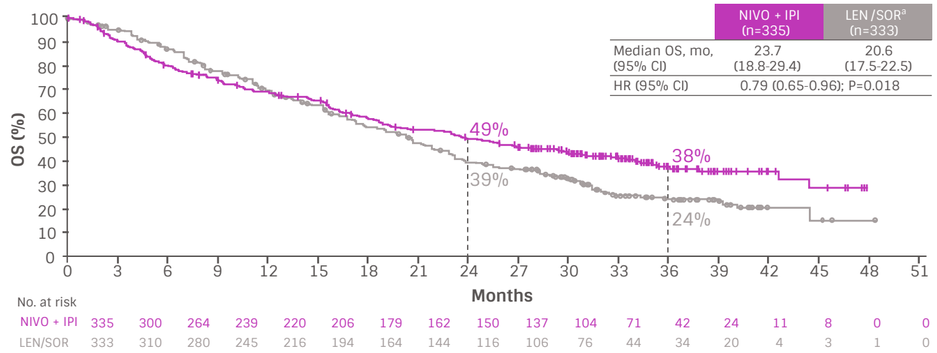
The safety profile of NIVO + IPI was manageable and consistent with the established safety profile of the regimen.[6]

Numerically higher PFS rates with NIVO + IPI versus LEN/SOR at:[7]
18 months **34%** versus **18%**
24 months **28%** versus **12%**

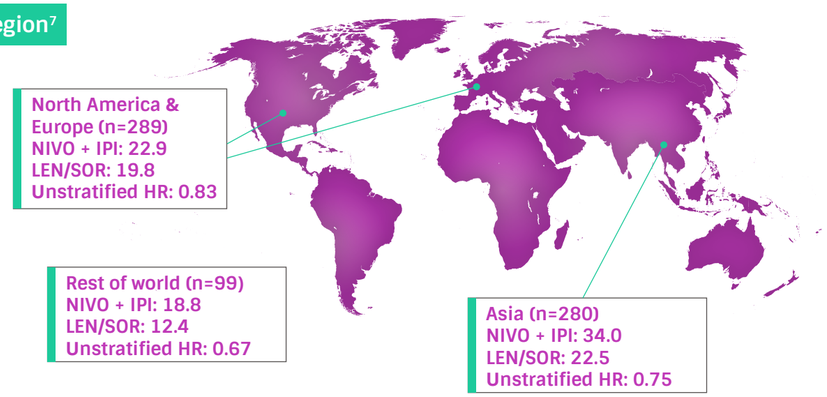
The benefit of NIVO + IPI was consistent in all regions, including Asia, North America/Europe, and the rest of the world.[7]

OS (median follow-up: 35.2 months)[8]

Statistically significant and clinically meaningful OS benefit (NIVO + IPI versus LEN/SOR)[8]



OS by region[7]



Key Takeaways

Results of CheckMate 8HW, NICHE-2, and CheckMate 9DW demonstrate the benefit of combination immunotherapy in CRC and HCC.[2-8]

CheckMate 8HW and CheckMate 9DW support first-line use of NIVO + IPI as a standard-of-care option for patients with MSI-H/dMMR mCRC and unresectable HCC.[3,7]